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Fluvoxamine versus other anti-depressive agents for depression (Review)

Omori IM, Watanabe N, Nakagawa A, Cipriani A, Barbui C, McGuire H, Churchill R, Furukawa TA

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[Intervention Review]

Fluvoxamine versus other anti-depressive agents for depression

Ichiro M Omori¹, Norio Watanabe², Atsuo Nakagawa³, Andrea Cipriani⁴, Corrado Barbui⁴, Hugh McGuire⁵, Rachel Churchill⁶, Toshi A Furukawa⁷

¹Department of Psychiatry, Toyokawa City Hospital, Aichi, Japan. ²Department of Psychiatry & Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan. ³Department of Psychiatry and the Center for Clinical Research, Keio University School of Medicine, Tokyo, Japan. ⁴Department of Public Health and Community Medicine, Section of Psychiatry, University of Verona, Verona, Italy. ⁵National Collaborating Centre for Women's and Children's Health, London, UK. ⁶Centre for Mental Health, Addiction and Suicide Research, School of Social and Community Medicine, University of Bristol, Bristol, UK. ⁷Departments of Health Promotion and Behavior Change and of Clinical Epidemiology, Kyoto University Graduate School of Medicine / School of Public Health, Kyoto, Japan

Contact: Ichiro M Omori, Department of Psychiatry, Toyokawa City Hospital, Koumei 1-19, Toyokawa, Aichi, 442-8561, Japan. ichiro.m.omori@gmail.com, mmds@sannet.ne.jp.

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ABSTRACT

Background

Fluvoxamine, one of the oldest selective serotonin reuptake inhibitors (SSRIs), is prescribed to patients with major depression in many countries. Several studies have previously reviewed the efficacy and tolerability of fluvoxamine for the treatment of major depression. However, these reviews are now outdated.

Objectives

Our objective is to evaluate the effectiveness, tolerability and side effect profile of fluvoxamine for major depression in comparison with other anti-depressive agents, including tricyclics (TCAs), heterocyclics, other SSRIs, SNRIs, other newer agents and other conventional psychotropic drugs.

Search methods

We searched the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register. Trial databases and ongoing trial registers in North America, Europe, Japan and Australia, were handsearched for randomised controlled trials. We checked reference lists of the articles included in the review, previous systematic reviews and major textbooks of affective disorder for published reports and citations of unpublished research. The date of last search was 31 August 2008.

Selection criteria

We included all randomised controlled trials, published in any language, that compared fluvoxamine with any other active antidepressants in the acute phase treatment of major depression.

Data collection and analysis

Two independent review authors inspected citations and abstracts, obtained papers, extracted data and assessed the risk of bias of included studies. We analysed dichotomous data using odds ratios (ORs) and continuous data using the standardised mean difference (SMD). A random effects model was used to combine studies.

Main results

A total of 54 randomised controlled trials ($n = 5122$) were included. No strong evidence was found to indicate that fluvoxamine was either superior or inferior to other antidepressants regarding response, remission and tolerability. However, differing side effect profiles were evident, especially with regard to gastrointestinal side effects of fluvoxamine when compared to other antidepressants. For example, fluvoxamine was generally associated with a higher incidence of vomiting/nausea (versus imipramine, OR 2.23, CI 1.59 to 3.14; versus clomipramine, OR 2.13, CI 1.06 to 4.27; versus amitriptyline, OR 2.86, CI 1.31 to 2.63).

Authors' conclusions

We found no strong evidence that fluvoxamine was either superior or inferior to any other antidepressants in terms of efficacy and tolerability in the acute phase treatment of depression. However, differing side effect profiles were evident. Based on these findings, we conclude that clinicians should focus on practical or clinically relevant considerations, including these differences in side effect profiles.

PLAIN LANGUAGE SUMMARY

Fluvoxamine versus other anti-depressive agents for depression

Major depression is a severe mental illness characterised by a persistent and unreactive low mood and loss of all interest and pleasure, usually accompanied by a range of symptoms including appetite change, sleep disturbance, fatigue, loss of energy, poor concentration, psychomotor symptoms, inappropriate guilt and morbid thoughts of death. Although pharmacological and psychological interventions are both effective for major depression, antidepressant (AD) drugs remain the mainstay for treatment of moderate or severe depression. Fluvoxamine is one of the oldest selective serotonin reuptake inhibitors (SSRIs) and is prescribed to patients with major depression in many countries. This review reports trials comparing fluvoxamine with other antidepressants for treatment of major depression. We found no strong evidence that fluvoxamine was either superior or inferior to any other antidepressants in terms of efficacy and tolerability in the acute phase treatment of depression. However, there is evidence of differing side-effect profiles, especially when comparing gastrointestinal side effects between fluvoxamine and tricyclic antidepressants (TCAs). Based on these findings, we conclude that clinicians should focus on practical or clinically relevant considerations including these differences in side effect profiles.

BACKGROUND

Description of the condition

Major depression is generally diagnosed when a persistent and unreactive low mood and loss of all interest and pleasure are usually accompanied by a range of symptoms including appetite change, sleep disturbance, fatigue, loss of energy, poor concentration, psychomotor symptoms, inappropriate guilt, and morbid thoughts of death (APA 1994). In 2002, major depression was the third leading health burden in the world, following only lower respiratory infections and HIV/AIDS, and accounting for 4.5% of total human suffering related to health concerns. Moreover, the incidence of depression is expected to rise during the next 20 years (WHO 2006). The depressed condition is associated with a marked personal, social and economic morbidity, coupled with a loss of functioning and productivity, which creates significant demands on health service provider workloads (NICE 2004). In the USA, Greenberg 2003 estimated the economic burden of depression to be just over \$83 billion in 2000. Of this total, \$26 billion came from direct treatment costs, \$5 billion came from suicide-related costs, and \$52 billion came from workplace costs. These figures were also suspected to underestimate the true economic burden of the disease, as they did not take into account factors such as the burden on family members and caregivers, the cost of lost productivity while at work, and costs associated with those who remain untreated (Greenberg 2005).

Description of the intervention

Fluvoxamine ((*E*)-5-methoxy-1-[4-(trifluoromethyl)phenyl]pentan-1-one *O*-2-aminoethyl oxime) is a selective serotonin reuptake inhibitor (SSRI) that has been available as an antidepressant since 1983 in many countries – 87 countries and regions as of 2006, including some European countries and Japan. It is also available in many countries for anxiety disorders, including obsessive-compulsive disorder and social anxiety disorder. Fluvoxamine is structurally different from the tricyclic antidepressants (TCAs), heterocyclics, and other classes of antidepressants, and also differs chemically from various other SSRIs. For example, fluvoxamine is the only monocyclic SSRI and it belongs to the 2-aminoethylloximethers of aralkylketones (Claassen 1977; Fuller 1987). Therefore, some differential clinical potency may be expected, not only between the drugs classes but also among the SSRIs.

How the intervention might work

Fluvoxamine is well absorbed after oral administration and is widely distributed throughout the body. Plasma protein binding of fluvoxamine is low (77%), compared with other SSRIs. Fluvoxamine displays nonlinear, steady-state pharmacokinetics throughout the therapeutic range, with disproportionately higher plasma concentrations at higher doses (Perucca 1994). However, plasma fluvoxamine concentrations show no clear relationship with patient responses to the antidepressant or to the severity of adverse effects. Fluvoxamine pharmacokinetics remains unaltered by increasing age or by renal impairment. Fluvoxamine is metabolized in the liver by the cytochrome P450 (CYP) enzyme system. It has a prominent affinity for the CYP1A2 isozyme, a lesser affinity for the CYP3A4 and CYP2C isozymes, and a minimal affinity for CYP2D6. Fluvoxamine impairs metabolic elimination of a number of drugs, including TCAs (tertiary, but not secondary,

amines), alprazolam, bromazepam, diazepam, theophylline, propranolol and, possibly, carbamazepine. It generates no active metabolites. Smoking is known to increase CYP1A2 activity, and smokers appear to have lower serum concentration of fluvoxamine compared with non-smokers (Spigset 1995). The drug is eliminated with a mean half-life of 15 hours, with a range from nine to 28 hours. Excretion is primarily in the urine, predominantly as metabolites (van Harten 1995).

Why it is important to do this review

Although pharmacological and psychological interventions are both effective for major depression, antidepressant (AD) drugs remain the mainstay for treatment of moderate or severe depression (APA 2000; Ellis 2004; NICE 2004). Many different AD agents are available, including TCAs, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs: venlafaxine, duloxetine, milnacipran), and other newer agents (mirtazapine, reboxetine, bupropion). In many Western countries, AD consumption has risen dramatically over the last 20 years, mainly because of the increasing consumption of SSRIs and newer ADs, which have progressively become the most commonly prescribed ADs (Ciuna 2004; Guaiana 2005). SSRIs are generally better tolerated than TCAs (Barbui 2000), and there is evidence of similar efficacy (Anderson 2000; Geddes 2000; Williams 2000). However, head-to-head comparisons have provided contrasting findings. Amitriptyline, for example, may have an edge over SSRIs in terms of efficacy (Guaiana 2007), while individual SSRIs and SNRIs may differ in terms of efficacy and tolerability (Cipriani 2005; Cipriani 2009; Puech 1997; Smith 2002;).

Two systematic reviews on fluvoxamine exist in current literature. Burton (Burton 1991) reviewed 17 double-blind comparative studies between fluvoxamine and other ADs in depressed patients. Ware (Ware 1997) reviewed 31 controlled trials of fluvoxamine in the pharmacotherapy of depression. These reviews are now quite outdated and neither has provided meta-analytic summaries.

A group of researchers therefore agreed to join forces under the rubric of the Meta-Analyses of New Generation Antidepressants Study Group (MANGA Study Group), in order to systematically review all available evidence for each specific newer antidepressant. As of February 2010, we have completed an individual review for fluoxetine (Cipriani 2006), mirtazapine (Watanabe 2008), milnacipran (Nakagawa 2007), escitalopram (Cipriani 2009a) and sertraline (Cipriani 2009b) and have published the protocols for citalopram (Imperadore 2007), duloxetine (Nose 2007), paroxetine (Cipriani 2007b), venlafaxine (Cipriani 2007c) and reboxetine (Churchill 2009). The multiple-treatment meta-analysis of 12 new-generation antidepressants has also been published (Cipriani 2009).

In the present review, we report head-to-head comparisons not only between fluvoxamine and the other 11 new-generation antidepressants, but also between fluvoxamine and older antidepressants, providing detailed accounts of their comparative side effect profiles.

OBJECTIVES

1. To determine the efficacy of fluvoxamine compared to other antidepressive agents, including older antidepressants such as TCAs

and newer ones such as SSRIs, in alleviating the acute symptoms of depression.

2. To review acceptability of treatment with fluvoxamine compared with that of other antidepressive agents.

3. To investigate the adverse effects of fluvoxamine compared to other antidepressive agents.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were included. Quasi-randomised trials, such as those allocating by using alternate days of the week, were excluded. For trials that have a crossover design, only results from the first randomisation period were considered.

Types of participants

The review included patients 18 or older, of both sexes, with a primary diagnosis of depression and studies adopting standardised criteria (DSM-III / DSM-III-R, DSM-IV (APA 2000), ICD-10 (WHO 1992), Feighner criteria (Feighner 1972) or Research Diagnostic Criteria (Spitzer 1972) to define patients suffering from unipolar major depression. Studies using ICD-9 were excluded, as it has only disease names and no diagnostic criteria.

We included the following subtypes of depression: chronic, with catatonic features, with melancholic features, with atypical features, with postpartum onset, and with seasonal pattern. We also included studies in which up to 20% patients presented depressive episodes in bipolar affective disorder. When depressive patients in the trial had psychotic features, we included those studies in which up to 20% patients presented psychotic features. A concurrent secondary diagnosis of another psychiatric disorder was not considered an exclusion criterion. A concurrent primary diagnosis of Axis I or II disorders was an exclusion criterion. AD trials in depressive patients with a serious concomitant medical illness were excluded.

Types of interventions

We have examined fluvoxamine intervention in comparison with conventional treatment of acute depression. We also examined fluvoxamine intervention in comparison with non-conventional (e.g., herbal products, such as Hypericum) antidepressive agents (Linde 2008). Trials in which fluvoxamine was compared to another type of psychopharmacological agent (i.e., anxiolytics, anticonvulsants, antipsychotics or mood-stabilizers) were excluded. We also excluded trials in which fluvoxamine was used as an augmentation strategy.

Eligible intervention:

1. Fluvoxamine: any dose and mode or pattern of administration.

Eligible comparators:

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

2.1 Tricyclics (TCAs)

2.2 Heterocyclics

2.3 SSRIs

2.4 SNRIs

2.5 MAOIs or newer antidepressants (ADs)

2.6 Other conventional psychotropic drugs

3. Non-conventional anti-depressive agents

3.1 Herbal products

3.2 Other non-conventional anti-depressive agents

Types of outcome measures

Primary outcomes

1. Response - acute phase

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

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

(i) Response - early phase: between 1 and 4 weeks, with the time point closest to 2 weeks given preference.

(ii) Response - acute phase: between 6 and 12 weeks, with preference given to the time point given in the original study as the study endpoint.

(iii) Response - follow-up phase: between 4 and 6 months, with the time point closest to 24 weeks given preference.

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

Secondary outcomes

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

2. Remission - early phase, acute phase, and follow-up phase

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

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

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

(Hall 1995)

5. Health-related quality of life (QOL)

We limited ourselves to SF-12 (Ware 1998); SF-36 (Ware 1992), HoNOS (Wing 1998) and the WHO 2009-QOL (WHOQOL Group 1998).

6. Costs to health care services.

7. Tolerability

7.1 Total dropout

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

7.2 Dropout due to inefficacy

Number of patients who dropped out during the trial because the fluvoxamine was ineffective as a proportion of the total number of randomised patients.

7.3 Dropout due to side effects

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

7.4 Number of patients experiencing at least one side effect

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

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

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

Search methods for identification of studies

Electronic searches

We initially identified RCTs on June 2, 2006 by following the Cochrane Collaboration Depression, Anxiety and Neurosis (CCDAN) criteria for search strategy using the register of CCDAN Review Group Controlled Trials Registers (CCDANCTR-Studies and CCDANCTR-References). The registers are compiled from systematic and regularly updated searches of the Cochrane Central Register of Controlled Trials (CENTRAL) - the most comprehensive source of reports of RCTs - , MEDLINE, EMBASE, CINAHL, PsycINFO,

PSYINDEX, and LILACS and handsearched of major psychiatric and medical journals as well as conference proceedings. Trial databases (e.g., the Medicines and Healthcare products Regulatory Agency in the UK) and ongoing trial registers (e.g., clinicaltrials.gov in the USA) in North America, Europe, Japan and Australia, were handsearched for published, unpublished and ongoing RCTs.

CCDANCTR-Studies was searched using the following search strategy:

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

Intervention = Fluvoxamine

CCDANCTR-References was searched using the following search strategy:

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

Free-Text = Fluvoxamine

The researchers conducted additional searches on the CCDAN Review Group Controlled Trials Registers, MEDLINE and checked various meta-analysis and review articles on the 26th October 2009 (CCDAN Registers up-to-date as of 31 August 2008).

Searching other resources

1. Handsearches

We searched trial databases of the following drug-approving agencies for published, unpublished and ongoing controlled trials: the Food and Drug Administration (FDA) in the USA, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, the European Medicines Agency (EMA) in the EU, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and the Therapeutic Goods Administration (TGA) in Australia. We also searched ongoing trial registers such as clinicaltrials.gov in the USA, International Standard Randomised Controlled Trial Number Register (ISRCTN) and the National Research Register in the UK, Nederland's Trial Register in the Netherlands, European Union Drug Regulating Authorities Clinical Trials (EudraCT) in the EU, UMIN-CTR in Japan and the Australian Clinical Trials Registry in Australia. These searches were undertaken in November 2007.

Appropriate journals and conference proceedings relating to fluvoxamine treatment for depression have already been handsearched and incorporated into the CCDANCTR databases.

2. Personal communication

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

3. Reference checking

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

Data collection and analysis

Selection of studies

HMG and another independent review author checked to ensure that studies relating to fluvoxamine generated by the search strategies of the CCDANCTR-References and the other complementary searches met the rough inclusion criteria, firstly based on the title and abstracts. All of the studies that were rated as possible candidates by either of the two review authors were added to the preliminary list, and their full texts were retrieved. TAF and IMO then assessed all of the full text articles in this preliminary list to see if they met the strict inclusion criteria. If the raters disagreed, the final rating was made by consensus with the involvement - if necessary - of another member of the review group. Non-congruence in selection of trials was reported as *akappa* statistic. Considerable care was taken to exclude duplicate publications.

Data extraction and management

IMO and NW extracted data from the included studies. Again, any disagreement was discussed, and decisions were documented. If necessary, we contacted authors of studies for clarification. We extracted the following data:

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

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

Assessment of risk of bias in included studies

Risk of bias was assessed independently by two review authors (IMO and NW) using criteria described in the Cochrane Collaboration Handbook (Higgins 2008). This set of criteria is based on evidence of associations between effect overestimation and a high risk of bias in an article, such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

The categories are defined below:

- YES - low risk of bias
- NO - high risk of bias
- UNCLEAR - uncertain risk of bias

Measures of treatment effect

All comparisons were performed between fluvoxamine and comparator ADs as a class and as individual ADs.

1. Dichotomous data

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

2. Continuous data

For continuous data, mean differences (MD) or standardized mean differences (SMD) - where different measurement scales, were calculated with its 95% CI.

Unit of analysis issues

1. Cross-over trials

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

2. Cluster-randomised trials

No cluster randomised trials were identified for this version of the review. Should they be identified in a future update, we plan to use the generic inverse variance technique, if such trials have been appropriately analysed taking into account intraclass correlation coefficients to adjust for cluster effects.

Dealing with missing data

1. Dichotomous data

Responders and remitters to treatment were calculated on the strict intention-to-treat (ITT) basis: dropouts were included in this analysis. Where participants have been excluded from the trial before the endpoint, we have assumed that they experienced a negative outcome by the end of the trial (e.g., failure to respond to treatment). We examined the validity of this decision in the sensitivity analyses by applying worst- and best-case scenarios. If a statistically significant difference was found, the number needed to treat (NNT) was calculated from an odds ratio obtained by a meta-analysis (Higgins 2008). We applied the loose ITT analyses for continuous variables, whereby all the patients with at least one post-baseline measurement were represented by their last observations carried forward (LOCF), with due consideration of the potential bias and uncertainty introduced.

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

2. Continuous data

When there were missing data and the method of "last observation carried forward" (LOCF) had been used to do an ITT analysis, then the LOCF data were used. When SDs were missing, we presented data descriptively.

Assessment of heterogeneity

Heterogeneity between studies was assessed by visual inspection of the results in the forest plots. Statistic (the I^2 statistic and the Q statistic) were interpreted with caution, since non-significant results of statistical tests for heterogeneity cannot be regarded as evidence of heterogeneity (Higgins 2008). If the CIs for the results of individual comparisons had poor overlap, I^2 was equal to or more than 50% and P values were smaller than 0.1 (Higgins 2003), potential sources of heterogeneity were investigated. We performed subgroup analyses to investigate heterogeneity (see [Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

Data from included studies were entered into a funnel plot (trial effect against trial variance) to investigate small-study effects (Sterne 2000). We used the tests for funnel plot asymmetry only when there were at least 10 studies included in the meta-analysis, and results were interpreted cautiously, with visual inspection of the funnel plots (Higgins 2008). When evidence of small-study effects was identified, possible reasons for funnel plot asymmetry, including publication bias, were investigated.

Data synthesis

The primary analysis used a random effects model (odds ratio [OR]), which had the highest generalisability in our empirical examination of summary effect measures for meta-analyses (Furukawa 2002a). The robustness of this summary measure was routinely examined by checking the fixed-effect model OR and the random effects model risk ratios (RRs). Material differences between the models were reported. A p value of less than 0.05 and a 95% confidence interval (CI) were considered statistically significant.

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

Subgroup analysis and investigation of heterogeneity

We performed the following subgroup analyses for primary outcome where possible, for the following *a priori* reasons. Results were interpreted with caution, since multiple comparisons could lead to false positive conclusions (Oxman 1992).

1. Fluvoxamine dosing (fixed low dosage, fixed standard dosage, fixed high dosage; flexible low dosage, flexible standard dosage, flexible high dosage)

Existing evidence implies that low dosage antidepressants may be associated with better outcomes - both in terms of effectiveness and side effects - than standard or high dosage antidepressants (Bollini 1999; Furukawa 2002b). In addition, a fixed versus flexible dosing schedule may affect estimates of treatment effectiveness (Khan 2003). In the case of fluvoxamine, based on the Defined Daily Dosage (DDD) by WHO (WHO 2009), low dosage is referred to as <100, standard dosage to ≥ 100 but <200, and high dosage to ≥ 200

mg/day. We categorized studies by intended maximum dosage of fluvoxamine.

2. Comparator dosing (low dosage, standard dosage, and high dosage)

It is easy to imagine that people taking a comparator drug are less likely to complete a study if they are taking a high dosage of the comparator drug. We categorized studies by the intended maximum dose of fluvoxamine based on the DDD. Since WHO 2009 does not report DDD of milnacipran, we categorized these studies based on previous reports (Lecrubier 1996; Lopez-Ibor 1996; Okamura 2006), where low dosage refers to <100, standard dosage to ≥ 100 but <150, and high dosage to ≥ 150 mg/day.

3. Depression severity (severe major depression, moderate/mild major depression)

"Severe major depression" was defined by a threshold baseline severity score for entry of 25 or more for HRSD and 31 or more for MADRS (Dozois 2004; Muller 2003).

4. Treatment settings (psychiatric inpatients, psychiatric outpatients, primary care)

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

5. Elderly patients (≥ 65 years of age), separately from other adult patients

Older people may be more vulnerable to side effects associated with antidepressants and decreased dosage is often recommended for them (Depression Guideline Panel 1993).

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

Sensitivity analysis

The following sensitivity analyses for primary outcome were planned *a priori*. By limiting the included studies to those with higher quality (analysis 1 to 5) or to those free from some "bias" (analysis 6 to 9), we examined whether the results changed and we intended to check for the robustness of the observed findings.

1. We excluded trials with unclear concealment of random allocation and/or unclear double blinding.
2. We excluded trials with a dropout rate greater than 20%.
3. We performed the worst-case scenario ITT: that all patients in the experimental group experience the negative outcome and all those in the comparison group experience the positive outcome.
4. We performed the best-case scenario ITT: that all patients in the experimental group experienced the positive outcome and all those in the comparison group experienced the negative outcome.

5. We excluded trials for which the response rates had to be calculated based on the imputation method (Furukawa 2005) and for which the SD had to be borrowed from other trials (Furukawa 2006).

6. We examined a "wish bias" by comparing the trials where fluvoxamine was used as an investigational drug, the drug that was used as a new compound, to the trials where fluvoxamine was used as a comparator, since some evidence suggests that a new antidepressant might perform worse when used as a comparator than when used as an investigational agent (Barbui 2004).

7. We excluded trials funded by, or with at least one author affiliated with, a pharmaceutical company marketing fluvoxamine. This sensitivity analysis is particularly important in light 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 increased over the past 20 years (Buchkowsky 2004).

8. We excluded studies that included patients with bipolar depression.

9. We excluded trials studies that included patients with psychotic features.

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

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

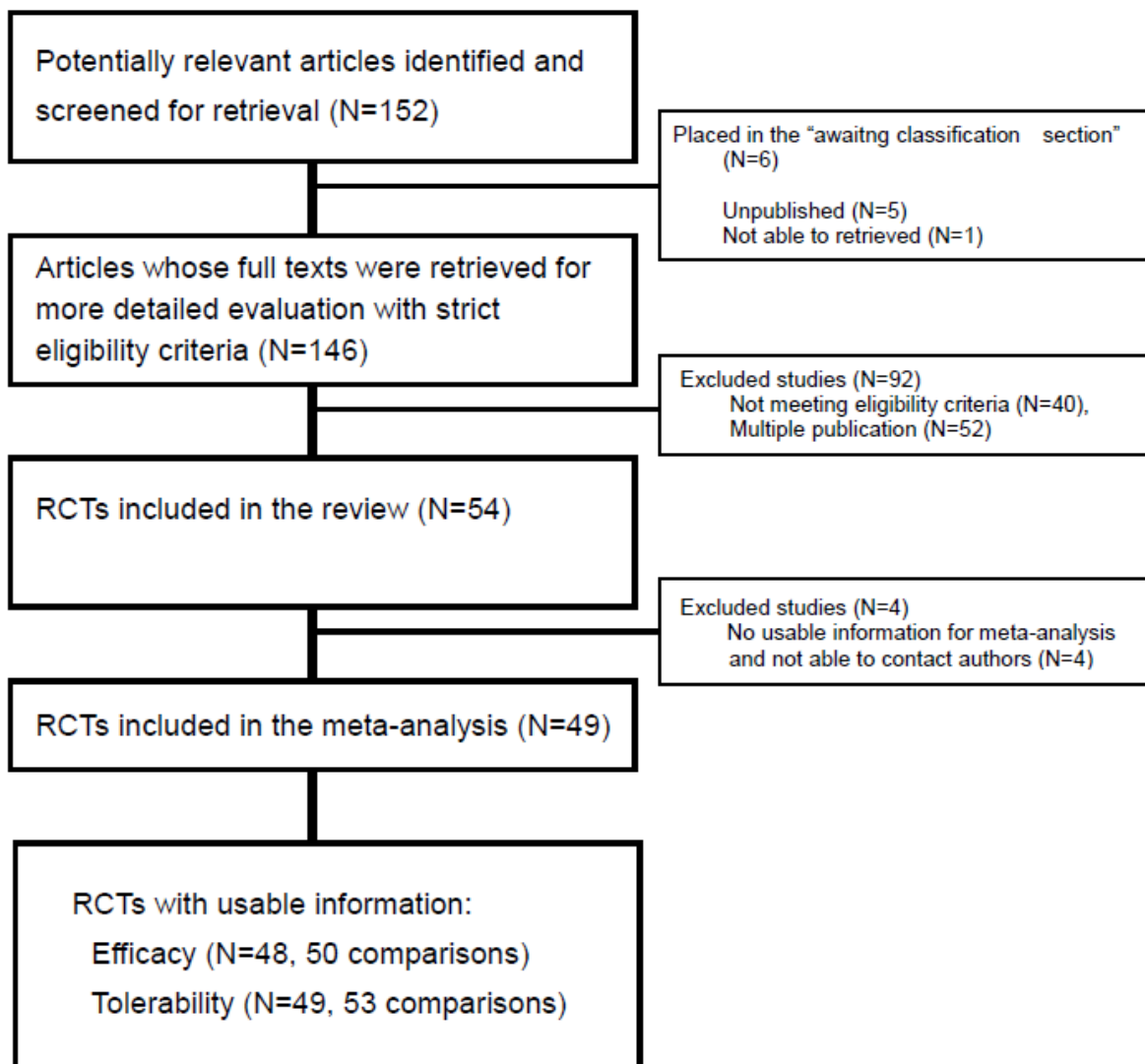
RESULTS

Description of studies

Results of the search

Initially, we identified 152 references considered relevant for our review. Of these, five trials were unpublished (Coleman 1981a; Coleman 1981b; Coleman 1983; Doogan 1981; van Beek 1981), and one trial was written in Hungarian and was not retrieved. These trials has been placed on the list of studies awaiting assessment (Faludi 1989). The remaining 146 references were retrieved for more detailed evaluation (Figure 1).

Figure 1. Flow diagram for the trials



RCT, randomised controlled trial

Additional searches conducted on the 26th October 2009 (CCDAN Registers up-to-date as of 31 August 2008) found 6 trials (Berlin 1998, Donovan 1993, Entsuah 2002b, Mallick 2003, Naito 2007, Ushiroyama 2004) which might be included in the an update of this review. We have placed these articles on the list of studies awaiting assessment.

Included studies

See: [Included studies](#), [Figure 1](#).

We were able to include 54 studies (56 comparisons). All studies included were randomised trials. The inter-rater reliability in selection of trials was satisfactory, with weighted *kappa* of 0.77.

We mailed or e-mailed or phoned the authors with known contact details to obtain extra information we sought. We had replies from

the authors of 23 trials. Among them, we were able to obtain unpublished data from 15 trials including 17 comparisons (Ansseau 1991a; Ansseau 1991b; Barge-Schaapveld 1995; Cassano 1986; Dalery 2003; Hackett 1998a; Hackett 1998b; Kasper 1990; Kato 2006; Nathan 1990; Nemeroff 1995; Otsubo 2005; Rechlin 1994; Remick 1994; Rossini 2005; Schoemaker 2002; Ueda 2002).

1. Length of studies

Duration of treatment was relatively brief, with a mean of 5.5 weeks (range 2 to 10 weeks). There was one 2-week study, 20 4-week studies, 24 6-week studies, five 7-week studies, three 8-week studies and one 10-week study.

2. Setting

For 18 studies, treatment occurred in a psychiatric inpatient setting; for 21 studies, treatment occurred in a psychiatric outpatient setting; and in seven studies, treatment occurred in a combined inpatient/outpatient setting. Two studies were based on primary care settings (Barge-Schaapveld 1995; Moon 1991), and six did not specify their treatment settings.

3. Participants

All trials reported that participants suffered from major depression defined by operationalised diagnostic criteria; however, some studies included less than 20% of patients with bipolar depression (Anseau 1991a; Anseau 1991b; Asakura 2005; de Wilde 1983; Guy 1984; Haffmans 1996; Itil 1983; Kasper 1990; March 1990; Murasaki 1998a; Ottevanger 1995; Rossini 2005). In addition, 18 studies used diagnostic criteria such as "major depressive episode" (DSM-III or IV), "major affective disorder" (DSM-III), "depression" (Feighner criteria), or "unipolar or bipolar disorder" (Feighner criteria), and did not exclude patients with bipolar depression. Consequently, some studies might include patients with bipolar depression who were not specifically taken into account (Anseau 1994; Barrelet 1991; Bocksberger 1993; Bougerol 1992; Brunner 1994; Cassano 1986; Coleman 1982; Dalery 2003; Dick 1983; Gonul 1999; Harris 1991a; Moon 1991; Mullin 1988; Perez 1990; Rahman 1991; Rapaport 1996; Rota 2005; Zohar 2003). Some studies included less than 20% of depressive patients with psychotic features (Anseau 1991a; Anseau 1991b; Anseau 1994; Asakura 2005; Bramanti 1988; Clerc 2001; Haffmans 1996; Kasper 1990). In 25 studies, some elderly subjects (over 65 years old) were included, but the actual number of elderly people was not reported in most trials. One trial was for elderly patients only (Bocksberger 1993), while seven studies did not include any elderly patients. One trial (Claghorn 1996) only included patients with severe depression, defined by a score higher than 25 on the HRSD-17 at baseline.

4. Study size

Two studies did not report the number of patients included (Kavoussi 1999; Rota 2005). The mean sample size for remaining studies was 93, ranging from 23 (Barge-Schaapveld 1995) to 481 (Cassano 1986). The majority of the studies (38 RCTs) recruited fewer than 100 participants.

5. Interventions

There were 30 studies comparing fluvoxamine with TCAs, five studies including heterocyclics, 10 including SSRIs, three including SNRIs, four including newer antidepressants, and one comparing fluvoxamine with sulpiride and one four-arm study comparing

fluvoxamine with amitriptyline, doxepine and paroxetine (Rechlin 1994). We could not find studies comparing fluvoxamine with non-conventional anti-depressive agents such as herbal products. Regarding fluvoxamine dosing, the trials included five fixed and 43 flexible schedules, and one study did not state dosing schedule. Standard doses were used in 22 studies, and high doses in 28 studies. Four studies did not state fluvoxamine dosing.

6. Outcomes

Of the included 54 studies, five studies (Brown 1986; Gonul 1999; Kavoussi 1999; Rechlin 1994; Rota 2005) did not report efficacy data, and four studies (Kavoussi 1999; Miller 2001; Rechlin 1994; Rota 2005) did not report tolerability data that could be entered into a meta-analysis. We were unable to obtain further data because we could not contact the authors by any means, nor could we obtain extra information from these authors. The majority of the identified studies (44 studies) used the HRSD as a primary or secondary outcome measure, while a minority of studies used the MADRS and Clinical Global Impression scale (CGI).

Among the 50 studies reporting dropouts due to any reason, 42 reported dropouts due to side effects. Forty-one studies reported the number of patients experiencing individual side effects. It was unclear how these adverse effects were measured in terms of either severity or duration.

Excluded studies

See: [Excluded studies](#).

By assessing the 146 retrieved full texts, we found 52 articles that were duplicate publications. We assessed the remaining 94 studies for their eligibility and we excluded 40 articles that did not meet our inclusion criteria. Among those excluded, 19 were not randomised trials; three did not use an operationalised criteria to diagnose major depression; three included more than 20% of participants who suffered from bipolar disorder; four included patients with major depression with psychotic features; five included an Axis I disorder other than major depression or bipolar disorder; two did not compare fluvoxamine with other antidepressants; two had a crossover design and clinical data for the first randomisation period were not reported; one reported clinical data for the maintenance phase only, with no data for the acute phase; one study compared fluvoxamine against imipramine and a placebo, but clinical data were shown for comparison between antidepressants and the placebo, not between fluvoxamine and imipramine.

Risk of bias in included studies

See: [Included studies](#), [Figure 2](#), [Figure 3](#).

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

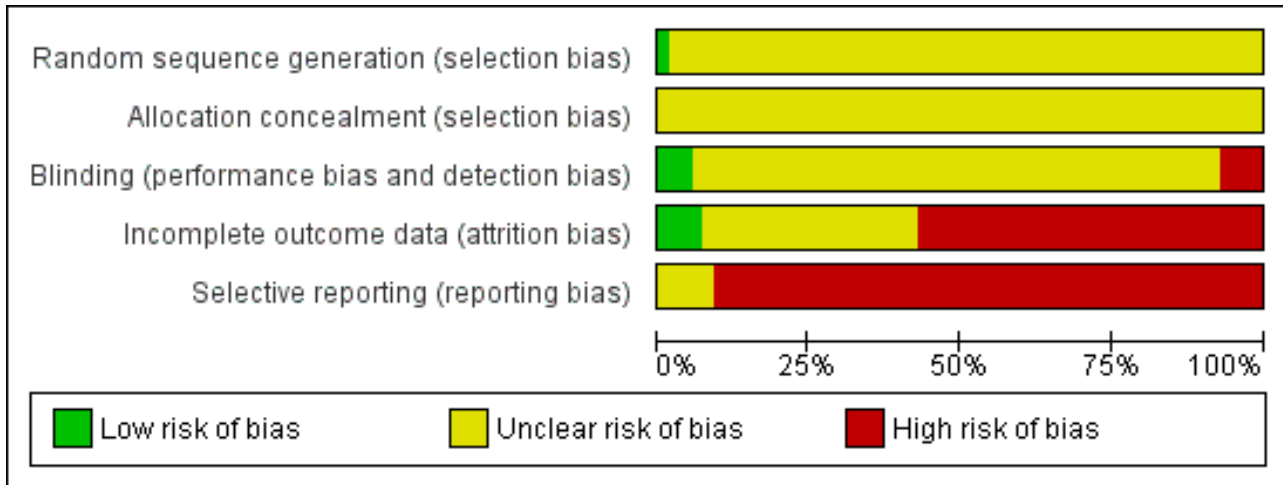


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Amore 1989	?	?	?	-	-
Ansseau 1991a	?	?	?	?	-
Ansseau 1991b	?	?	?	?	-
Ansseau 1994	?	?	?	-	-
Asakura 2005	?	?	?	?	?
Barge-Schaapveld 1995	?	?	-	-	-
Barrelet 1991	?	?	?	?	-
Bocksberger 1993	?	?	?	?	-
Bougerol 1992	?	?	?	-	-
Bramanti 1988	?	?	?	?	-
Brown 1986	?	?	?	?	-
Brunner 1994	?	?	-	?	-
Cassano 1986	?	?	?	-	-
Claghorn 1996	?	?	?	-	-
Clerc 2001	?	?	?	-	-
Coleman 1982	?	?	?	?	-
Dalery 2003	?	?	?	-	-
de Wilde 1983	?	?	?	+	-
Dick 1983	?	?	?	-	-
Fabre 1996	?	?	?	-	-
Feighner 1989	?	?	?	-	-
Gonul 1999	?	?	?	?	-

Figure 3. (Continued)

Gonul 1999	?	?	?	?	-
Guy 1984	?	?	?	?	-
Hackett 1998a	?	?	?	-	-
Hackett 1998b	?	?	?	-	-
Haffmans 1996	?	?	?	-	-
Harris 1991a	?	?	?	-	-
Itil 1983	?	?	?	-	-
Kasper 1990	?	?	?	?	-
Kato 2006	?	?	-	-	-
Kavoussi 1999	?	?	?	?	-
Kiev 1997	?	?	?	-	-
Koetsier 2002	?	?	?	?	-
Kostiukova 2003	?	?	?	-	-
Lydiard 1989	?	?	?	?	-
March 1990	?	?	?	-	-
Mendonca Lima 1997	?	?	-	+	-
Miller 2001	?	?	+	+	?
Moon 1991	?	?	?	-	-
Mullin 1988	?	?	?	-	-
Murasaki 1998a	?	?	?	-	-
Nathan 1990	?	?	?	?	-
Nemeroff 1995	?	?	?	-	-
Otsubo 2005	?	?	+	-	?
Ottevanger 1995	?	?	?	-	?
Perez 1990	?	?	?	-	-
Rahman 1991	?	?	?	-	-
Rapaport 1996	?	?	?	?	-
Rechlin 1994	?	?	?	?	-
Remick 1994	?	?	?	-	-
Rossini 2005	+	?	+	?	-
Rota 2005	?	?	?	-	-

Figure 3. (Continued)

Rota 2005	?	?	?	-	-
Schoemaker 2002	?	?	?	-	-
Tourigny-Rivard 1996	?	?	?	+	-
Ueda 2002	?	?	?	?	?
Zohar 2003	?	?	?	-	-

Our judgment about the overall risk of bias in the individual studies is illustrated in Figure 2 and Figure 3. The methodological quality of these included studies was judged as poor, although judging articles from some time ago by today's standard (Begg 1996; CONSORT) is problematic. Nevertheless, the reporting in these studies was not good. This type of reporting has been associated with an overestimate of the estimate of effect (Schulz 1995) and this should be considered when interpreting the results.

Allocation

Only one study reported the methods of generating random sequence, in which "a computer originated schedule" was used (Rossini 2005). No studies reported the method of allocation concealment. We were not assured that bias was minimised during the allocation procedure, yet 28 studies reported that the participants allocated to each treatment group were "similar", "the same", "not significantly different", "comparable" or "matched" (27/53 studies, 51%).

Blinding

Forty-three of the trials (80%) described their studies as "double blind"; however, no tests were conducted to ensure successful blinding. We rated only two studies among those 43 trials as having a "low risk of bias" (Miller 2001; Rossini 2005), as blinded raters conducted outcome assessment of those trials. In addition, one "single-blind" trial (Otsubo 2005) was rated as having a "low risk of bias" because its outcome assessment was blinded to the medication. Four trials were open trials that did not seek blinding (Barge-Schaapveld 1995; Brunner 1994; Kato 2006; Mendonca Lima 1997).

Incomplete outcome data

Total dropout rate was relatively high, ranging from 0% (de Wilde 1983; Mendonca Lima 1997; Miller 2001; Tourigny-Rivard 1996) to 59% (Claghorn 1996). There were twenty-seven studies (27/54, 50%) where the total dropout rates were more than 20%.

Selective reporting

The study protocol was not available for all studies. Four studies reported only "pituitary-adrenocortical status" (Brown 1986), "prolactin response to d-fenfluramine challenge" (Kavoussi 1999), "heart rate" (Rechlin 1994), or "hypothalamic-pituitary-adrenocortical axis activity" (Rota 2005) instead of reporting the clinical outcome for each intervention group. One study reported the clinical efficacy outcome only as "we could not find any significant difference" (Gonul 1999). Only ten studies reported SDs

of change scores (Asakura 2005; Harris 1991a; Kato 2006; Kiev 1997; Mendonca Lima 1997; Miller 2001; Nemeroff 1995; Otsubo 2005; Schoemaker 2002; Ueda 2002); 26 studies reported SDs of endpoint score of continuous efficacy variables.

Other potential sources of bias

Funding and wish bias

Most of the included studies (38 studies) were funded by industry. Among the 30 trials comparing fluvoxamine to TCAs, a great majority (21 trials) were sponsored by, or had at least one author affiliated with, a pharmaceutical company marketing fluvoxamine, and almost all of the trials (25 trials) set fluvoxamine as an investigational drug. Among the 24 trials comparing fluvoxamine with ADs other than TCAs, pharmaceutical companies marketing fluvoxamine sponsored 8 trials, and a company marketing the comparator drug funded 9 trials; only three trials set fluvoxamine as an investigational drug.

Effects of interventions

Of the 54 included studies (56 comparisons), 48 RCTs (50 comparisons) contributed usable data for the efficacy analyses and 49 RCTs (53 comparisons) did so for the tolerability analyses. No studies reported social adjustment/ functioning, health-related quality of life, and costs to health care services. ORs for the efficacy data larger than one (falling to the right of the midline) and those for the tolerability data smaller than one indicate a difference in favour of fluvoxamine. Negative SMDs (falling to the left of the midline) indicate a difference in favour of fluvoxamine.

To obtain response rate and remission, we used validated imputation methods, and if SDs were missing, we borrowed from other trials, if possible (See; Table 1, Table 2)

1. FLUVOXAMINE versus TCAs

Twenty-eight RCTs contributed usable data for the efficacy analyses and 28 RCTs for the tolerability analyses. Twenty-one trials reported dichotomous data for a number of patients who experienced each side effect.

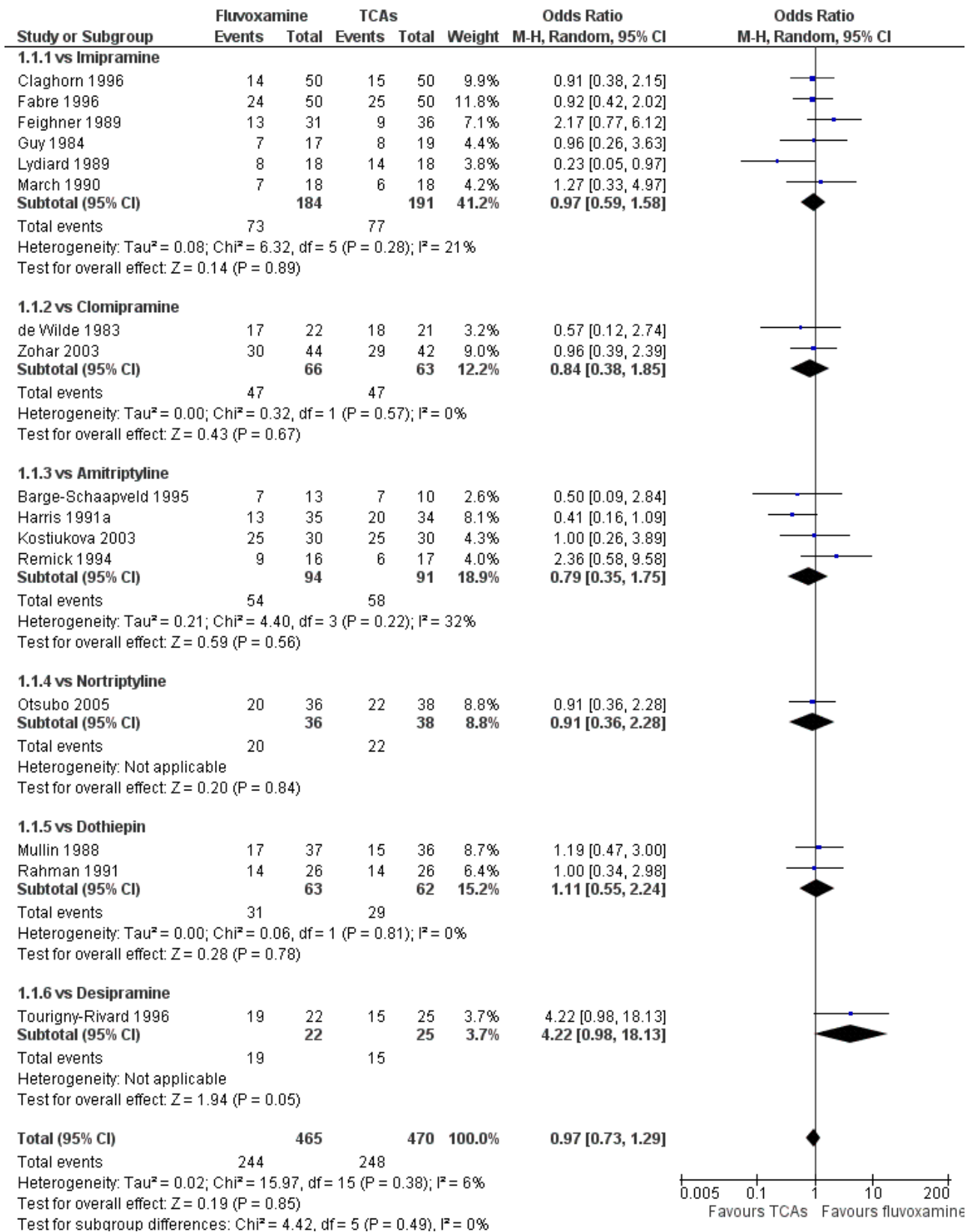
1.1 Response - acute phase (between 6 and 12 weeks); Primary outcome

Sixteen studies reported this outcome. Among them, imputation methods were used for 11 studies (Claghorn 1996; de Wilde 1983; Feighner 1989; Guy 1984; Harris 1991a; Lydiard 1989; March 1990; Mullin 1988; Rahman 1991; Remick 1994; Tourigny-Rivard 1996). There was no strong evidence that fluvoxamine was either superior

or inferior to TCAs except desipramine in terms of this dichotomous outcome in head-to-head comparisons. However, desipramine were less effective than fluvoxamine based on one small trial (OR:

4.22, 95% CI 0.98 to 18.13, $P=0.05$; 1 trial, 47 participants) ([Analysis 1.1, Figure 4](#)).

Figure 4. Forest plot of comparison: 1 Fluvoxamine vs TCAs, outcome: 1.1 Response (acute phase).



1.2 Response - early phase and follow-up phase

1.2.1 Early phase (between 1 and 4 weeks)

No strong evidence indicated that fluvoxamine was either superior or inferior to TCAs in terms of the dichotomous outcome between fluvoxamine and TCAs in head-to-head comparisons ([Figure 5](#)).

Figure 5. Forest plot of comparison: 1 Fluvoxamine vs TCAs, outcome: 1.2 Response (early phase).

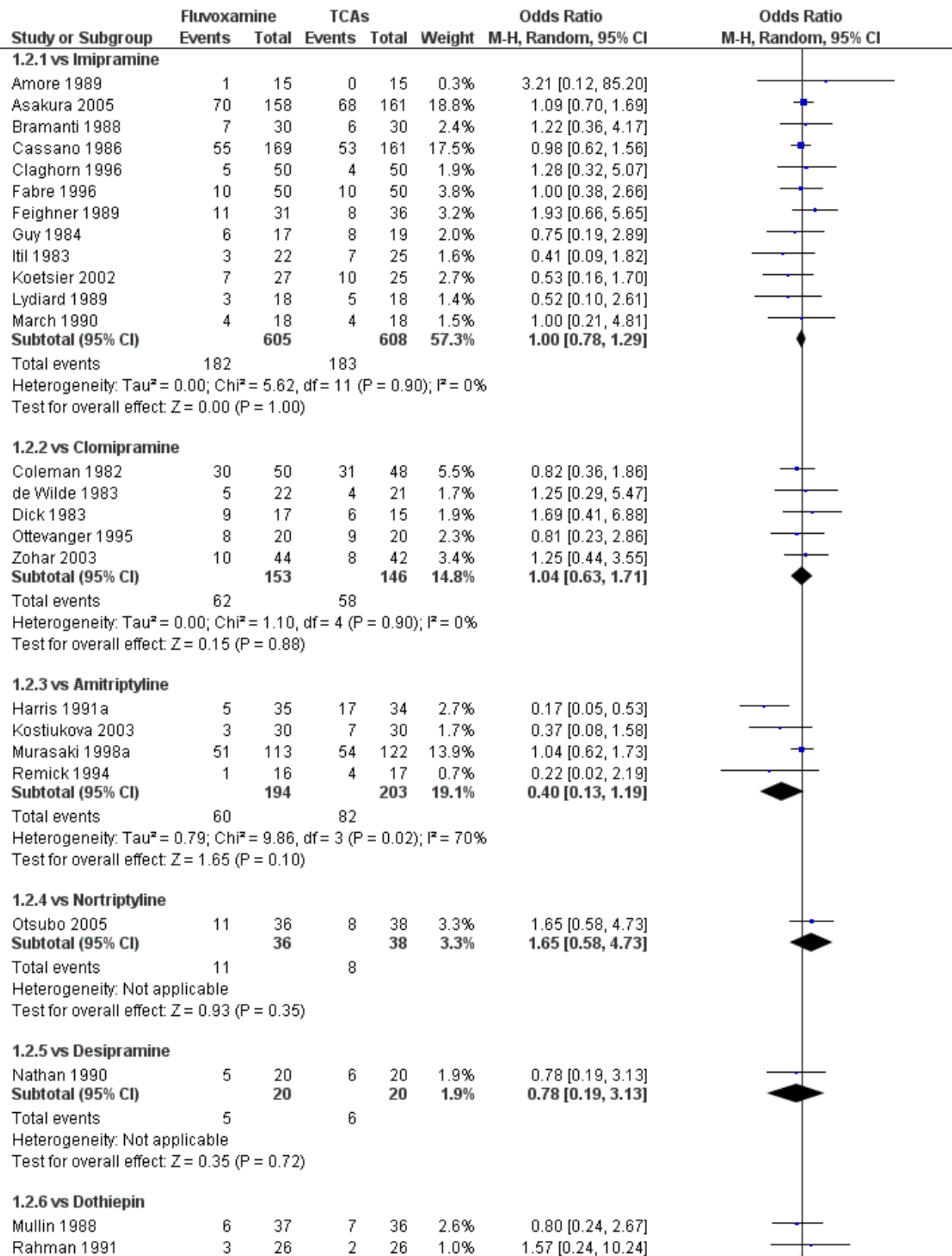
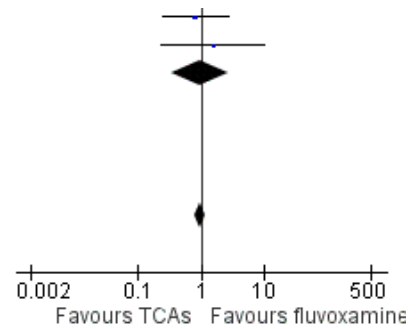


Figure 5. (Continued)

Mullin 1988	6	37	7	36	2.6%	0.80 [0.24, 2.67]
Rahman 1991	3	26	2	26	1.0%	1.57 [0.24, 10.24]
Subtotal (95% CI)		63		62	3.6%	0.97 [0.35, 2.68]
Total events	9		9			
Heterogeneity: Tau ² = 0.00; Chi ² = 0.35, df = 1 (P = 0.56); I ² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Total (95% CI)		1071		1077	100.0%	0.95 [0.78, 1.15]
Total events	329		346			
Heterogeneity: Tau ² = 0.00; Chi ² = 20.44, df = 24 (P = 0.67); I ² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Chi ² = 3.73, df = 5 (P = 0.59), I ² = 0%						



Substantial heterogeneity existed between trials comparing fluvoxamine to amitriptyline, based on four trials ($I^2 = 70\%$, $P = 0.02$, Analysis 1.2). Visual inspection revealed that, among these studies, three smaller ones using the imputation methods for response (Harris 1991a; Kostjukova 2003; Remick 1994) reported results favourable to amitriptyline. However, because of the small number of trials, sources of the heterogeneity cannot be further explained.

1.2.2 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

1.3 Remission

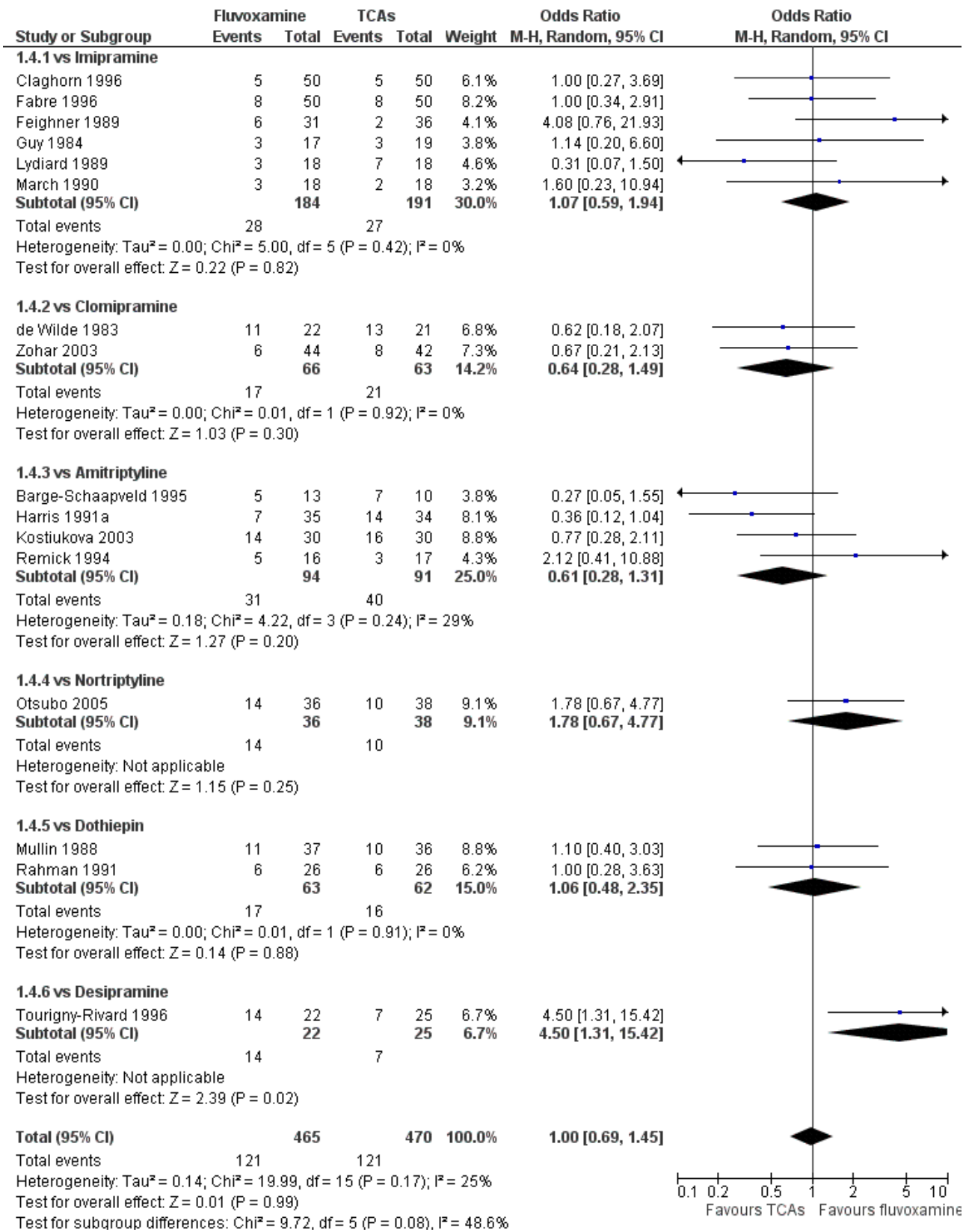
1.3.1 Early phase (between 1 and 4 weeks)

In terms of remission at the end of the early phase, the analysis found no strong evidence that fluvoxamine was either superior or inferior to TCA in head-to-head comparisons (Analysis 1.3).

1.3.2 Acute phase (between 6 and 12 weeks)

Fluvoxamine was found to be more effective than desipramine based on one trial (OR: 4.50, 95% CI 1.31 to 15.42, $P = 0.02$; 1 trial, 47 participants) (Tourigny-Rivard 1996); this small study did not report the actual number of patients who experienced remission, so we converted HRSD data expressed as mean and SD into the number of remitted patients, according to the validated imputation method (Furukawa 2005) (Figure 6).

Figure 6. Forest plot of comparison: 1 Fluvoxamine vs TCAs, outcome: 1.4 Remission (acute phase).



1.3.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

1.4 Endpoint score on depression scale

1.4.1 Early phase (between 1 and 4 weeks)

We meta-analysed non-skewed data only from 5 trials, and no strong evidence emerged that fluvoxamine was either superior or inferior to TCA as a class or in head-to-head comparisons ([Analysis 1.5](#)). However, data were skewed in six trials, and SDs were missing in 10 trials. We did not meta-analyse these data, and presented them descriptively ([Analysis 1.6](#)).

1.4.2 Acute phase (between 6 and 12 weeks)

Sixteen trials reported this outcome. However, we did not meta-analyse these data (data were skewed in three trials, and SDs were missing in 13 trials). We presented them descriptively ([Analysis 1.7](#)).

1.4.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

1.5. Change score on depression scale

1.5.1 Early phase (between 1 and 4 weeks)

We meta-analysed this outcome and found evidence that fluvoxamine was inferior to amitriptyline (SMD: 1.17, 95% CI 0.61 to 1.73, $P < 0.0001$; 1 trial, 58 participants) ([Analysis 1.8](#)). However, four other trials that compared fluvoxamine with amitriptyline did not

report SDs for this outcome and we did not meta-analyse these data ([Analysis 1.9](#)).

1.5.2 Acute phase (between 6 and 12 weeks).

We meta-analysed non-skewed data only from 3 trials, and there was no strong evidence that fluvoxamine was superior or inferior to TCA as a class or in head-to-head comparisons ([Analysis 1.10](#)). However, SDs were missing in 14 trials and we did not meta-analyse these data, and presented them descriptively instead ([Analysis 1.11](#)).

1.5.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

1.6 Tolerability

1.6.1 Dropout

No strong evidence emerged that fluvoxamine was more or less acceptable in terms of the total numbers of dropouts for any reason, a proxy measure of tolerability, between fluvoxamine and TCAs in head-to-head comparisons ([Figure 7](#)). Similarly, regarding patients who dropped out because of inefficacy, no strong evidence emerged that fluvoxamine was superior or inferior to TCAs in head-to-head comparisons ([Analysis 1.13](#)). The analysis of dropouts due to side effects revealed that amitriptyline (OR: 0.59, 95% CI 0.35 to 1.00, $P = 0.05$; 5 trials, 420 participants) and TCA as a class (OR: 0.79, 95% CI 0.60 to 1.04, $P = 0.09$; 21 trials, 1772 participants) were less tolerated than fluvoxamine ([Analysis 1.14](#), [Figure 8](#)).

Figure 7. Forest plot of comparison: 1 Fluvoxamine vs TCAs, outcome: 1.11 Total Dropout.

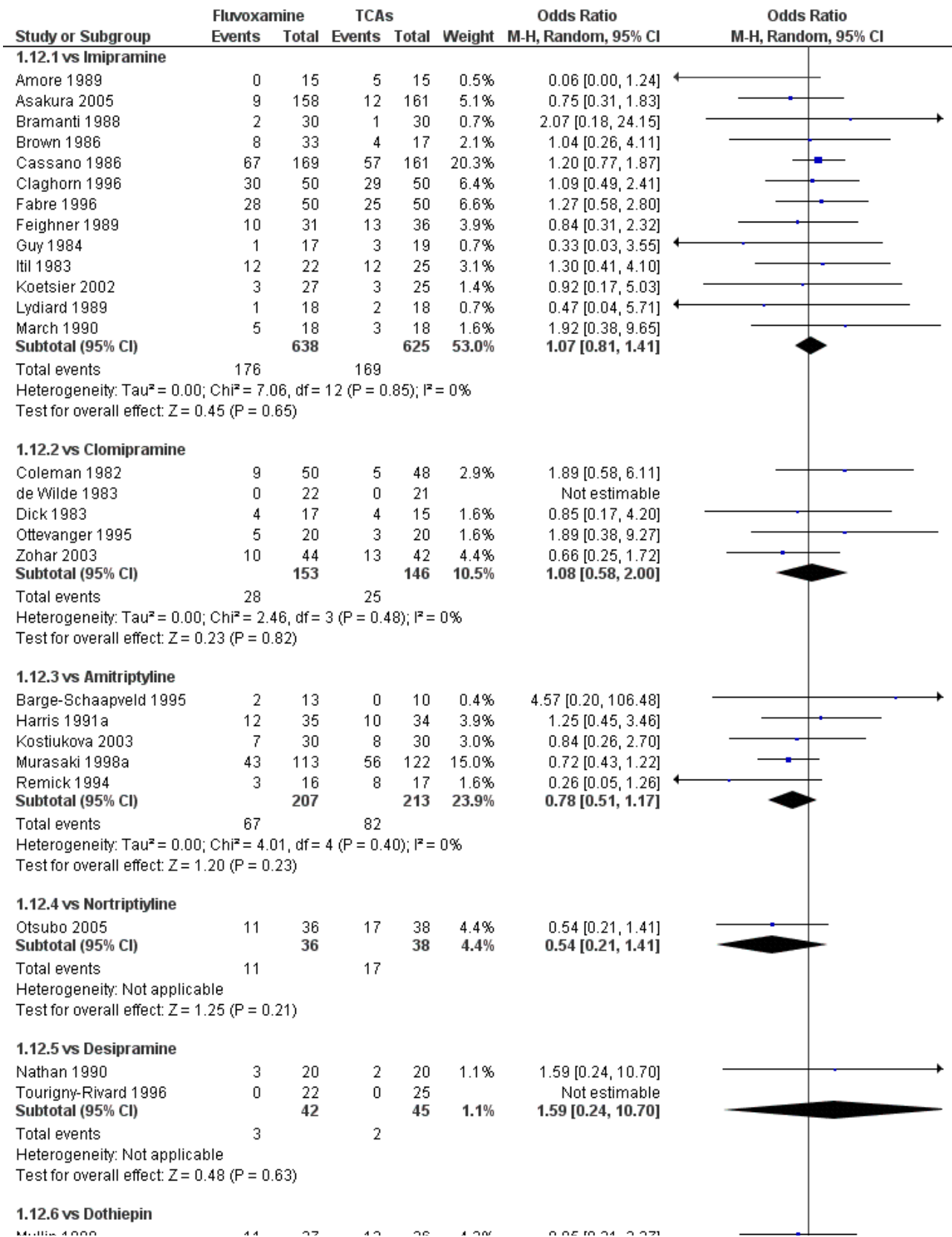


Figure 7. (Continued)

1.12.6 vs Dothiepin

Mullin 1988	11	37	12	36	4.2%	0.85 [0.31, 2.27]
Rahman 1991	9	26	7	26	2.9%	1.44 [0.44, 4.70]
Subtotal (95% CI)		63		62	7.0%	1.05 [0.49, 2.25]

Total events 20 19
Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 0.45$, $\text{df} = 1$ ($P = 0.50$); $I^2 = 0\%$
Test for overall effect: $Z = 0.13$ ($P = 0.90$)

Total (95% CI) 1139 1129 100.0% **0.96 [0.79, 1.18]**

Total events 305 314
Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 17.35$, $\text{df} = 25$ ($P = 0.87$); $I^2 = 0\%$
Test for overall effect: $Z = 0.36$ ($P = 0.72$)
Test for subgroup differences: $\text{Chi}^2 = 3.38$, $\text{df} = 5$ ($P = 0.64$), $I^2 = 0\%$

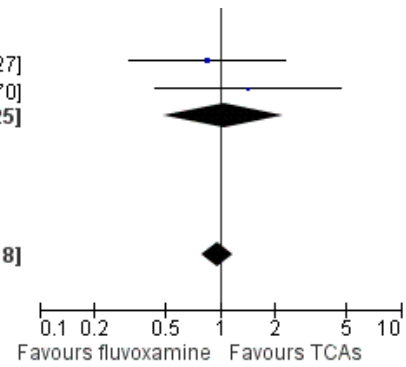


Figure 8. Forest plot of comparison: 1 Fluvoxamine vs TCAs, outcome: 1.13 Dropout due to side effects.

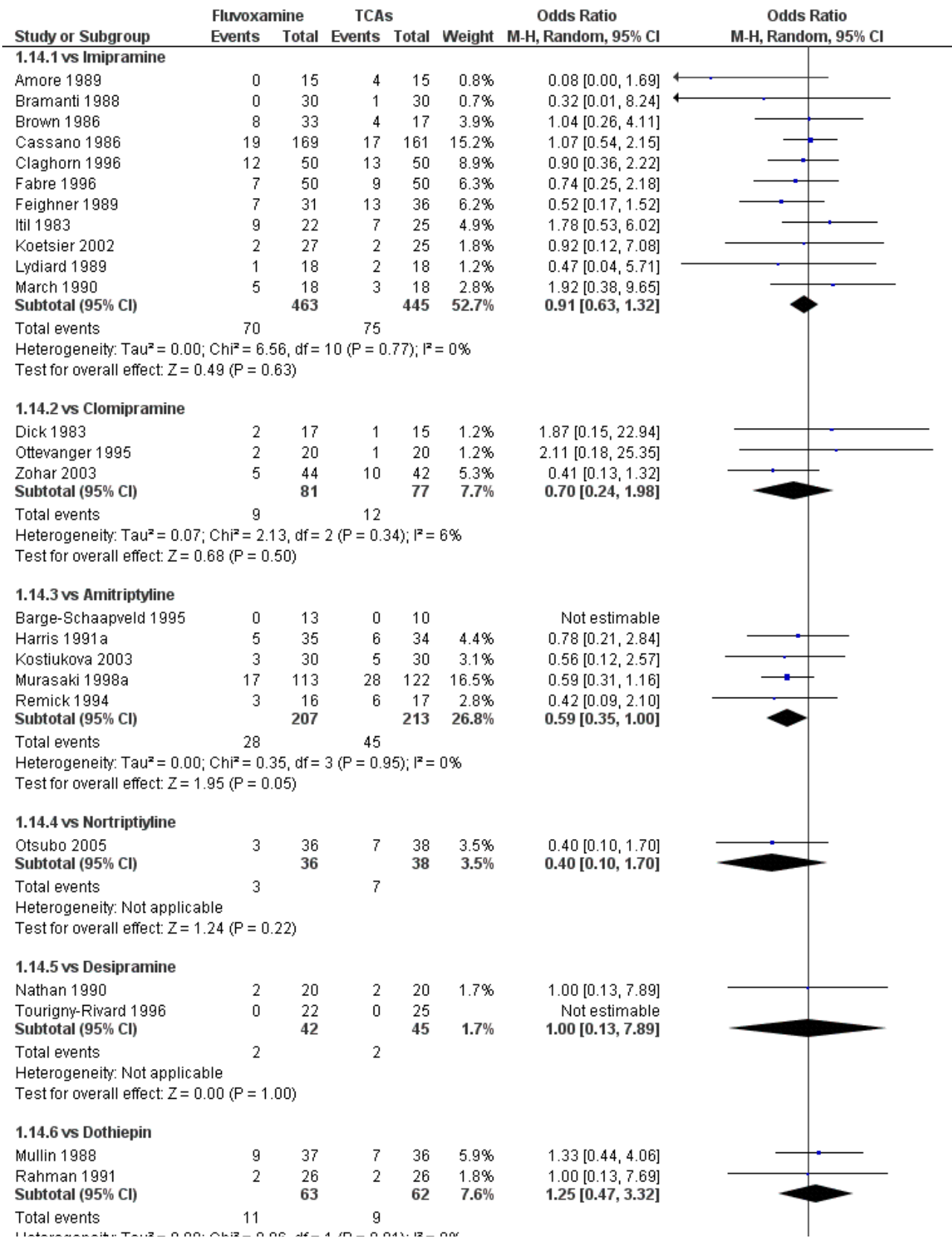
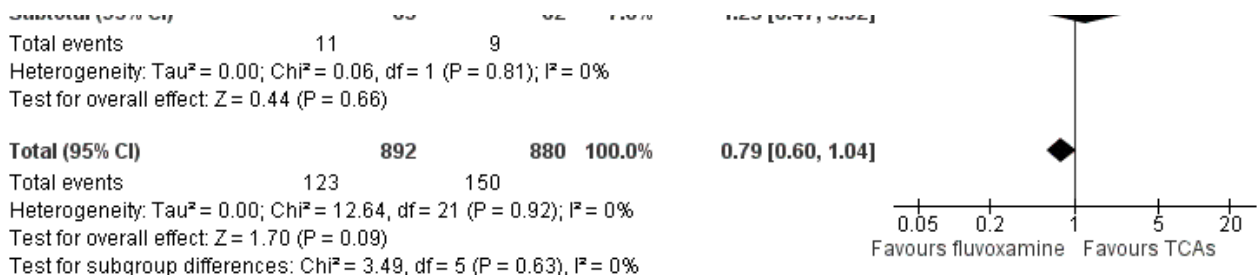


Figure 8. (Continued)

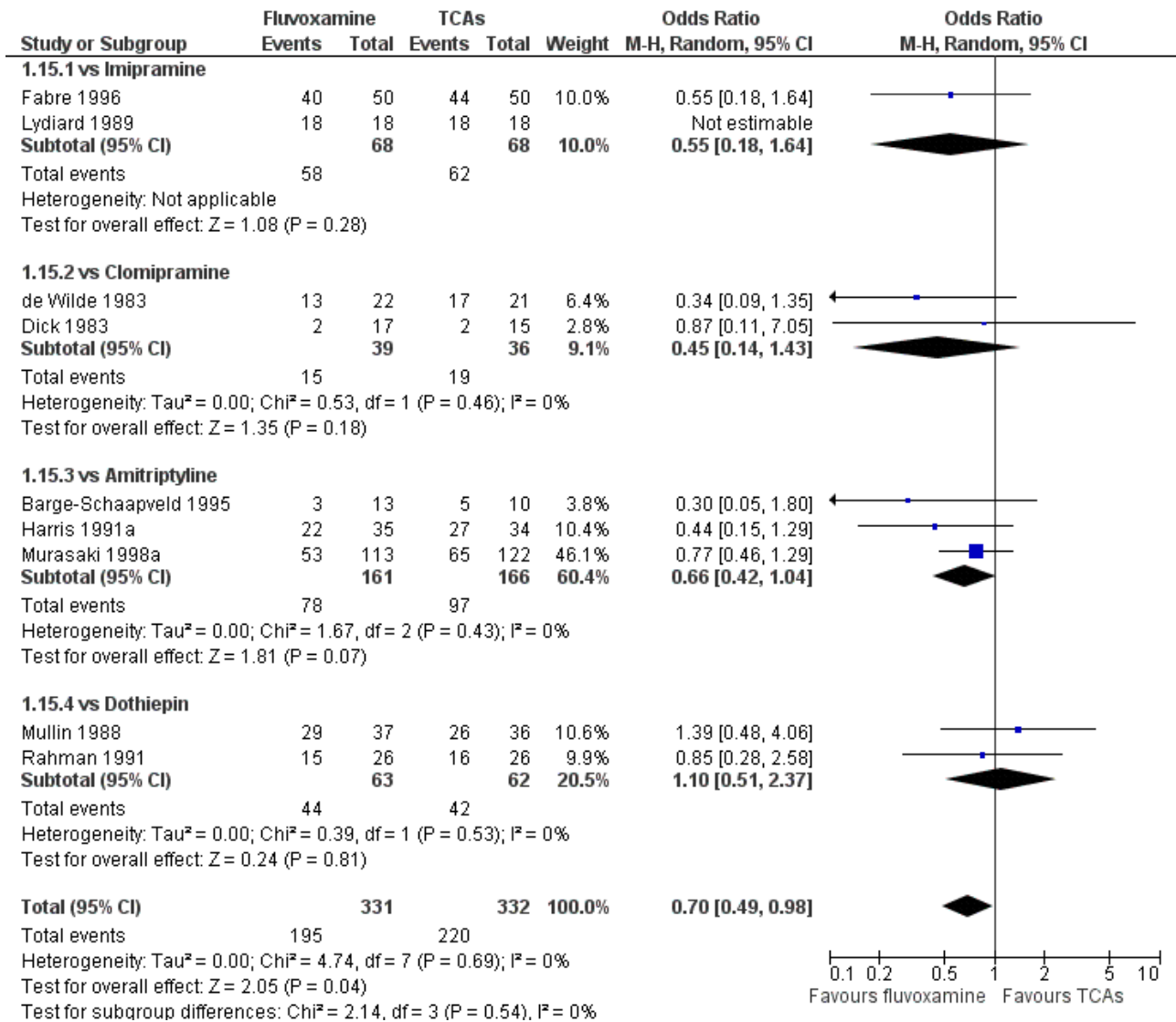


1.6.2 Number of patients experiencing at least one side effect

People allocated to amitriptyline were more likely to have at least one side effect during the trial, even though it was not statistically

significant (OR 0.66, 95%CI 0.42 to 1.04, P=0.07; 3 trials, 327 participants) (Analysis 1.15, Figure 9).

Figure 9. Forest plot of comparison: 1 Fluvoxamine vs TCAs, outcome: 1.14 Number of patients experiencing at least one side effect.



1.7 Side effects profile by body system

See: Table 3.

All specific side effects were grouped by organ system, as follows:
Cardiovascular: hypertension/tachycardia, hypotension/bradycardia.

Dermatological: dermatitis/rash, sweating.

Gastrointestinal: increased salivation, dry mouth, oral discomfort/taste disturbance, vomiting/nausea, constipation, diarrhoea, weight gain, weight loss, increased appetite, anorexia.

Neuropsychiatric: blurred vision, dizziness/vertigo/faintness, fatigue/tiredness/asthenia, headache, tremor, involuntary movement other than tremor, insomnia, sleepiness/drowsiness, agitation/anxiety, manic symptom, completed suicide, suicide wishes/gestures/attempts.

Genitourinary: problems urinating, sexual dysfunction.

1.7.1 Cardiovascular side effects

Reasonable evidence indicated that fluvoxamine was less likely to cause hypotension / bradycardia than was imipramine (OR 0.24, 95%CI 0.10 to 0.62, $P=0.003$; 4 trials, 560 participants) (Analysis 7.2). No strong evidence suggested that fluvoxamine was more or less likely to cause hypertension/tachycardia than TCAs.

1.7.2 Dermatological side effects

Sweating was more frequent in imipramine-treated patients (OR 0.32, 95%CI 0.16 to 0.66, $P=0.002$; 7 trials, 972 participants) than in fluvoxamine-treated patients (Analysis 7.4). No strong evidence was apparent to indicate that fluvoxamine was more or less likely to cause dermatitis/rash than were TCAs.

1.7.3 Gastrointestinal side effects

Dry mouth was more frequent in patients treated with imipramine (OR 0.24, 95%CI 0.16 to 0.34, $P<0.001$; 9 trials, 1055 participants), clomipramine (OR 0.43, 95%CI 0.22 to 0.81, $P=0.009$; 7 trials, 972 participants), and dothiepin (OR 0.08, 95%CI 0.01 to 0.70, $P=0.02$; 1 trial, 972 participants) than in those treated with fluvoxamine (Analysis 7.6). Constipation was more frequent in patients treated with imipramine (OR 0.50, 95%CI 0.27 to 0.93, $P=0.03$; 8 trials, 1008 participants) (Analysis 7.9).

In contrast, fluvoxamine was associated with higher rates of vomiting/nausea in participants than occurred with imipramine (OR 2.23, 95%CI 1.59 to 3.14, $p<0.001$; 9 trials, 1055 participants), clomipramine (OR 2.13, 95%CI 1.06 to 4.27, $P=0.03$; 3 trials, 216 participants), and amitriptyline (OR 2.86, 95%CI 1.31 to 6.23, $P=0.008$; 4 trials, 387 participants) (Analysis 7.8). Diarrhoea was more frequent in patients treated with fluvoxamine than in those treated with imipramine (OR 6.38, 95%CI 1.27 to 32.04, $P=0.02$; 2 trials, 136 participants) (Analysis 7.10).

In terms of the rate of other gastrointestinal side effects (i.e., increased salivation, oral discomfort/taste disturbance, weight gain, weight loss, increased appetite or anorexia), no strong evidence emerged that fluvoxamine was either more or less likely to cause these adverse events than were TCAs.

1.7.4 Neuropsychiatric side effects

Dizziness/vertigo/faintness were less common in recipients of fluvoxamine than in recipients of imipramine (OR 0.24, 95%CI 0.15 to 0.38, $p<0.001$; 9 trials, 1055 participants), clomipramine (OR 0.21, 95%CI 0.05 to 0.80, $P=0.02$; 1 trial, 86 participants), amitriptyline (OR 0.31, 95%CI 0.11 to 0.83, $P=0.02$; 2 trials, 304 participants), nortriptyline (OR 0.22, 95%CI 0.07 to 0.70, $P=0.01$; 1 trial, 73 participants) (Analysis 7.16).

In contrast, fluvoxamine was associated with higher rate of agitation/anxiety in participants than was imipramine (OR 2.24, 95%CI 1.01 to 4.97, $P=0.05$; 5 trials, 644 participants) (Analysis 7.23).

Recent research has pointed out that some antidepressants, in particular SSRIs, have caused the emergence or worsening of suicidal ideas in vulnerable patients (Barbui 2008; Hammad 2006). Only two trials (Dick 1983; Zohar 2003) among those comparing fluvoxamine with TCAs recorded completed suicide (Analysis 7.25), with two events among 61 patients taking fluvoxamine and no events among 57 those taking TCAs. Suicide wishes/gestures/attempts were reported in only three trials (Cassano 1986; Mullin 1988; Zohar 2003), with 3 events among 250 patients taking fluvoxamine and five among 239 patients taking TCAs.

In terms of the rate of participants experiencing other neuropsychiatric side effects (i.e., blurred vision, fatigue/tiredness/asthenia, headache, tremor, involuntary movement other than tremor, insomnia, sleepiness or manic symptoms), no strong evidence emerged that fluvoxamine was either more or less likely to cause these adverse events than were TCAs.

1.7.5 Genitourinary side effects

Urination problems were less common in recipients of fluvoxamine than in recipients of imipramine (OR 0.18, 95%CI 0.04 to 0.71, $P=0.01$; 2 trials, 409 participants) and TCAs as a class (OR 0.44, 95%CI 0.23 to 0.83, $P=0.01$; 6 trials, 818 participants) (Analysis 7.27). In terms of the rate of participants experiencing sexual dysfunction, no strong evidence emerged that fluvoxamine was more or less likely to cause these adverse events than were TCAs.

2. FLUVOXAMINE versus HETEROCYCLICS

Only five RCTs contributed usable data for efficacy and tolerability analyses (versus amineptine: Brunner 1994, versus maprotiline: Kasper 1990; Mendonca Lima 1997, versus mianserin: Moon 1991; Perez 1990). Four trials reported dichotomous data for a number of patients who experienced each side effect (versus maprotiline: Kasper 1990; Mendonca Lima 1997, versus mianserin: Moon 1991; Perez 1990).

2.1 Response - acute phase (between 6 and 12 weeks); Primary outcome

Two trials comparing fluvoxamine with mianserin reported this outcome. Imputation methods were used for Perez 1990. No strong evidence emerged that fluvoxamine was either superior or inferior to mianserin in terms of the response at end of the acute-phase treatment (Analysis 2.1).

2.2 Response - early phase and follow-up phase

2.2.1 Early phase (between 1 and 4 weeks)

No strong evidence emerged that fluvoxamine was either superior or inferior to amineptine or maprotiline in terms of the response at end of the acute-phase treatment. No trials comparing fluvoxamine with mianserin reported this outcome. See Analysis 2.2

2.2.2 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

2.3 Remission

2.3.1 Early phase (between 1 and 4 weeks)

No strong evidence emerged that fluvoxamine was either superior or inferior to amineptine or maprotiline in terms of the remission. No trials comparing fluvoxamine with mianserin reported this outcome. See [Analysis 2.3](#)

2.3.2 Acute phase (between 6 and 12 weeks)

Two trials that compared fluvoxamine with mianserin reported this outcome. No strong evidence emerged to indicate that fluvoxamine was either superior or inferior to mianserin in terms of this outcome. See [Analysis 2.4](#).

2.3.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

2.4 Endpoint score on depression scale

2.4.1 Early phase (between 1 and 4 weeks)

We meta-analysed non-skewed data only from 2 trials, and found no strong evidence that fluvoxamine was either superior or inferior to heterocyclics ([Analysis 2.5](#)). SDs were missing in one trial and we did not meta-analyse these data, presenting them descriptively instead ([Analysis 2.6](#)).

2.4.2 Acute phase (between 6 and 12 weeks)

Only one trial ([Perez 1990](#)) reported this continuous outcome, but SDs were missing ([Analysis 2.7](#)).

2.4.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

2.5 Change score on depression scale

2.5.1 Early phase (between 1 and 4 weeks)

We meta-analysed non-skewed data only from 1 trial and found no strong evidence that fluvoxamine was either superior or inferior to moprotiline ([Analysis 2.8](#)). SDs were missing in three trials and we did not meta-analyse these data, presenting them descriptively instead ([Analysis 2.9](#)).

2.5.2 Acute phase (between 6 and 12 weeks)

Two trials compared fluvoxamine with mianserin and reported this continuous outcome. However, SDs for this outcome were missing. Therefore, we presented the results descriptively ([Analysis 2.10](#)).

2.5.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

2.6 Tolerability

2.6.1 Dropout

We found no strong evidence that fluvoxamine was either more or less acceptable in terms of the total numbers of dropouts

for any reason when compared to heterocyclics (i.e., amineptine, maprotiline and mianserin) ([Analysis 2.11](#)). Similarly, regarding patients who dropped out because of inefficacy and due to side effects, we found no strong evidence that fluvoxamine was superior or inferior to heterocyclics ([Analysis 2.12](#), [Analysis 2.13](#)).

2.6.2 Number of patients experiencing at least one side effect

No strong evidence emerged that fluvoxamine was either superior or inferior to maprotiline or mianserin in terms of this dichotomous outcome ([Analysis 2.14](#)).

2.7 Side effects profile by body system

No trials comparing fluvoxamine with amineptine reported a number of patients who experienced a specific side effect. Only gastrointestinal side effects, such as dry mouth, vomiting/nausea and dizziness/vertigo/faintness were reported by four RCTs ([Kasper 1990](#); [Mendonca Lima 1997](#); [Moon 1991](#); [Perez 1990](#)). See [Table 3](#).

2.7.1 Cardiovascular side effects

No studies contributed data to this outcome.

2.7.2 Dermatological side effects

No studies contributed data to this outcome.

2.7.3 Gastrointestinal side effects

Reasonable evidence existed that fluvoxamine was associated with a higher rate of vomiting/nausea than was mianserin (OR 9.62, 95%CI 1.96 to 47.30, $p=0.009$; 4 trials, 207 participants). For further details, see [Analysis 8.1](#), [Analysis 8.2](#), [Analysis 8.3](#)). In terms of dry mouth or dizziness/vertigo/faintness, we found no strong evidence that fluvoxamine was either more or less likely to cause these adverse events than were heterocyclics.

2.7.4 Neuropsychiatric side effects

No studies contributed data to this outcome.

2.7.5 Genitourinary side effects

No studies contributed data to this outcome.

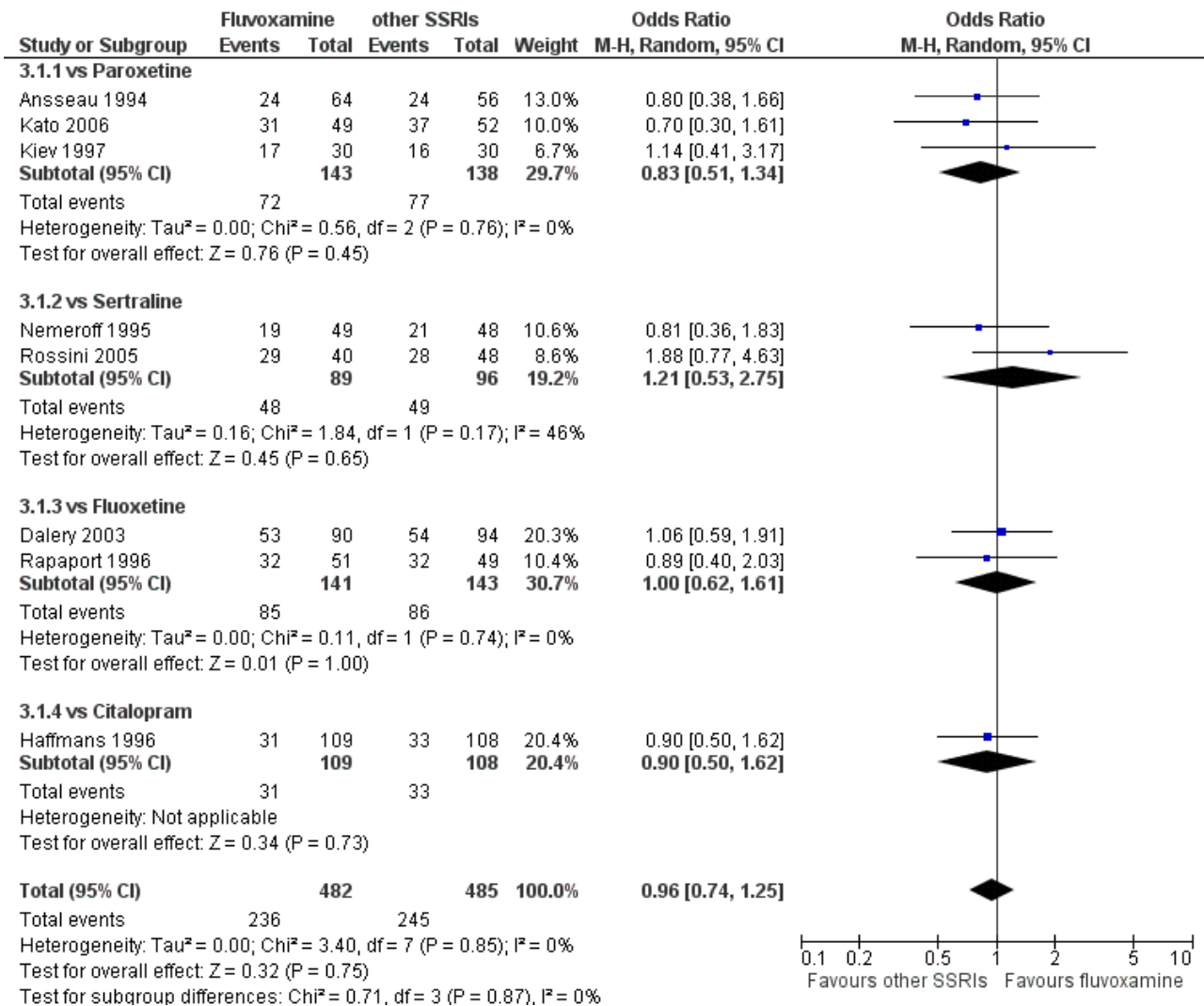
3. FLUVOXAMINE versus OTHER SSRIs

Eight RCTs contributed usable data for the efficacy analyses and nine RCTs contributed to the tolerability analyses. Eight trials reported dichotomous data for a number of patients who experienced each side effect.

3.1 Response - acute phase between 6 and 12 weeks; Primary outcome

Eight trials reported this outcome. Imputation methods were used for four trials ([Kiev 1997](#), [Nemeroff 1995](#), [Rossini 2005](#), [Rapaport 1996](#)). We found no strong evidence that fluvoxamine was either superior or inferior to other SSRIs (i.e., paroxetine, sertraline, fluoxetine and citalopram) in terms of this dichotomous outcome. See [Figure 10](#).

Figure 10. Forest plot of comparison: 3 Fluvoxamine vs other SSRIs, outcome: 3.1 Response (acute phase).



3.2 Response - early phase and follow-up phase

3.2.1 Early phase (between 1 and 4 weeks)

We found no strong evidence that fluvoxamine was either superior or inferior to other SSRIs in terms of this dichotomous outcome. See Analysis 3.2. Substantial heterogeneity existed between trials comparing fluvoxamine to fluoxetine based on two trials, Dalery 2003 and Rapaport 1996 (I² = 71%, P = 0.07, Analysis 3.2). However, because of the small number of trials, sources of the heterogeneity cannot be further explained.

3.2.2 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

3.3 Remission

3.3.1 Early phase (between 1 and 4 weeks)

We found no strong evidence that fluvoxamine was either superior or inferior to other SSRIs in terms of remission at the end of early phase. See Analysis 3.3.

3.3.2 Acute phase (between 6 and 12 weeks)

No strong evidence emerged that fluvoxamine was either superior or inferior to other SSRIs in terms of remission at the end of acute phase. See Analysis 3.4.

3.3.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

3.4 Endpoint score on depression scale

3.4.1 Early phase (between 1 and 4 weeks)

We meta-analysed non-skewed data only from 2 trials, and found no strong evidence that fluvoxamine was either superior or inferior to other SSRIs (Analysis 3.5). SDs were missing in five trials and we did not meta-analyse these data, and presenting them descriptively instead (Analysis 3.6).

3.4.2 Acute phase (between 6 and 12 weeks)

Eight trials reported this outcome. However, we did not meta-analyse these data (data were skewed in four trials, and SDs were

missing in four trials). We presented them descriptively ([Analysis 3.7](#)).

3.4.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

3.5 Change score on depression scale

3.5.1 Early phase (between 1 and 4 weeks)

We meta-analysed data only from one trial, and found no strong evidence that fluvoxamine was either superior or inferior to paroxetine ([Analysis 3.8](#)). SDs were missing in six trials and we did not meta-analyse these data, and presenting them descriptively instead ([Analysis 3.9](#)).

3.5.2 Acute phase (between 6 and 12 weeks)

We meta-analysed data only from three trials, and found no strong evidence that fluvoxamine was either superior or inferior to paroxetine or sertraline ([Analysis 3.10](#)). SDs were missing in five trials and we did not meta-analyse these data, presenting them descriptively instead ([Analysis 3.11](#)).

3.5.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

3.6. Tolerability

3.6.1 Dropout

We found no strong evidence that fluvoxamine was either more or less acceptable than were other SSRIs in terms of withdrawal due to any reason ([Analysis 3.12](#)). Similarly, regarding number of patients who dropped out because of inefficacy and because of adverse effects, no strong evidence emerged that fluvoxamine was either superior or inferior to other SSRIs ([Analysis 3.13](#) and [Analysis 3.14](#)). We found substantial heterogeneity between trials comparing fluvoxamine to sertraline, based on three trials ([Gonul 1999](#); [Nemeroff 1995](#); [Rossini 2005](#)) ($I^2 = 66\%$, $P = 0.05$, [Analysis 3.14.2](#)). Visual inspection revealed that, among these studies, [Nemeroff 1995](#) reported results favourable to sertraline. However, because of the small number of trials, sources of the heterogeneity cannot be further explained.

3.6.2 Number of patients experiencing at least one side effect

Only five trials reported this dichotomous outcome, and no strong evidence emerged that fluvoxamine was either superior or inferior to other SSRIs in terms of this outcome. See [Analysis 3.15](#).

3.7 Side effect profile by body system

Only one trial ([Haffmans 1996](#)) compared fluvoxamine with citalopram but did not report the number of patients who experienced specific side effects other than completed suicide or suicide attempts. See: [Table 3](#).

3.7.1 Cardiovascular side effects

In terms of the rate of participants experiencing hypertension/tachycardia or hypotension/bradycardia, we found no strong evidence that fluvoxamine was either superior or inferior to paroxetine ([Analysis 9.1](#), [Analysis 9.2](#)).

3.7.2 Dermatological side effects

Sweating was more frequent with paroxetine (OR 0.22, 95%CI 0.05 to 0.91, $P=0.04$; 1 trial, 60 participants) than in fluvoxamine-treated patients ([Analysis 9.4](#)). In terms of the rate of dermatitis/rash experienced by participants, no strong evidence emerged that fluvoxamine was either superior or inferior to sertraline in this respect ([Analysis 9.3](#)).

3.7.3 Gastrointestinal side effects

We found no evidence that fluvoxamine was either superior or inferior to other SSRIs in terms of the rate of gastrointestinal side effects experienced by participants ([Analysis 9.5](#), [Analysis 9.6](#), [Analysis 9.7](#), [Analysis 9.8](#) and [Analysis 9.9](#)).

No studies contributed data regarding increased salivation, oral discomfort/taste disturbance, weight gain, weight loss or increased appetite.

3.7.4 Neuropsychiatric side effects

We found no strong evidence that fluvoxamine, compared with other SSRIs, was either more or less likely to cause headache ([Analysis 9.12](#)), insomnia ([Analysis 9.14](#)), agitation/anxiety ([Analysis 9.16](#)), dizziness/vertigo/faintness ([Analysis 9.10](#)), fatigue/tiredness/asthenia ([Analysis 9.11](#)), tremor ([Analysis 9.13](#)), sleepiness/drowsiness ([Analysis 9.15](#)), manic symptom ([Analysis 9.17](#)). Only one trial compared fluvoxamine with citalopram ([Haffmans 1996](#)) recorded a completed suicide ([Analysis 7.25](#)), and cited one event among 108 patients taking citalopram and no events among 109 patients taking fluvoxamine. Suicide attempts/ideation were reported in only four trials ([Ansseau 1994](#); [Dalery 2003](#); [Rapaport 1996](#); [Haffmans 1996](#)), with 6 events among 314 patients taking fluvoxamine and 2 patients among 307 patients taking other SSRIs (i.e., paroxetine, fluoxetine and citalopram) ([Analysis 9.18](#), [Analysis 9.19](#)).

No studies contributed data to blurred vision and involuntary movement other than tremor.

3.7.5 Genitourinary side effects

Only four trials reported sexual dysfunction as a side effect. Some previous trials have reported that fluvoxamine was associated with a relatively low prevalence of sexual dysfunction compared to other SSRIs (i.e., paroxetine, sertraline and fluoxetine) ([Mackay 1997](#); [Montejo-Gonzalez 1997](#)). However, we found no strong evidence that fluvoxamine was either more or less likely to cause sexual dysfunction than were other SSRIs ([Analysis 9.20](#)). No studies contributed data to problems urinating.

4. FLUVOXAMINE versus SNRIs

Three RCTs (five comparisons) contributed usable data for the efficacy analyses and tolerability analyses for milnacipran or venlafaxine ([Ansseau 1991a](#); [Ansseau 1991b](#); [Clerc 2001](#); [Hackett 1998a](#); [Hackett 1998b](#)). Two RCTs (three comparisons) reported dichotomous data for a number of patients who experienced specific side effects ([Ansseau 1991a](#); [Ansseau 1991b](#); [Clerc 2001](#)).

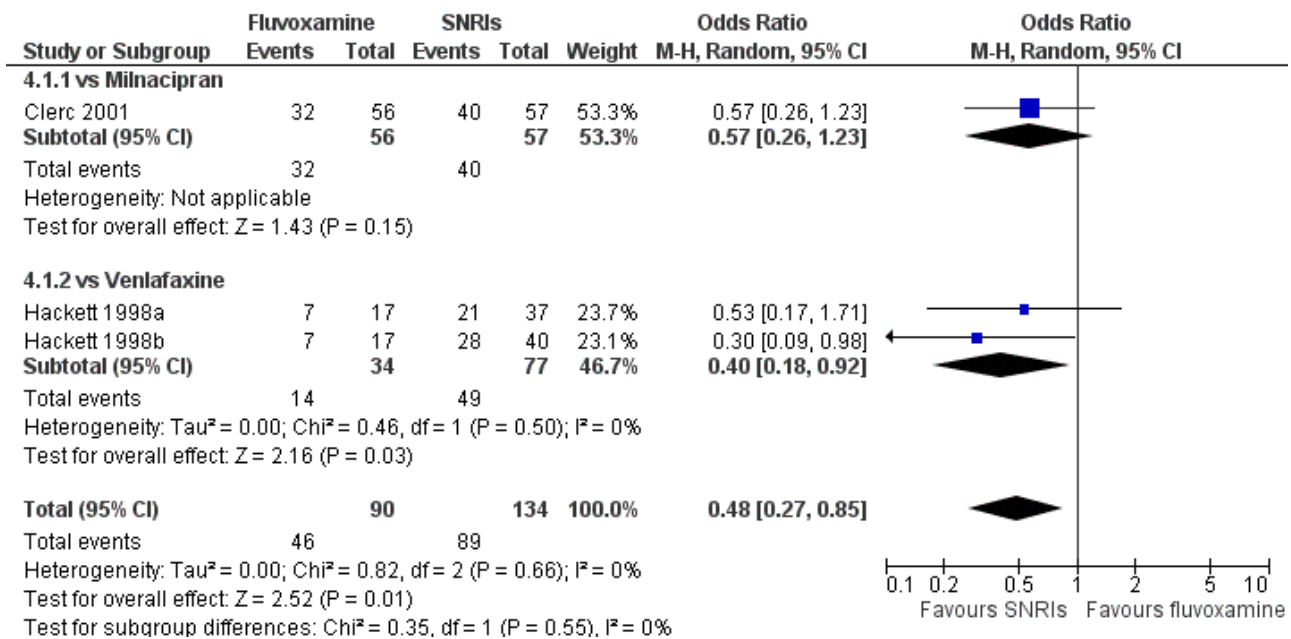
4.1 Response - acute phase (between 6 and 12 weeks); Primary outcome

Two trials (three comparisons) reported this outcome. Imputation methods were used for [Hackett 1998a](#) and [Hackett 1998b](#). Evidence emerged that fluvoxamine was less effective than was venlafaxine,

based on one trial (2 comparisons), for which the response had to be calculated based on the imputation method (Furukawa 2005) (OR: 0.40, 95% CI 0.18 to 0.92, P=0.03; 1 trial (2 comparisons),

111 participants) (Hackett 1998a; Hackett 1998b). We found no strong evidence that fluvoxamine was either superior or inferior to milnacipran in terms of this dichotomous outcome. See Figure 11.

Figure 11. Forest plot of comparison: 4 Fluvoxamine vs SNRIs, outcome: 4.1 Response (acute phase).



4.2 Response - early phase and follow-up phase

4.2.1 Early phase (between 1 and 4 weeks)

We found no strong evidence that fluvoxamine was either superior or inferior to SNRIs in terms of this dichotomous outcome. See Analysis 4.2.

4.2.2 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

4.3 Remission

4.3.1 Early phase (between 1 and 4 weeks)

No strong evidence emerged that fluvoxamine was either superior or inferior to SNRIs in terms of this dichotomous outcome. See Analysis 4.3.

4.3.2 Acute phase (between 6 and 12 weeks)

We found no strong evidence that fluvoxamine was either superior or inferior to SNRIs in terms of this dichotomous outcome. See Analysis 4.4.

4.3.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

4.4 Endpoint score on depression scale

4.4.1 Early phase (between 1 and 4 weeks)

We meta-analysed data only from 3 trials (four comparisons), and found no strong evidence that fluvoxamine was either superior or inferior to mianserin or venlafaxine (Analysis 4.5). SDs were missing in one trial and we did not meta-analyse the data, and presenting it descriptively instead (Analysis 4.6).

4.4.2 Acute phase (between 6 and 12 weeks)

One trial (two comparisons) reported this outcome. However, we did not meta-analyse these skewed data, instead presenting them descriptively (Analysis 4.7).

4.4.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

4.5 Change score on depression scale

4.5.1 Early phase (between 1 and 4 weeks)

Three trials (five comparisons) reported this outcome. However, we did not meta-analyse these data, since SDs were missing (Analysis 4.8).

4.5.2 Acute phase (between 6 and 12 weeks)

Two trials (three comparisons) reported this outcome. However, we did not meta-analyse these data, since SDs were missing (Analysis 4.9).

4.5.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

4.6 Tolerability

4.6.1 Dropout

We found no strong evidence that fluvoxamine was either more or less acceptable in terms of withdrawal due to any reason when compared with milnacipran. Venlafaxine was found to be less likely elicit withdrawal due to any reason (OR: 2.29, 95% CI 0.97 to 5.43, P=0.06; 1 trial (2 comparisons), 111 participants) (Analysis 4.10). Similarly, regarding the number of patients who dropped

out because of inefficacy and due to side effects, we found no strong evidence that fluvoxamine was either superior or inferior to milnacipran. ([Analysis 4.11](#), [Analysis 4.12](#)).

4.6.2 Number of patients experiencing at least one side effect

No studies contributed data to this outcome.

4.7 Side effects profile by body system

No studies comparing fluvoxamine to venlafaxine reported any number of patients experiencing specific side effects. See: [Table 3](#).

4.7.1 Cardiovascular side effects

In terms of the rate of hypertension/tachycardia or hypotension/bradycardia, we found no strong evidence that fluvoxamine was either superior or inferior to milnacipran in this respect ([Analysis 10.1](#), [Analysis 10.2](#)).

4.7.2 Dermatological side effects

In terms of the rate of dermatitis/rash or sweating experienced by participants, no strong evidence emerged that fluvoxamine was either superior or inferior to milnacipran. ([Analysis 10.3](#), [Analysis 10.4](#)).

4.7.3 Gastrointestinal side effects

We found evidence that fluvoxamine was associated with higher rate of vomiting/nausea experienced by participants than was milnacipran (OR 1.95, 95%CI 1.09 to 3.50, $P=0.02$; 2 trials (3 comparisons), 240 participants) ([Analysis 10.8](#)). In terms of the rate of increased salivation, dry mouth, oral discomfort/taste disturbance, vomiting/nausea, constipation, diarrhoea, weight gain, weight loss and anorexia experienced by participants receiving fluvoxamine compared to milnacipran, no strong evidence emerged to indicate that fluvoxamine was either superior or inferior to milnacipran. See [Analysis 10.5](#) to [Analysis 10.13](#).

No studies contributed data to increased appetite.

4.7.4 Neuropsychiatric side effects

In terms of the rate of blurred vision, dizziness/vertigo/faintness, fatigue/tiredness/asthenia, headache, tremor, involuntary movement other than tremor, insomnia, sleepiness/drowsiness and agitation/anxiety experienced by participants, we found no strong evidence that fluvoxamine was either superior or inferior to milnacipran. See [Analysis 10.14](#) to [Analysis 10.22](#).

No studies contributed data to manic symptom, completed suicide and suicide wishes/gestures/attempts.

4.7.5 Genitourinary side effects

We found no strong evidence that fluvoxamine was either more or less likely to cause urination problems than was milnacipran. See [Analysis 10.23](#)

No studies contributed data to sexual dysfunction.

5. FLUVOXAMINE versus NEWER ANTIDEPRESSANTS

Three RCTs comparing fluvoxamine to moclobemide ([Barrelet 1991](#); [Bocksberger 1993](#); [Bougerol 1992](#)) and one RCT comparing fluvoxamine to mirtazapine ([Schoemaker 2002](#)) contributed usable data for the efficacy analyses, tolerability analyses and for a number of patients who experienced specific side effects. These

two drugs have little chemically in common, we did not pool the results of these two drugs, presenting them separately instead.

5.1 Response - acute phase (between 6 and 12 weeks); Primary outcome

Schoemaker 2002 reported this outcome. Imputation methods were not used for this study. No strong evidence emerged that fluvoxamine was either superior or inferior to mirtazapine in terms of this dichotomous outcome. See [Analysis 5.1](#).

5.2 Response - early phase and follow-up phase

5.2.1 Early phase (between 1 and 4 weeks)

We found no strong evidence that fluvoxamine was either superior or inferior to moclobemide or mirtazapine in terms of this dichotomous outcome. See [Analysis 5.2](#).

5.2.2 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

5.3 Remission

5.3.1 Early phase (between 1 and 4 weeks)

We found no strong evidence that fluvoxamine was either superior or inferior to moclobemide or mirtazapine in terms of this dichotomous outcome. See [Analysis 5.3](#).

5.3.2 Acute phase (between 6 and 12 weeks)

We found no strong evidence that fluvoxamine was either superior or inferior to mirtazapine in terms of this dichotomous outcome. See [Analysis 5.4](#).

5.3.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

5.4 Endpoint score on depression scale

5.4.1 Early phase (between 1 and 4 weeks)

Two trials reported this outcome. However, we did not meta-analyse these data, since SDs were missing ([Analysis 5.5](#)).

5.4.2 Acute phase (between 6 and 12 weeks)

Two trials reported this outcome. However, we did not meta-analyse these data, since SDs were missing ([Analysis 5.6](#)).

5.4.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

5.5 Change score on depression scale

5.5.1 Early phase (between 1 and 4 weeks)

One trial that compared fluvoxamine with mirtazapine reported this outcome and showed strong evidence that fluvoxamine was inferior to mirtazapine (SMD 0.32, 95%CI 0.12 to 0.51, $P=0.002$; 1 trial, $n=402$) ([Analysis 5.7](#)). Three trials that compared fluvoxamine with moclobemide reported this outcome, but we did not meta-analyse these data since SDs were missing ([Analysis 5.8](#))

5.5.2 Acute phase (between 6 and 12 weeks)

One trial that compared fluvoxamine with mirtazapine reported this outcome but showed no strong evidence that fluvoxamine was

either inferior or superior to mirtazapine (SMD 0.08, 95%CI 0.12 to 0.28, $P=0.42$; 1 trial, $n=402$) ([Analysis 5.9](#)).

5.5.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

5.6 Tolerability

5.6.1 Dropout

We found no strong evidence that fluvoxamine was either more or less acceptable in terms of withdrawal due to any reason when compared with the newer ADs ([Analysis 5.10](#)). Similarly, regarding number of patients who dropped out because of inefficacy and due to side effects, we found no strong evidence that fluvoxamine was either more or less acceptable than the newer ADs ([Analysis 5.11](#), [Analysis 5.12](#)).

5.6.2 Number of patients experiencing at least one side effect

Fluvoxamine did appear to be associated with a higher number of participants experiencing at least one side effect when compared with moclobemide (OR 2.29, 95%CI 1.35 to 3.88, $P=0.002$; 3 trials, 231 participants) ([Analysis 5.13](#)).

5.7 Side effects profile by body system

See: [Table 3](#).

5.7.1 Cardiovascular side effects

In terms of the numbers of participants experiencing hypertension/tachycardia or hypotension/bradycardia, no strong evidence emerged that fluvoxamine was either more or less likely to cause these adverse events than was moclobemide ([Analysis 11.1](#)). No studies contributed data to hypertension/tachycardia.

5.7.2 Dermatological side effects

We found no strong evidence that fluvoxamine was either more or less likely to cause sweating than was moclobemide ([Analysis 11.2](#)). No studies contributed data to dermatitis/rash.

5.7.3 Gastrointestinal side effects

Fluvoxamine appeared to be associated with a higher number of participants who experienced vomiting/nausea when compared with mirtazapine (OR 3.43, 95%CI 1.90 to 6.19, $P<0.001$; 1 trial, 412 participants) or moclobemide (OR 2.01, 95%CI 1.03 to 3.92, $P=0.04$; 2 trials, 170 participants) ([Analysis 11.4](#)). We found evidence that fluvoxamine was associated with a higher number of participants who experienced dry mouth when compared with mirtazapine (OR 4.73, 95%CI 1.14 to 19.57, $P=0.03$; 1 trial, 412 participants) ([Analysis 11.3](#)).

No strong evidence emerged that fluvoxamine, compared with mirtazapine, was either more or less likely to cause constipation, diarrhoea, weight gain or increased appetite. See [Analysis 11.5](#) to [Analysis 11.8](#).

No studies contributed data to increased salivation, oral discomfort/taste disturbance, weight loss or anorexia.

5.7.4 Neuropsychiatric side effects

See [Analysis 11.9](#) to [Analysis 11.18](#).

Fluvoxamine appeared to be associated with lower numbers of participants who experienced sleepiness/drowsiness when compared with mirtazapine (OR 0.47, 95%CI 0.29 to 0.76, $P=0.002$; 1 trial, 412 participants) ([Analysis 11.15](#)). Fluvoxamine was associated with lower numbers of participants who experienced agitation/ anxiety when compared with mirtazapine (OR 0.17, 95%CI 0.05 to 0.61, $P=0.03$; 1 trial, 412 participants) ([Analysis 11.16](#)). Only one trial compared fluvoxamine with moclobemide ([Barrelet 1991](#)) and recorded completed suicide ([Analysis 11.18](#)), with one event among 30 patients taking fluvoxamine and no events among 31 patients taking moclobemide.

No studies contributed data to involuntary movements other than tremors or to suicide wishes/gestures/attempts.

5.7.5 Genitourinary side effects

No studies contributed data to genitourinary side effects.

6. FLUVOXAMINE versus OTHER CONVENTIONAL PSYCHOTROPIC DRUGS

Only one 4-week RCT comparing fluvoxamine to sulpiride ([Ueda 2002](#)) contributed usable data for the efficacy analyses and tolerability analyses.

6.1 Response - acute phase (between 6 and 12 weeks); Primary outcome

No studies contributed data to this outcome.

6.2 Response - early phase and follow-up phase

6.2.1 Early phase (between 1 and 4 weeks)

We found no strong evidence that fluvoxamine was either superior or inferior to sulpiride in terms of response at end of the acute-phase treatment. ([Analysis 6.1](#)).

6.2.2 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

6.3 Remission

6.3.1 Early phase (between 1 and 4 weeks)

We found no strong evidence that fluvoxamine was either superior or inferior to sulpiride in terms of remission at end of the early phase treatment. ([Analysis 6.2](#)).

6.3.2 Acute phase (between 6 and 12 weeks)

No studies contributed data to this outcome.

6.2.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

6.4 Endpoint score on depression scale

6.4.1 Early phase (between 1 and 4 weeks)

We found no strong evidence that fluvoxamine was either superior or inferior to sulpiride in terms of this continuous outcome ([Analysis 6.3](#)).

6.4.2 Acute phase (between 6 and 12 weeks)

No studies contributed data to this outcome.

6.4.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

6.5 Change score on depression scale

6.5.1 Early phase (between 1 and 4 weeks)

We found no strong evidence that fluvoxamine was either inferior or superior to sulpiride in terms of this continuous outcome (Analysis 6.4).

6.5.2 Acute phase (between 6 and 12 weeks)

No studies contributed data to this outcome.

6.5.3 Follow-up phase (between 4 and 6 months)

No studies contributed data to this outcome.

6.7 Tolerability

6.7.1 Dropout

We found no strong evidence that fluvoxamine was either more or less acceptable than was sulpiride in terms of withdrawal due to any

reason (Analysis 6.5). No studies contributed data to dropout due to inefficacy or due to side effects.

6.7.2 Numbers of patients experiencing at least one side effect

No studies contributed data to this outcome.

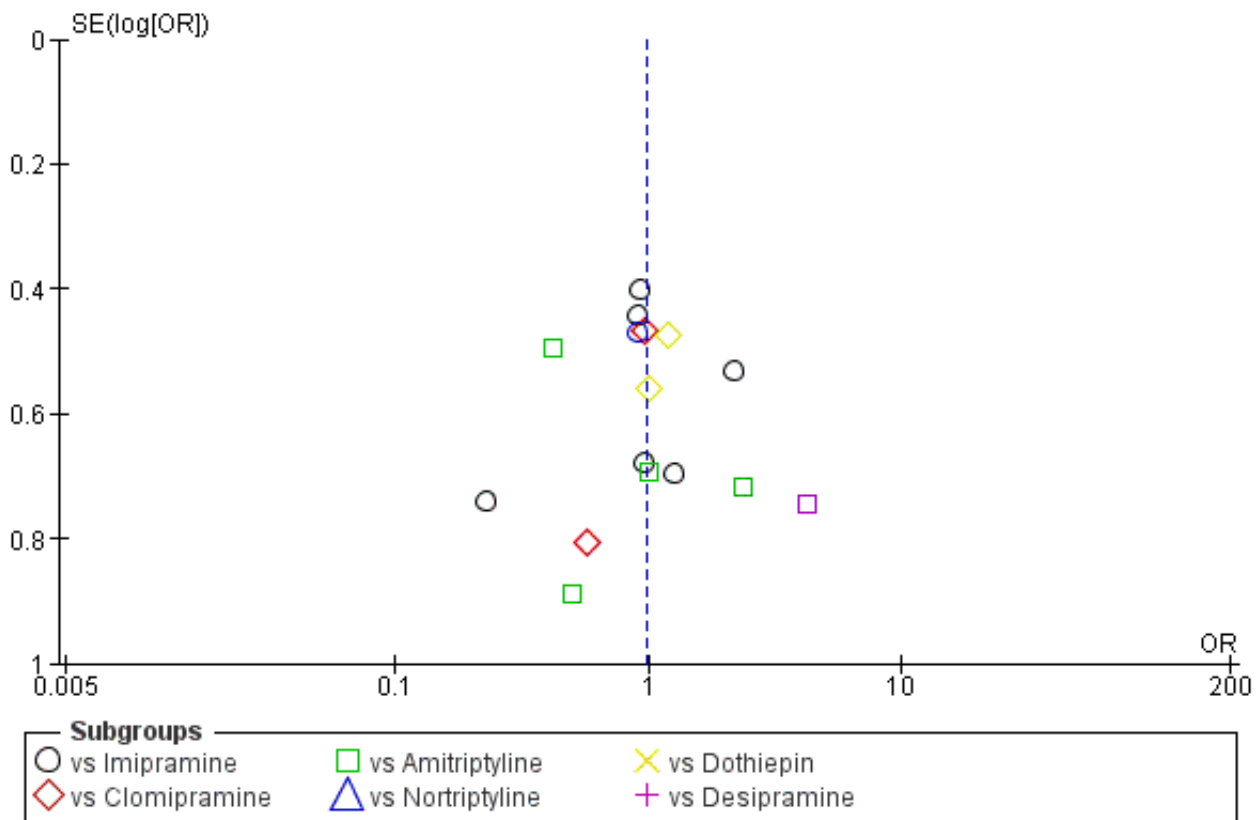
6.8 Side effects profile by body system

Ueda 2002 did not report specific side effects.

7. FUNNEL PLOT ANALYSES

Funnel plots were examined only for the comparison between fluvoxamine and TCAs as a class, since there were insufficient trials to allow meaningful formal assessment using funnel plots for other comparisons. Visual inspection did not reveal an asymmetrical appearance of the funnel plot (Figure 12). Tests for funnel plot asymmetry (Egger 1997) did not suggest any strong evidence of asymmetry (Egger's bias coefficient, number of trials= 16, bias = 0.09 (P = 0.94)). However, included trials were of similar size (sample size: 23 to 100) and similar standard errors of OR (SE of ln(OR): 0.40 to 0.89), and the test for funnel plots should not be used (Higgins 2008).

Figure 12. Funnel plot of comparison: 1 Fluvoxamine versus TCAs, outcome: 1.1 Response (acute phase): Primary outcome.



8. SUBGROUP ANALYSES

We conducted subgroup analyses only for fluvoxamine dosing - standard versus high dose (fluvoxamine versus TCAs, fluvoxamine versus other SSRIS), comparator dosing (fluvoxamine versus TCAs, fluvoxamine versus other SSRIS) and treatment settings

(fluvoxamine versus TCAs), since there were insufficient number of trials that could produce subgroups and useful findings. Differences in subgroups were reported only for response rates in acute phases.

8.1 Fluvoxamine dosing - standard dose versus high dose

8.1.1 Fluvoxamine versus TCAs

Only 6 trials used standard dose schedules, and 10 trials used high dose schedules. The magnitude of effects in the trials using standard doses of fluvoxamine (OR: 0.83, 95% CI 0.53 to 1.46) and high doses of fluvoxamine (OR: 1.07, 95% CI 0.74 to 1.55) were similar and their CIs were overlapped ([Analysis 1.16](#), [Analysis 1.17](#)).

8.1.2 Fluvoxamine versus other SSRIs

Only 5 trials used standard dose schedules, and 3 trials used high dose schedules. The magnitude of effects in the trials using standard doses of fluvoxamine (OR: 0.92, 95% CI 0.65 to 1.30) and high doses of fluvoxamine (OR: 1.02, 95% CI 0.65 to 1.60) were similar and their CIs were overlapped ([Analysis 3.16](#), [Analysis 3.17](#)).

8.2 Comparator dosing

8.2.1 Fluvoxamine versus TCAs

Only 4 trials used standard dose schedules and 15 trials used high dose schedules of comparator drugs. The magnitude of effects in the trials using standard dose comparator drugs (OR: 1.27, 95% CI 0.64 to 2.50) and high dose comparator drugs (OR: 0.99, 95% CI 0.74 to 1.33) were similar and their CIs were overlapped ([Analysis 1.18](#), [Analysis 1.19](#)).

8.2.2 Fluvoxamine versus other SSRIs

Only 2 trials used standard dose schedules, and 6 trials used high dose schedules of comparator drugs. The magnitude of effects in the trials using standard dose comparator drugs (OR: 0.95, 95% CI 0.60 to 1.50) and high dose of comparator drugs (OR: 0.96, 95% CI 0.70 to 1.33) were similar and their CIs were overlapped ([Analysis 3.18](#), [Analysis 3.19](#)).

8.3 Treatment settings

8.3.1 Fluvoxamine versus TCAs

Only 5 trials were conducted in inpatient settings and 9 trials were conducted in outpatient settings. The magnitude of effects in the trials that were conducted in inpatient settings (OR: 1.17, 95% CI 0.71 to 1.92) and the trials conducted in outpatient settings (OR: 0.84, 95% CI 0.58 to 1.20) were similar and their CIs were overlapped ([Analysis 1.20](#), [Analysis 1.21](#)).

9. SENSITIVITY ANALYSES

We reported the results of sensitivity analyses for efficacy outcome at the acute phase. In the main analyses, we found no evidence that fluvoxamine was either more or less effective than other ADs as a class. In head-to-head comparisons, fluvoxamine was more effective than desipramine (response rate at acute phase; OR: 4.22, 95% CI 0.98 to 18.13, $P=0.05$; 1 trial, 47 participants), while venlafaxine was more effective than fluvoxamine (response rate at acute phase; OR: 0.40, 95% CI 0.18 to 0.92, $P=0.03$; 1 trial (2 comparisons), 111 participants).

9.1 Excluding trials with unclear concealment of random allocation and/or unclear double blinding

We did not perform sensitivity analyses of excluded trials with unclear concealment of random allocation, as there were no studies that reported details of having conducted allocation concealment. In addition, we did not perform sensitivity analysis

of excluding with unclear double blinding as there were only two studies rated as being "low risk of bias" regarding blinding.

9.2 Excluding trials with dropout rates greater than 20%

No substantial change was found in the main findings when fluvoxamine and TCAs ([Analysis 1.22](#)) or fluvoxamine and other SSRIs ([Analysis 3.20](#)) were compared for sensitivity analysis. We did not perform sensitivity analysis for comparisons between fluvoxamine and heterocyclics, SNRIs or newer ADs because dropout rates greater than 20% were reported for all of the trials of these comparisons that reported primary outcome.

9.3 Performing the worst case scenario ITT

Based on sensitivity analysis, fluvoxamine was found to be less effective in terms of response at acute phase than were imipramine (OR 0.60 95%CI 0.39 to 0.90, $P=0.01$; 6 trials, 375 participants), amitriptyline (OR 0.34 95%CI 0.13 to 0.90, $P=0.03$; 4 trials, 185 participants), dothiepin (OR 0.34 95%CI 0.16 to 0.72, $P=0.005$; 2 trials, 125 participants) or venlafaxine (OR 0.11 95%CI 0.04 to 0.29, $P<0.001$; 1 trial (2 comparisons), 111 participants). See [Analysis 1.23](#), [Analysis 4.13](#).

9.4 Performing the best case scenario ITT

Based on sensitivity analysis, fluvoxamine was found to be more effective in terms of response at acute phase than were dothiepin (OR 4.04 95%CI 1.85 to 8.81, $P<0.001$; 2 trials, 125 participants) ([Analysis 1.24](#)), mianserin (OR 3.04 95%CI 1.20 to 7.67, $P=0.02$; 2 trials, 125 participants) ([Analysis 2.16](#)) or paroxetine (OR 1.77 95%CI 1.08 to 2.92, $P=0.02$; 3 trials, 281 participants) ([Analysis 3.22](#)). In addition, based on this sensitivity analysis, the superiority of venlafaxine over fluvoxamine in terms of response at acute phase was lost (OR 2.67 95%CI 0.98 to 7.26, $P=0.05$; 1 trial (2 comparisons), 111 participants) ([Analysis 4.14](#)).

9.5 Excluding trials for which the response rates had to be calculated based on the imputation method and for which the SD had to be borrowed from other trials

We conducted this sensitivity analysis only for comparison between fluvoxamine and TCAs, and between fluvoxamine and other SSRIs, since there were insufficient numbers of trials that could produce useful findings for other comparisons. No substantial change in the results was found by excluding trials with the imputation method for calculating responses ([Analysis 1.25](#), [Analysis 3.23](#)) or by excluding trials that borrowed SDs for imputation ([Analysis 1.26](#), [Analysis 3.24](#)).

9.6 Examination of "wish bias" by comparing fluvoxamine as an investigational drug versus fluvoxamine as a comparator

Examination of "wish bias" was impossible because no trials comparing fluvoxamine with TCAs set fluvoxamine as a comparator; among studies comparing fluvoxamine with ADs other than TCAs, only three trials set fluvoxamine as an investigational drug.

9.7 Excluding studies funded by or with at least one author affiliated with a pharmaceutical company marketing fluvoxamine

A sensitivity analysis to investigate the effect of commercial funding, excluding studies sponsored by pharmaceutical companies, was impossible, as almost all of the included trials

had been funded by the industry. For example, among 30 trials comparing fluvoxamine with TCAs, there were only two trials free from commercial funding. Therefore, it is impossible to obtain substantial results from this sensitivity analysis.

9.8 Excluding studies that included patients with bipolar depression

No substantial changes in the main findings were noted by these sensitivity analyses (Analysis 1.30, Analysis 2.20, Analysis 3.28, Analysis 4.18).

9.9 Excluding studies that included patients with psychotic features

No substantial changes in the main findings were noted by these sensitivity analyses (Analysis 1.31, Analysis 2.21, Analysis 3.29, Analysis 4.19, Analysis 5.21).

DISCUSSION

Summary of main results

The main results of our study revealed no strong evidence that fluvoxamine was either inferior or superior to other antidepressants, including TCAs such as amitriptyline or clomipramine, other SSRIs or other forms, in terms of either response or remission in any clinical setting, even though a small number of findings suggested a direction of effect in favour of fluvoxamine (versus desipramine) or in favour of control drug (venlafaxine) in terms of response and remission at acute phase. This was somewhat surprising because TCAs are sometimes believed to be more effective than SSRIs, particularly among hospitalized depressive patients (Anderson 1998).

We were also unable to find differences in dropouts for any reason, including side effects, between fluvoxamine and other antidepressive agents. Although the 95% CI are wide and we cannot exclude possibilities of meaningful differences between fluvoxamine and other antidepressive agents, our findings at least suggest a need for moderation of the general statement that holds that patients tolerate SSRIs better than TCAs. In addition, we included 10 trials involving fluvoxamine in our review, and from the pooled data, we were unable to find any differences in total dropouts or dropouts due to side effects between fluvoxamine and other SSRIs.

The analysis of individual side effects points to evidence of differing side effects profiles, especially when comparing gastrointestinal side effects between fluvoxamine and TCAs. Diarrhoea and weight loss were experienced significantly more frequently with fluvoxamine than with TCAs. Vomiting/nausea and weight loss/anorexia were also experienced significantly more frequently with fluvoxamine than with TCAs and some other antidepressive agents (e.g., mianserin, milnacipran and some newer antidepressants). However, constipation and decreased salivation/dry mouth were more common with TCAs than with fluvoxamine.

Not only are SSRIs chemically different from TCAs, heterocyclics and other antidepressive agents, but considerable structural differences also exist even among the various SSRIs. Therefore, some differential pharmacology between the drugs in the same class may be expected. However, head-to-head comparisons found no evidence to suggest side effect profile differences between

fluvoxamine and other SSRIs, except for sweating, which was more common in recipients of paroxetine than fluvoxamine in a single trial.

Overall completeness and applicability of evidence

This review has a number of limitations in overall completeness and applicability.

Participants

Severity of depression was believed to be associated with good treatment response in patients taking TCAs compared with those taking SSRIs (Anderson 1994). However, all of the studies included in this review, other than that of Claghorn 1996, were conducted for moderate/mild depression. For this reason, the findings from this review may not be representative of more severely affected patients.

In addition, the findings from this review may not be representative for the depressive elderly, since only one trial was found in which recruitment was wholly conducted for the depressive elderly (Bocksberger 1993). Elder patients with depression are recognized as being more vulnerable to adverse effects of antidepressants (Schneider 1995). If fluvoxamine is more or less acceptable than other antidepressants, this advantage/disadvantage might be obvious in trials focused on geriatric depression.

Twenty-five out of 54 trials explicitly included or might have included patients with major depressive episodes caused by bipolar disorder. However, we found no heterogeneity in the pooled results.

In many countries, including the UK, many patients with depression are treated solely in primary care (Spijker 2001, Goldberg 1991), and depressive disorder in primary care has a different profile than treated in secondary care (Suh 1997). However, we could find only two articles conducted in primary care settings (Barge-Schaapveld 1995; Moon 1991), and the relevance of the studies included in this review to primary care settings should be limited.

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 no studies that examined the long-term efficacy of fluvoxamine for major depression.

Outcomes

Treatments for major depression should be assessed not only by psychiatric symptoms, but also by general functioning and/or QOL. 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 borders on negligence. In addition, no studies included cost to health care services as an outcome. The choice of antidepressants may be influenced by factors such as safety of the medication in overdose and the propensity of the medication to be associated with withdrawal symptoms. However, we found no randomised trials that examined these factors in this review.

Quality of the evidence

Fifty-four trials with 4353 patients were included in this analysis; 2117 were randomised to fluvoxamine and 2236 to comparator drugs. These included trials had a number of methodological shortcomings.

Randomisation

All of the trials except one (Rossini 2005) failed to describe methods of random sequence generation. In addition, no trials reported the method of allocation concealment. Therefore, it is conceivable that selection bias might have occurred in the trials included in this review.

Blinding

Information on blinding was sought for many trials; however, no test of blinding success was conducted in any study. The use of an independent, blind assessor was explicitly described in only three studies (Miller 2001; Otsubo 2005; Rossini 2005). On the whole, little information was presented on the outcome assessment process, and the extent to which detection bias might have occurred was uncertain.

Selective outcome reporting

Forty-four out of the 54 included studies used the HRSD as a primary or secondary outcome measure, while a minority of studies used the MADRS and CGI. It is conceivable that the study authors did not report some outcomes in which results failed to show statistical significance. Therefore, the results of our meta-analyses could overestimate the intervention effect due to outcome reporting bias. In addition, only a few studies reported SDs for a change and endpoint score of any depression scale that we adopted as a secondary outcome, which meant that we had to borrow SDs from other trials that did report SDs for the outcomes.

High discontinuation rate

Twenty-seven of the 54 studies had dropout rates higher than 20%. This high attrition rate could have influenced treatment outcomes; for two studies with high attrition rate (Mullin 1988 and Rahman 1991), sensitivity analysis performing the worst case scenario revealed the statistically significant results in favour of the comparator and the best case scenario in favour of fluvoxamine.

Sample size

If we assumed that response rate for experimental antidepressants was 50% and that of the control was 35%, 183 participants would be needed in each treatment group to detect this type of difference at 80% power and 95% confidence. However, most trials included in this review were small; the majority of the studies (38 RCTs) recruited less than 100 participants in total. This made it difficult to interpret the negative finding. In addition, most trials did not discuss their low power or did not conduct sample size calculation

Potential biases in the review process

Strength

The comprehensiveness of our study search and the strict quality appraisal we required before any study could be included in the final pooling of the results contributed to the strength of our review. As a result, randomised evidence from unpublished (Schoemaker 2002) as well as published studies was included in the

review. Furthermore, our strong efforts made to obtain missing data resulted in additional data from investigators from 15 trials.

We also imputed response and remission outcomes by applying a threshold of the standard depression severity scales, such as the HRSD or MADRS, with a validated statistical method if they were not available in original trials (Furukawa 2005; Furukawa 2006). We believe our methodology can be used in future systematic reviews in order to minimise outcome reporting bias and to make the most use of information from the obtained trials.

Limitations

This systematic review is not without methodological problems.

First of all, although neither the funnel plot nor Egger's test detected small-study effects, we still cannot rule out the risk of publication bias. There were only 16 studies included in the funnel plots, and all studies were of similar size; therefore, it was difficult to find a meaningful result from funnel plots and their statistical tests. In addition, we have concerns about those five studies that only reported biochemical or physiological outcomes, instead of reporting clinical efficacy and/or tolerability outcomes. For example, one RCT reported prolactin responses to d-fenfluramine for depressive patients, before and after medication but included no clinical outcome at all (Kavoussi 1999). This trial formed part of an industry drug trial sponsored by Solvay, the primary fluvoxamine marketer. We were unable to locate a trial matching the description in this report, and we strongly suspect that we are missing a large trial sponsored by this company. We excluded a crossover trial that did not report the result of first randomisation period (Emrich 1987) and a trial that only reported the result of a maintenance period (White 1990). We tried to contact the original authors to obtain missing outcomes but our attempts were in vain. We believe that publication bias remained a very real risk in this review.

Second, pharmaceutical companies marketing fluvoxamine sponsored a large majority of the trials comparing fluvoxamine with TCAs; the majority of the authors of these trials set fluvoxamine as an investigational drug. Therefore, comparability between fluvoxamine and TCAs in efficacy and tolerability may not be unconditionally warranted; that is to say, the efficacy and tolerability of fluvoxamine over TCAs might be overestimated (Barbui 2004).

Third, although sensitivity analyses excluding trials for which the response rates had to be calculated based on the imputation method did not find any evidence that it changed the results of the main analyses, this could have happened for many reasons other than validity of the imputation methods. For example, there were few studies included in each analysis and most studies were small-sized trials that reported null effects; therefore, removing some trials is unlikely to have a large effect.

Finally, very few of the trials employed standardized instruments in the reporting of side effects. Many of the side effects experienced by patients taking antidepressants may be confused with symptoms and signs of depression. Many trials reported the number of patients who experienced unwanted symptoms during trials, but some articles defined side effects strictly as experiences that appeared for the first time during the treatment period, or experiences that appeared between screen and baseline, but

increased in severity during the treatment period. Some trials did not report a side effect profile at all. Obviously the emphasis on detecting side effects differs between trials, and this may explain some of the observed differences.

Agreements and disagreements with other studies or reviews

Edwards 1999 conducted a well-designed systematic review and meta-analysis of RCTs, involving direct comparisons between five SSRIs in the treatment of major depressive illness. The review reported that significantly more patients on fluvoxamine stopped treatment due to any reason and due to side effects compared with other SSRIs. However, this review included only five trials involving fluvoxamine, and these are outdated. The clinical guidelines released by the same authors (Anderson 2001) suggested that fluvoxamine was not the best SSRI choice in routine practice because of its relatively high discontinuation rate, but the results of our review do not provide any evidence that support or argue against this statement.

We have recently published a multiple-treatment meta-analysis (MTM) in which our data for fluvoxamine were merged with those for 11 other new generation antidepressants and both direct and indirect comparisons among them were statistically pooled (Cipriani 2009). The MTM offers a clinically meaningful synthesis when several competing treatments are available for one disease (Lumley 2002; Lu 2006; Salanti 2008), as is the case with major depression, while examining the overall strength and consistency of this network of evidence. The corresponding ORs and their 95%CI for response and total dropout are tabulated in Table 4.

We note that:

- 1) all of the confidence intervals overlap widely between direct comparisons and MTM (direct + indirect) comparisons, mainly because the 95%CI for direct comparisons are wide, generally indicating that the network of evidence is consistent.
- 2) When nominal superiority of fluvoxamine existed in direct comparisons (fluvoxamine over sertraline for response, and fluvoxamine over mirtazapine for dropout), this was lost in the MTM, although again their 95%CI overlapped widely.
- 3) When the ratio of ORs was greater than 1.5 or smaller than 0.67 (versus sertraline, versus milnacipran and versus venlafaxine for response, and versus venlafaxine for dropout), the MTM results were almost always less extreme (i.e., closer to 1.0) than the direct comparisons, very probably because of cancelling out possible sponsorship, publication and other biases.

The relative merits and demerits of direct versus MTM comparisons are still debatable (Bucher 1997; Song 2003; Ioannidis 2006) and we need to carefully weigh and synthesize the direct with the indirect comparisons.

AUTHORS' CONCLUSIONS

Implications for practice

The main finding of the present study is that the present review is based on poor quality evidence of primary studies and we found no strong evidence that fluvoxamine was either superior or inferior

to any other antidepressants, including TCAs and SSRIs, in terms of efficacy and tolerability during the treatment of depression in the acute phase. On the other hand, evidence is clear for differing side effect profiles, especially in terms of gastrointestinal side effects between fluvoxamine and TCAs. The results of the study led us to conclude that clinicians should focus on practical or clinically relevant considerations, including these differences in side effect profiles.

Implications for research

We could have learnt more about the effects of fluvoxamine if the studies included in the review had clearly described sequence generation, allocation concealment, blinding of outcome assessors, and reasons for dropout. In addition to assessment of depressive symptoms and levels of general functioning, QOL and patient satisfaction would be most informative. If continuous rating scales are to be employed, a concerted effort should be made to come up with an agreement as to which measures are the most useful. For analyses of side effect profiles, more reliable and consistent methods of monitoring and reporting side effects during the trial are needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Amore 1989

Methods	Four-week double blind, randomised study.
Participants	Psychiatric inpatients meeting DSM-III for major depression without psychotic features, with a minimum baseline score of 21 on the HDRS-21. Age range: 20-70 years old. Exclusion criteria: during pregnancy, lactation, or being of childbearing potential, serious diseases, alcohol or drug abuse, or treatment with any medications that might interact with antidepressant drugs.
Interventions	Fluvoxamine: 15 participants. Imipramine: 15 participants. Fluvoxamine dose range: 100-150 mg/day. Imipramine dose range: 100-150 mg/day. Benzodiazepine were allowed as additional medications.
Outcomes	Hamilton Rating Scale for Depression (HRSD) -21, Zung Self-Rating Depression Scale, Clinical Global Impression-severity (CGI-S) and Clinical Global Impression-improvement (CGI-I). Total dropout, dropout due to inefficiency, due to side effects, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.

Amore 1989 (Continued)

Fluvoxamine as an investigational or comparator drug

As an investigational drug.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "in a double blind fashion", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 5/15 missing from control group (4 due to adverse effects).
Selective reporting (reporting bias)	High risk	Standard deviations (SDs) of endpoint / change score for depression were not reported.

Ansseau 1991a

Methods	Four-week double blind, multicentre, randomised study.
Participants	Psychiatric inpatients meeting RDC for major depressive disorder, endogenous subtype, with a minimum baseline score of 25 on the Montgomery and Asberg Scale for Depression (MADRS). Age range: 20-70 years old. Exclusion criteria: patients presenting any evidence of contra-indications for a tricyclic antidepressant, or serious or uncontrolled medical illness.
Interventions	Fluvoxamine: 41 participants. Milnacipran: 42 participants. Fluvoxamine dose: 200 mg/day. Milnacipran dose: 300 mg/day for 2 weeks and 150mg/day during the 2 following weeks) The active period was preceded by a washout period of 4-7 days on placebo and lorazepam (up to 10 mg/day) and nitrazepam (up to 10 mg/day) if needed. These associated drugs could be maintained during the treatment period if necessary.
Outcomes	HRSD-24, CGI-I, CGI-S, CGI-efficacy index, Raskin Scale for Depression. Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets comparator drug.
Fluvoxamine as an investigational or comparator drug	As a comparator drug.

Fluvoxamine versus other anti-depressive agents for depression (Review)

Ansseau 1991a (Continued)

Notes 11/127 (8.7%) patients were with bipolar depression and 14/127 (11.0%) patients were with psychotic features.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	no details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Both participants and drug prescribing physicians were blinded. No further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 6/41 missing from fluvoxamine group (1 due to lack of efficacy, 5 due to adverse effects); 10/86 missing from control group (2 due to lack of efficacy, 7 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Ansseau 1991b

Methods	= Ansseau 1991a
Participants	= Ansseau 1991a
Interventions	Fluvoxamine: 41 participants. Milnacipran: 44 participants. Fluvoxamine dose: 200 mg/day. Milnacipran dose: 200 mg/day for 4 weeks. The active period was preceded by a washout period of 4-7 days on placebo and lorazepam (up to 10 mg/day) and nitrazepam (up to 10 mg/day) if needed. These associated drugs could be maintained during the treatment period if necessary.
Outcomes	= Ansseau 1991a
Funded by pharmaceutical companies	= Ansseau 1991a
Fluvoxamine as an investigational or comparator drug	= Ansseau 1991a
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	= Ansseau 1991a

Ansseau 1991b (Continued)

Allocation concealment (selection bias)	Unclear risk	=Ansseau 1991a
Blinding (performance bias and detection bias) All outcomes	Unclear risk	=Ansseau 1991a
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	=Ansseau 1991a
Selective reporting (reporting bias)	High risk	=Ansseau 1991a

Ansseau 1994

Methods	Six-week double blind, multicentre, randomised study.	
Participants	Psychiatric in- and outpatients meeting DSM-III-R for major depressive episode, with a minimum baseline score of 18 on the HRSD-21. Age range: 18-65 years old. Exclusion criteria: clinically significant co-existing diseases or other psychiatric disorders, history of alcohol or drug abuse, women of child bearing potential not employing adequate contraception, recent treatment with monoamine oxidase inhibitors, neuroleptics, or lithium, and current treatment with oral anticoagulants and type 1C antiarrhythmic.	
Interventions	Fluvoxamine: 64 participants. Paroxetine: 56 participants. Fluvoxamine dose range: 50-200 mg/day. Paroxetine dose range: 20-30 mg/day. For patients who had received benzodiazepines for at least two weeks prior to continue these agents, providing the dose remained unchanged throughout the study period. In addition, low dose lorazepam or chloral hydrate were permitted in case of severe insomnia.	
Outcomes	HRSD-21, CGI-S, Hamilton Rating Scale for Anxiety (HRSA). Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets comparator drug.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes	Patients with major depressive episode (DSM-III-R) were included, so there might be some bipolar depression, but correct number was not reported.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.

Fluvoxamine versus other anti-depressive agents for depression (Review)

Ansseau 1994 (Continued)

Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "the trial used a double-blind design", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 23/64 missing from fluvoxamine group (5 due to lack of efficacy, 13 due to adverse effects); 16/56 missing from control group (2 due to lack of efficacy, 3 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Asakura 2005

Methods	Four-week double blind, single-centre, randomised study.	
Participants	Psychiatric in- and outpatients meeting major depressive disorder or other affective disorder according to DSM-IV. Baseline HRSD score: 20.02 (SD 6.60). Age: 20 years old or more, mean 41.3 years old (SD 13.7). Exclusion criteria: treated with any antidepressants for the current depressive episode.	
Interventions	Fluvoxamine: 158 participants. Imipramine: 161 participants. Fluvoxamine dose range: 50-150 mg/day. Imipramine dose range: 75-150 mg/day.	
Outcomes	HRSD-17, CGI. Total dropout.	
Funded by pharmaceutical companies	Funded by pharmaceutical companies market fluvoxamine and comparator drug.	
Fluvoxamine as an investigational or comparator drug	As an investigational drug.	
Notes	Almost all the patients were drug naive outpatients. 17% (54/309) of participants were with dysthymic disorder, depressive disorder not otherwise specified, bipolar II disorder or major depressive disorder with psychotic features.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias)	Unclear risk	Quote: "double blind", no further details.

Fluvoxamine versus other anti-depressive agents for depression (Review)

Asakura 2005 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 9/158 missing from fluvoxamine group; 12/161 missing from control group.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Barge-Schaapveld 1995

Methods	Six-week open, multicentre, randomised study.	
Participants	Primary care outpatients meeting DSM-III-R for major depressive disorder, with a minimum baseline score of 18 on the HRSD-17. Patients were recruited in five primary care practices. Age range: 18-65 years old. Exclusion criteria: other psychiatric or medical conditions.	
Interventions	Fluvoxamine: 13 participants. Amitriptyline: 10 participants. Fluvoxamine dose: 100 mg/day. Amitriptyline dose: 150 mg/day.	
Outcomes	HRSD-17. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect.	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients were blinded. No blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 2/13 missing from fluvoxamine group.

Barge-Schaapveld 1995 (Continued)

Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.
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Barrelet 1991

Methods	Four-week double blind, multicentre, randomised study.
Participants	Psychiatric in- and outpatients meeting DSM-III for major depressive episode, with a minimum baseline score of 17 on the HRSD-17. Age: mean 54.2 years old (SD 14.6). Exclusion criteria: organic brain disorders, alcohol dependence, risk of suicide, with schizophrenic symptoms, severe medical illness.
Interventions	Fluvoxamine: 30 participants. Moclobemide: 31 participants. Fluvoxamine dose range: 100-200 mg/day. Moclobemide dose range: 300-450 mg/day. Benzodiazepine and lithium were allowed.
Outcomes	HRSD-17, HRSA, Widlocher Psychomotor Retardation Scale, Hospital Anxiety and Depression Scale. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets comparator drug.
Fluvoxamine as an investigational or comparator drug	As a comparator drug.
Notes	Patients with major affective disorder (DSM-III) were included, so there might be some bipolar depression, but correct number was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double aveugle", no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 5/30 missing from fluvoxamine group (4 due to adverse effects); 5/30 missing from control group (4 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Bocksberger 1993

Methods	Four-week double blind, single-centre, randomised study.
Participants	Psychiatric inpatients meeting DSM-III for major depressive episode, with a minimum baseline score of 20 on the MADRS. Age range: 65 years old or more. Exclusion criteria: marked suicidal tendency, symptoms of psychosis, severe organic disease, alcoholism, drug abuse.
Interventions	Fluvoxamine: 20 participants. Moclobemide: 20 participants. Fluvoxamine dose range: 100-200 mg/day. Moclobemide dose range: 300-450 mg/day. Patients receiving lithium were enrolled in the study, providing treatment had been stabilized for at least four weeks prior to entry. The use of concomitant psychotropic medication was prohibited, with the exception of lithium for patients on a previously established lithium regimen, or one benzodiazepine or chloral hydrate, if judged necessary by the investigator. Drugs that had been given regularly for somatic complaints were allowed to continue if there were no psychotropic effects.
Outcomes	MADRS, CGI-I, Widlocher Psychomotor Retardation Scale. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets comparator drug.
Fluvoxamine as an investigational or comparator drug	As a comparator drug.
Notes	Patients with major affective disorder (DSM-III) were included, so there might be some bipolar depression, but correct number was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "two randomized parallel groups", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "a double blind study", no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 2/20 missing from fluvoxamine group (1 due to adverse effects); 1/20 missing from control group.
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Bougerol 1992

Methods	Six-week double blind, multicentre, randomised study.
Participants	Psychiatric in- and outpatients meeting DSM-III for major depressive episode, with a minimum baseline score of 17 on the HRSD-17. Age range: 18 years old or more. Exclusion criteria: marked suicidal tendency, symptoms of psychosis; severe organic disease, patient undergoing electroshock therapy or structured psychotherapy, alcoholism, drug abuse.
Interventions	Fluvoxamine: 63 participants. Moclobemide: 67 participants. Fluvoxamine dose range: 100-200 mg/day. Moclobemide dose range: 300-450 mg/day. Patients receiving lithium were enrolled in the study, providing treatment had been stabilized for at least 4 weeks prior to entry. The use of concomitant psychotropic medication was prohibited, with the exception of lithium for patients on a previously established lithium regimen, or one benzodiazepine, if judged necessary by the investigator. Drugs that had been given regularly for somatic complaints were allowed to continue if there were no psychotropic effects. During the study, patients were not required to avoid tyramine-rich food.
Outcomes	HRSD-17, CGI-efficacy index, Widlocher Psychomotor Retardation Scale. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets comparator drug.
Fluvoxamine as an investigational or comparator drug	As a comparator drug.
Notes	Patients with major affective disorder (DSM-III) were included, so there might be some bipolar depression, but correct number was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "two randomized parallel groups", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 19/63 missing from fluvoxamine group (3 due to lack of efficacy, 9 due to adverse effects); 15/67 missing from control group (5 due to lack of efficacy, 6 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Bramanti 1988

Methods	Four-week double blind, multicentre, randomised study.
Participants	Patients suffering major depressive disorder according to DSM-III, with a minimum baseline score of 18 on the HRSD-21. Age range: 18 years old or more. Exclusion criteria: pregnancy or a risk of pregnancy, lactating women, severe impairment of liver or renal function, treatment with lithium, other antidepressants or MAO inhibitors in the previous two weeks before the study.
Interventions	Fluvoxamine: 30 participants. Imipramine: 30 participants. Fluvoxamine dose range: 100-150 mg/day. Imipramine dose range: 100-150 mg/day. Treatments with benzodiazepines was allowed, if necessary. No treatments with barbiturates, other antidepressants, or amphetamine were permitted.
Outcomes	HRSD-21, CGI-I, CGI-S. Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	5/60 (8%) patients were with psychotic features.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study medicines were dispensed in identical pharmaceutical forms, no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 2/30 missing from fluvoxamine group (2 due to lack of efficacy); 1/30 missing from control group (1 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Brown 1986

Methods	Six-week double blind, multicentre, randomised study.
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Brown 1986 (Continued)

Participants	Psychiatric outpatients meeting DSM-III-R for major depression, with a minimum baseline score of 20 on the HRSD-21. Age range: 21-60 years old. Exclusion criteria: clinically significant physical illness or were taking medication, such as anticonvulsants.
Interventions	Fluvoxamine: 33 participants. Imipramine: 17 participants. Fluvoxamine dose range: 200-300 mg/day. Imipramine dose range: 150-225 mg/day.
Outcomes	HRSD-21. Total dropout, dropout due to inefficiency, dropout due to side effects.
Funded by pharmaceutical companies	Unclear.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	Study authors examined pituitary-adrenocortical status in relation to medication. No clinical data were reported for imipramine group. No efficacy data could be entered in a meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 8/33 missing from fluvoxamine group (8 due to adverse effects); 4/17 missing from control group (4 due to adverse effects).
Selective reporting (reporting bias)	High risk	No clinical data were reported for imipramine group.

Brunner 1994

Methods	Four-week open, randomised study.
Participants	Psychiatric inpatients suffering from depression according to Feighner criteria, with a minimum baseline score of 17 on the HRSD-17. Age range: 18-70 years old.

Brunner 1994 (Continued)

Exclusion criteria: Woman who were pregnant or not taking adequate contraceptive measures, an initial depressive episode of less than two weeks' duration, depression secondary to another psychiatric condition, severe physical illness, or who had received lithium or shock therapy in the previous four weeks.

Interventions	Fluvoxamine: 20 participants. Amineptine: 20 participants. Fluvoxamine dose range: 100-300 mg/day. Amineptine dose range: 100-200 mg/day. Diazepam (sedative), flunitrazepam (hypnotic) and cymemazine (sedative neuroleptic) were allowed.
Outcomes	HRSD-17, CGI-I, CGI-S. Total dropout, dropout due to inefficiency, dropout due to side effects.
Funded by pharmaceutical companies	Unclear.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	Patients with depression (Feighner criteria) were included, so there might be some bipolar depression, but correct number was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized study", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "open study".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 2/20 missing from fluvoxamine group (1 due to adverse effects); 3/20 missing from control group (4 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Cassano 1986

Methods	Four-week double blind, multicentre, randomised study.
Participants	Psychiatric in- and outpatients meeting DSM-III for major affective disorder, with a minimum baseline score of 15 on the HDRS-17. Age range: 19-70 years old. Exclusion criteria: child bearing potential or pregnant women; antidepressant therapy in the past 2 weeks; ECT within the last month; depressive symptoms secondary to other psychiatric illness; dependence upon licit or illicit drugs; serious organic diseases; need for concurrent medications which could

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Cassano 1986 (Continued)

interact with the study drugs or obscure their effects; patients unwilling or unable to cooperate with the study.

Interventions	<p>Fluvoxamine: 169 participants. Imipramine: 161 participants. Placebo: 151 participants. Fluvoxamine dose range: 50-300 mg/day. Imipramine dose range: 50-300 mg/day.</p> <p>Chloral hydrate or flurazepam as hypnotics were allowed during the trial.</p>
Outcomes	<p>HDRS-17, CGI-I, CGI-severity, BPRS, SCL-90, SDS.</p> <p>Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.</p>
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	Patients with major affective disorder (DSM-III) were included, so there might be some bipolar depression, but correct number was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 67/169 missing from fluvoxamine group (12 due to lack of efficacy, 19 due to adverse effects); 57/161 missing from control group (10 due to lack of efficacy, 17 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Claghorn 1996

Methods	Six-week double blind, single-centre, randomised study.
Participants	<p>Psychiatric outpatients meeting DSM-III-R for major depressive disorder (single or recurrent episode without psychotic features or only mood-congruent psychotic features). Baseline symptom severity (mean (SD) for HRSD-21) was 26.1 (3.6). Age range: 18-65years old.</p>

Claghorn 1996 (Continued)

Exclusion criteria: any significant health problems, as determined by a physical examination and clinical laboratory tests (blood chemistry, hematology, urinalysis, serum pregnancy test) and electrocardiograms.

Interventions	Fluvoxamine: 50 participants. Imipramine: 50 participants. Placebo: 50 participants. Fluvoxamine dose range: 50-150 mg/day. Imipramine dose range: 80-240 mg/day.
Outcomes	HRSD-21, MADRS, CGI-I, Raskin Depression Scale and Covi Anxiety Scale, SCL-56. Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 30/50 missing from fluvoxamine group (4 due to lack of efficacy, 12 due to adverse effects); 29/50 missing from control group (3 due to lack of efficacy, 13 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Clerc 2001

Methods	Six-week, multicentre, randomised study.
Participants	Psychiatric in- and outpatients suffering from major depression according to DSM-III-R, with a minimum baseline score of 25 on the MADRS. Age range: 18-70 years old. Exclusion criteria: depression was associated with other conditions such as dysthymic disorder or schizophrenia, suicidal ideas or extreme anxiety, bipolar depression treated with lithium within the 3 months prior to the study, pregnancy or breastfeeding, serious medical conditions or treatment with drugs known to interact with fluvoxamine or milnacipran.
Interventions	Fluvoxamine: 56 participants.

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Clerc 2001 (Continued)

Milnacipran: 57 participants.
 Fluvoxamine dose: 200 mg/day.
 Milnacipran dose: 100 mg/day.

No other psychotropic drugs were permitted during the trial and any such drugs were withdrawn during the run-in period. Tranquilizers or hypnotics (other than nitrazepam or lorazepam) were withdrawn at least 3 days before starting medication, and antidepressants were withdrawn 7 days before the study (15 days for monoamine oxidase inhibitor). Intermediate-acting neuroleptic agents were withdrawn 7 days before the trial, and long-acting agents were withdrawn 1 month before. Nitrazepam or lorazepam, at daily doses up to 5 and 10 mg, respectively, or chloral hydrate syrup, could be given as necessary during the run-in and subsequent phases.

Outcomes	HRSD-17, HRSD-24, MADRS, CGI-I. Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets comparator drug.
Fluvoxamine as an investigational or comparator drug	As a comparator drug.
Notes	2/113 (1.8%) patients were with psychotic features.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Patients were blinded, no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 17/56 missing from fluvoxamine group (7 due to lack of efficacy, 4 due to adverse effects); 15/57 missing from control group (10 due to lack of efficacy, 1 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Coleman 1982

Methods	Four-week double blind, multicentre, randomised study.
Participants	Psychiatric inpatients suffering from both unipolar and bipolar depression, with the dysphoric mood accompanied by at least five of Feighner criteria. Age range: not stated. Exclusion criteria: not stated.
Interventions	Fluvoxamine: 50 participants. Clomipramine: 48 participants.

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Coleman 1982 (Continued)

Fluvoxamine dose range: 150-300 mg/day.
 Clomipramine dose range: 150-300mg/day.

Outcomes	HRSD, CGI-I, CGI-S. Total dropout, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	Patients with bipolar depression were included, but correct number was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 9/50 missing from fluvoxamine group; 5/48 missing from control group (due to lack of efficacy, due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Dalery 2003

Methods	Six-week double blind, multicentre, randomised study.
Participants	Psychiatric outpatients meeting DSM-III-R for major depressive episode, with a minimum baseline score of 17 on the HRSD-17. Age range: 18-70 years old. Exclusion criteria: acute suicidal ideation or a serious suicide attempt in the previous 6 months; dementia; a history of epilepsy or seizures; concurrent or recent (6 months) alcoholism, other psychoactive substance abuse or drug-induced psychosis, were pregnant, lactating or of childbearing potential and not taking adequate contraceptive measures, or if they had clinically uncontrolled hepatic, renal, pulmonary, endocrine or collagen disease. Also excluded were patients who had previously failed SSRI therapy or who required concomitant lithium, warfarin, hepatically metabolised antivitamin K agents, carbamazepine, theophylline, insulin or hypoglycaemic agents. Patients were required not to receive monoamine oxidase inhibitors or ECT in the 2 weeks prior to the study.
Interventions	Fluvoxamine: 90 participants. Fluoxetine: 94 participants. Fluvoxamine dose: 100 mg/day. Fluoxetine dose: 20 mg/day.

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Dalery 2003 (Continued)

Oxazepam or nitrazepam were permitted as necessary for night time sedation; no other psychotherapeutic treatments or ECT were permitted during the study.

Outcomes	HRSD-17, CGI-I, CGI-S, Clinical Anxiety Scale, Irritability, Depression and Anxiety scale, Beck's scale for suicide ideation score. Total dropout, side effect profile.
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Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
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Fluvoxamine as an investigational or comparator drug	Unclear.
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Notes	Patients with major depressive episode (DSM-III-R) were included, so there might be some bipolar depression, but correct number was not reported.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 24/90 missing from fluvoxamine group; 20/94 missing from control group (due to lack of efficacy, due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

de Wilde 1983

Methods	Six-week double blind, randomised study.
Participants	Psychiatric outpatients meeting Feighner criteria for depression, with a minimum baseline score of 16 on the HRSD-17. Age range: 18-70 years old. Exclusion criteria: significant concurrent organic disease, depression as a secondary manifestation of other psychiatric illnesses, pregnant or lactating women, patients who had received ECT or lithium within the last 4 weeks, patients with a high suicide risk and those with a history of drug allergy.
Interventions	Fluvoxamine: 22 participants. Clomipramine: 51 participants. Fluvoxamine dose range: 100-300 mg/day. Clomipramine dose range: 50-150 mg/day. During the treatment free period and the study period the following concurrent medication was allowed: benzodiazepines as hypnotics, sedatives or tranquilizers, chloral hydrate as a hypnotic, anti-

de Wilde 1983 (Continued)

otics, non-narcotic analgesics, antacids and laxatives. Antihypertensive agents, anticoagulants and alcohol were not allowed. Psychotropic medication other than the benzodiazepines or chloral hydrate were forbidden.

Outcomes	HRSD-17, CGI-S. Total dropout, number of patients experiencing at least one side effect, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	2/43 (4.7%) patients were with bipolar depression.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	High risk	SDs for endpoint score and change score were not reported.

Dick 1983

Methods	Four-week double blind, randomised study.
Participants	Psychiatric inpatients suffering from persistent alteration of mood (depressed mood), had to be accompanied by at least 5 characteristics as mentioned in the Feighner criteria, with a minimum baseline score of 16 on the HRSD-17. Age range: 34-64 years old. Exclusion criteria: not stated.
Interventions	Fluvoxamine: 17 participants. Clomipramine: 15 participants. Fluvoxamine dose: 150 mg/day. Clomipramine dose: 150 mg/day. The protocol did not allow drugs other than the study medication during the study period except, if necessary, limited use of diazepam, levomepromazine (methotrimeprazine) and flunitrazepam.
Outcomes	HRSD-17, CGI-S, CGI-change in condition score and a self rating scale.

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Dick 1983 (Continued)

Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.

Funded by pharmaceutical companies

Unclear.

Fluvoxamine as an investigational or comparator drug

As an investigational drug.

Notes

Patients with depression (Feighner criteria) were included, so there might be some bipolar depression, but correct number was not reported.
*The HRSD-17 items 'genital symptoms' and 'loss of weight' were not recorded, study authors analysed left 15 items only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 4/17 missing from fluvoxamine group (2 due to adverse effects); 4/15 missing from control group (1 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Fabre 1996

Methods	Six-week double blind, single-centre, randomised study.
Participants	Psychiatric outpatients meeting DSM-III-R for major depressive disorder, with a minimum baseline score of 20 on the HRSD-21. Age range: 18-65 years old. Exclusion criteria: any other primary psychiatric diagnosis, unstable medical conditions, clinically significant abnormal laboratory findings.
Interventions	Fluvoxamine: 50 participants. Imipramine: 50 participants. Placebo: 50 participants. Fluvoxamine dose range: 50-150 mg/day. Imipramine dose range: 80-240 mg/day. 101 received at least one concomitant medication during the double blind portion of the trial. Concomitant medication was limited, only chloral hydrate was allowed as a hypnotic during the first two weeks of therapy. No sedative hypnotic was permitted after week 2. The most frequently prescribed medications were acetaminophen, aspirin, and other non-steroidal anti-inflammatory agents or non-

Fabre 1996 (Continued)

sedating antihistamines, which should not have influenced the safety or efficacy outcome measures used in this study.

Outcomes	HRSD-21, MADRS, CGI-S, Raskin-Covi, SCL-56. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.
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Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
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Fluvoxamine as an investigational or comparator drug	As an investigational drug.
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 28/50 missing from fluvoxamine group (7 due to lack of efficacy, 7 due to adverse effects); 25/50 missing from control group (2 due to lack of efficacy, 9 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Feighner 1989

Methods	Six-week double blind, randomised study.
Participants	Psychiatric inpatients meeting DSM-III for major depression. All but one also quantified for melancholic subtype. Age range: 18-71 years old. Exclusion criteria: not reported.
Interventions	Fluvoxamine: 31 participants. Imipramine: 36 participants. Placebo: 19 participants. Fluvoxamine dose range: 150-300 mg/day. Imipramine dose range: 150-300 mg/day.
Outcomes	HRSD, CGI-S, BPRS, Zung Depression Scale, SCL-90. Total dropout, dropout due to side effects, side effect profile.

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Feighner 1989 (Continued)

Funded by pharmaceutical companies Unclear.

Fluvoxamine as an investigational or comparator drug As an investigational drug.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 10/31 missing from fluvoxamine group (7 due to adverse effects); 13/36 missing from control group (13 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Gonul 1999

Methods Four-week double blind, randomised study.

Participants Patients with major depression (DSM-IV).
 Age: mean 35.6 years old (SD 11.8).
 Exclusion criteria: psychotic symptoms, catatonia.

Interventions Fluvoxamine: 40 participants.
 Fluoxetine: 40 participants.
 Paroxetine: 40 participants.
 Sertraline: 40 participants.
 Fluvoxamine dose: 150 mg/day.
 Fluoxetine dose: 20 mg/day.
 Paroxetine dose: 20 mg/day.
 Sertraline dose: 50 mg/day.

Outcomes HRSD.
 Total dropout, dropout due to side effects.

Funded by pharmaceutical companies Unclear.

Gonul 1999 (Continued)

Fluvoxamine as an investigational or comparator drug Unclear.

Notes Patients with "major depression" (DSM-IV) were included, so there might be some bipolar depression, but correct number was not reported.

No clinical efficacy data could be entered in a meta-analysis; study authors reported only as "When the number of patients responding therapy was taken into account for the efficacy to each SSRI, we could not find any significant difference among them".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "single blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 3/40 missing from fluvoxamine group (3 due to adverse effects); 4/40 missing from fluoxetine group (4 due to adverse effects); 6/40 missing from paroxetine group (6 due to adverse effects); 4/40 missing from sertraline group (6 due to adverse effects).
Selective reporting (reporting bias)	High risk	Results of HRSD were not reported.

Guy 1984

Methods	Six-week double blind, randomised study.
Participants	Psychiatric inpatients meeting RDC for primary depression (unipolar or bipolar) and a persistent alteration of mood. Age range: 18-60 years old. Exclusion criteria: females not practicing contraception, significant medical illnesses, continuing alcohol/drug abuse, history of other psychiatric illness in which the depression was secondary.
Interventions	Fluvoxamine: 17 participants. Imipramine: 19 participants. Fluvoxamine dose range: 150-225 mg/day. Imipramine dose range: 150-225 mg/day.
	Remedial medications were administered in at least one occasion to approximately 80 % of the patients in each treatment group. Flurazepam for sleep disturbance and acetaminophen for headache were the most frequently prescribed medications. In both instances, a higher percent of fluvoxamine-treated patients (64%) received these medications than patients in the imipramine group. Less frequently and non differentially prescribed were medications for constipation, diet supplementation, coughs and colds, and minor infections.
Outcomes	HRSD-17, CGI-I, CGI-S, BPRS, NOSIE (Nurses' observation scale for independent evaluation), Zung self-rating depression scale.

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Guy 1984 (Continued)

Total dropout, side effect profile.

Funded by pharmaceutical companies	Unclear.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	7/36 (19.4%) bipolar patients were included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned by randomization list", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 1/17 missing from fluvoxamine group; 3/19 missing from control group.
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Hackett 1998a

Methods	Six-week double blind, multicentre, randomised study.
Participants	Psychiatric outpatients meeting DSM-III for major depression, with a minimum pre-study and baseline score of 24 on the MADRS and no more than 20 % decrease in those score from pre-study to baseline. Age range: not stated. Exclusion criteria: not stated.
Interventions	Fluvoxamine: 34 participants. Venlafaxine (twice a day): 37 participants. Fluvoxamine dose: 200 mg/day. Venlafaxine dose (twice a day): 100 mg/day.
Outcomes	HRSD, MADRS, CGI-I. Total dropout.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets comparator drug.
Fluvoxamine as an investigational or comparator drug	As a comparator drug.

Fluvoxamine versus other anti-depressive agents for depression (Review)

Hackett 1998a (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 13/34 missing from fluvoxamine group; 9/37 missing from venlafaxine (twice a day) group; 9/40 missing from venlafaxine (three times a day) group.
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Hackett 1998b

Methods	= Hackett 1998a
Participants	= Hackett 1998a
Interventions	Fluvoxamine: 34 participants. Venlafaxine (three times a day): 40 participants. Fluvoxamine dose: 200 mg/day. Venlafaxine dose (three times a day): 100 mg/day.
Outcomes	= Hackett 1998a
Funded by pharmaceutical companies	= Hackett 1998a
Fluvoxamine as an investigational or comparator drug	= Hackett 1998a
Notes	= Hackett 1998a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	= Hackett 1998a
Allocation concealment (selection bias)	Unclear risk	= Hackett 1998a

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Hackett 1998b (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	=Hackett 1998a
Incomplete outcome data (attrition bias) All outcomes	High risk	=Hackett 1998a
Selective reporting (reporting bias)	High risk	=Hackett 1998a

Haffmans 1996

Methods	Six-week double blind, multicentre, randomised study.	
Participants	Psychiatric outpatients meeting DSM-III-R for major depression, with a minimum baseline score of 16 on the HRSD-17. Age range: 18-70 years old. Exclusion criteria: patients who had been treated with MAO-I or fluoxetine within the last 3 weeks or with other psychotropic drugs within the last week, with the exception of benzodiazepines; primary psychiatric diagnosis; a history of epilepsy, alcohol and/or drug abuse; pregnant or lactating women and women of childbearing potential failing to use standard birth control methods; renal, hepatic, cardiovascular, neurological or somatic disorders and/or significant abnormal laboratory findings; mental retardation.	
Interventions	Fluvoxamine: 109 participants. Citalopram: 108 participants. Fluvoxamine dose range: 150-200 mg/day. Citalopram dose range: 30-40 mg/day. Selected benzodiazepines as permitted concomitant medication at baseline could be continued during the study. Patients who were receiving other benzodiazepines were switched to one of the following permitted drugs. The maximum dose of the benzodiazepines which could be given during the study were; oxazepam at 50 mg daily, lormethazepam at 4 mg daily, temazepam at 20 mg daily, lorazepam at 4 mg daily, flurazepam at 15 mg daily. Preferably, the daily dose was stable during the study period. All non psychotropic medication was allowed but the regime was to be kept stable. In case of severe nausea and/or vomiting, domperidone could be given.	
Outcomes	HRSD-17, CGI-S, Zung Self-Rating Depression scale. Total dropout, dropout due to side effects, side effect profile.	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets comparator drug.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes	6/217 (2.8%) patients were with bipolar depression and 4/217 (1.8%) patients with psychotic features.	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Haffmans 1996 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 29/109 missing from fluvoxamine group (26 due to adverse effects); 22/108 missing from control group (16 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Harris 1991a

Methods	Six-week double blind, multicentre, randomised study.	
Participants	Psychiatric outpatients meeting DSM-III for major depressive episode, with a minimum baseline score of 17 on the HRSD-17. Age range: 18-65 years old. Exclusion criteria: pregnant or at risk of pregnancy or breast feeding, epilepsy; patients receiving other antidepressants therapy, adrenergic neuron blockers, clonidine, sympathomimetic or anticholinergic drugs; severe impairment of renal or cardiovascular function, prostatic hypertrophy, urinary retention, narrow angle glaucoma, increased intraocular pressure, hyperthyroidism; severe suicidal risk.	
Interventions	Fluvoxamine: 35 participants. Amitriptyline: 34 participants. Fluvoxamine dose range: 50-150 mg/day. Amitriptyline dose range: 50-150 mg/day. The use of other antidepressants was prohibited, but benzodiazepine previously described as hypnotics or anxiolytics were permitted. Other concurrent medication had to be kept to a minimum and be fully documented.	
Outcomes	HRSD-17, CGI-I. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.	
Fluvoxamine as an investigational or comparator drug	As an investigational drug.	
Notes	Patients with major depressive episode (DSM-III) were included, so there might be some bipolar depression, but correct number was not reported.	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Harris 1991a (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 12/35 missing from fluvoxamine group (1 due to lack of efficacy, 5 due to adverse effects); 10/34 missing from control group (4 due to lack of efficacy, 6 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint score for depression were not reported.

Itil 1983

Methods	Six-week double blind, randomised study.	
Participants	Psychiatric outpatients meeting RDC for depression, with a minimum baseline score of 15 on the HRSD-17. Age range: 18-65 years old. Exclusion criteria: Pregnant women and women of childbearing potential; patients whose depression was secondary to another illness; patients receiving imipramine, MAO inhibitors within 2 weeks of study commencement, ECT within 4 weeks of study commencement, lithium carbonate, or any short or long term medication which might interact with study drug.	
Interventions	Fluvoxamine: 22 participants. Imipramine: 25 participants. Placebo: 22 participants. Fluvoxamine dose range: 50-300 mg/day Imipramine dose range: 50-300 mg/day.	
Outcomes	HRSD-16, CGI-I, CGI-S, SCL-90, Beck depression inventory (BDI). Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.	
Fluvoxamine as an investigational or comparator drug	As an investigational drug.	
Notes	3/69 (4.3%) were with bipolar depression. * Study authors stated the using 'HRSD-16'.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.

Itil 1983 (Continued)

Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 12/22 missing from fluvoxamine group (9 due to adverse effects); 12/25 missing from control group (1 due to lack of efficacy, 7 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Kasper 1990

Methods	Six-week double blind, randomised study.	
Participants	Psychiatric inpatients meeting RDC for major depression, with a minimum baseline score of 18 on the HRSD-21. Age range: 28-71 years old. Exclusion criteria: medical illness examined by complete medical and neurological evaluations; alcohol and drug abuse; pathological signs of EEG, ECG, and laboratory examinations.	
Interventions	Fluvoxamine: 21 participants. Maprotiline: 21 participants. Fluvoxamine dose range: 100-300 mg/day. Maprotiline dose range: 100-300 mg/day. Following admission to the study, all psychotropic drugs were discontinued (wash out phase: 7 days) and patients remained drug free except for chlor-hydrate, which was given for agitation or insomnia. Patients underwent a TSD (total sleep deprivation) at day 0 and day 8. All patients were deprived of sleep for one total night (40 hours).	
Outcomes	HRSD-21, CGI. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.	
Funded by pharmaceutical companies	Unclear.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes	2/42 (5%) patients were with bipolar depression and 2/42 (5%) patients were with psychotic features.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.

Kasper 1990 (Continued)

Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", "capsules of either fluvoxamine or maprotiline in identical presentation", no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 1/21 missing from control group (due to lack of efficacy, due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Kato 2006

Methods	Six-week open, single-centre, randomised study.	
Participants	Patients meeting DSM-IV for major depressive disorder. Age: mean 44.8 years old (SD 14.9). Exclusion criteria: additional diagnoses on Axis I and Axis II, pregnancy, and medical and neurological disorders.	
Interventions	Fluvoxamine: 49 participants. Paroxetine: 52 participants. Fluvoxamine dose range: 50-150 mg/day. Paroxetine dose range: 20-40 mg/day. Patients who had been receiving benzodiazepines for at least 10 days before entering the study were permitted to continue these agents, providing that dose remained unchanged throughout the study period. A low dose sleep inducing hypnotic agent, either brotizolam or triazolam, was permitted for severe insomnia as an additional medication.	
Outcomes	HRSD-21. Total dropout, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.	
Funded by pharmaceutical companies	Funded by pharmaceutical companies market fluvoxamine and comparator drug.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes	Study authors examined the association between 5HTT gene-linked polymorphic region genotype and SSRI treatment response.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.

Kato 2006 (Continued)

Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "open-label study", "HRSD score evaluations were administered at weekly intervals by trained raters, who were blind to genotyping".
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 8/49 missing from fluvoxamine group (4 due to adverse effects); 13/52 missing from control group (6 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint score for depression were not reported.

Kavoussi 1999

Methods	Eight-week double blind, multicentre, randomised study.	
Participants	Psychiatric outpatients meeting DSM-IV for major depressive disorder, with a minimum baseline score of 20 on the HRSD-21. Age (mean (SD)): 35.4 (7.7). Exclusion criteria: other Axis I disorders (current or past), any Axis II disorder; had ever been actively suicidal, or had a history of substance dependence within 6 months of the study; had been previously treated with fluoxetine or fluvoxamine.	
Interventions	Fluvoxamine: number of participants not stated. Fluoxetine: number of participants not stated. Fluvoxamine dose range: 100-150 mg/day Fluoxetine dose range: 20-80 mg/day.	
Outcomes	No efficacy and tolerability data could be entered in a meta-analysis were reported.	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes	Study authors examined prolactin response to d-fenfluramine challenge before and after antidepressant treatment.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", "the medications were blindly titrated", no further details.

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Kavoussi 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details.
Selective reporting (reporting bias)	High risk	No clinical outcome data were reported.

Kiev 1997

Methods	Seven-week double blind, multicentre, randomised study.	
Participants	Psychiatric outpatients meeting DSM-III-R for recurrent major depressive disorder, with a minimum baseline score of 20 on the HRSD-21. Age range: 18-65 years old. Exclusion criteria: woman of childbearing potential were required to use appropriate birth control methods, and no pregnant or nursing patients were included the study; patients who were not fluent in written or oral English; had a history of medication noncompliance or substance abuse within the previous 6 months (other than nicotine); had been treated within 30 days with a drug with anticipated major organ toxicity; had a severe risk of suicide or displayed auto-aggressive behavior during the current depressive episode; hypersensitivity to SSRIs; participation in previous fluvoxamine studies; significant organic disease; clinically significant laboratory abnormalities; other primary psychiatric diagnoses; patients who would not be able to return for assessment due to transportation difficulties.	
Interventions	Fluvoxamine: 30 participants. Paroxetine: 30 participants. Fluvoxamine dose range: 50-150 mg/day. Paroxetine dose range: 20-50 mg/day. Sufficient washout from other investigational drugs prior psychotropic drugs, and ECT was assured, and concomitant use of any psychotropic medication was prohibited. While medications to treat gastrointestinal disturbances (antacids, laxatives), and headache (acetaminophen, aspirin, ibuprofen) and to provide nighttime sedation (chloral hydrate only) were permitted, all other medication use was prohibited unless approved by the study physician.	
Outcomes	HRSD-21, CGI-I, CGI-S, HRSA, SCL-56. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.

Kiev 1997 (Continued)

Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 11/30 missing from fluvoxamine group (1 due to lack of efficacy, 2 due to adverse effects); 9/30 missing from control group (3 due to lack of efficacy, 5 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint score for depression were not reported.

Koetsier 2002

Methods	Four-week double blind, single-centre, randomised study.	
Participants	Psychiatric inpatients suffering from major depressive disorder according to DSM-IV, with a minimum baseline score of 14 on the HRSD-17. Age range: 32-65 years old. Exclusion criteria: history of a treatment with a TCA with adequate plasma levels during 4 weeks.	
Interventions	Fluvoxamine: 27 participants. Imipramine: 25 participants. Fluvoxamine dose range: not stated. Imipramine dose range: not stated. During the treatment period no psychotropic drugs were allowed besides the study medication.	
Outcomes	HRSD-17, SPRS (Salpetriere retardation rating scale), shortened version of POMS (Profile of mood state). Total dropout, dropout due to inefficiency, dropout due to side effects.	
Funded by pharmaceutical companies	Unclear.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias)	Unclear risk	Quote: "double blind", no further details

Fluvoxamine versus other anti-depressive agents for depression (Review)

Koetsier 2002 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 3/27 missing from fluvoxamine group (2 due to adverse effects); 3/25 missing from control group (2 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Kostiukova 2003

Methods	Six-week, single-centre, randomised study.
Participants	Psychiatric inpatients meeting ICD-10 for recurrent depressive disorder without psychotic features, with a minimum baseline score of 19 on the HRSD-17. Age range: 18-65 years old. Exclusion criteria: not stated.
Interventions	Fluvoxamine: 30 participants. Amitriptyline: 30 participants. Fluvoxamine dose range: 50-300 mg/day. Amitriptyline dose range: 50-250 mg/day.
Outcomes	HRSD-17. Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.
Funded by pharmaceutical companies	Unclear.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 7/30 missing from fluvoxamine group (4 due to lack of efficacy, 3 due to adverse effects); 8/30 missing from control group (3 due to lack of efficacy, 5 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Lydiard 1989

Methods	Six-week double blind, multicentre, randomised study.
Participants	Psychiatric outpatients meeting DSM-III for major depressive disorder, with a minimum baseline score of 22 on the HRSD-17. Age range: 23-80 years old. Exclusion criteria: not physically healthy, were psychotic or had organic brain syndrome, had a history of bipolar affective disorder, exhibited current depressive symptomatology of less than 1 month and greater than 18 month in duration, were currently taking any psychotropic medication, were substance abusers, or exhibited a clear suicidal intent.
Interventions	Fluvoxamine: 18 participants. Imipramine: 18 participants. Placebo: 18 participants. Fluvoxamine dose range: 100-300 mg/day. Imipramine dose range: 100-300 mg/day.
Outcomes	HRSD-17, MADRS, CGI-I. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 1/18 missing from fluvoxamine group (1 due to adverse effects); 2/18 missing from control group (2 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

March 1990

Methods	Six-week double blind, randomised study.
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Fluvoxamine versus other anti-depressive agents for depression (Review)

March 1990 (Continued)

Participants	<p>Psychiatric outpatients meeting DSM-III for major affective disorder, with a minimum baseline score of 22 on the HRSD-17.</p> <p>Age range: 18-67 years old.</p> <p>Exclusion criteria: pregnant women, lactating women, or women of childbearing potential who were taking inadequate contraceptive measures; patients with schizophrenia, psychotic symptoms, organic dementias, or a diagnosis within 1 year of substance abuse or alcoholism; patients with cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, or other systematic diseases that could interfere with the diagnosis, treatment, or assessment of depression; patients who required treatment with any concurrent medication that might interact with or obscure the action of the study medications; patients with clinically significant abnormalities in ECG or laboratory results; patients with multiple drug allergies; patients who had received monoamine oxidase inhibitors or lithium in the 2 weeks preceding study entry or who had received any other antidepressant drugs in the preceding 1 week; patients who had received any investigational drug or ECT in the previous 4 weeks.</p>
Interventions	<p>Fluvoxamine: 18 participants.</p> <p>Imipramine: 18 participants.</p> <p>Placebo: 18 participants.</p> <p>Fluvoxamine dose range: 100-300 mg/day.</p> <p>Imipramine dose range: 100-300 mg/day.</p>
Outcomes	<p>HRSD-17. MADRS, CGI-I, 58 items Hopkins symptom checklist (HSCL).</p> <p>Total dropout, dropout due to inefficiency, dropout due to side effects.</p>
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	1/54 (2%) patients were with bipolar depression.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", "fluvoxamine, imipramine, and placebo were provided in identical gray capsules," no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 5/18 missing from fluvoxamine group (5 due to adverse effects); 3/18 missing from control group (3 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Mendonca Lima 1997

Methods	Four-week open, single-centre, randomised study.
Participants	<p>Patients meeting DSM-III-R for major depression or dysthymia, with a minimum baseline score of 25 on the MADRS.</p> <p>Age: mean 35.6 years old (SD 8.3).</p> <p>Exclusion criteria: hepatic, renal, endocrine, cardiac disease; taking any medication that could affect thyroid function.</p>
Interventions	<p>Fluvoxamine: 20 participants.</p> <p>Maprotiline: 20 participants.</p> <p>Fluvoxamine dose: 100 mg/day</p> <p>Maprotiline dose: 75 mg/day.</p> <p>Only bromazepam (at most 18 mg/day) were allowed.</p>
Outcomes	<p>MADRS, Newcastle Diagnostic Scale.</p> <p>Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.</p>
Funded by pharmaceutical companies	Unclear.
Fluvoxamine as an investigational or comparator drug	Unclear.
Notes	There were some patients with dysthymia, but correct number was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "en ouvert" (open study), no further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	High risk	SDs of endpoint score for depression were not reported.

Miller 2001

Methods	Six-week double blind, randomised study.
Participants	<p>Psychiatric outpatients meeting DSM-III for major depression.</p> <p>Age range: not reported.</p>

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Miller 2001 (Continued)

Exclusion criteria: not reported.

Interventions	Fluvoxamine: 13 participants. Imipramine: 11 participants. Placebo: 13 participants. Fluvoxamine dose range: not stated. Imipramine dose range: not stated.
Outcomes	HRSD (change score only). No tolerability data could be entered in a meta-analysis were reported.
Funded by pharmaceutical companies	No funding by pharmaceutical companies.
Fluvoxamine as an investigational or comparator drug	Unclear.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind", "HRSD score were obtained by a research clinician unaware of treatment assignment".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Moon 1991

Methods	Six-week double blind, single-centre, randomised study.
Participants	Primary care outpatients meeting DSM-III for major depressive episode, with a minimum baseline score of 24 on the MADRS. Age range: 18-65 years old. Exclusion criteria: clinically important impairment of hepatic or renal function; history of epilepsy; severe suicide risk; pregnant females or those at risk of becoming pregnant.
Interventions	Fluvoxamine: 31 participants. Mianserin: 31 participants. Fluvoxamine dose range: 100-300 mg/day. Mianserin dose range: 60-180 mg/day.

Moon 1991 (Continued)

During the study, from entry into the placebo period onwards, no other psychotropic medication (antidepressant, tranquillisers or hypnotics) were allowed, Patients were asked to keep other concurrent drugs to a minimum and to abstain from alcohol.

Outcomes	MADRS, CGI-I. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	Patients with major depressive episode (DSM-III) were included, so there might be some bipolar depression, but correct number was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 3/31 missing from fluvoxamine group (3 due to adverse effects); 10/31 missing from control group (7 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Mullin 1988

Methods	Six-week double blind, multicentre, randomised study.
Participants	Psychiatric inpatients meeting DSM-III for major depressive episode, with a minimum baseline score of 17 on the HRSD-17. Age range: 20-69 years old. Exclusion criteria: pregnant or breast feeding; receiving other anti-depressive therapy which could not be discontinued for the duration of the trial; severe impairment of liver or renal function; history of recent myocardial infarction, any degree of heart block or any other cardiac arrhythmia, as such conditions contraindicate the use of dothiepin; history of narrow angle glaucoma, prostatic hypertrophy or epilepsy, as dothiepin should be avoided in these patients.
Interventions	Fluvoxamine: 37 participants. Dothiepin: 36 participants. Fluvoxamine dose range: 100-300 mg/day.

Mullin 1988 (Continued)

	Dothiepin dose range: 75-225 mg/day.
Outcomes	HRSD-17, CGI-I. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	Patients with major depressive episode (DSM-III) were included, so there might be some bipolar depression, but correct number was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomisation", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 11/37 missing from fluvoxamine group (2 due to lack of efficacy, 9 due to adverse effects); 12/36 missing from control group (4 due to lack of efficacy, 7 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs for endpoint score and change score were not reported.

Murasaki 1998a

Methods	Four-week double blind, multicentre, randomised study.
Participants	Psychiatric in- and outpatients meeting DSM-III for major depressive episode, with a minimum baseline score of 16 on the HRSD-17. 186 out of 218 all allocated patients (85%) were with major depressive disorder. Age range: 18-70 years old. Exclusion criteria: schizophrenia; history of epilepsy; depressive state due to organic brain disorder; treatment with lithium or MAO inhibitors in the previous two weeks before the study; treatment with ECT in the previous three months before the study; dysuria, glaucoma, endocrine disorder including hypothyroidism; history of drug allergy; severe cardiac, hepatic, renal, hematological disorder; pregnant, at risk of pregnant, breastfeeding female.
Interventions	Fluvoxamine: 113 participants. Amitriptyline: 122 participants. Fluvoxamine dose range: 50-150 mg/day. Amitriptyline dose range: 50-150 mg/day.

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Murasaki 1998a (Continued)

Outcomes	HRSD-21. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical companies market fluvoxamine and comparator drug.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	15/218 (6.9%) patients were with bipolar depression, 11/218 (5.0%) were with dysthymia and 6/218 (2.8%) with depressive disorder not otherwise specified.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 43/113 missing from fluvoxamine group (1 due to lack of efficacy, 17 due to adverse effects); 56 missing from control group (2 due to lack of efficacy, 28 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Nathan 1990

Methods	Four-week double blind, multicentre, randomised study.
Participants	Psychiatric inpatients meeting DSM-III for major depressive episode, with a minimum baseline score of 15 on the HRSD-17. Age: mean 39.7 years old (SD 13.7). Exclusion criteria: history of bipolar disorder; evidence of psychosis; concurrent medical diseases.
Interventions	Fluvoxamine: 20 participants. Desipramine: 20 participants. Fluvoxamine dose range: not stated. Desipramine dose range: not stated.
Outcomes	HRSD-17, Raskin, somatic symptoms scale, BDI. Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.

Fluvoxamine versus other anti-depressive agents for depression (Review)

Nathan 1990 (Continued)

Fluvoxamine as an investigational or comparator drug As an investigational drug.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", "patients were rated by an independent clinician", no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 3/20 missing from fluvoxamine group (2 due to adverse effects); 2/20 missing from control group (2 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Nemeroff 1995

Methods	Seven-week double blind, multicentre, randomised study.
Participants	Psychiatric outpatients meeting DSM-III-R for major depression, with a minimum baseline score of 20 on the HRSD-21. Age range: 22-62 years old. Exclusion criteria: pregnant or nursing female; did not have written and oral fluency in the English language; history of noncompliance; had been treated within 30 days with a drug having possible toxic effects on major organs; severe risk of suicide; intolerant to SSRI side effects; had participated in previous fluvoxamine studies; had other significant organic disease or other primary psychotic diagnoses.
Interventions	Fluvoxamine: 49 participants. Sertraline: 48 participants. Fluvoxamine dose range: 50-150 mg/day Sertraline dose range: 50-200 mg/day. Concomitant use of any psychotropic medications, other than chloral hydrate for nighttime sedation, was prohibited. While medications to treat gastrointestinal disturbances and headache were permitted, all other medication use was prohibited unless approved by the study physician. Lactobacillus acidophilus was used to treat SSRI-induced diarrhoea.
Outcomes	HRSD-21, CGI-I, HRSA, Raskin and Covi, SCL-56. Total dropout, dropout due to inefficiency, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.

Fluvoxamine versus other anti-depressive agents for depression (Review)

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Nemeroff 1995 (Continued)

Fluvoxamine as an investigational or comparator drug

Unclear.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", study drugs were identical in appearance, no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 21/49 missing from fluvoxamine group (2 due to lack of efficacy, 9 due to adverse effects); 9/48 missing from control group (1 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint score for depression were not reported.

Otsubo 2005

Methods	Eight-week open, single-centre, randomised study.
Participants	Psychiatric outpatients meeting DSM-IV for major depressive disorder. Age range: 20-69 years old. Exclusion criteria: patients who had failed to respond to 2 or more prior antidepressant trials in their current episode; medical contraindications to antidepressant therapy; significant hematologic, endocrine, or cardiovascular disease or conditions that might impair the study drug absorption, metabolism, or excretion; acute suicidal tendencies; history of a seizure disorder; history or presence of any psychotic disorder not associated with depression; history of drug or alcohol dependence within the past 2 years; experiences of receiving fluvoxamine or nortriptyline treatment.
Interventions	Fluvoxamine: 36 participants. Nortriptyline: 38 participants. Fluvoxamine dose range: 25-150 mg/day. Nortriptyline dose range: 25-150 mg/day. Patients were allowed to take lormethazepam 1-2 mg/day at bedtime for sleep whenever necessary.
Outcomes	HRSD-17, CGI-I, CGI-S. Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.
Funded by pharmaceutical companies	No funding by pharmaceutical companies.

Otsubo 2005 (Continued)

Fluvoxamine as an investigational or comparator drug

As an investigational drug.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "the patients were able to identify the drugs prescribed from their distinct appearance", however. "the doctor in charge was blind to the medical settings", "the raters were completely blind to the medication settings".
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 11/36 missing from fluvoxamine group (4 due to lack of efficacy, 3 due to adverse effects); 17/38 missing from control group (2 due to lack of efficacy, 7 due to adverse effects).
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Ottevanger 1995

Methods	Four-week double blind, multicentre, randomised study.
Participants	Psychiatric inpatients meeting Feighner criteria for depression, with a minimum baseline score of 17 on the HRSD-17. Age: mean 54.2 years old (SD 14.0). Exclusion criteria: patients receiving lithium or had undergone shock therapy during the previous 4 weeks; symptoms of depression which were only secondary manifestation of some other psychiatric condition; already on monoamine oxidase inhibitors or other antidepressants.
Interventions	Fluvoxamine: 20 participants. Clomipramine: 20 participants. Fluvoxamine dose range: 100-300 mg/day. Clomipramine dose range: 50-150 mg/day. The use of diazepam (5-35mg/day) for sedation, and flunitrazepam (2 -4 mg/day) for insomnia was permitted.
Outcomes	HRSD-17, CGI-S. Total dropout, dropout due to inefficiency, dropout due to side effects.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.

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Ottevanger 1995 (Continued)

Notes 1/40 (3%) patients were with bipolar depression.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 5/20 missing from fluvoxamine group (1 due to lack of efficacy, 2 due to adverse effects); 3/20 missing from control group (2 due to lack of efficacy, 1 due to adverse effects).
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Perez 1990

Methods	Six-week double blind, multicentre, randomised study.
Participants	Psychiatric outpatients meeting DSM-III for major depressive episode, with a minimum baseline score of 30 on the MADRS. Age range: 18 years old or more; mean 41.6 years old. Exclusion criteria: pregnant or at risk of becoming pregnant, breast feeding; strong suicide potential; major physical disorders such as epilepsy, hepatic or renal disease.
Interventions	Fluvoxamine: 30 participants. Mianserin: 33 participants. Fluvoxamine dose range: 100-300 mg/day Mianserin dose range: 60-180 mg/day. No other form of antidepressant medication was allowed during the trial period.
Outcomes	MADRS, CGI-I, Leeds Sleep Evaluation Questionnaire. Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.
Fluvoxamine as an investigational or comparator drug	Unclear.
Notes	Patients with major depressive episode (DSM-III) were included, so there might be some bipolar depression, but correct number was not reported.

Risk of bias

Perez 1990 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 9/30 missing from fluvoxamine group (1 due to lack of efficacy, 6 due to adverse effects); 9/33 missing from control group (2 due to lack of efficacy, 5 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Rahman 1991

Methods	Six-week double blind, multicentre, randomised study.	
Participants	Patients meeting DSM-III for major depressive episode, with a minimum baseline score of 29 on the MADRS. Age range: 61-86 years old. Exclusion criteria: concurrent depressive delusions or stupor; depression secondary to other psychiatric illness, according to DSM-III; narrow angle glaucoma; symptoms suggestive of prostatic hypertrophy; history of epilepsy, myocardial infarct within 3 months of entry into the study or any degree of heart block or other clinically significant arrhythmia.	
Interventions	Fluvoxamine: 26 participants. Dothiepin: 26 participants. Fluvoxamine dose range: 100-200 mg/day. Dothiepin dose range: 100-200 mg/day. Hypnotic and anxiolytic medication was allowed during the study, but other antidepressants were not.	
Outcomes	MADRS, CGI-I, Newcastle Scale. Total dropout, dropout due to side effects, number of patients experiencing at least one side effect.	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes	Patients with major depressive episode (DSM-III) were included, so there might be some bipolar depression, but correct number was not reported.	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Fluvoxamine versus other anti-depressive agents for depression (Review)

Rahman 1991 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 9/26 missing from fluvoxamine group (2 due to adverse effects); 7/26 missing from control group (2 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs for endpoint score and change score were not reported.

Rapaport 1996

Methods	Seven-week double blind, multicentre, randomised study.	
Participants	Psychiatric outpatients meeting DSM-III-R for major depressive episode, with a minimum baseline score of 20 on the HRSD-21. Age range: 22-61 years old. Exclusion criteria: pregnant or nursing patients; unstable medical conditions; other axis I diagnoses; acute suicidality; history of substance dependence within 6 months of the study; history of a seizure disorder; had been treated with either fluvoxamine or fluoxetine before enrolment.	
Interventions	Fluvoxamine: 51 participants. Fluoxetine: 49 participants. Fluvoxamine dose range: 100-150 mg/day. Fluoxetine dose range: 20-80 mg/day. Only chloral hydrate (up to a maximum of 1000 mg/day) was allowed as adjuvant medication for insomnia during the study.	
Outcomes	HRSD-21, CGI-I, CGI-S, HRSA, Raskin-Covi scale, SCL-56. Total dropout, dropout due to side effects, number of patients experiencing at least one side effect, side effect profile.	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes	Patients with major depressive episode (DSM-III-R) were included, so there might be some bipolar depression, but correct number was not reported.	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Rapaport 1996 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", "study medication was provided in identical-appearing green capsules", no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 7/51 missing from fluvoxamine group (2 due to adverse effects); 8/49 missing from control group (2 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Rechlin 1994

Methods	Two-week, randomised study.	
Participants	Psychiatric inpatients meeting DSM-III-R for major depression, with a minimum baseline score of 20 on the HRSD. Age range: 24-75 years old. Exclusion criteria: diabetes mellitus, polyneuropathy, alcoholism, cardiac diseases, neurologic diseases.	
Interventions	Fluvoxamine: 8 participants. Amitriptyline: 8 participants. Doxepine: 8 participants. Paroxetine: 8 participants. Fluvoxamine dose: 150 mg/day. Amitriptyline dose: 150 mg/day. Doxepine dose: 150 mg/day. Paroxetine dose: 20 mg/day. No other psychopharmacologic drugs were allowed except for the continuation of lithium prophylaxis.	
Outcomes	No efficacy and tolerability data could be entered in a meta-analysis were reported.	
Funded by pharmaceutical companies	Unclear.	
Fluvoxamine as an investigational or comparator drug	Unclear.	
Notes	Study authors examined whether or not the application of SSRI in therapeutic doses influence heart rate variability.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated", no further details.

Rechlin 1994 (Continued)

Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details.
Selective reporting (reporting bias)	High risk	No clinical outcomes were reported.

Remick 1994

Methods	Seven-week double blind, randomised study.	
Participants	Psychiatric outpatients meeting DSM-III-R for major depressive disorder, with a minimum baseline score of 20 on the HRSD-17. Age range: 18-65 years old. Exclusion criteria: any significant abnormalities detected on physical and laboratory examinations (hematology, urinalysis, clinical chemistry, ECG); a diagnosis of schizophrenia, other psychiatric disorders, or a principal diagnosis of panic disorder; history of epilepsy or seizures; history of alcohol or drug abuse within 6 months of study start; a woman who were pregnant or lactating.	
Interventions	Fluvoxamine: 16 participants. Amitriptyline: 17 participants. Fluvoxamine dose range: 50-300 mg/day. Amitriptyline dose range: 50-300 mg/day.	
Outcomes	HRSD-17, CGI-I, CGI-S, CGI-Efficacy, Patient Global Improvement Scale (PGI), HRSA, Raskin-Covi scale, BDI. Total dropout, dropout due to inefficiency, dropout due to side effects.	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.	
Fluvoxamine as an investigational or comparator drug	As an investigational drug.	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.

Remick 1994 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 3/16 missing from fluvoxamine group (3 due to adverse effects); 8/17 missing from control group (2 due to lack of efficacy, 6 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Rossini 2005

Methods	Seven-week double blind, single-centre, randomised study.	
Participants	Psychiatric inpatients suffering from major depressive episode according to DSM-IV, with a minimum baseline score of 22 on the HRSD-21. Age range: 59 years old or more. Exclusion criteria: presence of any concomitant axis I diagnosis; presence of psychotic features together with somatic or neurological illnesses impairing psychiatric evaluation; mini mental state examination score less than 23.	
Interventions	Fluvoxamine: 40 participants. Sertraline: 48 participants. Fluvoxamine dose: 200 mg/day. Sertraline dose: 150 mg/day. Subjects had not taken nonreversible monoamine oxidase inhibitors or slow release neuroleptics for at least 1 month before entering the study. All bipolar patients were under maintenance with mood stabilizers, the treatment remained unchanged during the present trial. No other psychotropic medication was allowed with the exception of flurazepam (up to 30 mg at bed time)	
Outcomes	HRSD-21. Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.	
Funded by pharmaceutical companies	Unclear.	
Fluvoxamine as an investigational or comparator drug	As an investigational drug.	
Notes	17/84 (17%) patients were with bipolar depression.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed by a computer originated schedule".
Allocation concealment (selection bias)	Unclear risk	No details.

Rossini 2005 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind", outcome assessors were blind to the treatment option.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study endpoint: 1/40 missing from fluvoxamine group (1 due to adverse effects); 3/48 missing from control group (3 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of change score for depression were not reported.

Rota 2005

Methods	Six-week, randomised study.
Participants	Psychiatric inpatients suffering from major depressive episode according to DSM-IV, with a minimum baseline score of 17 on the HRSD-21. Age range: 28-65 years old. Exclusion criteria: comorbidity with other DSM-IV axis I disorder; endocrinopathy or major medical illness; ocular glaucoma; prostatic hypertrophy; recent ECT or surgical event; use of psychoactive drugs or hormonal therapies; suicidal ideations.
Interventions	Fluvoxamine: number of participants not stated. Amitriptyline: number of participants not stated. Fluvoxamine dose: 200 mg/day. Amitriptyline dose: 150 mg/day.
Outcomes	HRSD-21, CGI, BDI.
Funded by pharmaceutical companies	Unclear.
Fluvoxamine as an investigational or comparator drug	Unclear.
Notes	Patients with major depressive episode (DSM-IV) were included, so there might be some bipolar depression, but correct number was not reported. Study authors assessed the time course changes in basal hypothalamic-pituitary-adrenocortical axis activity during the trial. Clinical outcome were reported only as "no difference between the two drugs", so those data could not be entered in a meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details.

Rota 2005 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants not stated.
Selective reporting (reporting bias)	High risk	Clinical outcome were reported only as "no difference between the two drugs".

Schoemaker 2002

Methods	Six-week double blind, multicentre, randomised study.
Participants	<p>Psychiatric outpatients meeting DSM-IV for major depressive disorder, with a minimum baseline score of 18 on the HRSD-17.</p> <p>Age range: 20-73 years old.</p> <p>Exclusion criteria: Patients were excluded from the study; if their current depressive episode was present for longer than one year; if they were pregnant or lactating or women of childbearing potential not practicing a reliable method of contraception; had an actual suicide risk; had a history or present condition of: bipolar disorder, schizophrenia or psychotic symptoms, schizotypal or borderline personality disorder, or organic mental disorders; had a present condition of anxiety disorders (according to DSM-IV), eating disorders, postpartum depression, epilepsy or a history of seizure disorder or ever received treatment with anticonvulsant medication for epilepsy or seizures; alcohol or substance abuse (according to DSM-IV) during the last 6 months; had any clinically meaningful non-stable renal, hepatic, cardiovascular respiratory, cerebrovascular disease or other serious, progressive physical disease; had any clinically meaningful abnormal finding uncovered during the physical examination, ECG and/or clinically significant abnormal laboratory results at screening; had participated in other clinical trials within the last three months, suffered from withdrawal symptoms at screening as a result of drug discontinuation; had a body mass index greater than 30 or less than 18, had a known allergy or hypersensitivity to mirtazapine or fluvoxamine; had been treated during the present episode with either mirtazapine or fluvoxamine; required treatment with terfenadine, astemizole, warfarin, theophylline, or cisapride.</p>
Interventions	<p>Fluvoxamine: 207 participants. Mirtazapine: 205 participants. Fluvoxamine dose range: 50-150 mg/day. Mirtazapine dose range: 15-45 mg/day.</p> <p>Concomitant intake of psychotropic was prohibited with the exception of a low dose hypnotic or anxiolytic (10 mg diazepam or equivalent dosage). Previous antidepressant treatment, including electroconvulsive therapy (ECT), had to be discontinued well in advance of randomization, excluding interference with study observations.</p>
Outcomes	<p>HRSD-17, HRSD-21, CGI-I, CGI-S.</p> <p>Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.</p>
Funded by pharmaceutical companies	Funded by pharmaceutical company markets comparator drug.
Fluvoxamine as an investigational or comparator drug	As a comparator drug.
Notes	

Risk of bias

Schoemaker 2002 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 41/207 missing from fluvoxamine group (8 due to lack of efficacy, 16 due to adverse effects); 47/205 missing from control group (4 due to lack of efficacy, 25 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint score for depression were not reported.

Tourigny-Rivard 1996

Methods	Ten-week double blind, multicentre, randomised study.
Participants	Patients meeting DSM-III-R for major depression, with a minimum baseline score of 18 on the HRSD-17. Age range: 60-82 years old.
Interventions	Fluvoxamine: 22 participants. Desipramine: 25 participants. Fluvoxamine dose range: to 150 mg/day. Desipramine dose range: to 150 mg/day.
Outcomes	HRSD, Geriatric Depression Scale, CGI, Brief Symptom Inventory. Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.
Funded by pharmaceutical companies	Unclear.
Fluvoxamine as an investigational or comparator drug	As an investigational drug.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias)	Unclear risk	Quote: "double blind", no further details.

Fluvoxamine versus other anti-depressive agents for depression (Review)

Tourigny-Rivard 1996 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Ueda 2002

Methods	Four-week, randomised study.
Participants	Patients meeting DSM-IV for major depressive disorder, with a minimum baseline score of 17 on the HRSD-17. Age range: 18-77 years old. Exclusion criteria: history of alcohol or drug abuse or dependency; physical complications; manic state or psychotic features before study.
Interventions	Fluvoxamine: 24 participants. Sulpiride: 24 participants. Fluvoxamine dose range: not stated. Sulpiride dose range: not stated. None had been administered any antidepressants for at least one month before participating in the study. No drugs were taken other than BZP hypnotics, and the dosages of BZP were kept constant throughout the study period.
Outcomes	HRSD-17. Total dropout.
Funded by pharmaceutical companies	No funding by pharmaceutical companies.
Fluvoxamine as an investigational or comparator drug	Unclear.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias)	Unclear risk	Study endpoint: 4/24 missing from fluvoxamine group; 4/24 missing from control group.

Ueda 2002 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
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Zohar 2003

Methods	Eight-week double blind, multicentre, randomised study.	
Participants	<p>Psychiatric inpatients suffering from major depressive episode, with or without mood congruent psychotic features not requiring antipsychotic treatment according to DSM-IV, with a minimum baseline score of 25 on the HRSD-17.</p> <p>Age range: 18-70 years old.</p> <p>Exclusion criteria: psychosis, a history of other psychiatric diagnosis; epilepsy or seizures; severe suicide risk; pregnant, lactating or of childbearing potential and not taking adequate contraceptive measures; clinically relevant/unstable disease which could affect the diagnosis and/or treatment of depression; hepatic or renal disease, severe heart disease, glaucoma, adrenal tumor, micturition disturbances, prostate hypertrophy; clinically relevant laboratory test abnormalities; multiple drug allergies; had been treated unsuccessfully with 2 or more antidepressants during the current episode of depression; had been treated with fluvoxamine or clomipramine during the current episode of depression.</p>	
Interventions	<p>Fluvoxamine: 44 participants. Clomipramine: 42 participants. Fluvoxamine dose range: 100-250 mg/day. Clomipramine dose range: 100-250 mg/day.</p> <p>Patients were required not to have received any antidepressants in the week prior to active treatment (5 weeks in the case of fluoxetine) or lithium, monoamine oxidase inhibitors, antipsychotics or ECT in the 2 weeks prior to active treatment. With the exception of oxazepam, which could be given for night-time sedation or control of anxiety, no other psychopharmacological treatments or ECT were permitted during the study.</p>	
Outcomes	<p>HRSD-17, MADRS, CGI-I, CGI-S.</p> <p>Total dropout, dropout due to inefficiency, dropout due to side effects, side effect profile.</p>	
Funded by pharmaceutical companies	Funded by pharmaceutical company markets fluvoxamine.	
Fluvoxamine as an investigational or comparator drug	As an investigational drug.	
Notes	Patients with major depressive episode (DSM-III-R) were included, so there might be some bipolar depression, but correct number was not reported.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	No details.

Zohar 2003 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study endpoint: 10/44 missing from fluvoxamine group (1 due to lack of efficacy, 5 due to adverse effects); 13/42 missing from control group (10 due to adverse effects).
Selective reporting (reporting bias)	High risk	SDs of endpoint/change score for depression were not reported.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baischer 1991	Allocation: randomised. Interventions: fluvoxamine versus placebo
Bellini 1992	Participants: those with bipolar disorder and major depression with psychotic features.
Blier 1997	Allocation: not randomised.
Davis 1991	Interventions: amitriptyline versus fluoxetine.
de Jonghe 1991	Participants: those with major depression (n=22) and dysthymic disorder (n=26).
de Kemp 2002	Participants: those with primary depression (n=40) and primary anxiety disorder (n=38).
de Wilde 1982	Participants: those with unipolar depression (n=21) and bipolar depression (n=9).
Emrich 1987	Allocation: randomised, crossover. Participants: those with major depressive disorder. Interventions: fluvoxamine versus oxaprotilene. Outcome: clinical data not presented for first phase of crossover.
Entsuaeh 2002a	Allocation: not randomised. meta-analysis.
Franchini 1997	Allocation: randomised. Participants: those with major depression in remission state (not acute phase).
Gasperini 1992	Allocation: randomised. Participants: those with major depression (n=38) and those with bipolar depression (n=18).
Gonella 1990	Allocation: randomised. Participants: those with major depression (n=13), bipolar depressive disorder (n=1) and dysthymia (n=6).
Goto 2006	Allocation: not randomised.
Guelfi 1983	Allocation: randomised. Participants: depressed patients. not presented operational diagnostic criteria.
Harris 1991b	Allocation: not randomised.

Study	Reason for exclusion
Hewer 1994	Allocation: not randomised.
Hochberg 1995	Allocation: randomised. Participants: depressed outpatients. Interventions: fluvoxamine versus TCAs versus placebo. Outcomes: clinical data reported for maintenance phase only; no data presented for acute phase.
Khan 1989	Allocation: randomised. Participants: those with major depression. Interventions: fluvoxamine versus imipramine versus placebo. Outcomes: clinical data presented only for the comparison between antidepressants and placebo, no data presented between fluvoxamine and imipramine.
Klok 1981	Allocation: randomised. Participants: those with vital depressive syndromes; not presented operational diagnostic criteria.
Lara-Munoz 1996	Allocation: not randomised.
Manfredonia 1992	Allocation: randomised. Participants: those with major depression (n=32) and bipolar disorder (n=16).
Muck-Seler 1991	Allocation: not randomised.
Murasaki 1998b	Allocation: not randomised. Participants: those with major depressive disorder (n=129) and those with bipolar disorder (n=15), dysthymic disorder (n=17) and depressive disorder not otherwise specified (n=5).
Namiki 1996	Allocation: not randomised. Participants: those with major depressive disorder (n=101) and those with bipolar disorder (n=8), dysthymic disorder (n=58) cyclothymic disorder (n=1) and depressive disorder not otherwise specified (n=39).
Nicolini 1996	Allocation: not randomised.
Nolen 1988	Allocation: not randomised. Participants: those with major depressive episode without psychotic features (n=51) and those with psychotic features (n=20).
Phanjoo 1991	Allocation: not randomised.
Poldinger 1991	Allocation: randomised. Participants: those with any form of depression as diagnosed by the investigator, not presented any diagnostic criteria.
Price 1986	Allocation: not randomised.
Ravindran 1995	Allocation: randomised. Participants: those with major depression (n=17), dysthymia (n=18) and healthy controls (n=18).
Sacchetti 1994	Allocation: not randomised.
Sacchetti 1997	Allocation: randomised. Participants: those with major depression with mood congruent psychotic features.
Schanda 1979	Allocation: not randomised. Participants: those with depression; not presented operational diagnostic criteria.

Study	Reason for exclusion
Serretti 2004	Allocation: not randomised.
Sheline 1997	Allocation: not randomised.
van den Broek 2004	Allocation: randomised. Participants: those with major depression without psychotic features (n=90), with psychotic features (n=48).
Vandel 1995	Allocation: not randomised.
White 1990	Allocation: randomised, crossover. Participants: those with major depression. Interventions: fluvoxamine versus desipramine versus placebo. Outcome: clinical data not presented for first phase of crossover.
Yu 2001	Allocation: quasi randomised (sequence generated by odd or even hospital record number) Participants: those with major depressive disorder (n=33) and those depressive neurosis (n=27).
Zanardi 2000	Allocation: randomised. Participants: those with major depressive episode with psychotic features.

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

[Berlin 1998](#)

Methods	Awaiting assessment.
Participants	
Interventions	
Outcomes	
Notes	

[Coleman 1981a](#)

Methods	Unpublished.
Participants	
Interventions	
Outcomes	
Notes	

Coleman 1981b

Methods	Unpublished.
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Participants

Interventions

Outcomes

Notes

Coleman 1983

Methods	Unpublished.
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Participants

Interventions

Outcomes

Notes

Donovan 1993

Methods	Awaiting assessment.
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Participants

Interventions

Outcomes

Notes

Doogan 1981

Methods	Unpublished.
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Participants

Interventions

Outcomes

Notes

Entsuah 2002b

Methods	Awaiting assessment.
Participants	
Interventions	
Outcomes	
Notes	

Faludi 1989

Methods	Paper is not yet available.
Participants	
Interventions	
Outcomes	
Notes	

Mallick 2003

Methods	Awaiting assessment.
Participants	
Interventions	
Outcomes	
Notes	

Naito 2007

Methods	Awaiting assessment.
Participants	
Interventions	
Outcomes	
Notes	

Ushiroyama 2004

Methods	Awaiting assessment.
Participants	
Interventions	
Outcomes	
Notes	

van Beek 1981

Methods	Unpublished.
Participants	
Interventions	
Outcomes	
Notes	

DATA AND ANALYSES
Comparison 1. Fluvoxamine versus TCAs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response (acute phase): Primary outcome	16	935	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.29]
1.1 vs Imipramine	6	375	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.59, 1.58]
1.2 vs Clomipramine	2	129	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.38, 1.85]
1.3 vs Amitriptyline	4	185	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.35, 1.75]
1.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
1.5 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.55, 2.24]
1.6 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]
2 Response (early phase)	25	2148	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.15]
2.1 vs Imipramine	12	1213	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.78, 1.29]
2.2 vs Clomipramine	5	299	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.63, 1.71]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 vs Amitriptyline	4	397	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.13, 1.19]
2.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	1.65 [0.58, 4.73]
2.5 vs Desipramine	1	40	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.19, 3.13]
2.6 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.35, 2.68]
3 Remission (early phase)	25	2148	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.73, 1.22]
3.1 vs Imipramine	12	1213	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.71, 1.42]
3.2 vs Clomipramine	5	299	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.40, 1.41]
3.3 vs Amitriptyline	4	397	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.10, 1.76]
3.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	2.33 [0.54, 10.14]
3.5 vs Desipramine	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.89]
3.6 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.18, 5.16]
4 Remission (acute phase)	16	935	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.69, 1.45]
4.1 vs Imipramine	6	375	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.59, 1.94]
4.2 vs Clomipramine	2	129	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.28, 1.49]
4.3 vs Amitriptyline	4	185	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.28, 1.31]
4.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	1.78 [0.67, 4.77]
4.5 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.48, 2.35]
4.6 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.5 [1.31, 15.42]
5 Depression scale - Endpoint score: low=good (early phase)	5	186	Std. Mean Difference (IV, Random, 95% CI)	0.28 [-0.01, 0.57]
5.1 vs Imipramine	1	58	Std. Mean Difference (IV, Random, 95% CI)	0.52 [-0.00, 1.05]
5.2 vs Amitriptyline	2	53	Std. Mean Difference (IV, Random, 95% CI)	0.47 [-0.08, 1.02]
5.3 vs Desipramine	1	35	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.49, 0.84]
5.4 vs Dothiepin	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.83, 0.41]
6 Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 vs Imipramine			Other data	No numeric data
6.2 vs Clomipramine			Other data	No numeric data
6.3 vs Amitriptyline			Other data	No numeric data
6.4 vs Nortriptyline			Other data	No numeric data
7 Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data			Other data	No numeric data
7.1 vs Imipramine			Other data	No numeric data
7.2 vs Clomipramine			Other data	No numeric data
7.3 vs Amitriptyline			Other data	No numeric data
7.4 vs Nortriptyline			Other data	No numeric data
7.5 vs Dothiepin			Other data	No numeric data
7.6 vs Desipramine			Other data	No numeric data
8 Depression scale - Change score: decrease=good (early phase)	2	119	Std. Mean Difference (IV, Random, 95% CI)	0.66 [-0.33, 1.64]
8.1 vs Amitriptyline	1	58	Std. Mean Difference (IV, Random, 95% CI)	1.17 [0.61, 1.73]
8.2 vs Nortriptyline	1	61	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.34, 0.66]
9 Depression scale - Change score: decrease=good (early phase) - missing SDs			Other data	No numeric data
9.1 vs Imipramine			Other data	No numeric data
9.2 vs Clomipramine			Other data	No numeric data
9.3 vs Amitriptyline			Other data	No numeric data
9.4 vs Desipramine			Other data	No numeric data
9.5 vs Dothiepine			Other data	No numeric data
10 Depression scale - Change score: decrease=good (acute phase)	3	372	Std. Mean Difference (IV, Random, 95% CI)	0.28 [-0.22, 0.79]
10.1 vs Imipramine	2	322	Std. Mean Difference (IV, Random, 95% CI)	0.17 [-0.46, 0.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 vs Amitriptyline	1	50	Std. Mean Difference (IV, Random, 95% CI)	0.55 [-0.01, 1.12]
11 Depression scale - Change score: decrease=good (acute phase) - missing SDs			Other data	No numeric data
11.1 vs Imipramine			Other data	No numeric data
11.2 vs Clomipramine			Other data	No numeric data
11.3 vs Amitriptyline			Other data	No numeric data
11.4 vs Desipramine			Other data	No numeric data
11.5 vs Dothiepine			Other data	No numeric data
12 Total Dropout	28	2268	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.79, 1.18]
12.1 vs Imipramine	13	1263	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.81, 1.41]
12.2 vs Clomipramine	5	299	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.58, 2.00]
12.3 vs Amitriptyline	5	420	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.51, 1.17]
12.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.21, 1.41]
12.5 vs Desipramine	2	87	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.24, 10.70]
12.6 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.49, 2.25]
13 Dropout due to inefficacy	22	1651	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.68, 1.83]
13.1 vs Imipramine	10	841	Odds Ratio (M-H, Random, 95% CI)	1.48 [0.77, 2.86]
13.2 vs Clomipramine	3	158	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.13, 6.69]
13.3 vs Amitriptyline	5	420	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.20, 1.74]
13.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	2.25 [0.39, 13.12]
13.5 vs Desipramine	2	85	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.6 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.08, 2.67]
14 Dropout due to side effects	24	1772	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.60, 1.04]
14.1 vs Imipramine	11	908	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.63, 1.32]
14.2 vs Clomipramine	3	158	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.24, 1.98]
14.3 vs Amitriptyline	5	420	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.35, 1.00]
14.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.10, 1.70]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.5 vs Desipramine	2	87	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.89]
14.6 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.47, 3.32]
15 Number of patients experiencing at least one side effect	9	663	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.49, 0.98]
15.1 vs Imipramine	2	136	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.18, 1.64]
15.2 vs Clomipramine	2	75	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.14, 1.43]
15.3 vs Amitriptyline	3	327	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.42, 1.04]
15.4 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.51, 2.37]
16 Subgroup analysis - Response (acute phase) 1. Fluvoxamine dosing - Standard dosage	6	413	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.53, 1.46]
16.1 vs Imipramine	2	200	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.51, 1.64]
16.2 vs Amitriptyline	1	69	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.16, 1.09]
16.3 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
16.4 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]
16.5 vs Amitriptyline	1	23	Odds Ratio (M-H, Random, 95% CI)	0.5 [0.09, 2.84]
17 Subgroup analysis - Response (acute phase) 1. Fluvoxamine dosing - High dosage	10	522	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.74, 1.55]
17.1 vs Imipramine	4	175	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.38, 2.40]
17.2 vs Clomipramine	2	129	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.38, 1.85]
17.3 vs Amitriptyline	2	93	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.57, 4.02]
17.4 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.55, 2.24]
18 Subgroup analysis - Response (acute phase) 2. Comparator dosing - Standard dosage	4	215	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.64, 2.50]
18.1 vs Clomipramine	1	43	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.12, 2.74]
18.2 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.55, 2.24]
18.3 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]

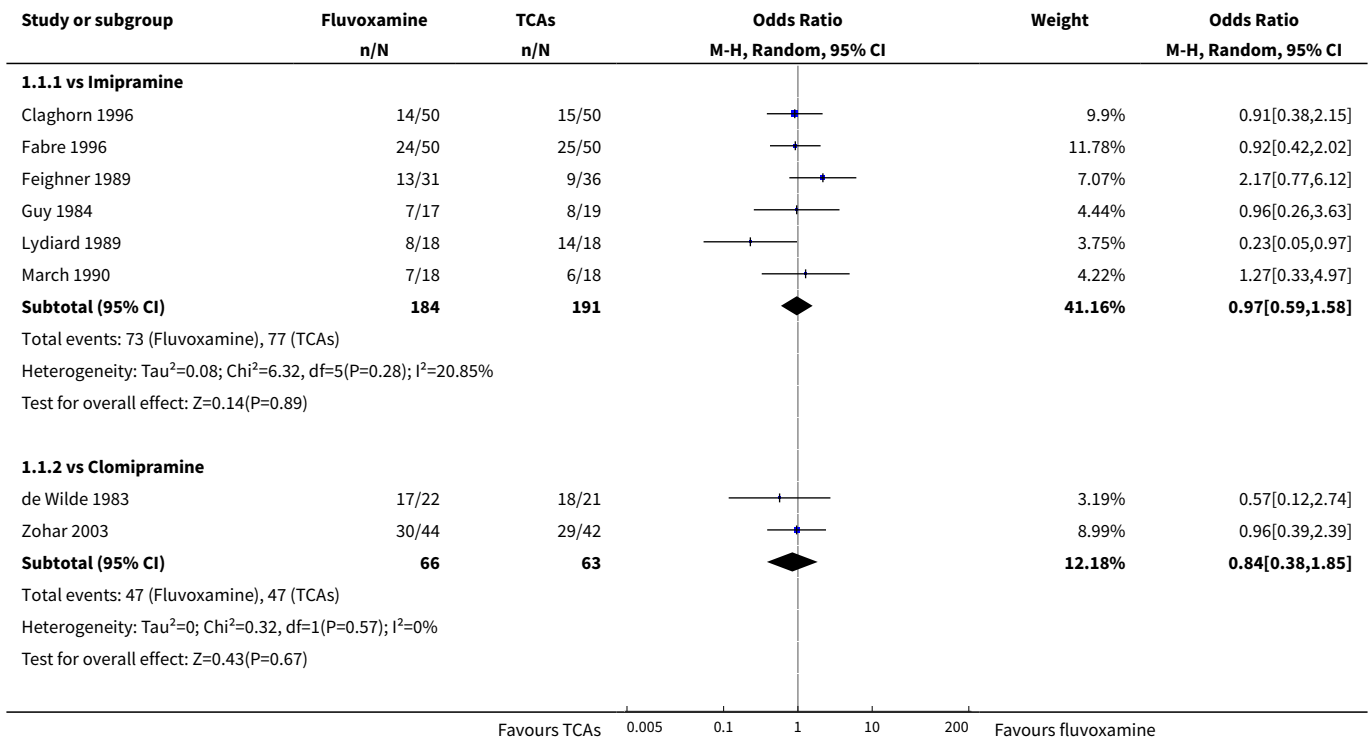
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19 Subgroup analysis - Response (acute phase) 2. Comparator dosing - High dosage	15	892	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.74, 1.33]
19.1 vs Imipramine	6	375	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.59, 1.58]
19.2 vs Clomipramine	1	86	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.39, 2.39]
19.3 vs Amitriptyline	4	185	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.35, 1.75]
19.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
19.5 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.55, 2.24]
19.6 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]
20 Subgroup analysis - Response (acute phase) 4. Treatment settings - Inpatient	5	301	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.71, 1.92]
20.1 vs Imipramine	2	103	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.70, 3.61]
20.2 vs Clomipramine	1	86	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.39, 2.39]
20.3 vs Amitriptyline	1	60	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.26, 3.89]
20.4 vs Dothiepin	1	52	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.34, 2.98]
21 Subgroup analysis - Response (acute phase) 4. Treatment settings - Outpatients	9	564	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.58, 1.20]
21.1 vs Imipramine	4	272	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.46, 1.39]
21.2 vs Clomipramine	1	43	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.12, 2.74]
21.3 vs Amitriptyline	2	102	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.17, 5.00]
21.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
21.5 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.47, 3.00]
22 Sensitivity analysis - Response (acute phase) 2. Excluding trials dropout rate >20%	5	185	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.30, 2.07]
22.1 vs Imipramine	2	72	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.12, 1.98]
22.2 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]
22.3 vs Clomipramine	1	43	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.12, 2.74]
22.4 vs Amitriptyline	1	23	Odds Ratio (M-H, Random, 95% CI)	0.5 [0.09, 2.84]

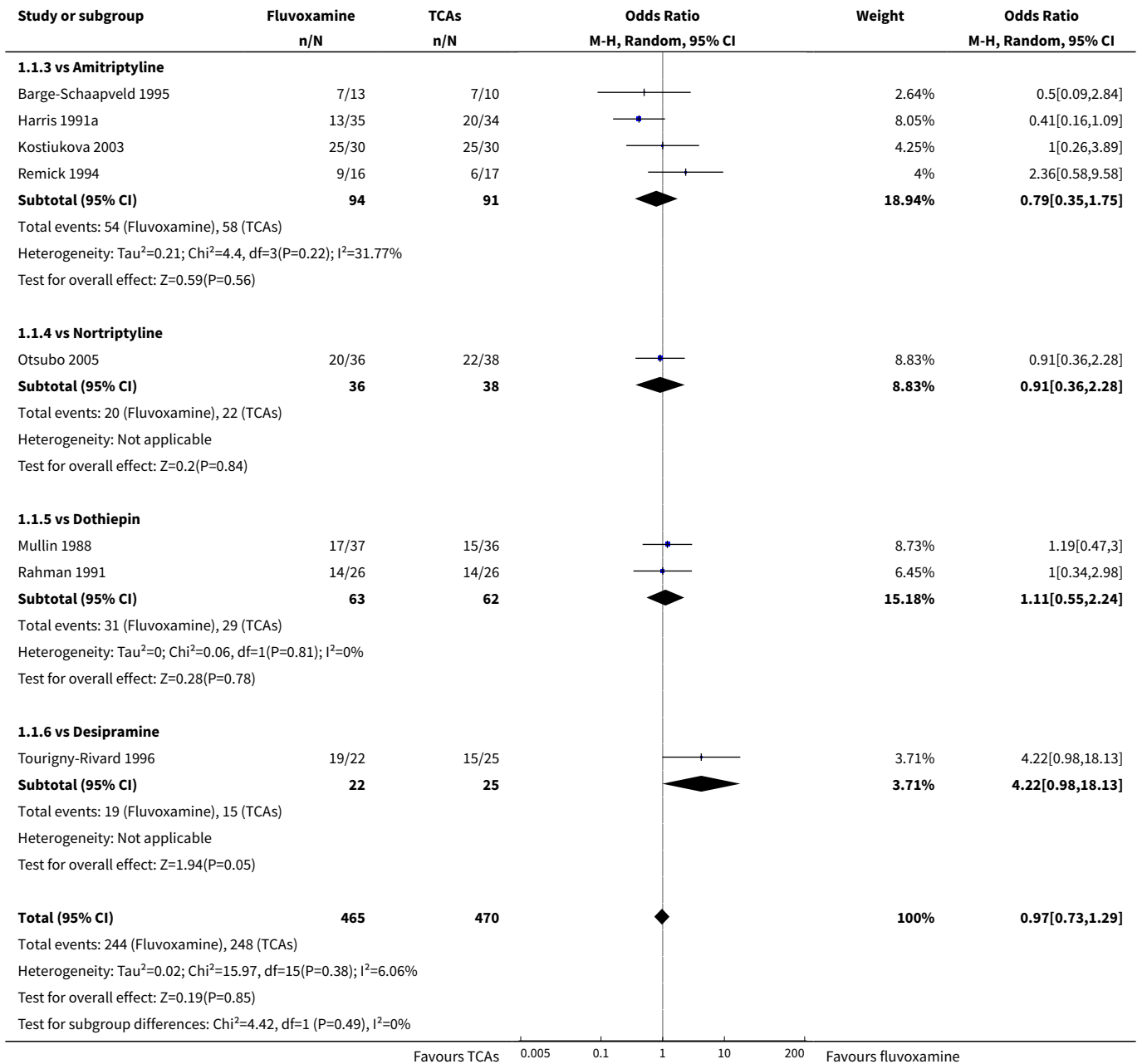
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23 Sensitivity analysis - Response (acute phase) 3. Worst case scenario ITT	16	935	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.40, 0.81]
23.1 vs Imipramine	6	375	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.39, 0.90]
23.2 vs Clomipramine	2	129	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.38, 1.85]
23.3 vs Amitriptyline	4	185	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.13, 0.90]
23.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
23.5 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.16, 0.72]
23.6 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]
24 Sensitivity analysis - Response (acute phase) 4. Best case scenario ITT	16	935	Odds Ratio (M-H, Random, 95% CI)	1.78 [1.18, 2.69]
24.1 vs Imipramine	6	375	Odds Ratio (M-H, Random, 95% CI)	1.75 [0.78, 3.92]
24.2 vs Clomipramine	2	129	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.44, 2.20]
24.3 vs Amitriptyline	4	185	Odds Ratio (M-H, Random, 95% CI)	1.67 [0.82, 3.37]
24.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
24.5 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	4.04 [1.85, 8.81]
24.6 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]
25 Sensitivity analysis - Response (acute phase) 5. Excluding trials with imputation methods for calculating response	5	343	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.57, 1.41]
25.1 vs Imipramine	1	100	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.42, 2.02]
25.2 vs Clomipramine	1	86	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.39, 2.39]
25.3 vs Amitriptyline	2	83	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.26, 2.24]
25.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
26 Sensitivity analysis - Mean change from baseline (acute phase) 5. Excluding trials for which the SD had to be borrowed from other trials	3	148	Std. Mean Difference (IV, Random, 95% CI)	0.39 [0.07, 0.72]
26.1 vs Imipramine	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.64 [-0.19, 1.47]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.2 vs Amitriptyline	1	50	Std. Mean Difference (IV, Random, 95% CI)	0.55 [-0.01, 1.12]
26.3 vs Nortriptyline	1	74	Std. Mean Difference (IV, Random, 95% CI)	0.22 [-0.24, 0.67]
27 Sensitivity analysis - Response (acute phase) 6. Wish bias - Fluvoxamine as an investigational drug	14	860	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.72, 1.36]
27.1 vs Imipramine	6	375	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.59, 1.58]
27.2 vs Clomipramine	2	129	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.38, 1.85]
27.3 vs Amitriptyline	3	162	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.32, 2.50]
27.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
27.5 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.47, 3.00]
27.6 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]
28 Sensitivity analysis - Response (acute phase) 7. Funding - Excluding trials funded by the fluvoxamine marketing company	5	284	Odds Ratio (M-H, Random, 95% CI)	1.42 [0.82, 2.43]
28.1 vs Imipramine	2	103	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.70, 3.61]
28.2 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]
28.3 vs Amitriptyline	1	60	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.26, 3.89]
28.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
29 Sensitivity analysis - Response (acute phase) 7. Funding - Trials funded by the fluvoxamine marketing company	11	651	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.61, 1.16]
29.1 vs Imipramine	4	272	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.46, 1.39]
29.2 vs Clomipramine	2	129	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.38, 1.85]
29.3 vs Amitriptyline	3	125	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.25, 2.29]
29.4 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.55, 2.24]
30 Sensitivity analysis - Response (acute phase) 8. Excluding trials that might include patients with bipolar depression	9	540	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.68, 1.73]

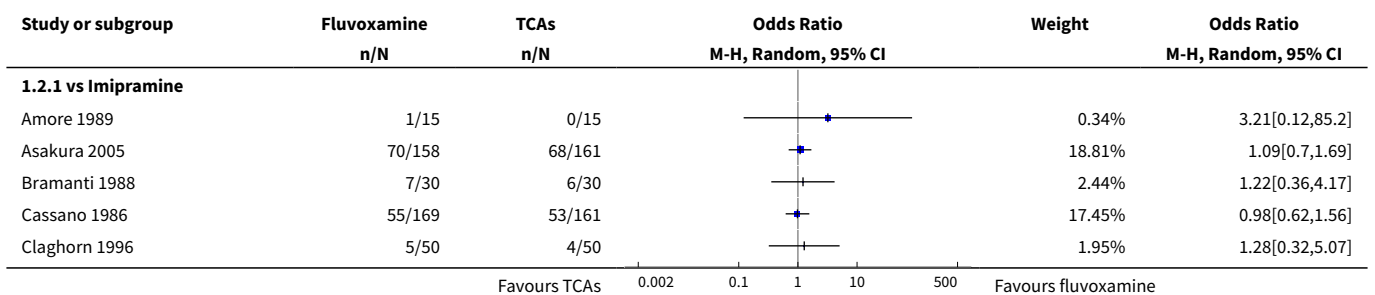
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30.1 vs Imipramine	4	303	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.44, 1.83]
30.2 vs Amitriptyline	3	116	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.50, 2.72]
30.3 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
30.4 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]
31 Sensitivity analysis - Response (acute phase) 9. Excluding trials that included patients with psychotic features	16	935	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.29]
31.1 vs Imipramine	6	375	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.59, 1.58]
31.2 vs Clomipramine	2	129	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.38, 1.85]
31.3 vs Amitriptyline	4	185	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.35, 1.75]
31.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
31.5 vs Dothiepin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.55, 2.24]
31.6 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.98, 18.13]

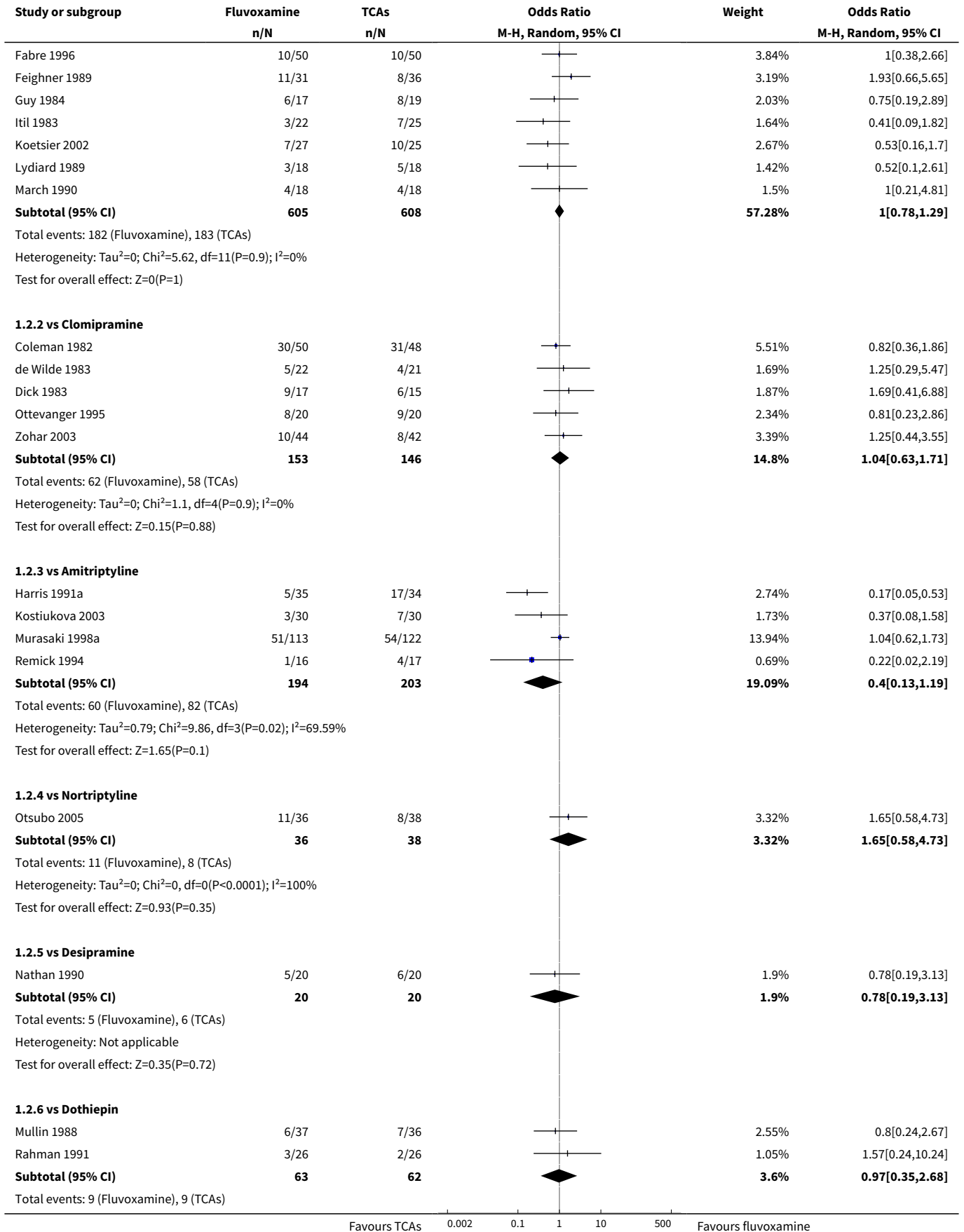
Analysis 1.1. Comparison 1 Fluvoxamine versus TCAs, Outcome 1 Response (acute phase): Primary outcome.

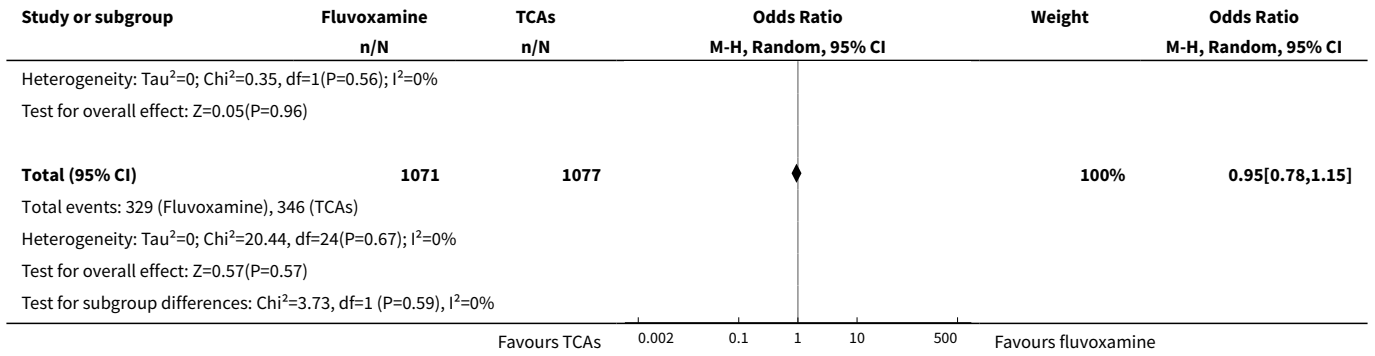




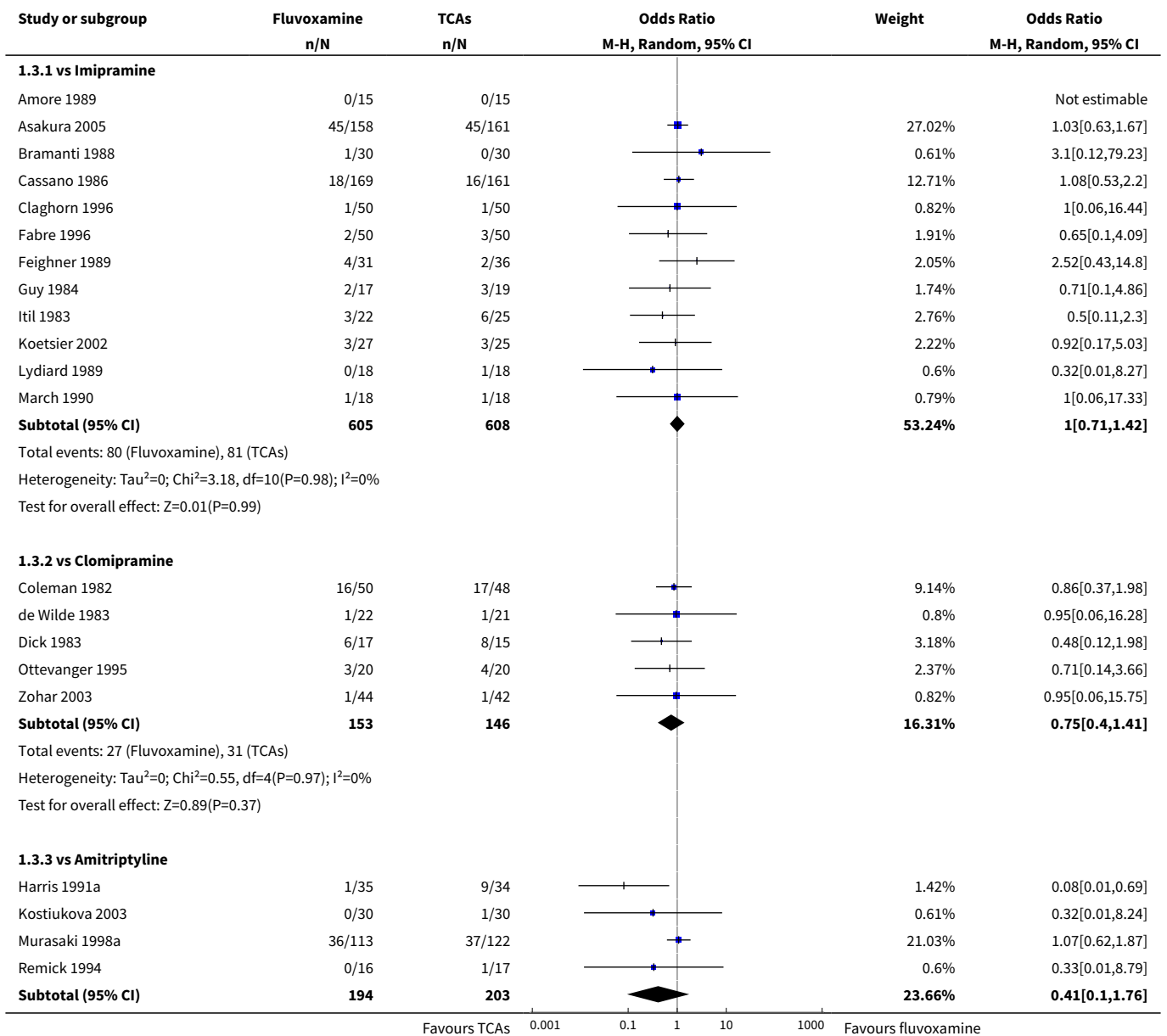
Analysis 1.2. Comparison 1 Fluvoxamine versus TCAs, Outcome 2 Response (early phase).

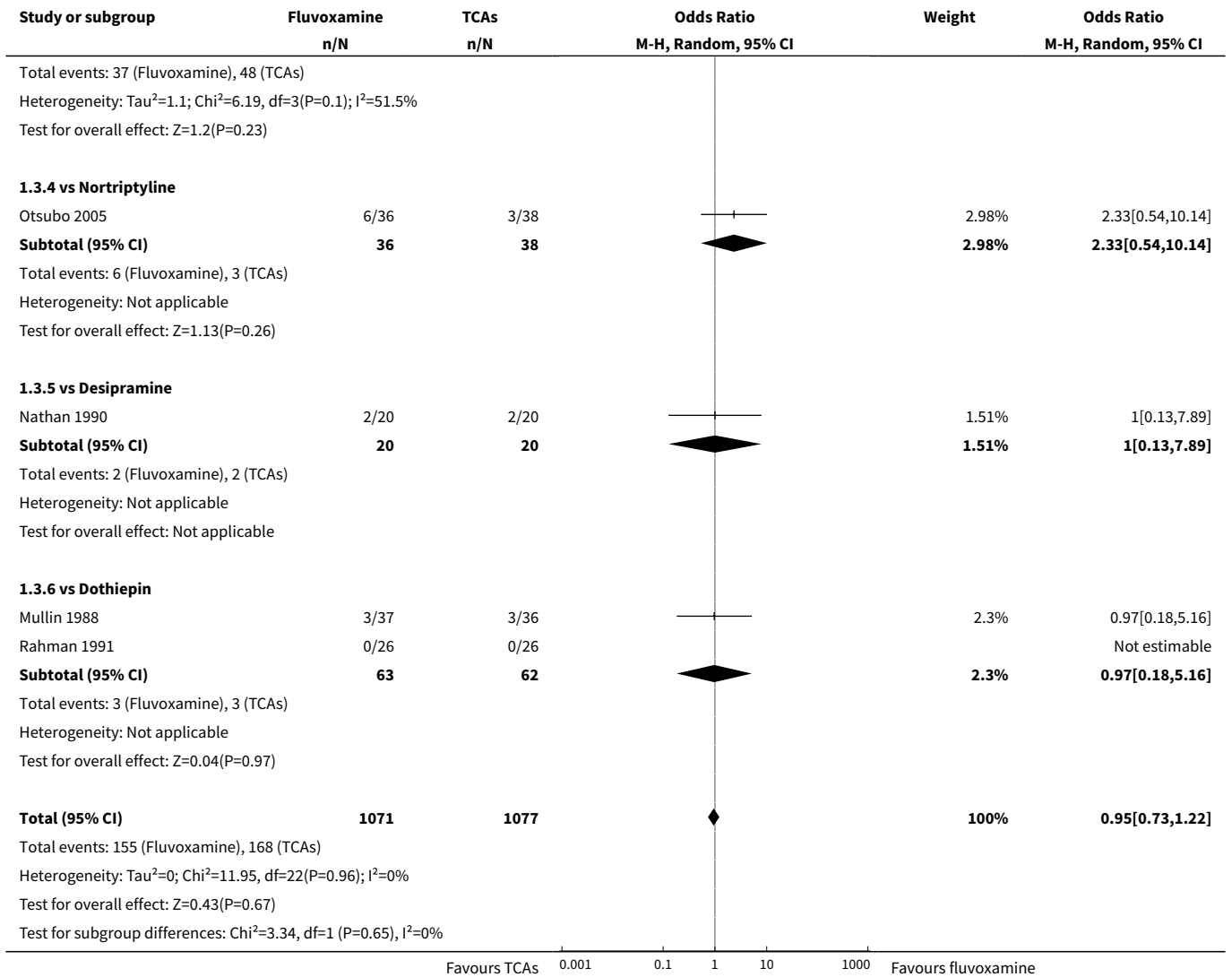




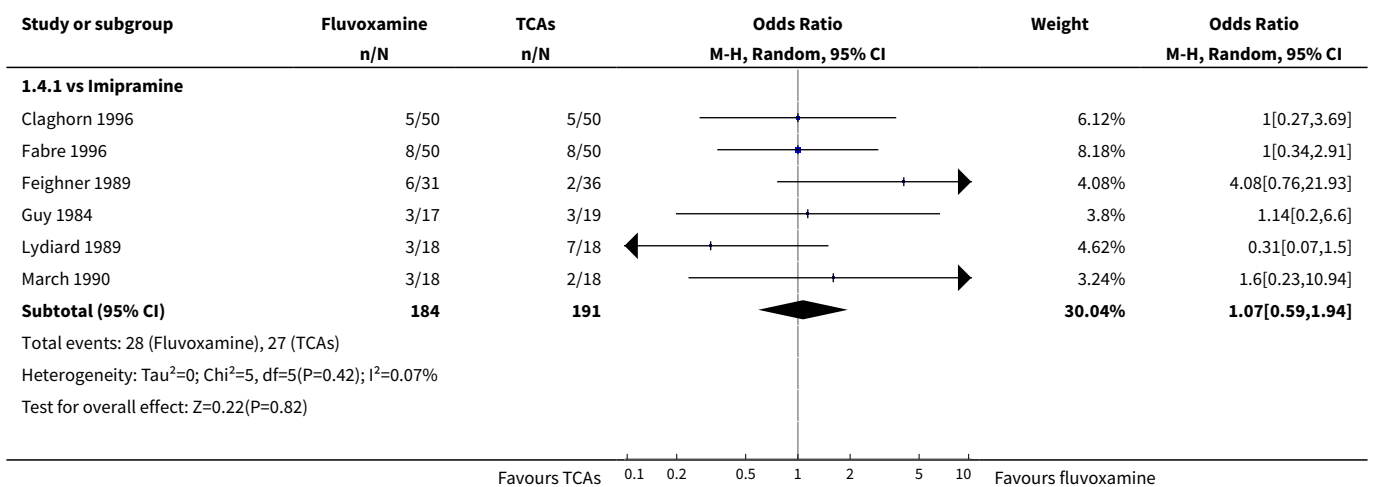


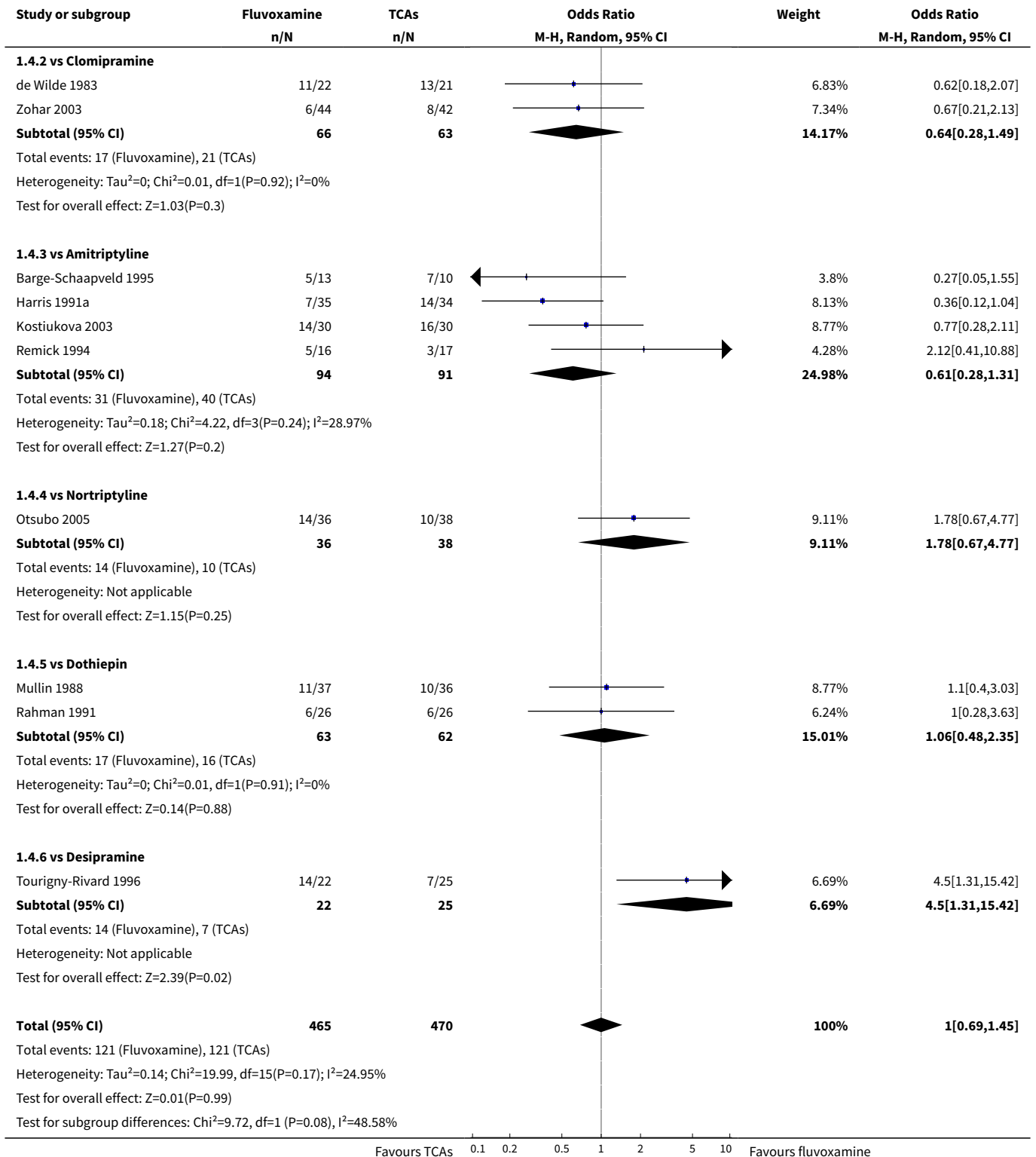
Analysis 1.3. Comparison 1 Fluvoxamine versus TCAs, Outcome 3 Remission (early phase).



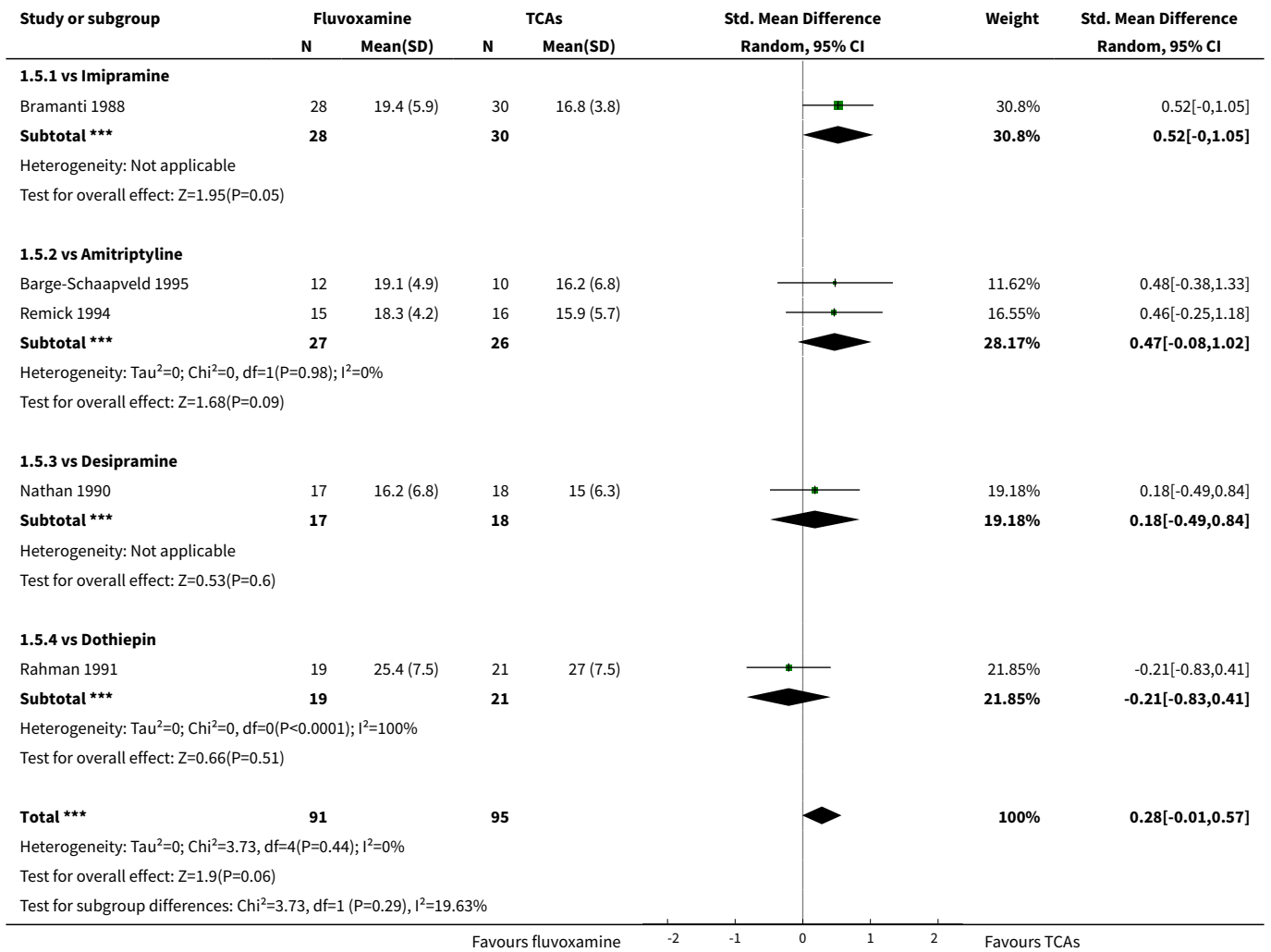


Analysis 1.4. Comparison 1 Fluvoxamine versus TCAs, Outcome 4 Remission (acute phase).





Analysis 1.5. Comparison 1 Fluvoxamine versus TCAs, Outcome 5 Depression scale - Endpoint score: low=good (early phase).



Analysis 1.6. Comparison 1 Fluvoxamine versus TCAs, Outcome 6 Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data.


Study	Depression scale	Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Imipramine								
Amore 1989	HRSD-21	22.6	missing	15	25.4	missing	11	
Asakura 2005	HRSD-17	10.7	7.0	149	10.6	7.1	149	skewed.
Cassano 1986	HRSD-17	13.4	missing	120	13.7	missing	119	
Claghorn 1996	HRSD-21	21.1	missing	44	21.3	missing	44	
Fabre 1996	HRSD-21	19	missing	46	18.3	missing	48	
Feighner 1989	HRSD-17	12.5	missing	21	16.6	missing	27	
Guy 1984	HRSD-17	14.2	missing	17	13	missing	16	
Itil 1983	HRSD-16	12.7	8.2	9	10.4	6.8	14	skewed.
Koetsier 2002	HRSD-17	19.4	9.7	27	15.5	8.0	25	skewed.
Lydiard 1989	HRSD-17	18.6	missing	17	17.2	missing	18	
March 1990	HRSD-17	15.9	missing	13	17.1	missing	15	

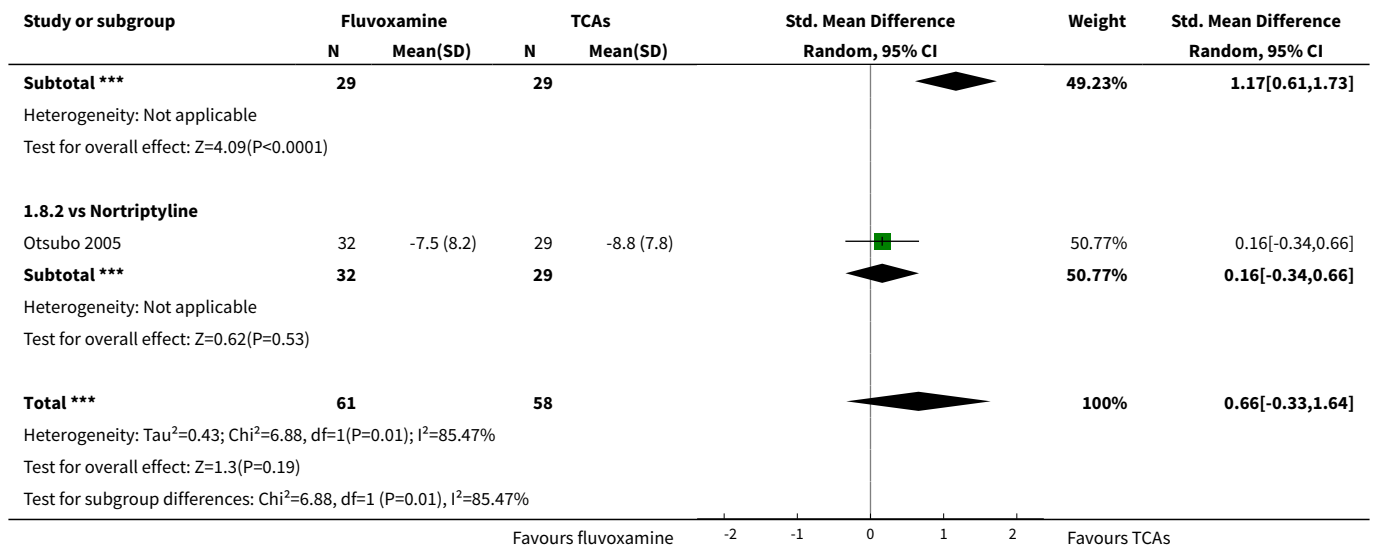
Study	Depression scale	Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Clomipramine								
Coleman 1982	HRSD-17	8.8	missing	41	8.6	missing	43	
Ottevanger 1995	HRSD-17	15.1	8.1	20	13.9	7.4	20	skewed.
vs Amitriptyline								
Harris 1991a	HRSD-17	17.1	missing	29	10.0	missing	29	
Murasaki 1998a	HRSD-17	14.5	7.8	80	16.1	7.6	83	skewed.
vs Nortriptyline								
Otsubo 2005	HRSD-17	13.5	7.7	32	15.7	6.5	29	skewed.

Analysis 1.7. Comparison 1 Fluvoxamine versus TCAs, Outcome 7 Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data.

Study	Depression scale	Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Imipramine								
Claghorn 1996	HRSD-21	16	missing	44	15.5	missing	44	
Fabre 1996	HRSD-21	14.2	missing	46	14.3	missing	48	
Feighner 1989	HRSD-17	10.5	missing	21	16.4	missing	27	
Guy 1984	HRSD-17	13.0	missing	16	12.1	missing	16	
Lydiard 1989	HRSD-17	12.8	missing	17	9.0	missing	18	
March 1990	HRSD-17	12.5	missing	13	13.8	missing	15	
vs Clomipramine								
de Wilde 1983	HRSD-17	6.4	missing	21	5.1	missing	21	
Zohar 2003	HRSD-17	13.4	missing	42	12.3	missing	42	
vs Amitriptyline								
Barge-Schaapveld 1995	HRSD-17	10.0	5.2	11	8.6	8.0	10	skewed.
Harris 1991a	HRSD-17	10.4	missing		6.6	missing	26	
Kostiukova 2003	HRSD-17	7.4	missing	30	6.7	missing	30	
Remick 1994	HRSD-17	8.7	7.2	13	10.3	6.0	10	skewed.
vs Nortriptyline								
Otsubo 2005	HRSD-17	11.9	8.9	36	12.1	5.9	38	skewed.
vs Dothiepin								
Mullin 1988	HRSD-17	8.3	missing	26	8.5	missing	24	
Rahman 1991	MADRS	13.5	missing	19	14.4	missing	21	
vs Desipramine								
Tourigny-Rivard 1996	HRSD-17	4.9	missing	22	10.8	missing	25	

Analysis 1.8. Comparison 1 Fluvoxamine versus TCAs, Outcome 8 Depression scale - Change score: decrease=good (early phase).

Study or subgroup	Fluvoxamine		TCAs		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
1.8.1 vs Amitriptyline							
Harris 1991a	29	-5.6 (7)	29	-12.8 (5)		49.23%	1.17[0.61,1.73]
Favours fluvoxamine					-2 -1 0 1 2	Favours TCAs	

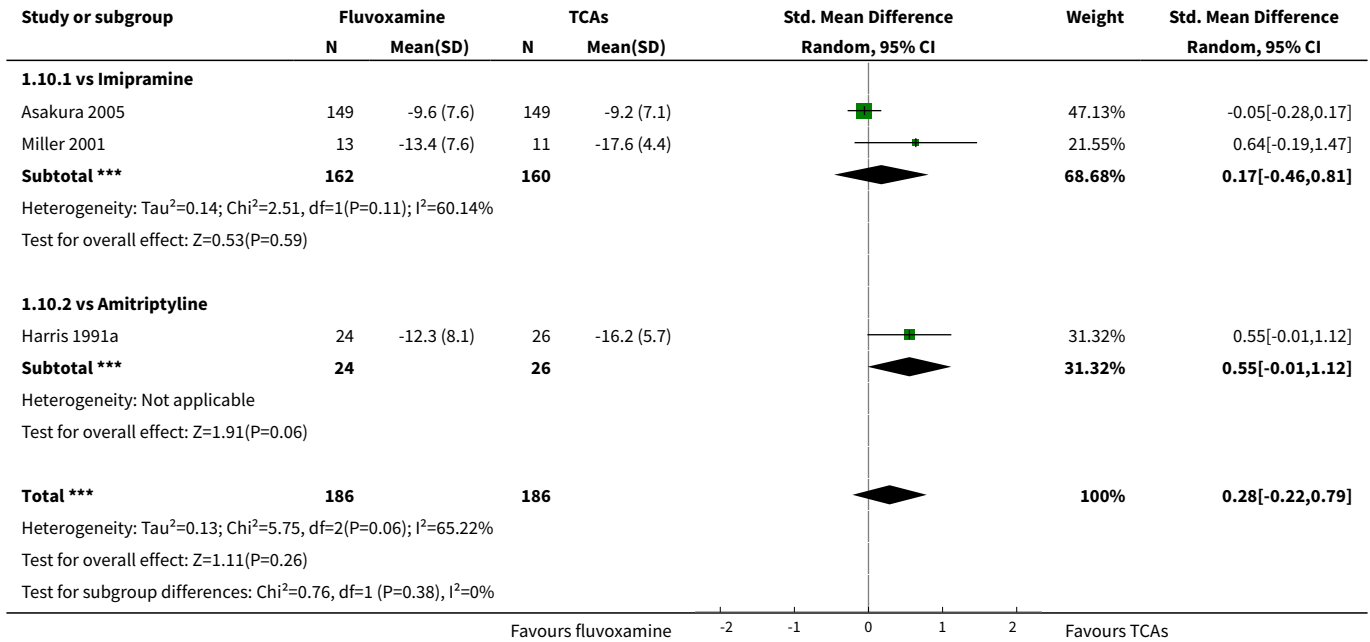


**Analysis 1.9. Comparison 1 Fluvoxamine versus TCAs, Outcome 9
Depression scale - Change score: decrease=good (early phase) - missing SDs.**

Depression scale - Change score: decrease=good (early phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
vs Imipramine								
Amore 1989	HRSD-21	-3.1	missing	15	-3.4	missing	11	
Bramanti 1988	HRSD-21	-11.1	missing	28	-10.4	missing	30	
Cassano 1986	HRSD-17	-12.2	missing	120	-12.2	missing	119	
Claghorn 1996	HRSD-21	-5	missing	44	-4.6	missing	44	
Fabre 1996	HRSD-21	-8.7	missing	46	-8.2	missing	48	
Feighner 1989	HRSD-17	-12.5	missing	21	-10.6	missing	27	
Guy 1984	HRSD-17	-10.4	missing	17	-12.1	missing	16	
Itil 1983	HRSD-17	-7.6	missing	9	-11.5	missing	14	
Koetsier 2002	HRSD-17	-7.6	missing	27	-12.2	missing	25	
Lydiard 1989	HRSD-17	-5.9	missing	17	-8.2	missing	18	
March 1990	HRSD-17	-9.1	missing	13	-8.4	missing	15	
vs Clomipramine								
Coleman 1982	HRSD-17	-16.6	missing	41	-16	missing	43	
de Wilde 1983	HRSD-17	-6.9	missing	22	-6.5	missing	21	
Dick 1983	HRSD-17	-11.7	missing	15	-8.6	missing	13	
Ottevanger 1995	HRSD-17	-11.3	missing	20	-11.8	missing	20	
Zohar 2003	HRSD-17	-10.8	missing	42	-9.8	missing	42	
vs Amitriptyline								
Barge-Schaapveld 1995	HRSD-17	-6.6	missing	12	-8.2	missing	10	
Kostiukova 2003	HRSD-17	-5.3	missing	30	-8.6	missing	30	
Murasaki 1998a	HRSD-17	-8.4	missing	80	-7.5	missing	83	
Remick 1994	HRSD-17	-6.6	missing	13	-6.9	missing	9	
vs Desipramine								
Nathan 1990	HRSD-17	-8.4	missing	17	-9.3	missing	18	
vs Dothiepine								
Mullin 1988	HRSD-17	-6.5	missing	26	-7.2	missing	24	

Depression scale - Change score: decrease=good (early phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
Rahman 1991	MADRS	-10.2	missing	19	-7.9	missing	21	

Analysis 1.10. Comparison 1 Fluvoxamine versus TCAs, Outcome 10 Depression scale - Change score: decrease=good (acute phase).

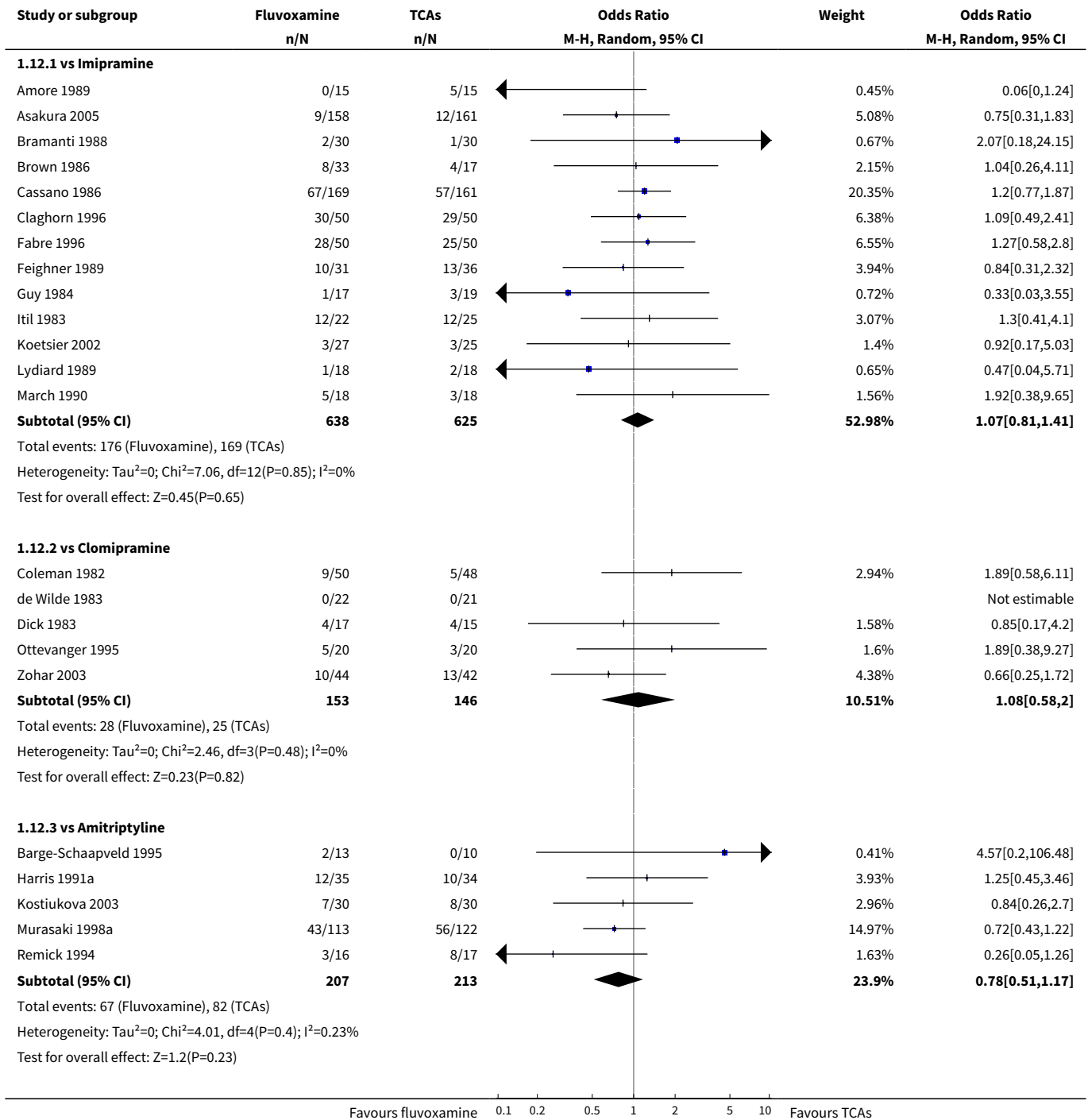


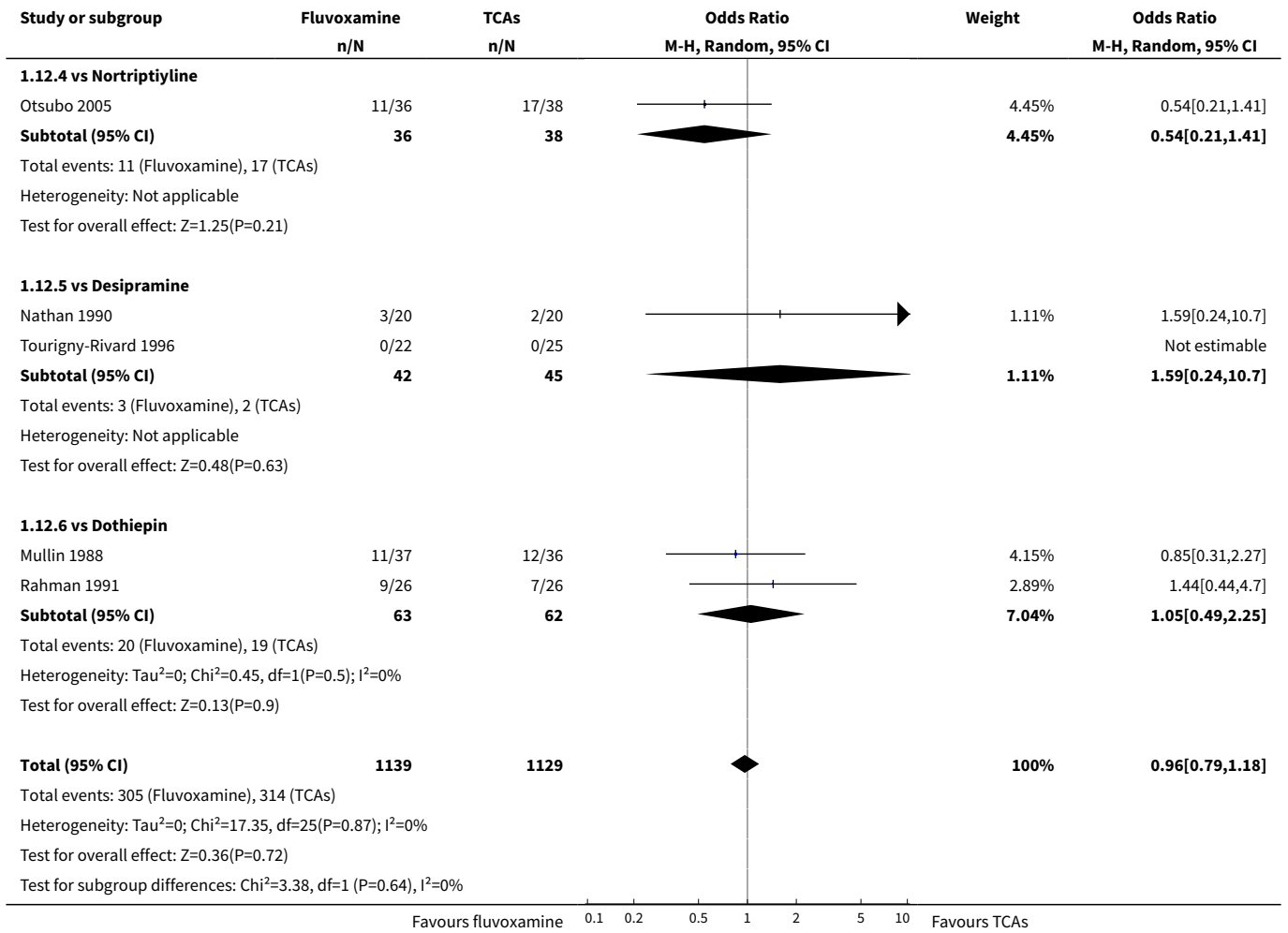
Analysis 1.11. Comparison 1 Fluvoxamine versus TCAs, Outcome 11 Depression scale - Change score: decrease=good (acute phase) - missing SDs.

Depression scale - Change score: decrease=good (acute phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
vs Imipramine								
Claghorn 1996	HRSD-21	-10.1	missing	44	-10.4	missing	44	
Fabre 1996	HRSD-21	-13.5	missing	46	-12.2	missing	48	
Feighner 1989	HRSD-17	-14.5	missing	21	-10.8	missing	27	
Guy 1984	HRSD-17	-11.6	missing	16	-13	missing	16	
Lydiard 1989	HRSD-17	-11.7	missing	17	-17.4	missing	18	
March 1990	HRSD-17	-12.5	missing	13	-11.7	missing	15	
vs Clomipramine								
de Wilde 1983	HRSD-17	-17	missing	21	-19.1	missing	21	
Zohar 2003	HRSD-17	-17.2	missing	42	-18.2	missing	42	
vs Amitriptyline								
Barge-Schaapveld 1995	HRSD-17	-15.7	missing	11	-15.8	missing	10	
Kostiukova 2003	HRSD-17	-18.9	missing	30	-19	missing	30	
Remick 1994	HRSD-17	-16.3	missing	13	-14.3	missing	9	
vs Desipramine								
Nathan 1990	HRSD-17	-19.2	missing	22	-13.5	missing	25	

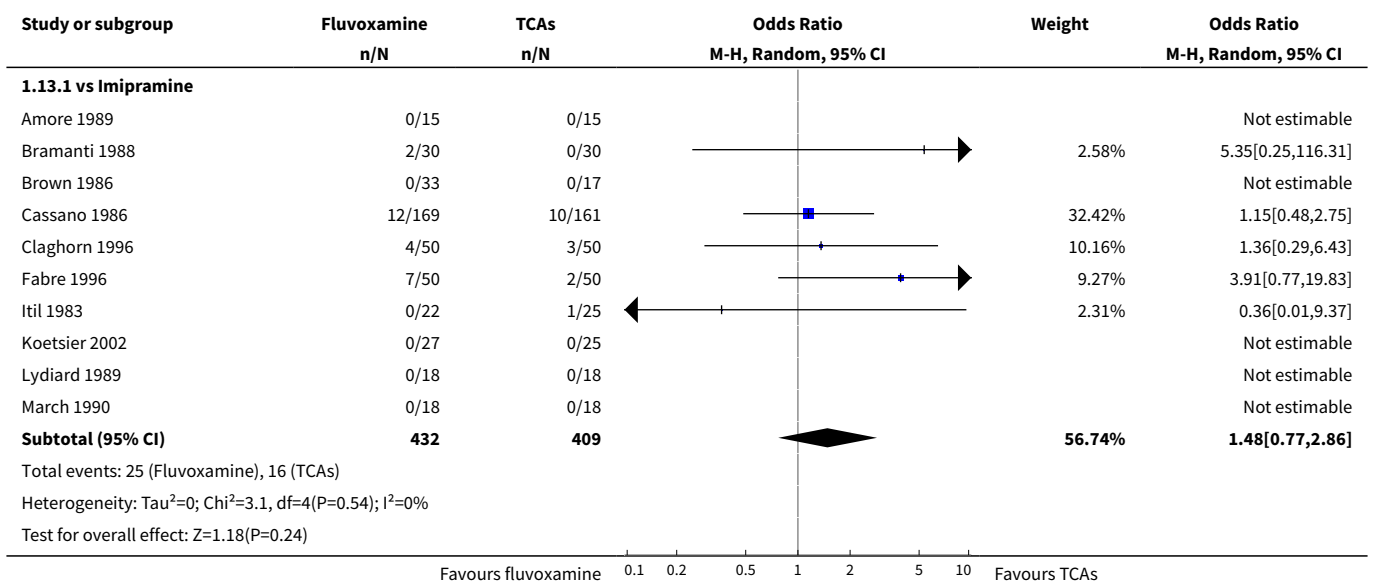
Depression scale - Change score: decrease=good (acute phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
vs Dothiepine								
Mullin 1988	HRSD-17	-13	missing	26	-12.7	missing	24	
Rahman 1991	MADRS	-22.1	missing	19	-20.5	missing	21	

Analysis 1.12. Comparison 1 Fluvoxamine versus TCAs, Outcome 12 Total Dropout.

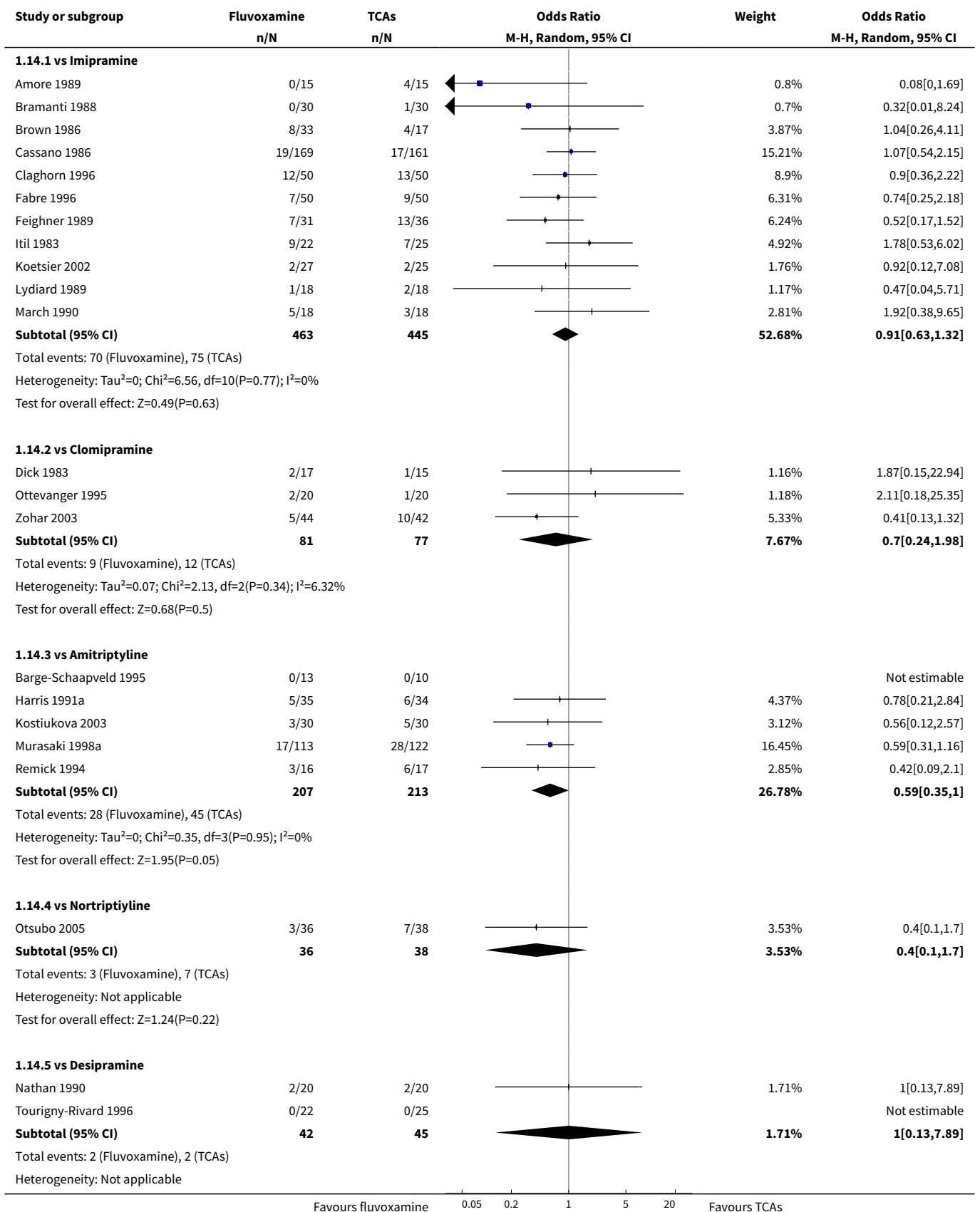


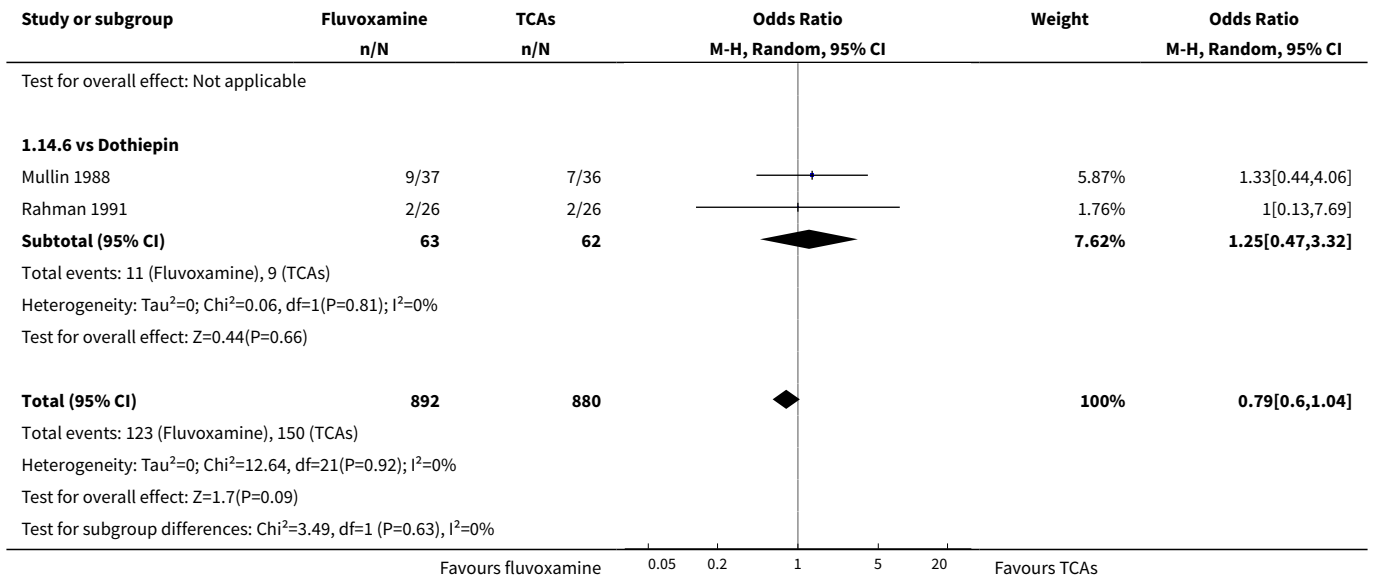


Analysis 1.13. Comparison 1 Fluvoxamine versus TCAs, Outcome 13 Dropout due to inefficacy.

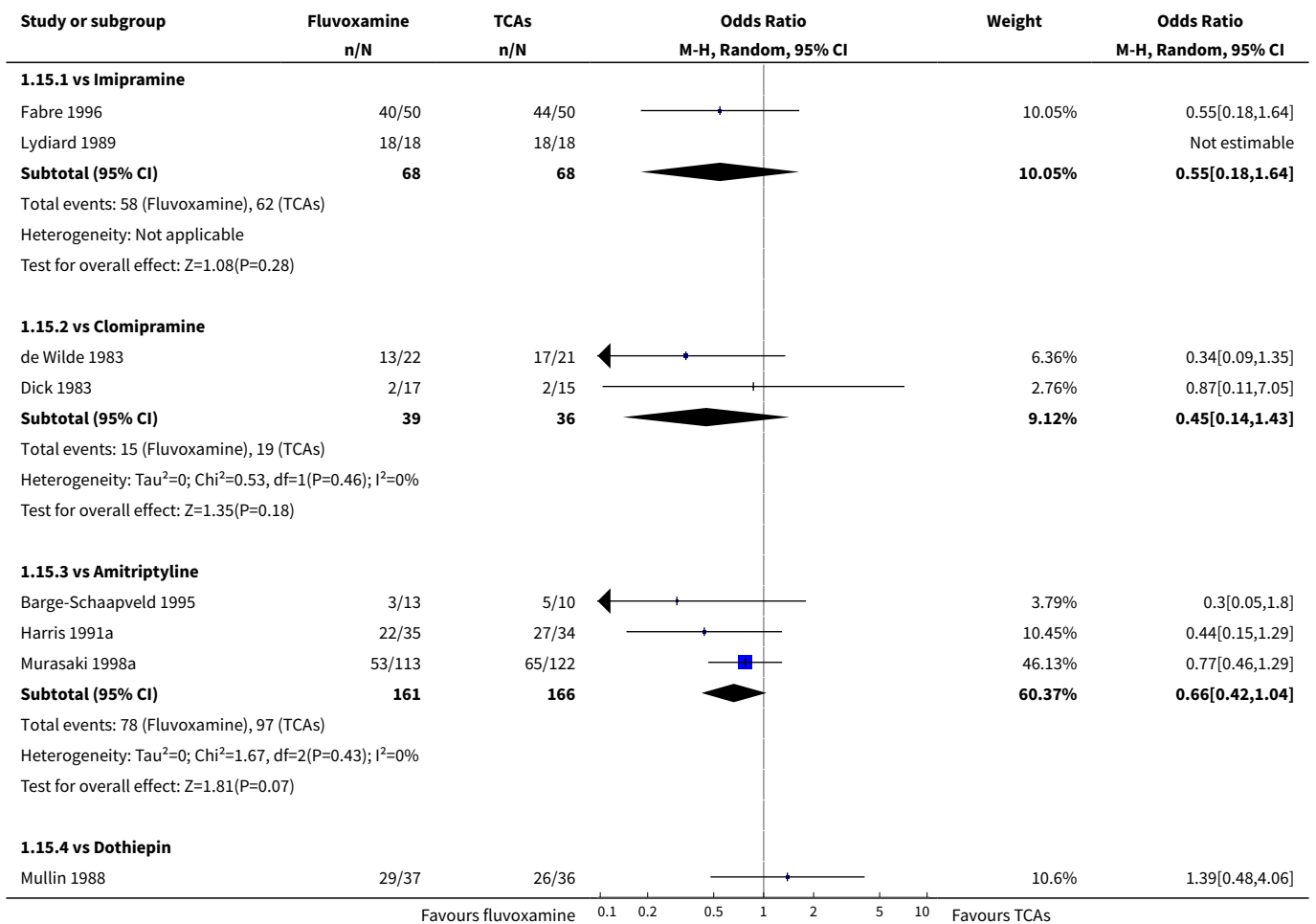


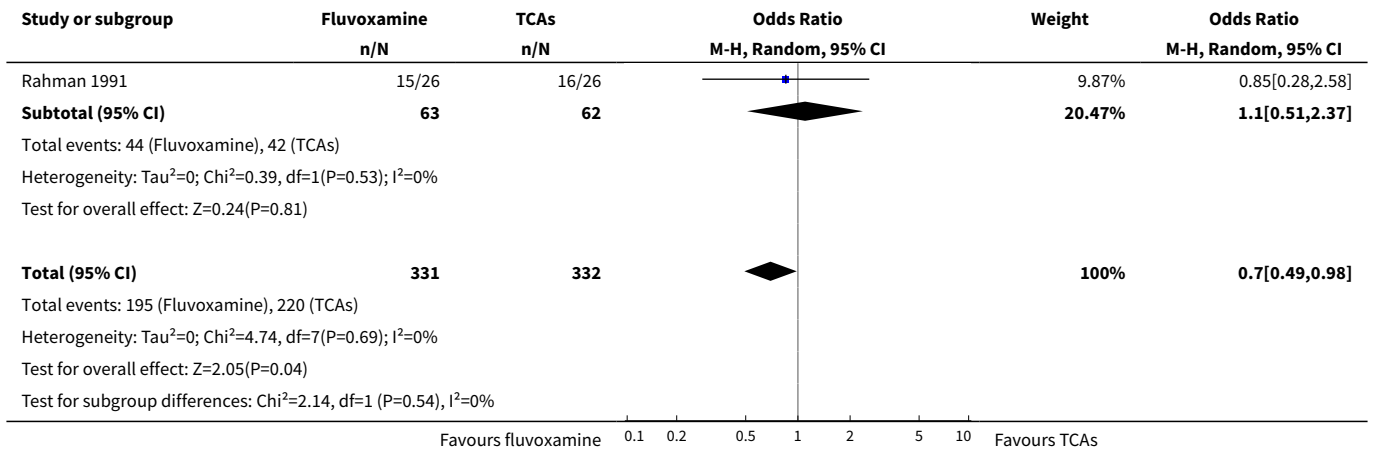
Analysis 1.14. Comparison 1 Fluvoxamine versus TCAs, Outcome 14 Dropout due to side effects.



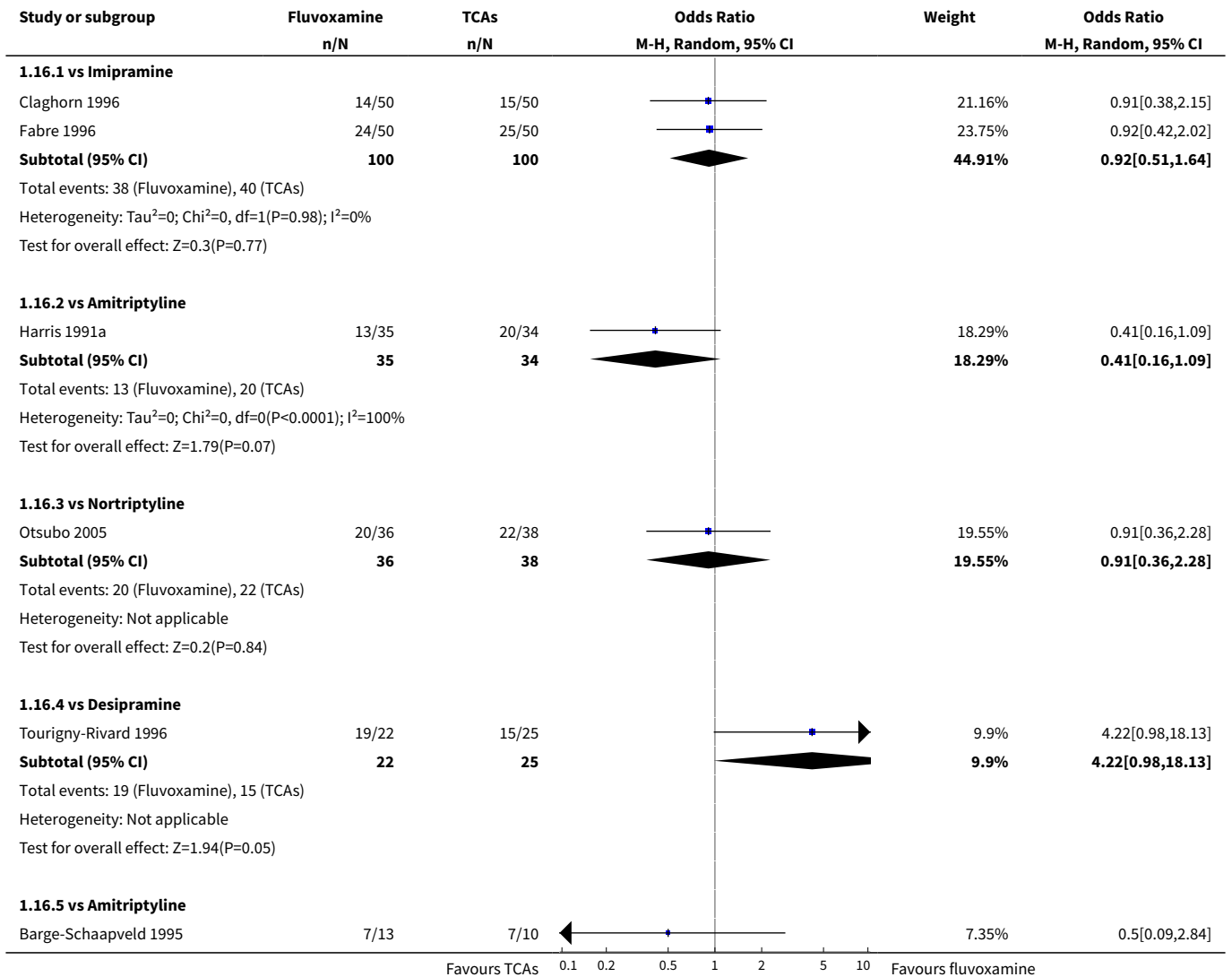


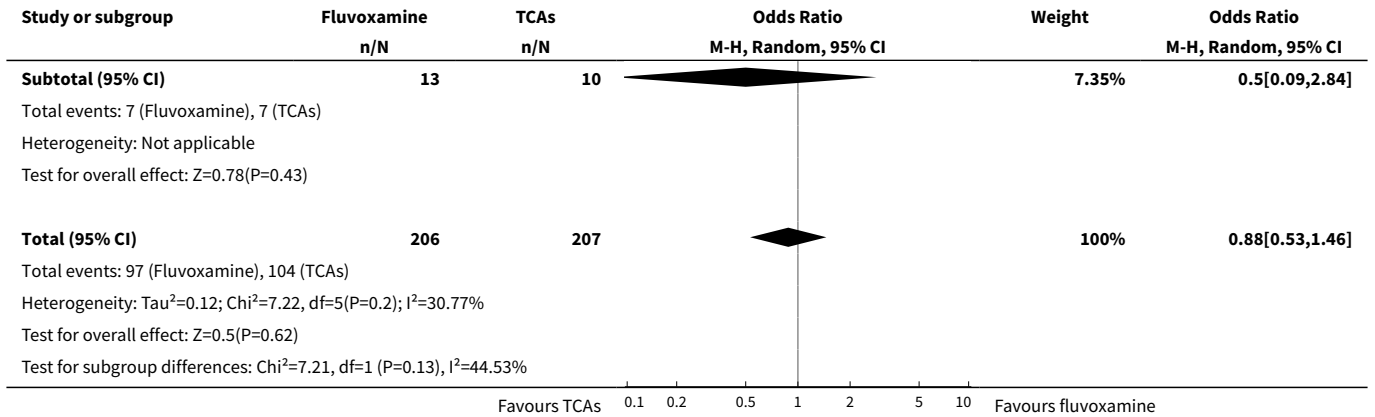
Analysis 1.15. Comparison 1 Fluvoxamine versus TCAs, Outcome 15 Number of patients experiencing at least one side effect.



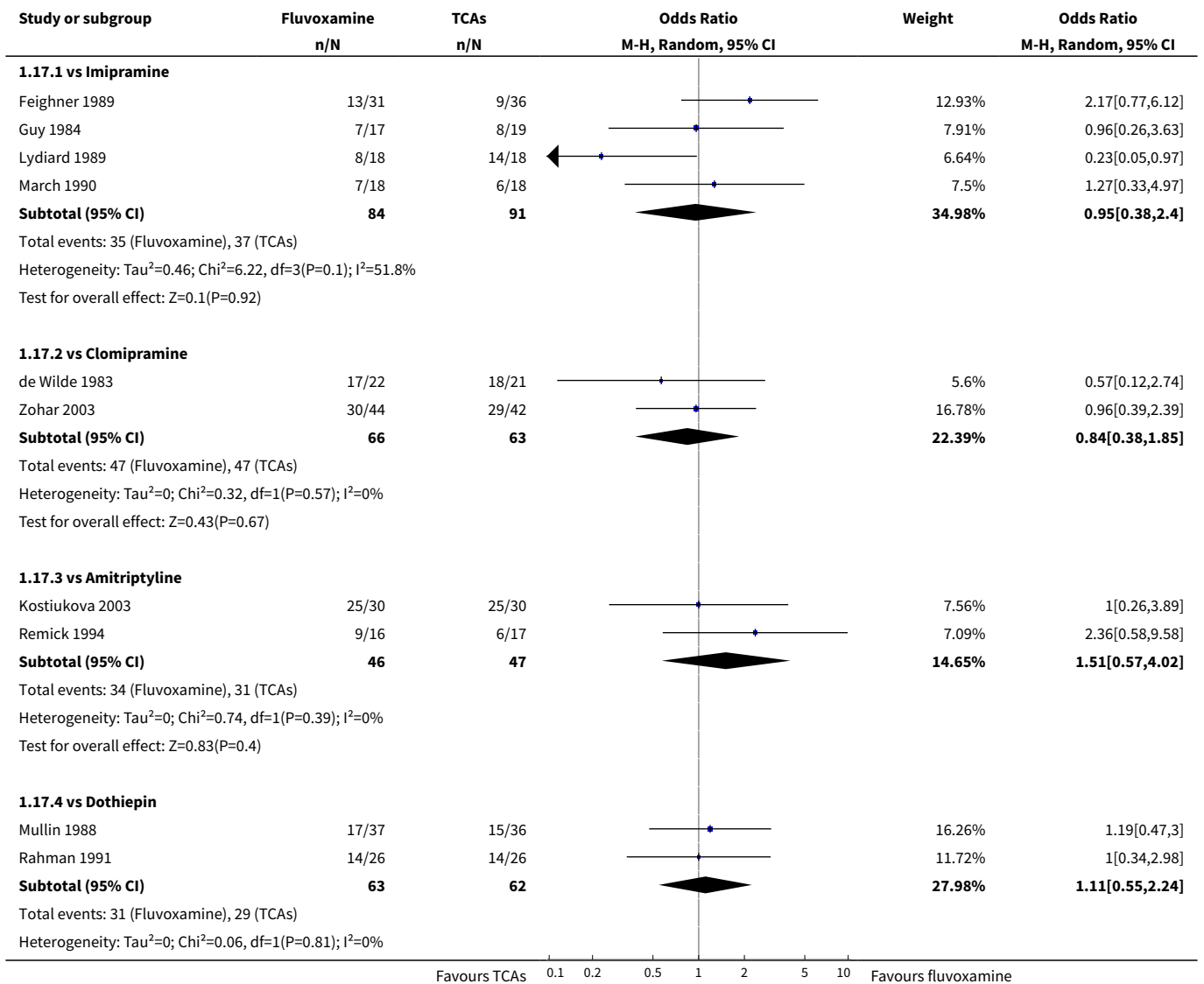


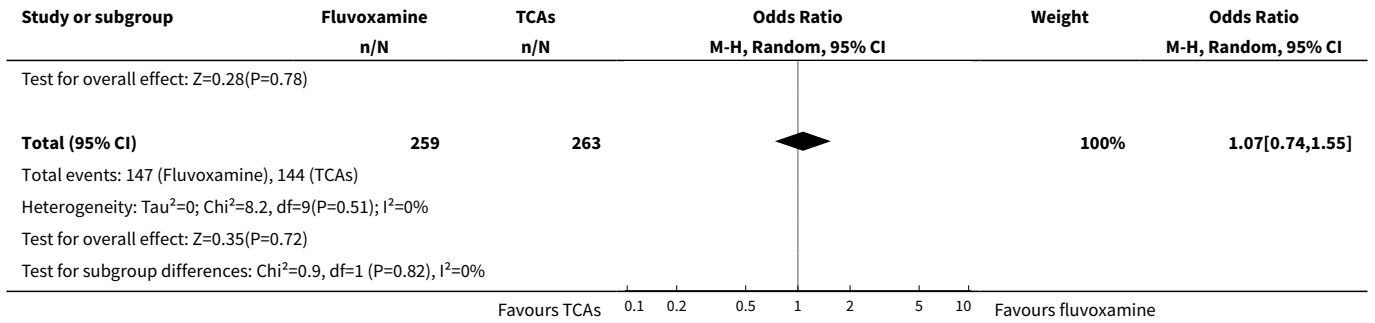
Analysis 1.16. Comparison 1 Fluvoxamine versus TCAs, Outcome 16 Subgroup analysis - Response (acute phase) 1. Fluvoxamine dosing - Standard dosage.



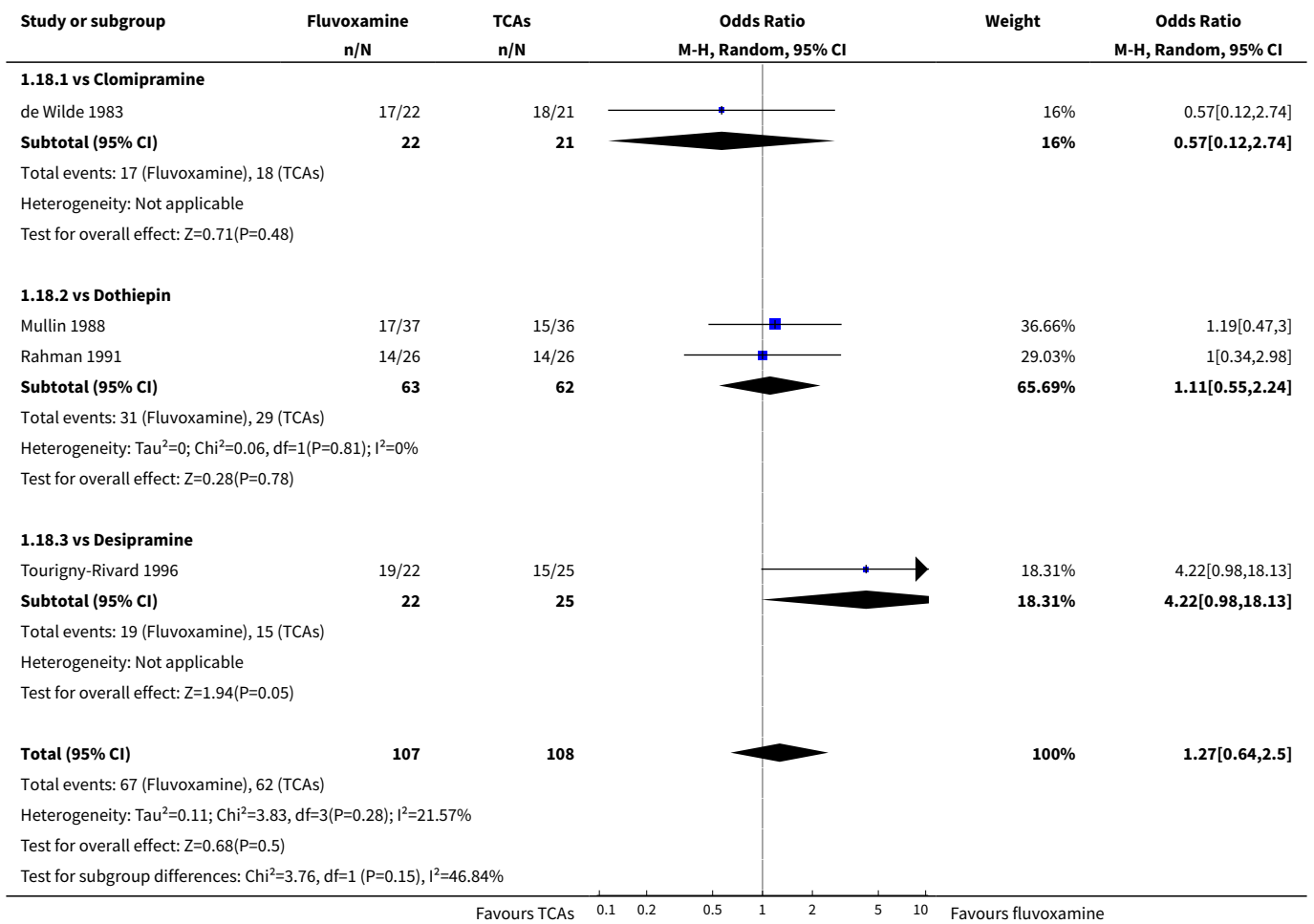


Analysis 1.17. Comparison 1 Fluvoxamine versus TCAs, Outcome 17 Subgroup analysis - Response (acute phase) 1. Fluvoxamine dosing - High dosage.

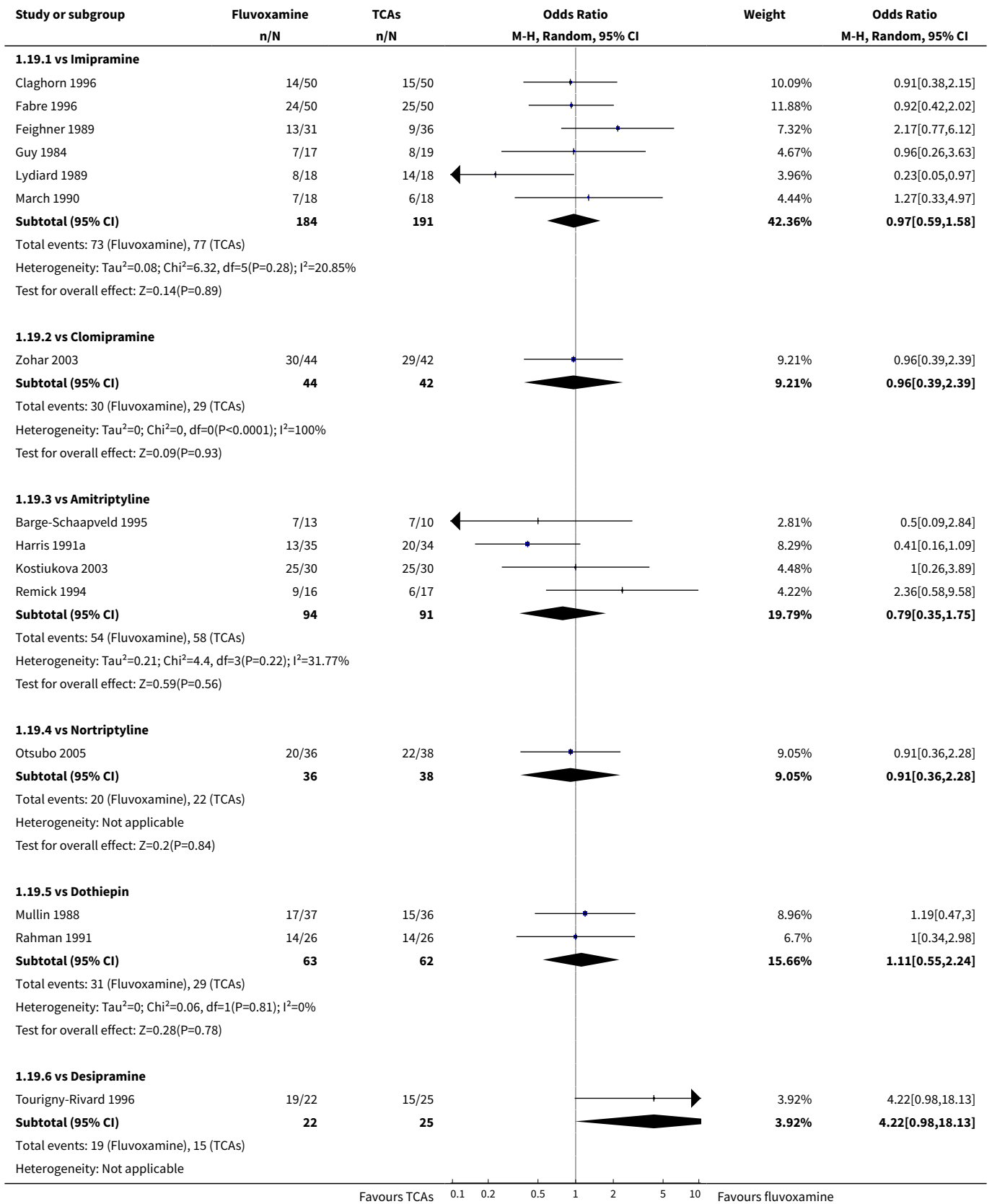


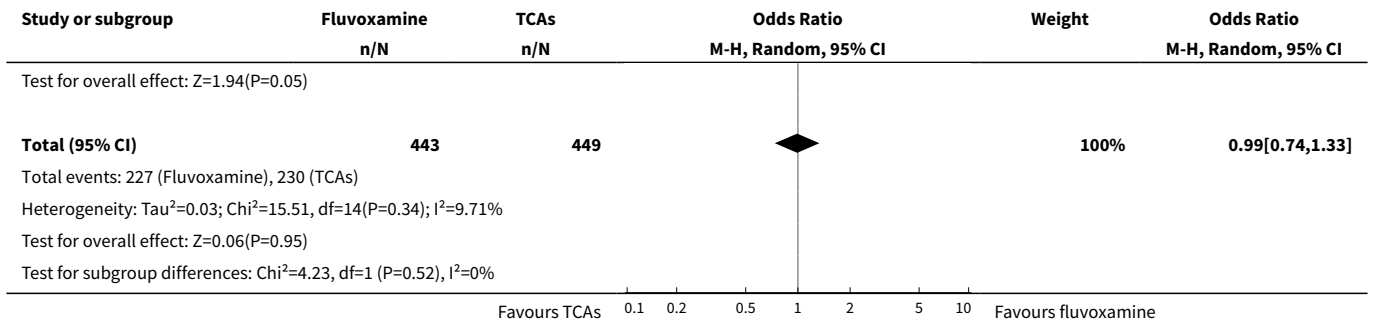


Analysis 1.18. Comparison 1 Fluvoxamine versus TCAs, Outcome 18 Subgroup analysis - Response (acute phase) 2. Comparator dosing - Standard dosage.

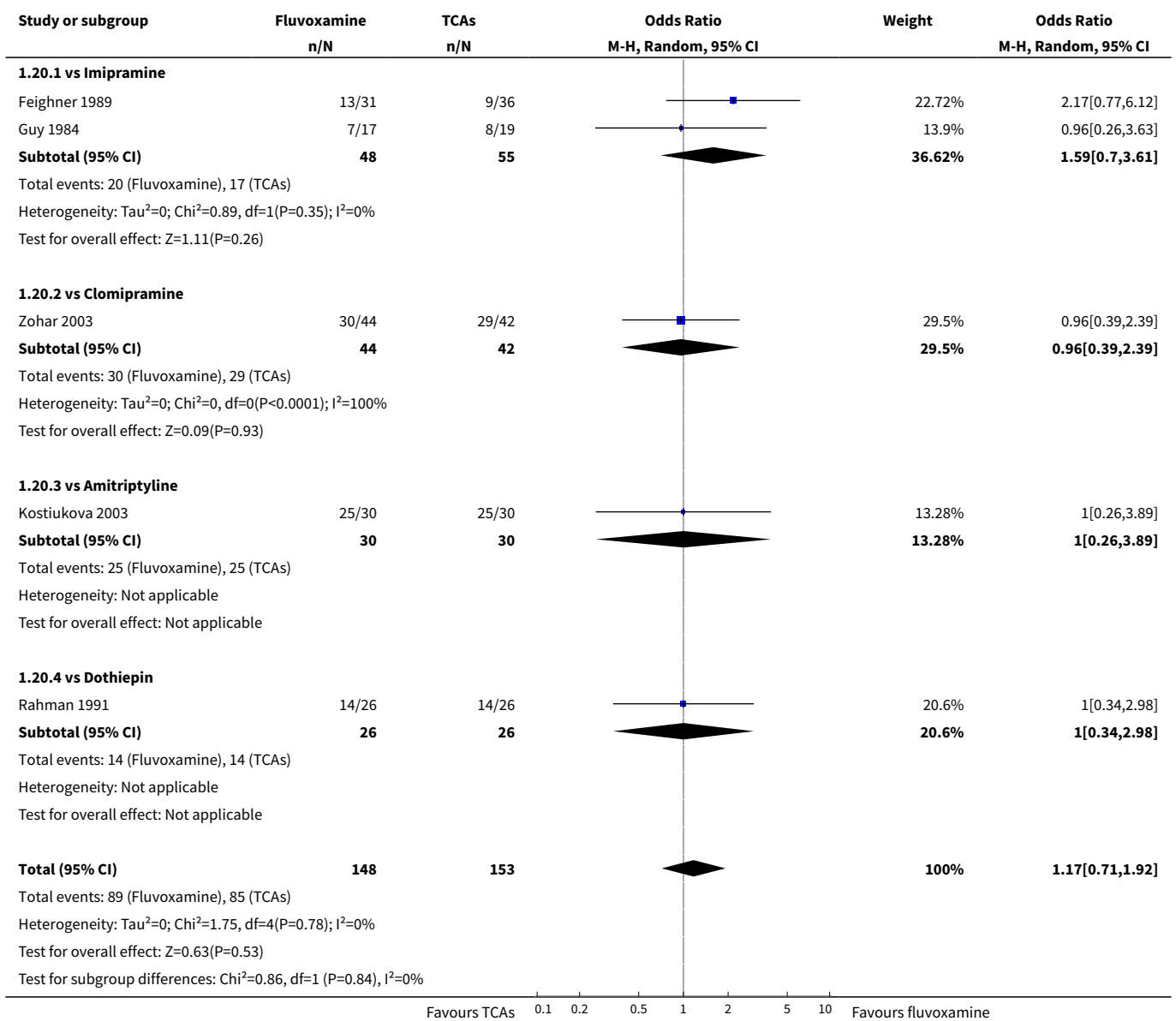


Analysis 1.19. Comparison 1 Fluvoxamine versus TCAs, Outcome 19 Subgroup analysis - Response (acute phase) 2. Comparator dosing - High dosage.

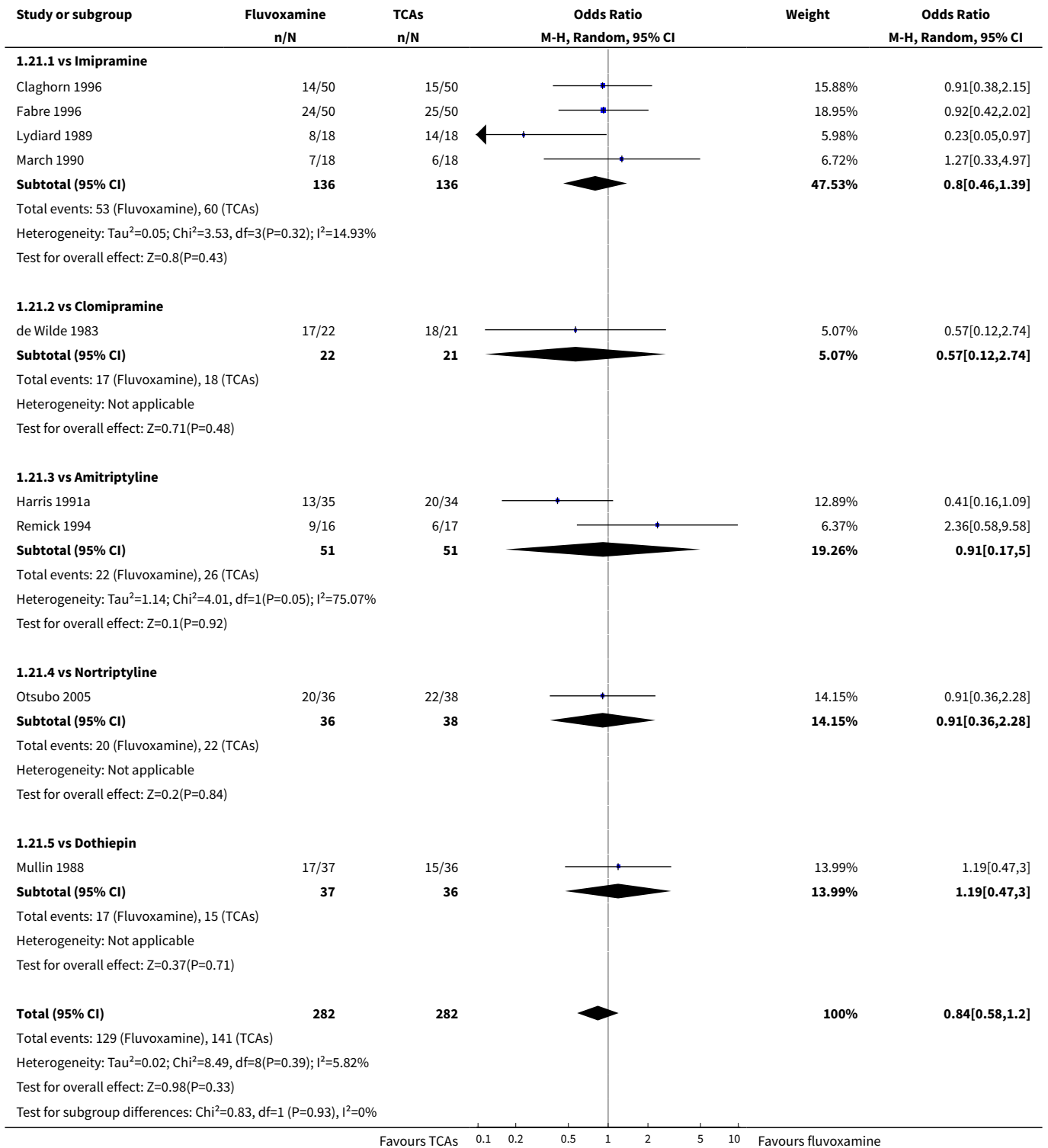




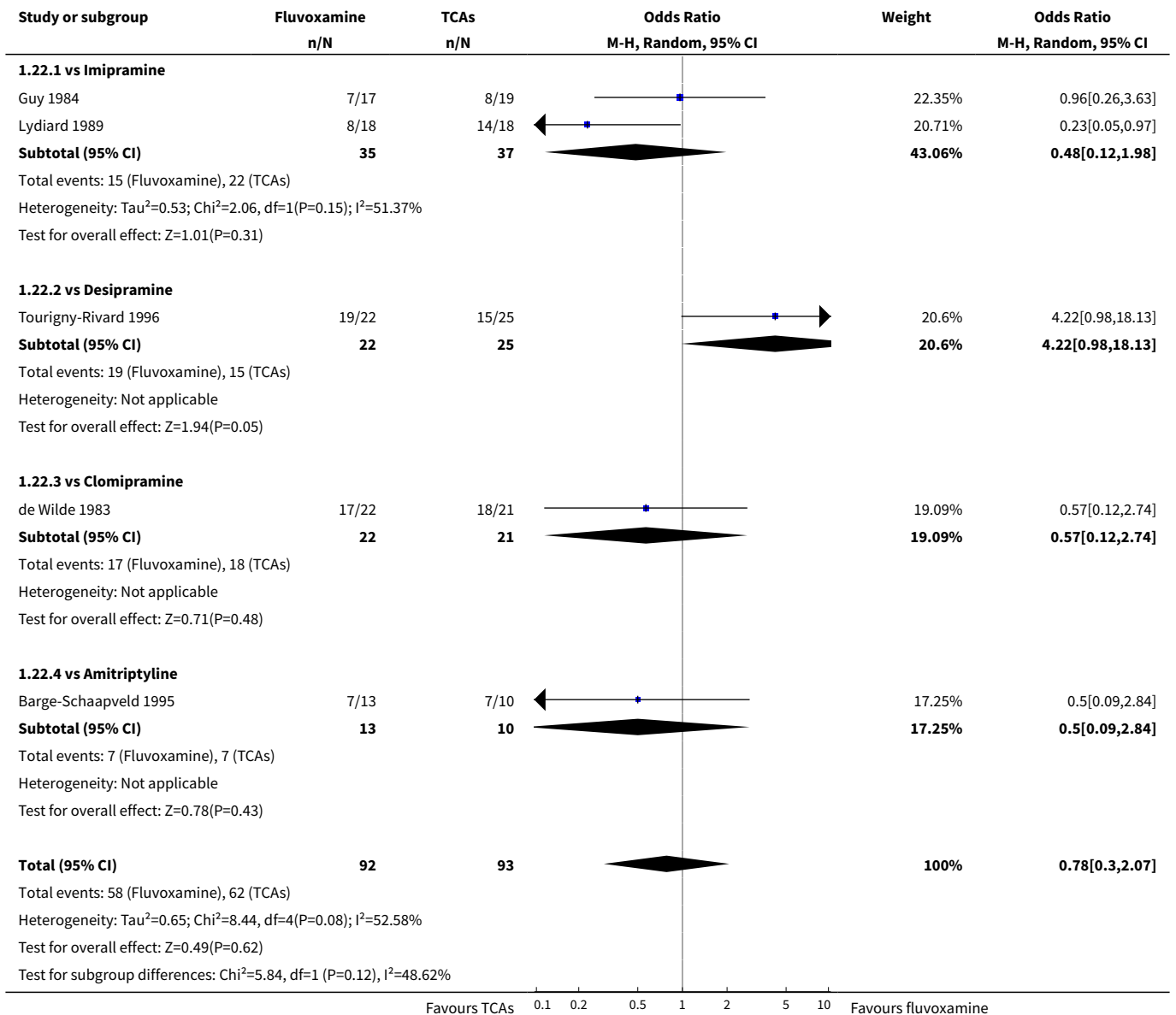
**Analysis 1.20. Comparison 1 Fluvoxamine versus TCAs, Outcome 20
Subgroup analysis - Response (acute phase) 4. Treatment settings - Inpatient.**



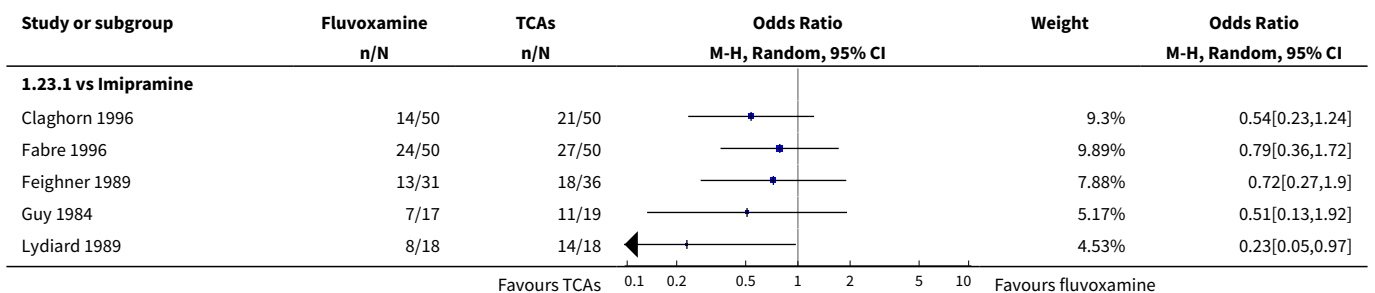
Analysis 1.21. Comparison 1 Fluvoxamine versus TCAs, Outcome 21 Subgroup analysis - Response (acute phase) 4. Treatment settings - Outpatients.

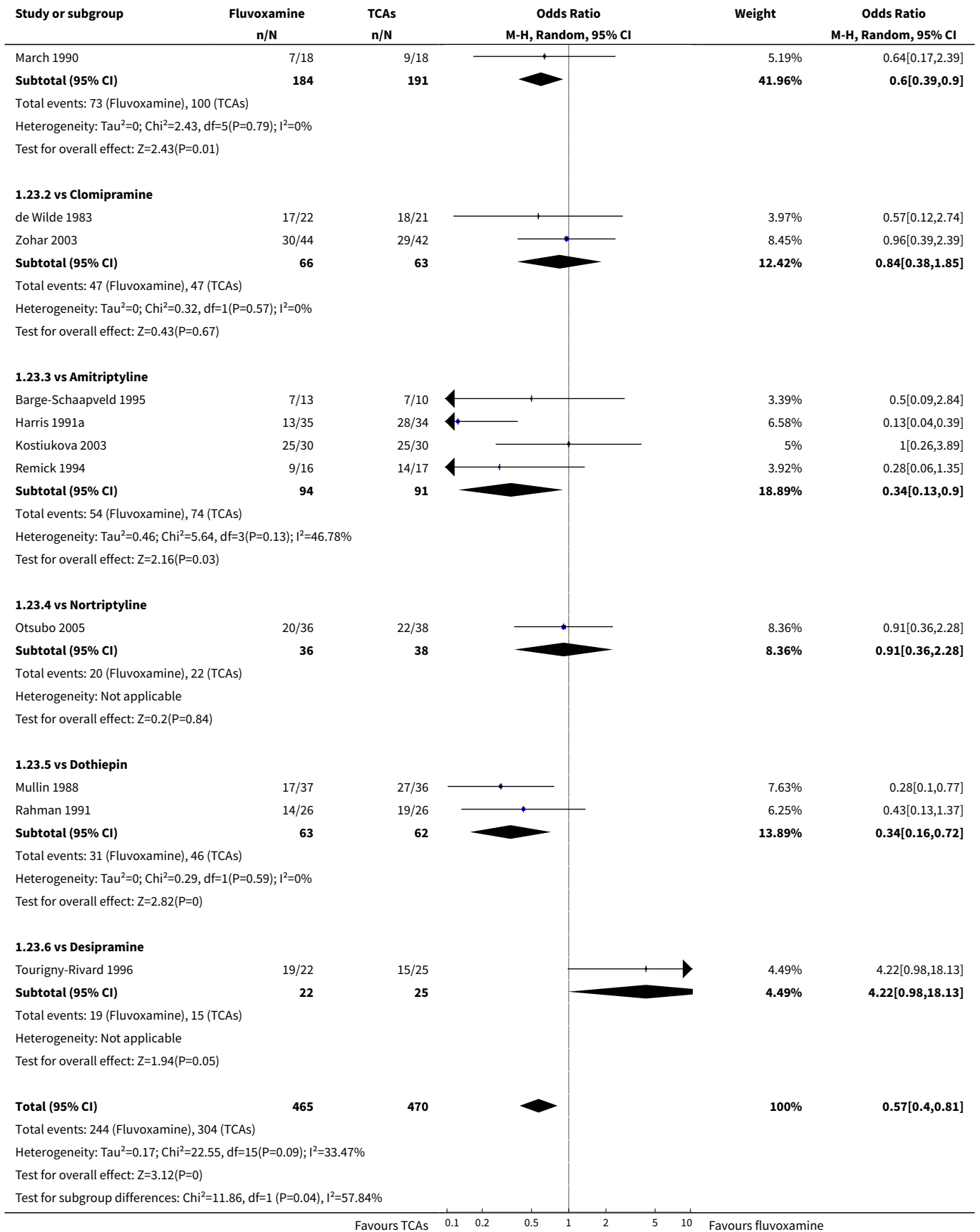


Analysis 1.22. Comparison 1 Fluvoxamine versus TCAs, Outcome 22 Sensitivity analysis - Response (acute phase) 2. Excluding trials dropout rate >20%.

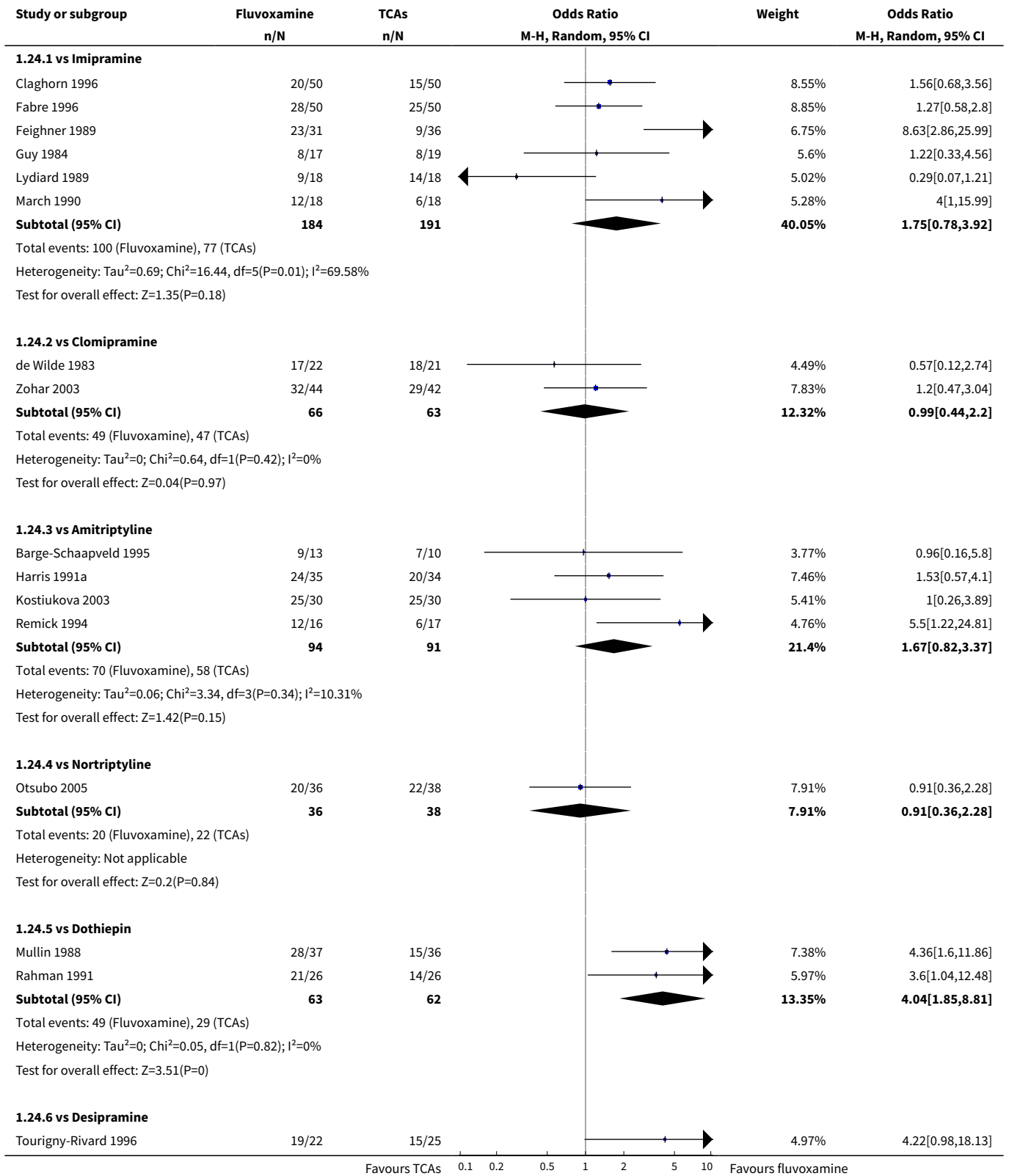


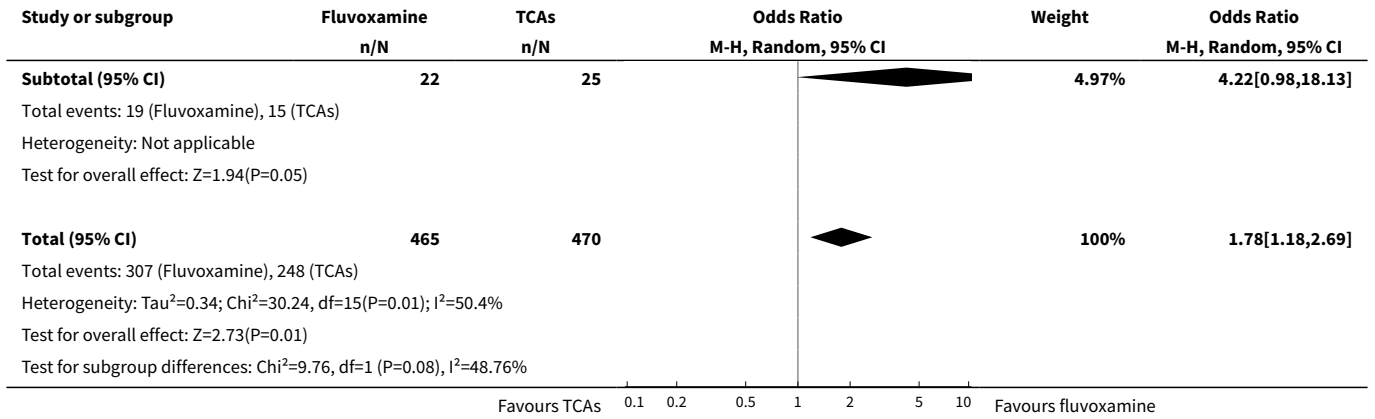
Analysis 1.23. Comparison 1 Fluvoxamine versus TCAs, Outcome 23 Sensitivity analysis - Response (acute phase) 3. Worst case scenario ITT.



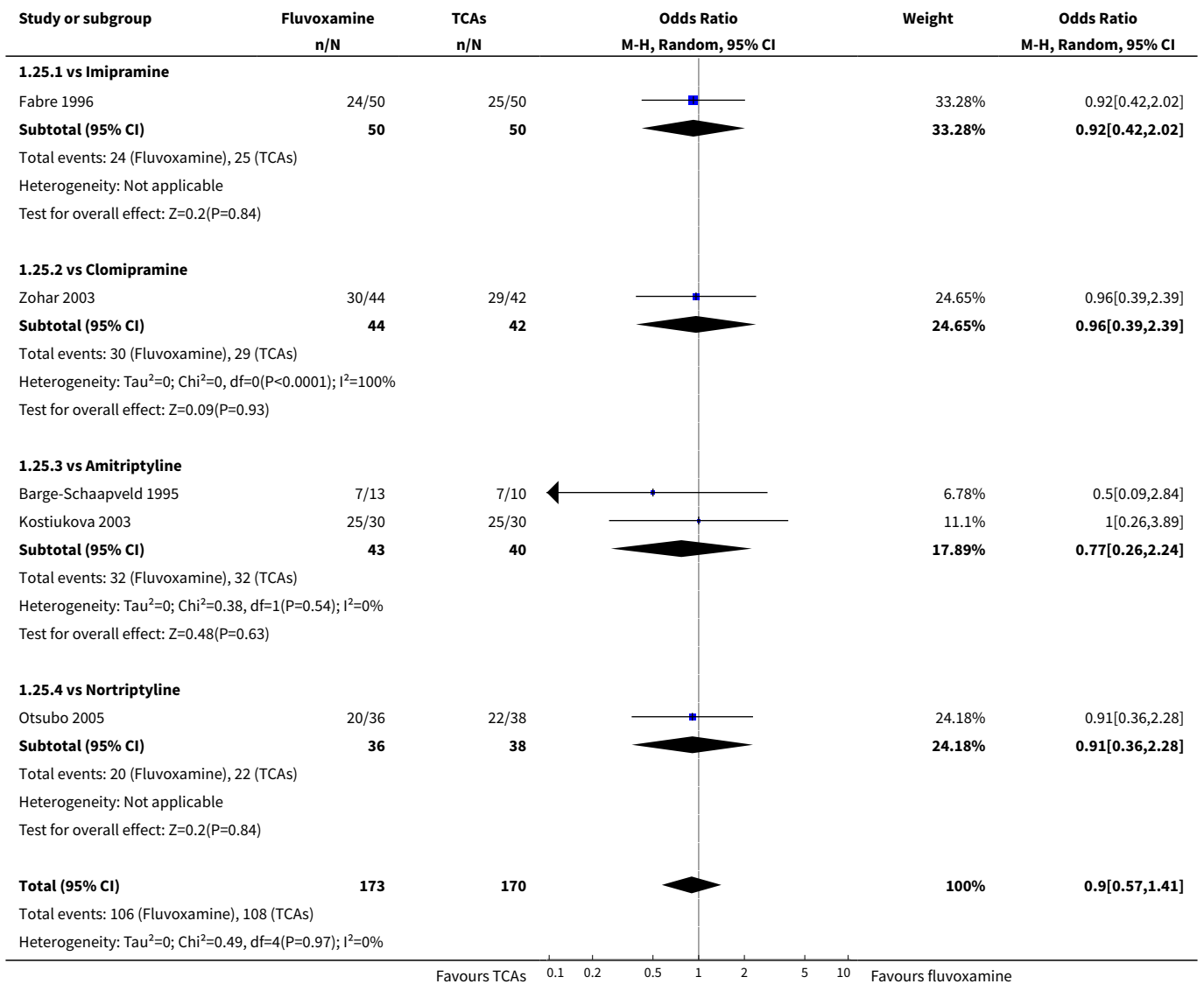


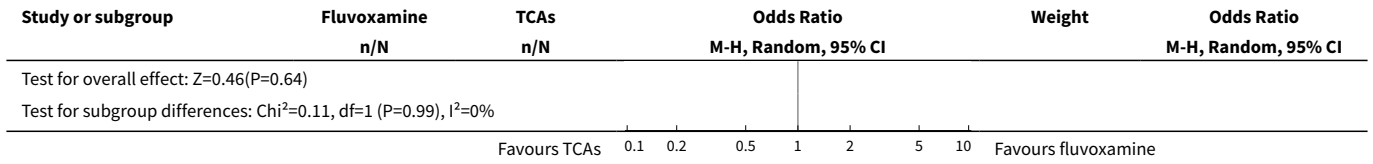
Analysis 1.24. Comparison 1 Fluvoxamine versus TCAs, Outcome 24 Sensitivity analysis - Response (acute phase) 4. Best case scenario ITT.



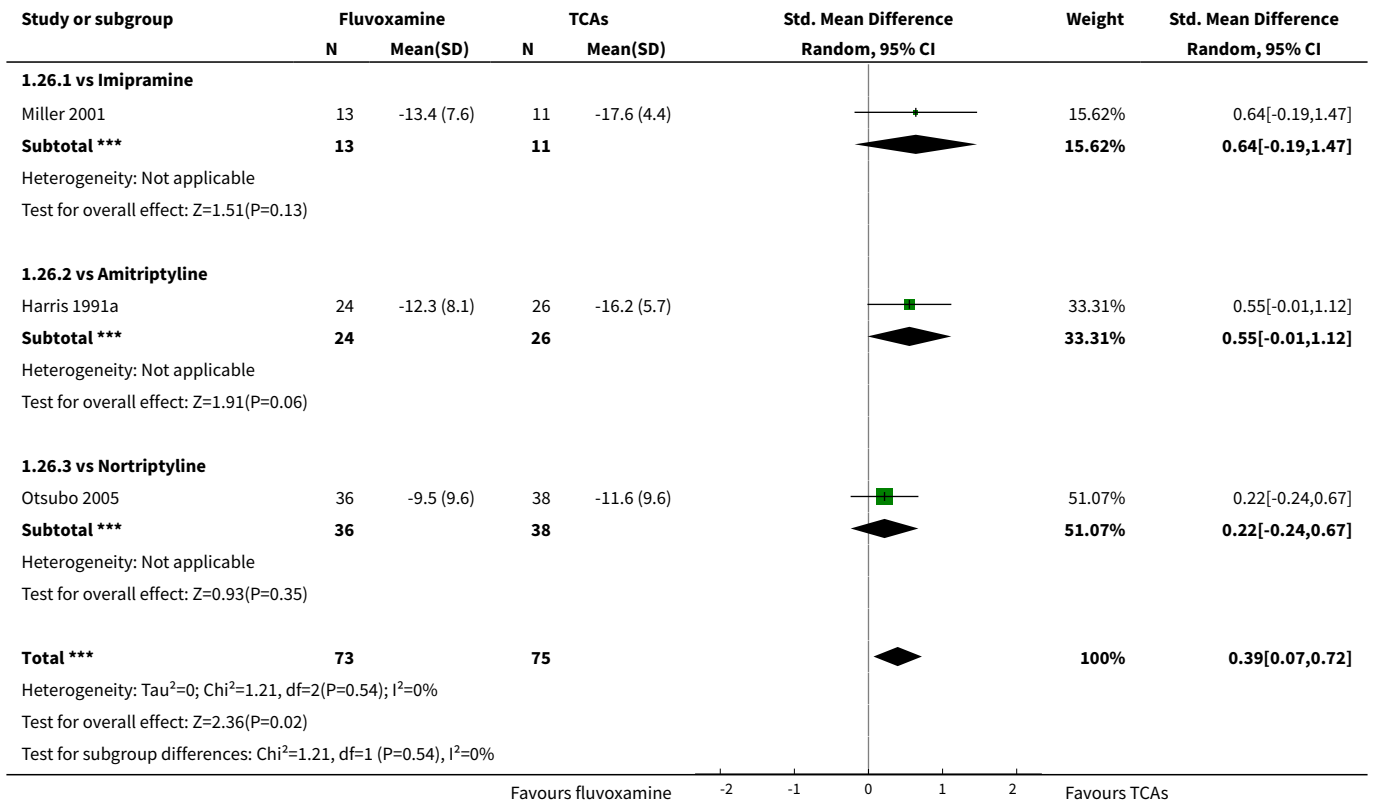


Analysis 1.25. Comparison 1 Fluvoxamine versus TCAs, Outcome 25 Sensitivity analysis - Response (acute phase) 5. Excluding trials with imputation methods for calculating response.

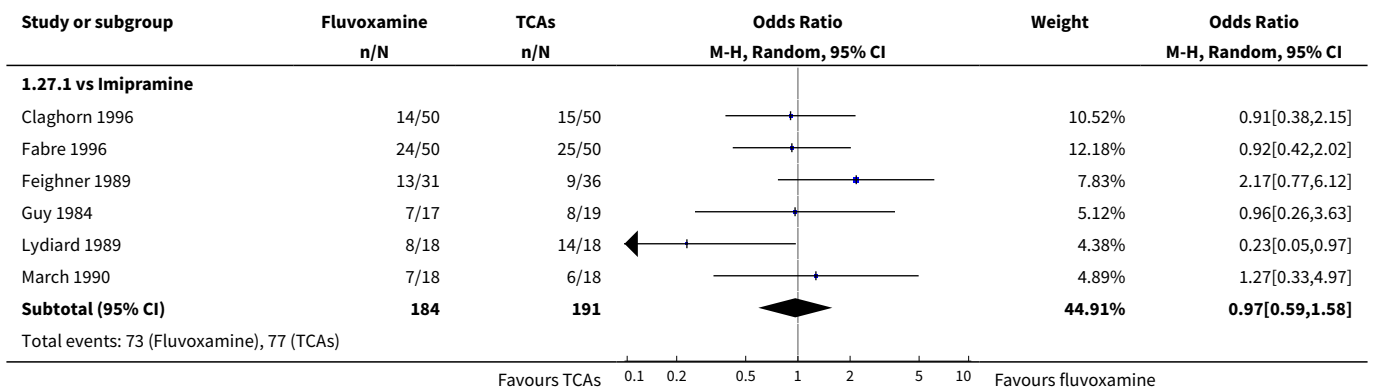


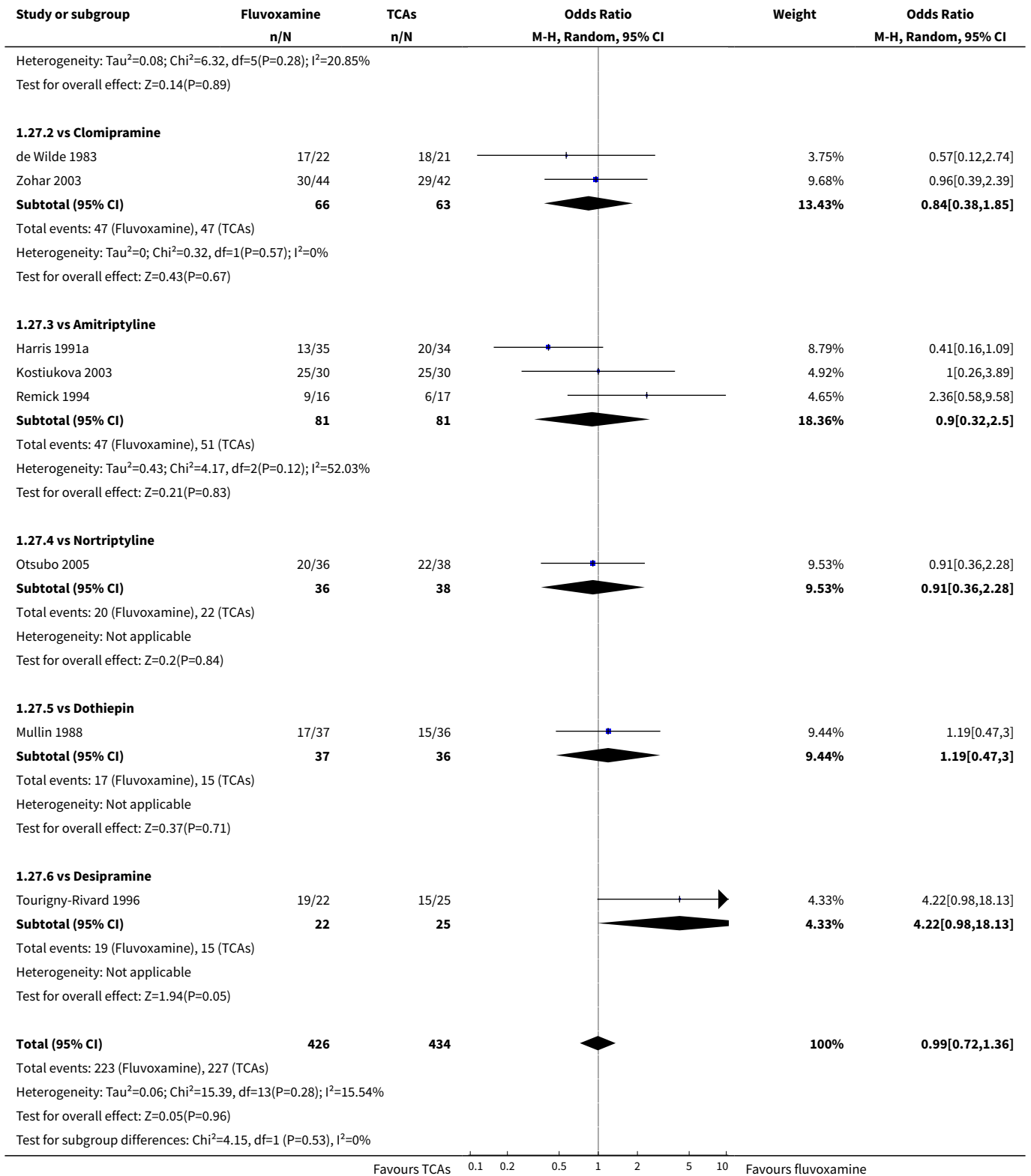


Analysis 1.26. Comparison 1 Fluvoxamine versus TCAs, Outcome 26 Sensitivity analysis - Mean change from baseline (acute phase) 5. Excluding trials for which the SD had to be borrowed from other trials.

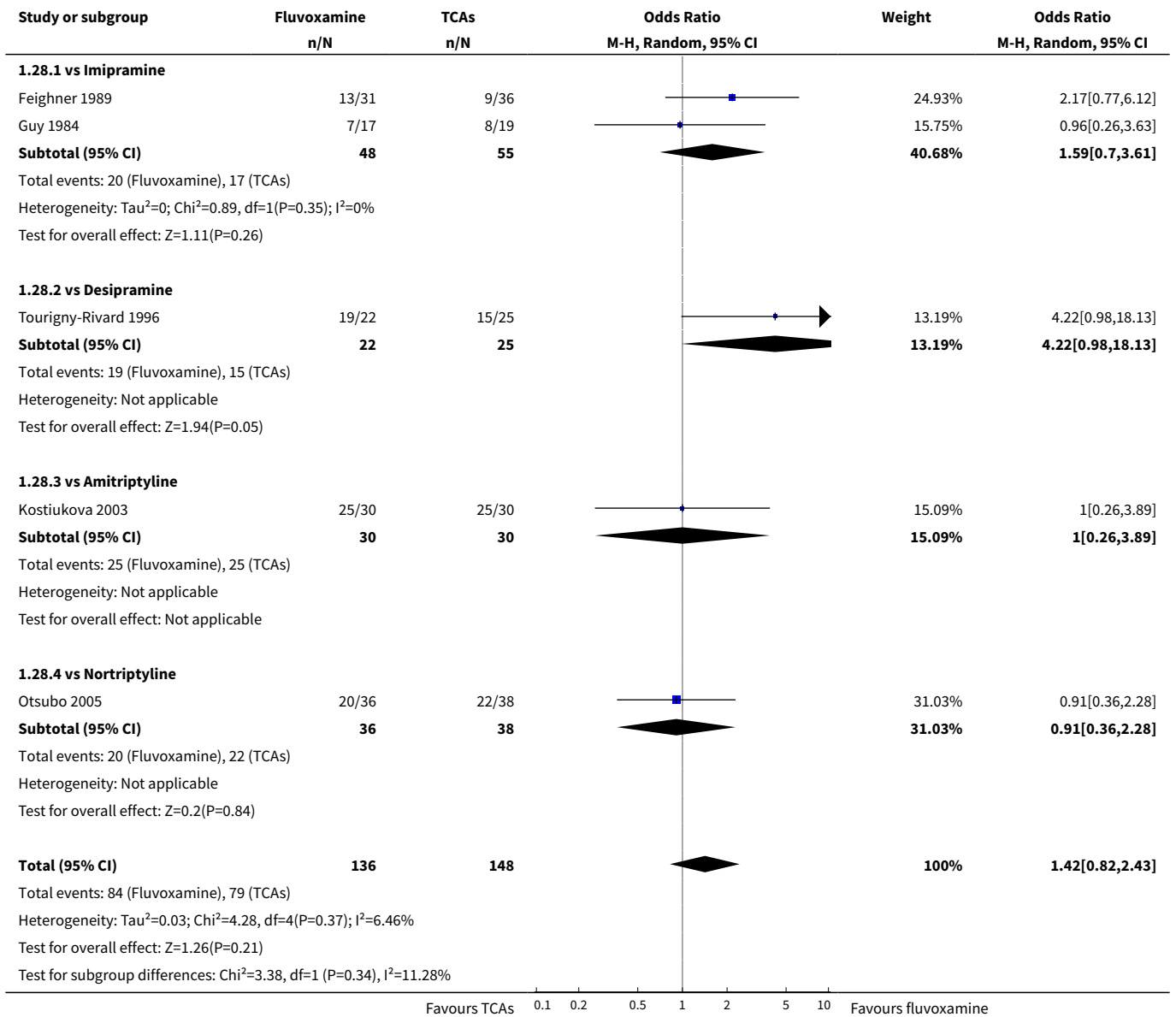


Analysis 1.27. Comparison 1 Fluvoxamine versus TCAs, Outcome 27 Sensitivity analysis - Response (acute phase) 6. Wish bias - Fluvoxamine as an investigational drug.

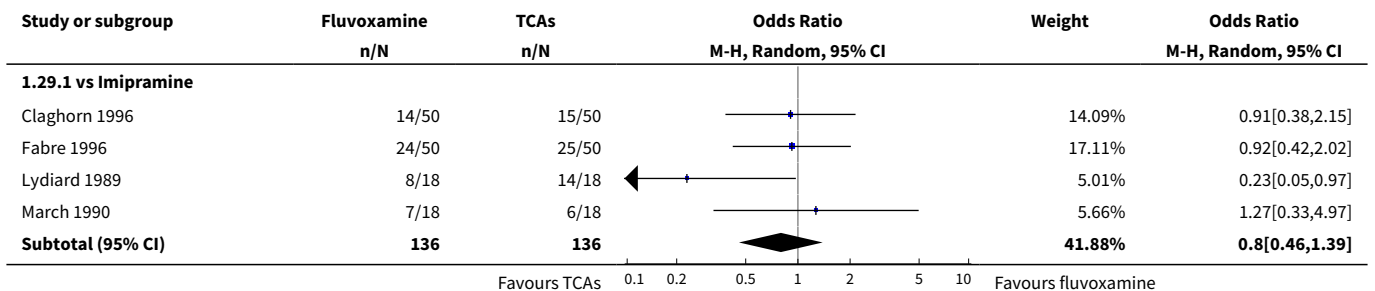


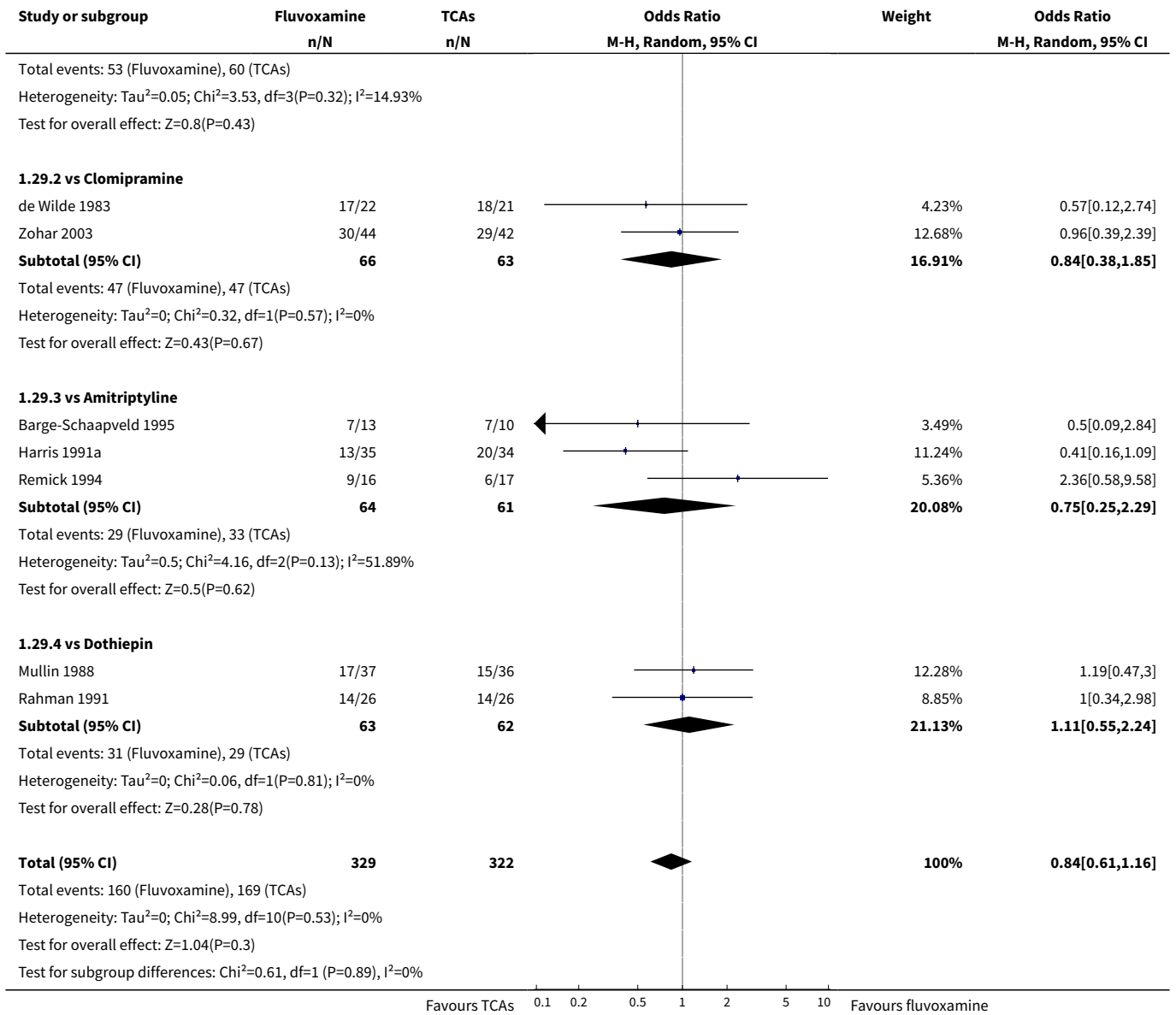


Analysis 1.28. Comparison 1 Fluvoxamine versus TCAs, Outcome 28 Sensitivity analysis - Response (acute phase) 7. Funding - Excluding trials funded by the fluvoxamine marketing company.

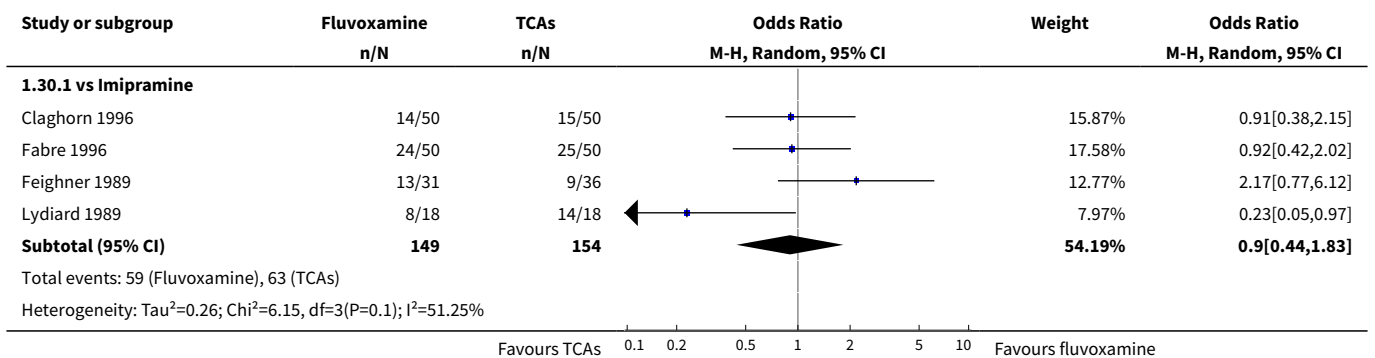


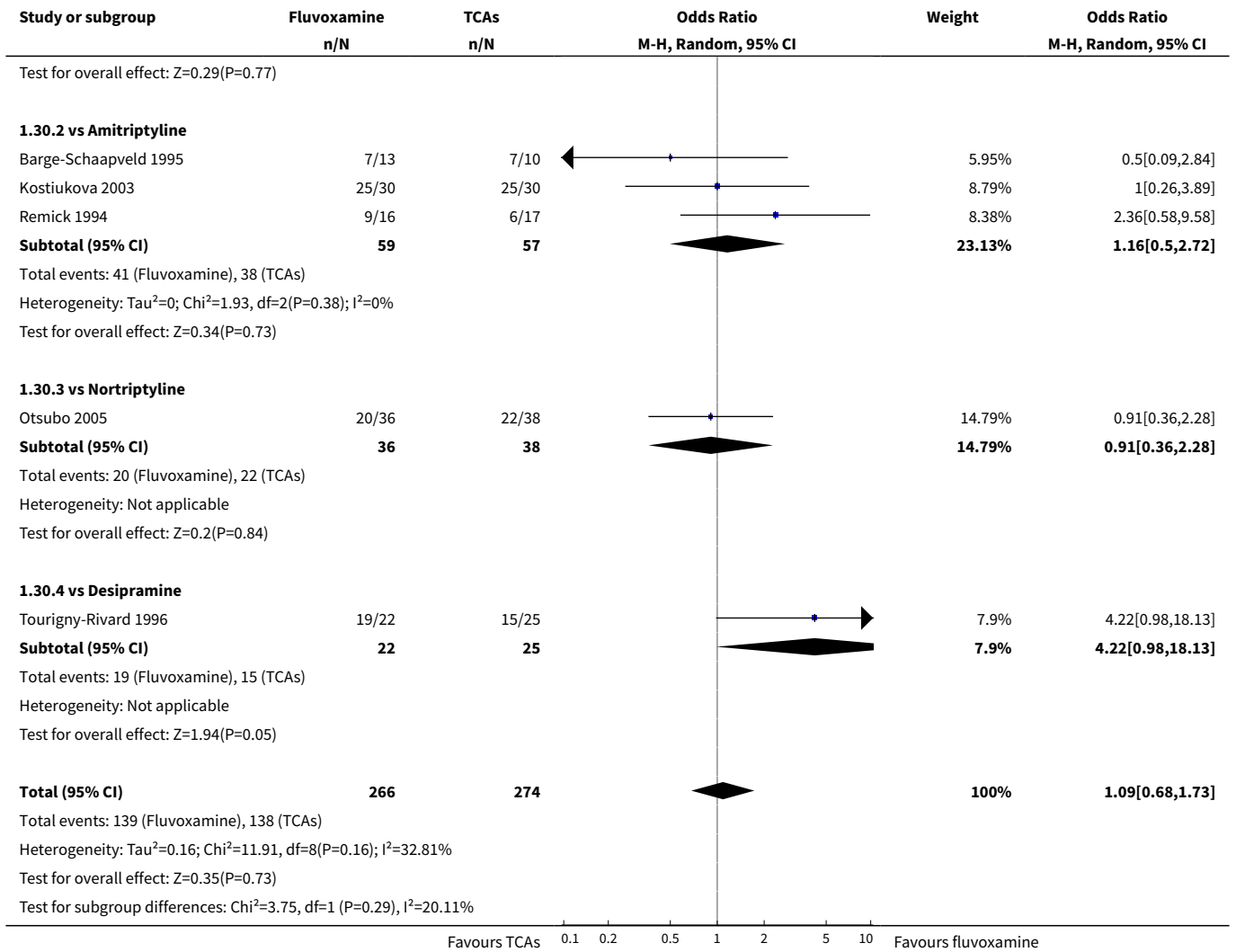
Analysis 1.29. Comparison 1 Fluvoxamine versus TCAs, Outcome 29 Sensitivity analysis - Response (acute phase) 7. Funding - Trials funded by the fluvoxamine marketing company.



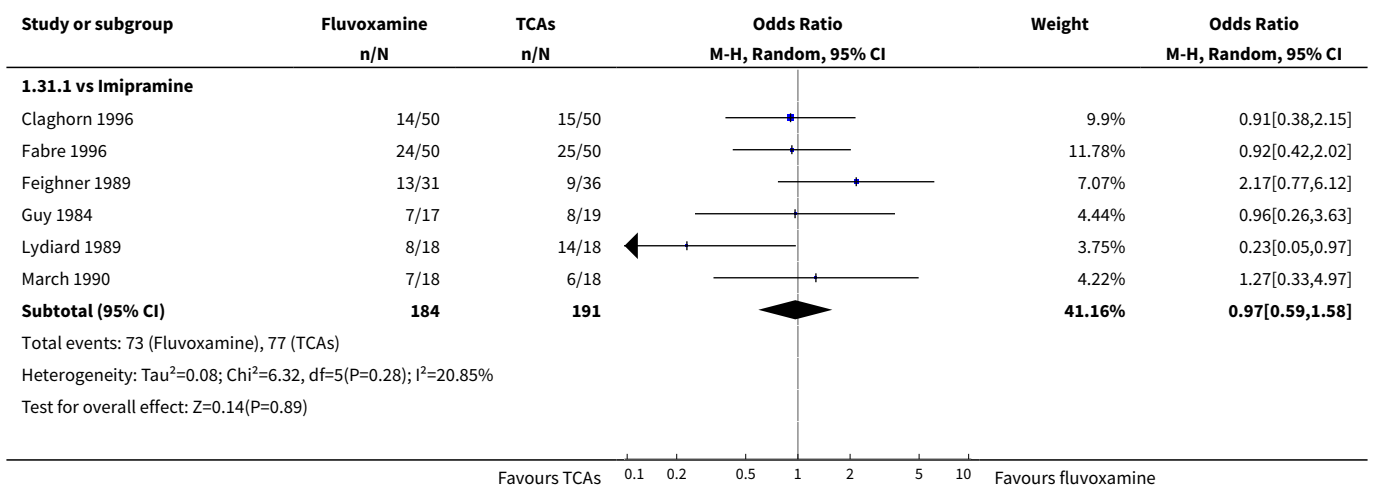


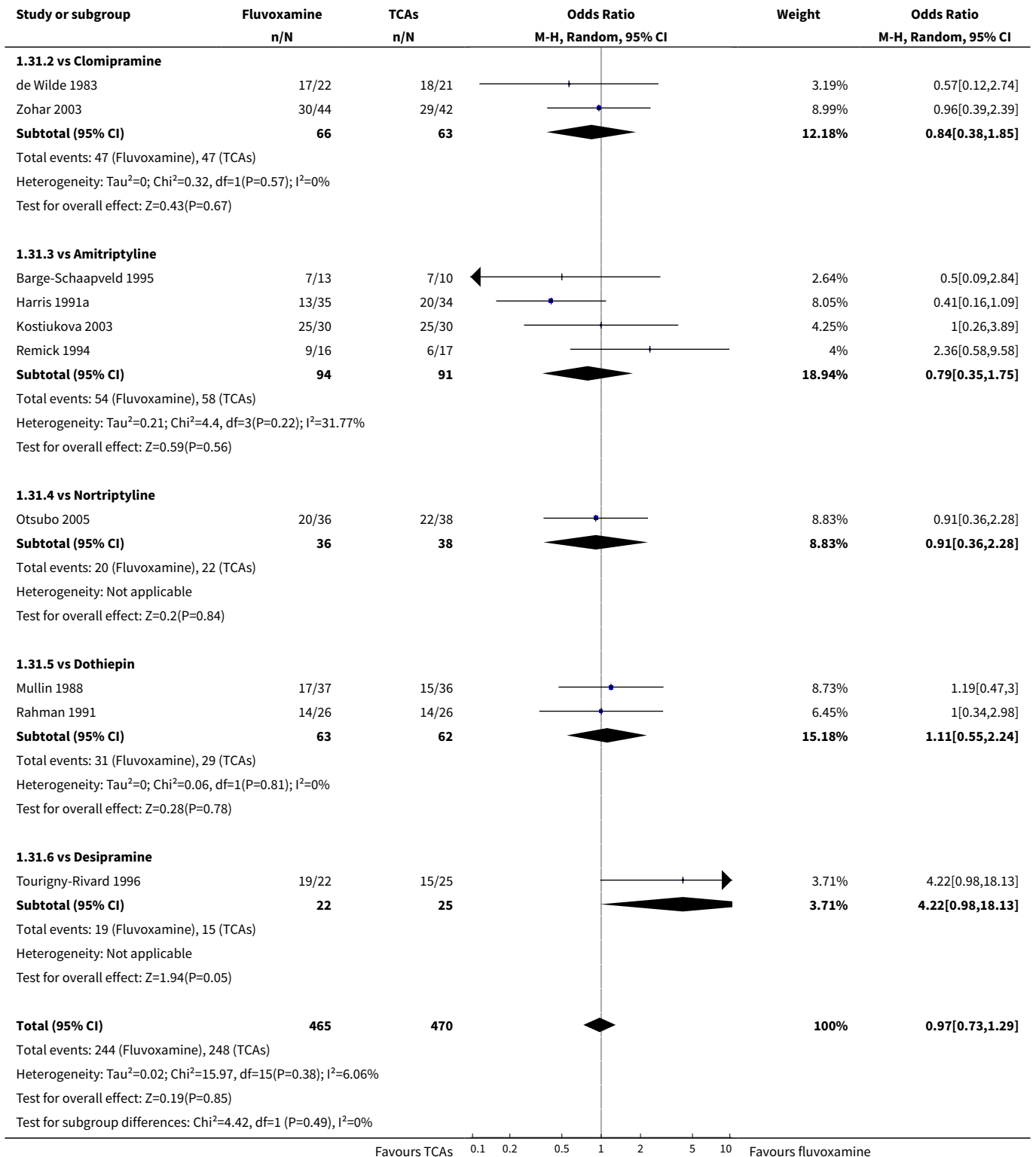
Analysis 1.30. Comparison 1 Fluvoxamine versus TCAs, Outcome 30 Sensitivity analysis - Response (acute phase) 8. Excluding trials that might include patients with bipolar depression.





Analysis 1.31. Comparison 1 Fluvoxamine versus TCAs, Outcome 31 Sensitivity analysis - Response (acute phase) 9. Excluding trials that included patients with psychotic features.





Comparison 2. Fluvoxamine versus Heterocyclics

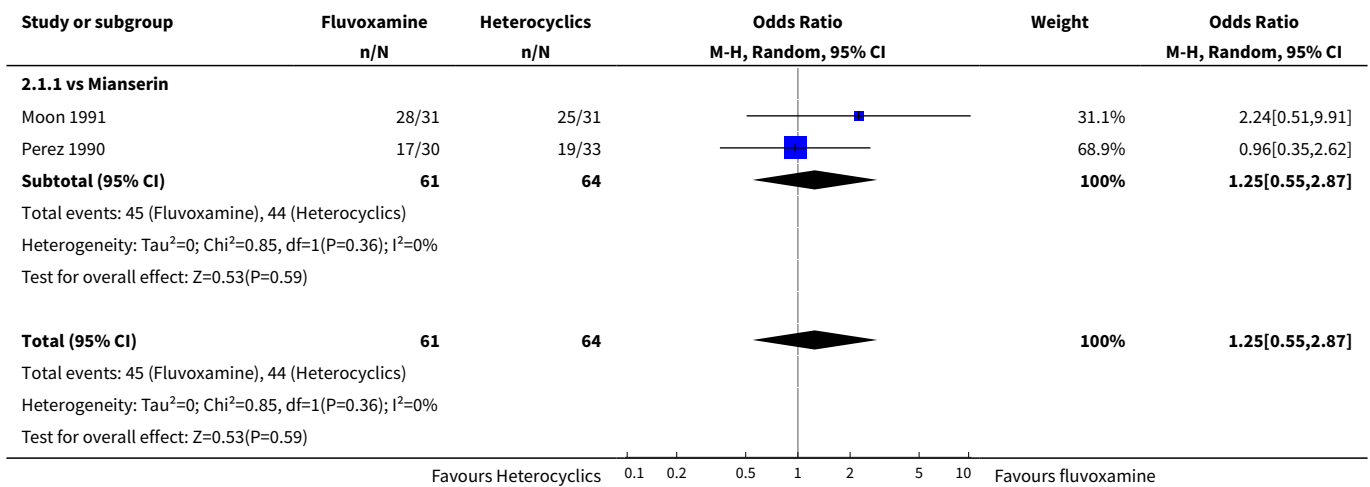
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response (acute phase): Primary outcome	2	125	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.55, 2.87]
1.1 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.55, 2.87]
2 Response (early phase)	3	122	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.45, 1.94]
2.1 vs Amineptine	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.26, 3.87]
2.2 vs Maprotiline	2	82	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.38, 2.17]
3 Remission (early phase)	3	122	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.50, 3.13]
3.1 vs Amineptine	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.89]
3.2 vs Maprotiline	2	82	Odds Ratio (M-H, Random, 95% CI)	1.32 [0.47, 3.69]
4 Remission (acute phase)	2	125	Odds Ratio (M-H, Random, 95% CI)	2.02 [0.55, 7.39]
4.1 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	2.02 [0.55, 7.39]
5 Depression scale - Endpoint score: low=good (early phase)	2	80	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.54, 0.34]
5.1 vs Amineptine	1	39	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.90, 0.36]
5.2 vs Maprotiline	1	41	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.56, 0.66]
6 Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data			Other data	No numeric data
6.1 vs Maprotiline			Other data	No numeric data
7 Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data			Other data	No numeric data
7.1 vs Mianserin			Other data	No numeric data
8 Depression scale - Change score: decrease=good (early phase)	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.61, 0.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 vs Maprotiline	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.61, 0.63]
9 Depression scale - Change score: decrease=good (early phase) - missing SDs			Other data	No numeric data
9.1 vs Amineptine			Other data	No numeric data
9.2 vs Maprotiline			Other data	No numeric data
9.3 vs Mianserin			Other data	No numeric data
10 Depression scale - Change score: decrease=good (acute phase) - missing SDs			Other data	No numeric data
10.3 vs Mianserin			Other data	No numeric data
11 Total Dropout	5	247	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.25, 1.34]
11.1 vs Amineptine	1	40	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.09, 4.24]
11.2 vs Maprotiline	2	82	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.26]
11.3 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.11, 2.65]
12 Dropout due to inefficacy	5	247	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.06, 3.14]
12.1 vs Amineptine	1	40	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.26]
12.2 vs Maprotiline	2	82	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.05, 6.21]
13 Dropout due to side effects	5	247	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.33, 1.97]
13.1 vs Amineptine	1	40	Odds Ratio (M-H, Random, 95% CI)	3.15 [0.12, 82.16]
13.2 vs Maprotiline	2	82	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.26]
13.3 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.20, 2.77]

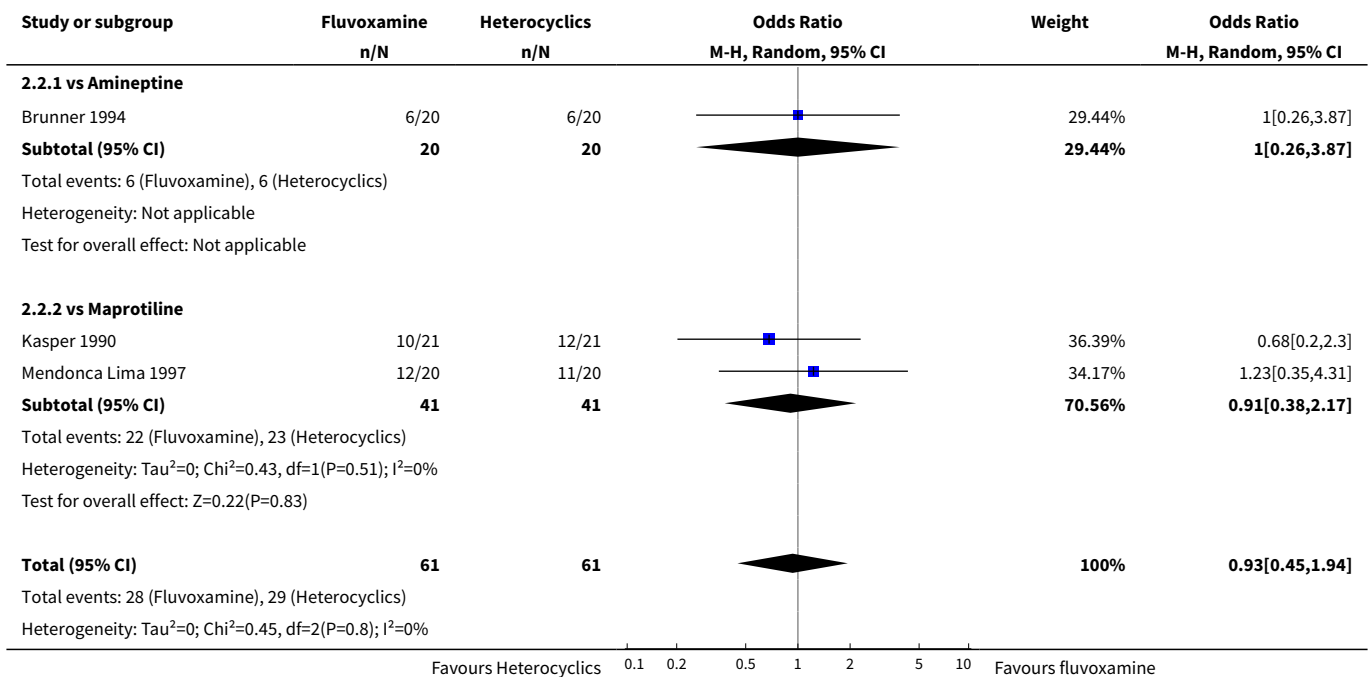
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Number of patients experiencing at least one side effect	3	144	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.46, 3.31]
14.1 vs Maprotiline	2	82	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.17, 6.00]
14.2 vs Mianserin	1	62	Odds Ratio (M-H, Random, 95% CI)	1.77 [0.62, 5.06]
15 Sensitivity analysis - Response (acute phase) 3. Worst case scenario ITT	2	125	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.10, 5.62]
15.1 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.10, 5.62]
16 Sensitivity analysis - Response (acute phase) 4. Best case scenario ITT	2	125	Odds Ratio (M-H, Random, 95% CI)	3.04 [1.20, 7.67]
16.1 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	3.04 [1.20, 7.67]
17 Sensitivity analysis - Response (acute phase) 5. Excluding trials with imputation methods for calculating response	1	62	Odds Ratio (M-H, Random, 95% CI)	2.24 [0.51, 9.91]
17.1 vs Mianserin	1	62	Odds Ratio (M-H, Random, 95% CI)	2.24 [0.51, 9.91]
18 Sensitivity analysis - Response (acute phase) 6. Wish bias - Fluvoxamine as an investigational drug	1	62	Odds Ratio (M-H, Random, 95% CI)	2.24 [0.51, 9.91]
18.1 vs Mianserin	1	62	Odds Ratio (M-H, Random, 95% CI)	2.24 [0.51, 9.91]
19 Sensitivity analysis - Response (acute phase) 7. Funding - Trials funded by the fluvoxamine marketing company	2	125	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.55, 2.87]
19.1 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.55, 2.87]
20 Sensitivity analysis - Response (acute phase) 8. Excluding trials that might include patients with bipolar depression	2	125	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.55, 2.87]
20.1 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.55, 2.87]
21 Sensitivity analysis - Response (acute phase) 9. Excluding trials that	2	125	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.55, 2.87]

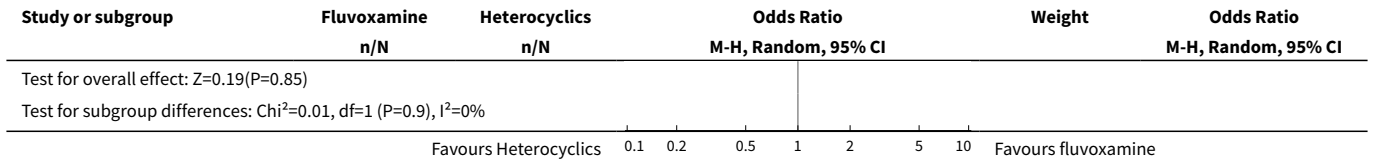
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
included patients with psychotic features				
21.1 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.55, 2.87]

Analysis 2.1. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 1 Response (acute phase): Primary outcome.

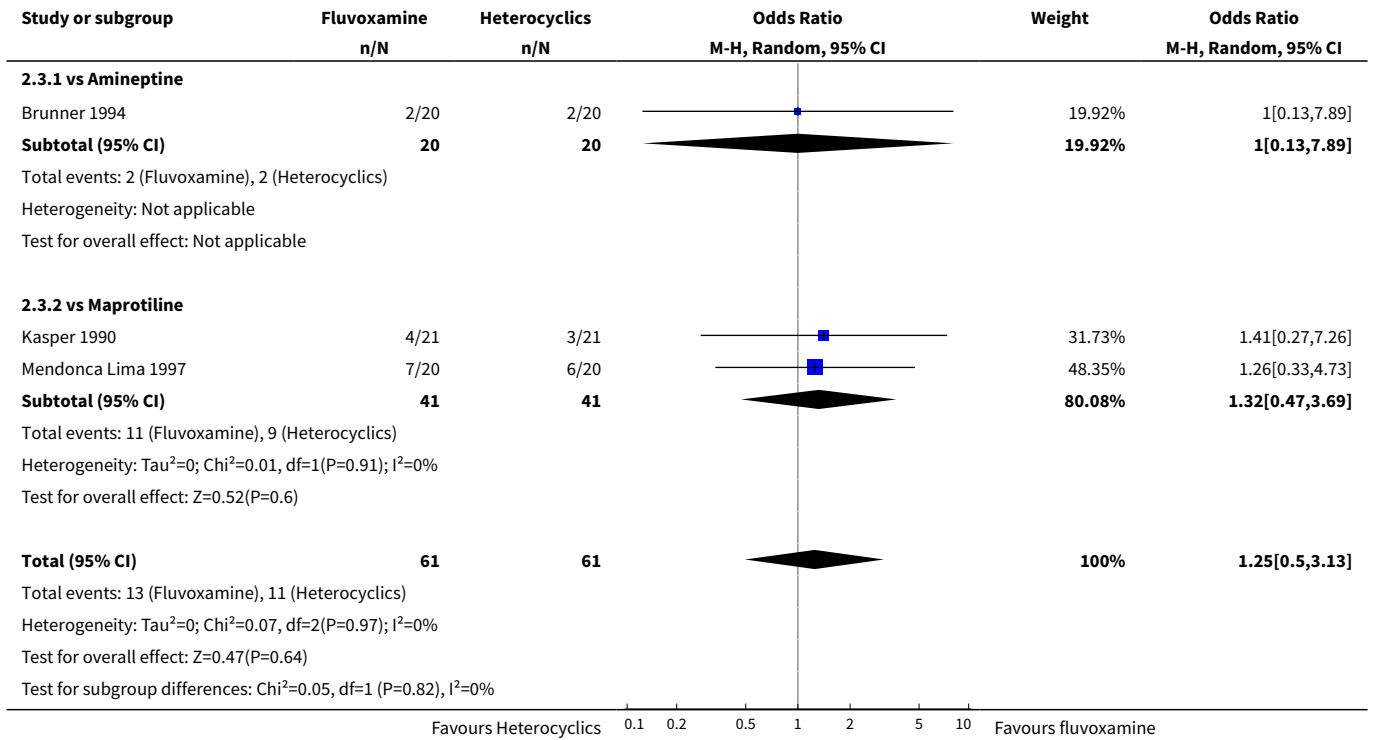


Analysis 2.2. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 2 Response (early phase).

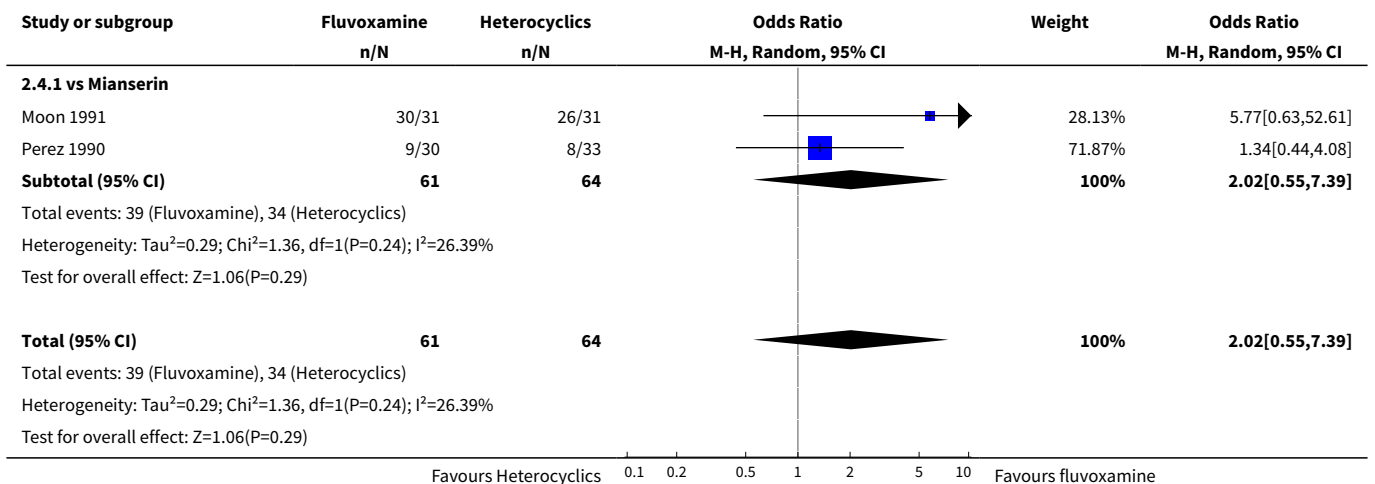




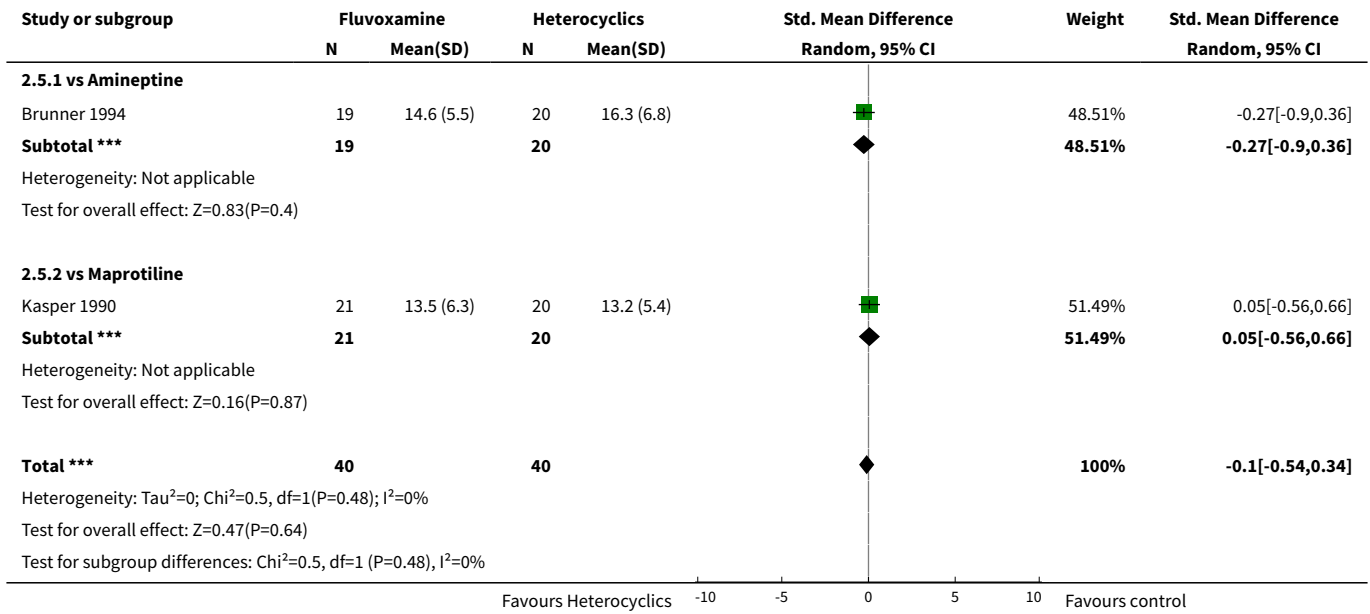
Analysis 2.3. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 3 Remission (early phase).



Analysis 2.4. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 4 Remission (acute phase).



Analysis 2.5. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 5 Depression scale - Endpoint score: low=good (early phase).



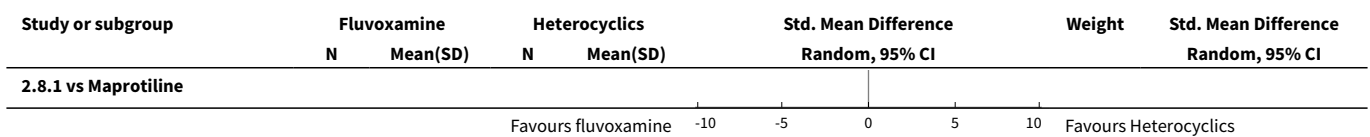
Analysis 2.6. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 6 Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data.

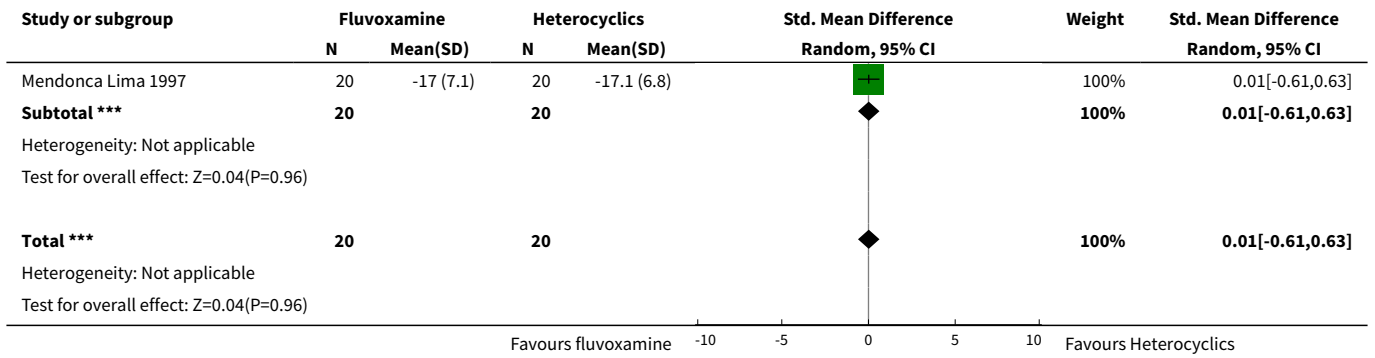
Study	Depression scale	Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Maprotiline								
Mendonca Lima 1997	MADRS	13.4	missing	20	14.0	missing	20	

Analysis 2.7. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 7 Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data.

Study	Depression scale	Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Mianserin								
Perez 1990	MADRS	11.9	7.5	22	13.6	7.5	25	skewed.

Analysis 2.8. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 8 Depression scale - Change score: decrease=good (early phase).





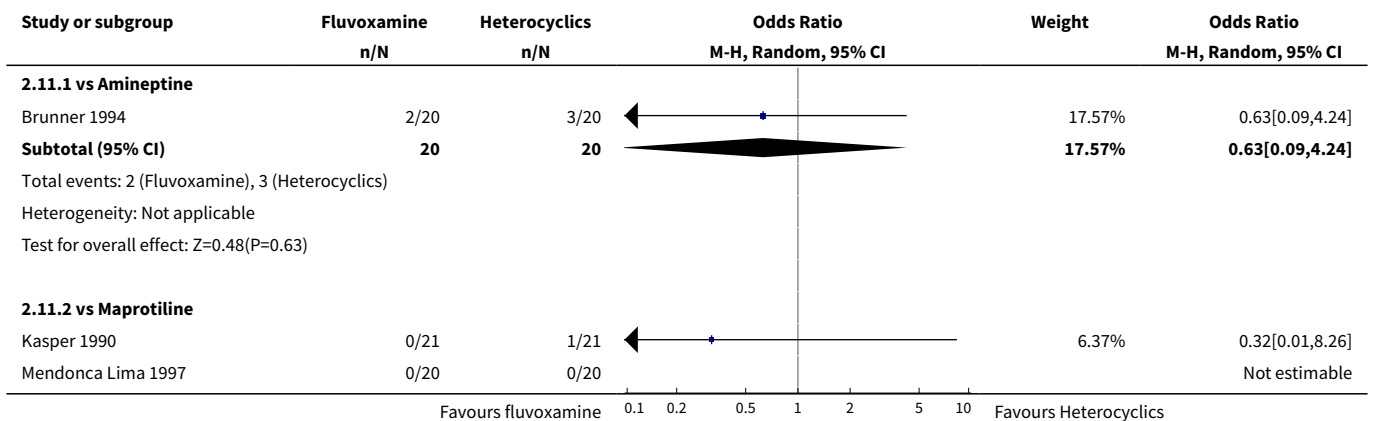
Analysis 2.9. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 9 Depression scale - Change score: decrease=good (early phase) - missing SDs.

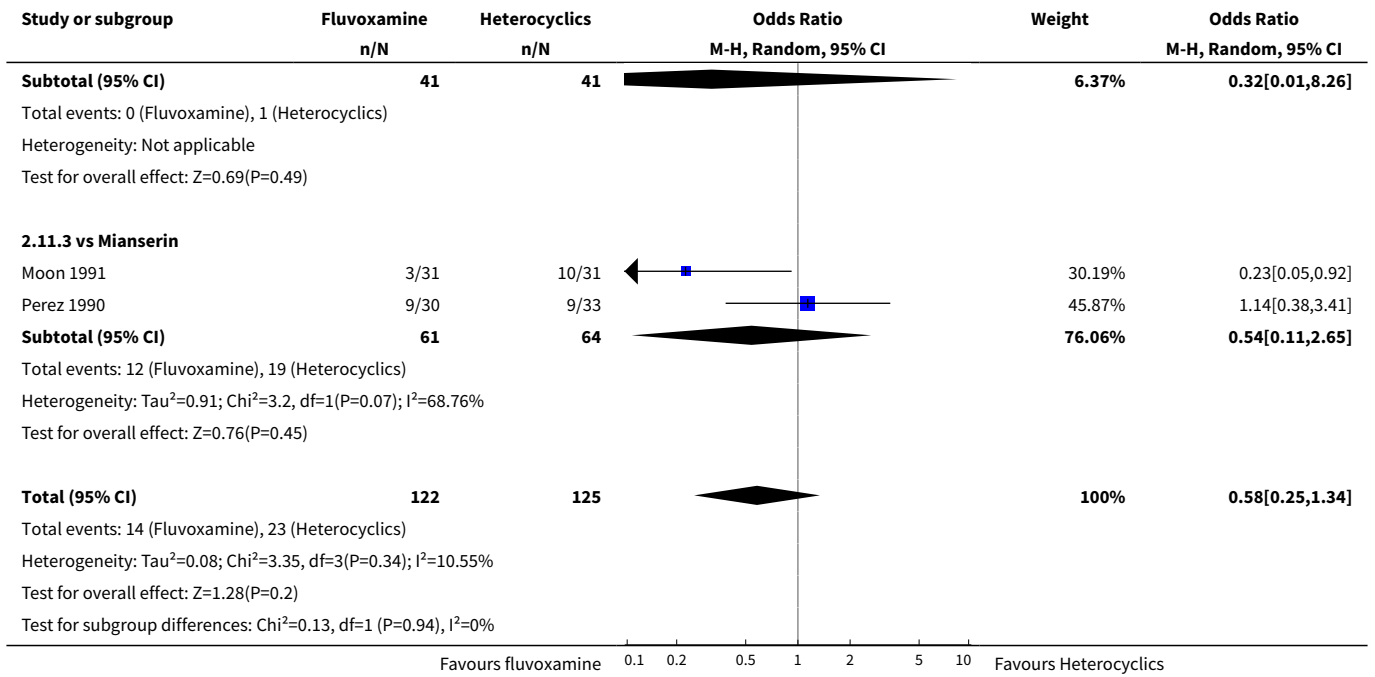
Depression scale - Change score: decrease=good (early phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
vs Amineptine								
Brunner 1994	HRSD-17	-9.7	missing	19	-8.5	missing	20	
vs Maprotiline								
Kasper 1990	HRSD-21	-12.5	missing	21	-15.4	missing	20	
vs Mianserin								
Moon 1991	MADRS	-10	missing	28	-11.5	missing	21	

Analysis 2.10. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 10 Depression scale - Change score: decrease=good (acute phase) - missing SDs.

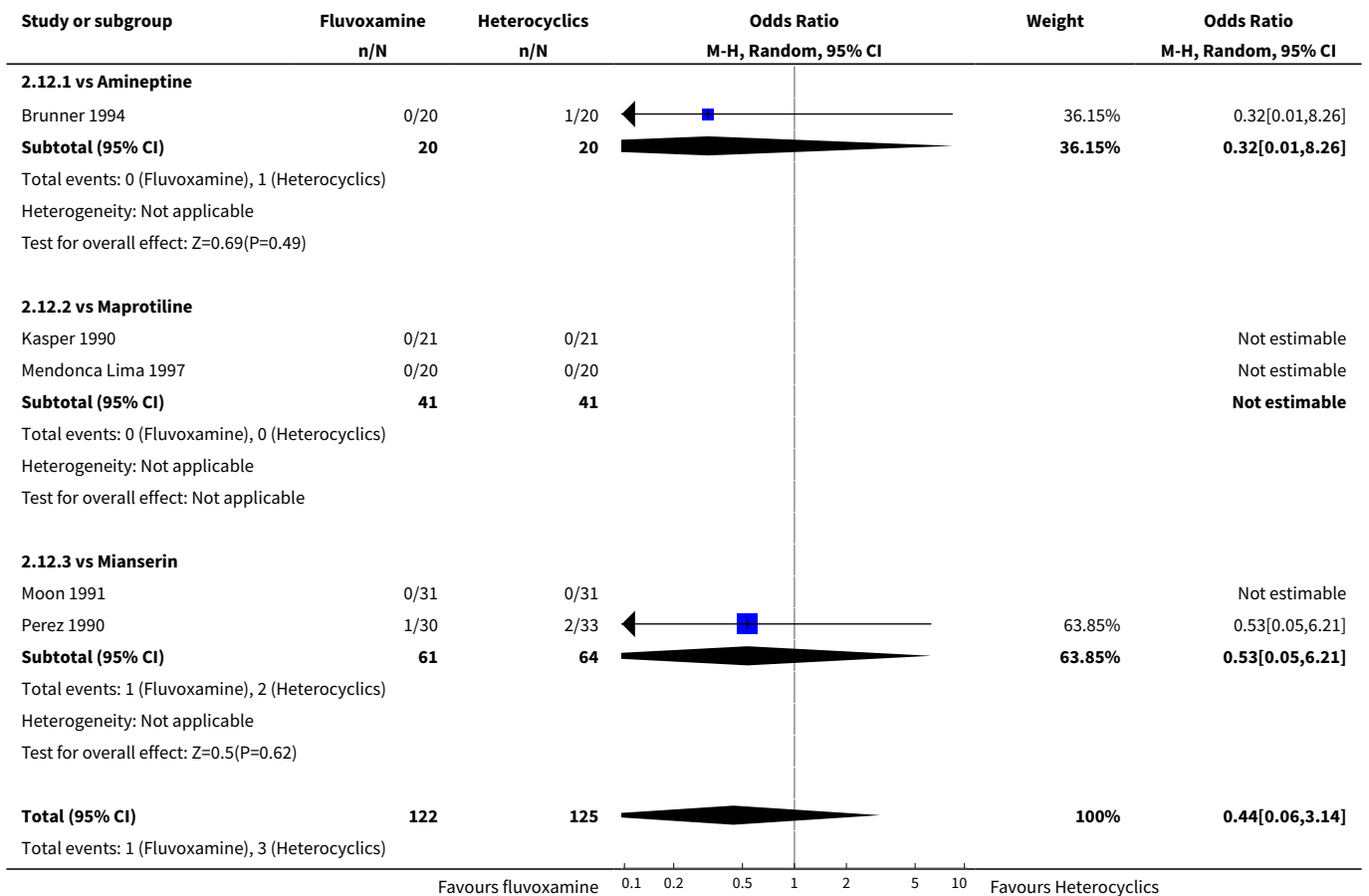
Depression scale - Change score: decrease=good (acute phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
vs Mianserin								
Moon 1991	MADRS	-22	missing	28	-24.1	missing	21	
Perez 1990	MADRS	-23.9	missing	22	-23.6	missing	25	

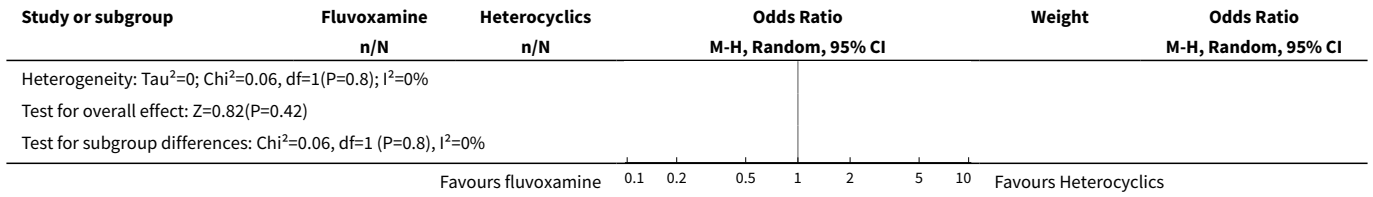
Analysis 2.11. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 11 Total Dropout.



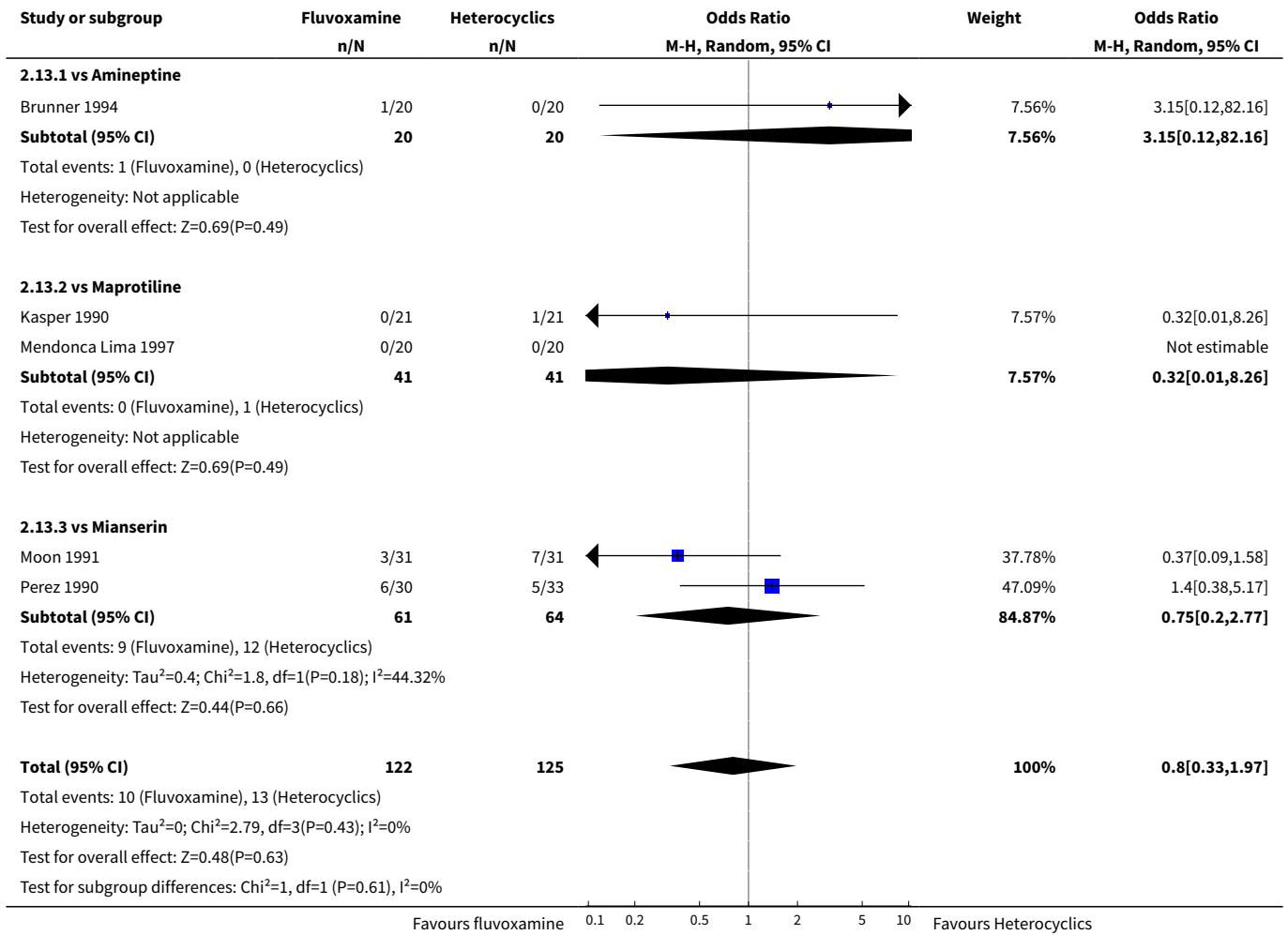


Analysis 2.12. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 12 Dropout due to inefficacy.

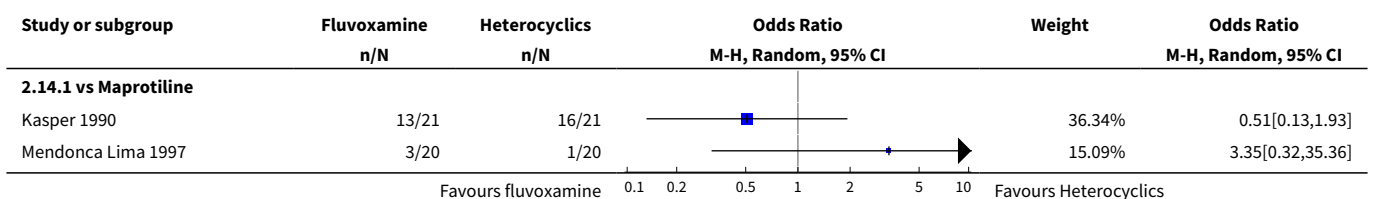


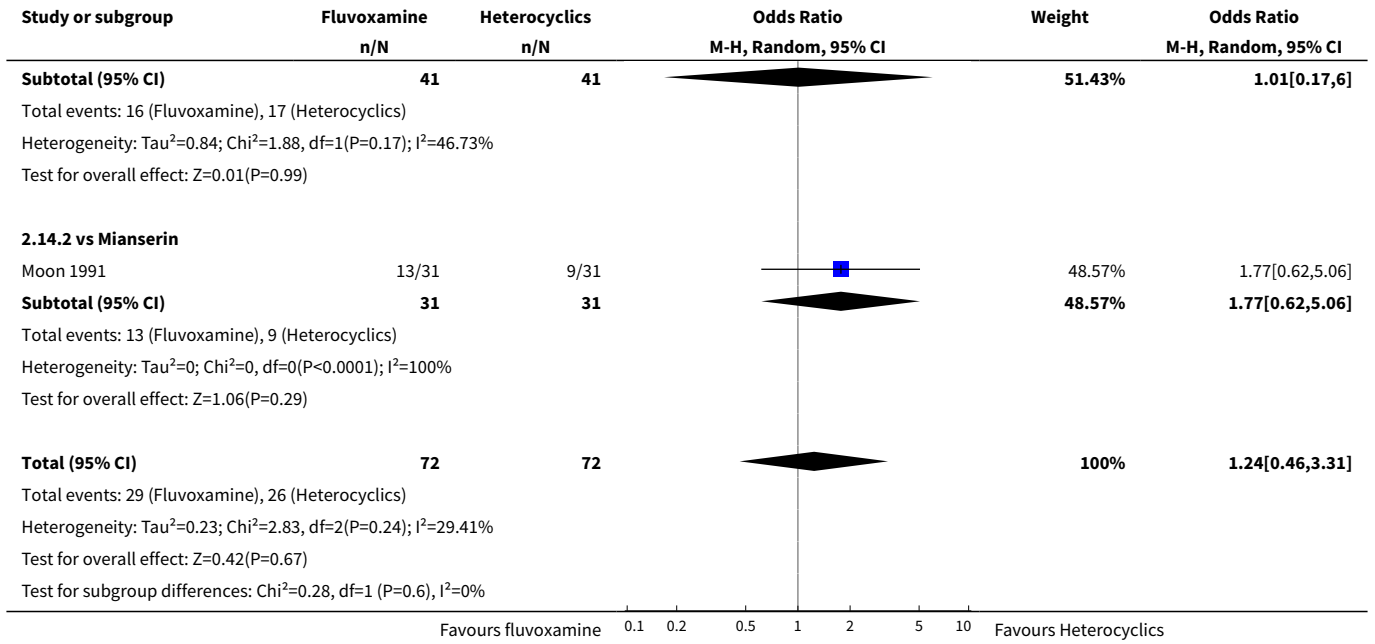


Analysis 2.13. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 13 Dropout due to side effects.

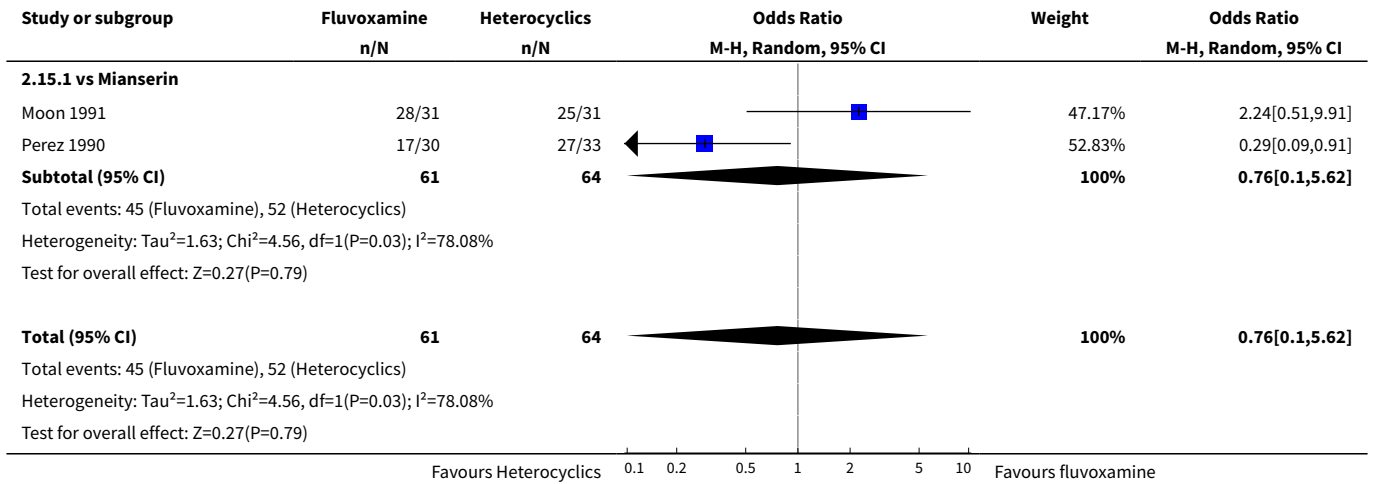


Analysis 2.14. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 14 Number of patients experiencing at least one side effect.

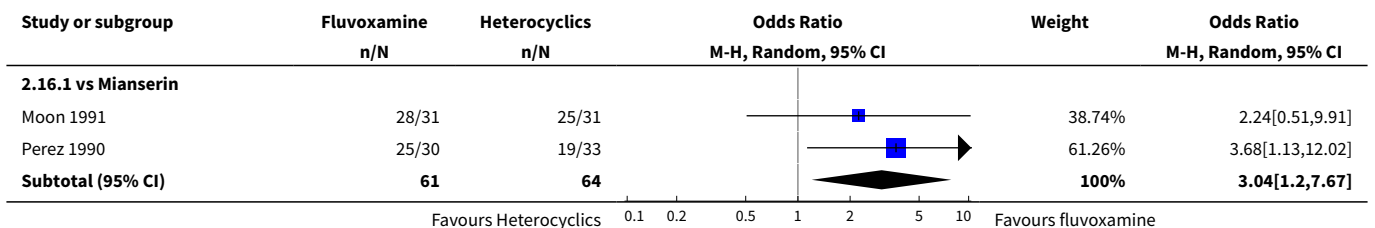


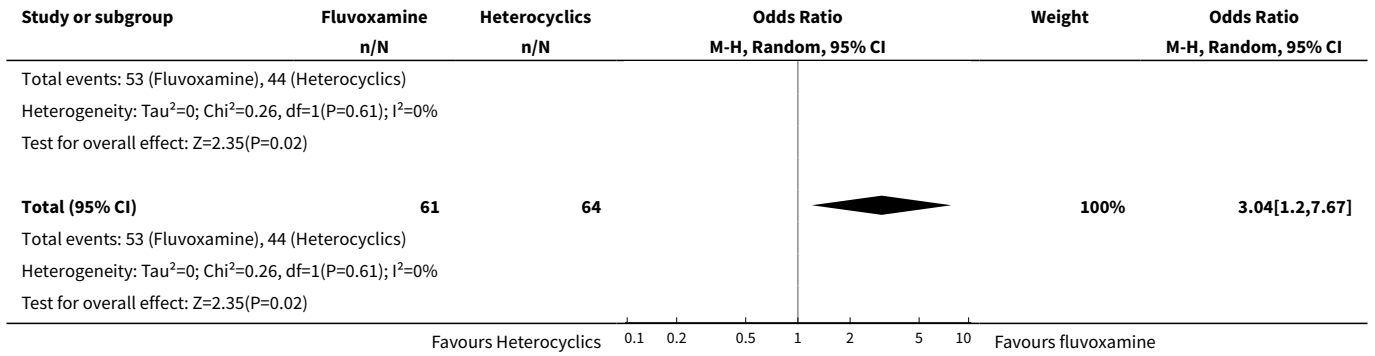


Analysis 2.15. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 15 Sensitivity analysis - Response (acute phase) 3. Worst case scenario ITT.

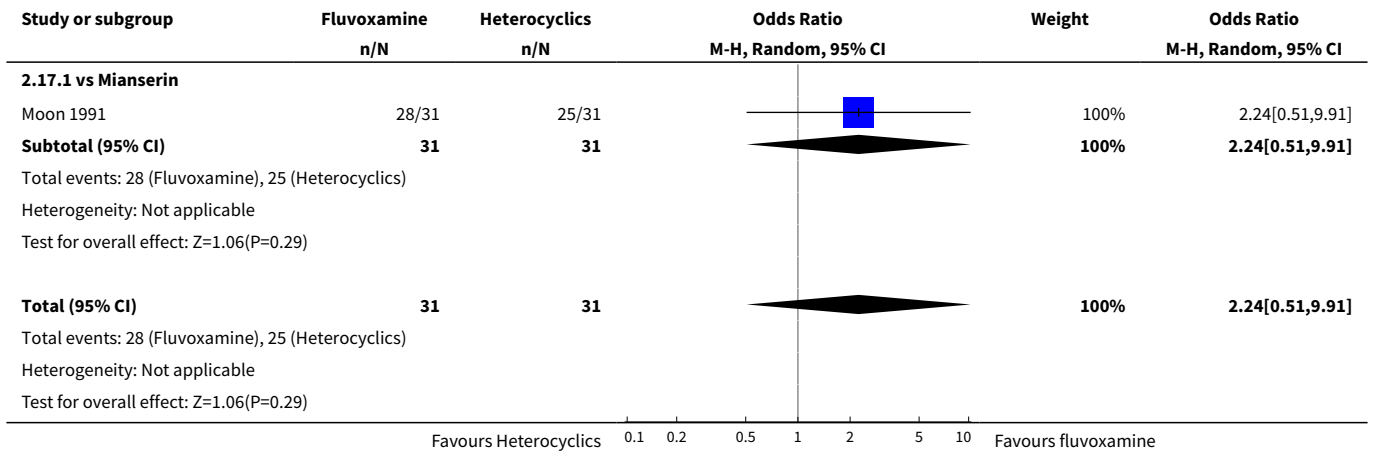


Analysis 2.16. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 16 Sensitivity analysis - Response (acute phase) 4. Best case scenario ITT.

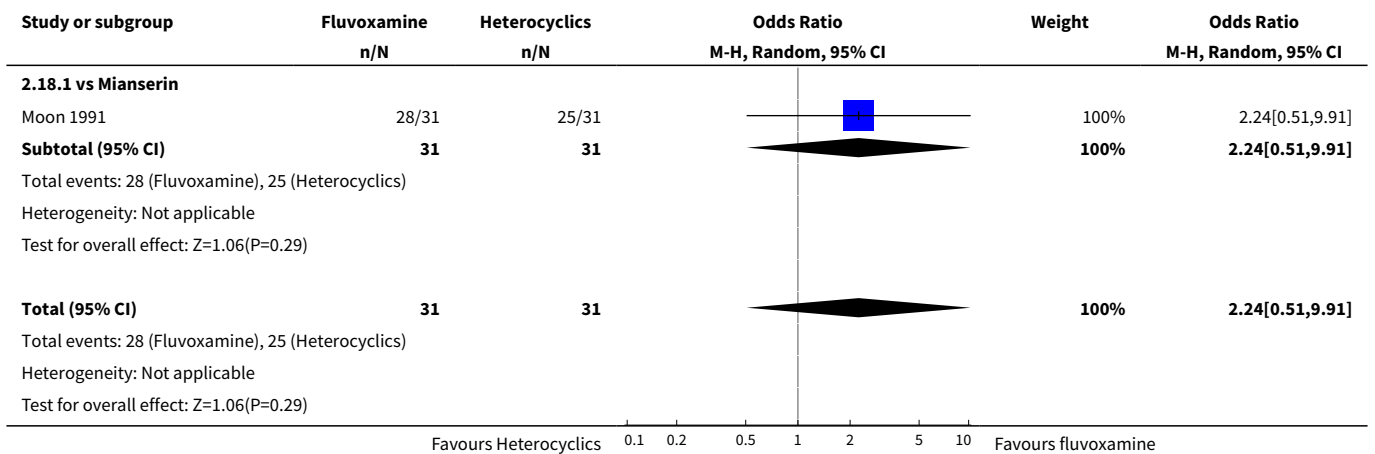




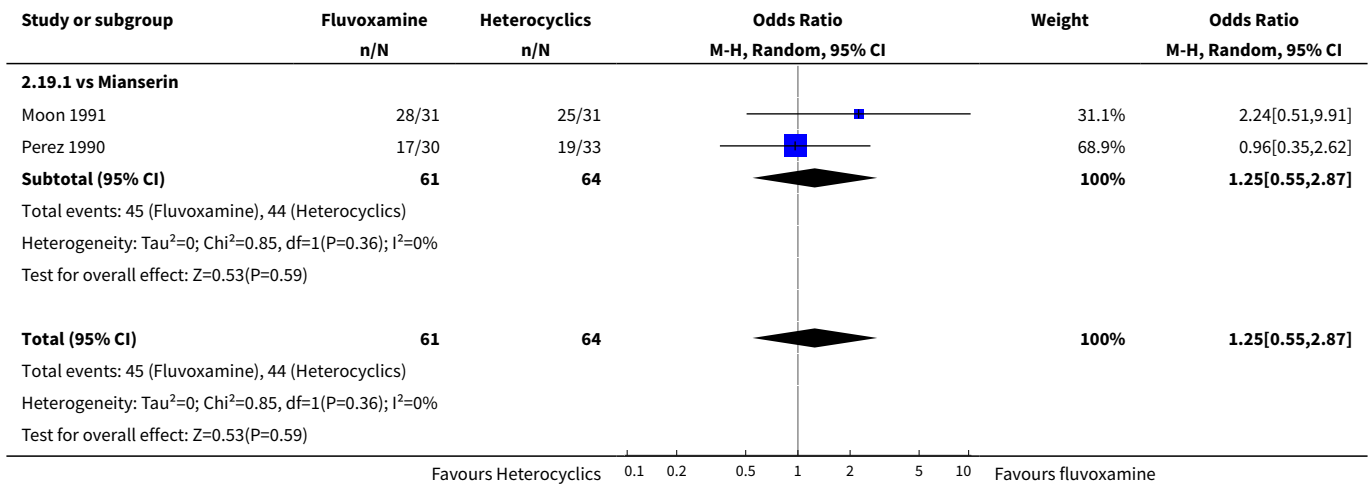
Analysis 2.17. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 17 Sensitivity analysis - Response (acute phase) 5. Excluding trials with imputation methods for calculating response.



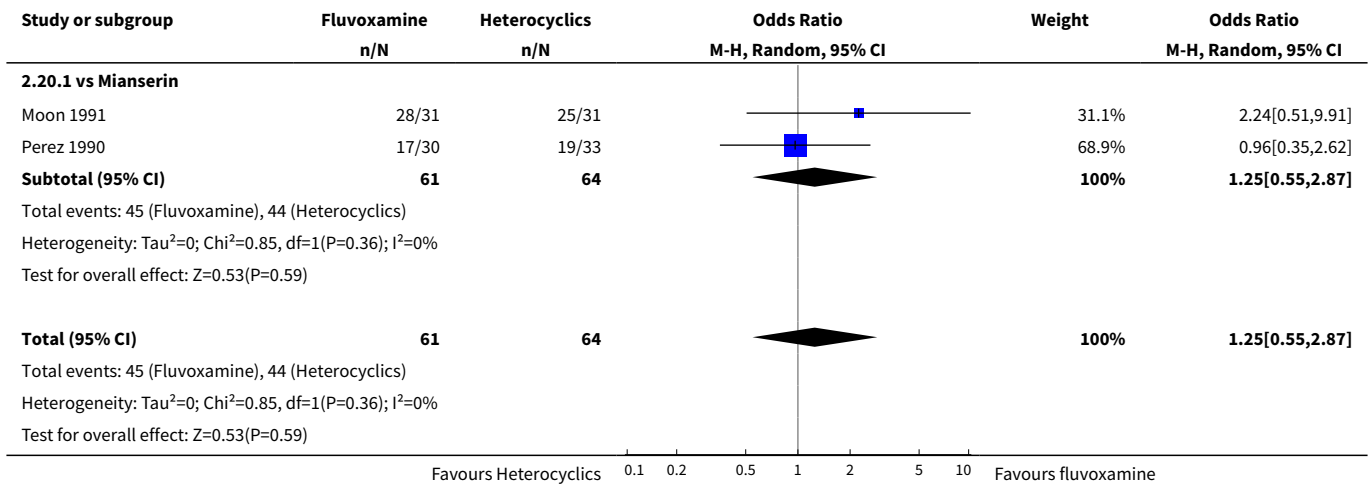
Analysis 2.18. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 18 Sensitivity analysis - Response (acute phase) 6. Wish bias - Fluvoxamine as an investigational drug.



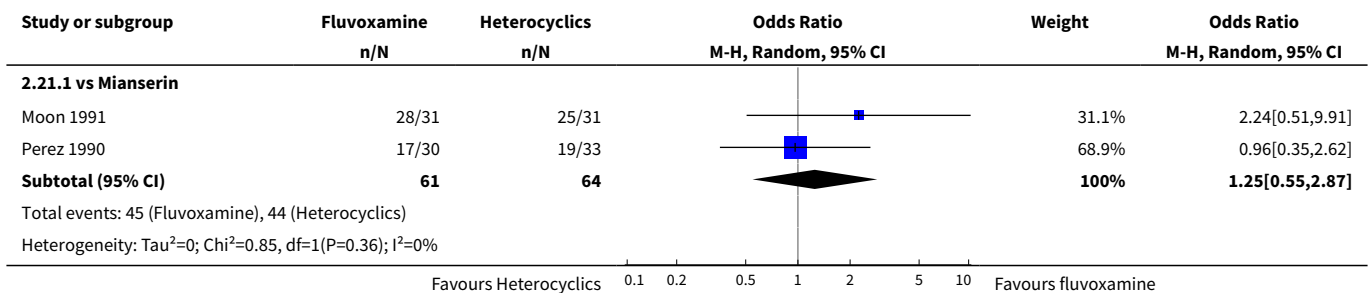
Analysis 2.19. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 19 Sensitivity analysis - Response (acute phase) 7. Funding - Trials funded by the fluvoxamine marketing company.

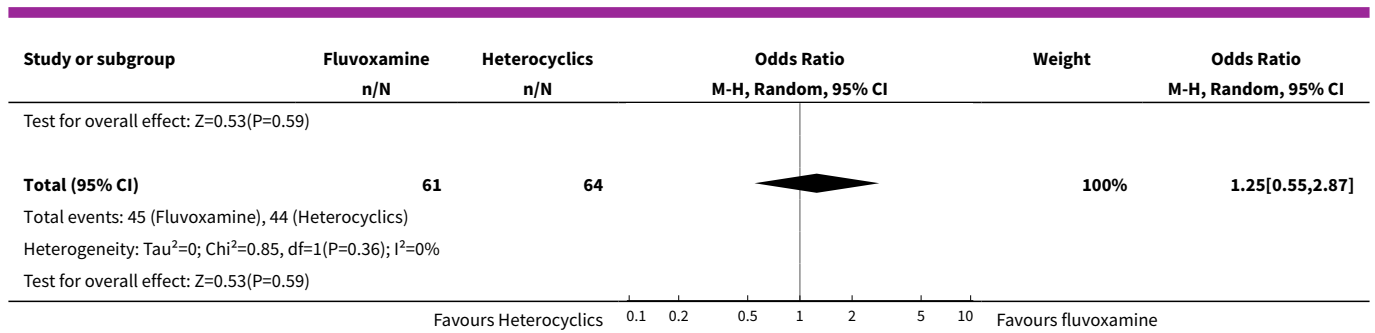


Analysis 2.20. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 20 Sensitivity analysis - Response (acute phase) 8. Excluding trials that might include patients with bipolar depression.



Analysis 2.21. Comparison 2 Fluvoxamine versus Heterocyclics, Outcome 21 Sensitivity analysis - Response (acute phase) 9. Excluding trials that included patients with psychotic features.





Comparison 3. Fluvoxamine versus other SSRIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response (acute phase): Primary outcome	8	967	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.74, 1.25]
1.1 vs Paroxetine	3	281	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.51, 1.34]
1.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.53, 2.75]
1.3 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.62, 1.61]
1.4 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.50, 1.62]
2 Response (early phase)	8	967	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.68, 1.42]
2.1 vs Paroxetine	3	281	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.41, 1.24]
2.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	1.32 [0.58, 2.98]
2.3 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.45, 3.41]
2.4 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.19, 1.90]
3 Remission (early phase)	7	783	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.42, 1.38]
3.1 vs Paroxetine	3	281	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.25, 1.67]
3.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.29, 2.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 vs Fluoxetine	1	100	Odds Ratio (M-H, Random, 95% CI)	0.8 [0.25, 2.57]
3.4 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.06, 16.04]
4 Remission (acute phase)	8	967	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.71, 1.37]
4.1 vs Paroxetine	3	281	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.45, 1.33]
4.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.48, 3.57]
4.3 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.74, 2.06]
4.4 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.23, 1.34]
5 Depression scale - Endpoint score: low=good (early phase)	2	177	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.35, 0.24]
5.1 vs Paroxetine	1	93	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.47, 0.34]
5.2 vs Sertraline	1	84	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.46, 0.39]
6 Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data			Other data	No numeric data
6.1 vs Paroxetine			Other data	No numeric data
6.2 vs Sertraline			Other data	No numeric data
6.3 vs Citalopram			Other data	No numeric data
6.4 vs Fluoxetine			Other data	No numeric data
7 Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data			Other data	No numeric data
7.1 vs Paroxetine			Other data	No numeric data
7.2 vs Sertraline			Other data	No numeric data
7.3 vs Fluoxetine			Other data	No numeric data
7.4 vs Citalopram			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Depression scale - Change score: decrease=good (early phase)	1	80	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.24, 0.64]
8.1 vs Paroxetine	1	80	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.24, 0.64]
9 Depression scale - Change score: decrease=good (early phase) - missing SDs			Other data	No numeric data
9.1 vs Paroxetine			Other data	No numeric data
9.2 vs Sertraline			Other data	No numeric data
9.3 vs Citalopram			Other data	No numeric data
9.4 vs Fluoxetine			Other data	No numeric data
10 Depression scale - Change score: decrease=good (acute phase)	3	230	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.23, 0.42]
10.1 vs Paroxetine	2	138	Std. Mean Difference (IV, Random, 95% CI)	0.19 [-0.31, 0.68]
10.2 vs Sertraline	1	92	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.47, 0.35]
11 Depression scale - Change score: decrease=good (acute phase) - missing SDs			Other data	No numeric data
11.1 vs Paroxetine			Other data	No numeric data
11.2 vs Sertraline			Other data	No numeric data
11.3 vs Citalopram			Other data	No numeric data
11.4 vs Fluoxetine			Other data	No numeric data
12 Total Dropout	9	1126	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.93, 1.69]
12.1 vs Paroxetine	4	334	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.62, 1.73]
12.2 vs Sertraline	3	238	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.24, 5.37]
12.3 vs Fluoxetine	3	337	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.65, 2.00]
12.4 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	1.42 [0.75, 2.67]

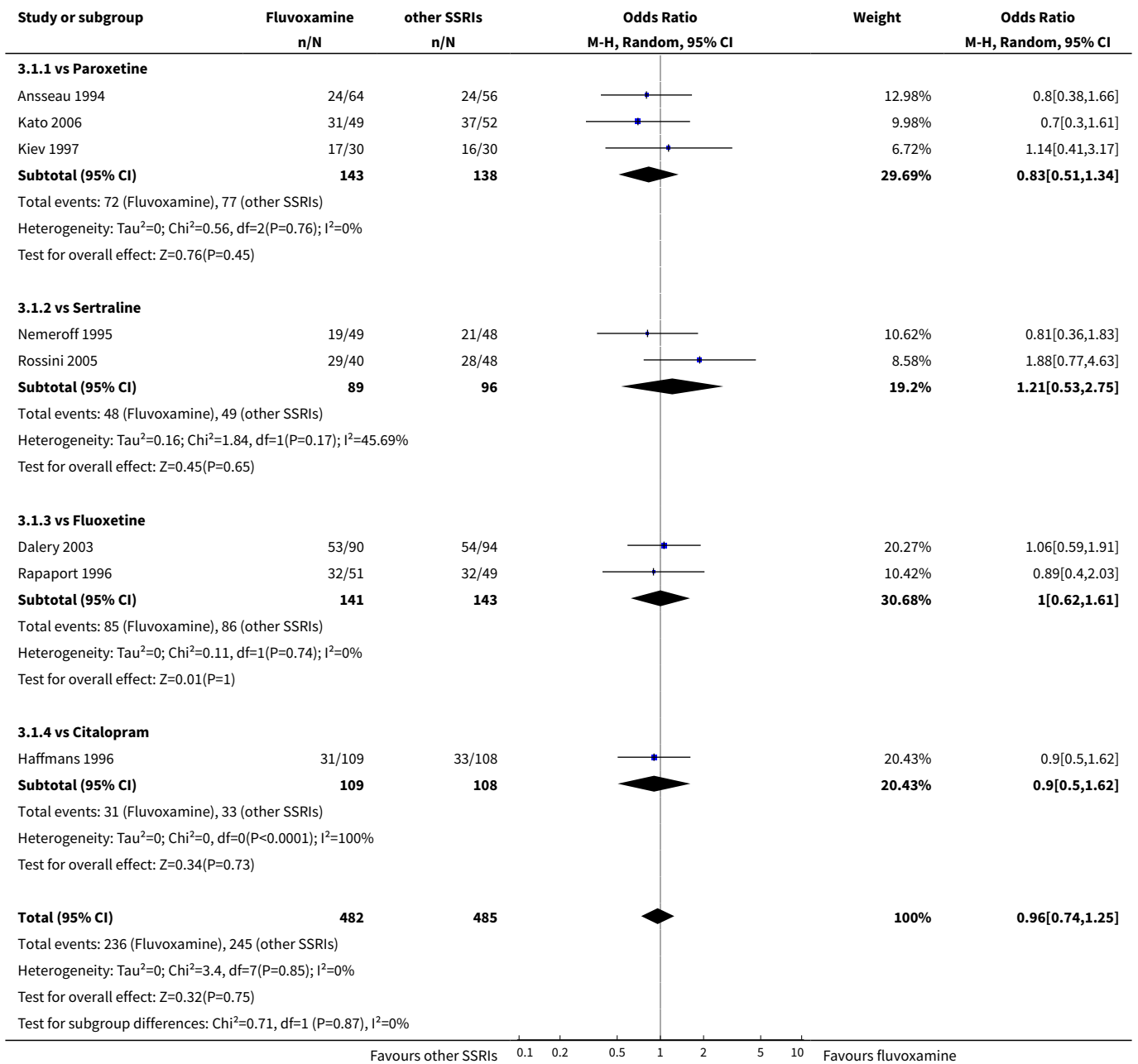
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Dropout due to inefficacy	4	365	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.33, 6.33]
13.1 vs Paroxetine	2	180	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.14, 6.87]
13.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	5.11 [0.24, 109.17]
14 Dropout due to side effects	8	942	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.62, 2.28]
14.1 vs Paroxetine	4	334	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.28, 3.26]
14.2 vs Sertraline	3	238	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.15, 11.33]
14.3 vs Fluoxetine	2	153	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.19, 3.89]
14.4 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	1.80 [0.90, 3.59]
15 Number of patients experiencing at least one side effect	5	478	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.53, 1.51]
15.1 vs Paroxetine	3	281	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.41, 2.23]
15.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.21, 2.37]
15.3 vs Fluoxetine	1	100	Odds Ratio (M-H, Random, 95% CI)	0.5 [0.09, 2.86]
16 Subgroup analysis - Response (acute phase) 1. Fluvoxamine dosing - Standard dosage	5	542	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.65, 1.30]
16.1 vs Paroxetine	2	161	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.45, 1.62]
16.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.36, 1.83]
16.3 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.62, 1.61]
17 Subgroup analysis - Response (acute phase) 1. Fluvoxamine dosing - High dosage	3	425	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.65, 1.60]
17.1 vs Paroxetine	1	120	Odds Ratio (M-H, Random, 95% CI)	0.8 [0.38, 1.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.2 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.50, 1.62]
17.3 vs Sertraline	1	88	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.77, 4.63]
18 Subgroup analysis - Response (acute phase) 2. Comparator dosing - Standard dosage	2	304	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.60, 1.50]
18.1 vs Paroxetine	1	120	Odds Ratio (M-H, Random, 95% CI)	0.8 [0.38, 1.66]
18.2 vs Fluoxetine	1	184	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.59, 1.91]
19 Subgroup analysis - Response (acute phase) 2. Comparator dosing - High dosage	6	663	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.33]
19.1 vs Paroxetine	2	161	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.45, 1.62]
19.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.53, 2.75]
19.3 vs Fluoxetine	1	100	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.40, 2.03]
19.4 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.50, 1.62]
20 Sensitivity analysis - Response (acute phase) 2. Excluding trials dropout rate >20%	2	188	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.61, 2.62]
20.1 vs Sertraline	1	88	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.77, 4.63]
20.2 vs Fluoxetine	1	100	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.40, 2.03]
21 Sensitivity analysis - Response (acute phase) 3. Worst case scenario ITT	8	967	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.43, 1.05]
21.1 vs Paroxetine	3	281	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.09, 1.15]
21.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.47, 1.99]
21.3 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.52, 1.35]

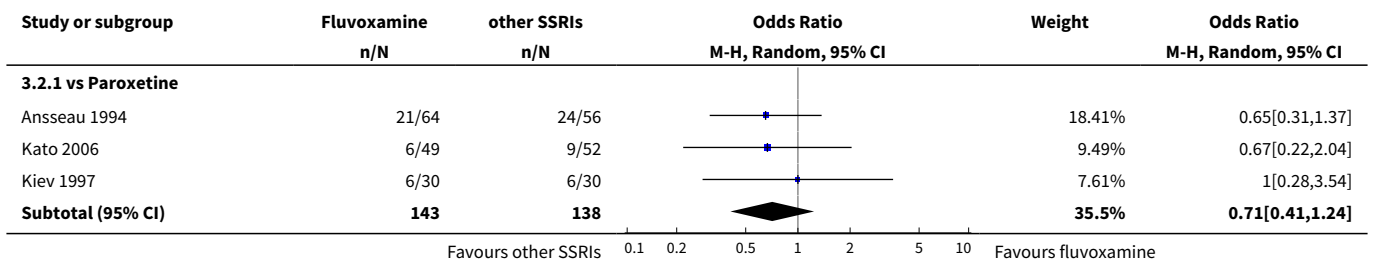
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.4 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.50, 1.62]
22 Sensitivity analysis - Response (acute phase) 4. Best case scenario ITT	8	967	Odds Ratio (M-H, Random, 95% CI)	1.33 [1.02, 1.74]
22.1 vs Paroxetine	3	281	Odds Ratio (M-H, Random, 95% CI)	1.77 [1.08, 2.92]
22.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.72, 2.90]
22.3 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.79, 2.07]
22.4 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.50, 1.62]
23 Sensitivity analysis - Response (acute phase) 5. Excluding trials with imputation methods for calculating response	4	622	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.24]
23.1 vs Paroxetine	2	221	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.43, 1.31]
23.2 vs Fluoxetine	1	184	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.59, 1.91]
23.3 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.50, 1.62]
24 Sensitivity analysis - Mean change from baseline (acute phase) 5. Excluding trials for which the SD had to be borrowed from other trials	3	230	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.23, 0.42]
24.1 vs Paroxetine	2	138	Std. Mean Difference (IV, Random, 95% CI)	0.19 [-0.31, 0.68]
24.2 vs Sertraline	1	92	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.47, 0.35]
25 Sensitivity analysis - Response (acute phase) 6. Wish bias - Fluvoxamine as an investigational drug	1	88	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.77, 4.63]
25.1 vs Sertraline	1	88	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.77, 4.63]
26 Sensitivity analysis - Response (acute phase) 7. Funding - Exclud-	3	425	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.65, 1.60]

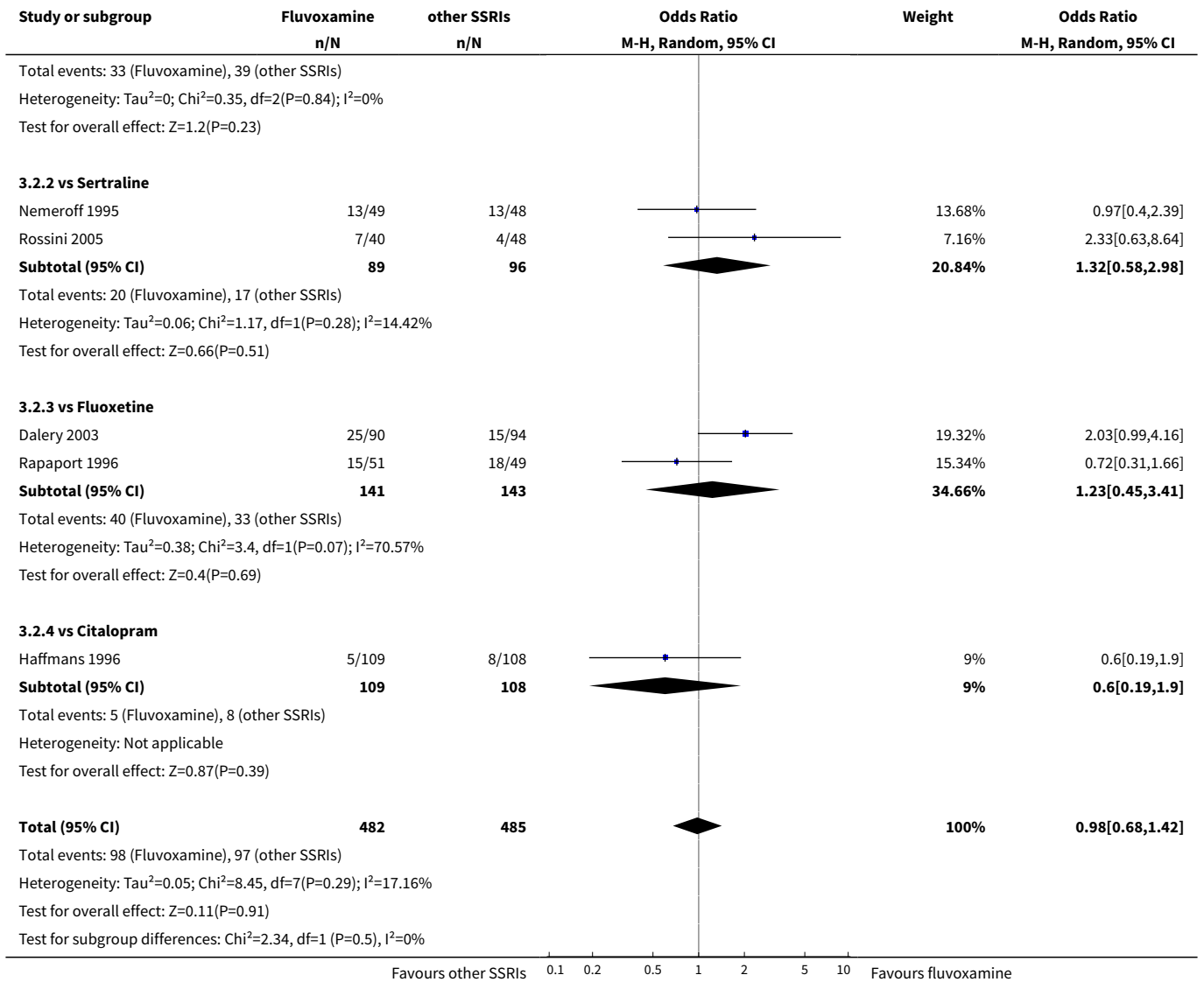
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
ing trials funded by the fluvoxamine marketing company				
26.1 vs Paroxetine	1	120	Odds Ratio (M-H, Random, 95% CI)	0.8 [0.38, 1.66]
26.2 vs Sertraline	1	88	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.77, 4.63]
26.3 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.50, 1.62]
27 Sensitivity analysis - Response (acute phase) 7. Funding - Trials funded by the fluvoxamine marketing company				
27.1 vs Paroxetine	2	161	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.45, 1.62]
27.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.36, 1.83]
27.3 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.62, 1.61]
28 Sensitivity analysis - Response (acute phase) 8. Excluding trials that might include patients with bipolar depression				
28.1 vs Paroxetine	2	161	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.45, 1.62]
28.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.36, 1.83]
29 Sensitivity analysis - Response (acute phase) 9. Excluding trials that included patients with psychotic features				
29.1 vs Paroxetine	2	161	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.45, 1.62]
29.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.53, 2.75]
29.3 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.62, 1.61]

Analysis 3.1. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 1 Response (acute phase): Primary outcome.

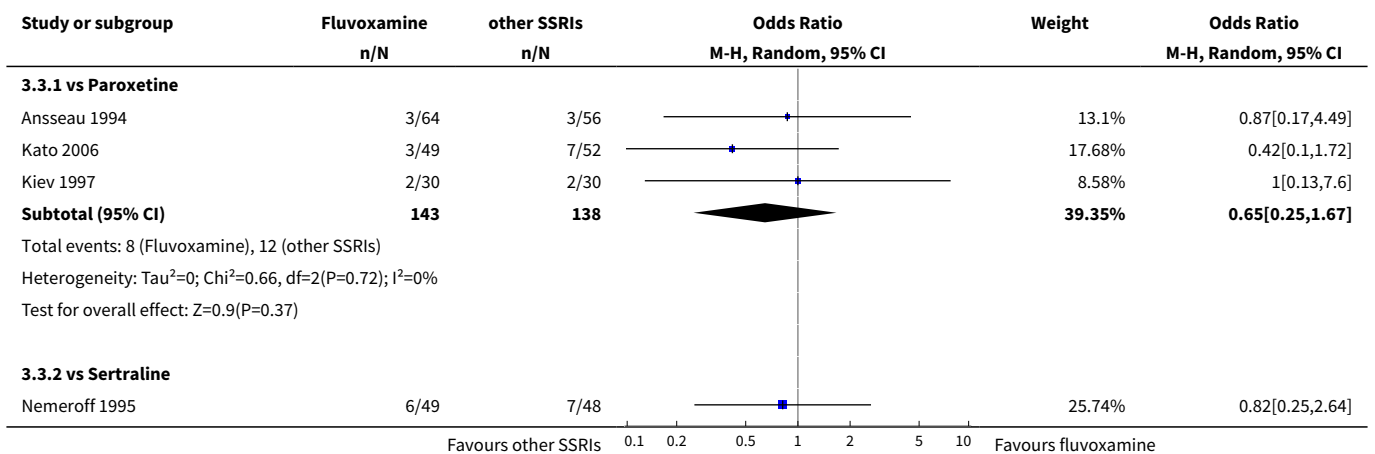


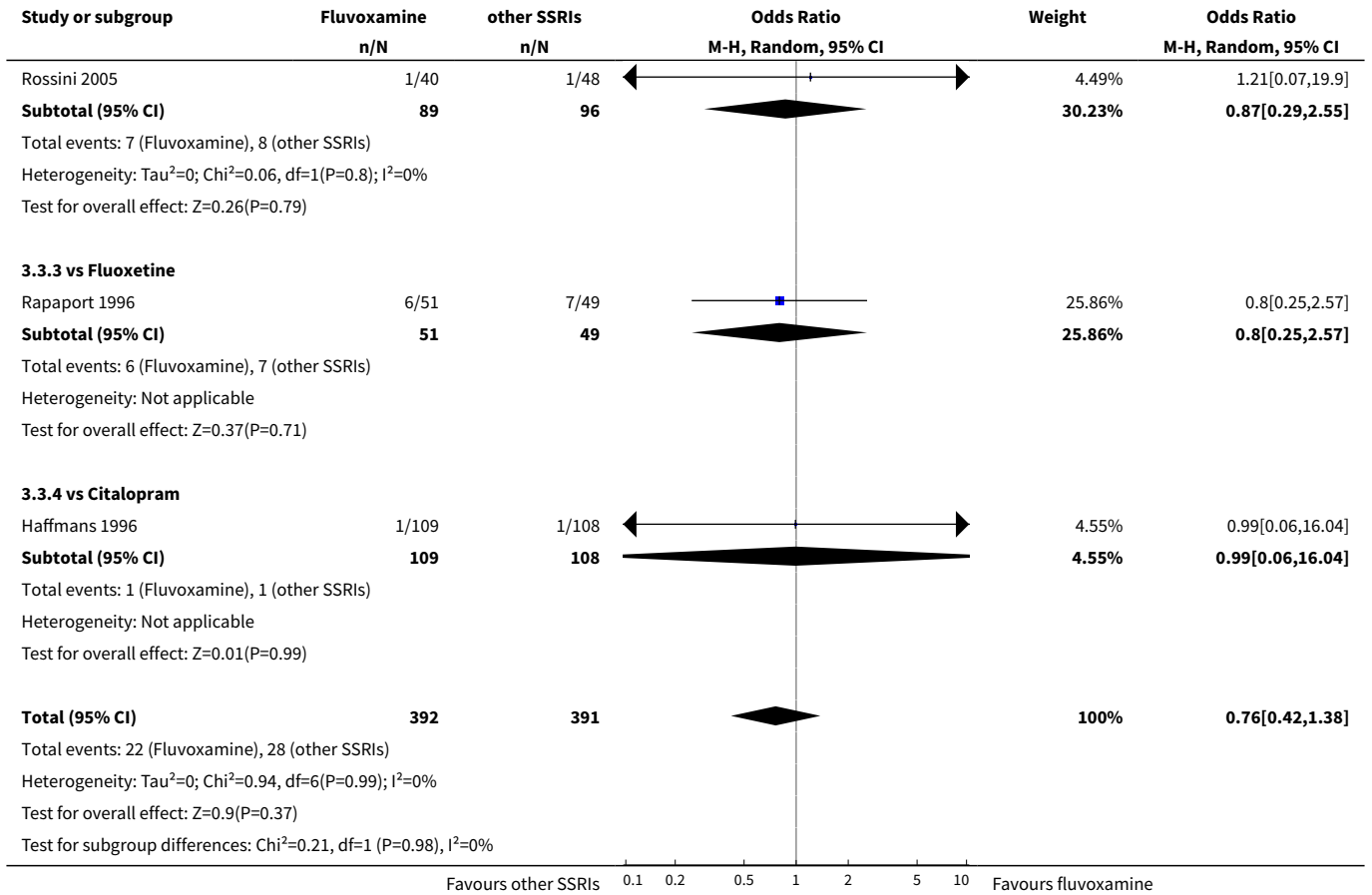
Analysis 3.2. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 2 Response (early phase).



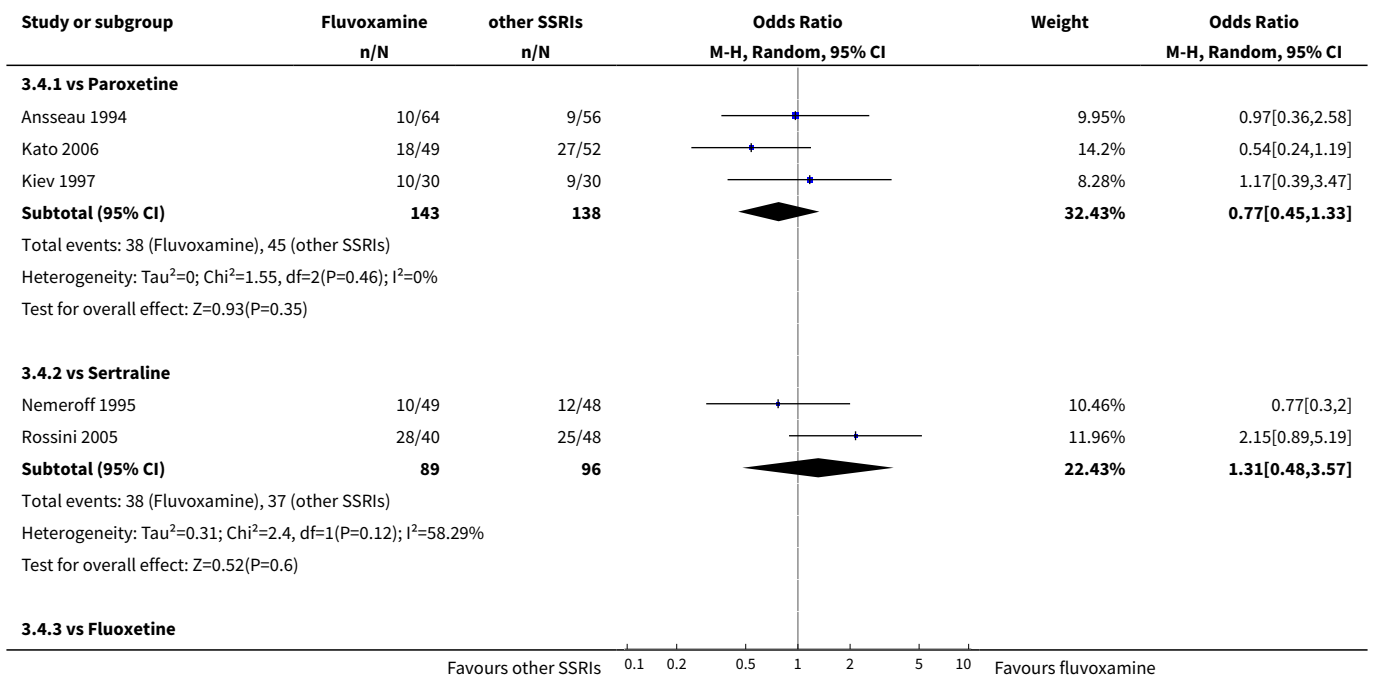


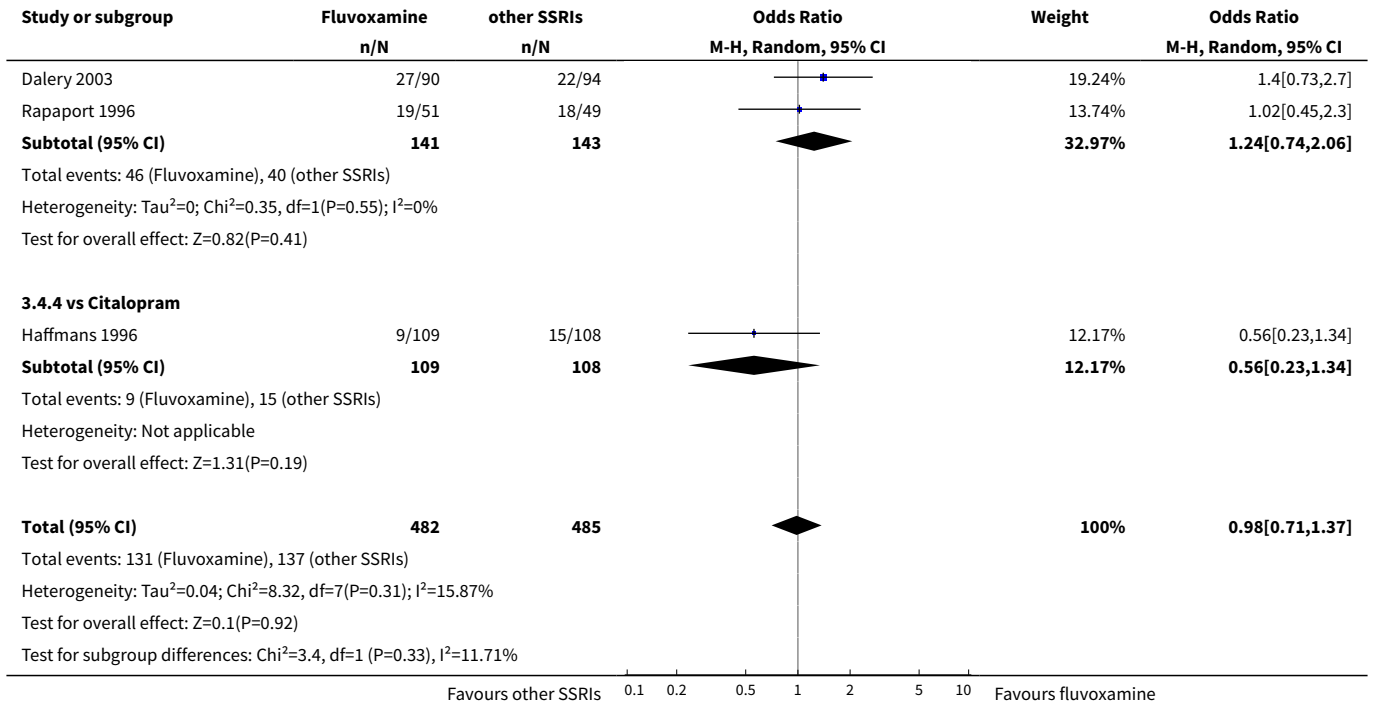
Analysis 3.3. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 3 Remission (early phase).



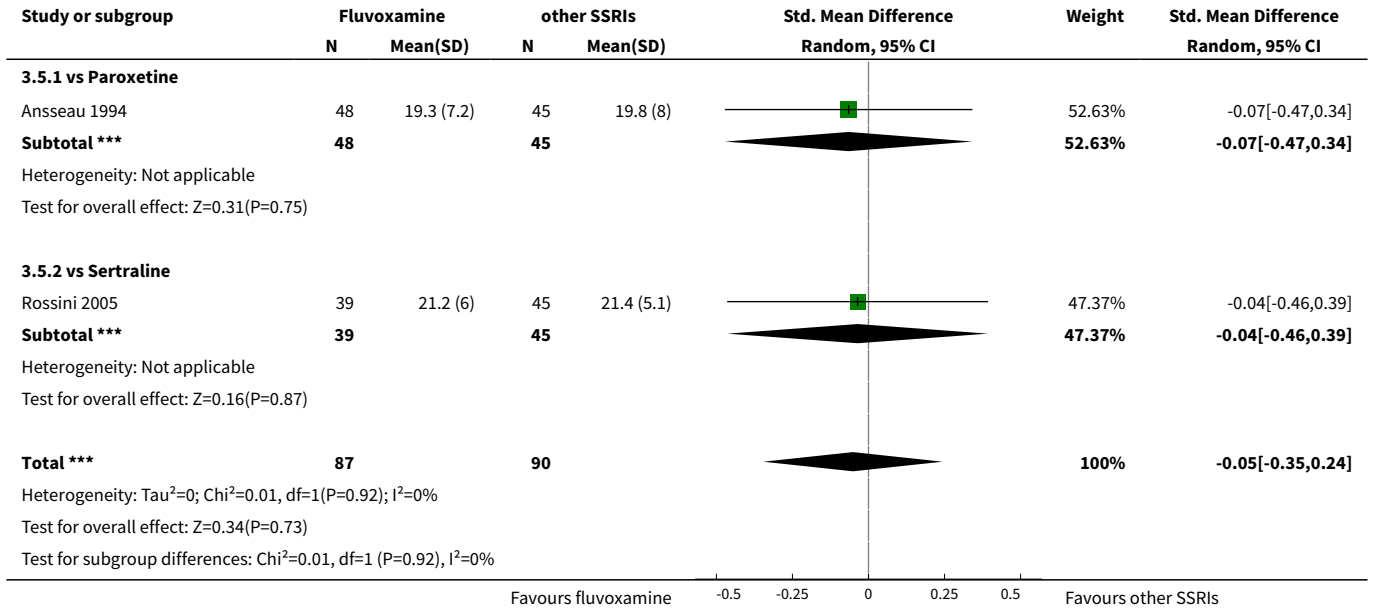


Analysis 3.4. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 4 Remission (acute phase).





Analysis 3.5. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 5 Depression scale - Endpoint score: low=good (early phase).



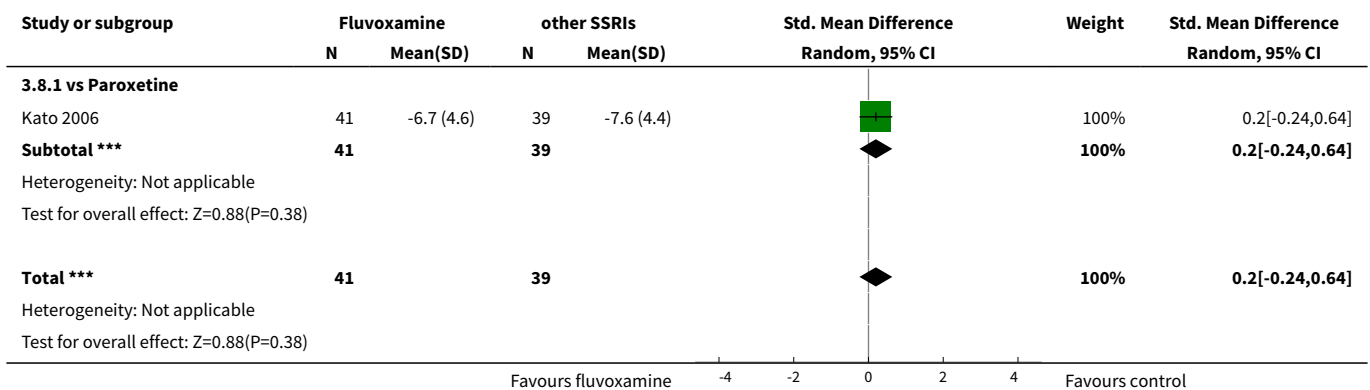
Analysis 3.6. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 6 Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data.

Study	Depression scale	Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Paroxetine								
Kato 2006	HRSD-21	17.2	missing	41	13.9	missing	39	
Kiev 1997	HRSD-21	17.1	missing	29	17.4	missing	29	
vs Sertraline								
Nemeroff 1995	HRSD-21	16.8	missing	46	15.8	missing	46	
vs Citalopram								
Haffmans 1996	HRSD-17	22.3	missing	109	21.2	missing	108	
vs Fluoxetine								
Rapaport 1996	HRSD-21	15.5	missing	47	14.4	missing	46	

Analysis 3.7. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 7 Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data.

Study	Depression scale	Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Paroxetine								
Ansseau 1994	HRSD-21	13.2	7.3	43	13.7	7.9	38	skewed.
Kato 2006	HRSD-21	9.0	missing	41	4.6	missing	39	
Kiev 1997	HRSD-21	10.9	7.3	29	11.5	7.4	29	skewed.
vs Sertraline								
Nemeroff 1995	HRSD-21	14.0	7.6	46	12.2	6.5	46	skewed.
Rossini 2005	HRSD-21	7.6	12.3	39	11.3	11.3	45	skewed.
vs Fluoxetine								
Dalery 2003	HRSD-17	10.0	missing	86	11.3	missing	91	
Rapaport 1996	HRSD-21	9.6	missing	47	9.7	missing	46	
vs Citalopram								
Haffmans 1996	HRSD-17	18.0	missing	109	16.6	missing	108	

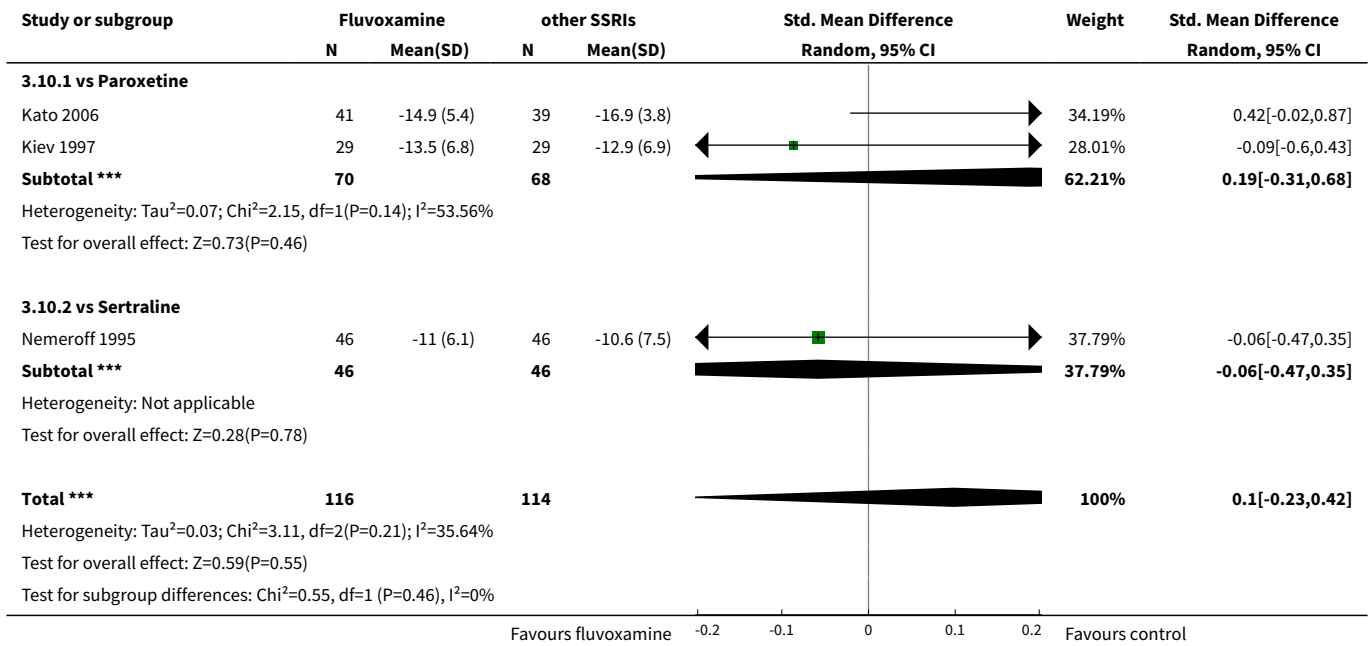
Analysis 3.8. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 8 Depression scale - Change score: decrease=good (early phase).



Analysis 3.9. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 9 Depression scale - Change score: decrease=good (early phase) - missing SDs.

Depression scale - Change score: decrease=good (early phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
vs Paroxetine								
Ansseau 1994	HRSD-21	-7.2	missing	48	-6.2	missing	45	
Kiev 1997	HRSD-21	-7.3	missing	29	-7	missing	29	
vs Sertraline								
Nemeroff 1995	HRSD-21	-7.8	missing	46	-7.4	missing	46	
Rossini 2005	HRSD-21	-10.1	missing	39	-7.8	missing	45	
vs Citalopram								
Haffmans 1996	HRSD-17	-2.2	missing	109	-3.5	missing	108	
vs Fluoxetine								
Rapaport 1996	HRSD-21	-9.7	missing	47	-11.2	missing	46	

Analysis 3.10. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 10 Depression scale - Change score: decrease=good (acute phase).

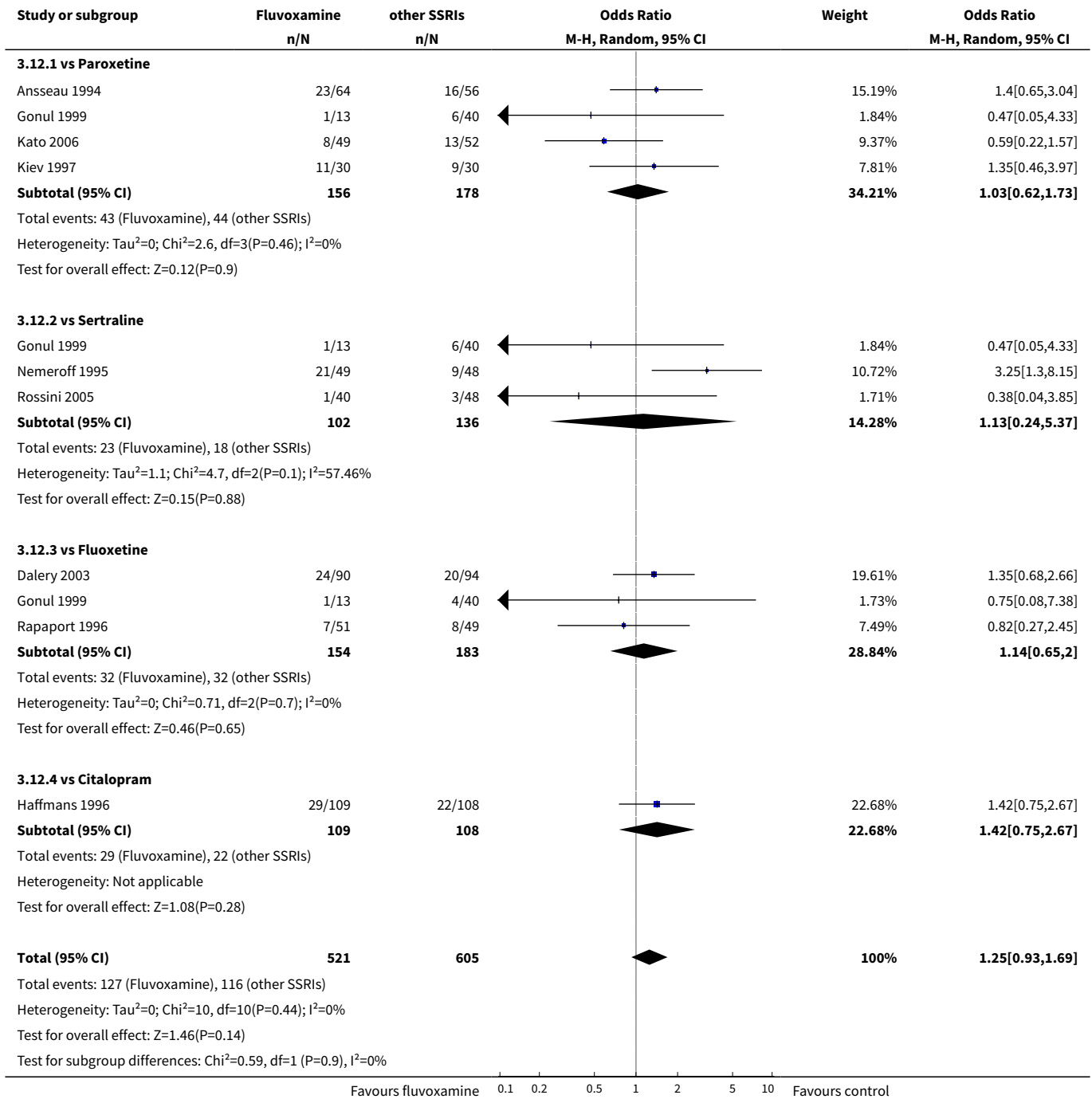


Analysis 3.11. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 11 Depression scale - Change score: decrease=good (acute phase) - missing SDs.

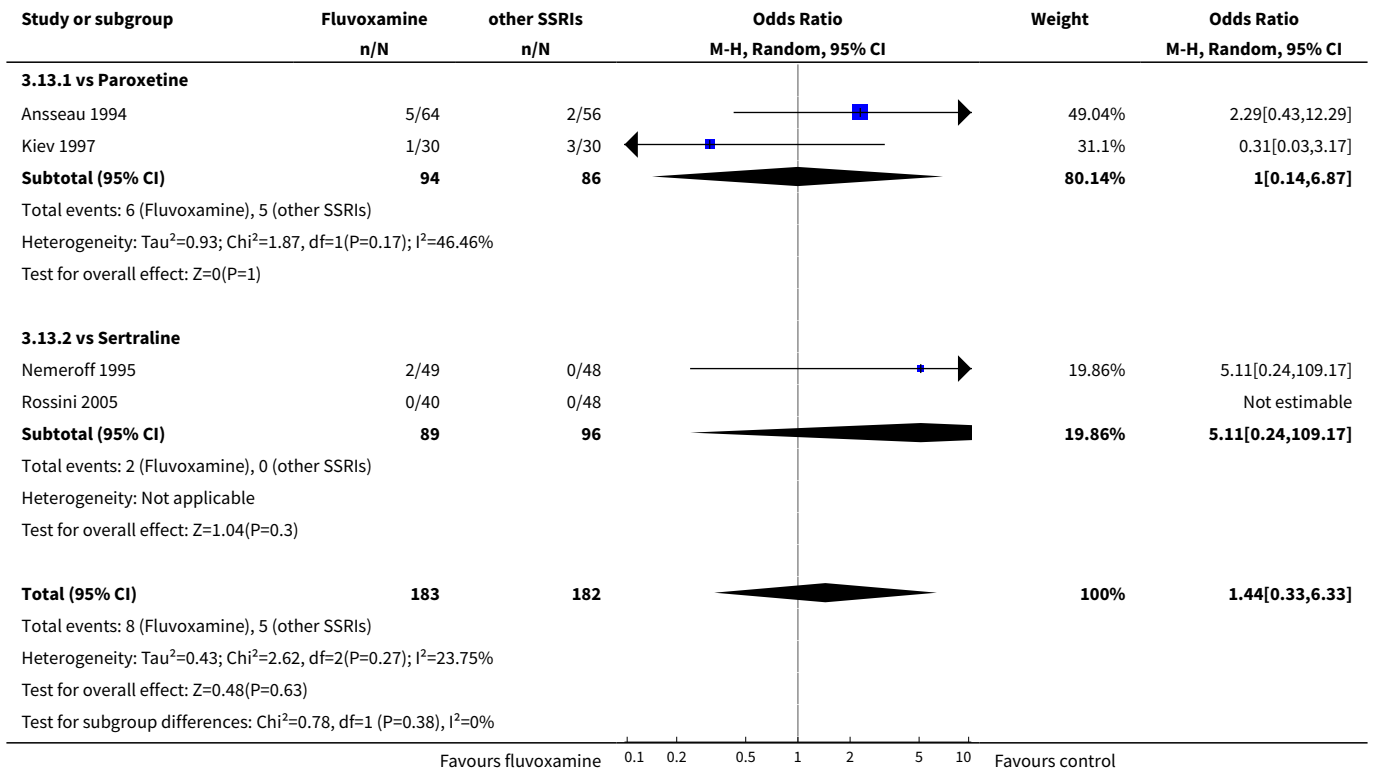
Depression scale - Change score: decrease=good (acute phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
vs Paroxetine								
Ansseau 1994	HRSD-21	-13.3	missing	43	-12.3	missing	38	
vs Sertraline								
Rossini 2005	HRSD-21	-23.7	missing	39	-18	missing	45	
vs Citalopram								
Haffmans 1996	HRSD-17	-6.5	missing	109	-8.1	missing	108	

Depression scale - Change score: decrease=good (acute phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
vs Fluoxetine								
Dalery 2003	HRSD-17	-12.3	missing	86	-10.9	missing	91	
Rapaport 1996	HRSD-21	-15.6	missing	47	-15.9	missing	46	

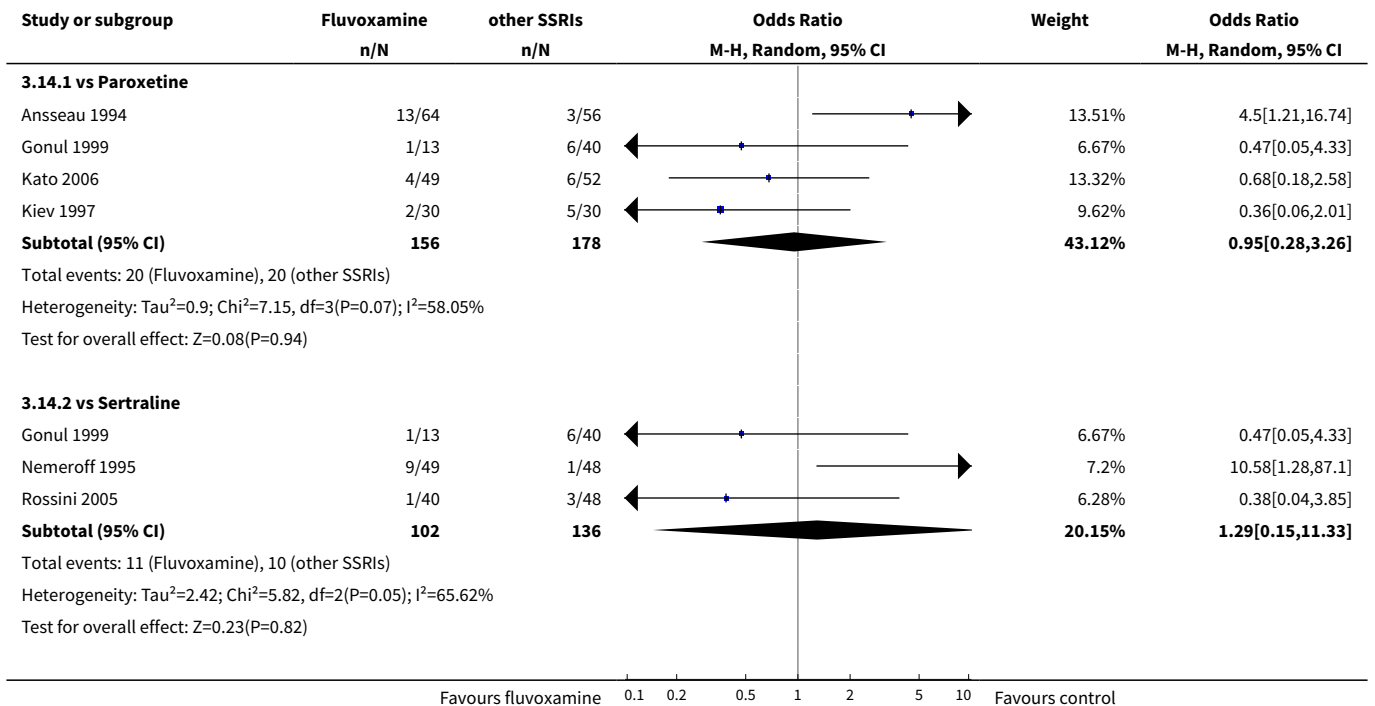
Analysis 3.12. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 12 Total Dropout.

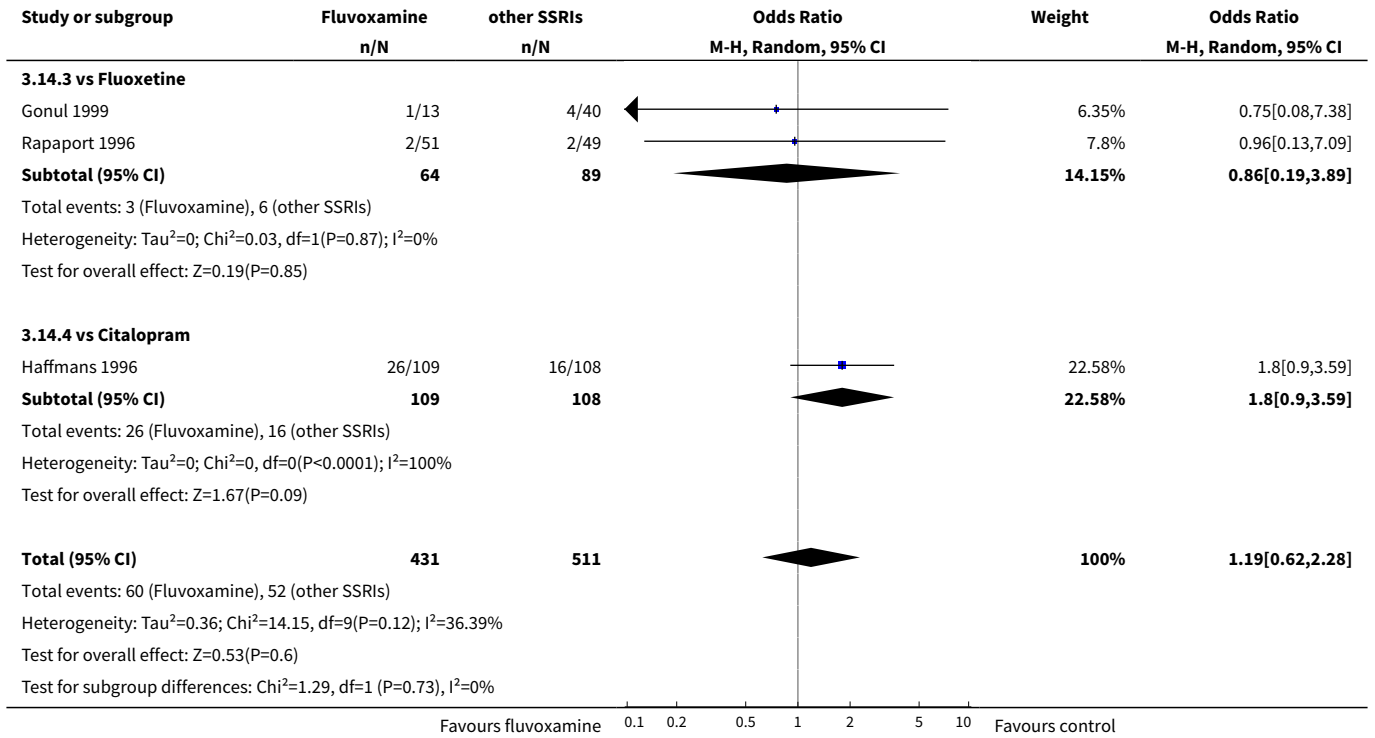


Analysis 3.13. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 13 Dropout due to inefficacy.

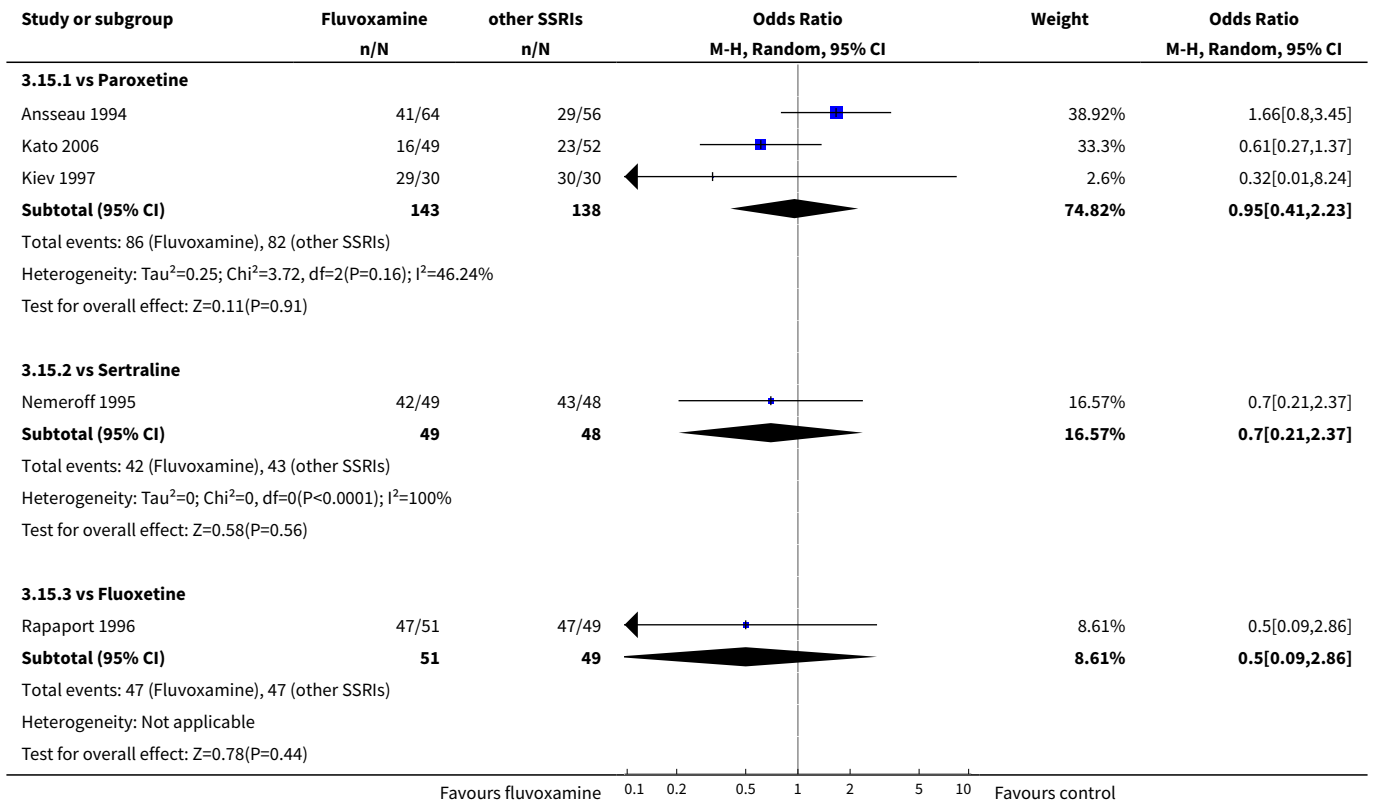


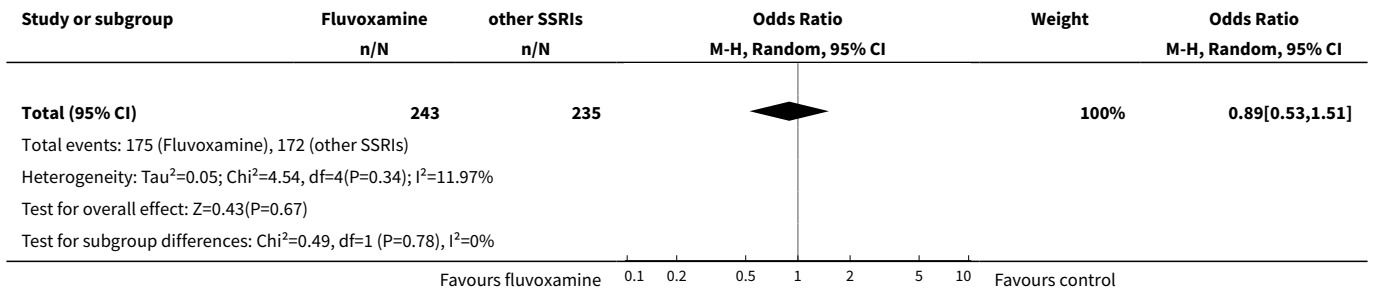
Analysis 3.14. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 14 Dropout due to side effects.



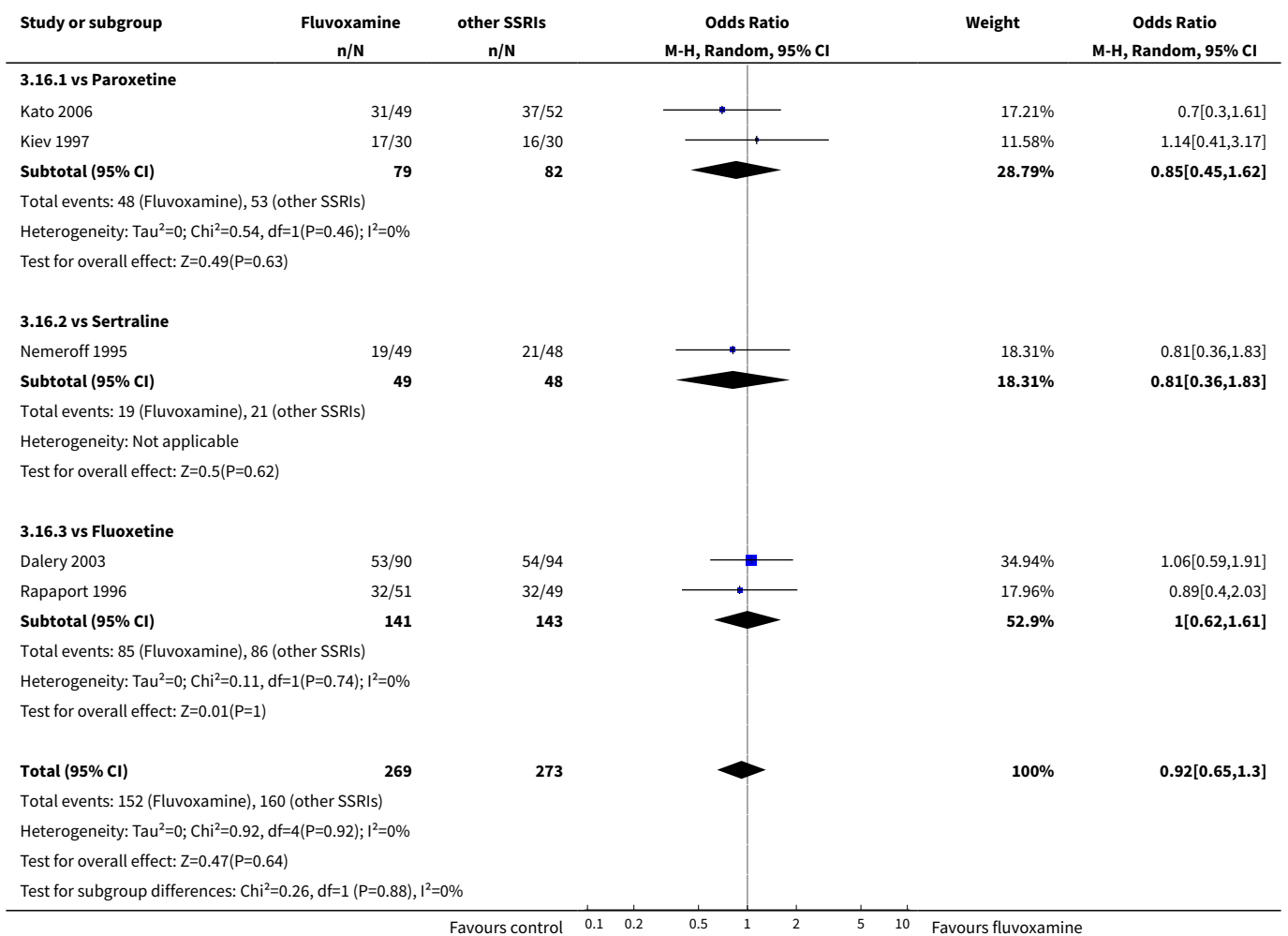


Analysis 3.15. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 15 Number of patients experiencing at least one side effect.

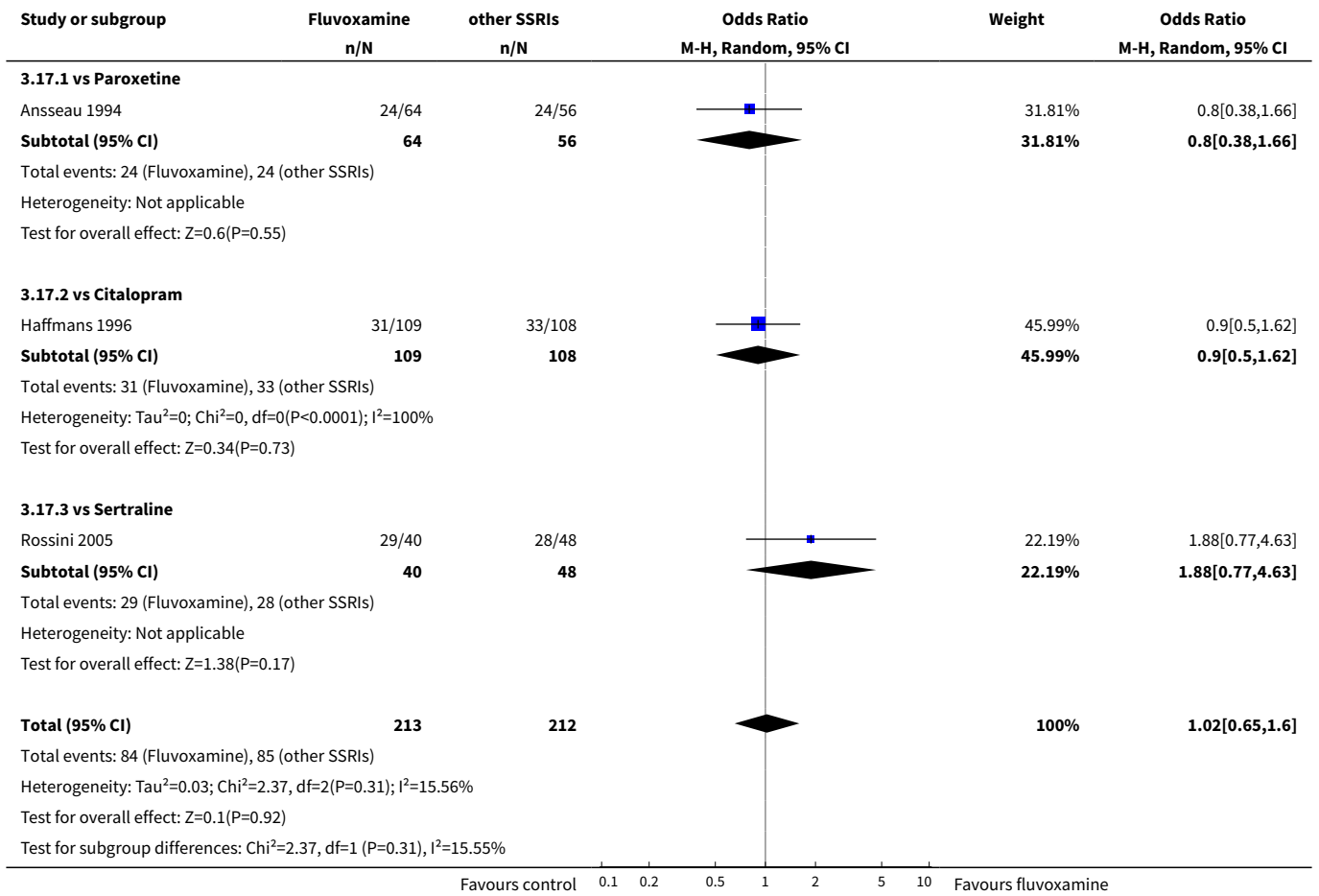




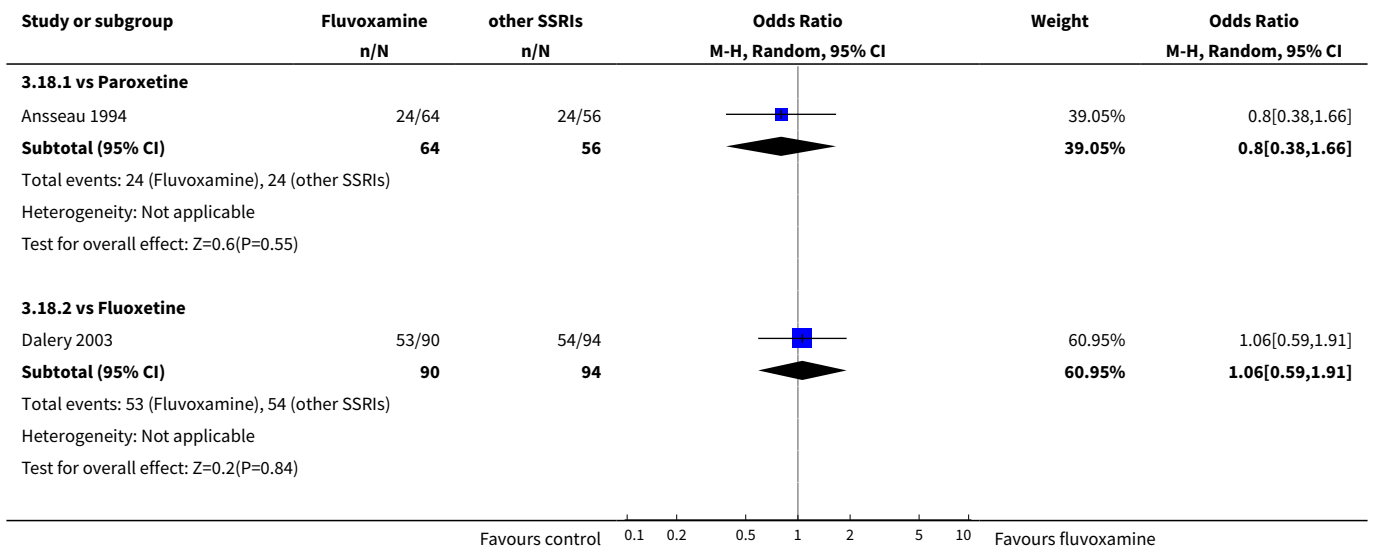
Analysis 3.16. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 16 Subgroup analysis - Response (acute phase) 1. Fluvoxamine dosing - Standard dosage.

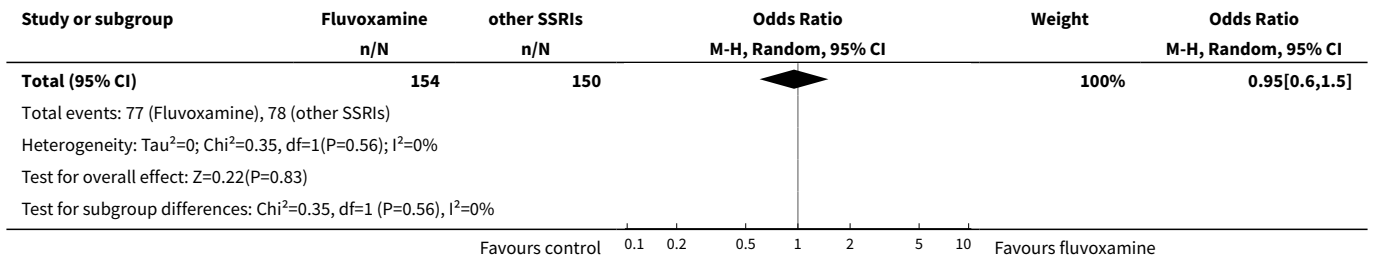


Analysis 3.17. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 17 Subgroup analysis - Response (acute phase) 1. Fluvoxamine dosing - High dosage.

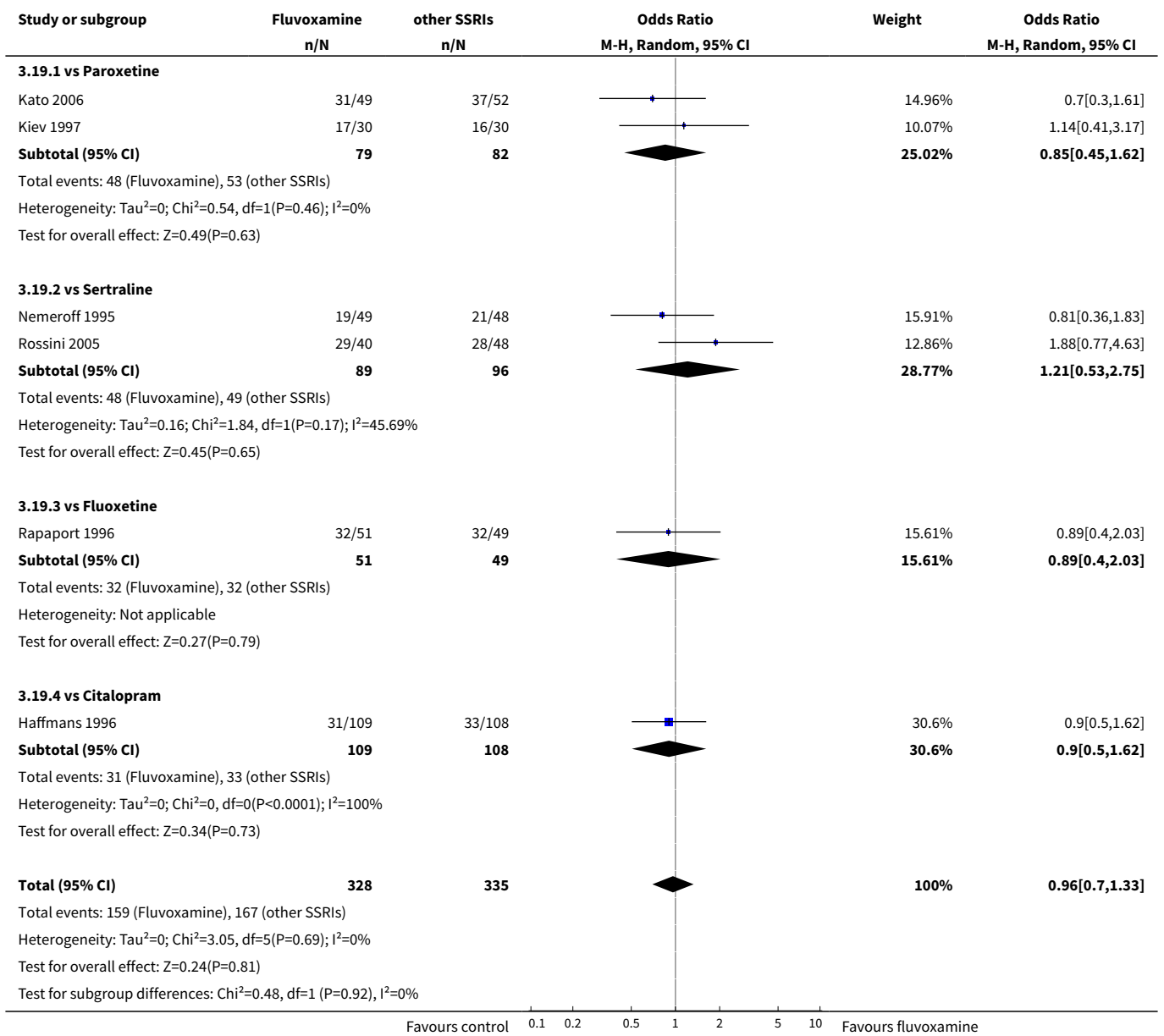


Analysis 3.18. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 18 Subgroup analysis - Response (acute phase) 2. Comparator dosing - Standard dosage.

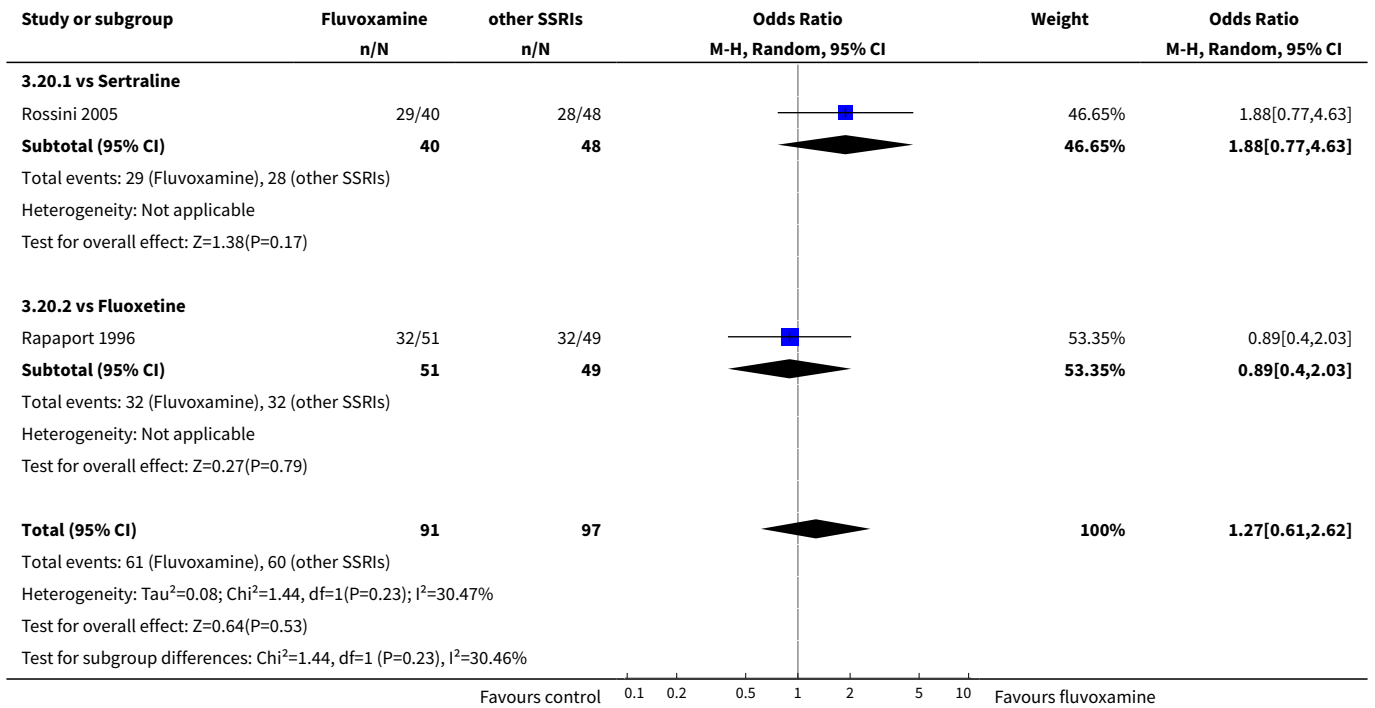




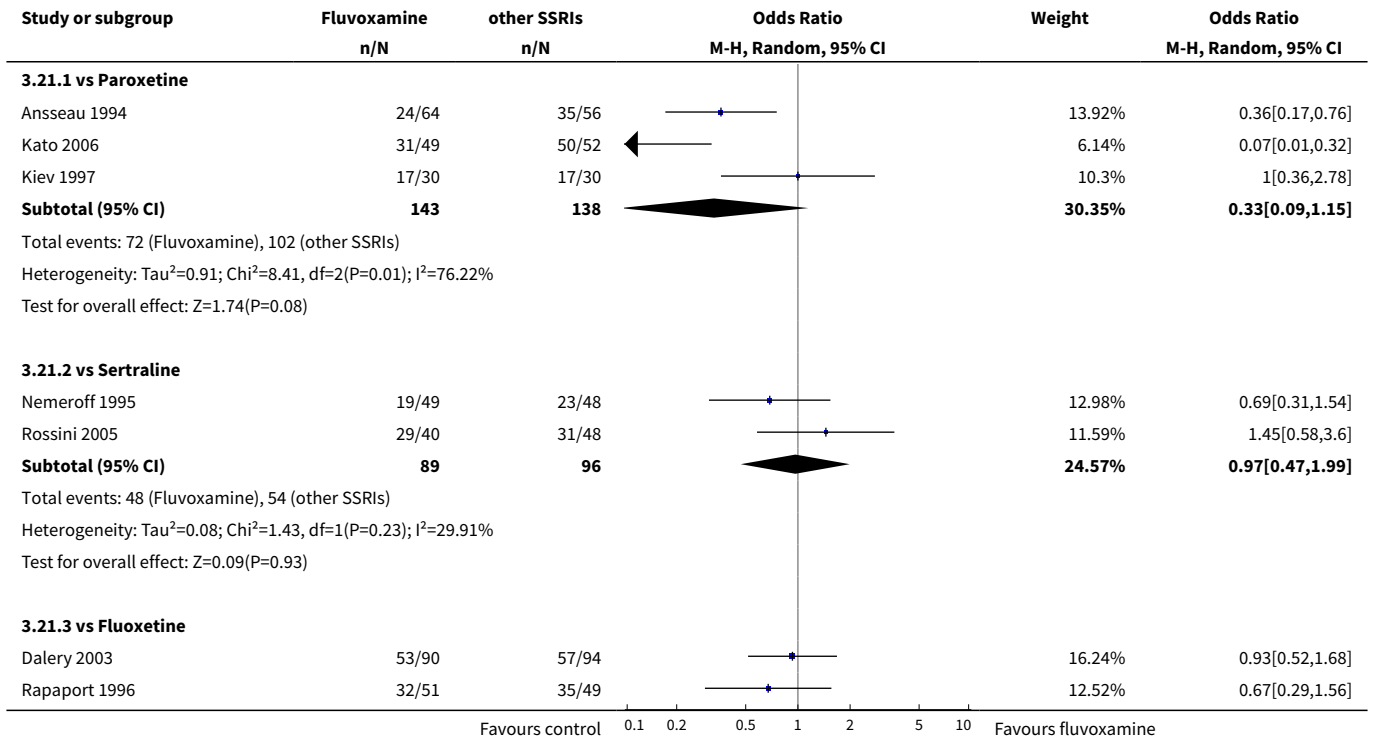
**Analysis 3.19. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 19
Subgroup analysis - Response (acute phase) 2. Comparator dosing - High dosage.**

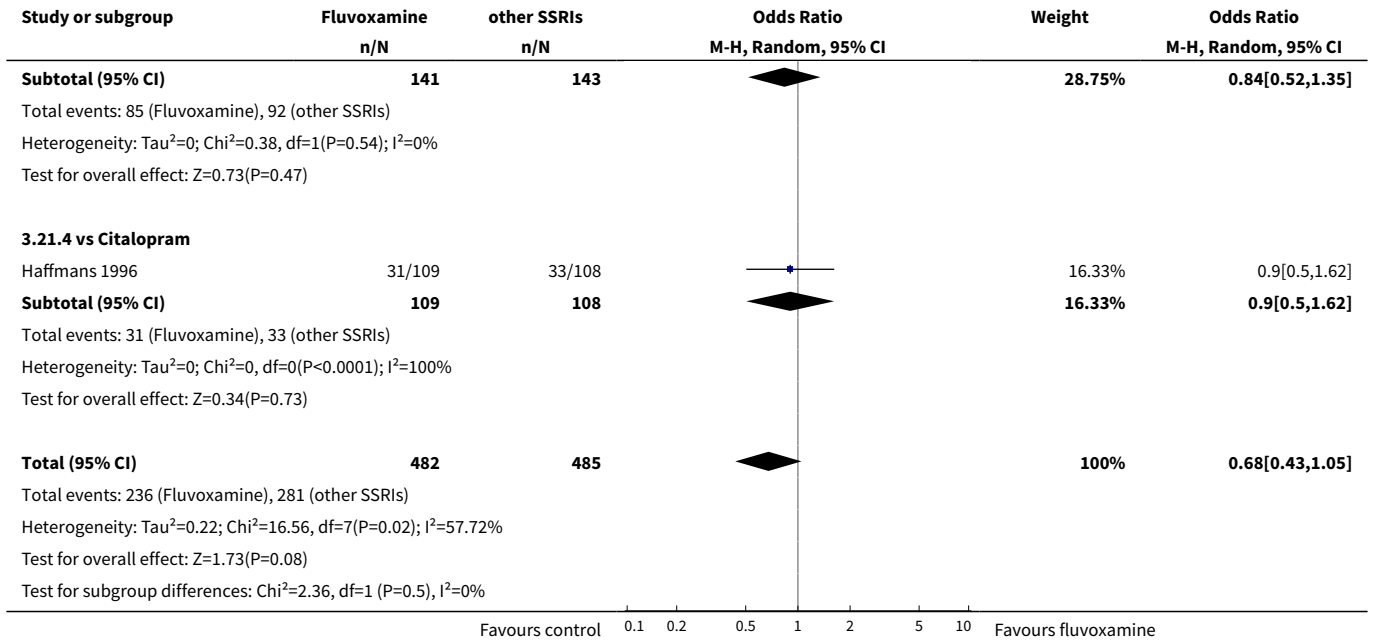


Analysis 3.20. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 20 Sensitivity analysis - Response (acute phase) 2. Excluding trials dropout rate >20%.

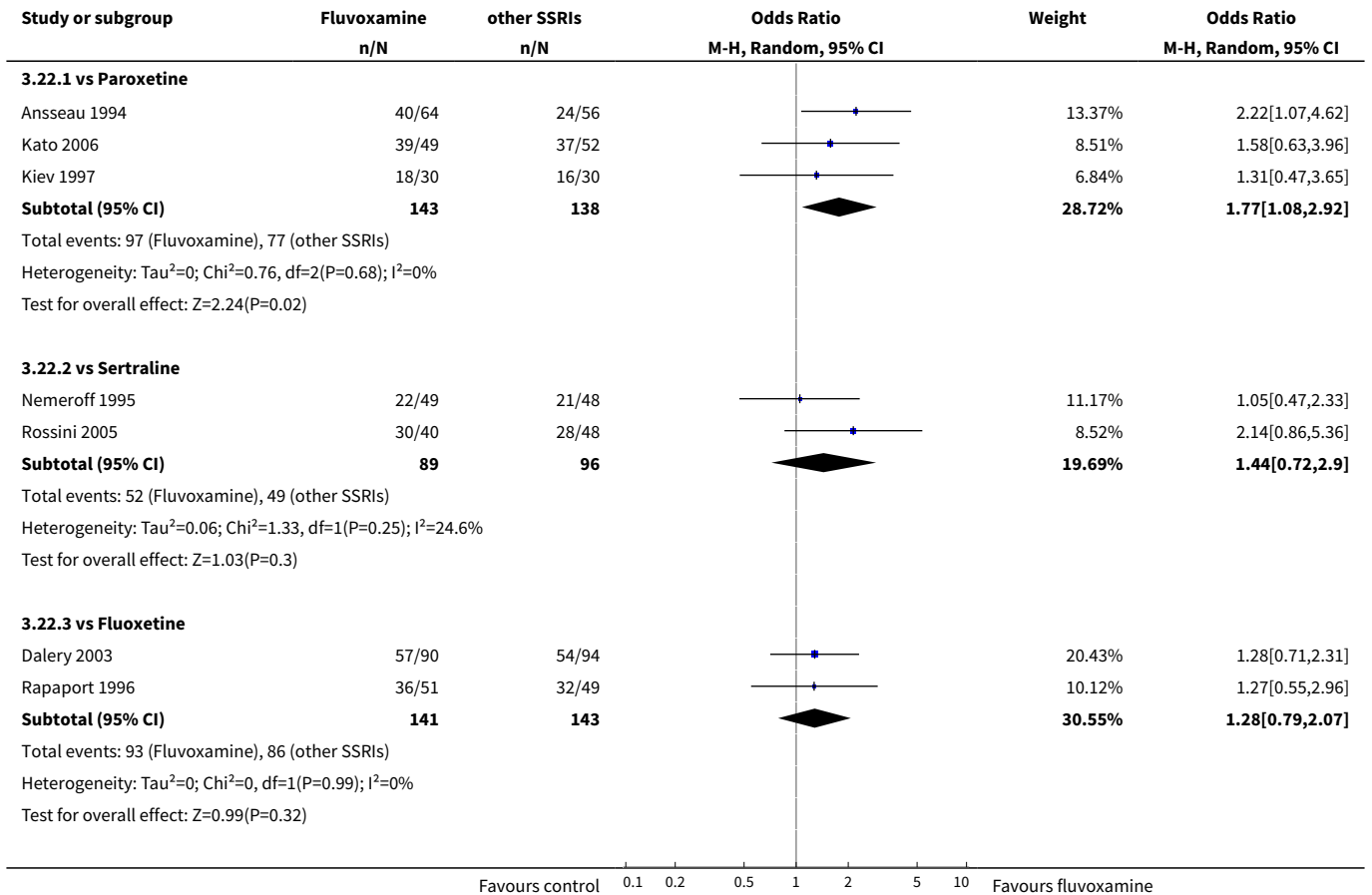


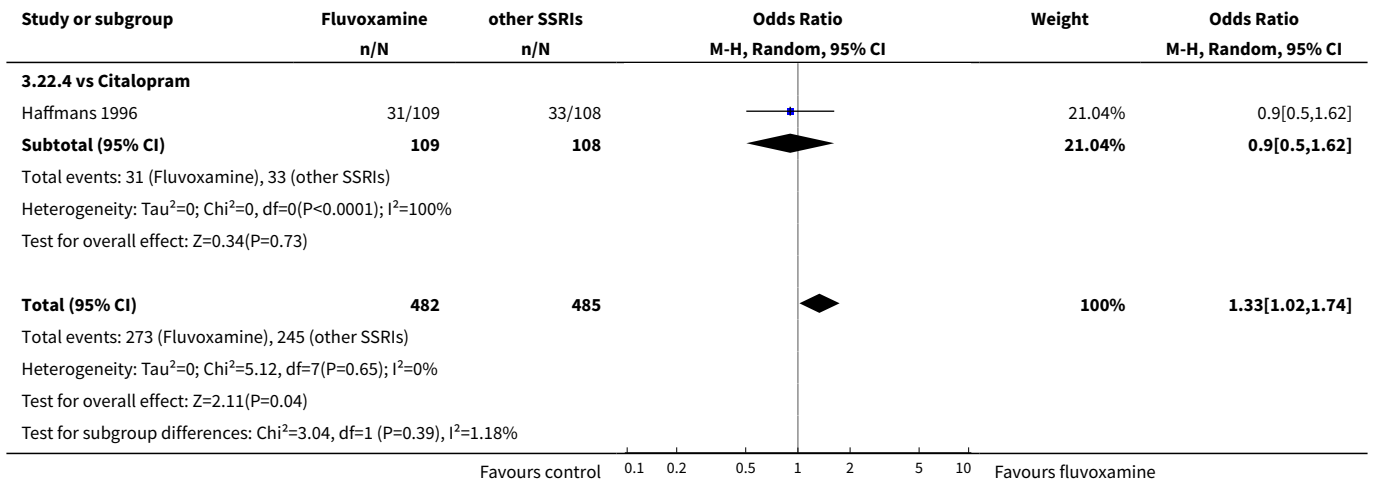
Analysis 3.21. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 21 Sensitivity analysis - Response (acute phase) 3. Worst case scenario ITT.



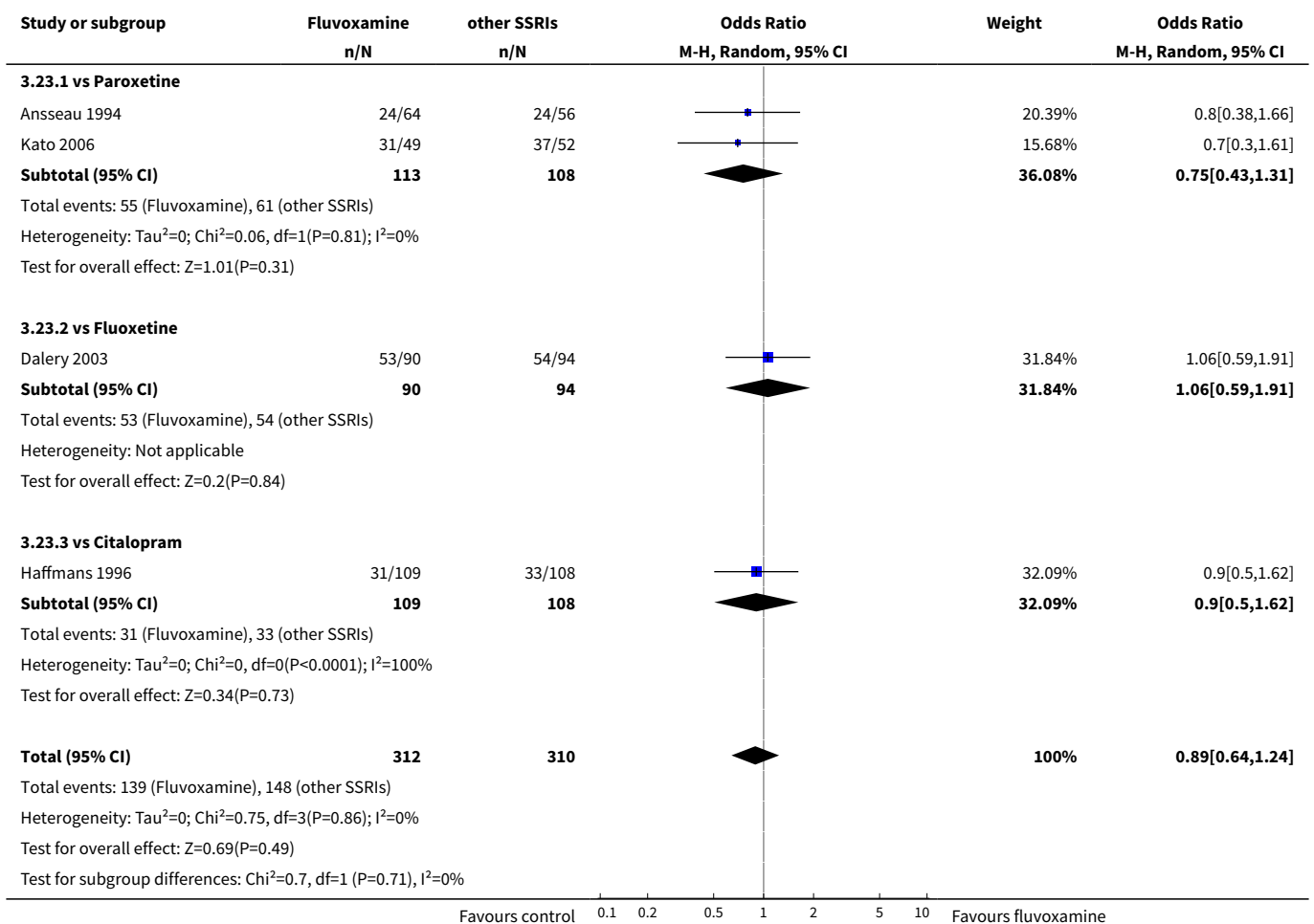


Analysis 3.22. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 22 Sensitivity analysis - Response (acute phase) 4. Best case scenario ITT.

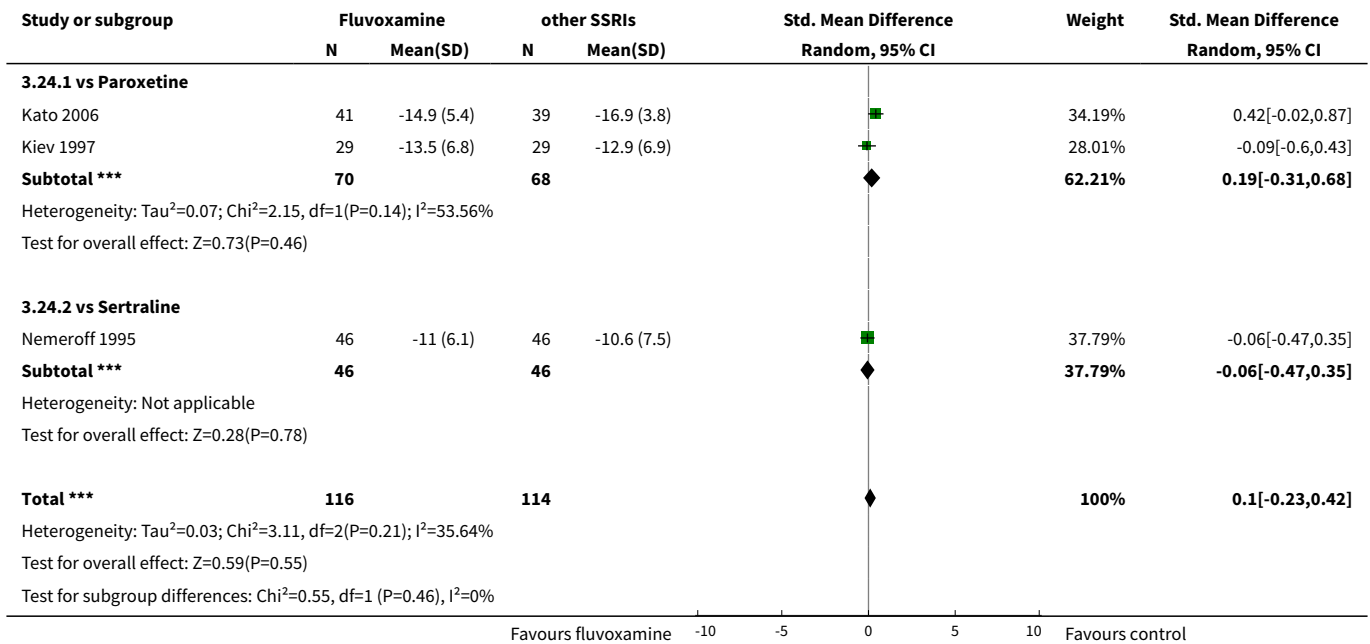




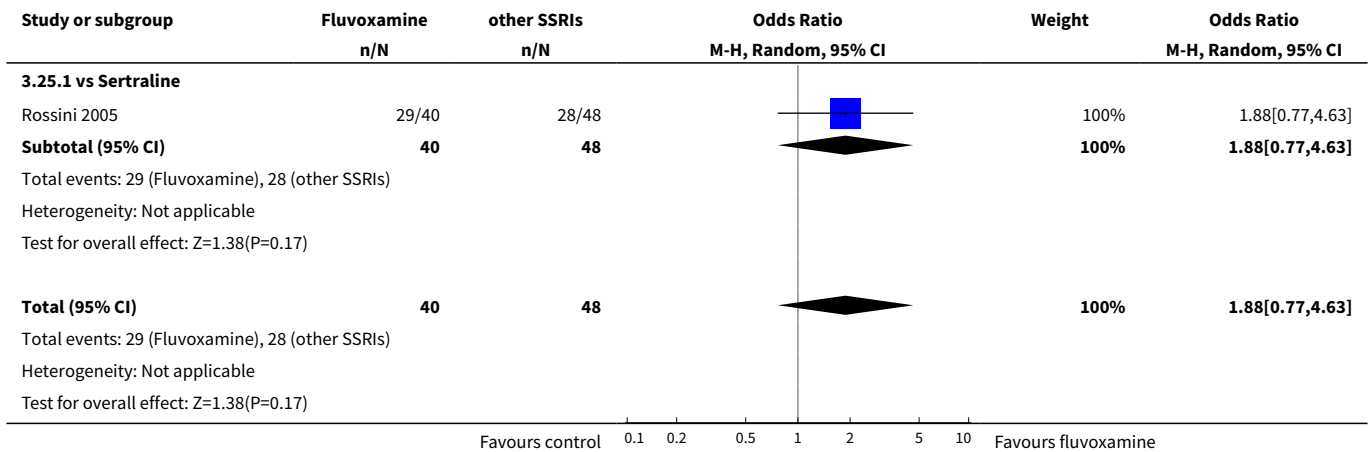
Analysis 3.23. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 23 Sensitivity analysis - Response (acute phase) 5. Excluding trials with imputation methods for calculating response.



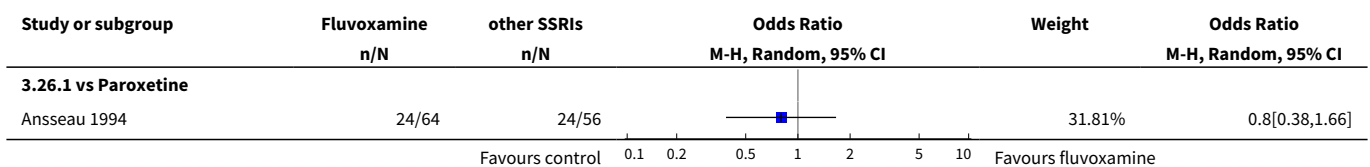
Analysis 3.24. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 24 Sensitivity analysis - Mean change from baseline (acute phase) 5. Excluding trials for which the SD had to be borrowed from other trials.

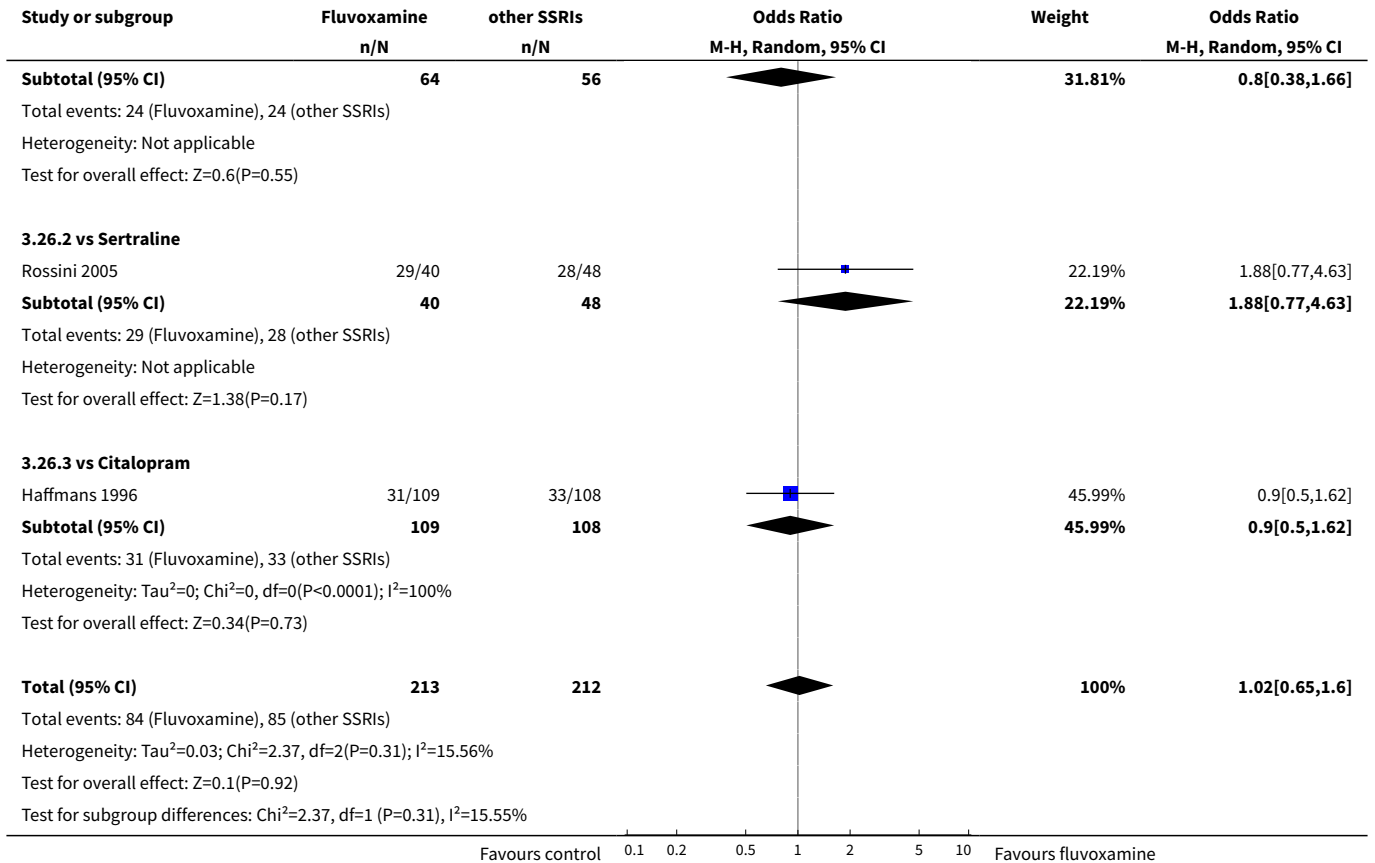


Analysis 3.25. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 25 Sensitivity analysis - Response (acute phase) 6. Wish bias - Fluvoxamine as an investigational drug.

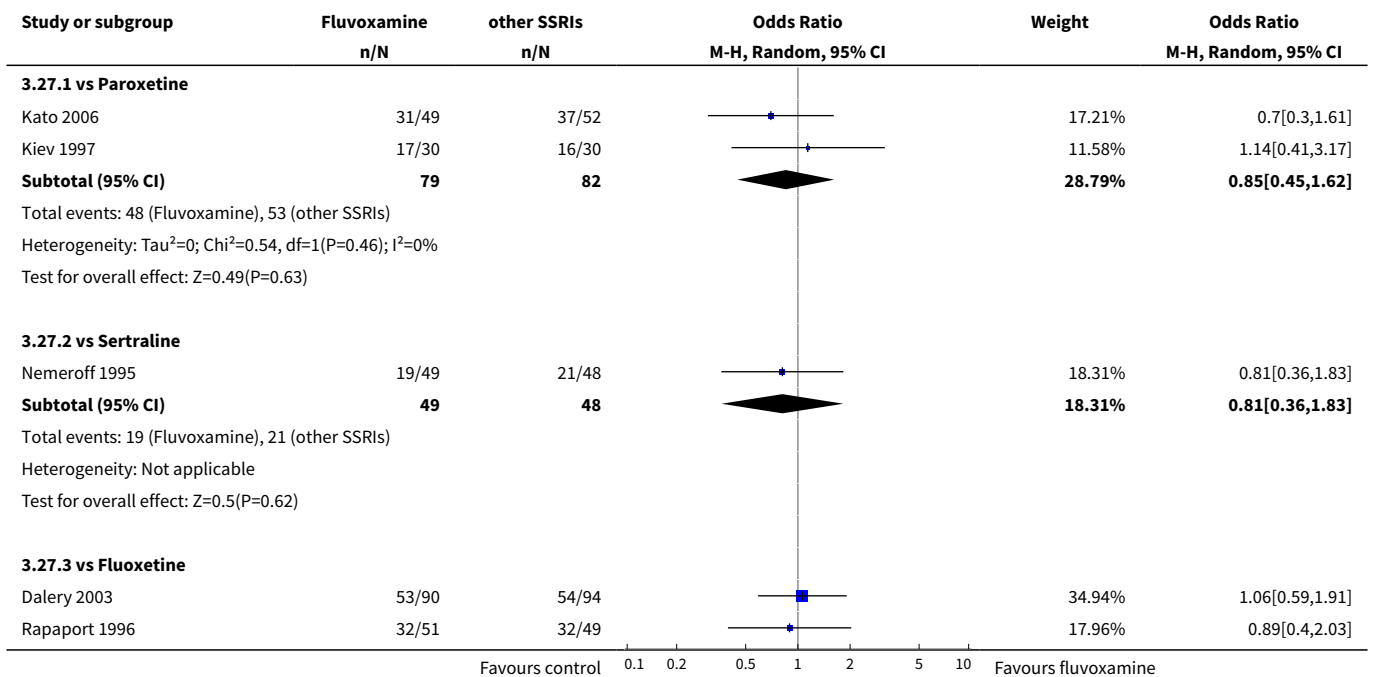


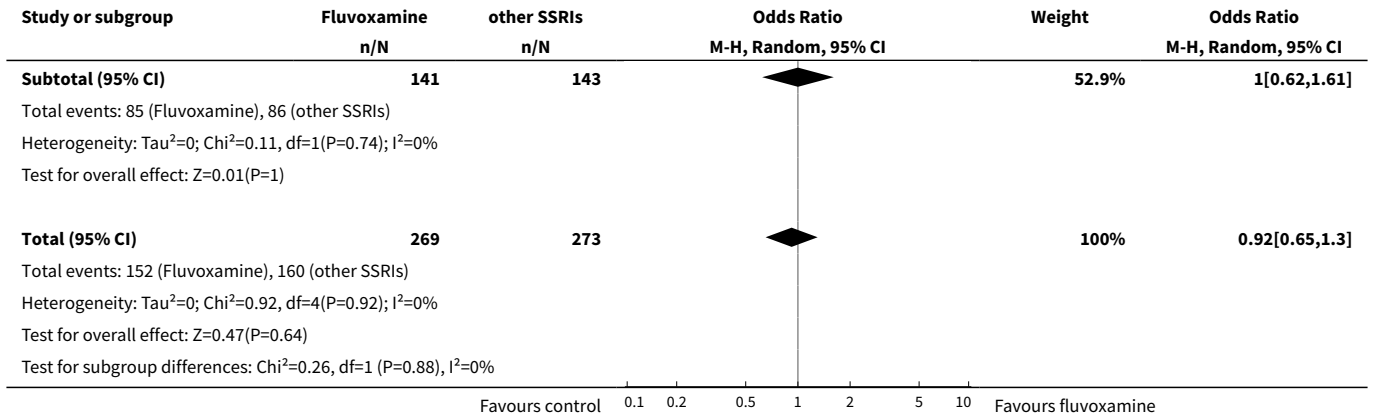
Analysis 3.26. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 26 Sensitivity analysis - Response (acute phase) 7. Funding - Excluding trials funded by the fluvoxamine marketing company.



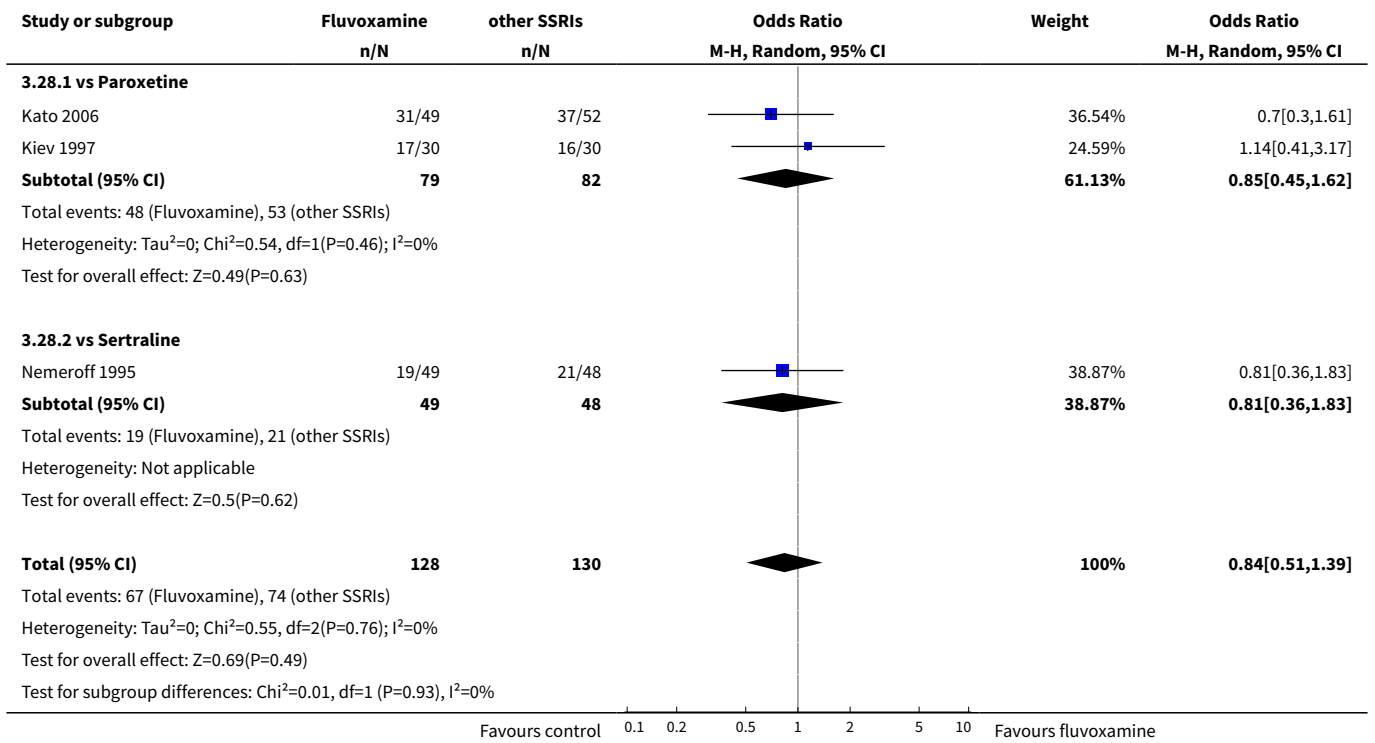


Analysis 3.27. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 27 Sensitivity analysis - Response (acute phase) 7. Funding - Trials funded by the fluvoxamine marketing company.

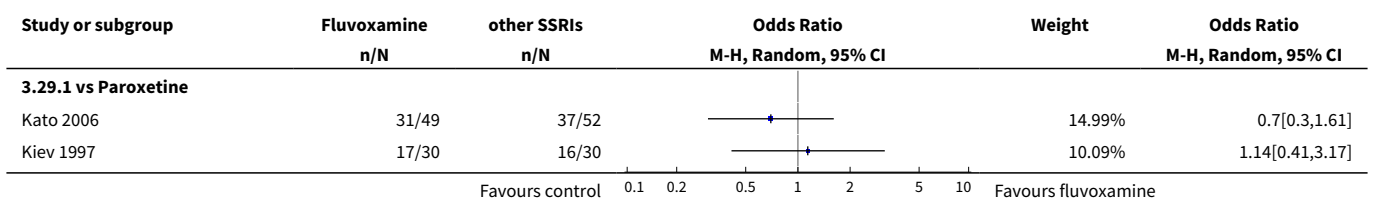


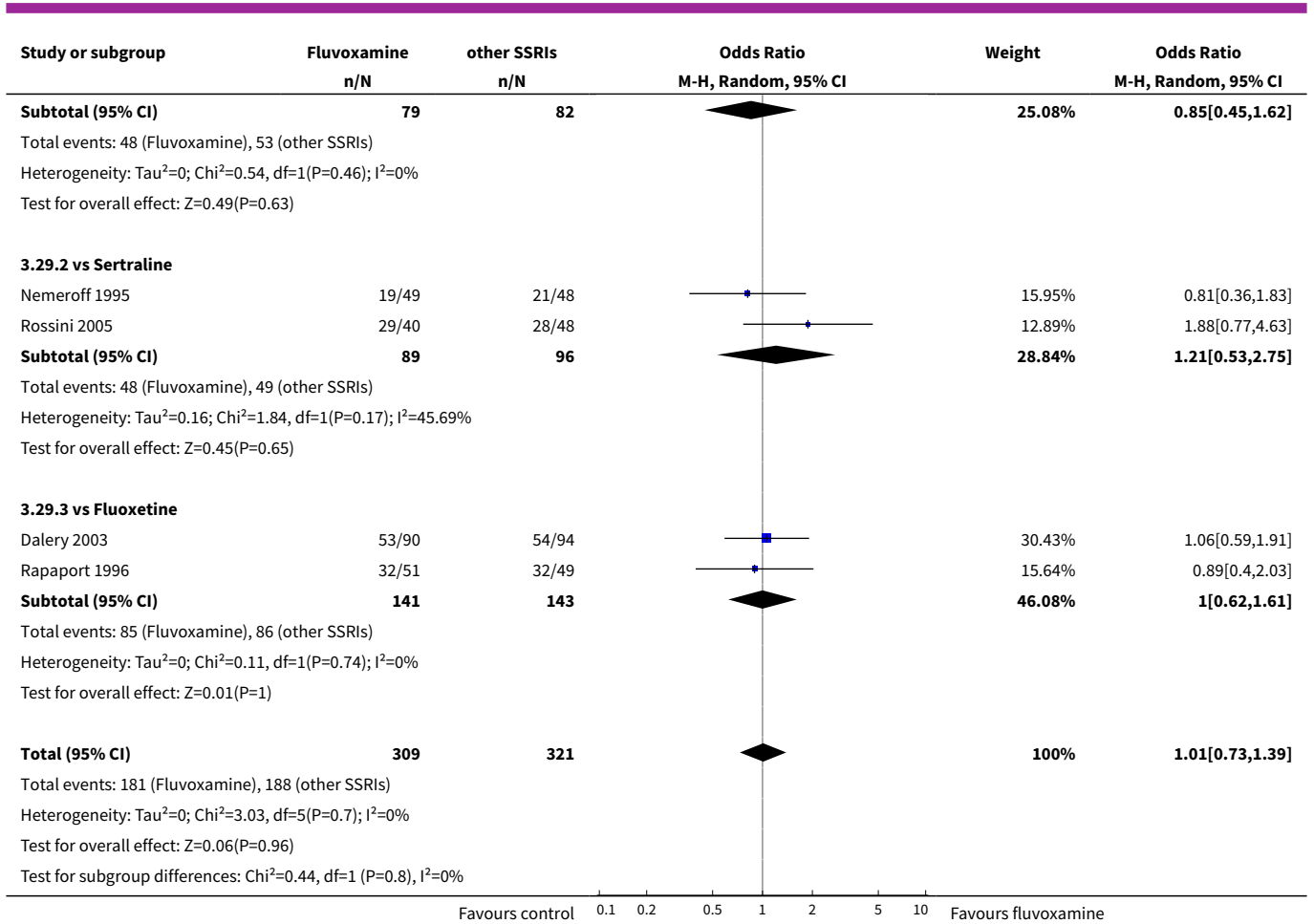


Analysis 3.28. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 28 Sensitivity analysis - Response (acute phase) 8. Excluding trials that might include patients with bipolar depression.



Analysis 3.29. Comparison 3 Fluvoxamine versus other SSRIs, Outcome 29 Sensitivity analysis - Response (acute phase) 9. Excluding trials that included patients with psychotic features.





Comparison 4. Fluvoxamine versus SNRIs

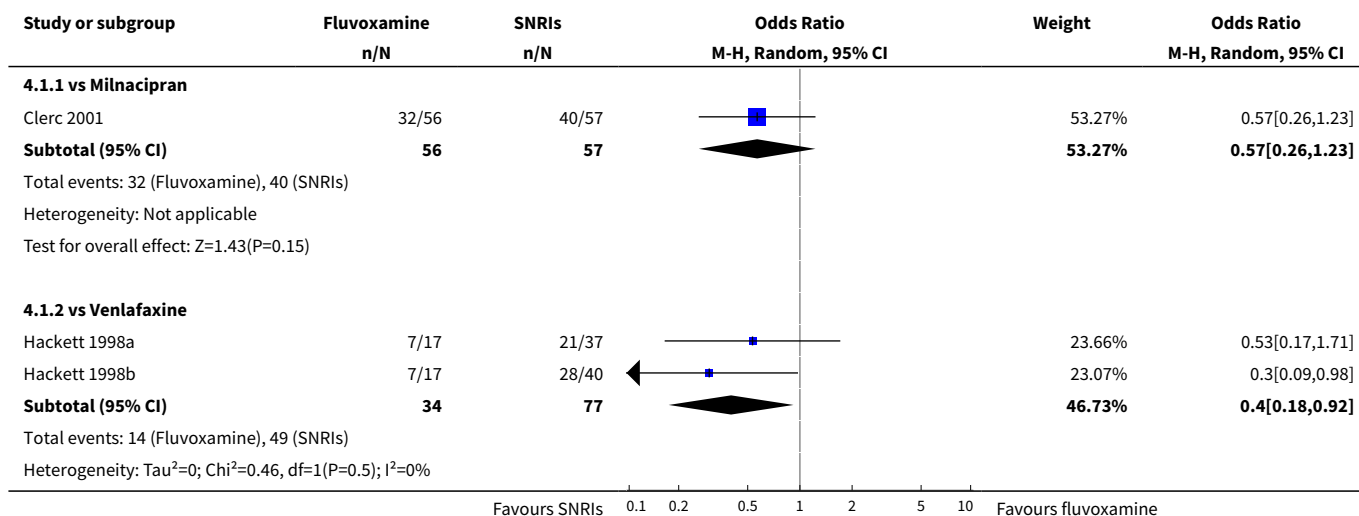
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response (acute phase): Primary outcome	3	224	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.27, 0.85]
1.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.23]
1.2 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.18, 0.92]
2 Response (early phase)	5	351	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.45, 1.19]
2.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.37, 1.15]
2.2 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.39, 2.63]

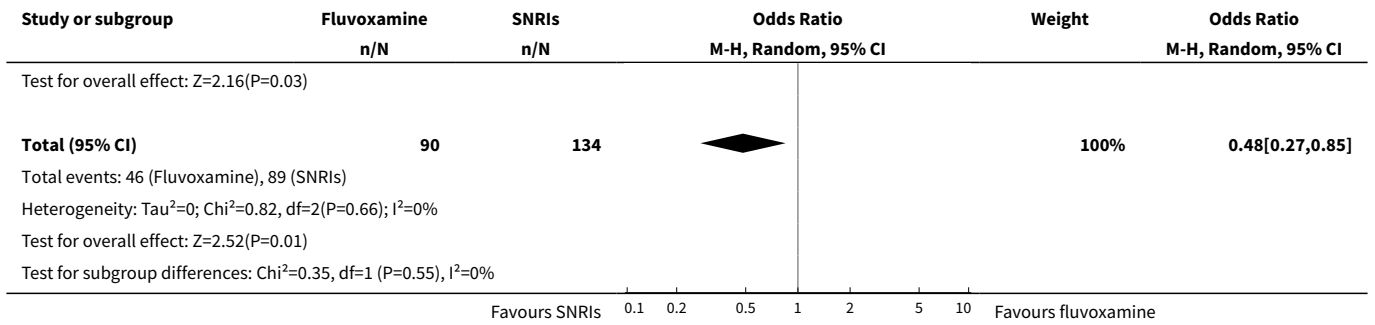
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Remission (early phase)	5	351	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.35, 1.86]
3.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.22, 1.74]
3.2 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	1.54 [0.22, 10.74]
4 Remission (acute phase)	3	224	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.34, 1.08]
4.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.30, 1.51]
4.2 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.23, 1.24]
5 Depression scale - Endpoint score: low=good (early phase)	4	274	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.17, 0.32]
5.1 vs Milnacipran	2	172	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.30, 0.31]
5.2 vs Venlafaxine	2	102	Std. Mean Difference (IV, Random, 95% CI)	0.21 [-0.21, 0.63]
6 Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data			Other data	No numeric data
6.1 vs Milnacipran			Other data	No numeric data
7 Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data			Other data	No numeric data
7.1 vs Venlafaxine			Other data	No numeric data
8 Depression scale - Change score: decrease=good (early phase) - missing SDs			Other data	No numeric data
8.1 vs Milnacipran			Other data	No numeric data
8.3 vs Venlafaxine			Other data	No numeric data
9 Depression scale - Change score: decrease=good (acute phase) - missing SDs			Other data	No numeric data
9.1 vs Milnacipran			Other data	No numeric data
9.3 vs Venlafaxine			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Total Dropout	5	351	Odds Ratio (M-H, Random, 95% CI)	1.57 [0.93, 2.67]
10.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.65, 2.45]
10.2 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	2.29 [0.97, 5.43]
11 Dropout due to inefficacy	3	240	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.34, 2.16]
11.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.34, 2.16]
12 Dropout due to side effects	3	240	Odds Ratio (M-H, Random, 95% CI)	2.38 [0.73, 7.78]
12.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	2.38 [0.73, 7.78]
13 Sensitivity analysis - Response (acute phase) 3. Worst case scenario ITT	3	224	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.05, 0.76]
13.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.23]
13.2 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	0.11 [0.04, 0.29]
14 Sensitivity analysis - Response (acute phase) 4. Best case scenario ITT	3	224	Odds Ratio (M-H, Random, 95% CI)	1.41 [0.43, 4.66]
14.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.23]
14.2 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	2.67 [0.98, 7.26]
15 Sensitivity analysis - Response (acute phase) 5. Excluding trials with imputation methods for calculating response	1	113	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.23]
15.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.23]
16 Sensitivity analysis - Response (acute phase) 6. Wish bias - Fluvoxamine as a comparator drug	3	224	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.27, 0.85]
16.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.23]

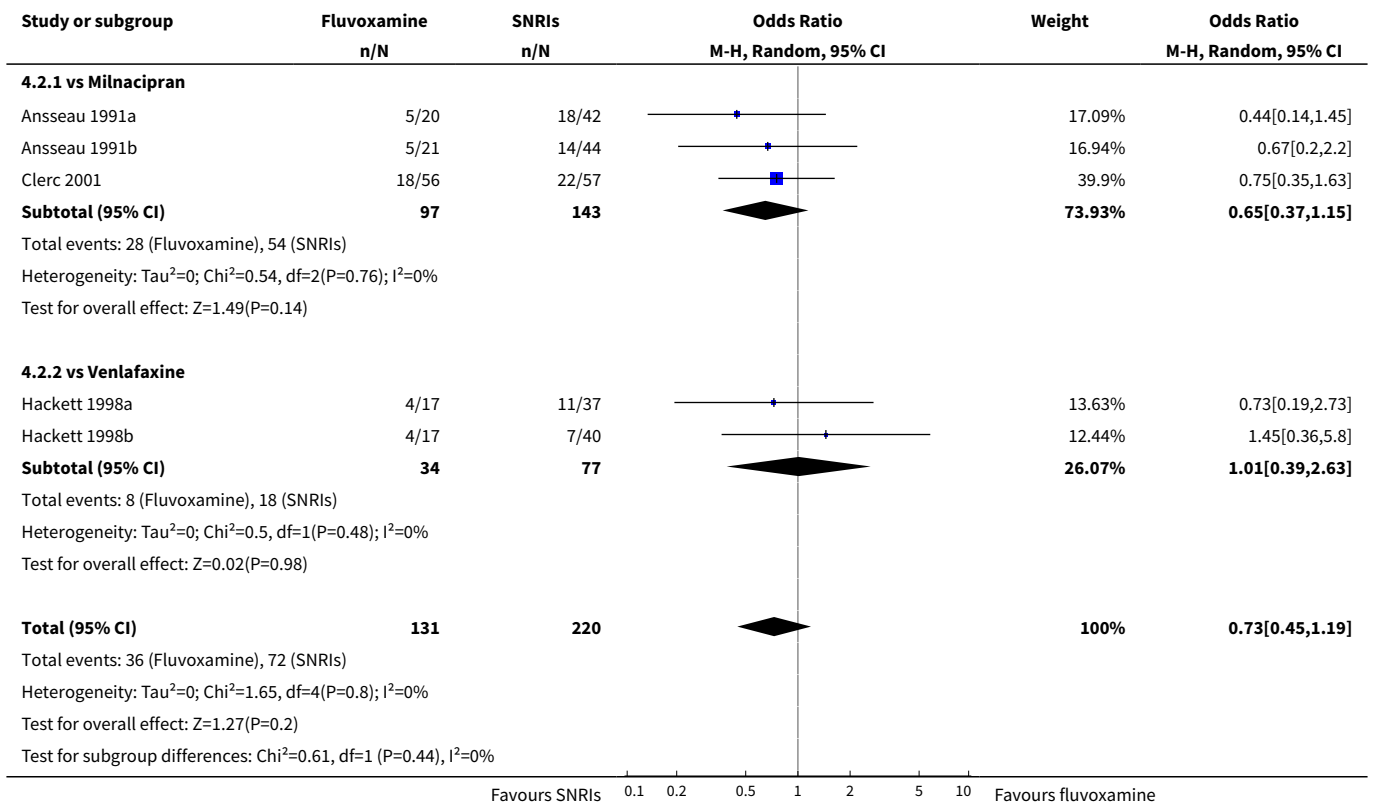
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.18, 0.92]
17 Sensitivity analysis - Response (acute phase) 7. Funding - Excluding trials funded by the fluvoxamine marketing company	3	224	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.27, 0.85]
17.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.23]
17.2 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.18, 0.92]
18 Sensitivity analysis - Response (acute phase) 8. Excluding trials that might include patients with bipolar depression	3	224	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.27, 0.85]
18.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.23]
18.2 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.18, 0.92]
19 Sensitivity analysis - Response (acute phase) 9. Excluding trials that included patients with psychotic features	2	111	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.18, 0.92]
19.1 vs Venlafaxine	2	111	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.18, 0.92]

Analysis 4.1. Comparison 4 Fluvoxamine versus SNRIs, Outcome 1 Response (acute phase): Primary outcome.

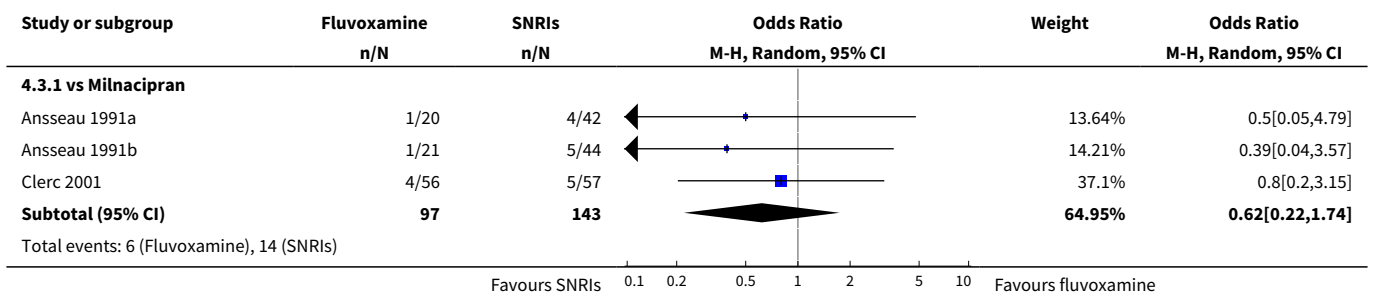


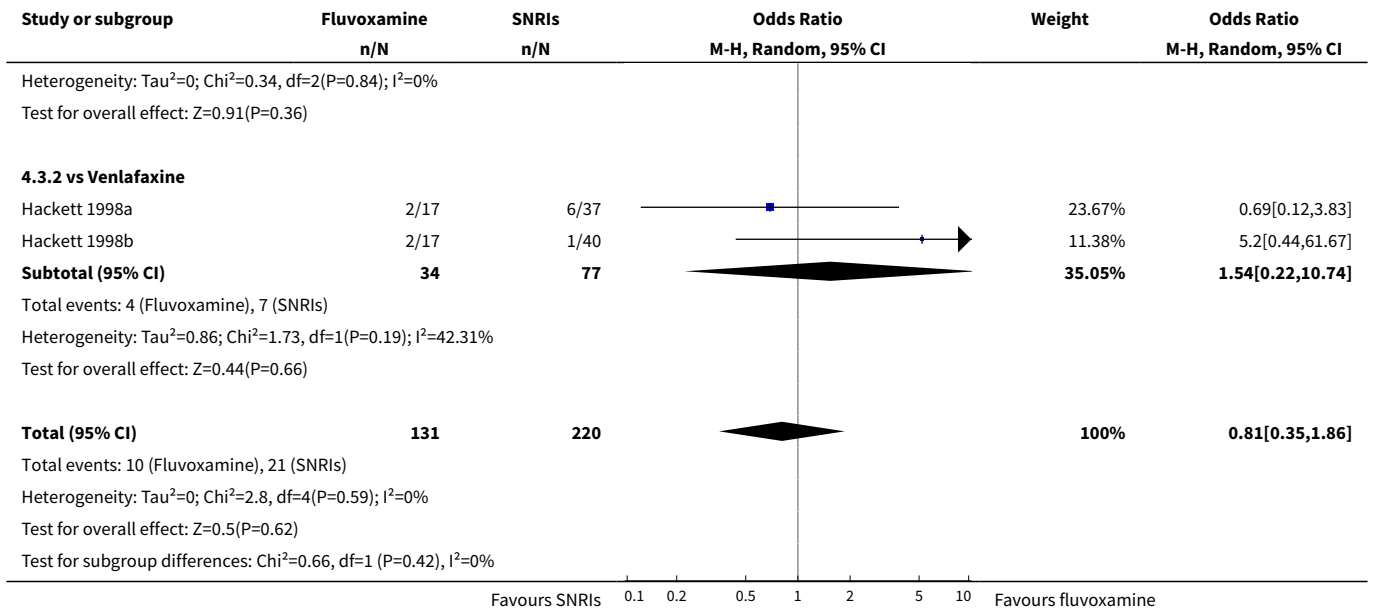


Analysis 4.2. Comparison 4 Fluvoxamine versus SNRIs, Outcome 2 Response (early phase).

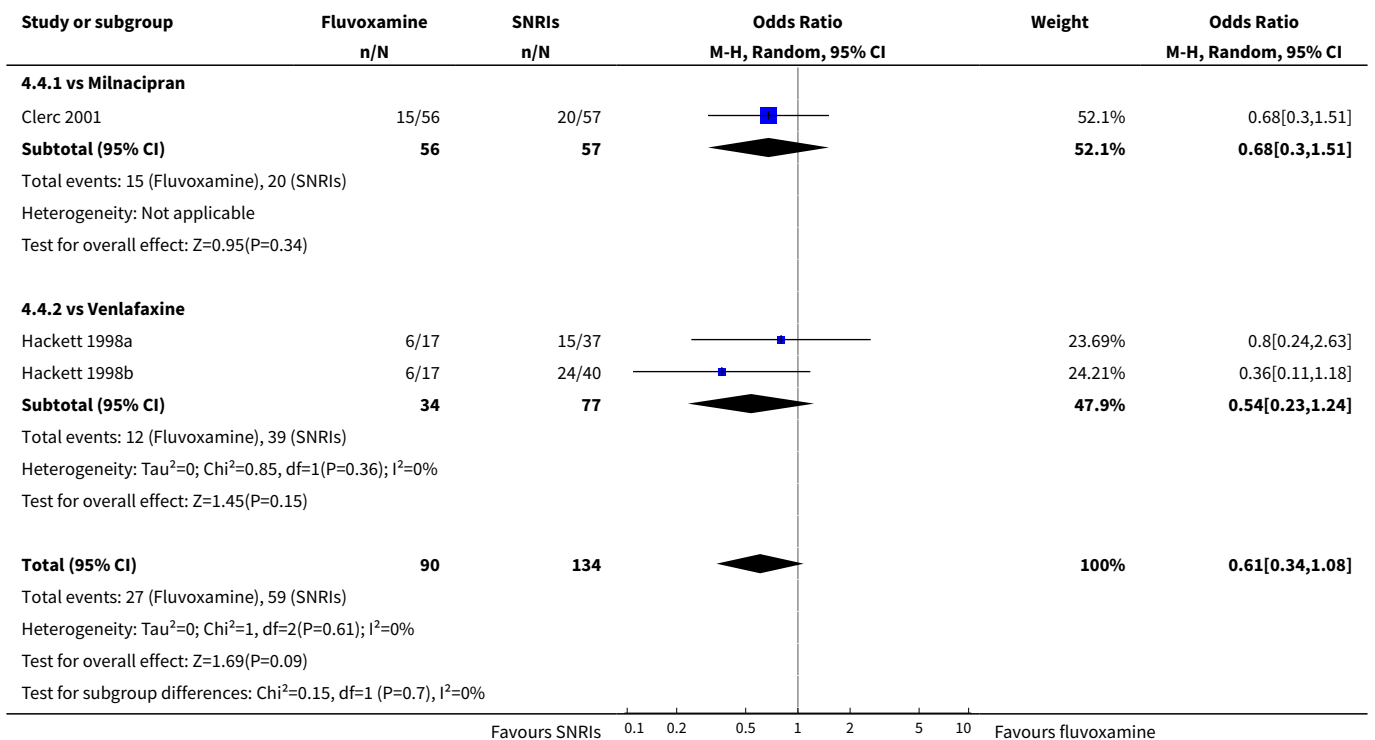


Analysis 4.3. Comparison 4 Fluvoxamine versus SNRIs, Outcome 3 Remission (early phase).

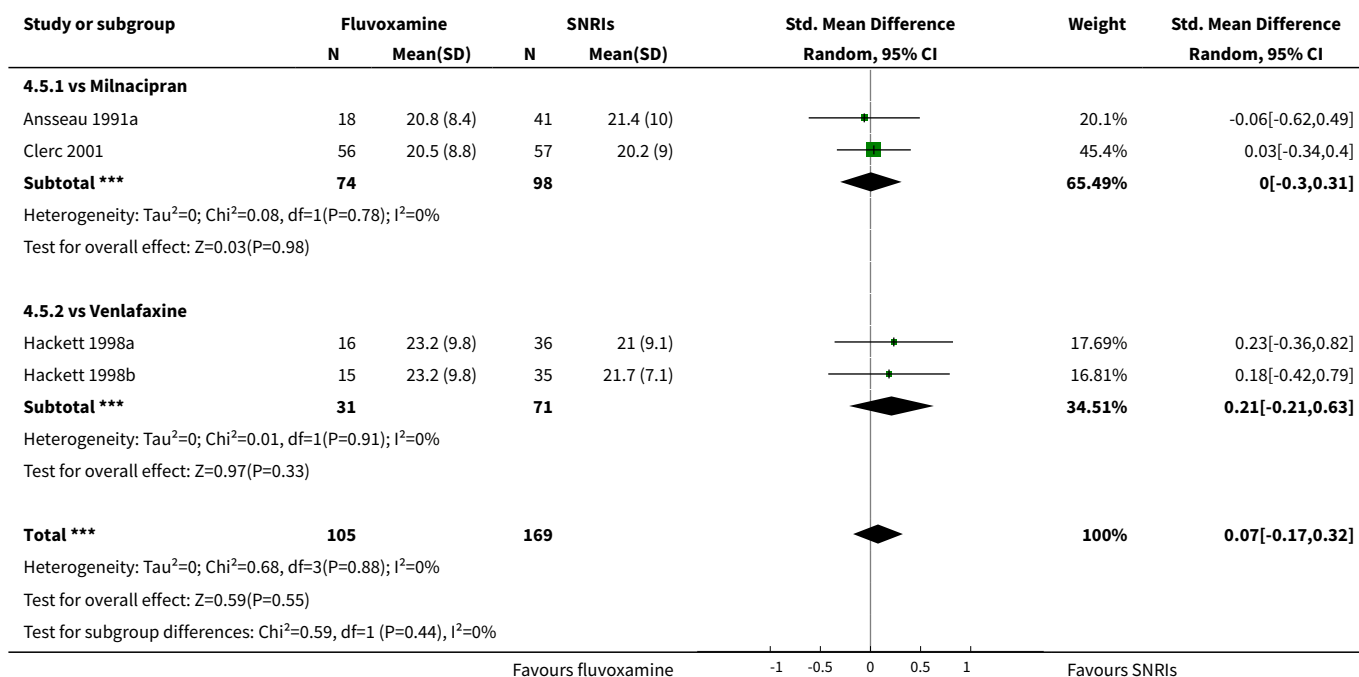




Analysis 4.4. Comparison 4 Fluvoxamine versus SNRIs, Outcome 4 Remission (acute phase).



Analysis 4.5. Comparison 4 Fluvoxamine versus SNRIs, Outcome 5 Depression scale - Endpoint score: low=good (early phase).



Analysis 4.6. Comparison 4 Fluvoxamine versus SNRIs, Outcome 6 Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data.

Study	Depression scale	Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Milnacipran								
Anseau 1991b	HRSD-24	20.8	8.4	19	20.1	10.1	42	skewed.

Analysis 4.7. Comparison 4 Fluvoxamine versus SNRIs, Outcome 7 Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data.

Study	Depression scale	Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Venlafaxine								
Hackett 1998a	MADRS	10.5	11.1	11	7.6	6.8	31	skewed.
Hackett 1998b	MADRS	10.5	11.1	10	10.5	9.3	28	skewed.

Analysis 4.8. Comparison 4 Fluvoxamine versus SNRIs, Outcome 8 Depression scale - Change score: decrease=good (early phase) - missing SDs.

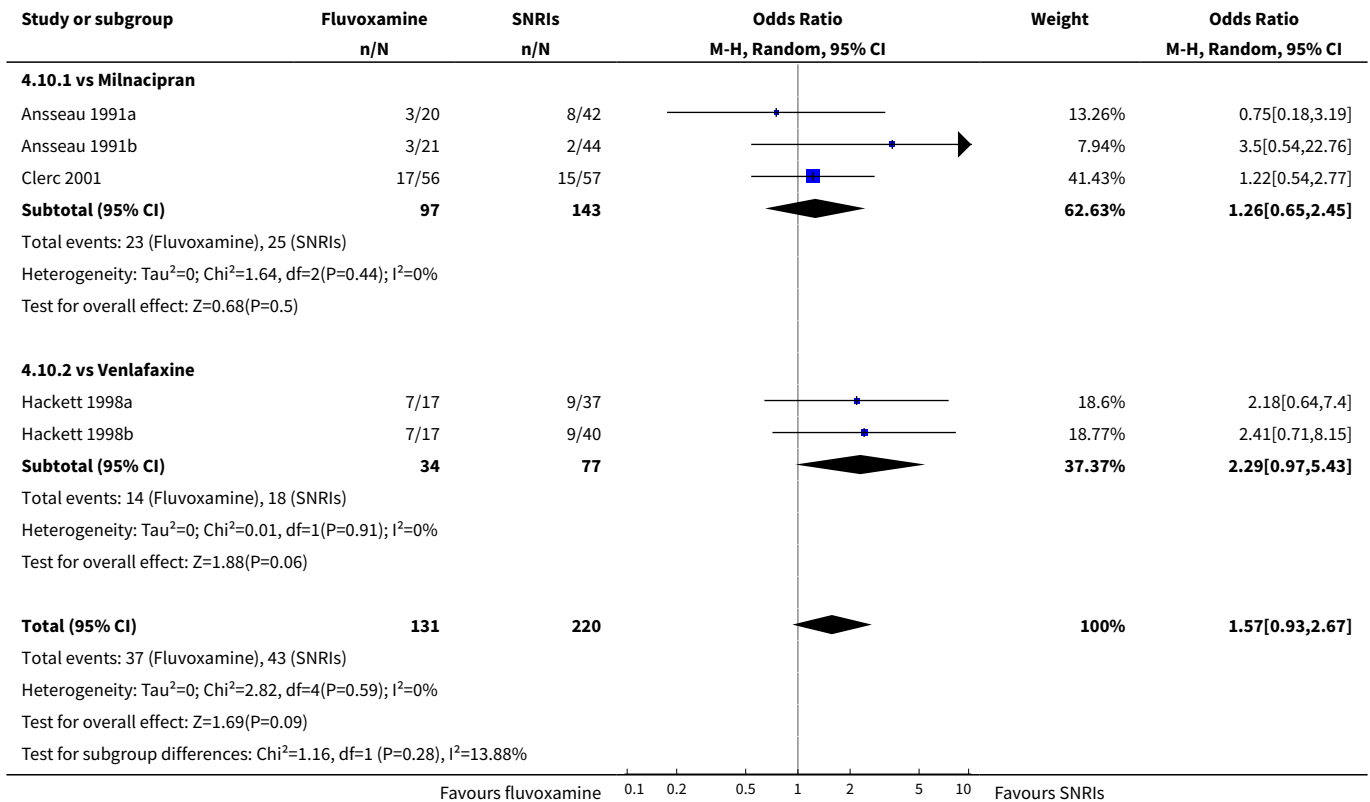
Study	Depression scale	Depression scale - Change score: decrease=good (early phase) - missing SDs						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Milnacipran								
Anseau 1991a	HRSD-21	-11.7	missing	19	-11.6	missing	42	

Depression scale - Change score: decrease=good (early phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
Anseau 1991b	HRSD-21	-11.7	missing	18	-12.4	missing	41	
Clerc 2001	HRSD-21	-10.9	missing	56	-12.6	missing	57	
vs Venlafaxine								
Hackett 1998a	MADRS	-8.4	missing	16	-11.7	missing	36	
Hackett 1998b	MADRS	-8.4	missing	15	-10	missing	35	

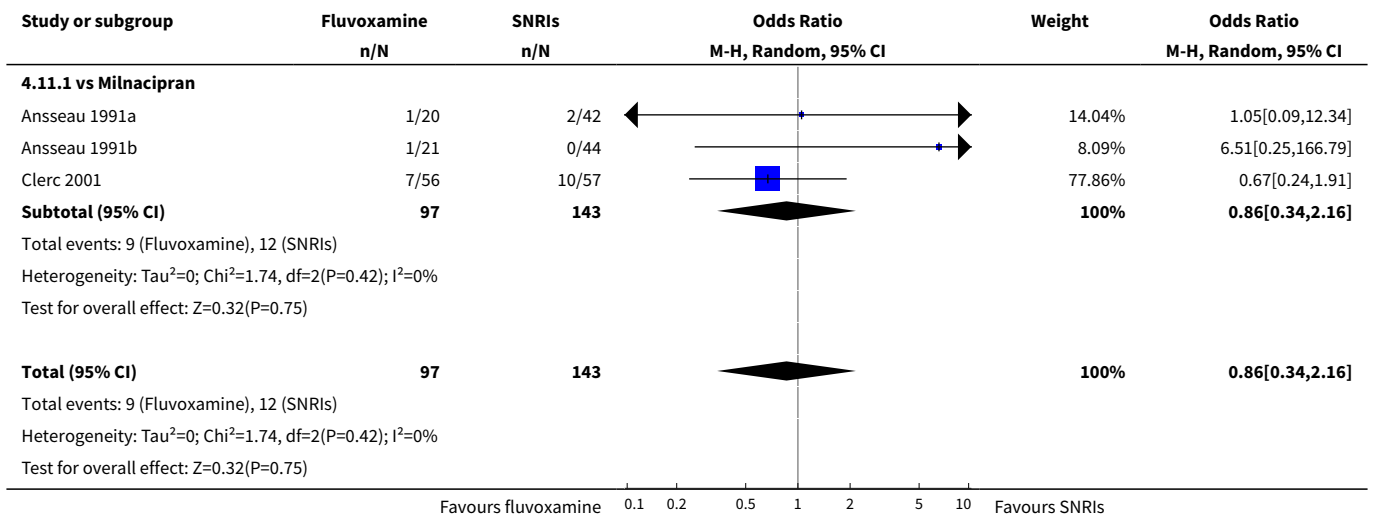
Analysis 4.9. Comparison 4 Fluvoxamine versus SNRIs, Outcome 9 Depression scale - Change score: decrease=good (acute phase) - missing SDs.

Depression scale - Change score: decrease=good (acute phase) - missing SDs								
Study	Depression scale	Fluvoxamine; mean	SD	n	comparator; mean	SD	n	Note
vs Milnacipran								
Clerc 2001	HRSD-21	-15.9	missing	56	-20.7	missing	57	
vs Venlafaxine								
Hackett 1998a	MADRS	-21.1	missing	10	-22.2	missing	28	
Hackett 1998b	MADRS	-21.1	missing	11	-24.1	missing	31	

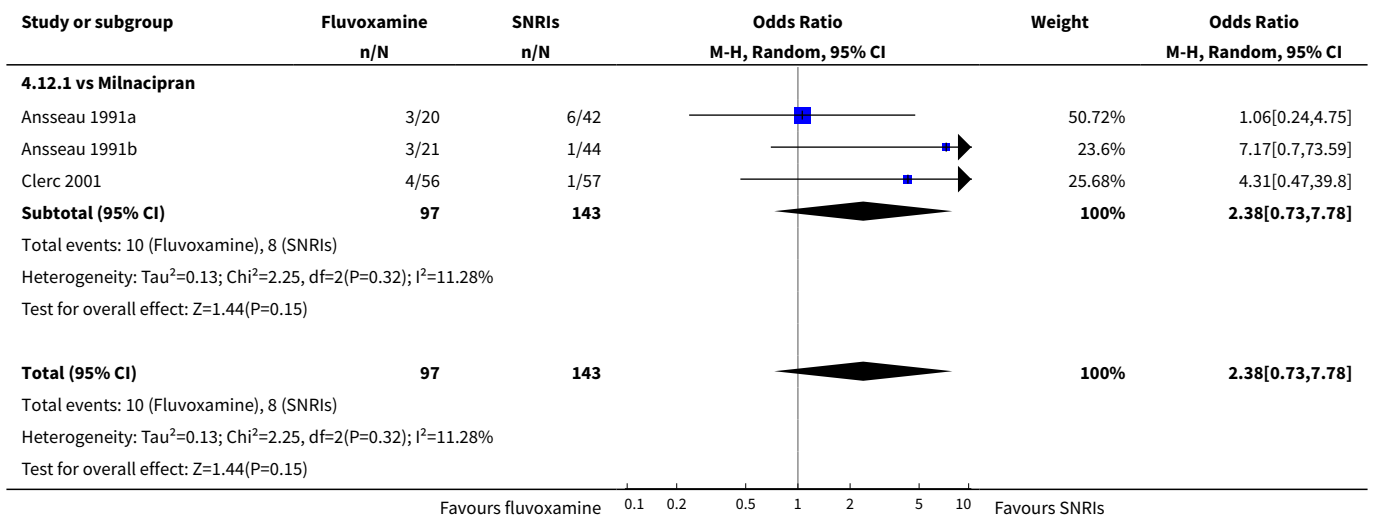
Analysis 4.10. Comparison 4 Fluvoxamine versus SNRIs, Outcome 10 Total Dropout.



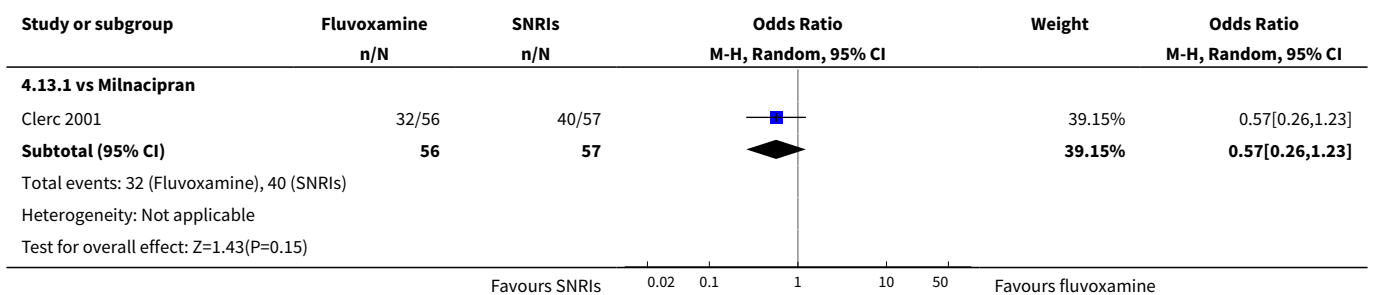
Analysis 4.11. Comparison 4 Fluvoxamine versus SNRIs, Outcome 11 Dropout due to inefficacy.

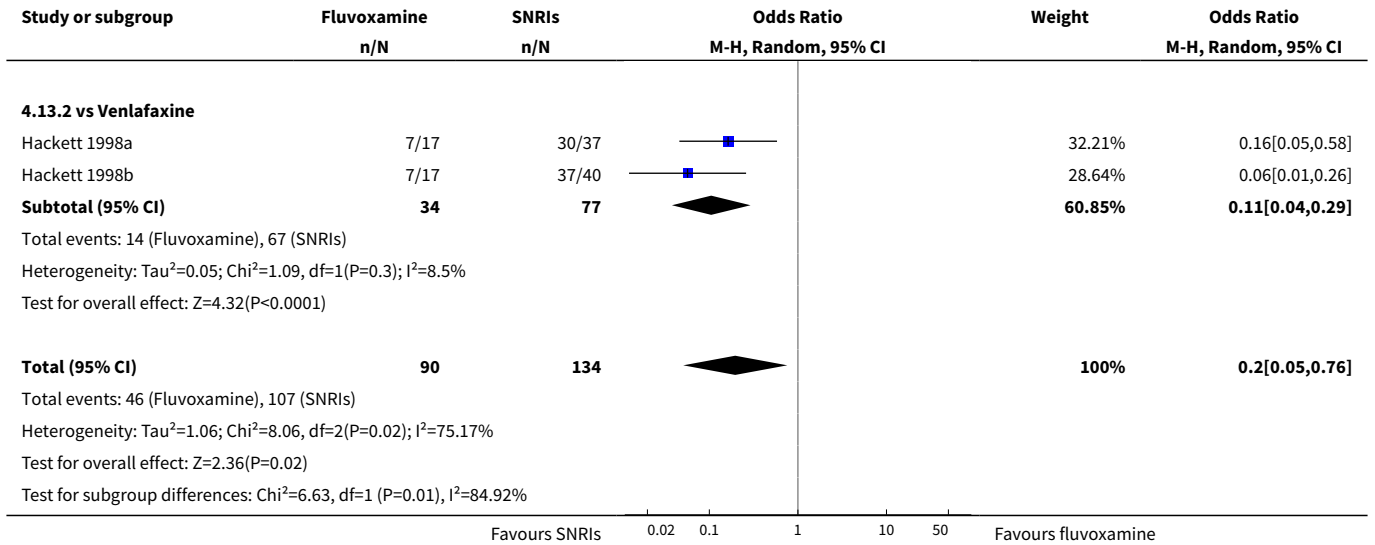


Analysis 4.12. Comparison 4 Fluvoxamine versus SNRIs, Outcome 12 Dropout due to side effects.

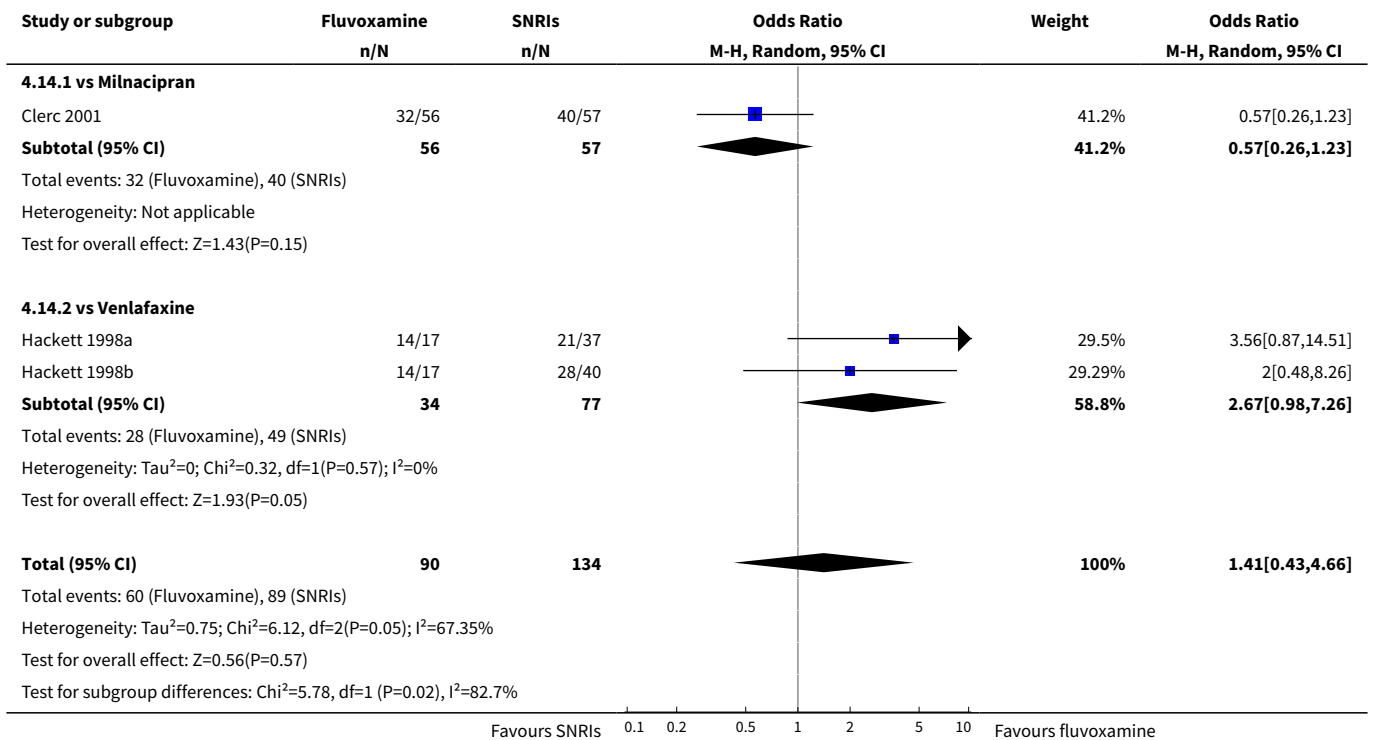


Analysis 4.13. Comparison 4 Fluvoxamine versus SNRIs, Outcome 13 Sensitivity analysis - Response (acute phase) 3. Worst case scenario ITT.

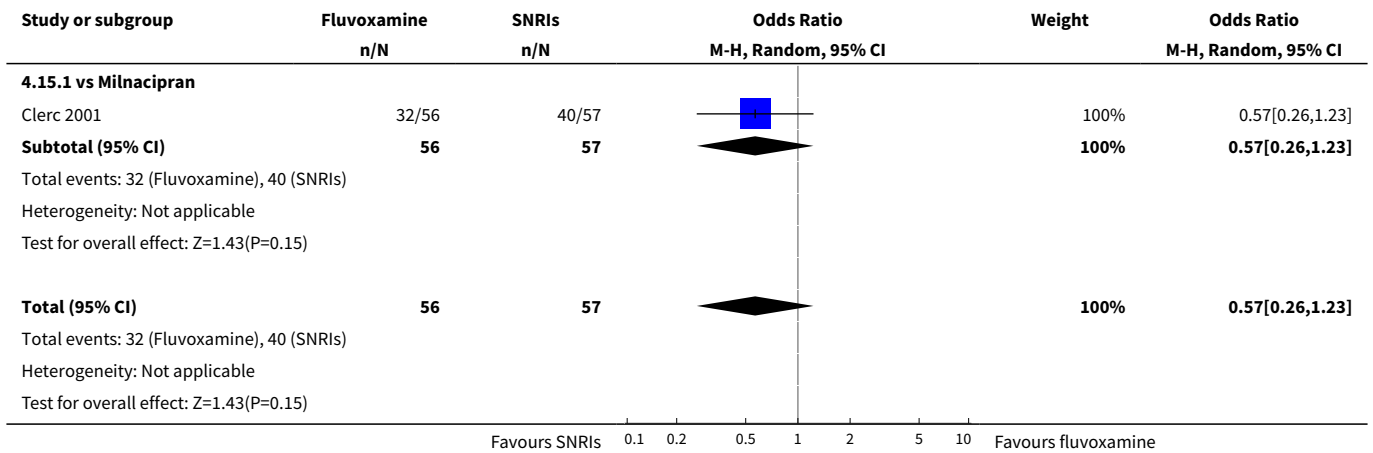




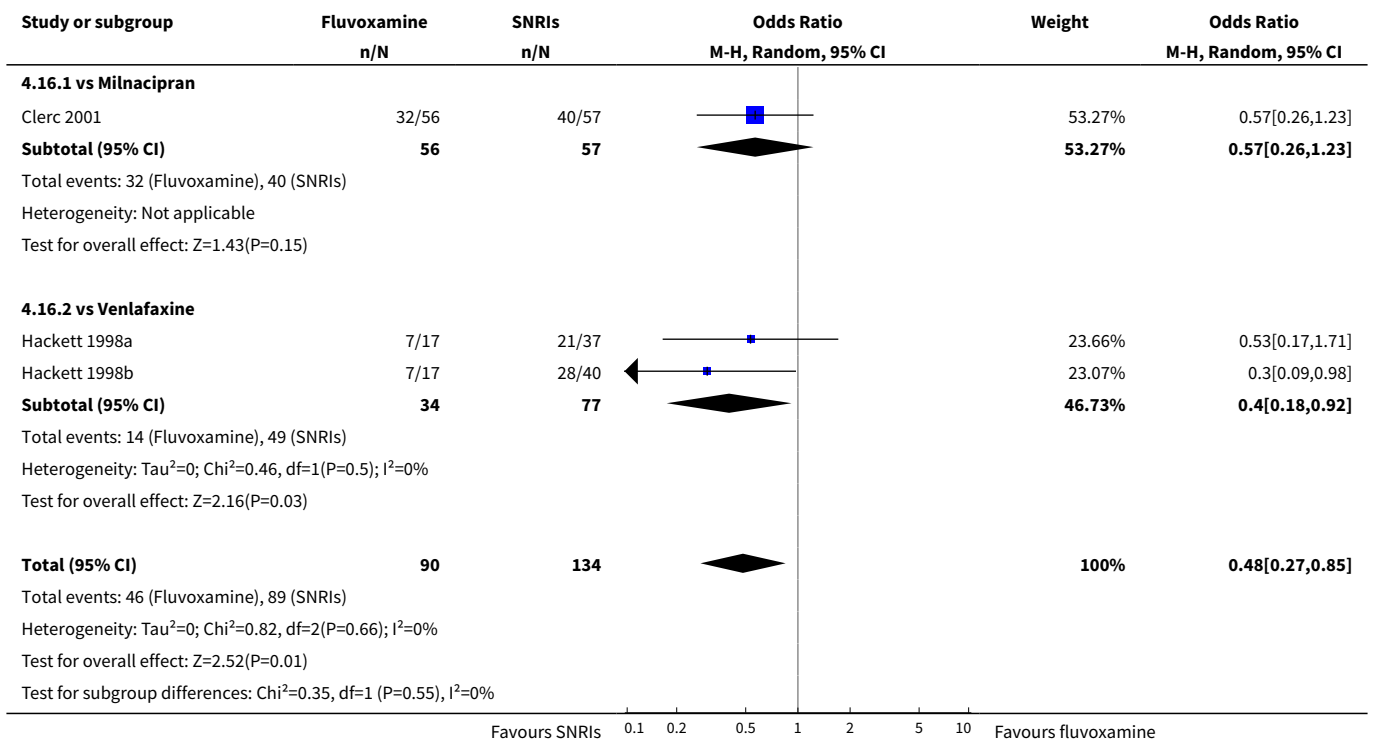
Analysis 4.14. Comparison 4 Fluvoxamine versus SNRIs, Outcome 14 Sensitivity analysis - Response (acute phase) 4. Best case scenario ITT.



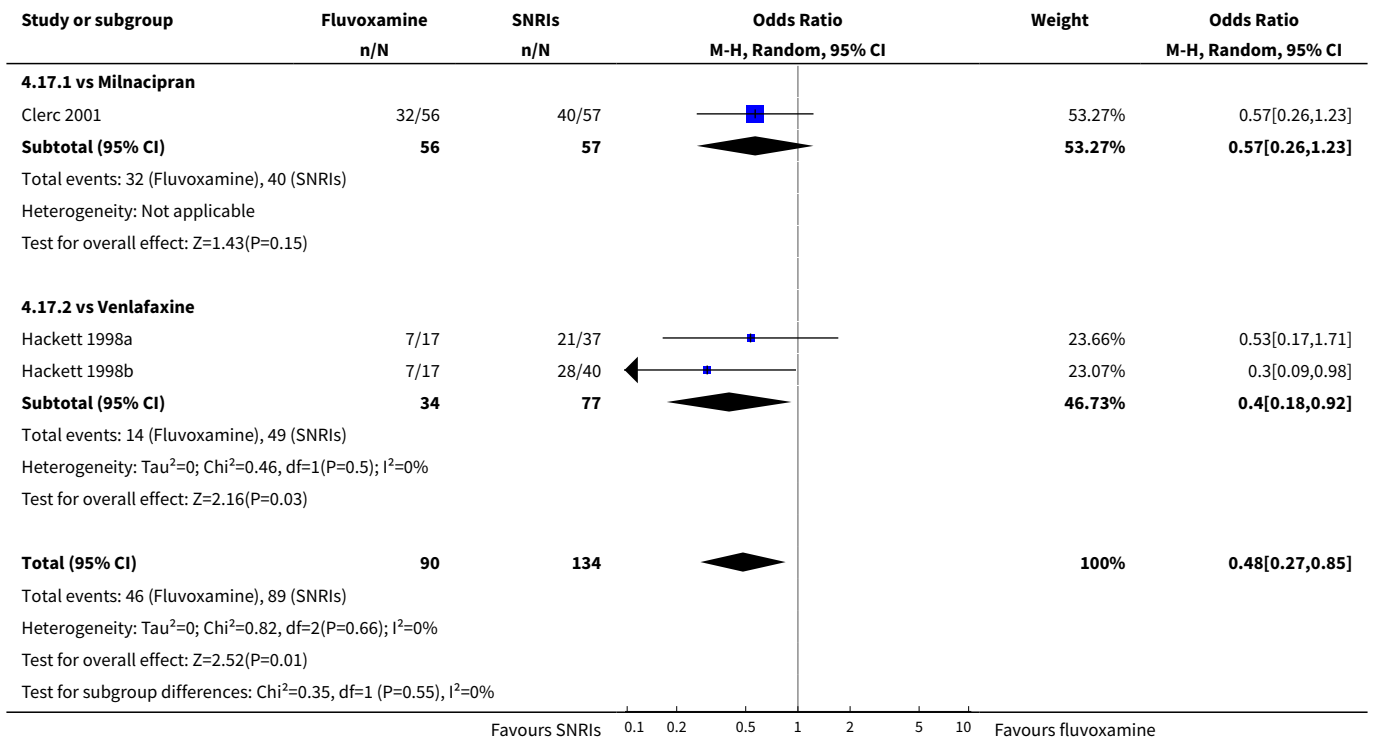
Analysis 4.15. Comparison 4 Fluvoxamine versus SNRIs, Outcome 15 Sensitivity analysis - Response (acute phase) 5. Excluding trials with imputation methods for calculating response.



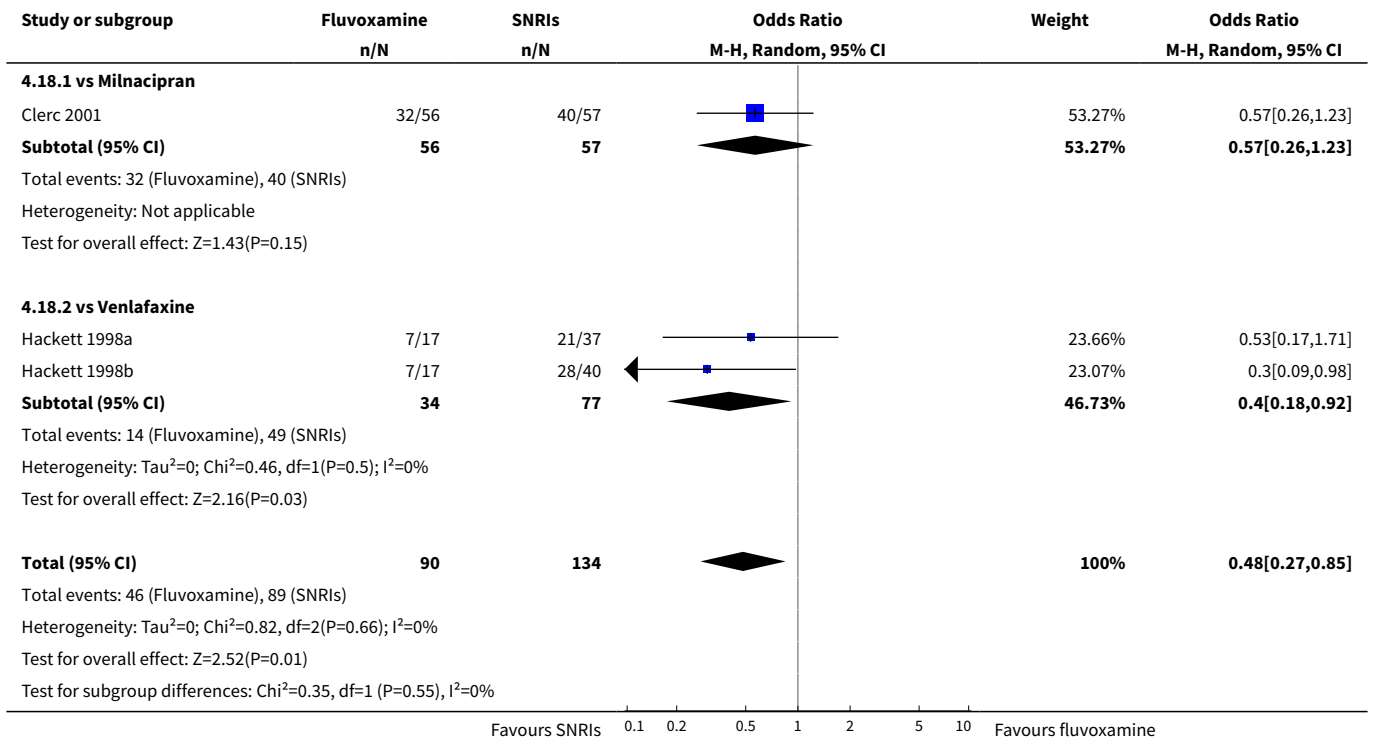
Analysis 4.16. Comparison 4 Fluvoxamine versus SNRIs, Outcome 16 Sensitivity analysis - Response (acute phase) 6. Wish bias - Fluvoxamine as a comparator drug.



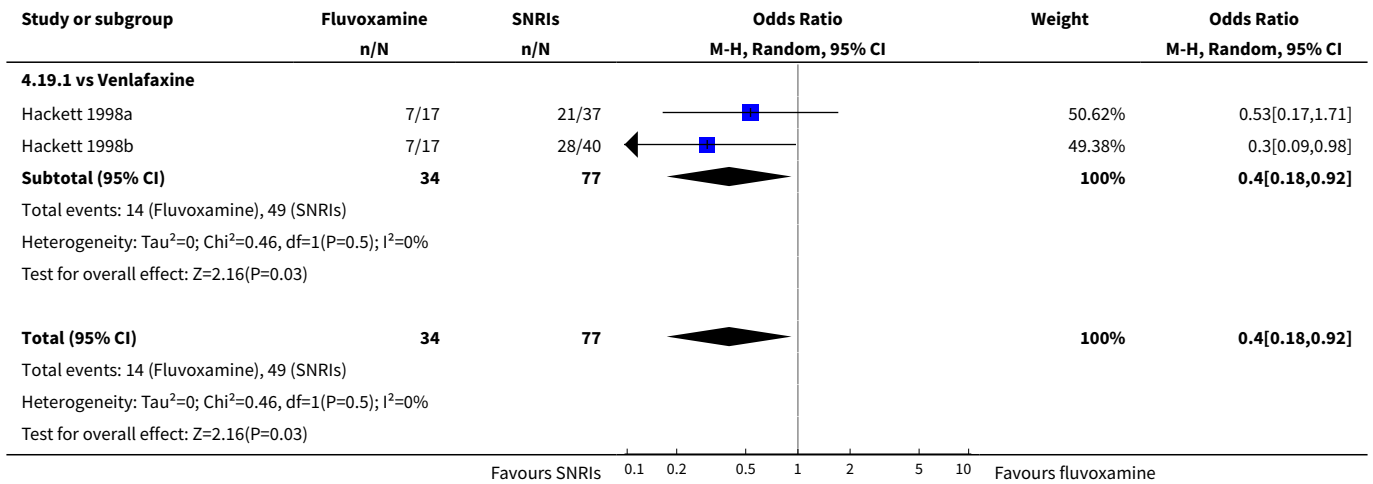
Analysis 4.17. Comparison 4 Fluvoxamine versus SNRIs, Outcome 17 Sensitivity analysis - Response (acute phase) 7. Funding - Excluding trials funded by the fluvoxamine marketing company.



Analysis 4.18. Comparison 4 Fluvoxamine versus SNRIs, Outcome 18 Sensitivity analysis - Response (acute phase) 8. Excluding trials that might include patients with bipolar depression.



Analysis 4.19. Comparison 4 Fluvoxamine versus SNRIs, Outcome 19 Sensitivity analysis - Response (acute phase) 9. Excluding trials that included patients with psychotic features.



Comparison 5. Fluvoxamine versus newer ADs

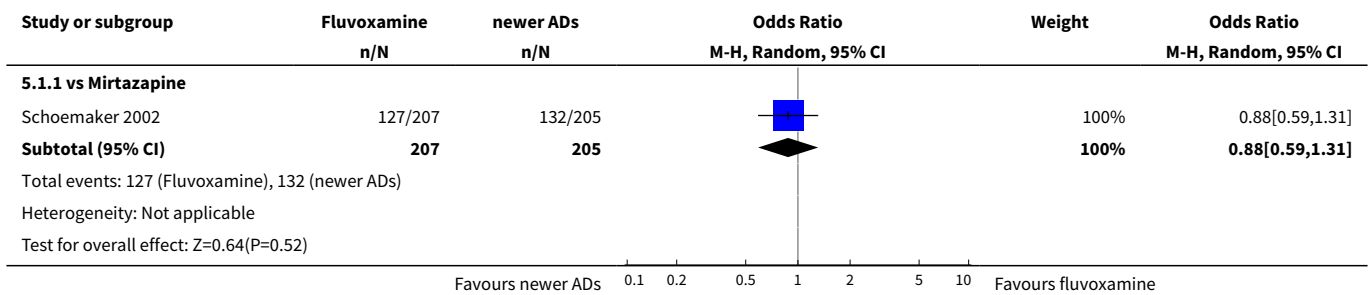
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response (acute phase): Primary outcome	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.31]
2 Response (early phase)	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.47, 1.11]
2.2 vs Moclobemide	3	231	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.26, 1.36]
3 Remission (early phase)	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.36, 1.30]
3.2 vs Moclobemide	3	231	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.16, 1.35]
4 Remission (acute phase)	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.81, 1.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data			Other data	No numeric data
5.1 vs Mirtazapine			Other data	No numeric data
5.2 vs Moclobemide			Other data	No numeric data
6 Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data			Other data	No numeric data
6.1 vs Mirtazapine			Other data	No numeric data
6.2 vs Moclobemide			Other data	No numeric data
7 Depression scale - Change score: decrease=good (early phase)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 vs Mirtazapine	1	402	Std. Mean Difference (IV, Random, 95% CI)	0.32 [0.12, 0.51]
8 Depression scale - Change score: decrease=good (early phase) - missing SDs			Other data	No numeric data
8.2 vs Moclobemide			Other data	No numeric data
9 Depression scale - Change score: decrease=good (acute phase)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 vs Mirtazapine	1	402	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.12, 0.28]
10 Total Dropout	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.33]
10.2 vs Moclobemide	3	231	Odds Ratio (M-H, Random, 95% CI)	1.41 [0.73, 2.71]
11 Dropout due to inefficacy	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	2.02 [0.60, 6.82]
11.2 vs Moclobemide	3	231	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.14, 2.71]
12 Dropout due to side effects	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

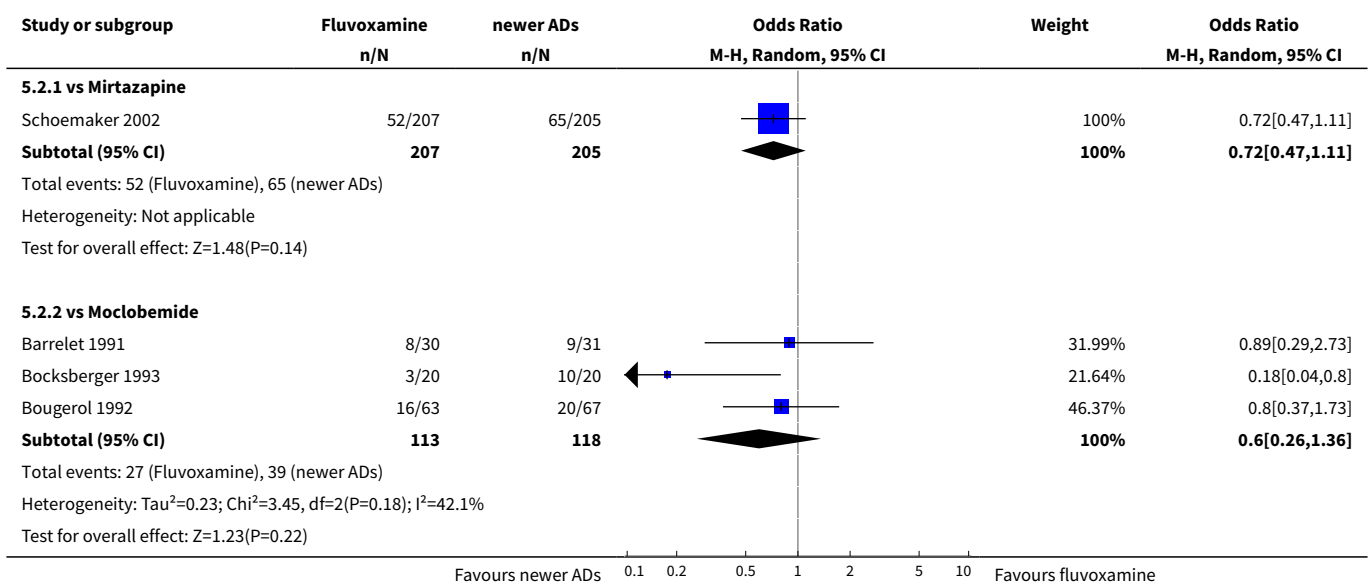
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.31, 1.17]
12.2 vs Moclobemide	3	231	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.64, 3.53]
13 Number of patients experiencing at least one side effect	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 vs Moclobemide	3	231	Odds Ratio (M-H, Random, 95% CI)	2.29 [1.35, 3.88]
14 Sensitivity analysis - Response (acute phase) 3. Worst case scenario ITT	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.51, 1.15]
15 Sensitivity analysis - Response (acute phase) 4. Best case scenario ITT	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.64, 1.42]
16 Sensitivity analysis - Response (acute phase) 5. Excluding trials with imputation methods for calculating response	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.31]
17 Sensitivity analysis - Mean change from baseline (acute phase) 5. Excluding trials for which the SD had to be borrowed from other trials	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 vs Mirtazapine	1	402	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.12, 0.28]
18 Sensitivity analysis - Response (acute phase) 6. Wish bias - Fluvoxamine as a comparator drug	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.31]
19 Sensitivity analysis - Response (acute phase) 8. Excluding trials that might include patients with bipolar depression	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20 Sensitivity analysis - Response (acute phase) 7. Funding - Excluding trials funded by the fluvoxamine marketing company	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.31]
21 Sensitivity analysis - Response (acute phase) 9. Excluding trials that included patients with psychotic features	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.31]

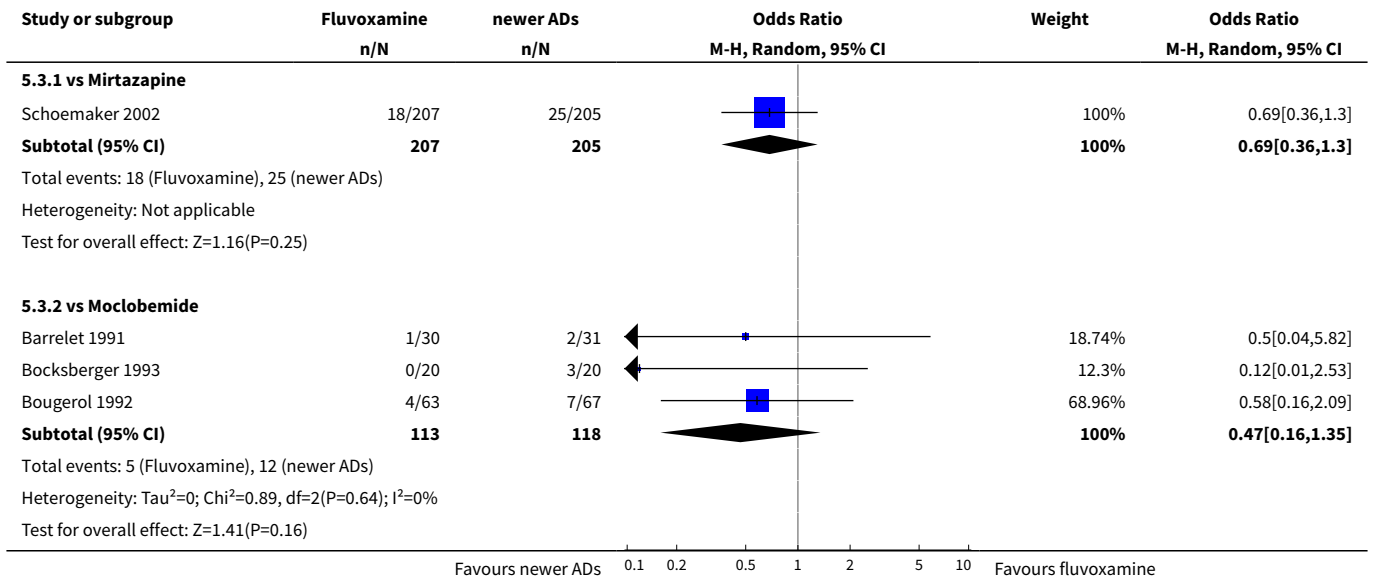
Analysis 5.1. Comparison 5 Fluvoxamine versus newer ADs, Outcome 1 Response (acute phase): Primary outcome.



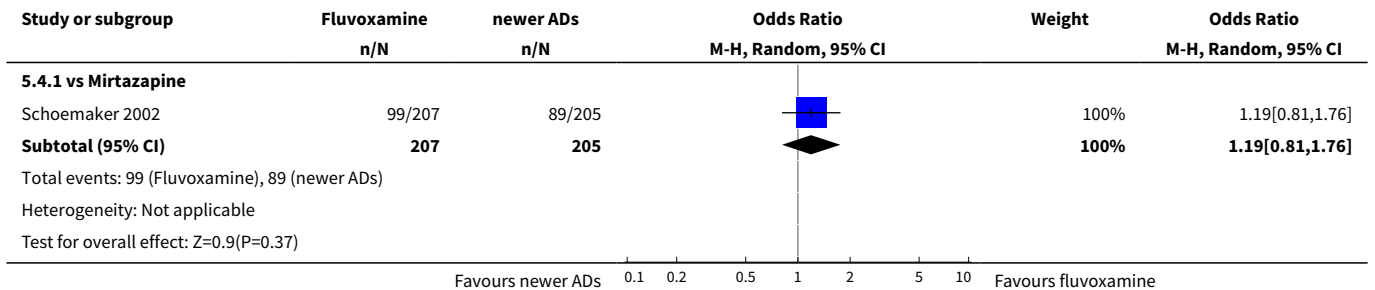
Analysis 5.2. Comparison 5 Fluvoxamine versus newer ADs, Outcome 2 Response (early phase).



Analysis 5.3. Comparison 5 Fluvoxamine versus newer ADs, Outcome 3 Remission (early phase).



Analysis 5.4. Comparison 5 Fluvoxamine versus newer ADs, Outcome 4 Remission (acute phase).



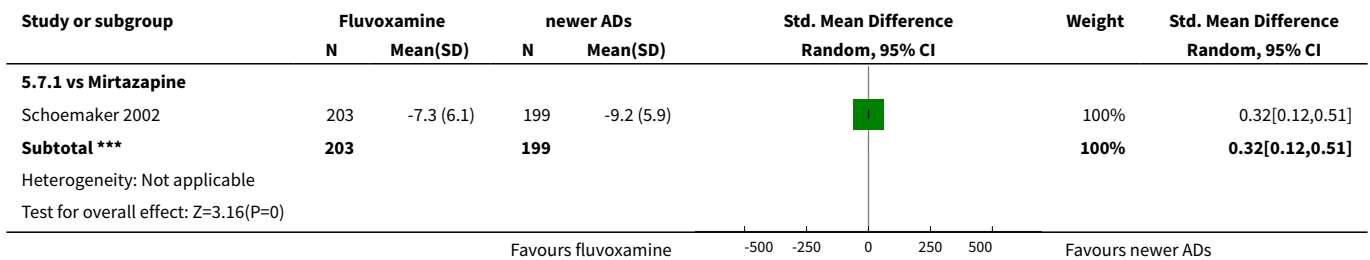
Analysis 5.5. Comparison 5 Fluvoxamine versus newer ADs, Outcome 5 Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data.

Study	Depression scale	Depression scale - Endpoint score: low=good (early phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Mirtazapine								
Schoemaker 2002	HRSD-17	16.5	missing	203	14.8	missing	199	
vs Moclobemide								
Bocksberger 1993	MADRS	31.5	9.8	19	20.0	10.8	19	skewed.

Analysis 5.6. Comparison 5 Fluvoxamine versus newer ADs, Outcome 6 Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data.

Study	Depression scale	Depression scale - Endpoint score: low=good (acute phase) - missing SDs or skewed data						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Mirtazapine								
Schoemaker 2002	HRSD-17	16.5	missing	203	14.8	missing	199	
vs Moclobemide								
Bocksberger 1993	MADRS	31.5	9.8	19	20.0	10.8	19	skewed.

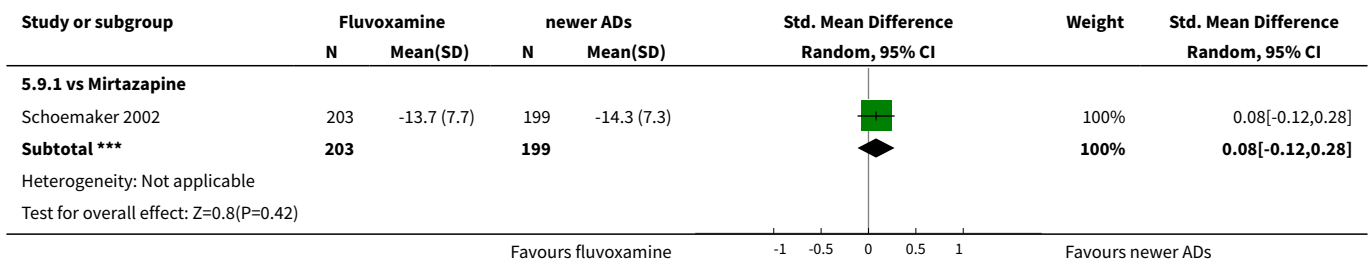
Analysis 5.7. Comparison 5 Fluvoxamine versus newer ADs, Outcome 7 Depression scale - Change score: decrease=good (early phase).



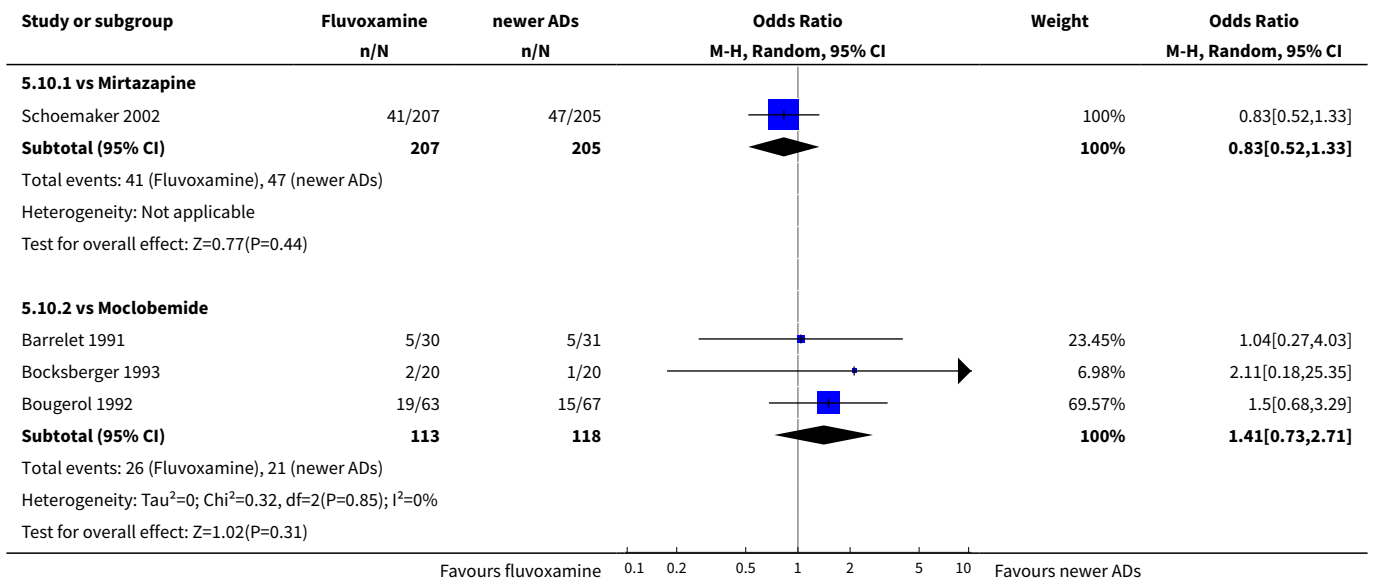
Analysis 5.8. Comparison 5 Fluvoxamine versus newer ADs, Outcome 8 Depression scale - Change score: decrease=good (early phase) - missing SDs.

Study	Depression scale	Depression scale - Change score: decrease=good (early phase) - missing SDs						Note
		Fluvoxamine; mean	SD	n	comparator; mean	SD	n	
vs Moclobemide								
Barrelet 1991	HRSD-17	-10.3	missing	25	-10.1	missing	26	
Bocksberger 1993	NADRS	-11.8	missing	19	-21.9	missing	19	
Bougerol 1992	HRSD-17	-8.4	missing	61	-9.0	missing	65	

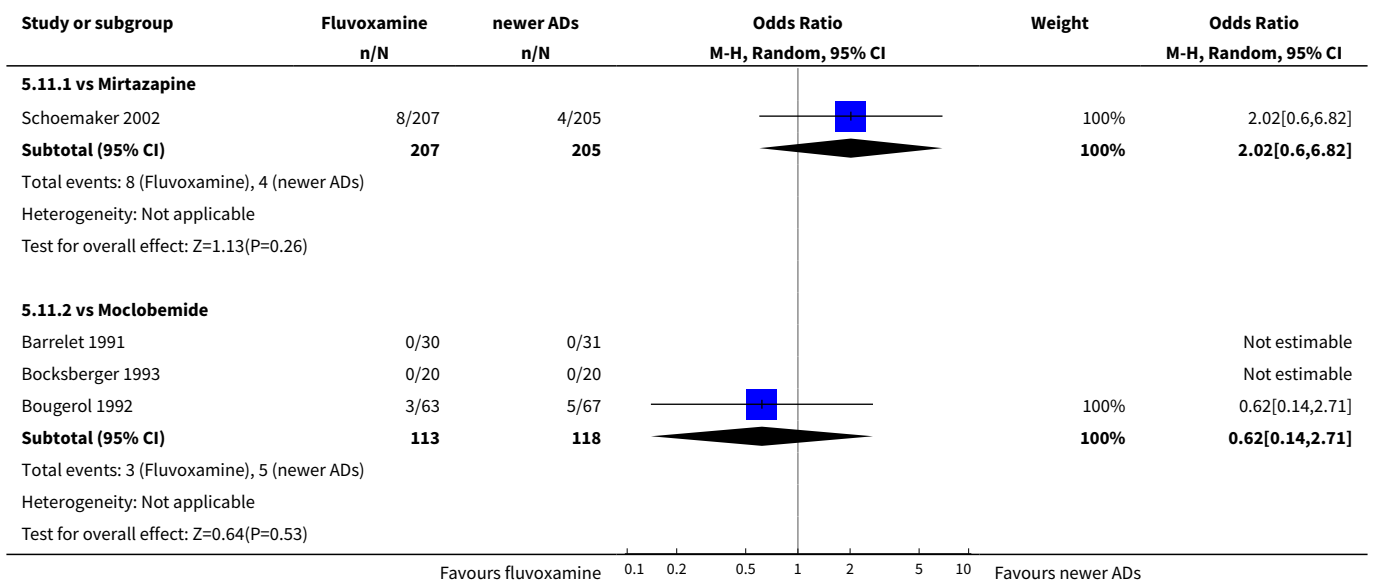
Analysis 5.9. Comparison 5 Fluvoxamine versus newer ADs, Outcome 9 Depression scale - Change score: decrease=good (acute phase).



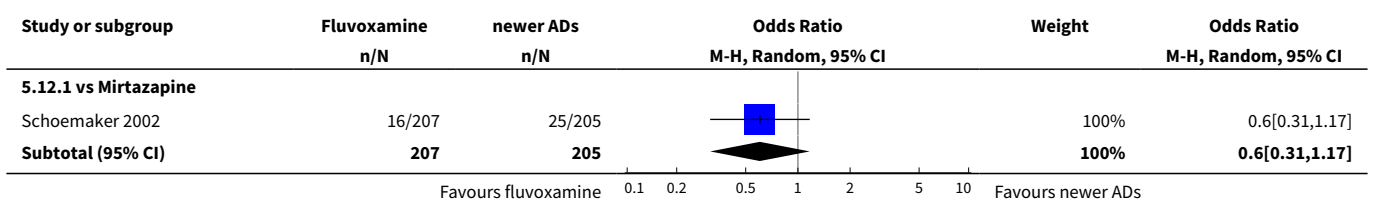
Analysis 5.10. Comparison 5 Fluvoxamine versus newer ADs, Outcome 10 Total Dropout.

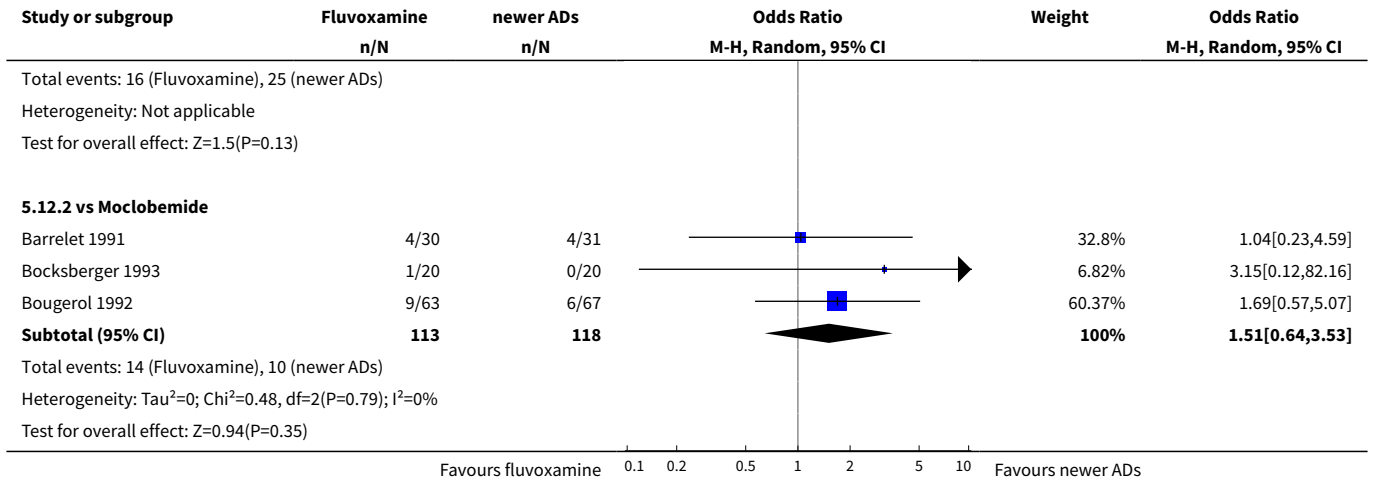


Analysis 5.11. Comparison 5 Fluvoxamine versus newer ADs, Outcome 11 Dropout due to inefficacy.

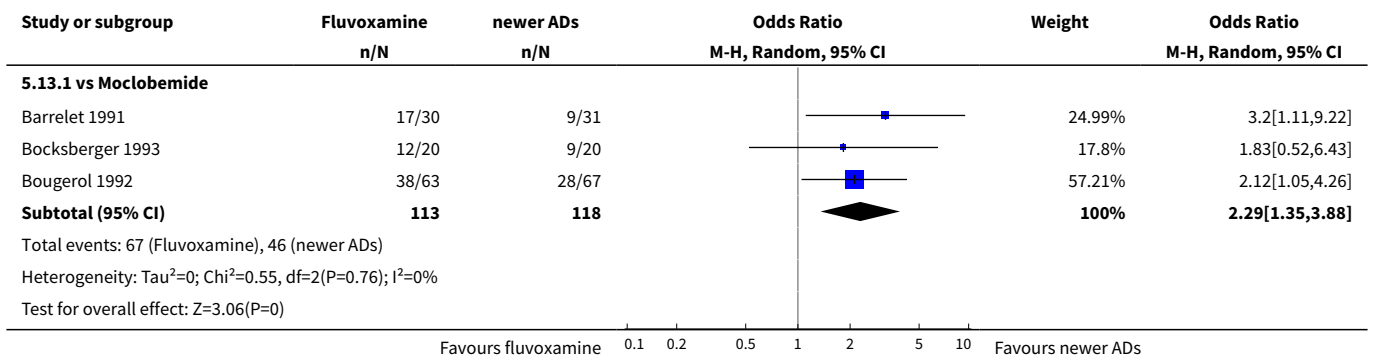


Analysis 5.12. Comparison 5 Fluvoxamine versus newer ADs, Outcome 12 Dropout due to side effects.

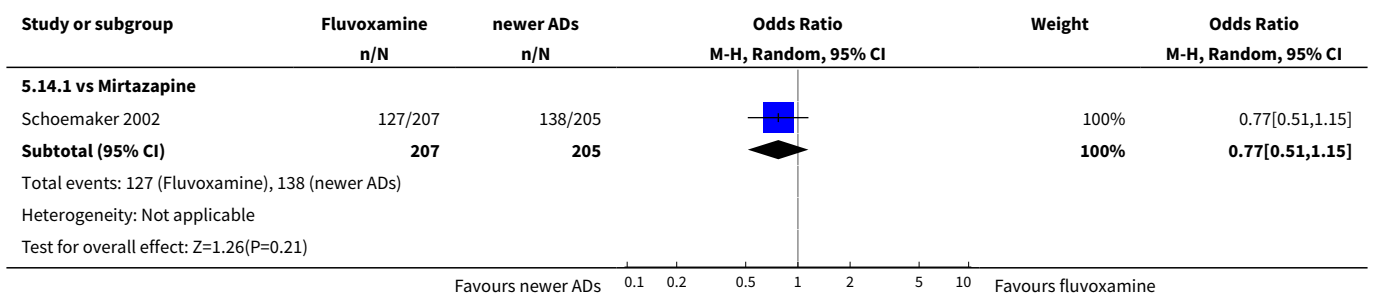




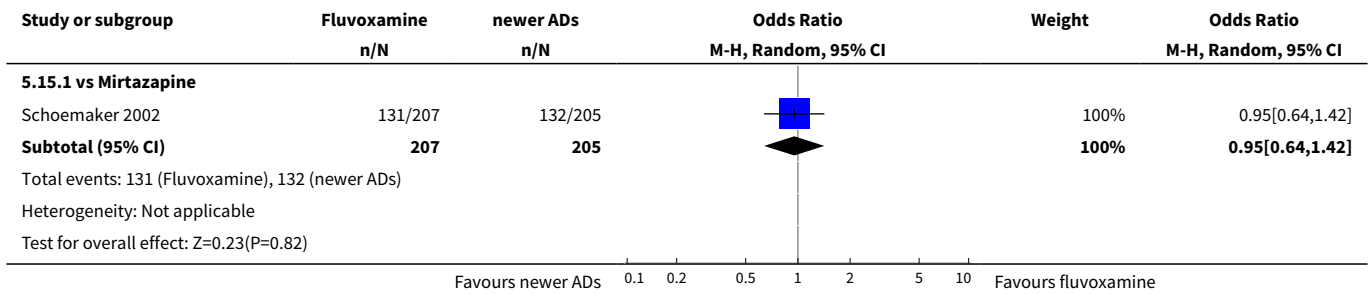
Analysis 5.13. Comparison 5 Fluvoxamine versus newer ADs, Outcome 13 Number of patients experiencing at least one side effect.



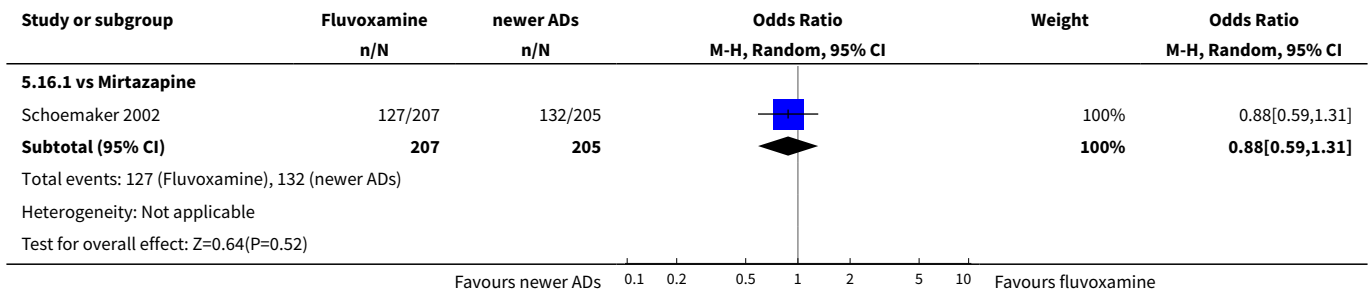
Analysis 5.14. Comparison 5 Fluvoxamine versus newer ADs, Outcome 14 Sensitivity analysis - Response (acute phase) 3. Worst case scenario ITT.



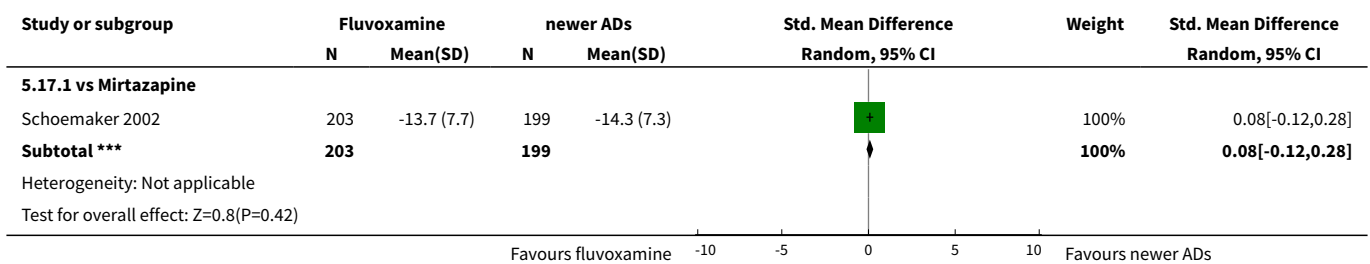
Analysis 5.15. Comparison 5 Fluvoxamine versus newer ADs, Outcome 15 Sensitivity analysis - Response (acute phase) 4. Best case scenario ITT.



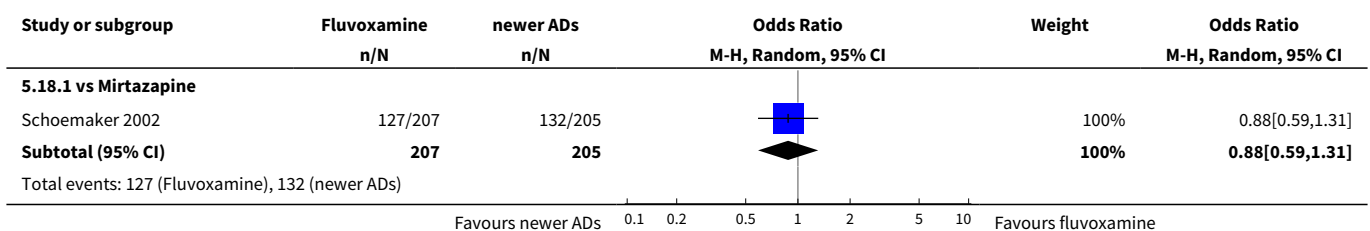
Analysis 5.16. Comparison 5 Fluvoxamine versus newer ADs, Outcome 16 Sensitivity analysis - Response (acute phase) 5. Excluding trials with imputation methods for calculating response.

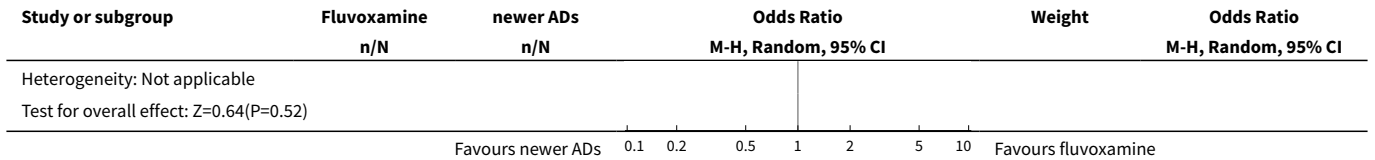


Analysis 5.17. Comparison 5 Fluvoxamine versus newer ADs, Outcome 17 Sensitivity analysis - Mean change from baseline (acute phase) 5. Excluding trials for which the SD had to be borrowed from other trials.

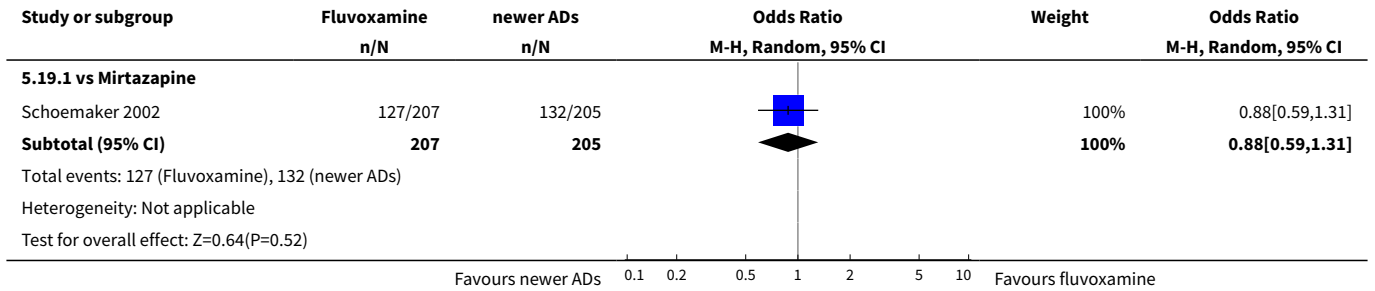


Analysis 5.18. Comparison 5 Fluvoxamine versus newer ADs, Outcome 18 Sensitivity analysis - Response (acute phase) 6. Wish bias - Fluvoxamine as a comparator drug.

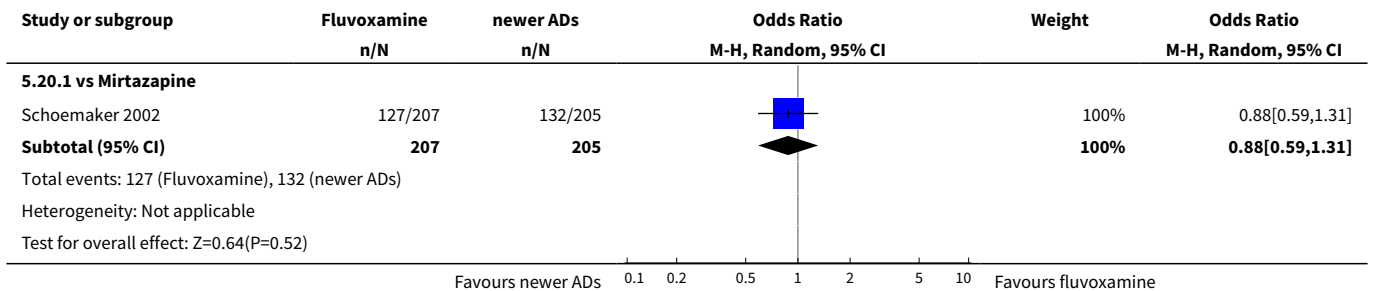




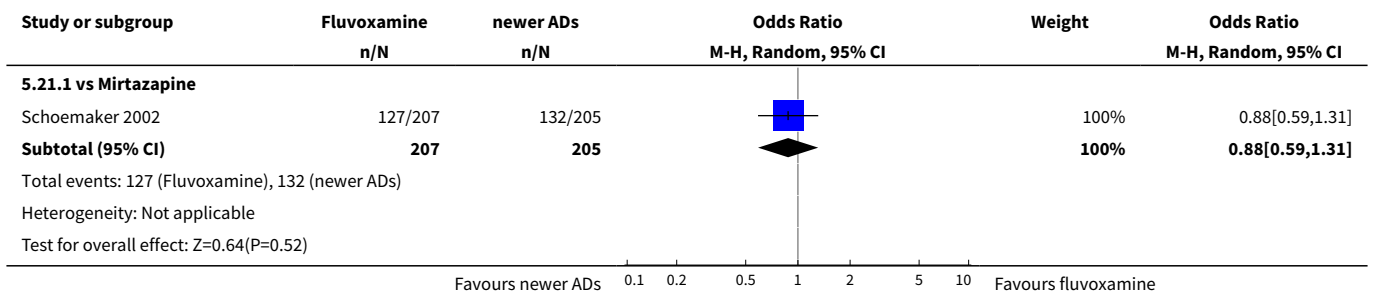
Analysis 5.19. Comparison 5 Fluvoxamine versus newer ADs, Outcome 19 Sensitivity analysis - Response (acute phase) 8. Excluding trials that might include patients with bipolar depression.



Analysis 5.20. Comparison 5 Fluvoxamine versus newer ADs, Outcome 20 Sensitivity analysis - Response (acute phase) 7. Funding - Excluding trials funded by the fluvoxamine marketing company.



Analysis 5.21. Comparison 5 Fluvoxamine versus newer ADs, Outcome 21 Sensitivity analysis - Response (acute phase) 9. Excluding trials that included patients with psychotic features.



Comparison 6. Fluvoxamine versus other conventional psychotropic drugs

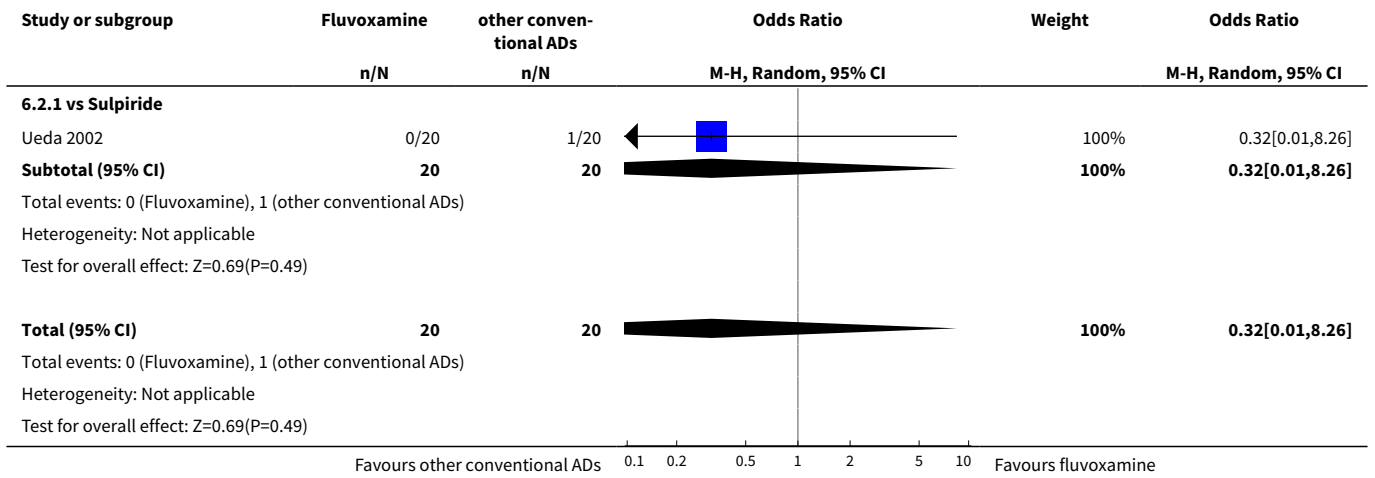
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response (early phase)	1	40	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.1 vs Sulpiride	1	40	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Remission (early phase)	1	40	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.26]
2.1 vs Sulpiride	1	40	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.26]
3 Depression scale - End-point score: low=good (early phase)	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.47 [-0.16, 1.10]
3.1 vs Sulpiride	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.47 [-0.16, 1.10]
4 Depression scale - Change score: decrease=good (early phase)	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.52 [-0.11, 1.15]
4.1 vs Sulpiride	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.52 [-0.11, 1.15]
5 Total Dropout	1	40	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.1 vs Sulpiride	1	40	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Fluvoxamine versus other conventional psychotropic drugs, Outcome 1 Response (early phase).

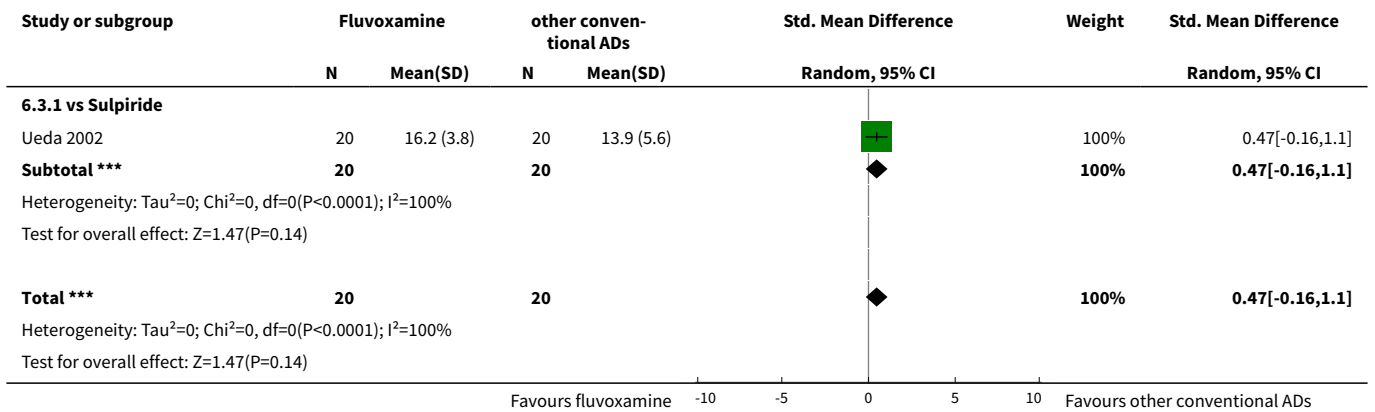
Study or subgroup	Fluvoxamine	other conventional ADs	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
	n/N	n/N			
6.1.1 vs Sulpiride					
Ueda 2002	0/20	0/20			Not estimable
Subtotal (95% CI)	20	20			Not estimable
Total events: 0 (Fluvoxamine), 0 (other conventional ADs)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	20	20			Not estimable
Total events: 0 (Fluvoxamine), 0 (other conventional ADs)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours other conventional ADs 0.01 0.1 1 10 100 Favours fluvoxamine

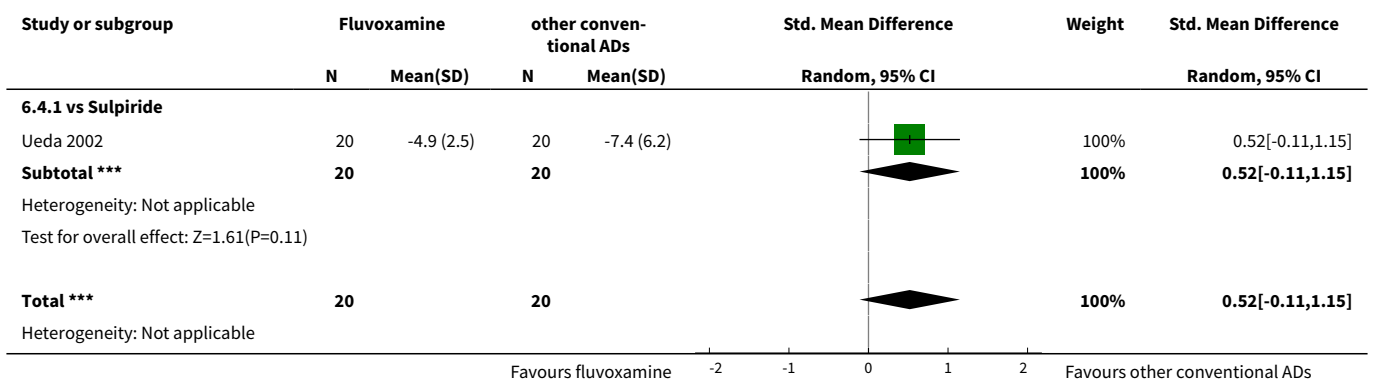
Analysis 6.2. Comparison 6 Fluvoxamine versus other conventional psychotropic drugs, Outcome 2 Remission (early phase).

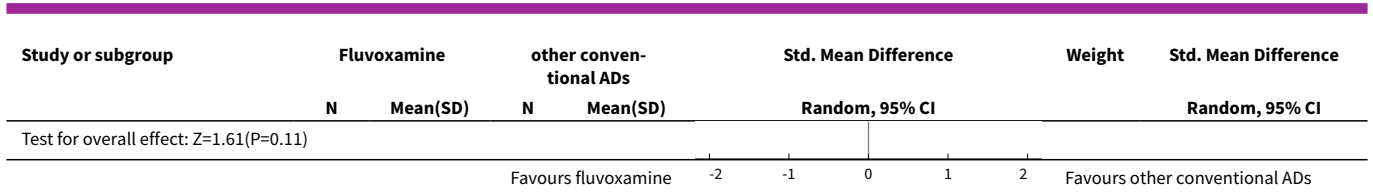


Analysis 6.3. Comparison 6 Fluvoxamine versus other conventional psychotropic drugs, Outcome 3 Depression scale - Endpoint score: low=good (early phase).

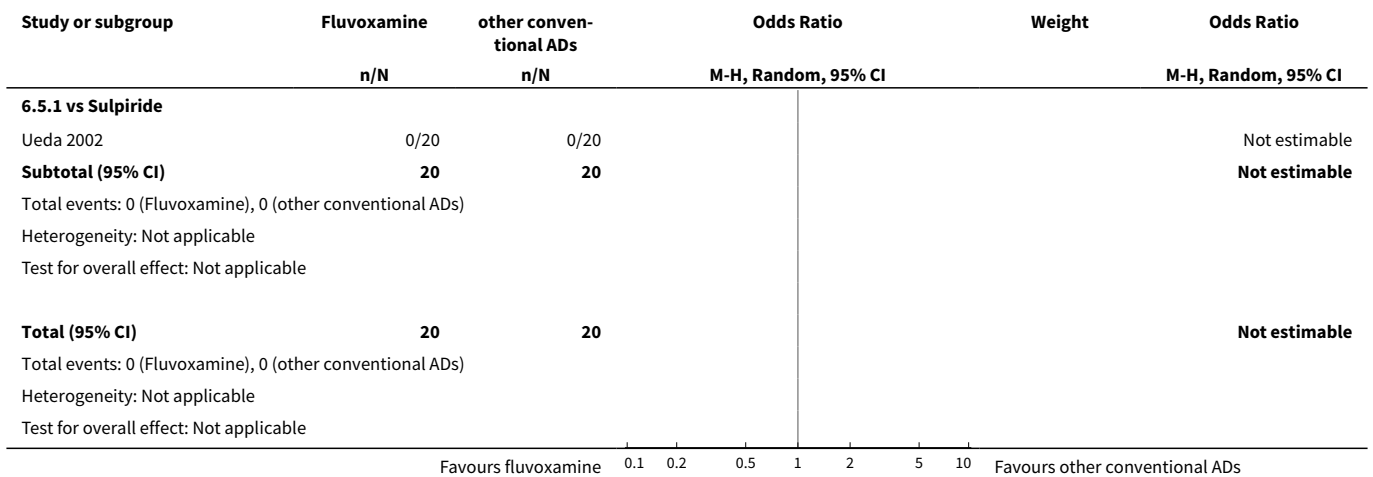


Analysis 6.4. Comparison 6 Fluvoxamine versus other conventional psychotropic drugs, Outcome 4 Depression scale - Change score: decrease=good (early phase).





Analysis 6.5. Comparison 6 Fluvoxamine versus other conventional psychotropic drugs, Outcome 5 Total Dropout.



Comparison 7. Side effect profile: Fluvoxamine vs TCAs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular - Hypertension / tachycardia	4	363	Odds Ratio (M-H, Random, 95% CI)	1.56 [0.51, 4.78]
1.1 vs Imipramine	1	36	Odds Ratio (M-H, Random, 95% CI)	1.64 [0.31, 8.68]
1.2 vs Clomipramine	1	32	Odds Ratio (M-H, Random, 95% CI)	5.0 [0.22, 112.88]
1.3 vs Amitriptyline	2	295	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.19, 5.81]
2 Cardiovascular - Hypotension / bradycardia	8	930	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.79]
2.1 vs Imipramine	4	560	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.10, 0.62]
2.2 vs Clomipramine	2	75	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.38, 4.02]
2.3 vs Amitriptyline	2	295	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.03, 1.18]
3 Dermatological - Dermatitis / rash	3	348	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.17, 4.61]
3.1 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.05, 5.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 vs Desipramine	1	40	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.26]
3.3 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	5.14 [0.24, 110.89]
4 Dermatological - Sweating	11	1248	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.28, 0.88]
4.1 vs Imipramine	7	972	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.16, 0.66]
4.2 vs Clomipramine	3	216	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.45, 1.73]
4.3 vs Amitriptyline	1	60	Odds Ratio (M-H, Random, 95% CI)	2.07 [0.18, 24.15]
5 Gastrointestinal - Increased salivation	1	30	Odds Ratio (M-H, Random, 95% CI)	9.33 [0.96, 90.94]
5.1 vs Imipramine	1	30	Odds Ratio (M-H, Random, 95% CI)	9.33 [0.96, 90.94]
6 Gastrointestinal - Dry mouth	17	1736	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.19, 0.38]
6.1 vs Imipramine	9	1055	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.16, 0.34]
6.2 vs Clomipramine	3	216	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.22, 0.81]
6.3 vs Amitriptyline	3	318	Odds Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.06]
6.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.16, 1.06]
6.5 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	0.08 [0.01, 0.70]
7 Gastrointestinal - Oral discomfort / taste disturbance	2	308	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.06, 2.98]
7.1 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.01, 8.85]
7.2 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.04, 5.45]
8 Gastrointestinal - Vomiting / nausea	18	1805	Odds Ratio (M-H, Random, 95% CI)	2.35 [1.80, 3.07]
8.1 vs Imipramine	9	1055	Odds Ratio (M-H, Random, 95% CI)	2.23 [1.59, 3.14]
8.2 vs Clomipramine	3	216	Odds Ratio (M-H, Random, 95% CI)	2.13 [1.06, 4.27]
8.3 vs Amitriptyline	4	387	Odds Ratio (M-H, Random, 95% CI)	2.86 [1.31, 6.23]
8.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	3.01 [1.00, 9.11]
8.5 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	2.71 [0.90, 8.19]
9 Gastrointestinal - Constipation	15	1666	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.80]
9.1 vs Imipramine	8	1008	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.27, 0.93]

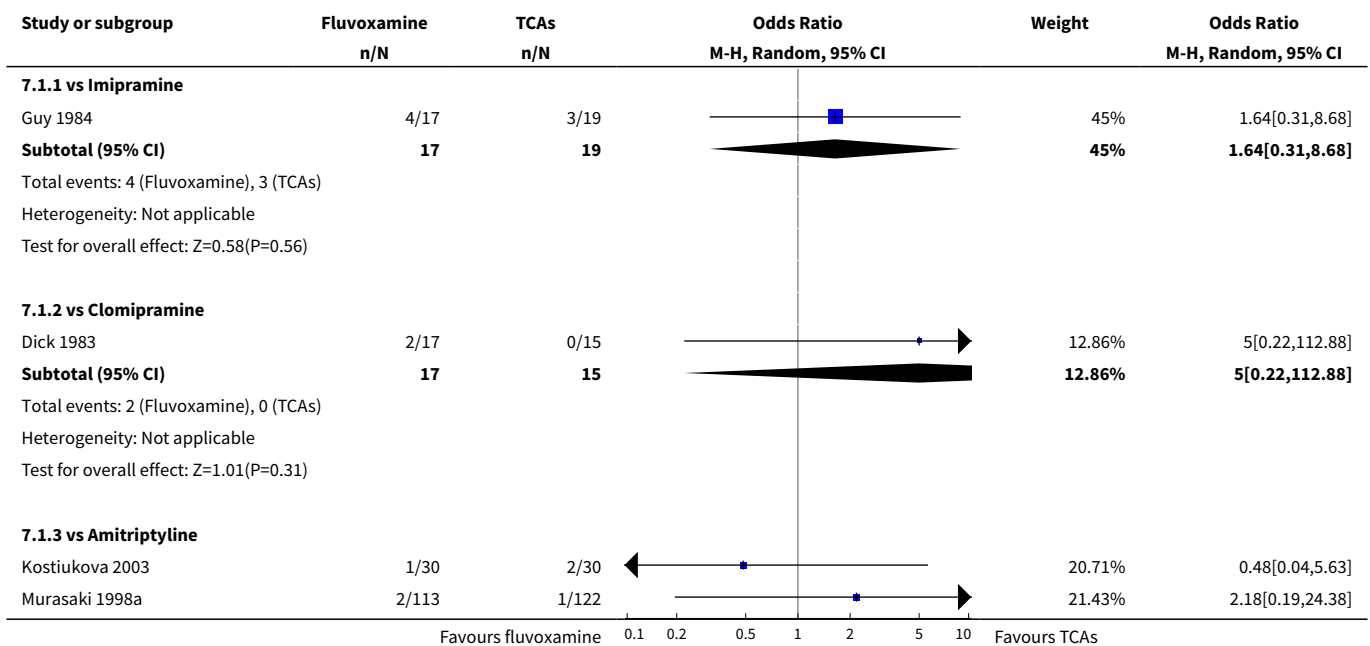
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 vs Clomipramine	3	216	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.27, 1.09]
9.3 vs Amitriptyline	2	295	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.25]
9.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.25, 1.60]
9.5 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.03, 3.08]
10 Gastrointestinal - Diarrhoea	5	518	Odds Ratio (M-H, Random, 95% CI)	2.98 [1.08, 8.20]
10.1 vs Imipramine	2	136	Odds Ratio (M-H, Random, 95% CI)	6.38 [1.27, 32.04]
10.2 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.01, 8.85]
10.3 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	1.82 [0.66, 5.00]
10.4 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	9.81 [0.51, 189.07]
11 Gastrointestinal - Weight gain	4	425	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.25, 1.09]
11.1 vs Imipramine	1	30	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.23, 4.31]
11.2 vs Clomipramine	1	86	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.05, 1.22]
11.3 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	3.27 [0.13, 81.01]
11.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.16, 1.21]
12 Gastrointestinal - Weight loss	4	226	Odds Ratio (M-H, Random, 95% CI)	2.76 [1.20, 6.34]
12.1 vs Imipramine	2	66	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.53, 6.67]
12.2 vs Clomipramine	1	86	Odds Ratio (M-H, Random, 95% CI)	7.76 [0.91, 66.05]
12.3 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	2.83 [0.79, 10.21]
13 Gastrointestinal - Increased appetite	2	335	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.08, 7.04]
13.1 vs Imipramine	1	100	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.18]
13.2 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	3.27 [0.13, 81.01]
14 Gastrointestinal - Anorexia	6	1104	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.54, 2.53]
14.1 vs Imipramine	5	869	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.47, 2.68]
14.2 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	2.18 [0.19, 24.38]

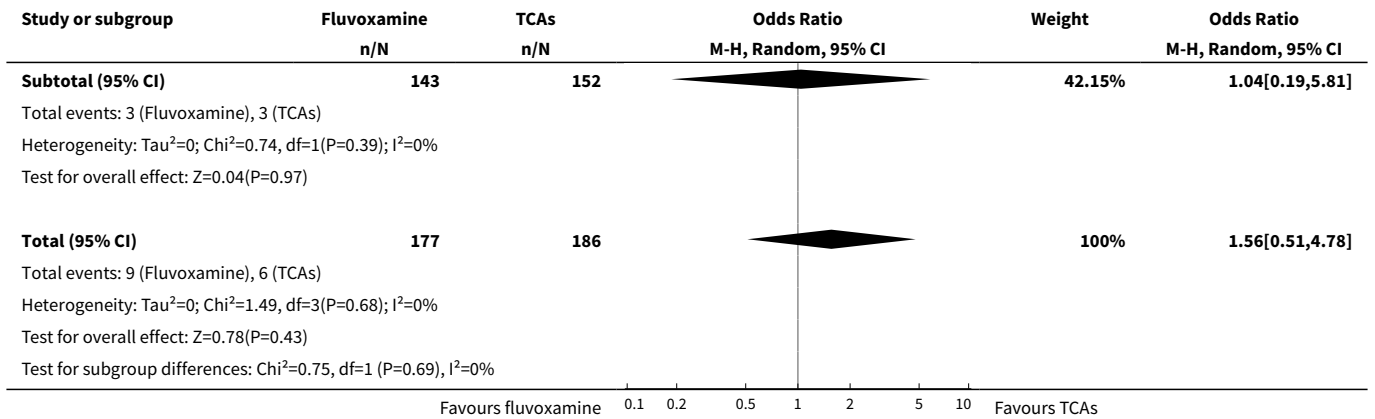
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 Neuropsychiatric - Blurred vision	5	500	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.23, 0.97]
15.1 vs Clomipramine	2	118	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.06, 2.30]
15.2 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.03, 2.39]
15.3 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.21, 1.56]
15.4 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.04, 5.45]
16 Neuropsychiatric - Dizziness / vertigo / faintness	14	1592	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.19, 0.38]
16.1 vs Imipramine	9	1055	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.15, 0.38]
16.2 vs Clomipramine	1	86	Odds Ratio (M-H, Random, 95% CI)	0.21 [0.05, 0.80]
16.3 vs Amitriptyline	2	304	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.11, 0.83]
16.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.07, 0.70]
16.5 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.18, 3.06]
17 Neuropsychiatric - Fatigue / tiredness / asthenia	5	565	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.52, 1.73]
17.1 vs Imipramine	2	200	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.25, 4.56]
17.2 vs Clomipramine	2	130	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.40, 1.85]
17.3 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	1.64 [0.27, 9.98]
18 Neuropsychiatric - Headache	16	1621	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.73, 1.62]
18.1 vs Imipramine	8	1008	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.71, 2.01]
18.2 vs Clomipramine	1	32	Odds Ratio (M-H, Random, 95% CI)	1.5 [0.33, 6.83]
18.3 vs Amitriptyline	4	387	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.07, 1.11]
18.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	1.82 [0.66, 5.00]
18.5 vs Desipramine	1	47	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.26, 2.79]
18.6 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	1.5 [0.24, 9.55]
19 Neuropsychiatric - Tremor	12	1247	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.33, 0.75]
19.1 vs Imipramine	6	663	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.32, 1.13]
19.2 vs Clomipramine	3	216	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.15, 1.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.3 vs Amitriptyline	2	295	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.08, 1.88]
19.4 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.03, 3.08]
20 Neuropsychiatric - Involuntary movement other than tremor	3	499	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.32, 3.47]
20.1 vs Imipramine	2	430	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.36, 4.58]
20.2 vs Amitriptyline	1	69	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.99]
21 Neuropsychiatric - Insomnia	9	1039	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.82, 1.92]
21.1 vs Imipramine	6	674	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.87, 2.39]
21.2 vs Clomipramine	2	130	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.37, 1.81]
21.3 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	5.49 [0.26, 115.67]
22 Neuropsychiatric - Sleepiness / drowsiness	15	1585	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.66, 1.33]
22.1 vs Imipramine	8	1019	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.80, 1.46]
22.2 vs Clomipramine	1	32	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.25, 4.71]
22.3 vs Amitriptyline	4	387	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.05, 1.21]
22.4 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.22, 1.42]
22.5 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	1.55 [0.40, 6.02]
23 Neuropsychiatric - Agitation / anxiety	8	984	Odds Ratio (M-H, Random, 95% CI)	1.64 [0.94, 2.84]
23.1 vs Imipramine	5	644	Odds Ratio (M-H, Random, 95% CI)	2.24 [1.01, 4.97]
23.2 vs Clomipramine	1	32	Odds Ratio (M-H, Random, 95% CI)	1.87 [0.15, 22.94]
23.3 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.19, 2.58]
23.4 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.31, 5.08]
24 Neuropsychiatric - Manic symptom	2	565	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.06, 11.58]
24.1 vs Imipramine	1	330	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.03, 2.11]
24.2 vs Amitriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	3.3 [0.34, 32.19]
25 Neuropsychiatric - Completed suicide	2	118	Odds Ratio (M-H, Random, 95% CI)	2.87 [0.29, 28.65]

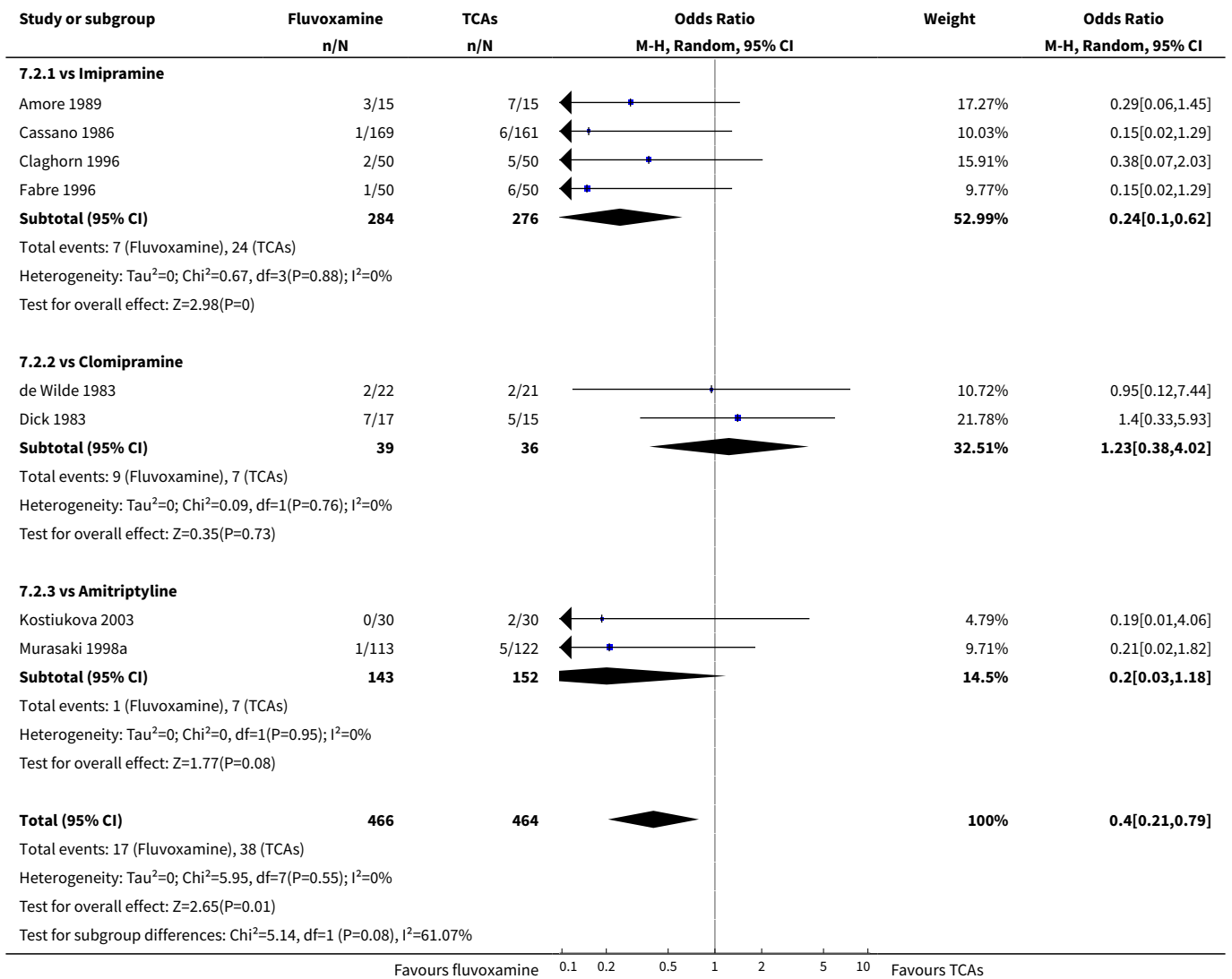
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 vs Clomipramine	2	118	Odds Ratio (M-H, Random, 95% CI)	2.87 [0.29, 28.65]
26 Neuropsychiatric - Suicide wishes / gestures / attempts	3	489	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.17, 2.48]
26.1 vs Imipramine	1	330	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.80]
26.2 vs Clomipramine	1	86	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.18, 5.00]
26.3 vs Dothiepin	1	73	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.00]
27 Genitourinary - Problems urinating	6	818	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.23, 0.83]
27.1 vs Imipramine	2	409	Odds Ratio (M-H, Random, 95% CI)	0.18 [0.04, 0.71]
27.2 vs Amitriptyline	2	295	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.10, 2.94]
27.3 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.19, 1.38]
27.4 vs Desipramine	1	40	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.26]
28 Genitourinary - Sexual dysfunction	1	74	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.29, 1.99]
28.1 vs Nortriptyline	1	74	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.29, 1.99]

Analysis 7.1. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 1 Cardiovascular - Hypertension / tachycardia.

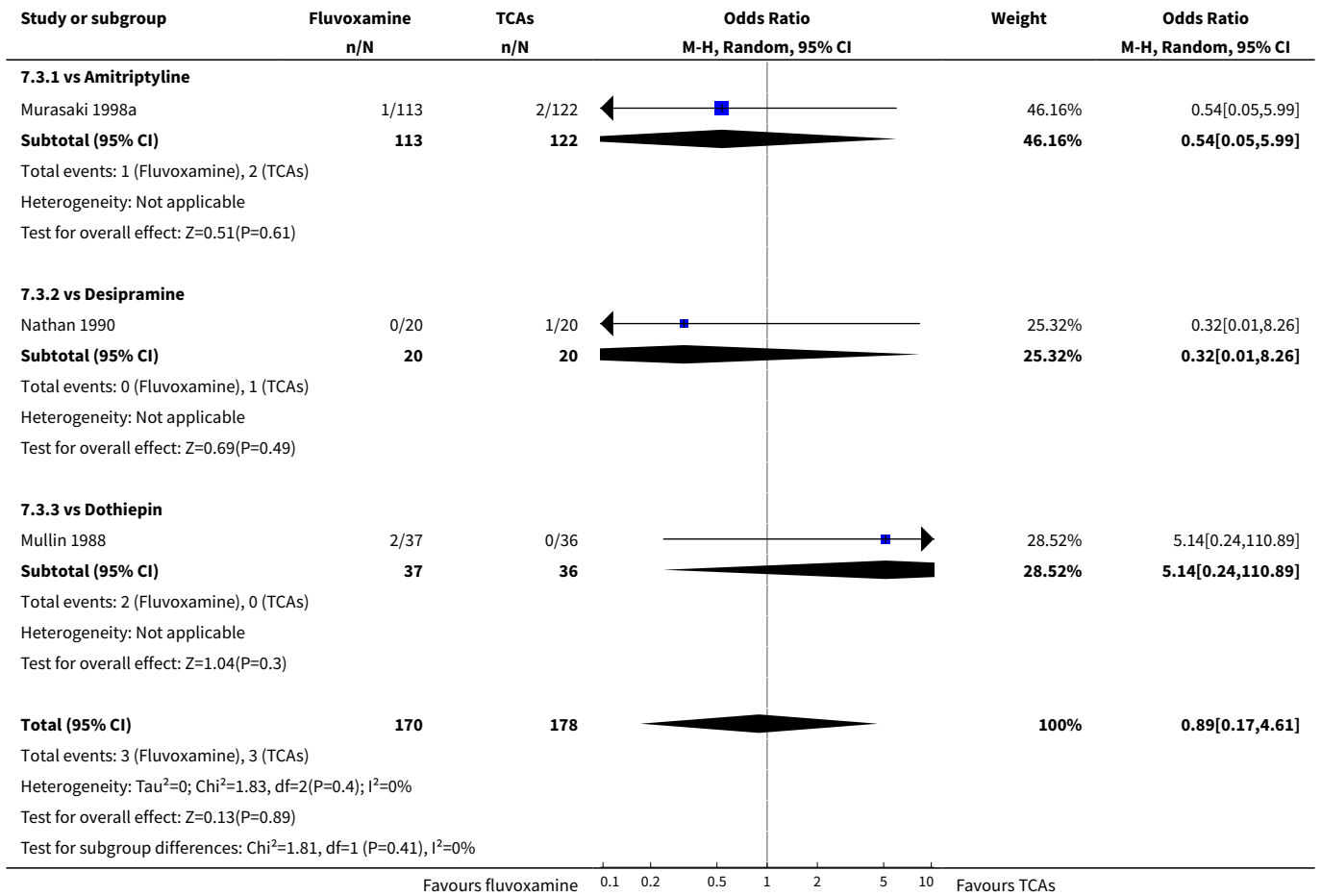




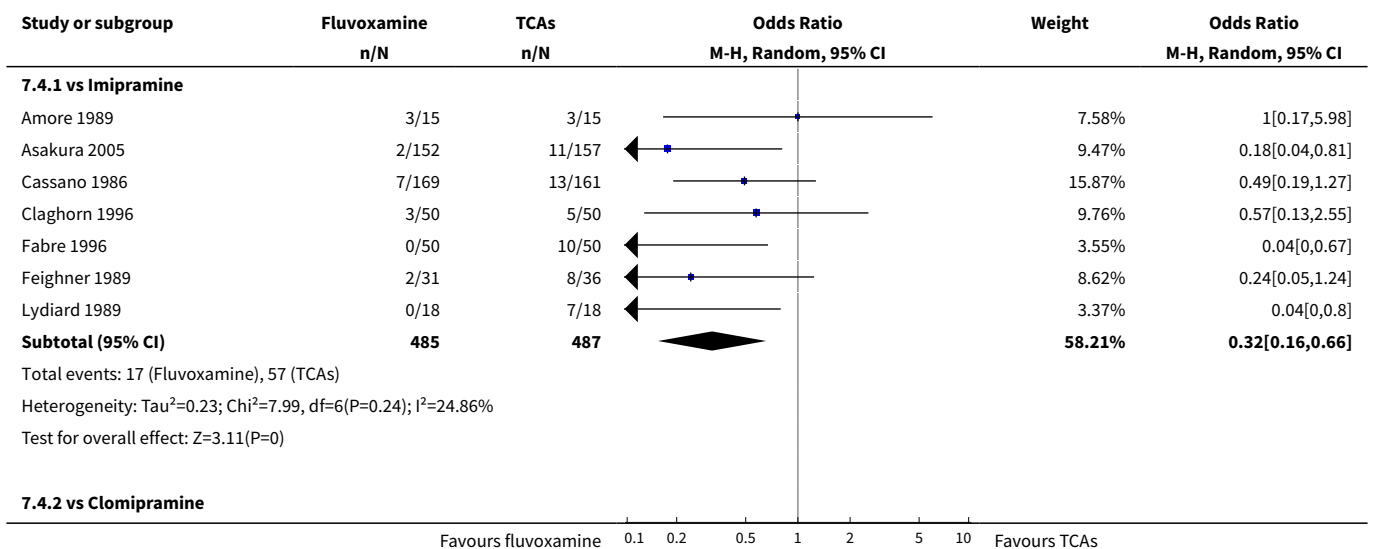
Analysis 7.2. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 2 Cardiovascular - Hypotension / bradycardia.

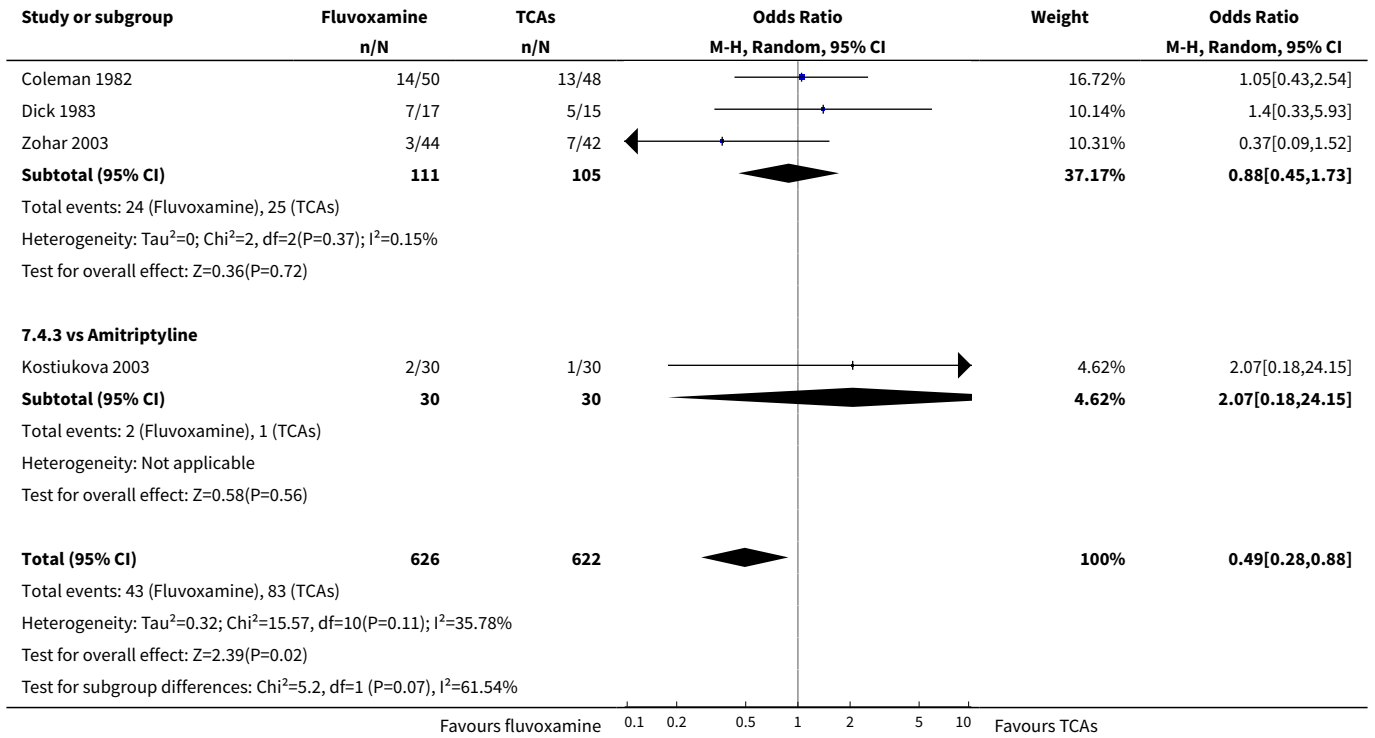


Analysis 7.3. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 3 Dermatological - Dermatitis / rash.

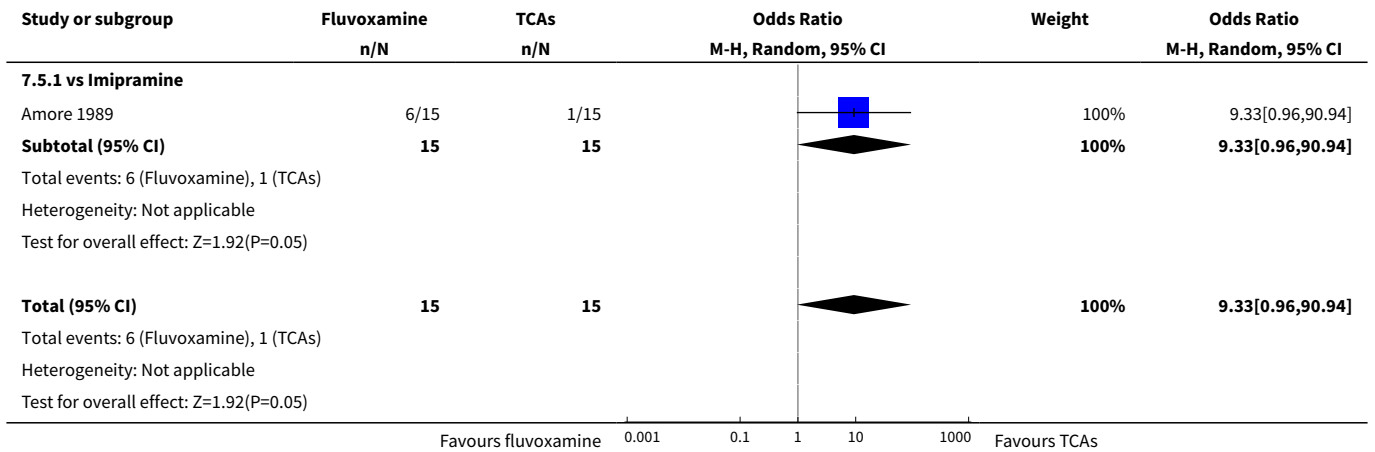


Analysis 7.4. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 4 Dermatological - Sweating.

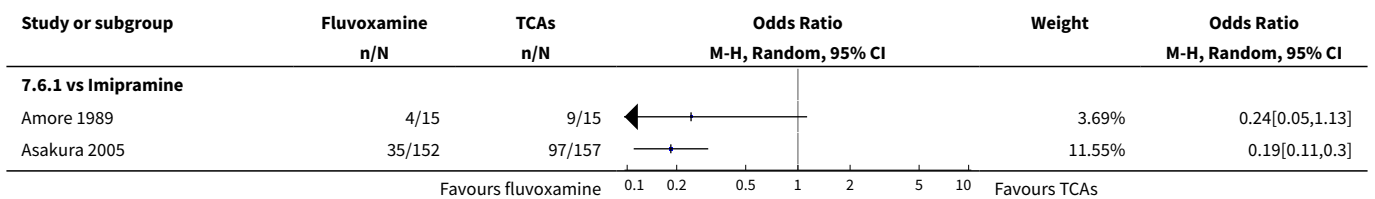


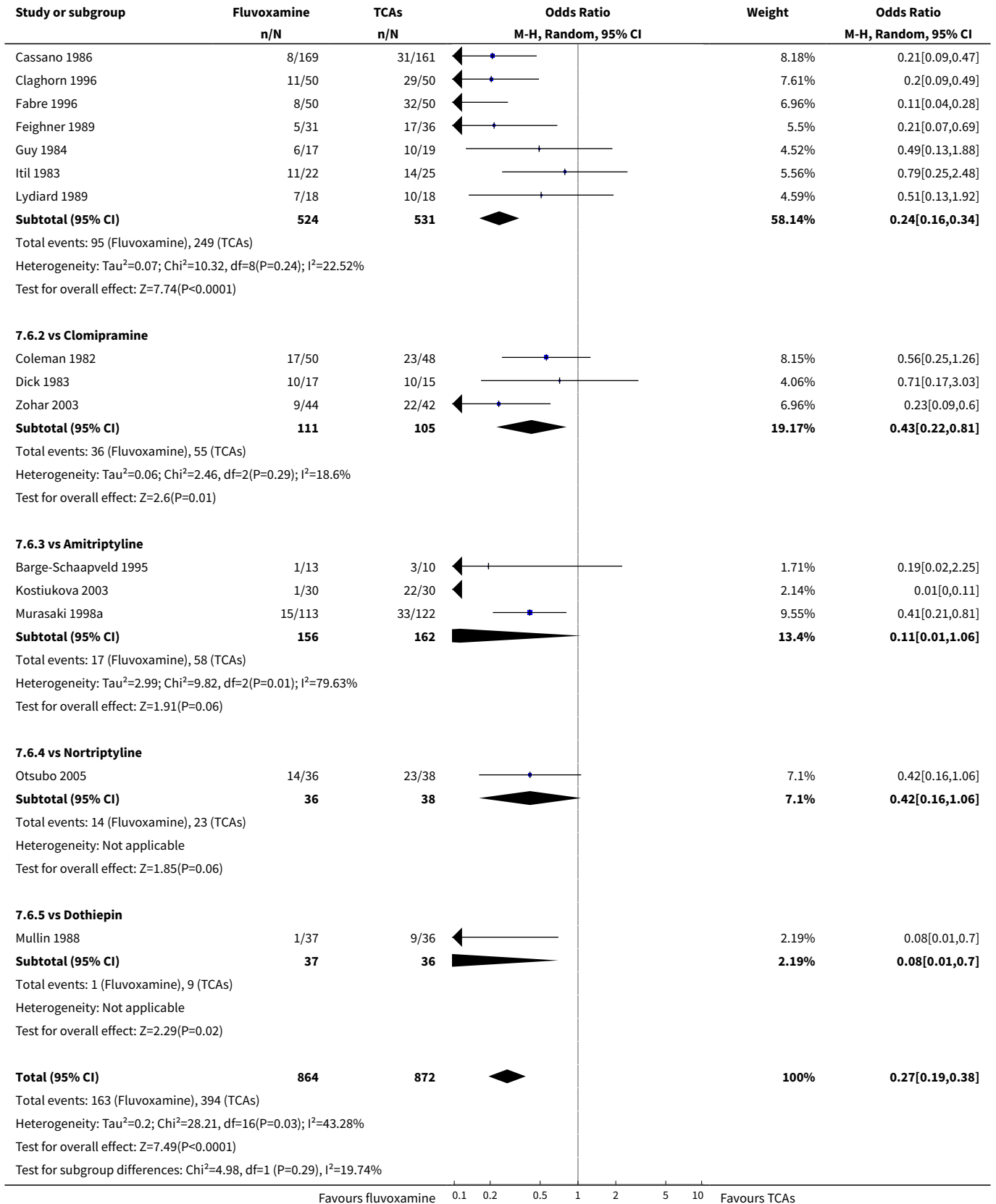


Analysis 7.5. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 5 Gastrointestinal - Increased salivation.

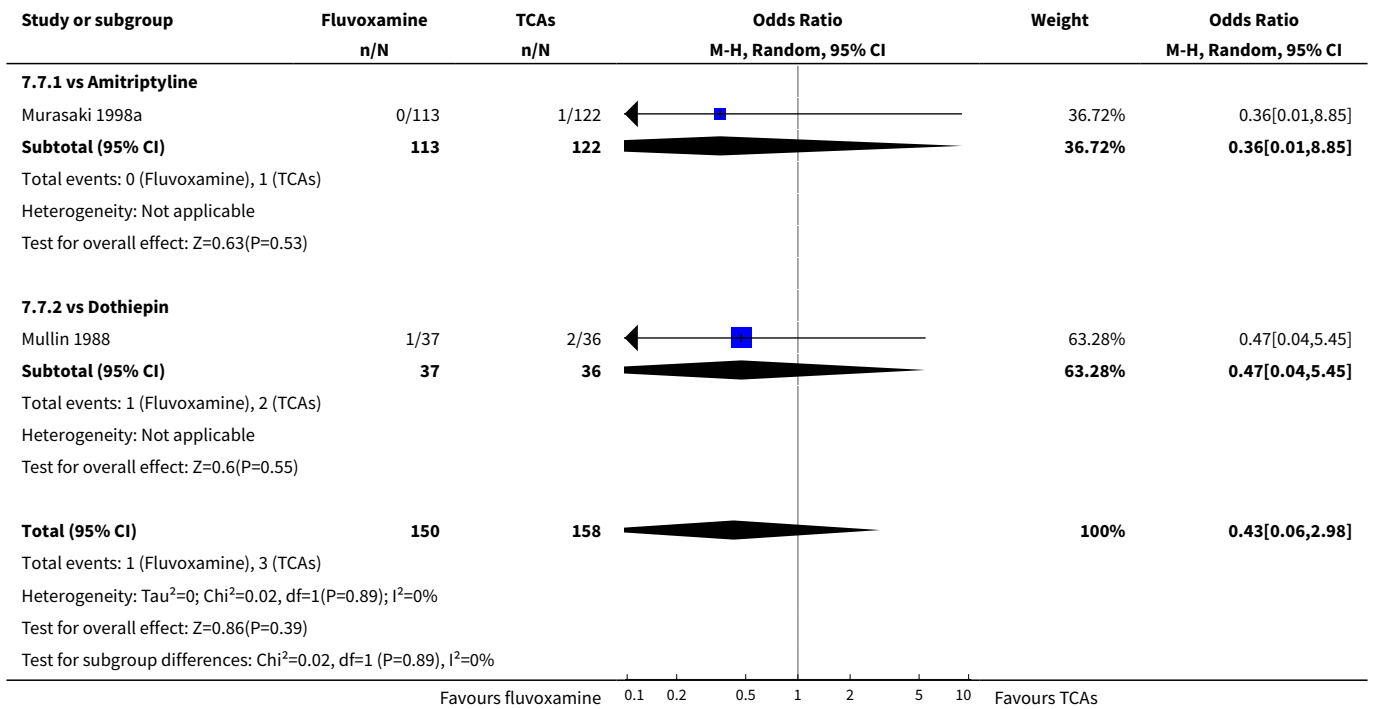


Analysis 7.6. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 6 Gastrointestinal - Dry mouth.

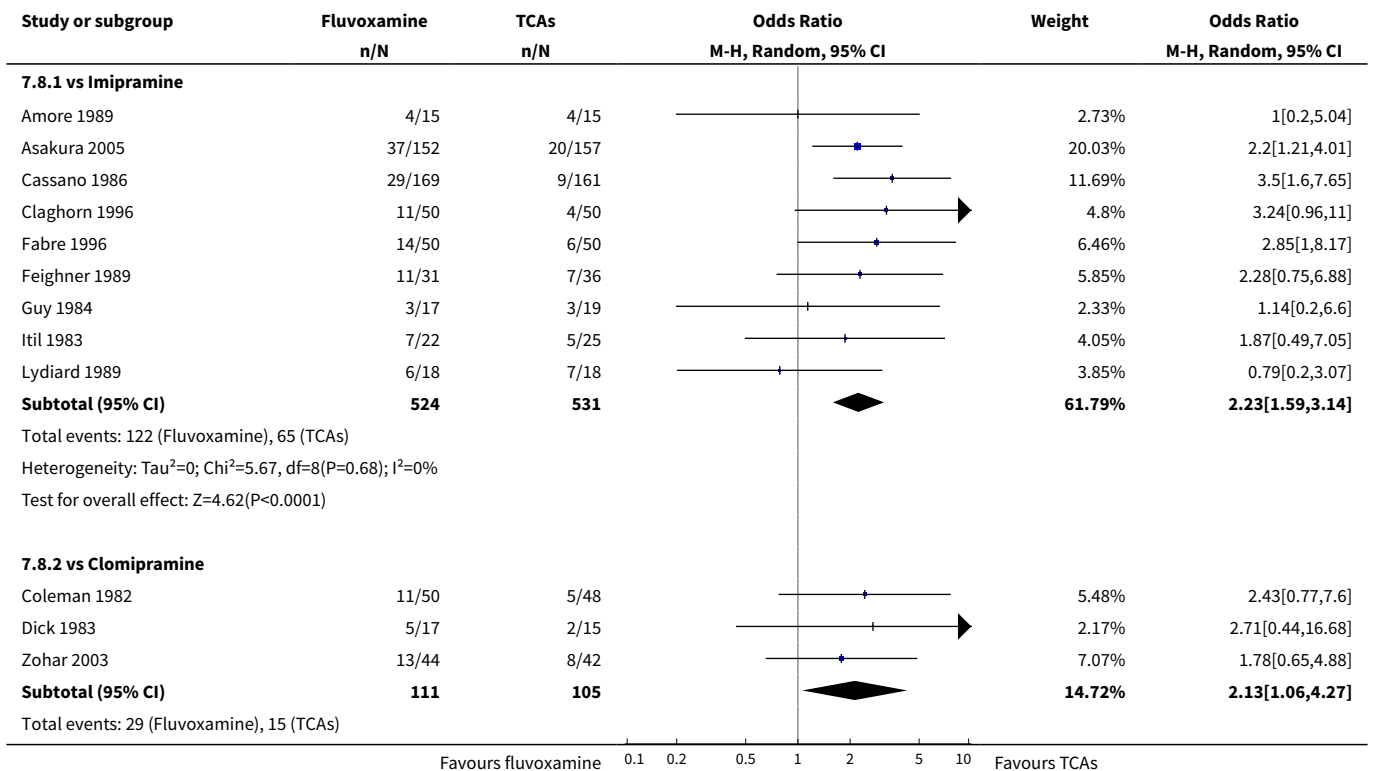


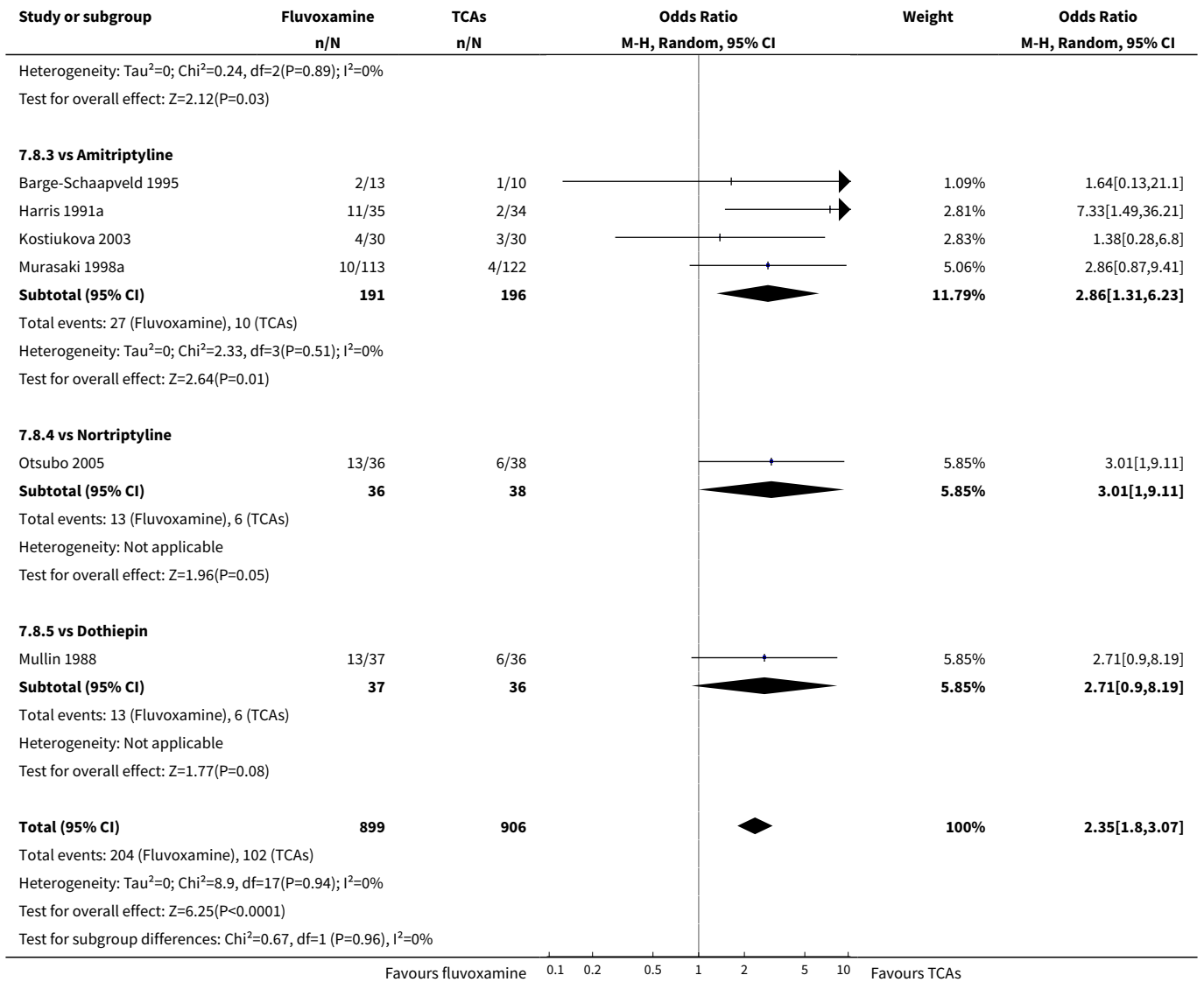


Analysis 7.7. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 7 Gastrointestinal - Oral discomfort / taste disturbance.

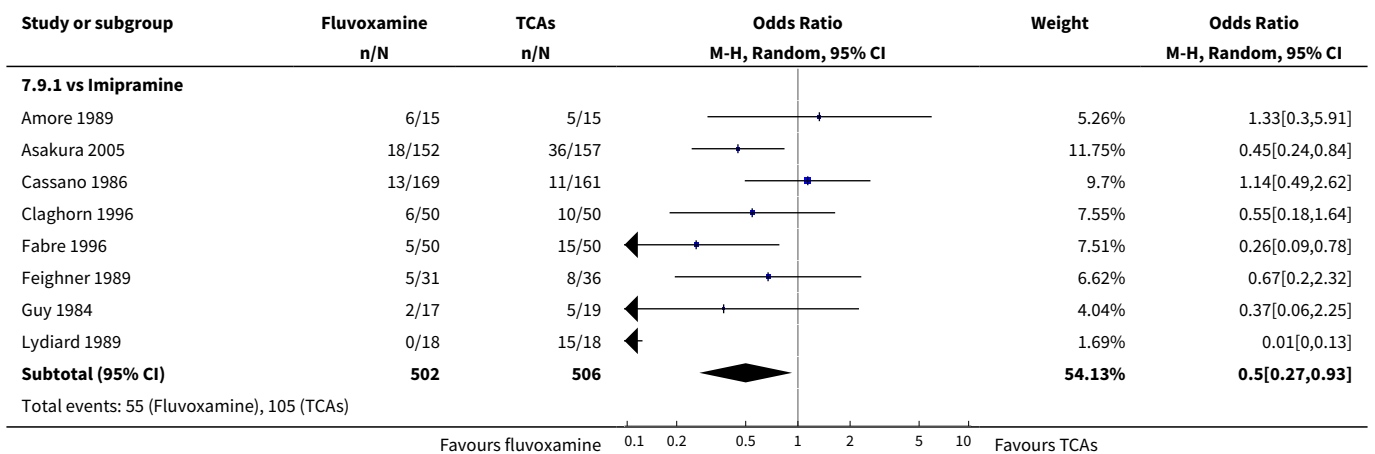


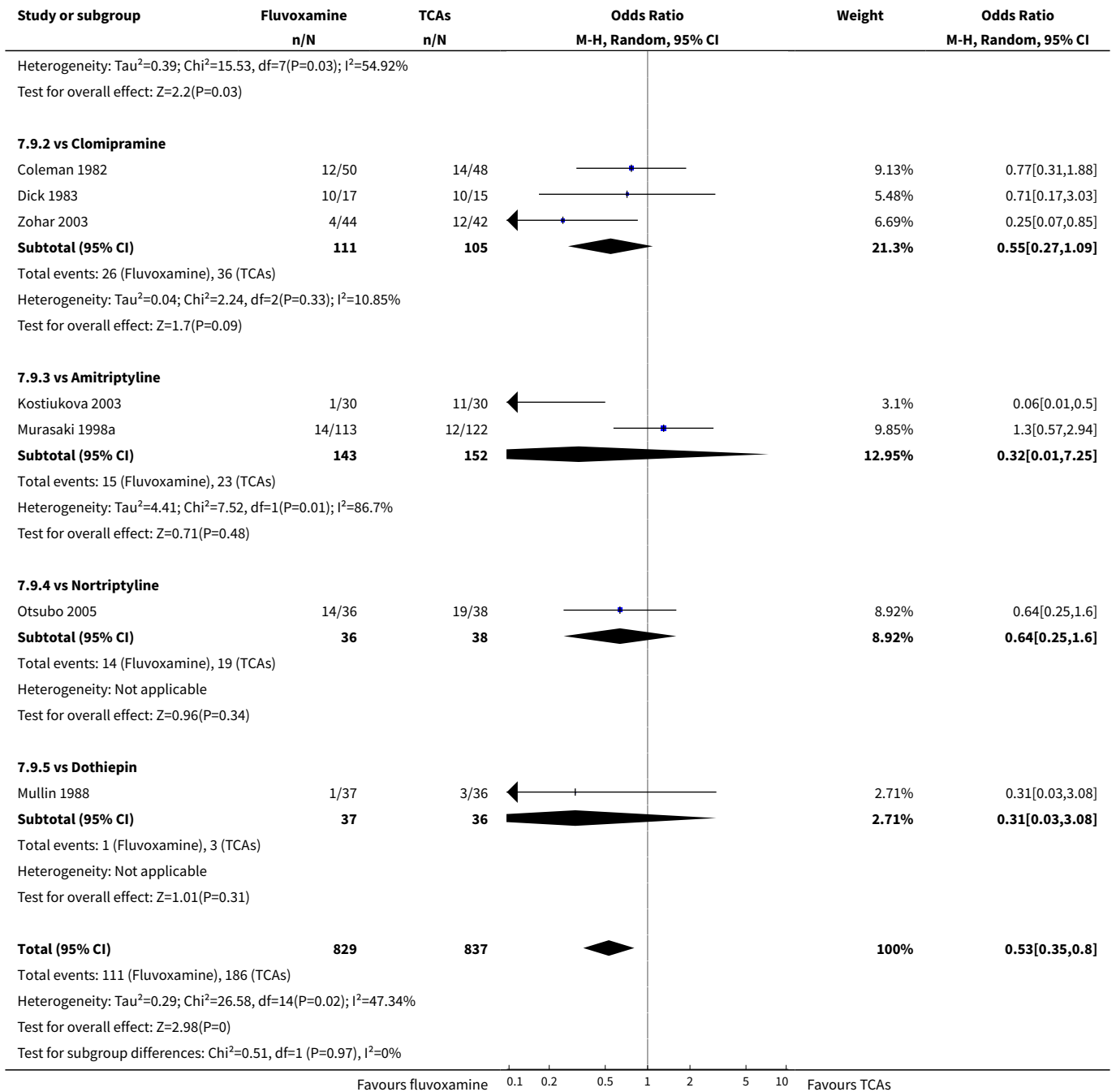
Analysis 7.8. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 8 Gastrointestinal - Vomiting / nausea.



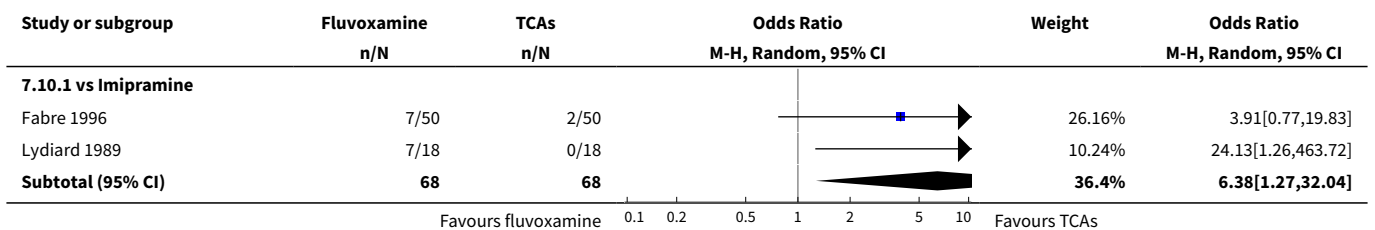


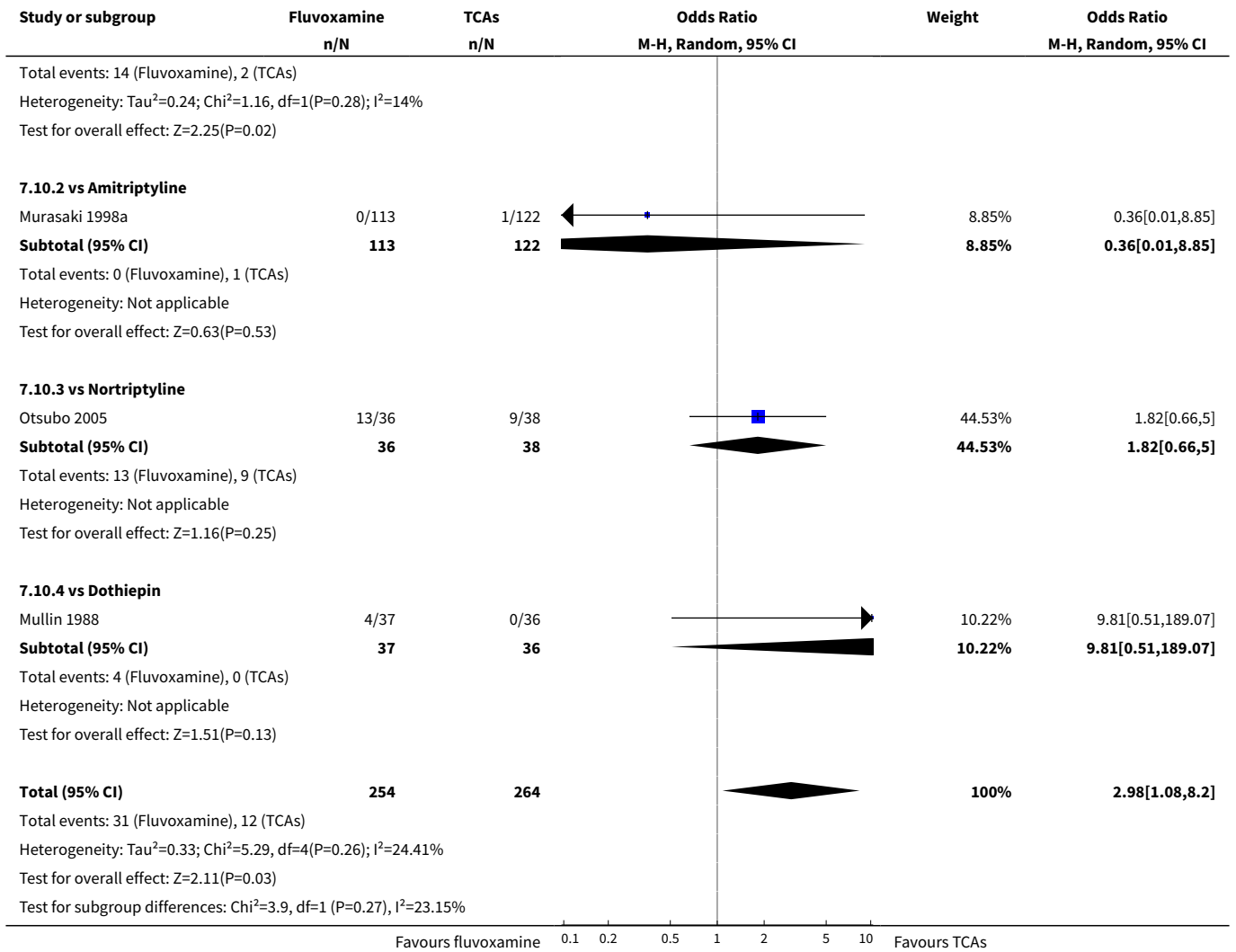
Analysis 7.9. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 9 Gastrointestinal - Constipation.



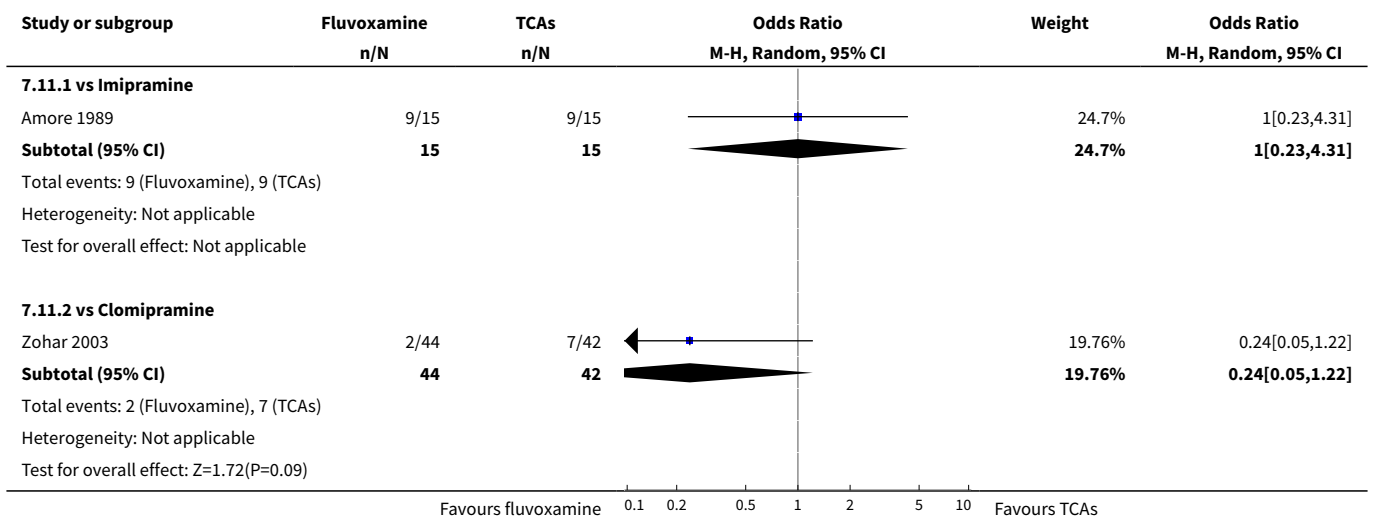


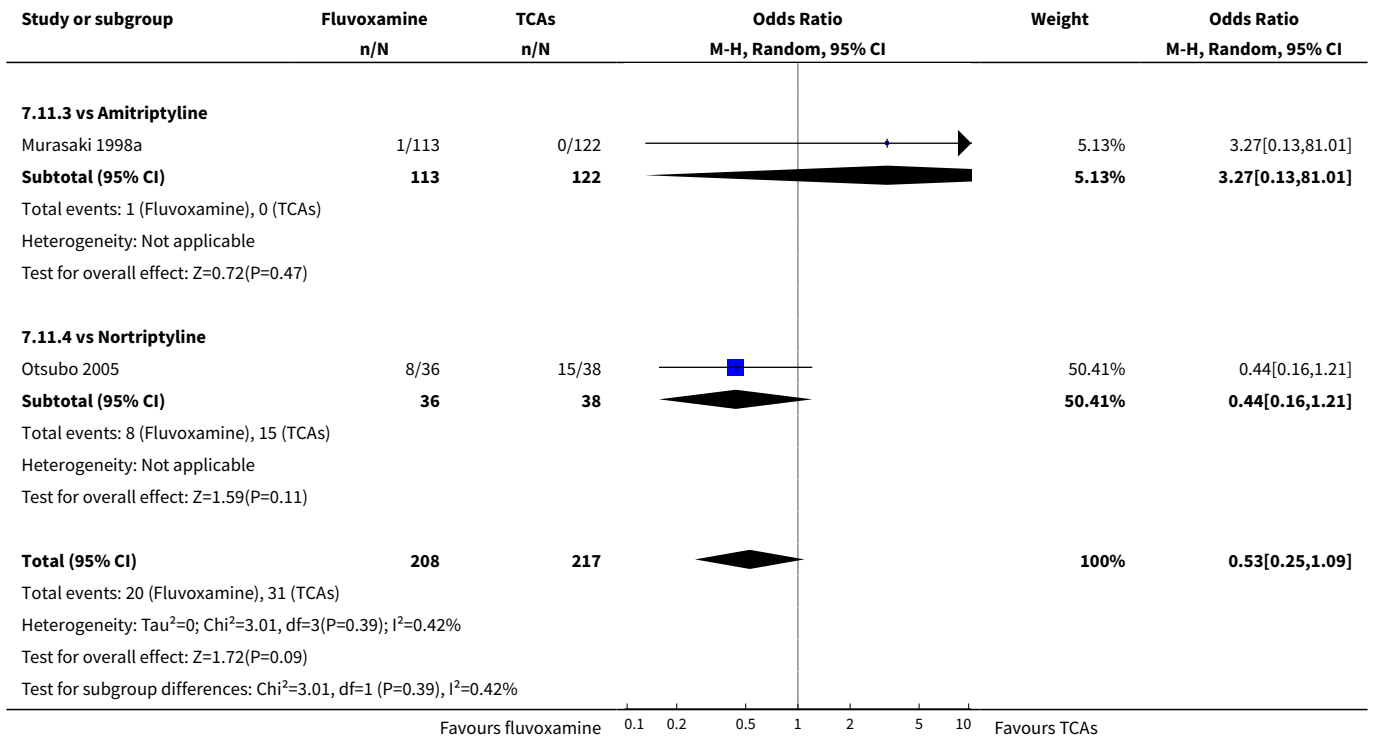
Analysis 7.10. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 10 Gastrointestinal - Diarrhoea.



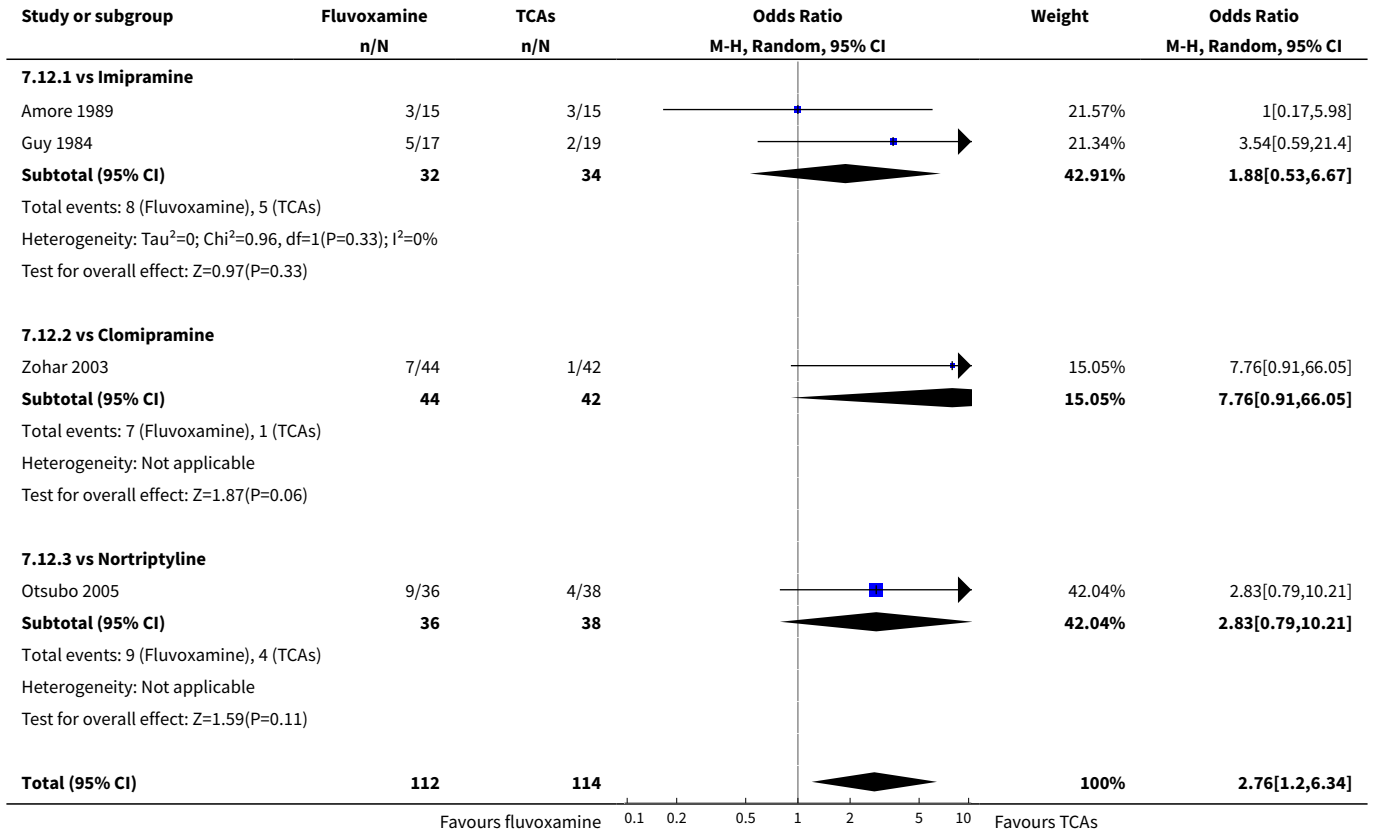


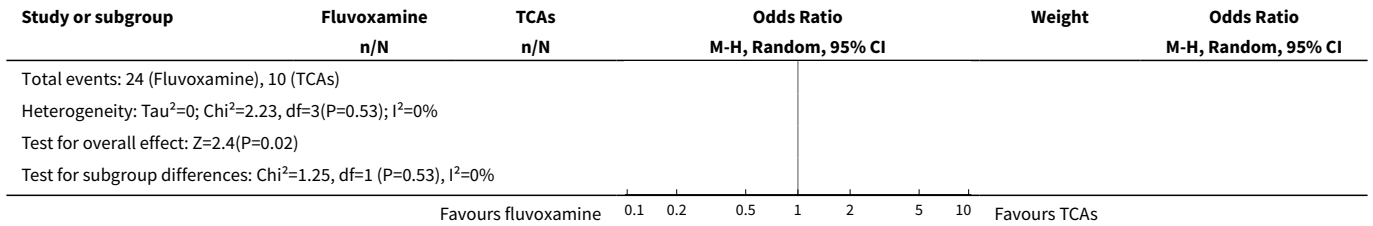
Analysis 7.11. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 11 Gastrointestinal - Weight gain.



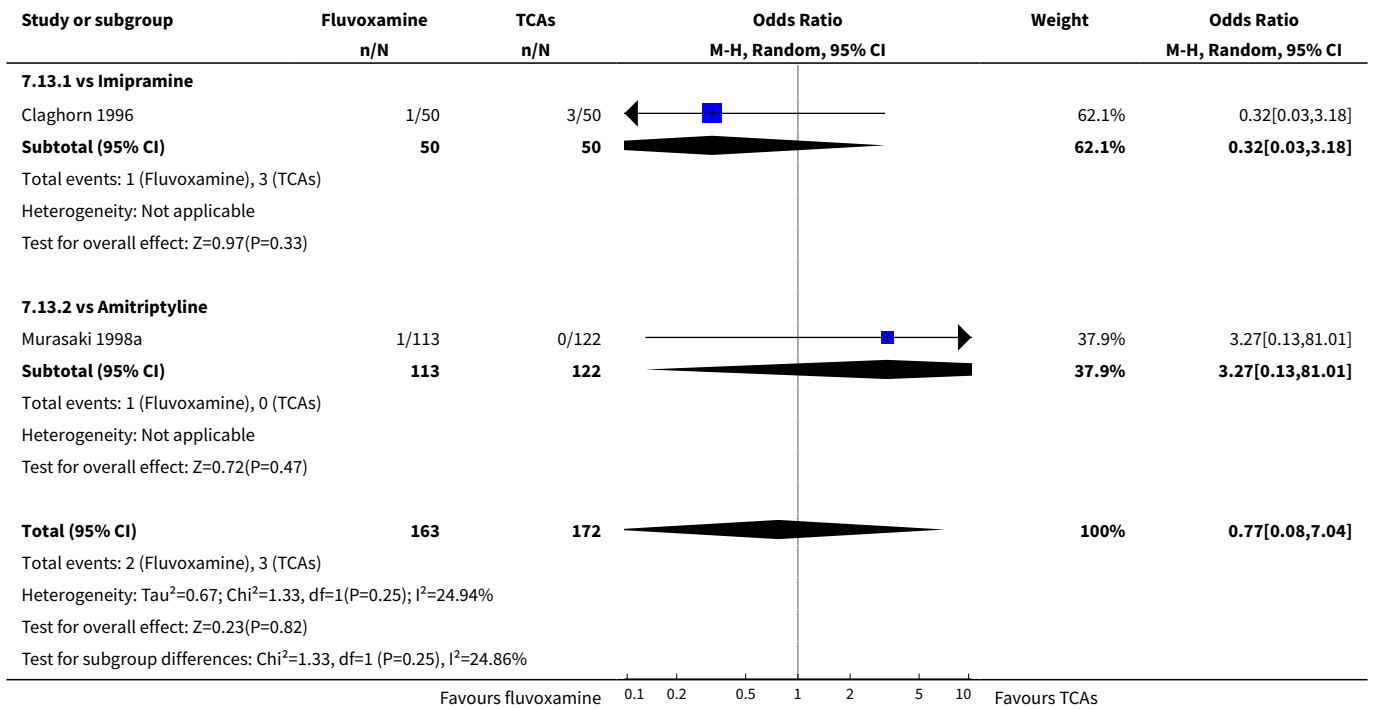


Analysis 7.12. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 12 Gastrointestinal - Weight loss.

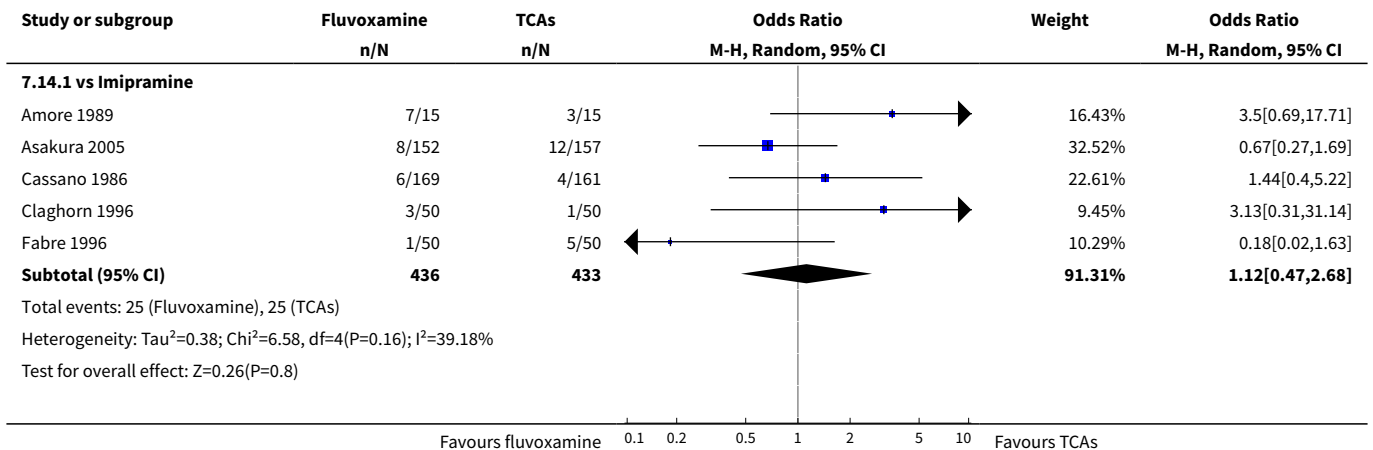


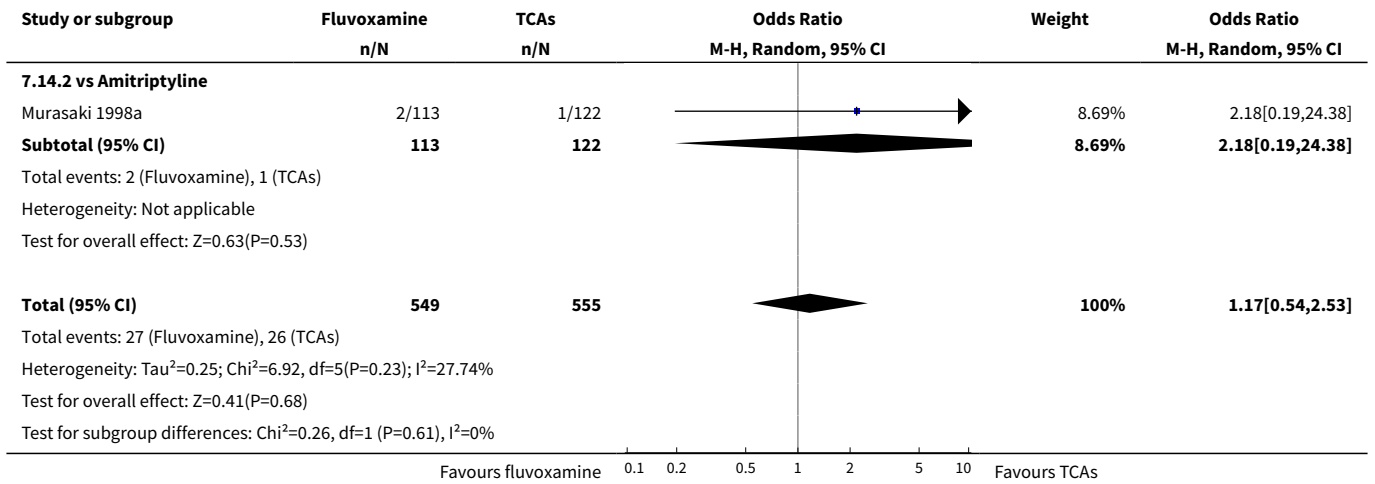


Analysis 7.13. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 13 Gastrointestinal - Increased appetite.

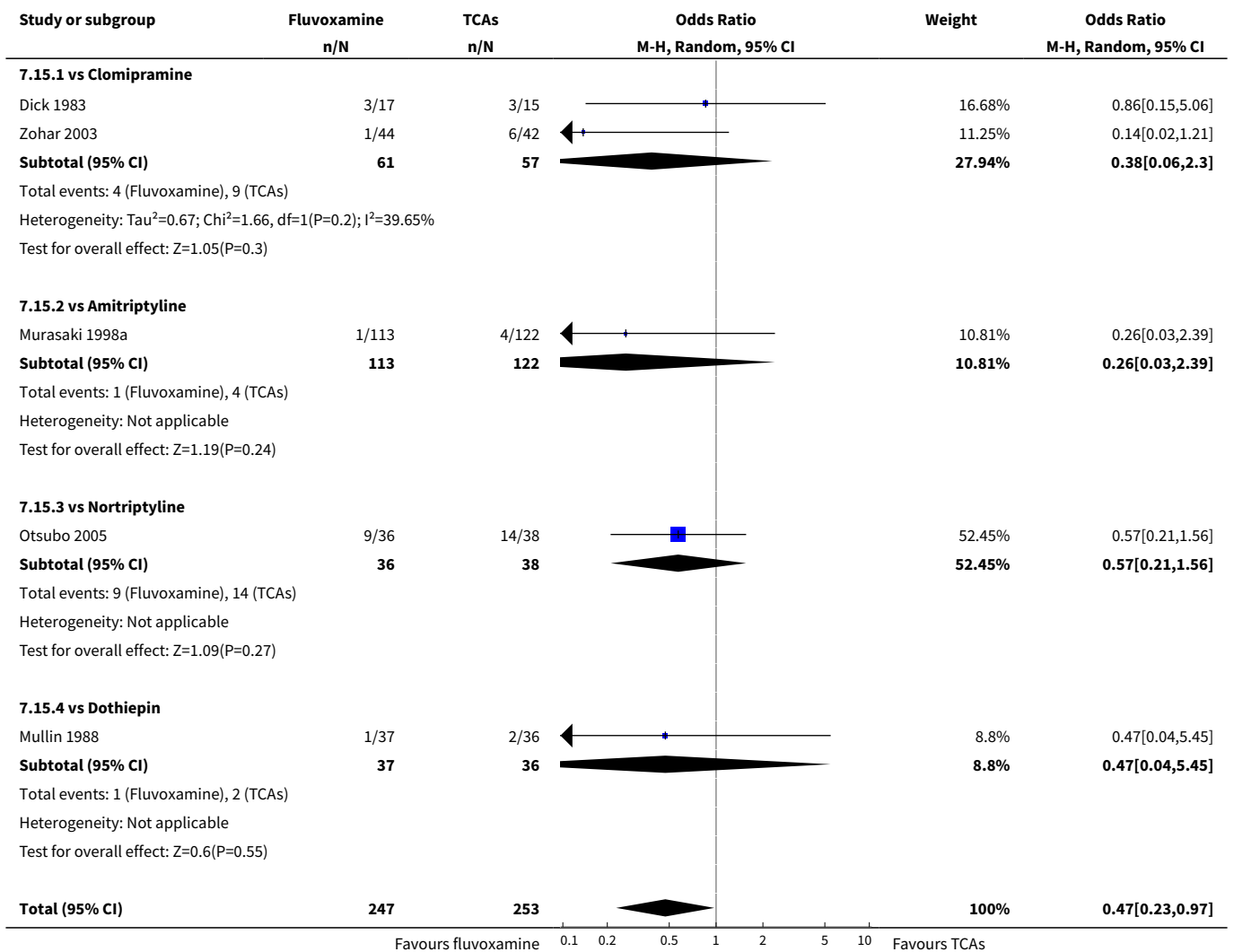


Analysis 7.14. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 14 Gastrointestinal - Anorexia.





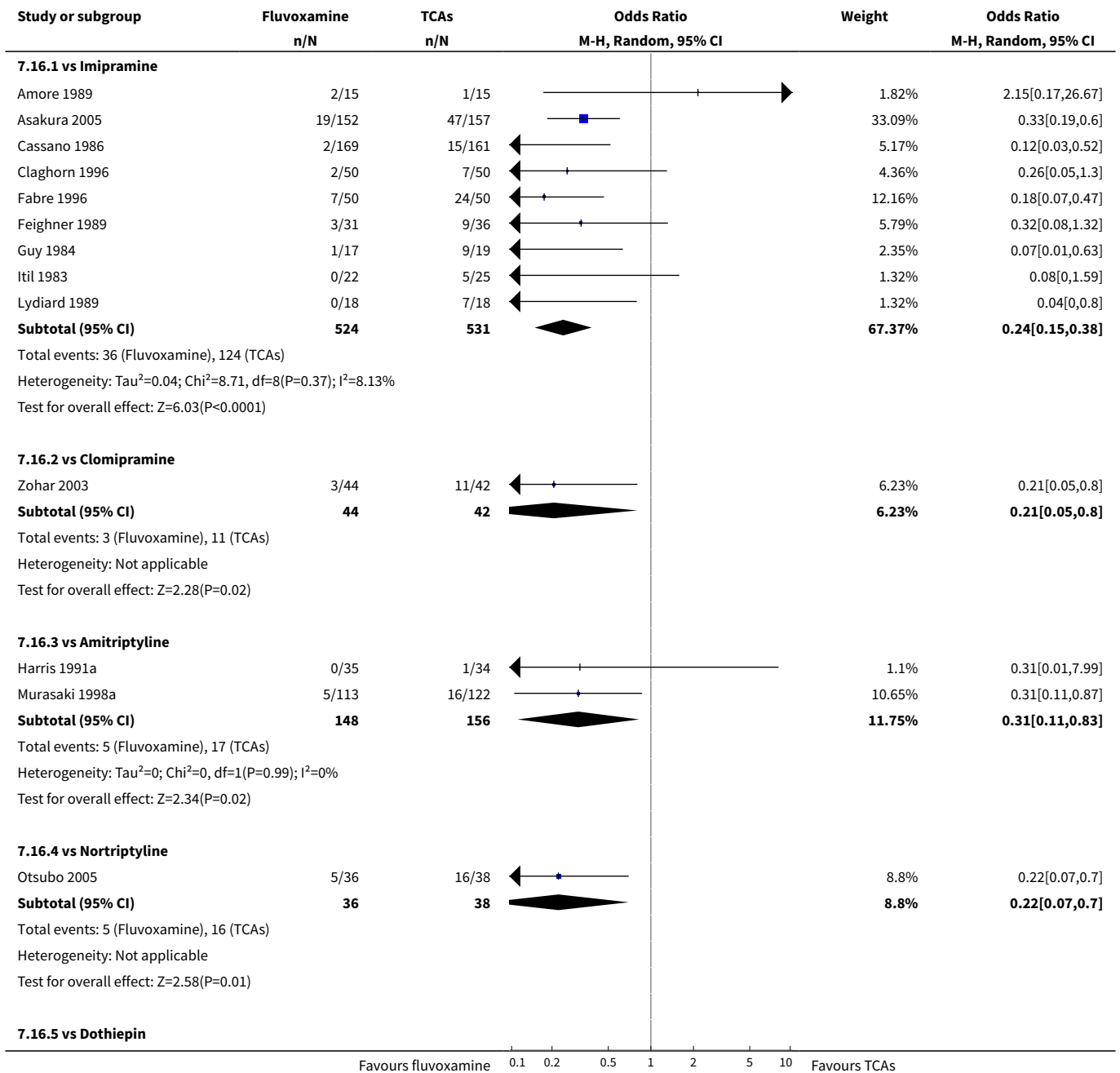
Analysis 7.15. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 15 Neuropsychiatric - Blurred vision.



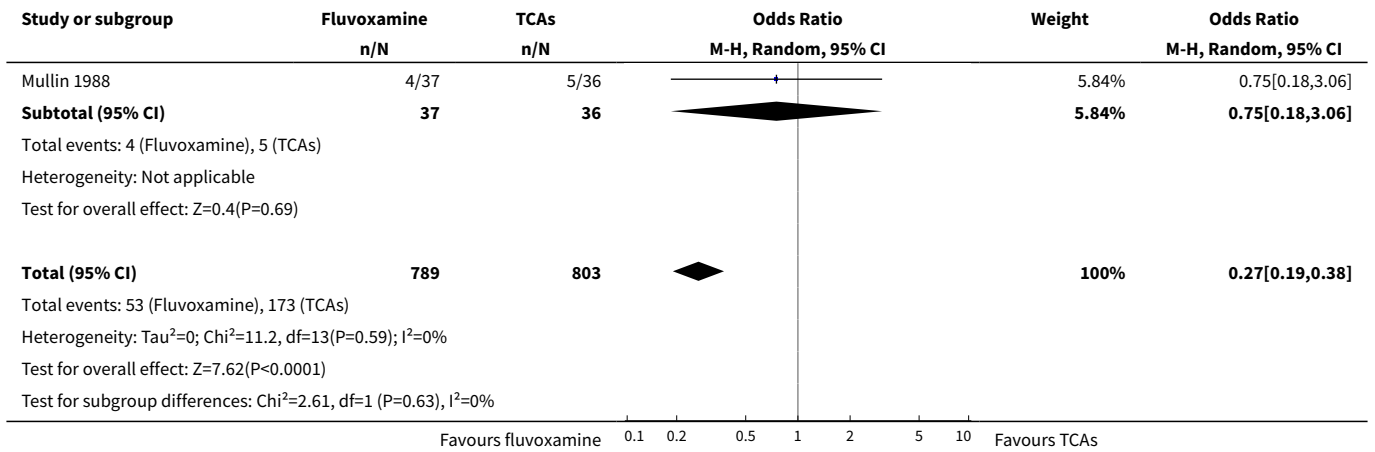
Study or subgroup	Fluvoxamine n/N	TCAs n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Total events: 15 (Fluvoxamine), 29 (TCAs)					
Heterogeneity: Tau ² =0; Chi ² =2.09, df=4(P=0.72); I ² =0%					
Test for overall effect: Z=2.03(P=0.04)					
Test for subgroup differences: Chi ² =0.46, df=1 (P=0.93), I ² =0%					

Favours fluvoxamine 0.1 0.2 0.5 1 2 5 10 Favours TCAs

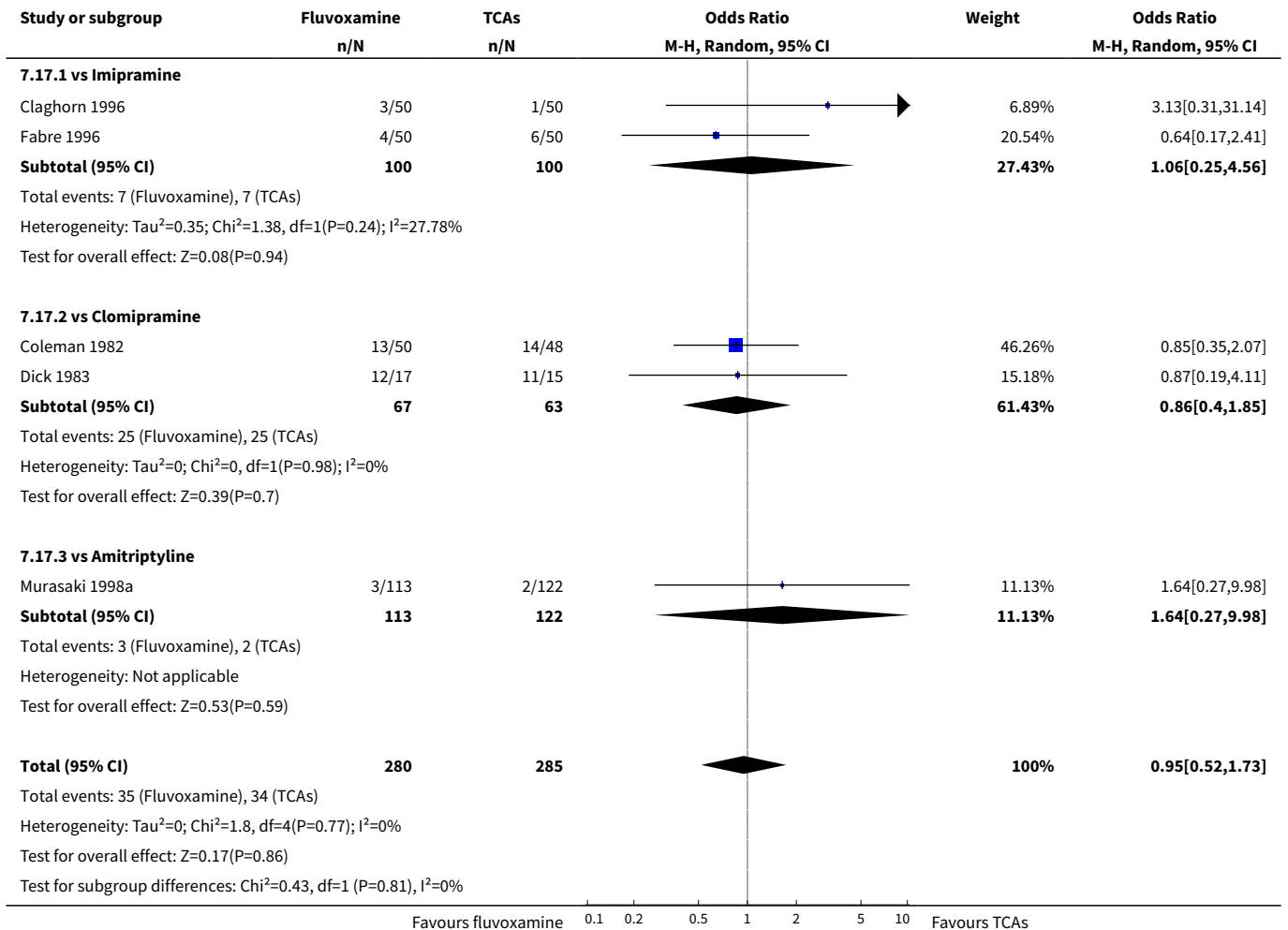
Analysis 7.16. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 16 Neuropsychiatric - Dizziness / vertigo / faintness.



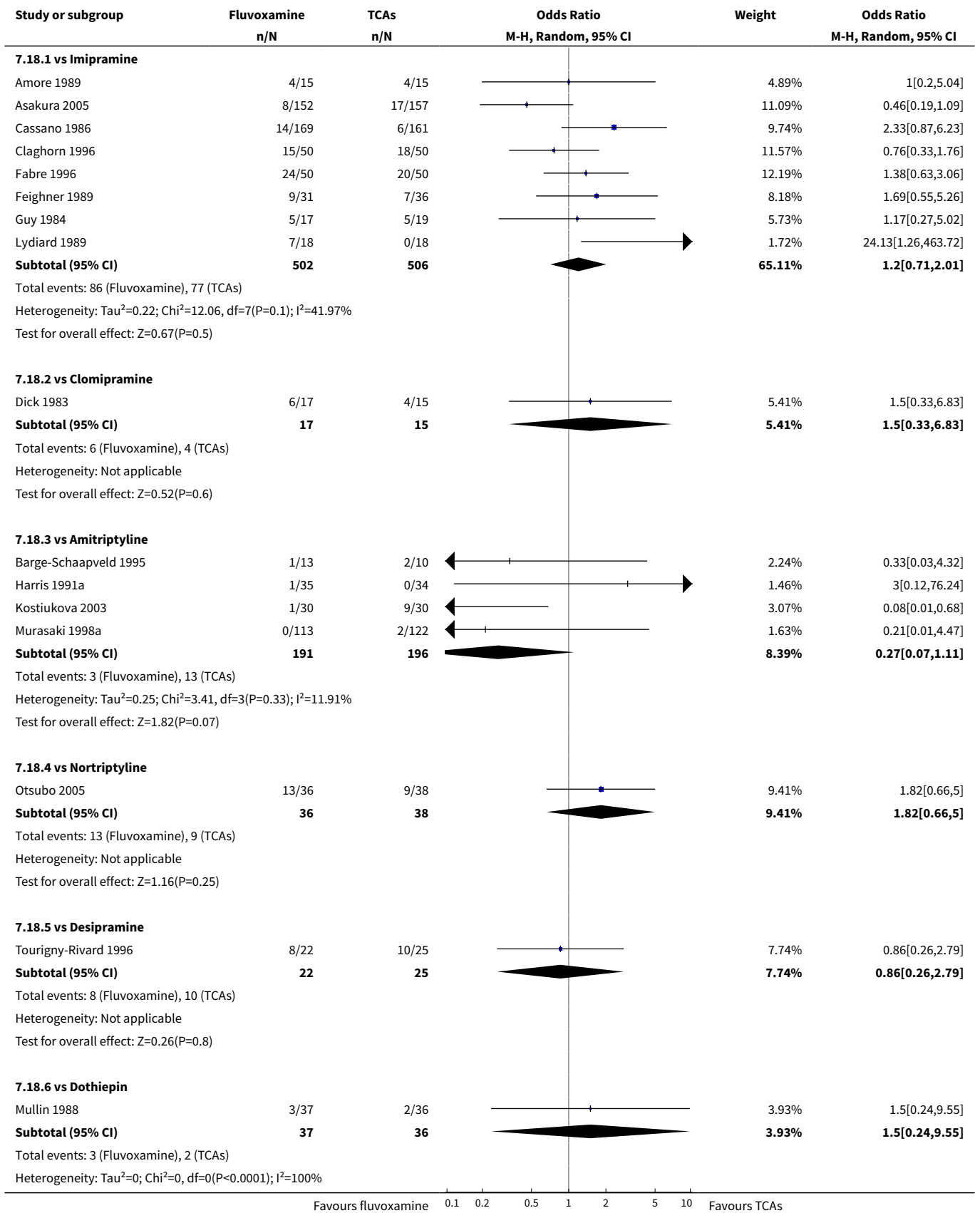
Favours fluvoxamine 0.1 0.2 0.5 1 2 5 10 Favours TCAs

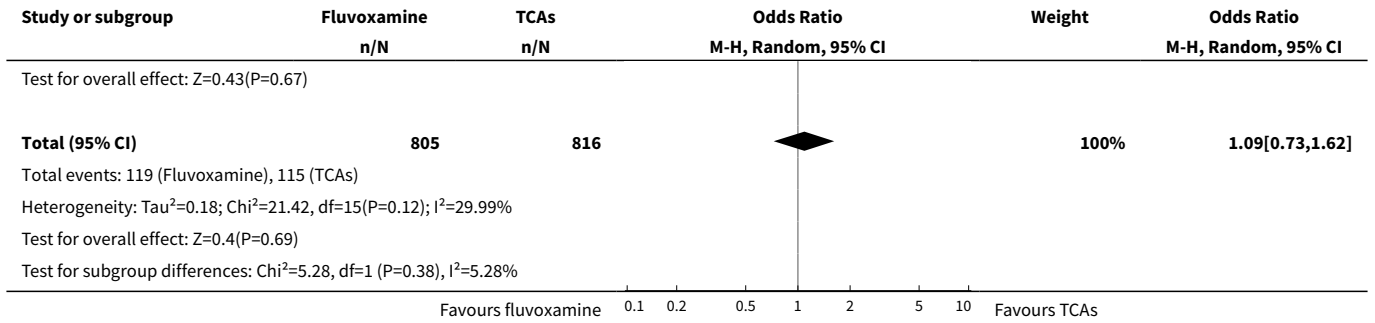


Analysis 7.17. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 17 Neuropsychiatric - Fatigue / tiredness / asthenia.

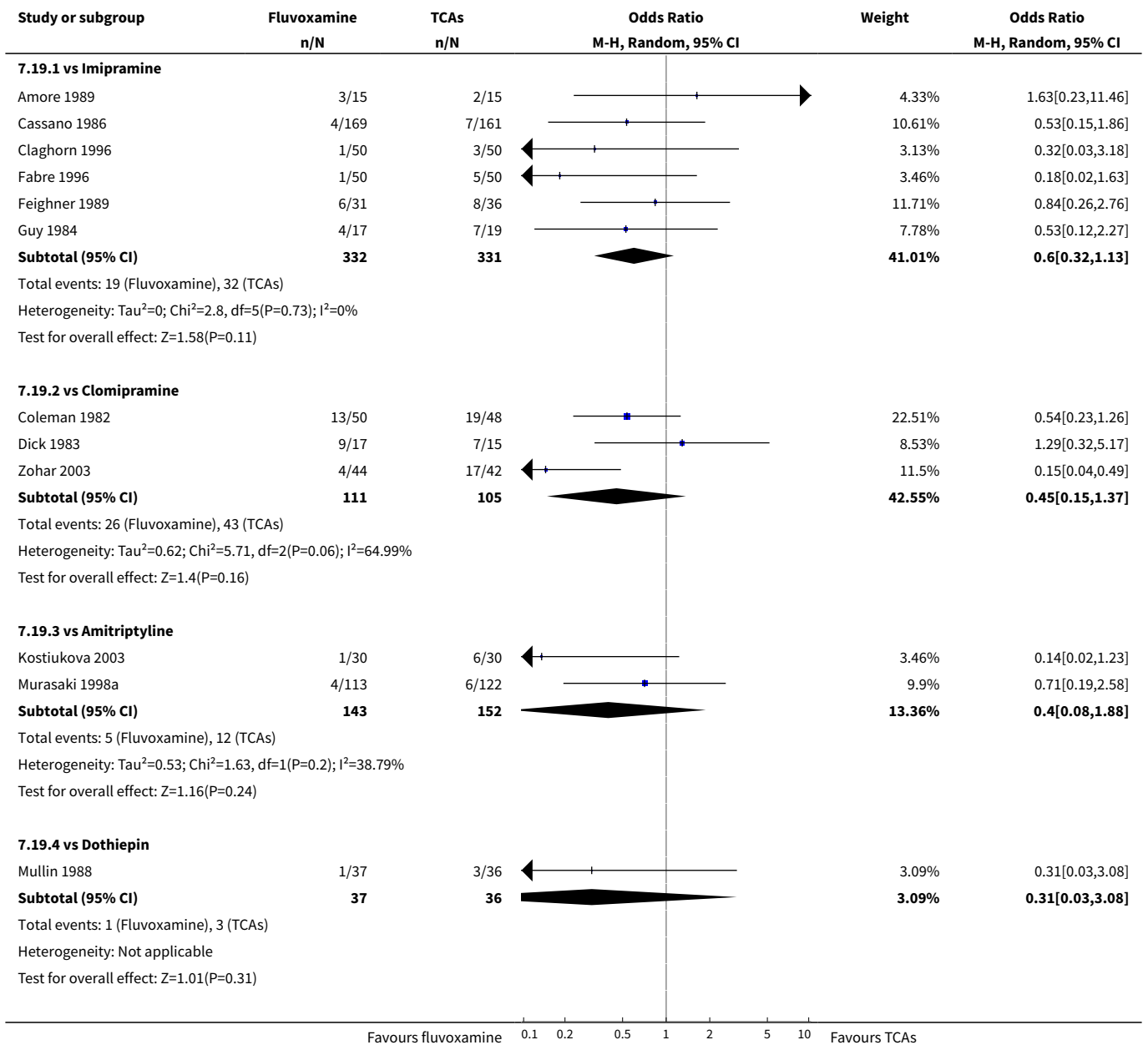


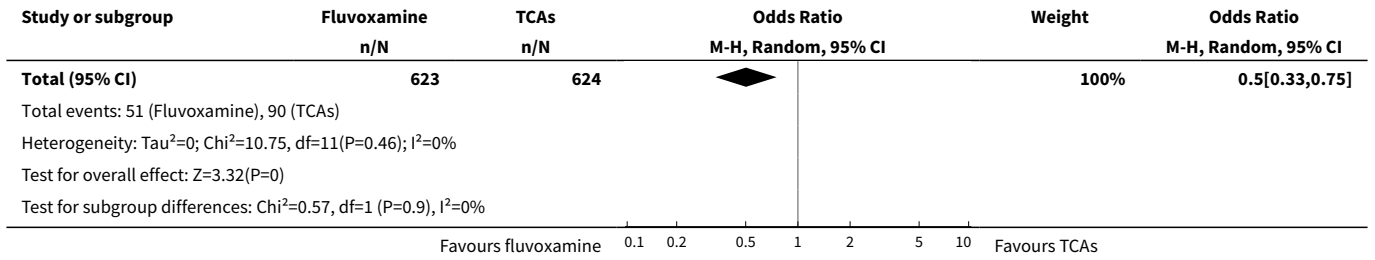
Analysis 7.18. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 18 Neuropsychiatric - Headache.



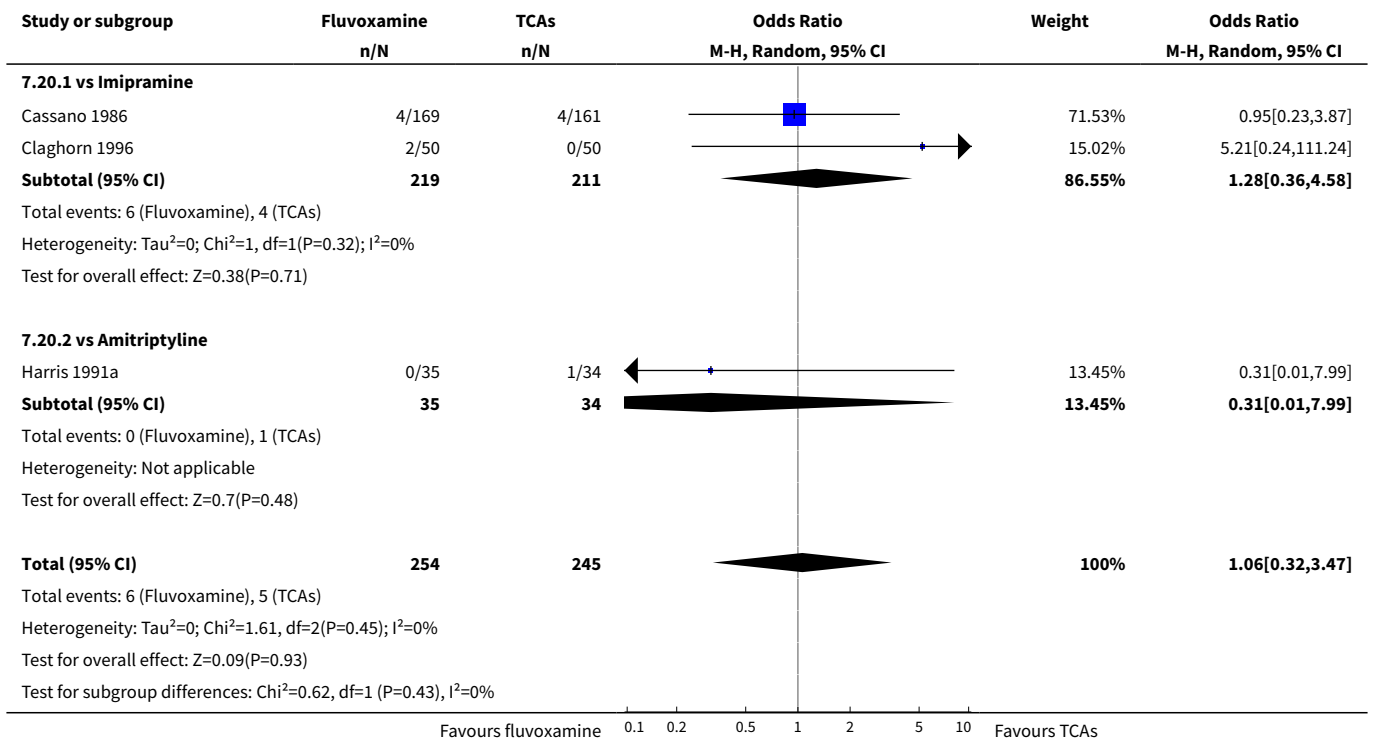


Analysis 7.19. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 19 Neuropsychiatric - Tremor.

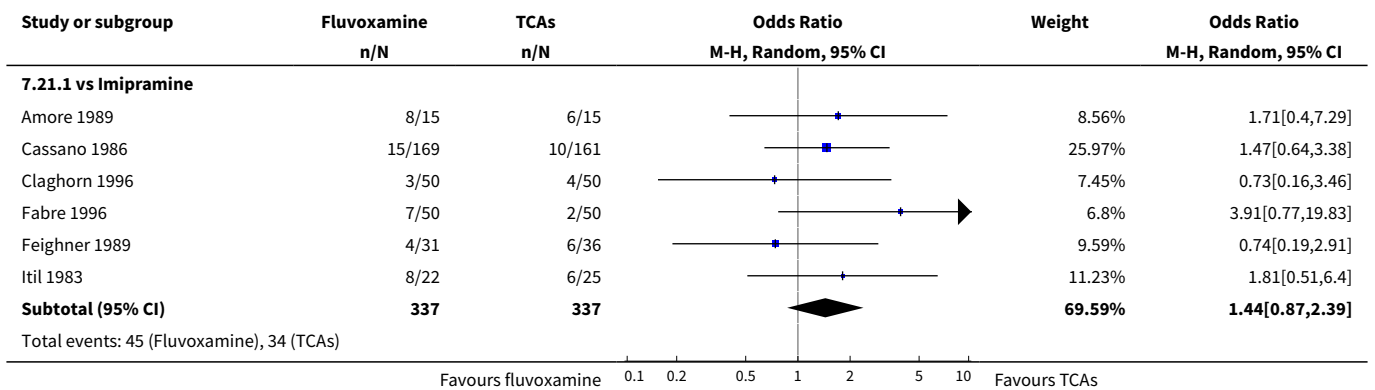


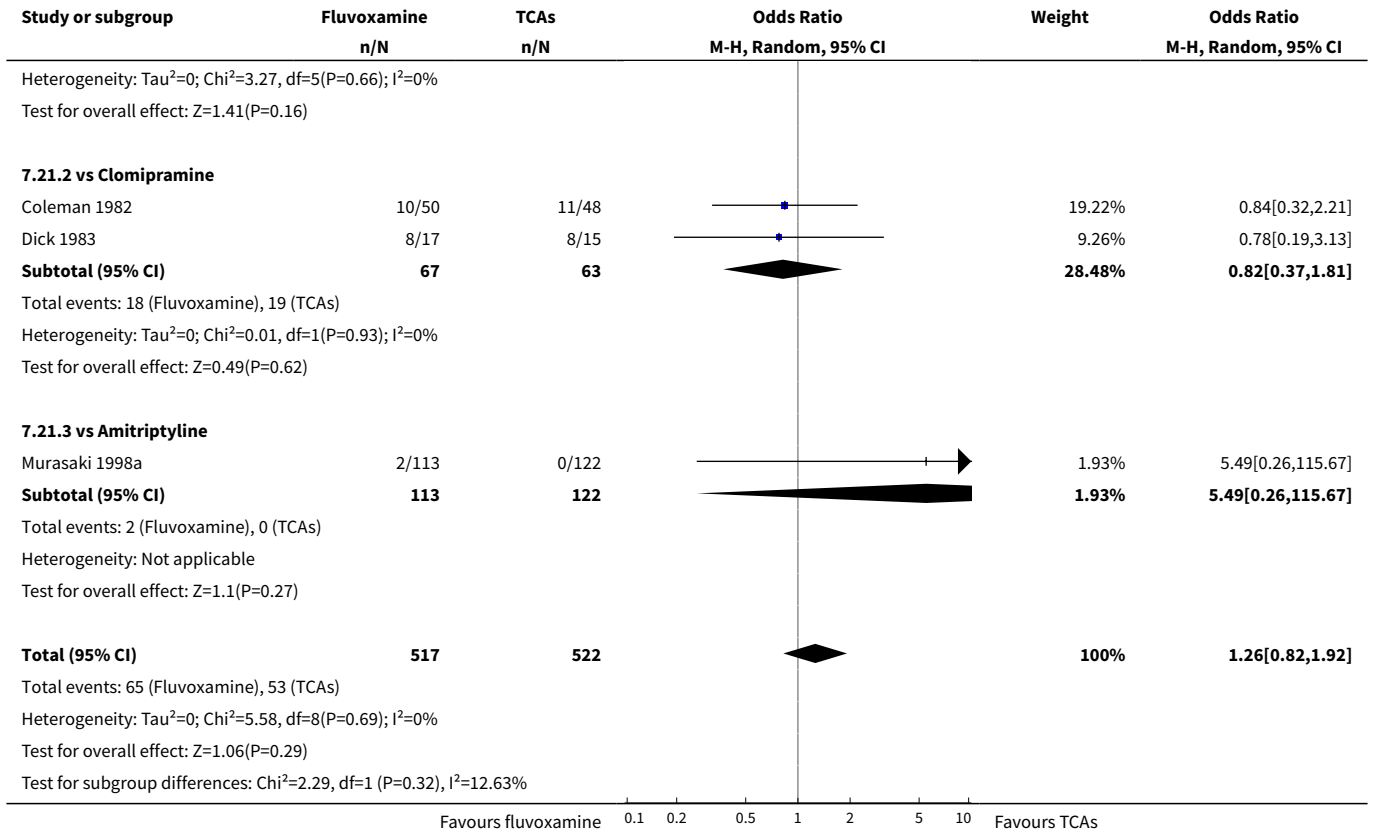


Analysis 7.20. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 20 Neuropsychiatric - Involuntary movement other than tremor.

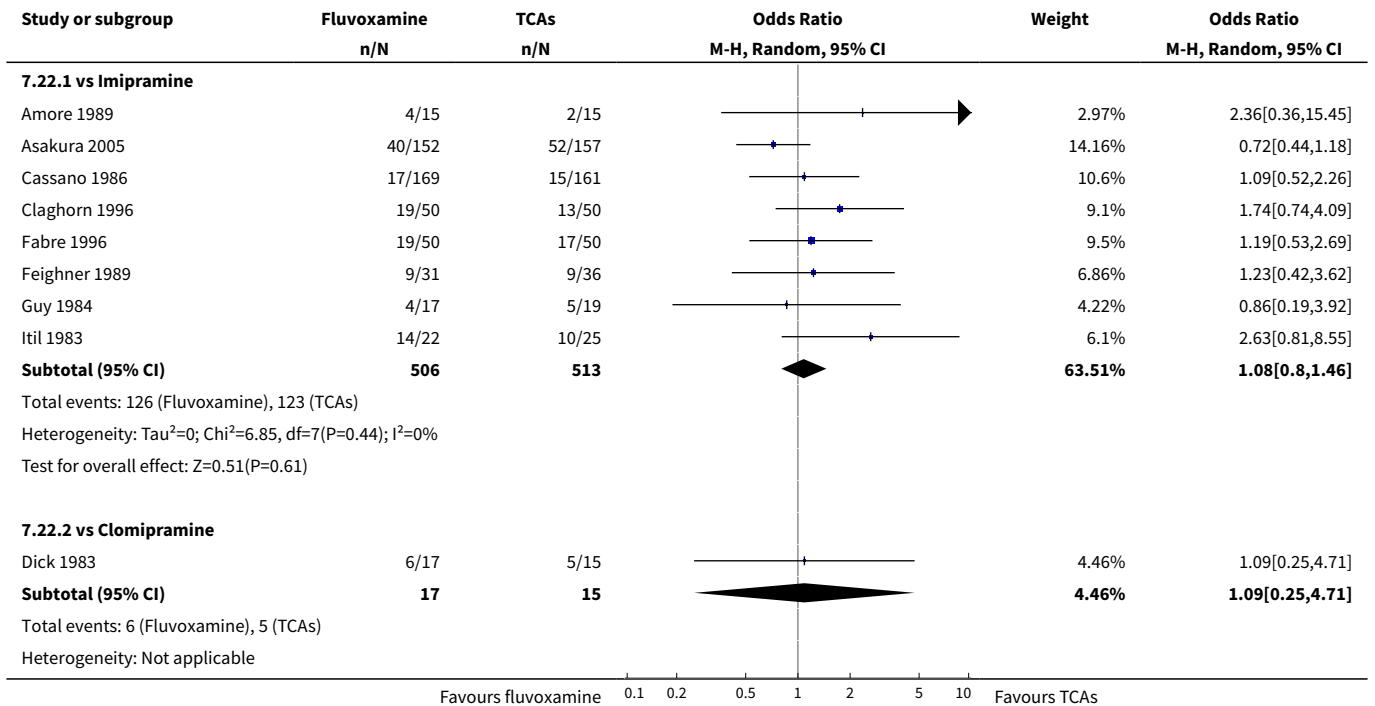


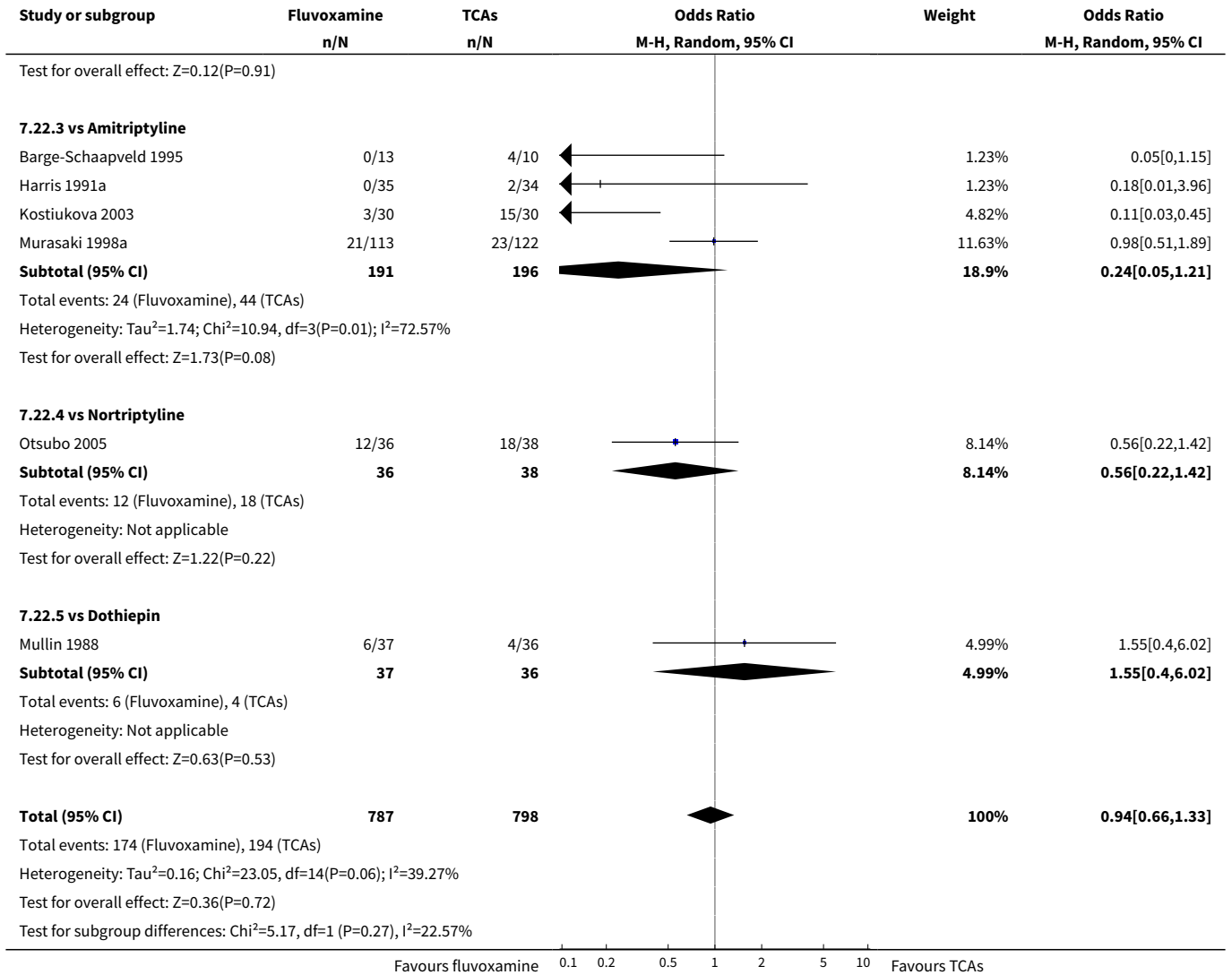
Analysis 7.21. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 21 Neuropsychiatric - Insomnia.



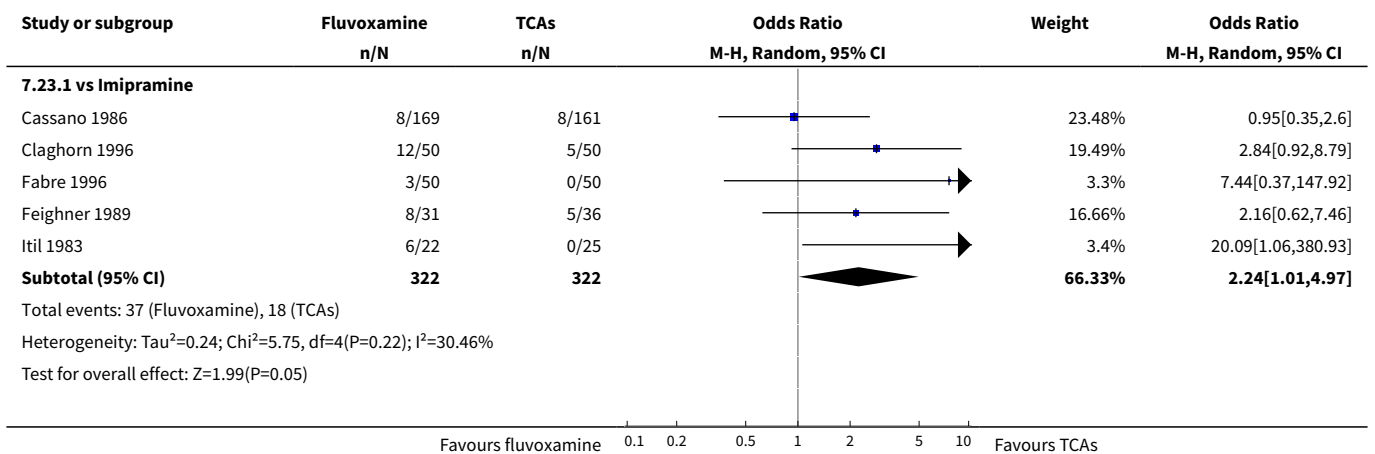


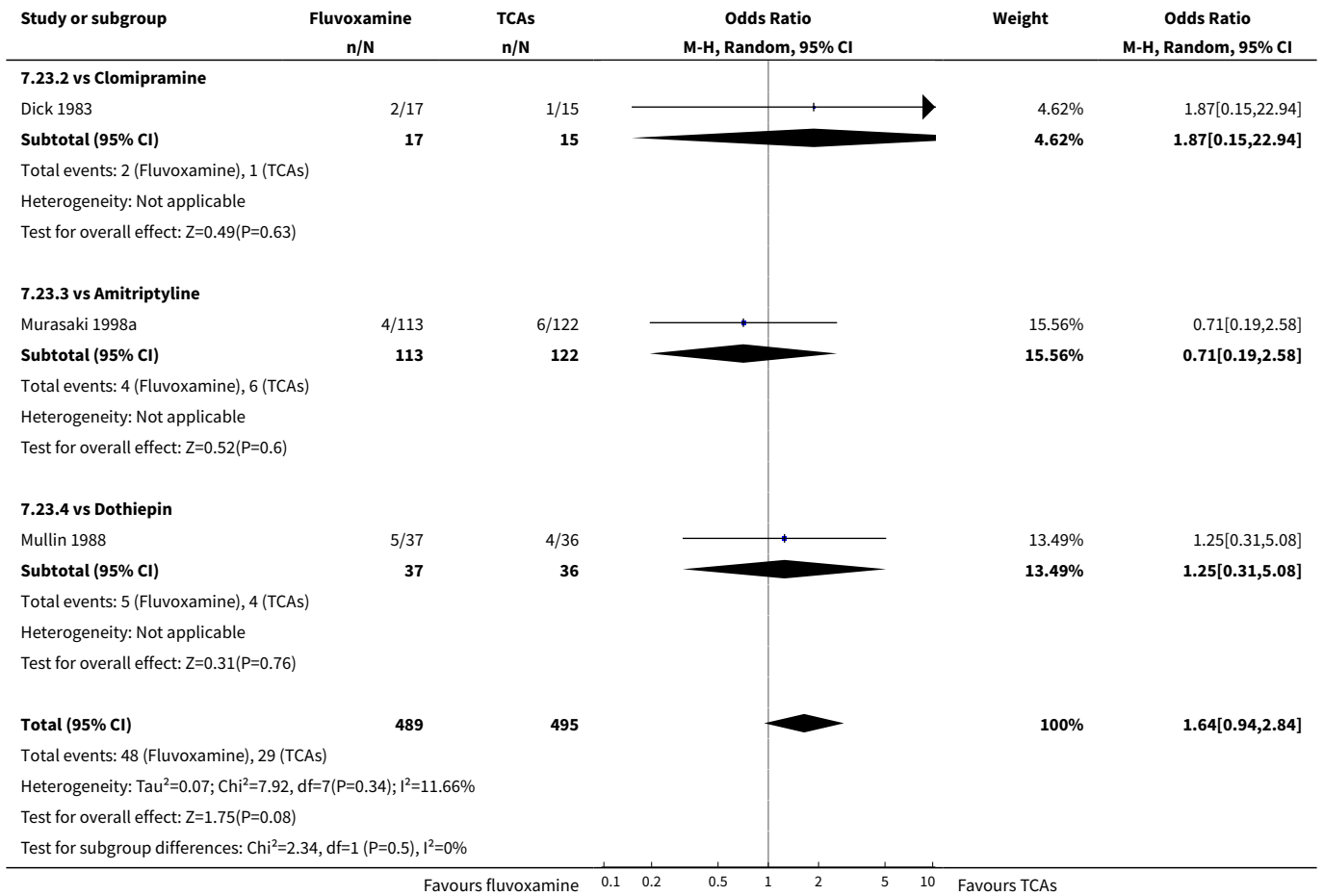
Analysis 7.22. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 22 Neuropsychiatric - Sleepiness / drowsiness.



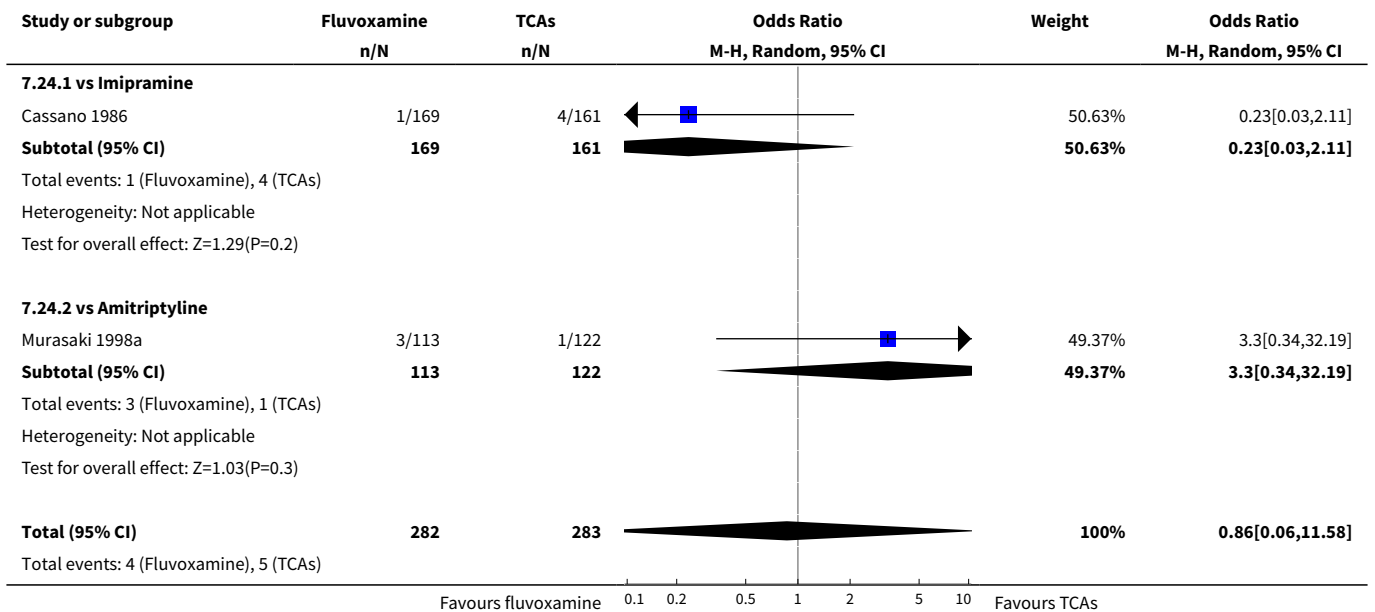


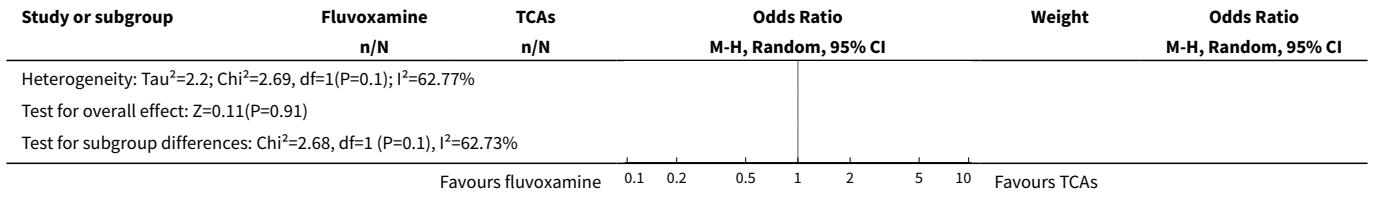
Analysis 7.23. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 23 Neuropsychiatric - Agitation / anxiety.



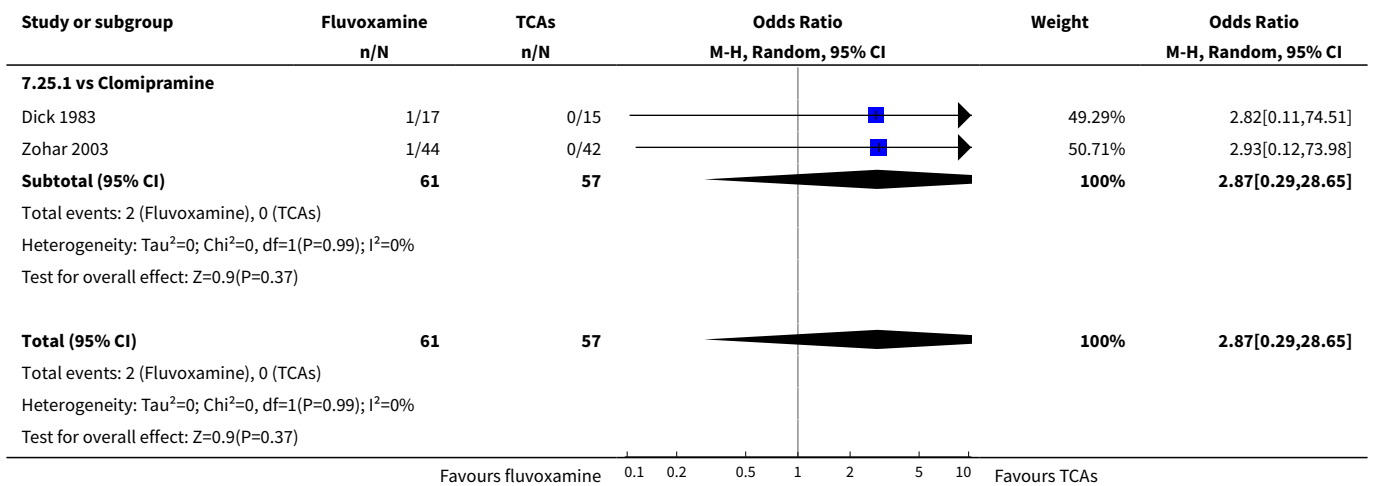


Analysis 7.24. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 24 Neuropsychiatric - Manic symptom.

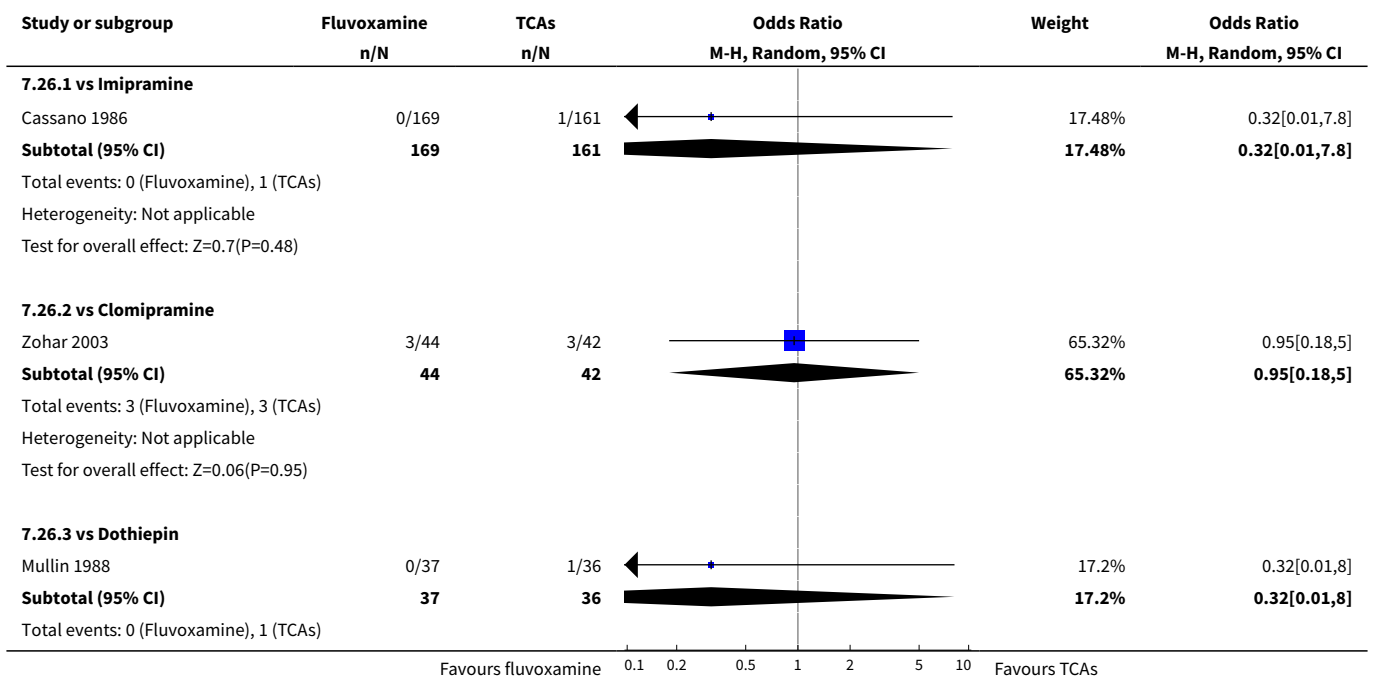


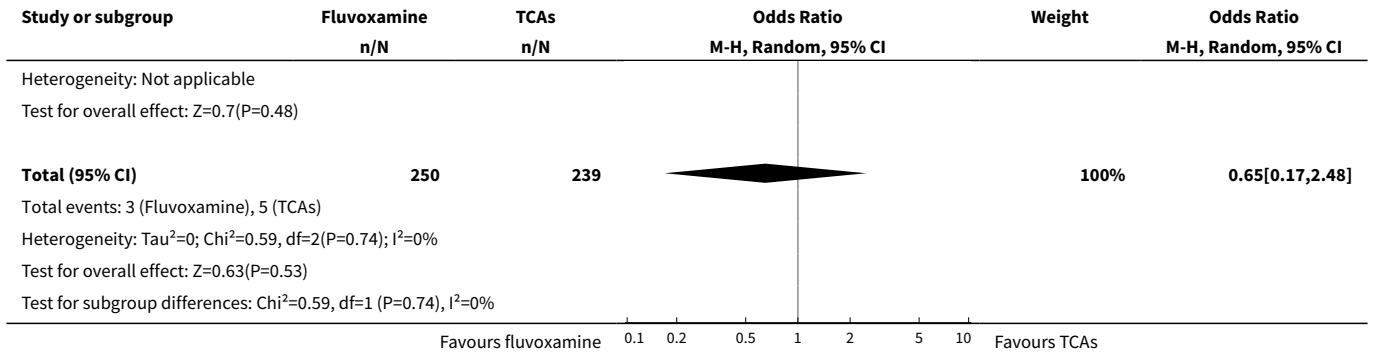


Analysis 7.25. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 25 Neuropsychiatric - Completed suicide.

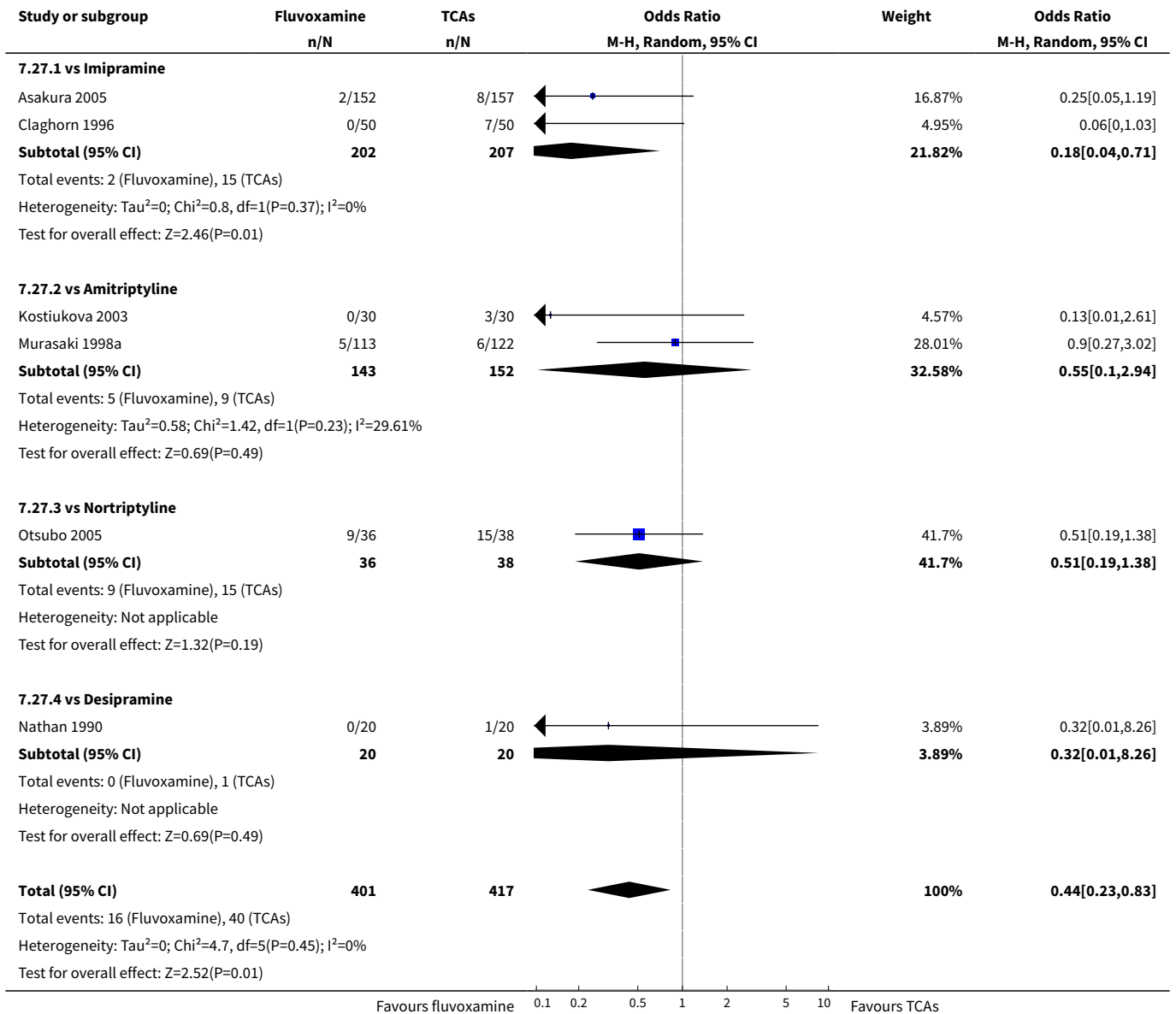


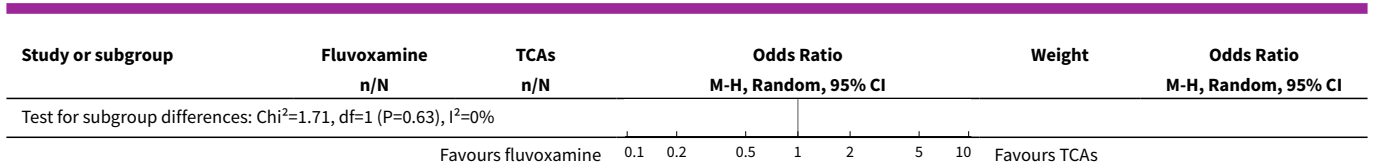
Analysis 7.26. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 26 Neuropsychiatric - Suicide wishes / gestures / attempts.



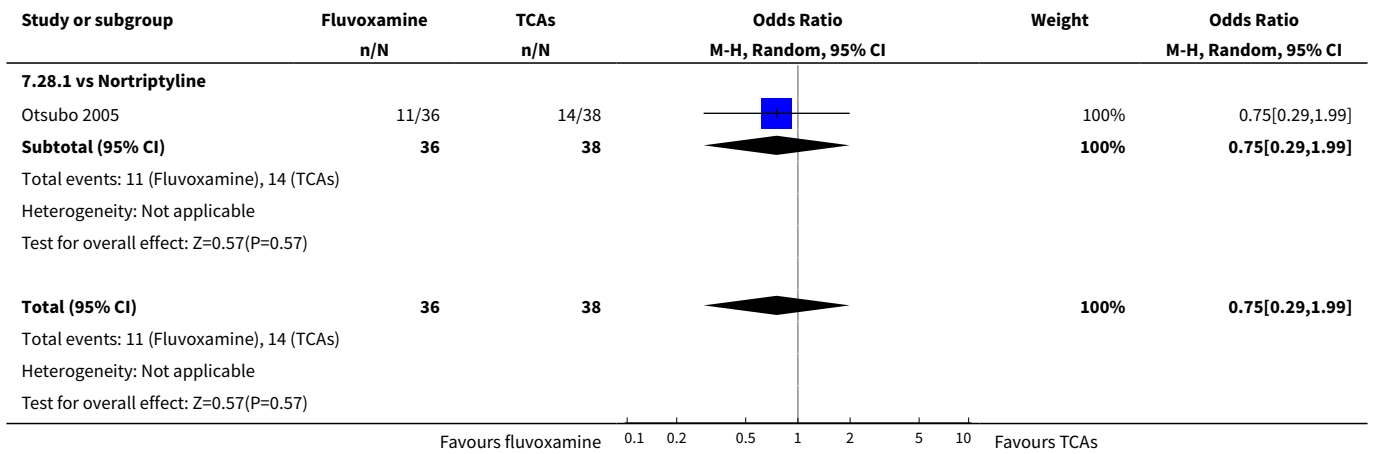


Analysis 7.27. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 27 Genitourinary - Problems urinating.





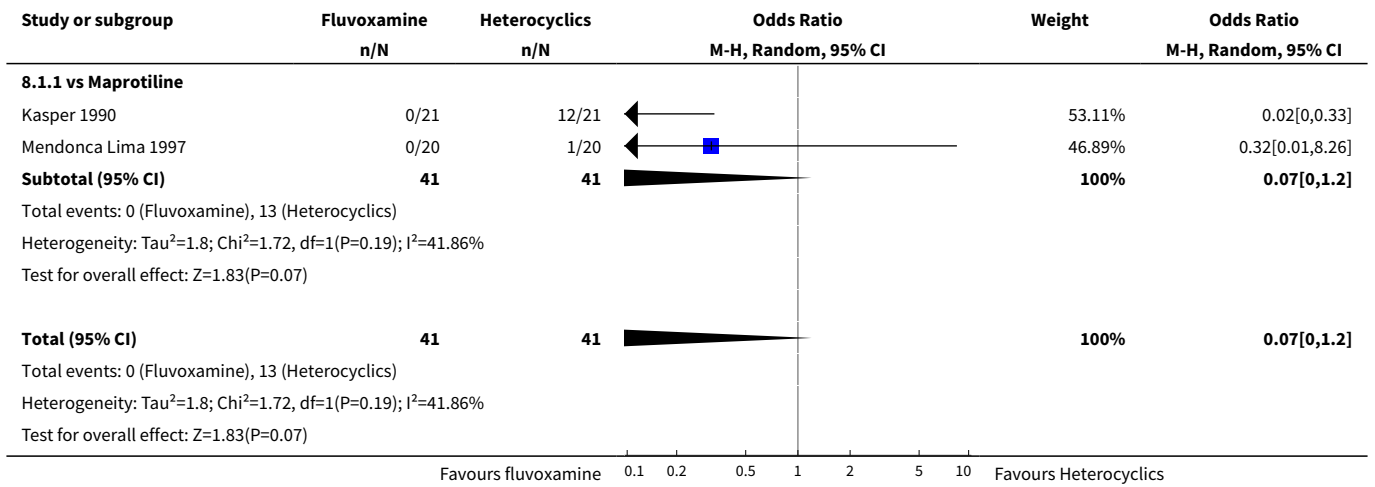
Analysis 7.28. Comparison 7 Side effect profile: Fluvoxamine vs TCAs, Outcome 28 Genitourinary - Sexual dysfunction.



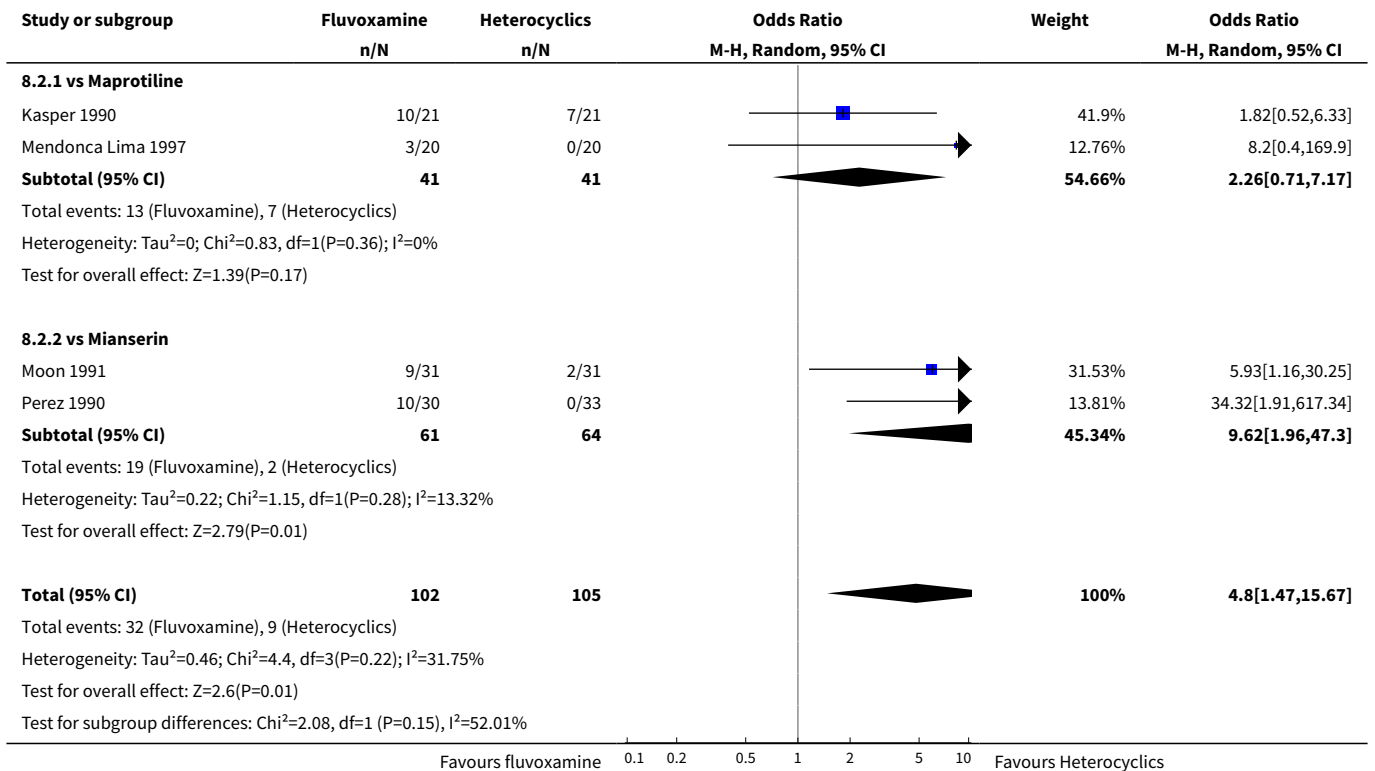
Comparison 8. Side effect profile: Fluvoxamine vs Heterocyclics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastrointestinal - Dry mouth	2	82	Odds Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.20]
1.1 vs Maprotiline	2	82	Odds Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.20]
2 Gastrointestinal - Vomiting / nausea	4	207	Odds Ratio (M-H, Random, 95% CI)	4.80 [1.47, 15.67]
2.1 vs Maprotiline	2	82	Odds Ratio (M-H, Random, 95% CI)	2.26 [0.71, 7.17]
2.2 vs Mianserin	2	125	Odds Ratio (M-H, Random, 95% CI)	9.62 [1.96, 47.30]
3 Neuropsychiatric - Dizziness / vertigo / faintness	2	104	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.04, 0.48]
3.1 vs Maprotiline	1	42	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.03, 0.56]
3.2 vs Mianserin	1	62	Odds Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.58]

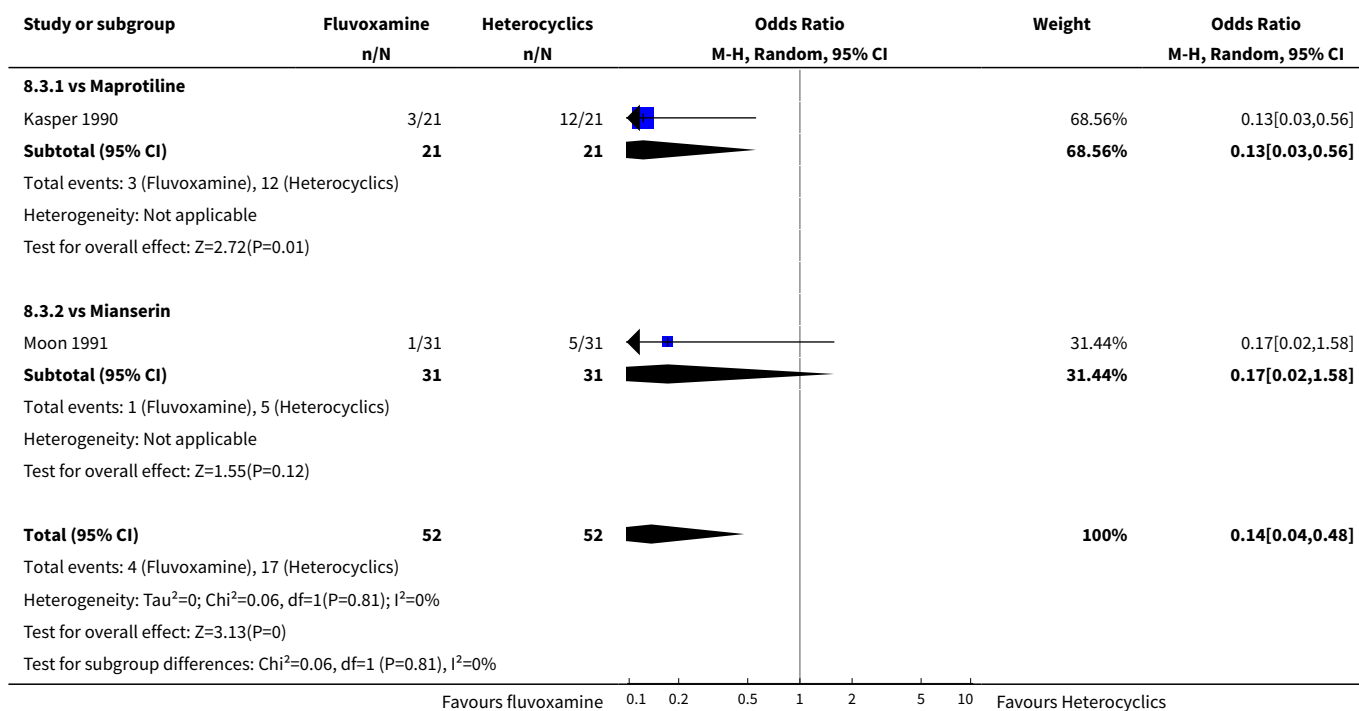
Analysis 8.1. Comparison 8 Side effect profile: Fluvoxamine vs Heterocyclics, Outcome 1 Gastrointestinal - Dry mouth.



Analysis 8.2. Comparison 8 Side effect profile: Fluvoxamine vs Heterocyclics, Outcome 2 Gastrointestinal - Vomiting / nausea.



Analysis 8.3. Comparison 8 Side effect profile: Fluvoxamine vs Heterocyclics, Outcome 3 Neuropsychiatric - Dizziness / vertigo / faintness.



Comparison 9. Side effect profile: Fluvoxamine vs other SSRIs

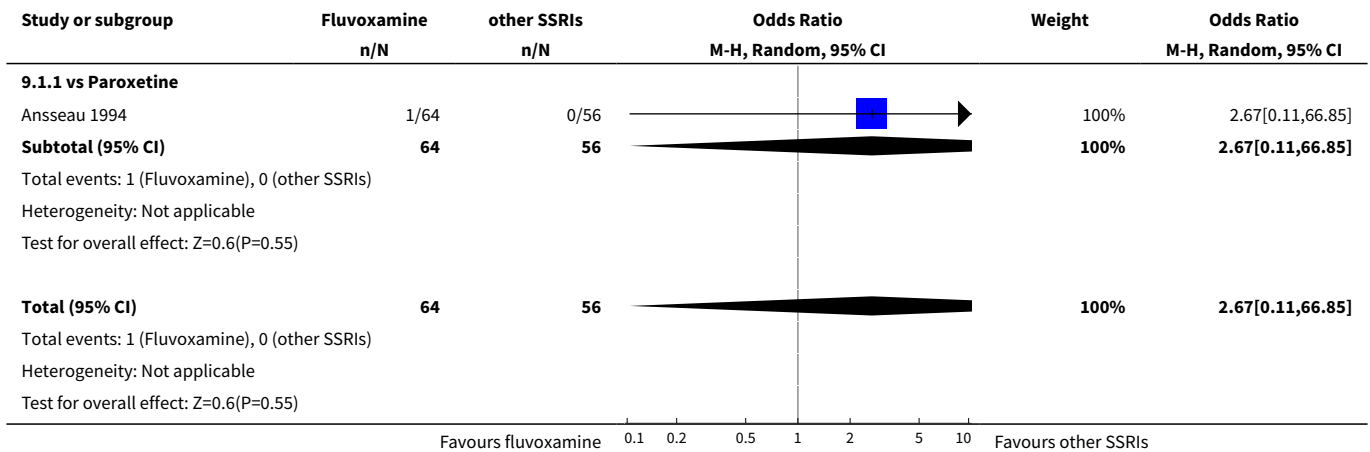
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular - Hypertension / tachycardia	1	120	Odds Ratio (M-H, Random, 95% CI)	2.67 [0.11, 66.85]
1.1 vs Paroxetine	1	120	Odds Ratio (M-H, Random, 95% CI)	2.67 [0.11, 66.85]
2 Cardiovascular - Hypotension / bradycardia	1	120	Odds Ratio (M-H, Random, 95% CI)	4.66 [0.53, 41.16]
2.1 vs Paroxetine	1	120	Odds Ratio (M-H, Random, 95% CI)	4.66 [0.53, 41.16]
3 Dermatological - Dermatitis / rash	1	88	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.01, 4.92]
3.1 vs Sertraline	1	88	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.01, 4.92]
4 Dermatological - Sweating	2	157	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.12, 0.96]
4.1 vs Paroxetine	1	60	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.05, 0.91]
4.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.13, 2.49]
5 Gastrointestinal - Dry mouth	2	157	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.54, 2.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 vs Paroxetine	1	60	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.53, 4.77]
5.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.31, 2.33]
6 Gastrointestinal - Vomiting / nausea	6	649	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.46, 1.36]
6.1 vs Paroxetine	2	180	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.46, 1.78]
6.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	1.78 [0.73, 4.33]
6.3 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.21, 1.13]
7 Gastrointestinal - Constipation	1	60	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.08, 2.75]
7.1 vs Paroxetine	1	60	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.08, 2.75]
8 Gastrointestinal - Diarrhoea	3	257	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.23, 0.82]
8.1 vs Paroxetine	1	60	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.10, 1.33]
8.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.20, 1.59]
8.3 vs Fluoxetine	1	100	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.13, 1.07]
9 Gastrointestinal - Anorexia	2	281	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.17, 1.95]
9.1 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.16, 2.36]
9.2 vs Fluoxetine	1	184	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.56]
10 Neuropsychiatric - Dizziness / vertigo / faintness	3	238	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.33, 1.60]
10.1 vs Paroxetine	2	141	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.22, 1.92]
10.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.25, 2.64]
11 Neuropsychiatric - Fatigue / tiredness / asthenia	2	157	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.19, 1.64]
11.1 vs Paroxetine	1	60	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.15, 3.54]
11.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.11, 1.94]
12 Neuropsychiatric - Headache	6	642	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.31]
12.1 vs Paroxetine	3	261	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.37, 2.52]
12.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.33, 1.92]

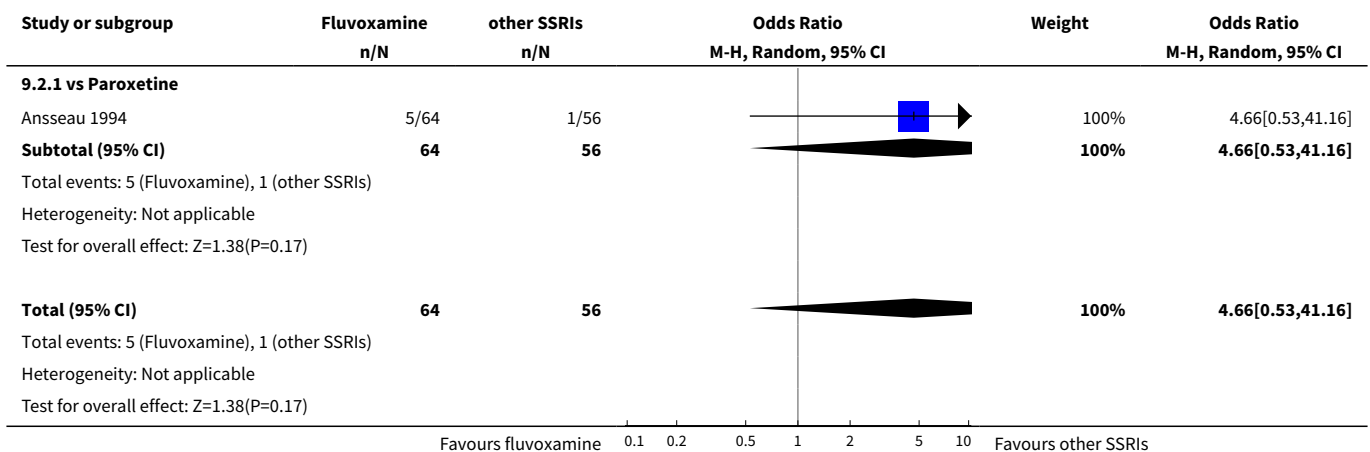
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.50, 1.60]
13 Neuropsychiatric - Tremor	3	277	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.21, 1.63]
13.1 vs Paroxetine	2	180	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.14, 2.51]
13.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.13, 2.49]
14 Neuropsychiatric - Insomnia	3	257	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.68, 2.01]
14.1 vs Paroxetine	1	60	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.52, 5.62]
14.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.30, 1.73]
14.3 vs Fluoxetine	1	100	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.64, 3.55]
15 Neuropsychiatric - Sleepiness / drowsiness	3	277	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.32, 3.46]
15.1 vs Paroxetine	2	180	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.02, 9.92]
15.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	1.62 [0.60, 4.41]
16 Neuropsychiatric - Agitation / anxiety	5	465	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.40, 1.35]
16.1 vs Paroxetine	2	180	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.13, 12.78]
16.2 vs Sertraline	2	185	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.45, 2.80]
16.3 vs Fluoxetine	1	100	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.21, 1.05]
17 Neuropsychiatric - Manic symptom	1	120	Odds Ratio (M-H, Random, 95% CI)	2.67 [0.11, 66.85]
17.1 vs Paroxetine	1	120	Odds Ratio (M-H, Random, 95% CI)	2.67 [0.11, 66.85]
18 Neuropsychiatric - Completed suicide	1	217	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.12]
18.1 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.12]
19 Neuropsychiatric - Suicide wishes / gestures / attempts	4	621	Odds Ratio (M-H, Random, 95% CI)	1.99 [0.39, 10.05]
19.1 vs Paroxetine	1	120	Odds Ratio (M-H, Random, 95% CI)	2.67 [0.11, 66.85]
19.2 vs Fluoxetine	2	284	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.05, 10.05]
19.3 vs Citalopram	1	217	Odds Ratio (M-H, Random, 95% CI)	9.26 [0.49, 174.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20 Genitourinary - Sexual dysfunction	4	422	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.26, 1.14]
20.1 vs Paroxetine	2	141	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.29, 1.91]
20.2 vs Sertraline	1	97	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.07, 1.12]
20.3 vs Fluoxetine	1	184	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.80]

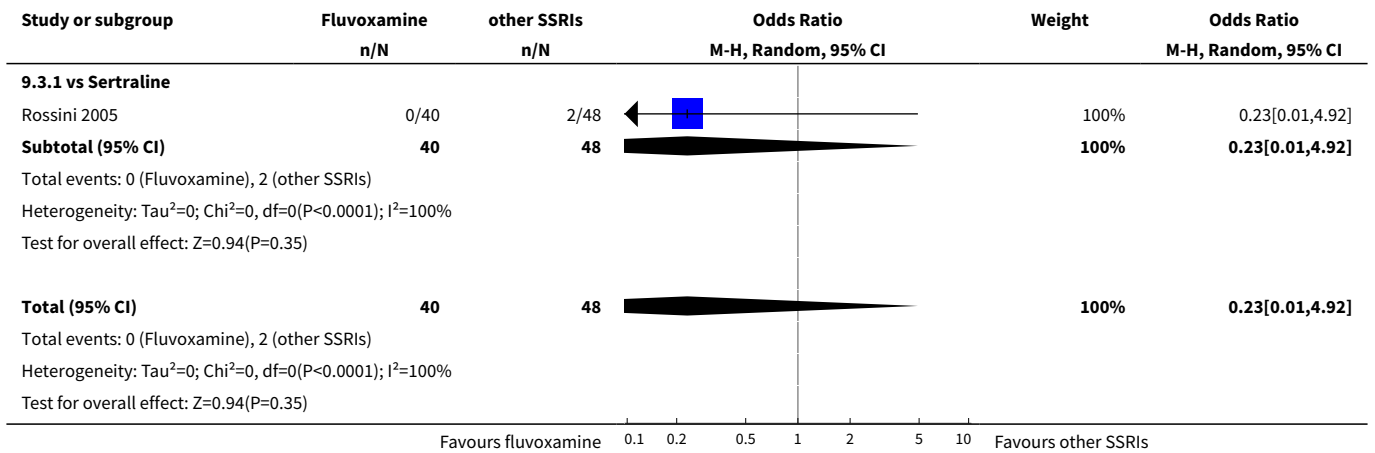
Analysis 9.1. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 1 Cardiovascular - Hypertension / tachycardia.



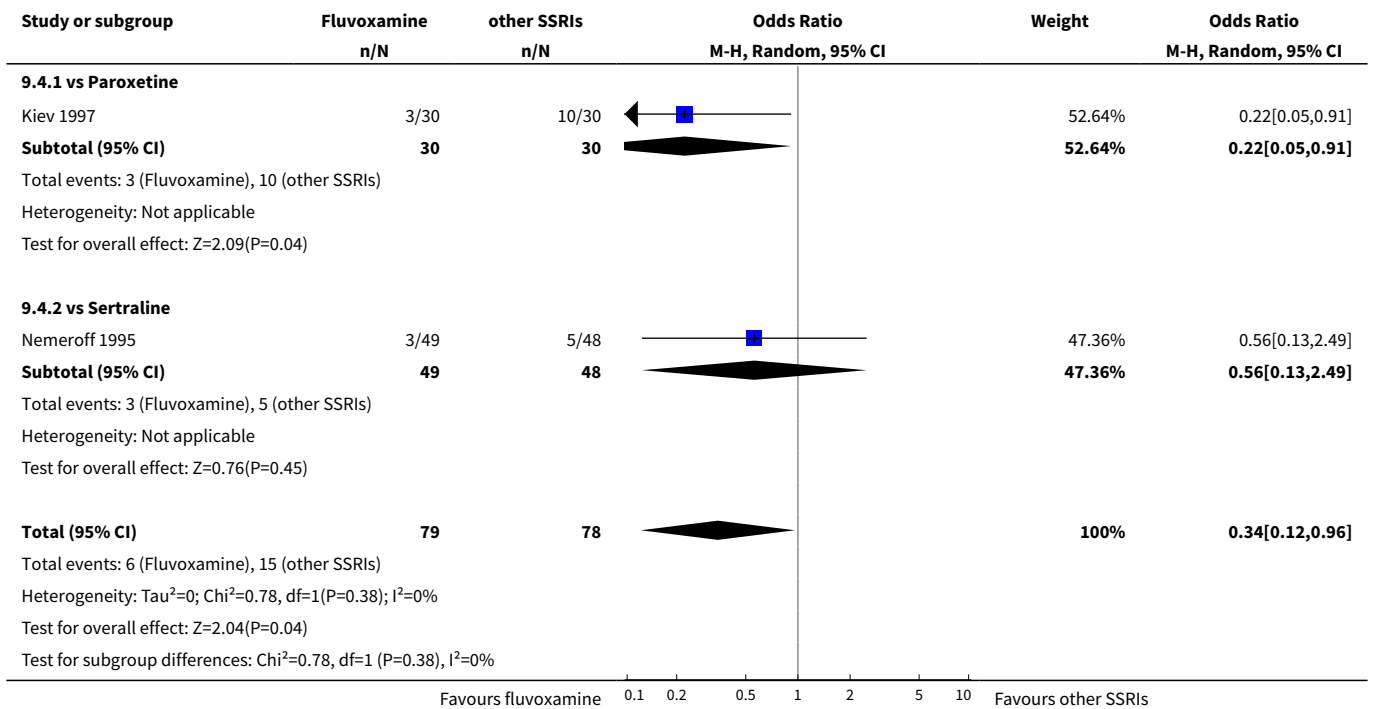
Analysis 9.2. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 2 Cardiovascular - Hypotension / bradycardia.



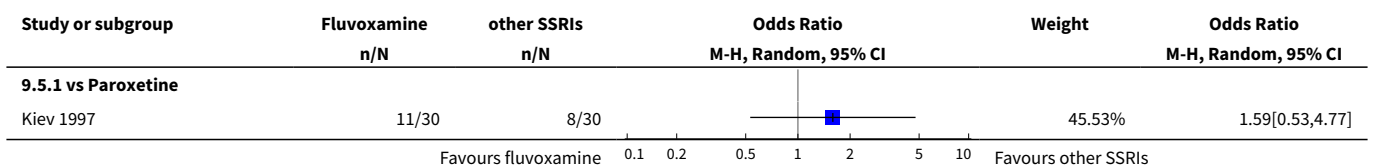
Analysis 9.3. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 3 Dermatological - Dermatitis / rash.

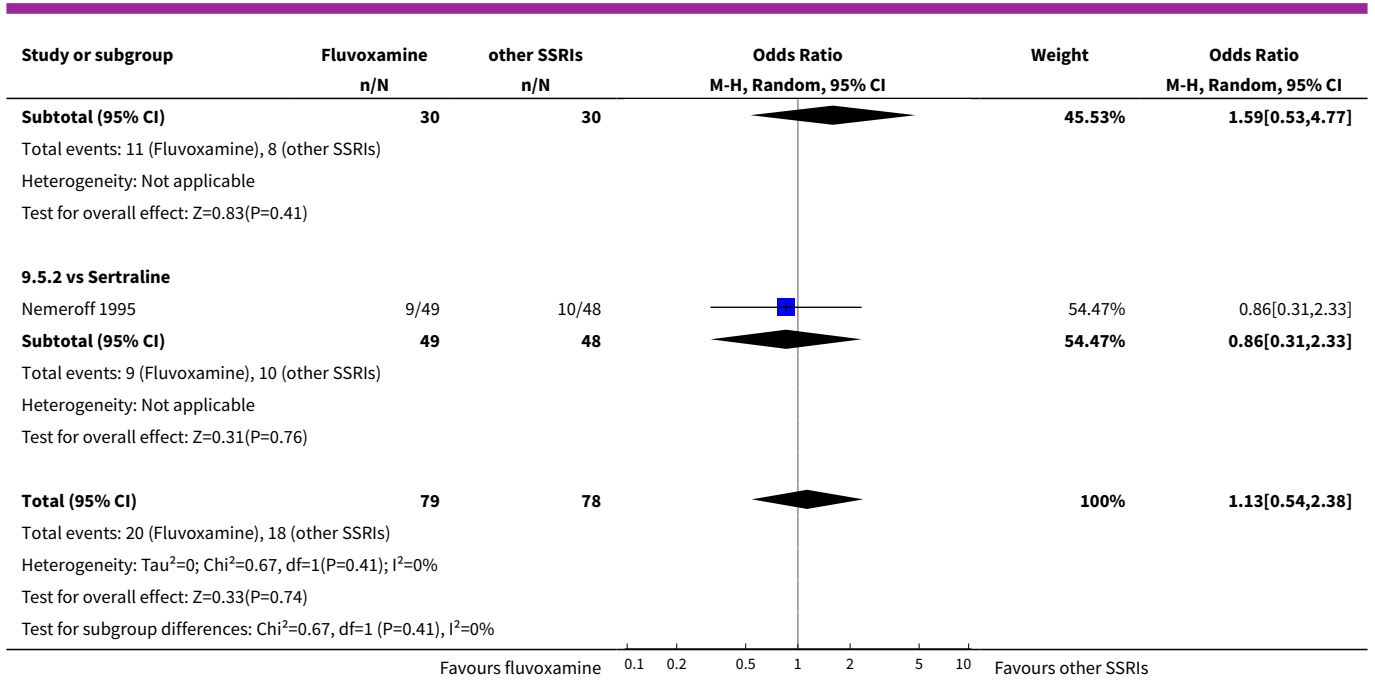


Analysis 9.4. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 4 Dermatological - Sweating.

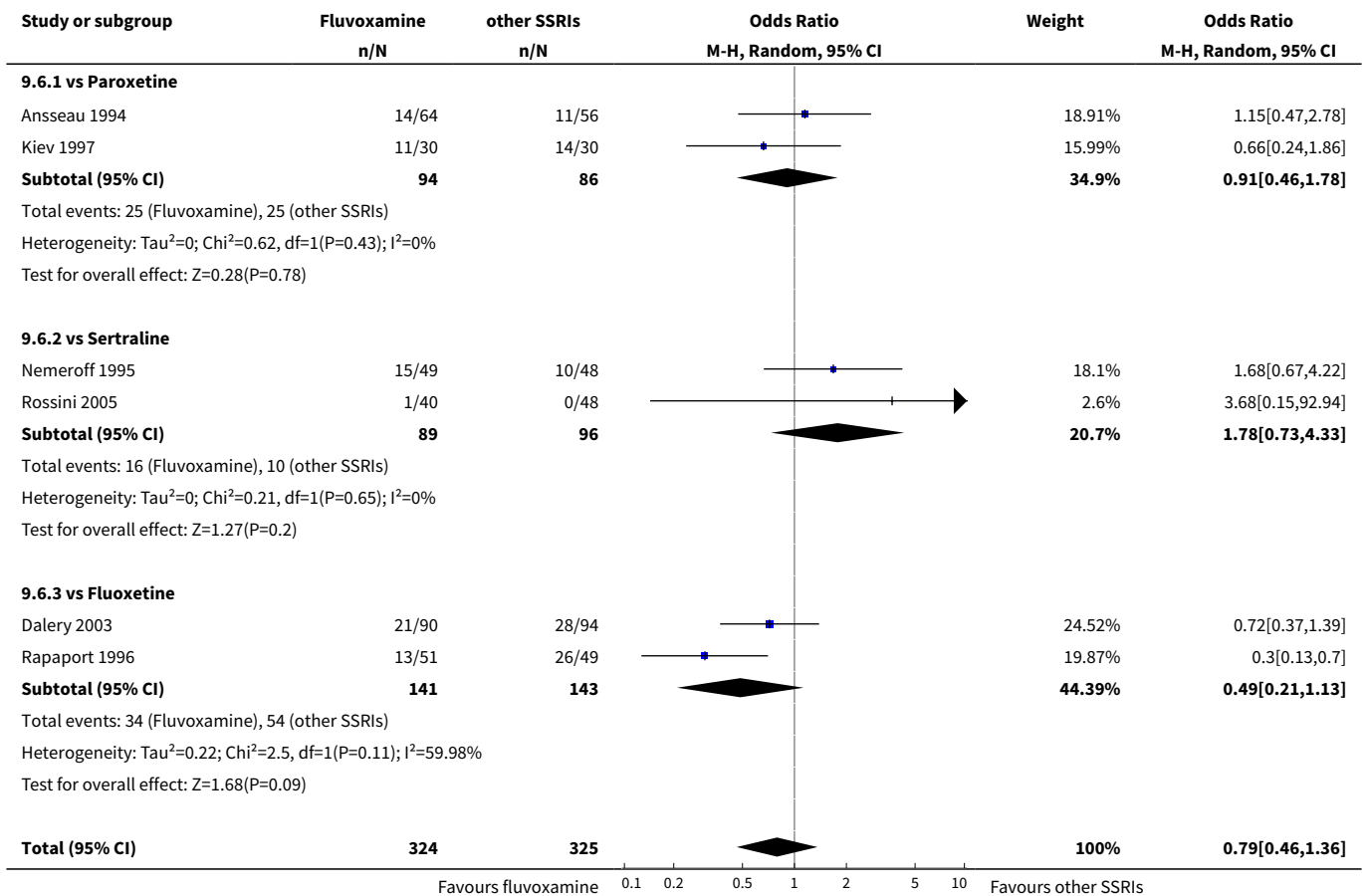


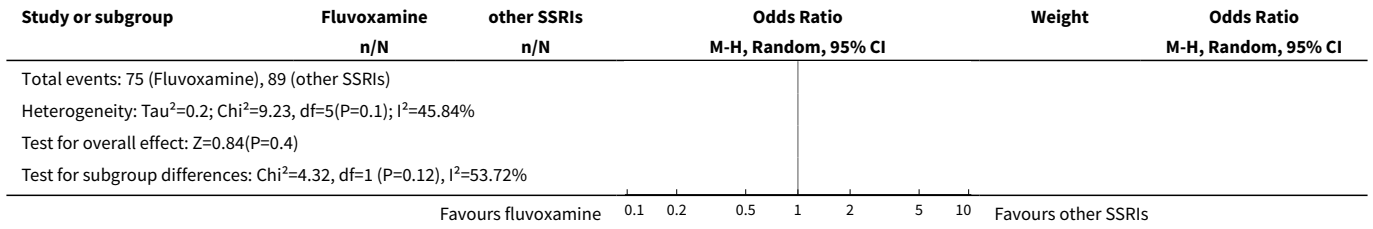
Analysis 9.5. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 5 Gastrointestinal - Dry mouth.



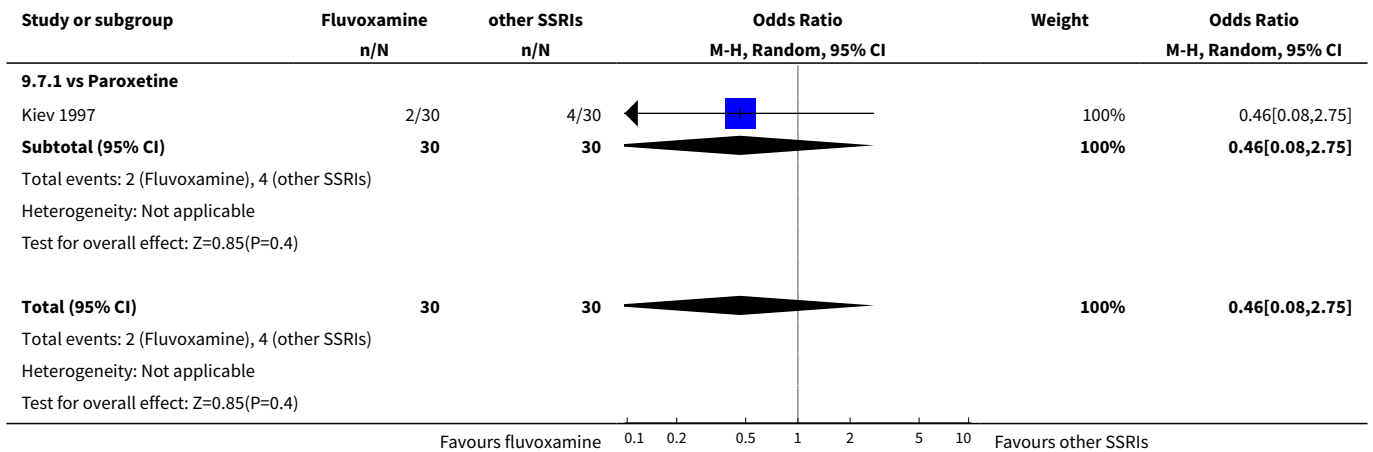


Analysis 9.6. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 6 Gastrointestinal - Vomiting / nausea.

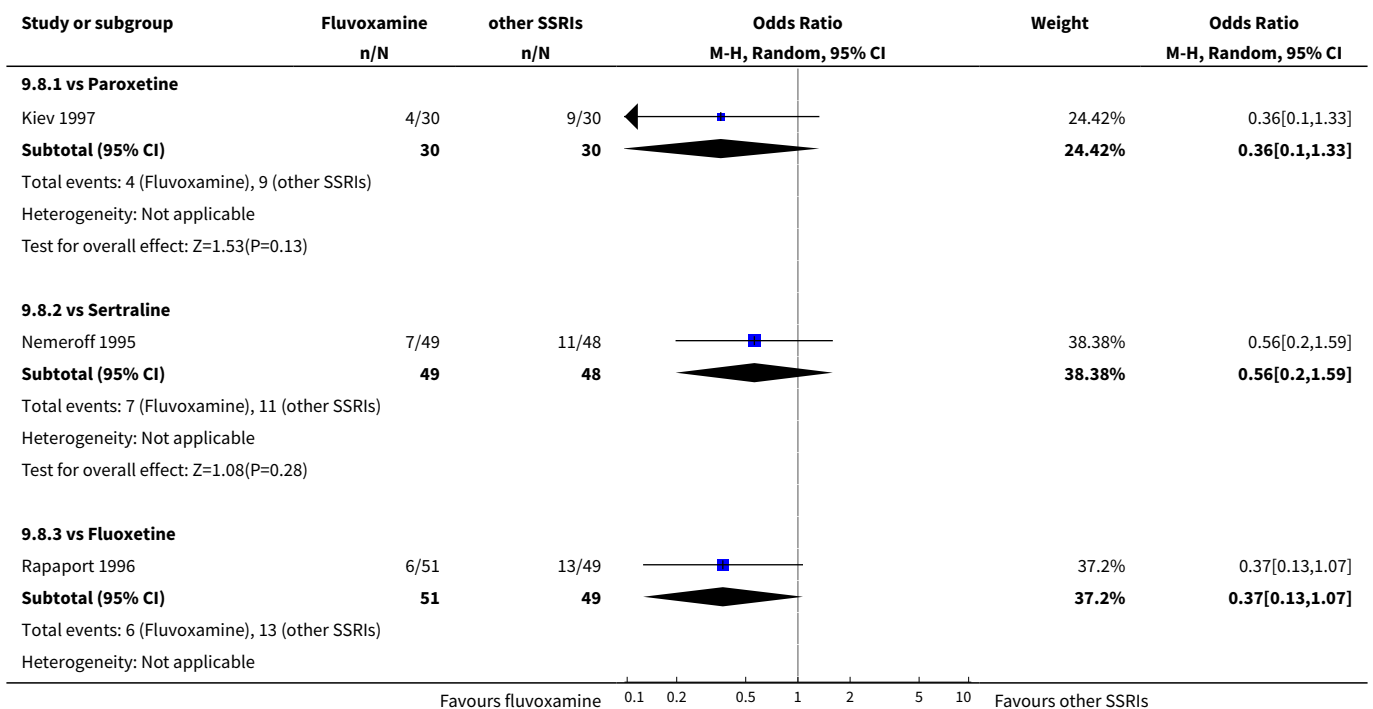


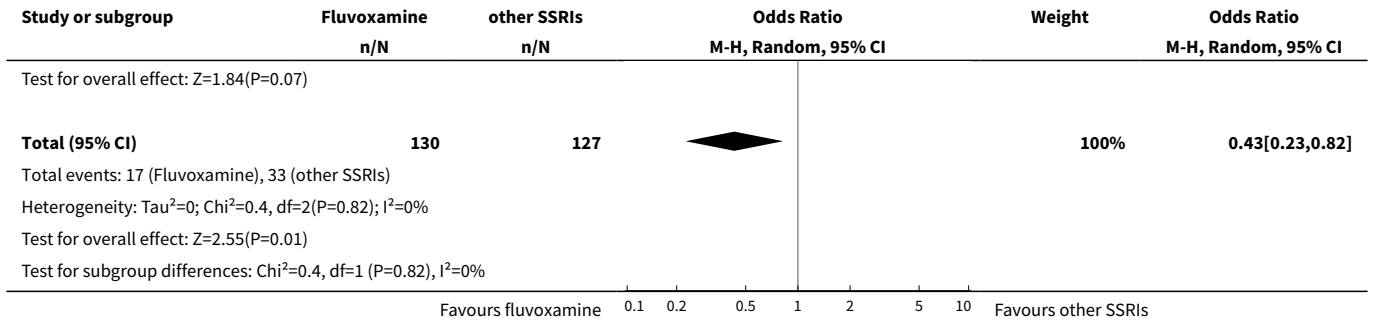


Analysis 9.7. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 7 Gastrointestinal - Constipation.

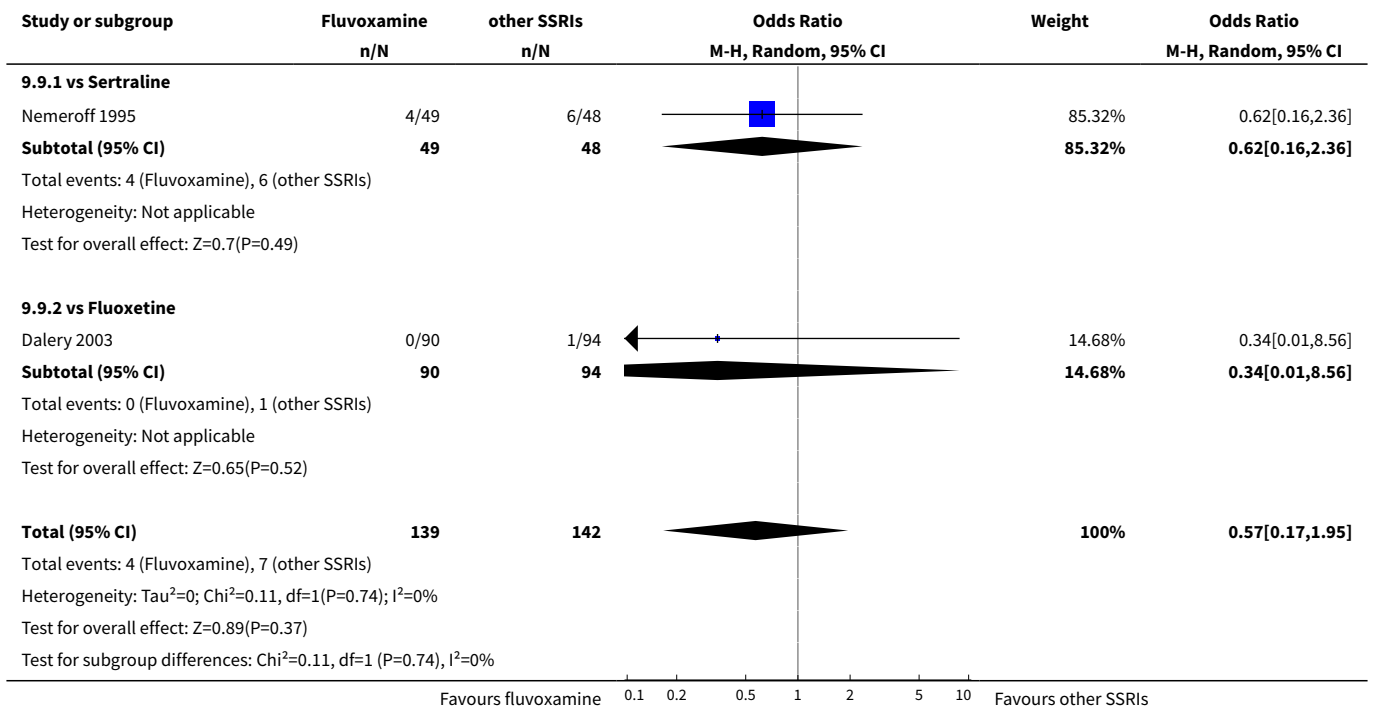


Analysis 9.8. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 8 Gastrointestinal - Diarrhoea.

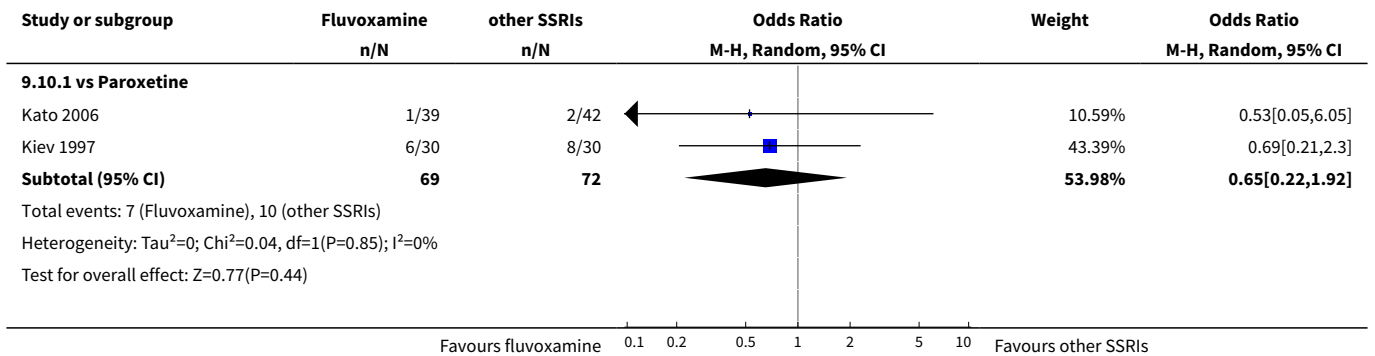


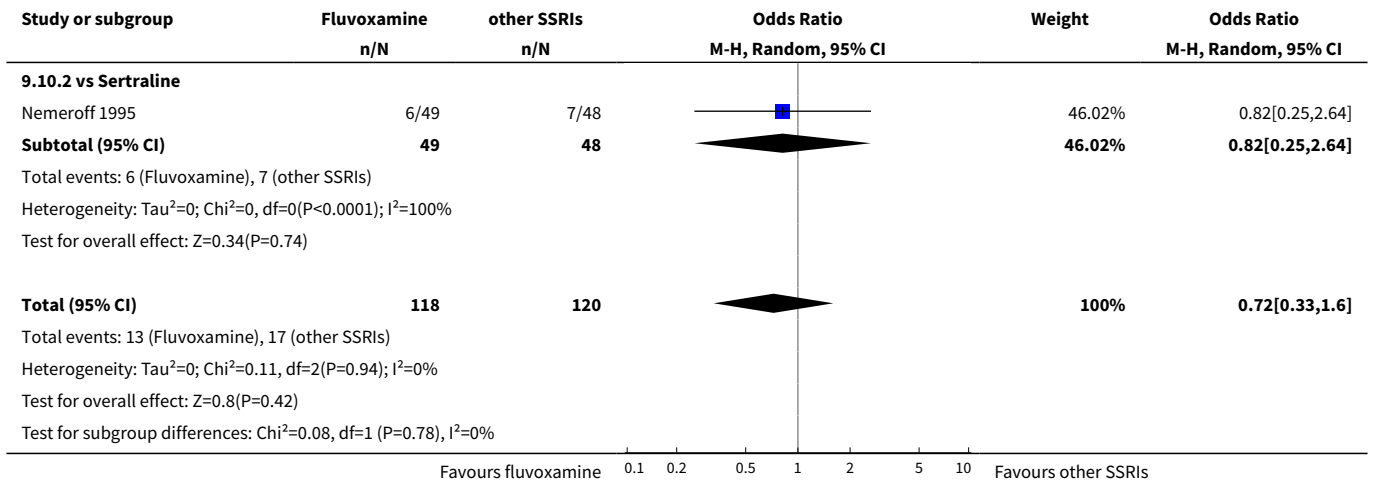


Analysis 9.9. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 9 Gastrointestinal - Anorexia.

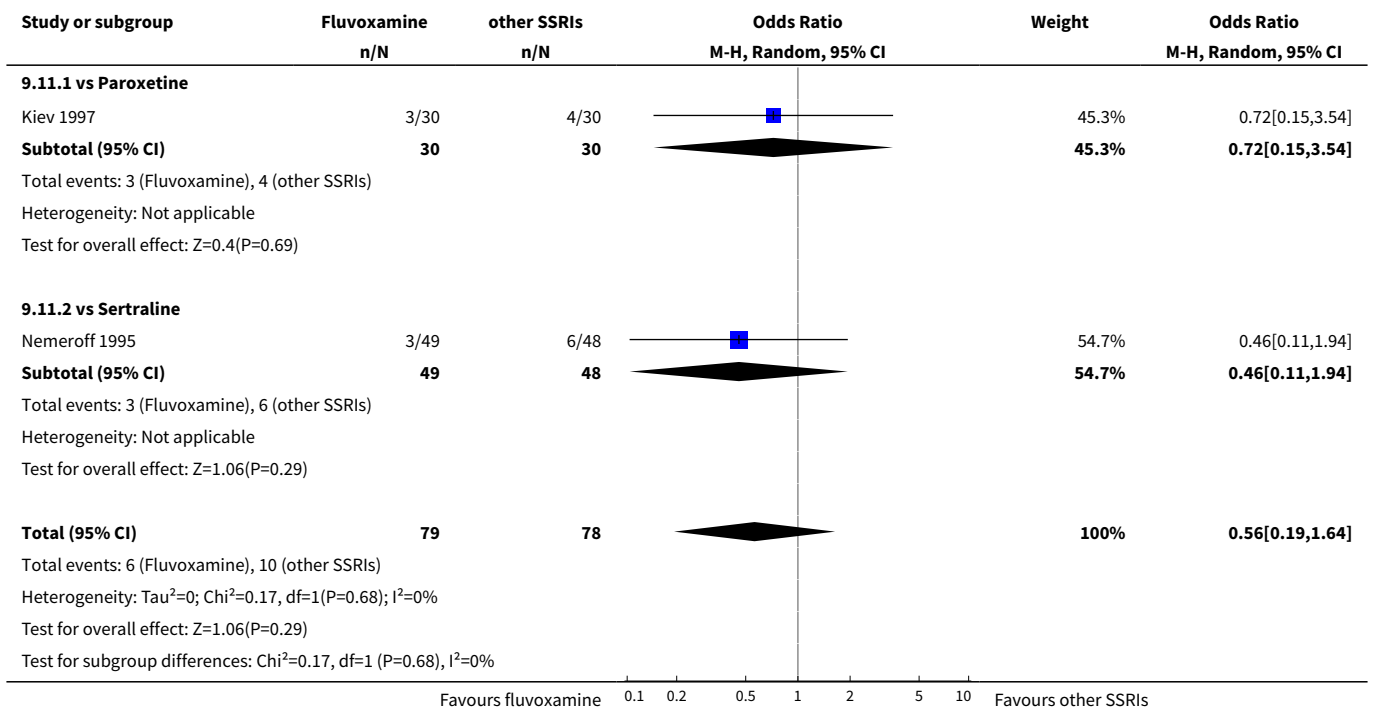


Analysis 9.10. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 10 Neuropsychiatric - Dizziness / vertigo / faintness.

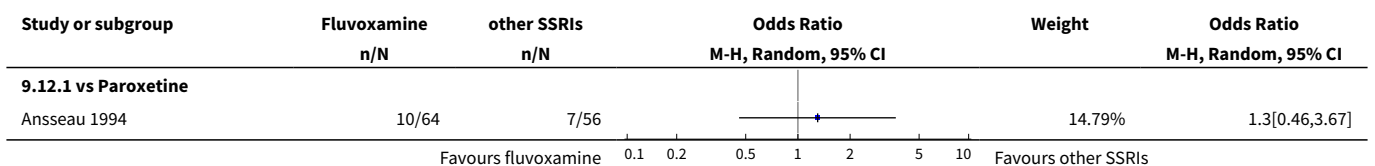


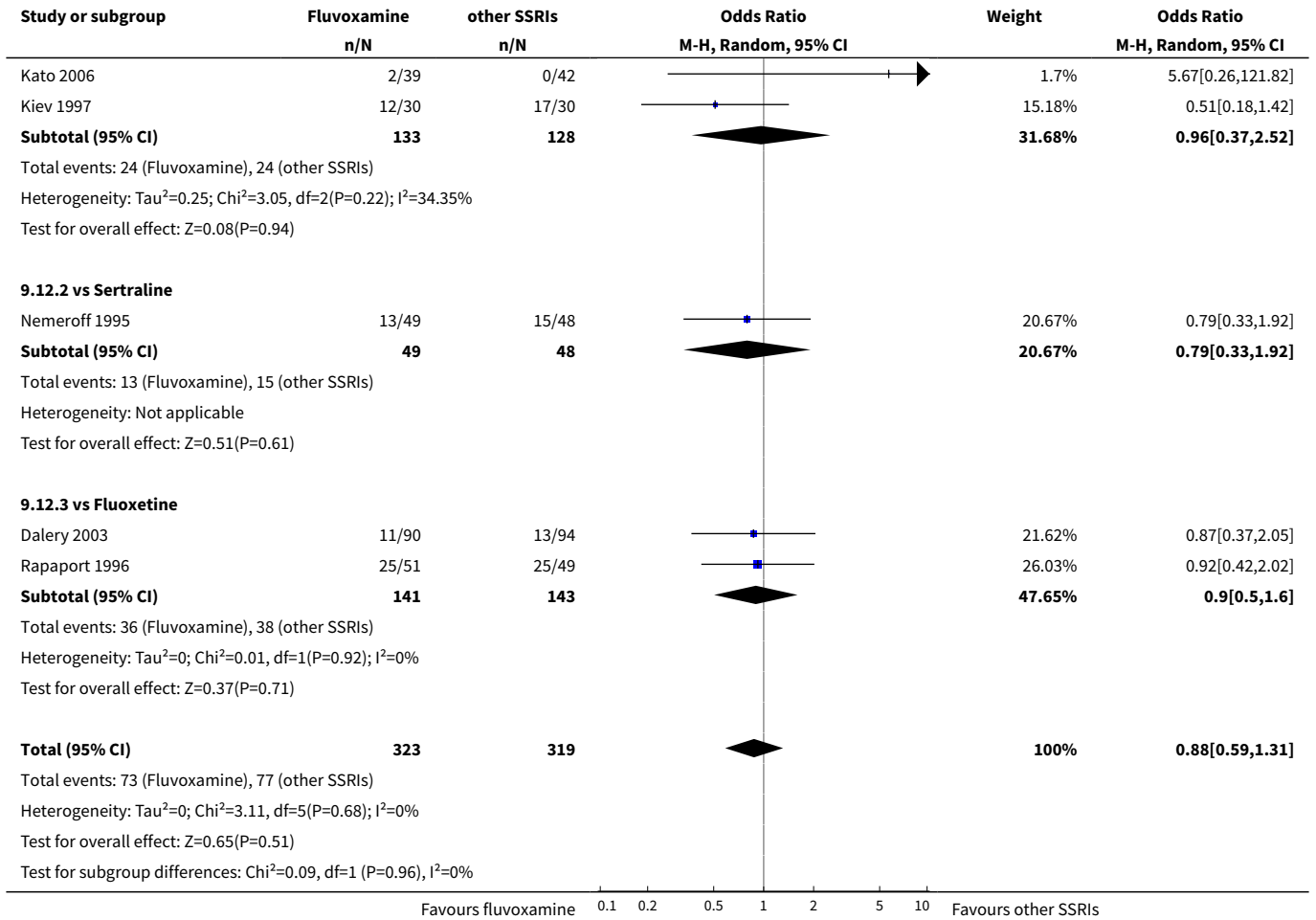


Analysis 9.11. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 11 Neuropsychiatric - Fatigue / tiredness / asthenia.

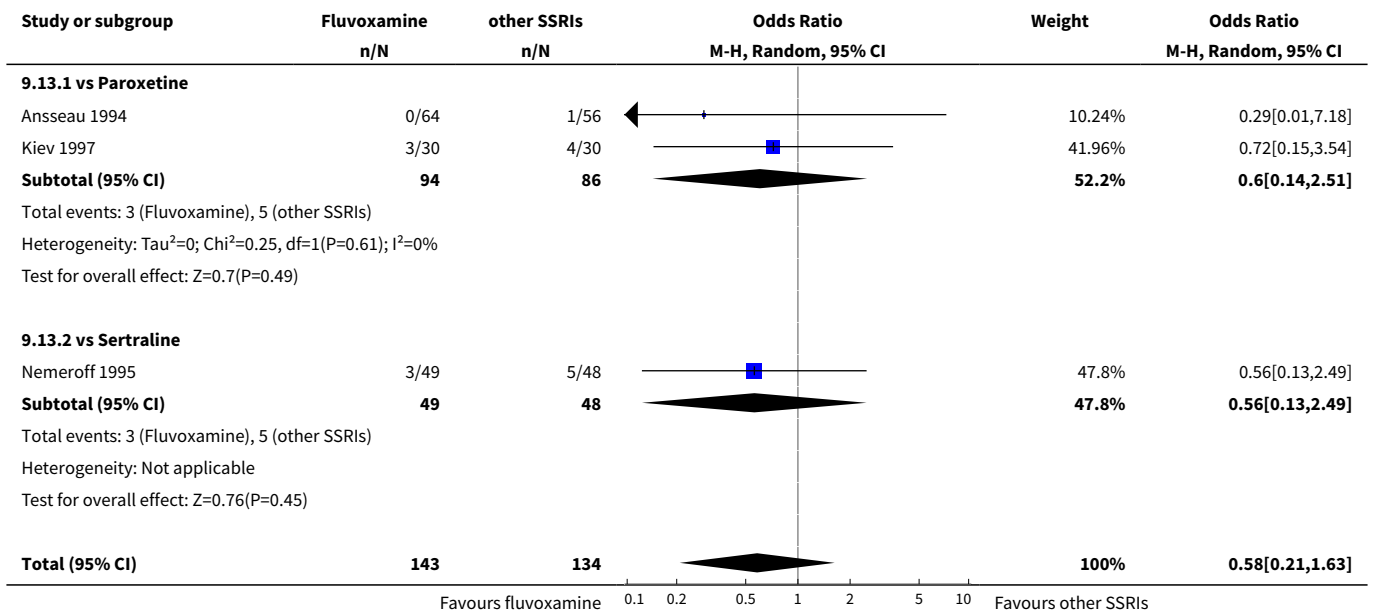


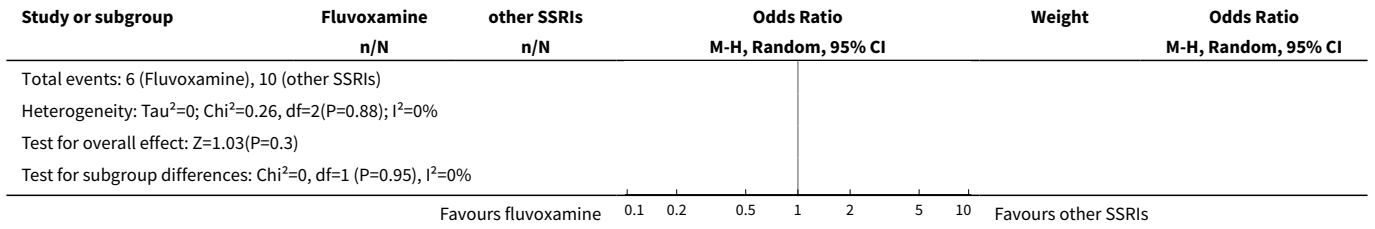
Analysis 9.12. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 12 Neuropsychiatric - Headache.



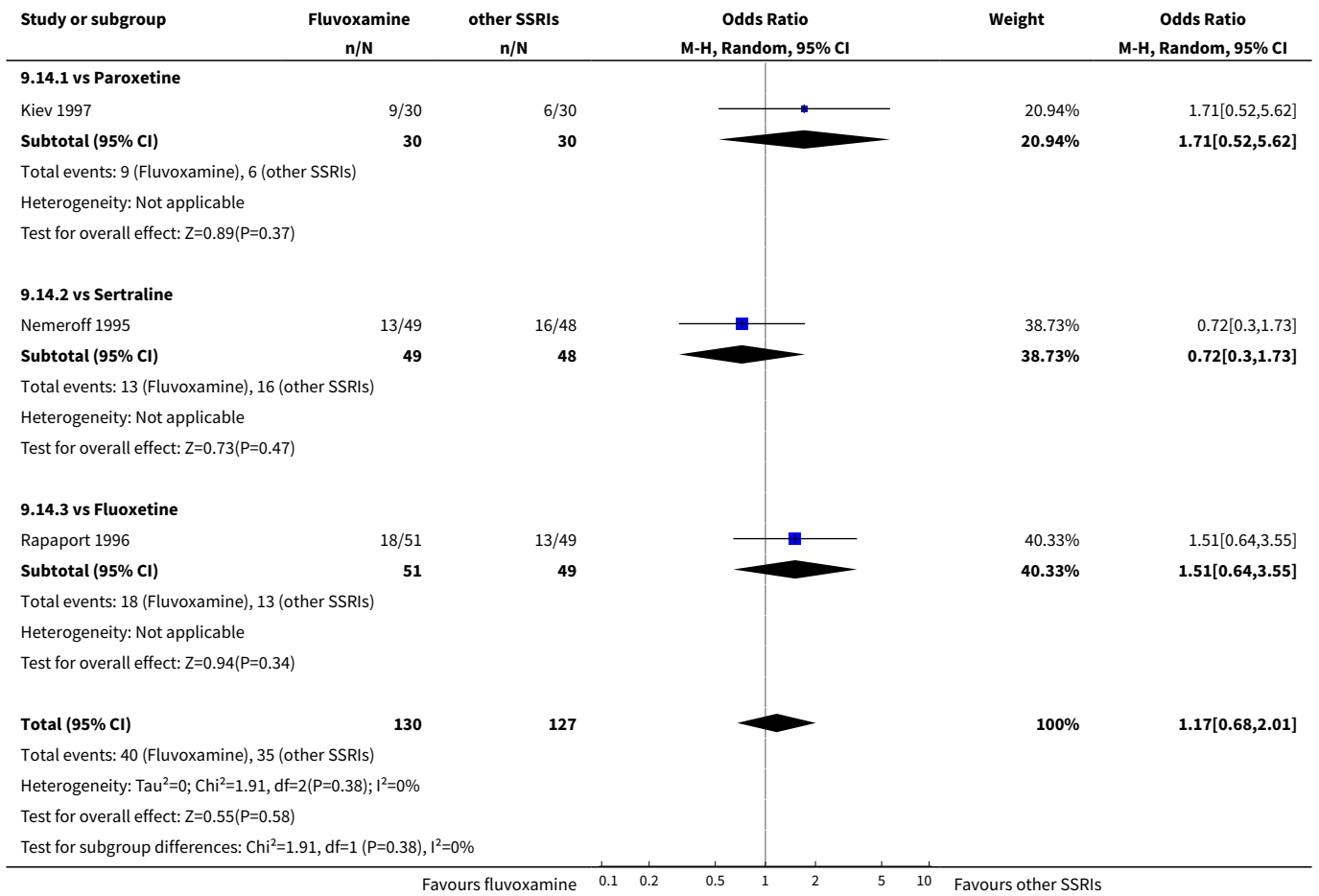


Analysis 9.13. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 13 Neuropsychiatric - Tremor.

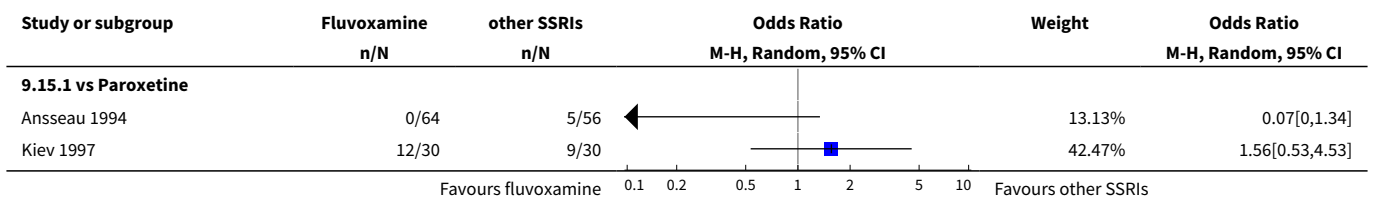


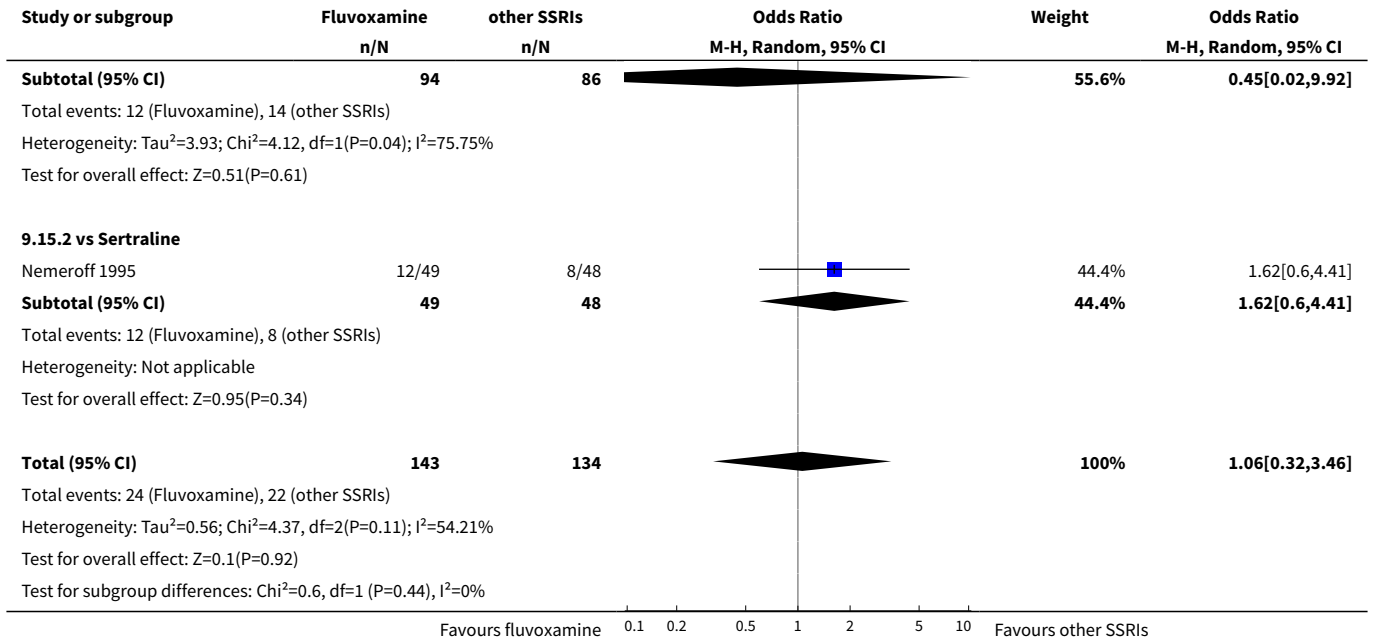


Analysis 9.14. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 14 Neuropsychiatric - Insomnia.

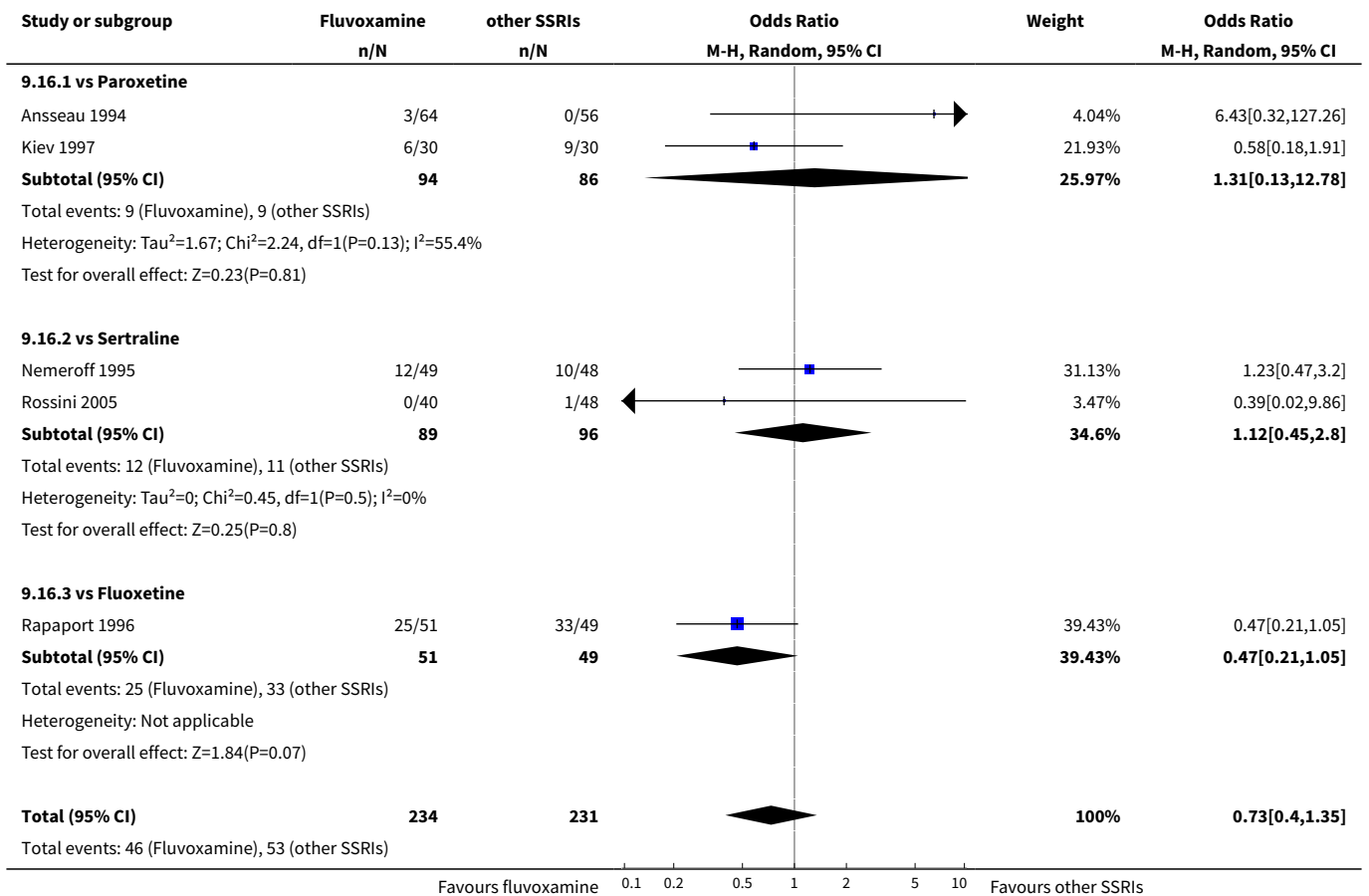


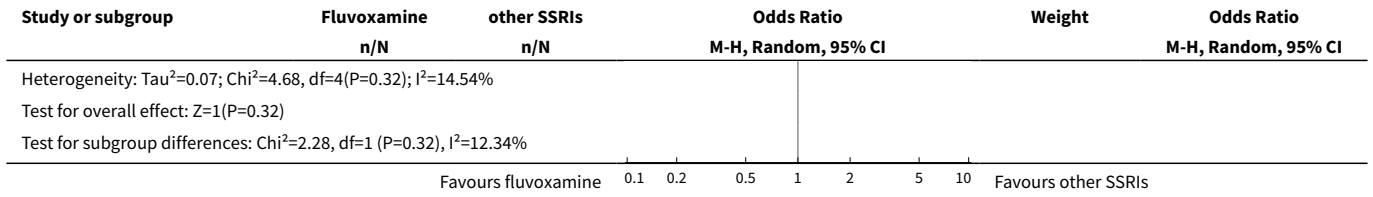
Analysis 9.15. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 15 Neuropsychiatric - Sleepiness / drowsiness.



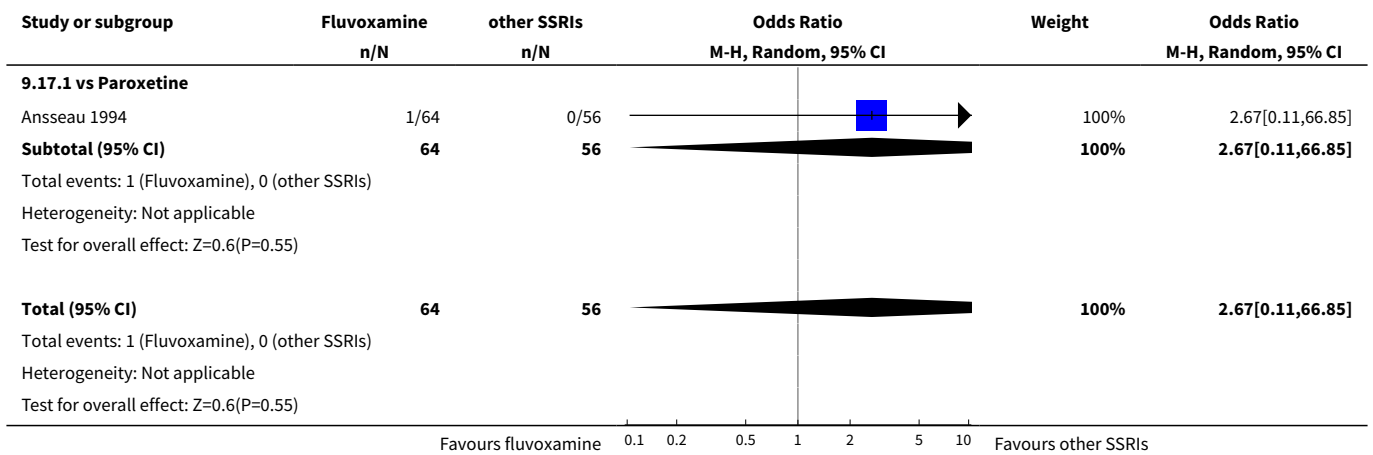


Analysis 9.16. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 16 Neuropsychiatric - Agitation / anxiety.

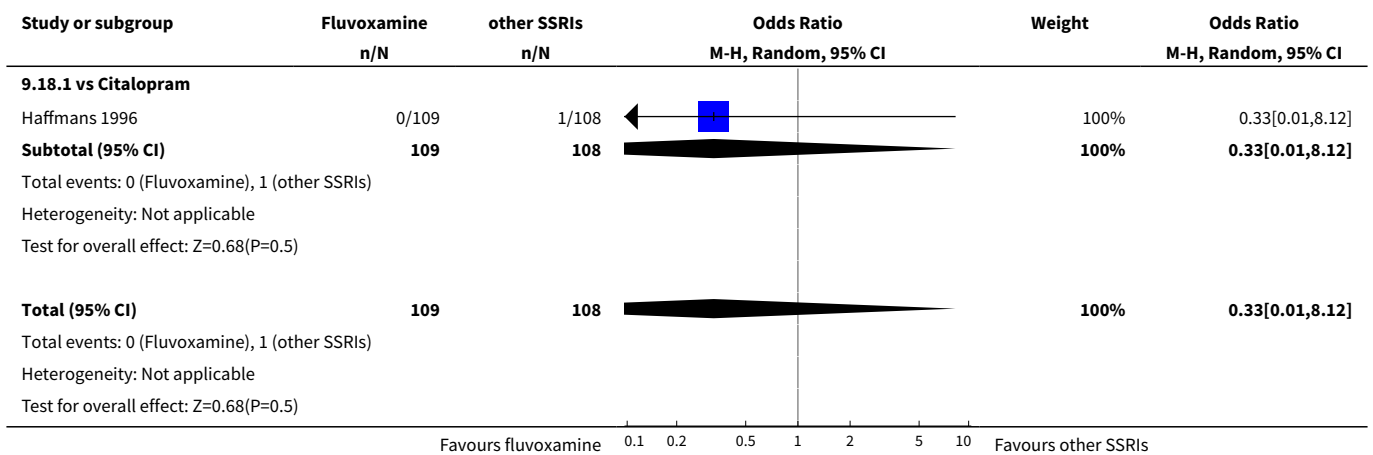




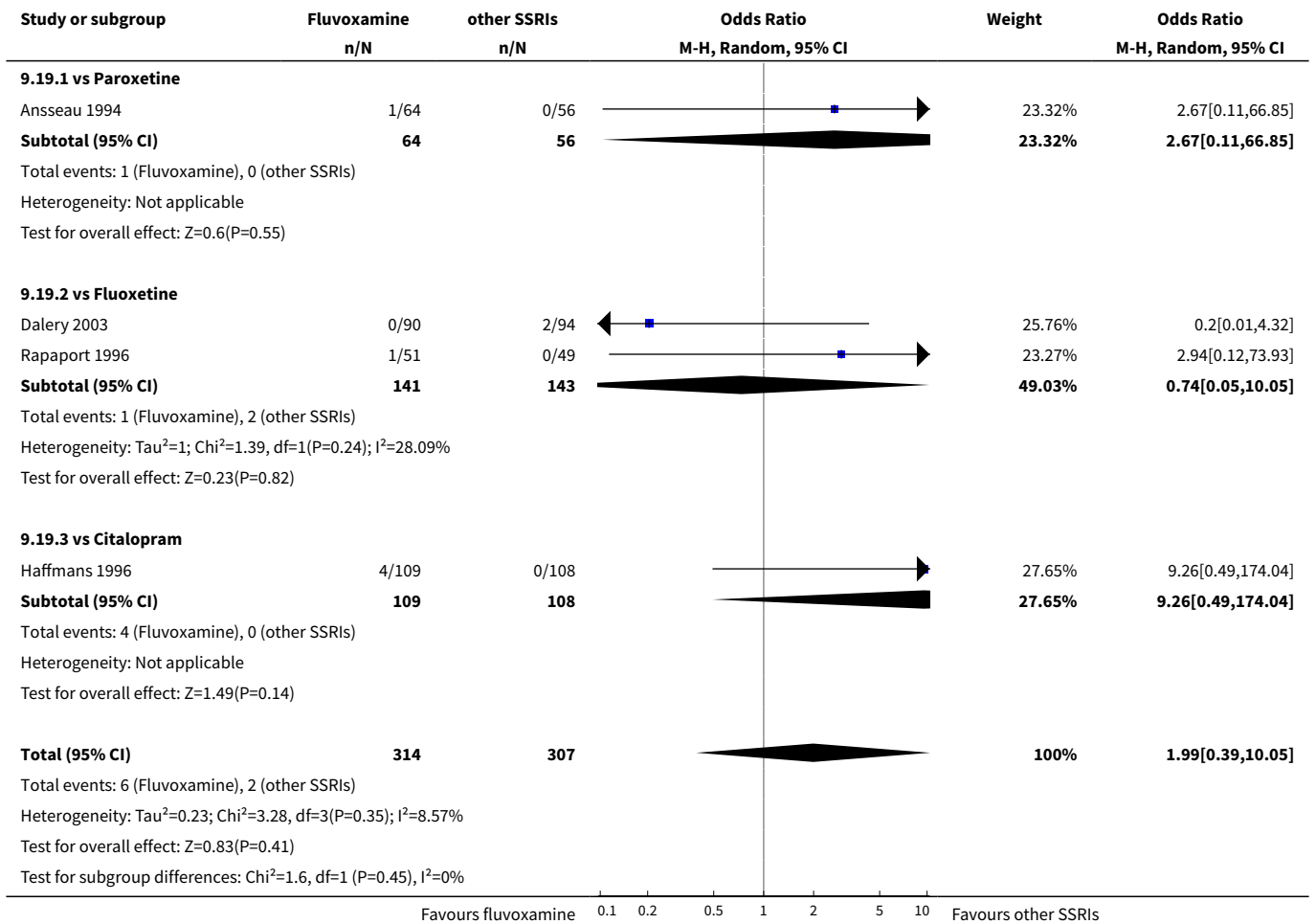
Analysis 9.17. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 17 Neuropsychiatric - Manic symptom.



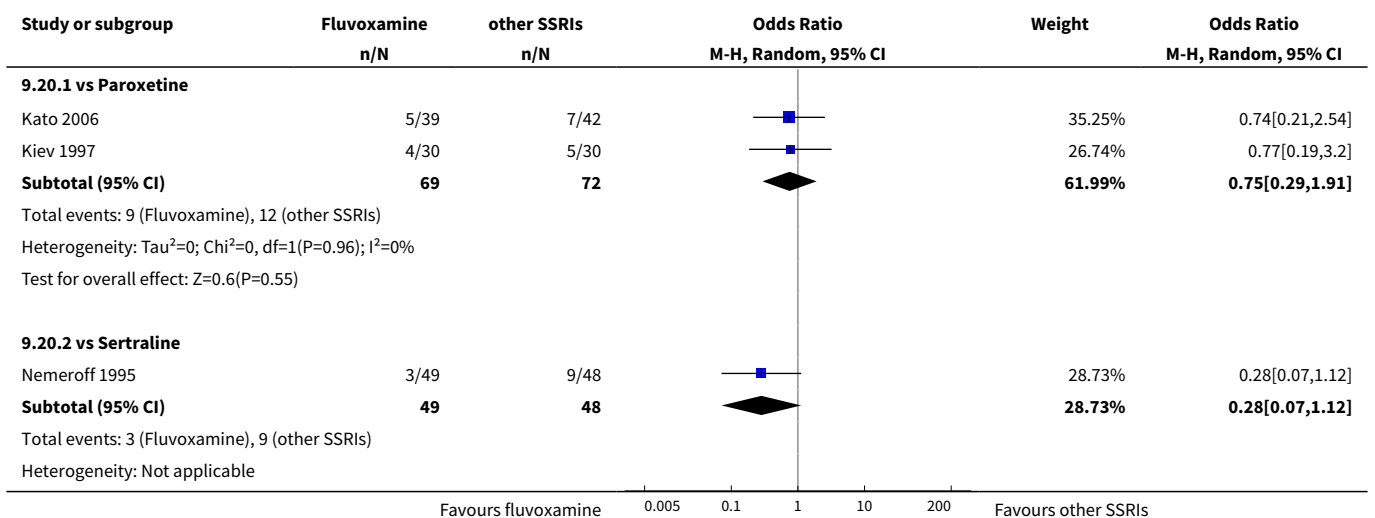
Analysis 9.18. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 18 Neuropsychiatric - Completed suicide.

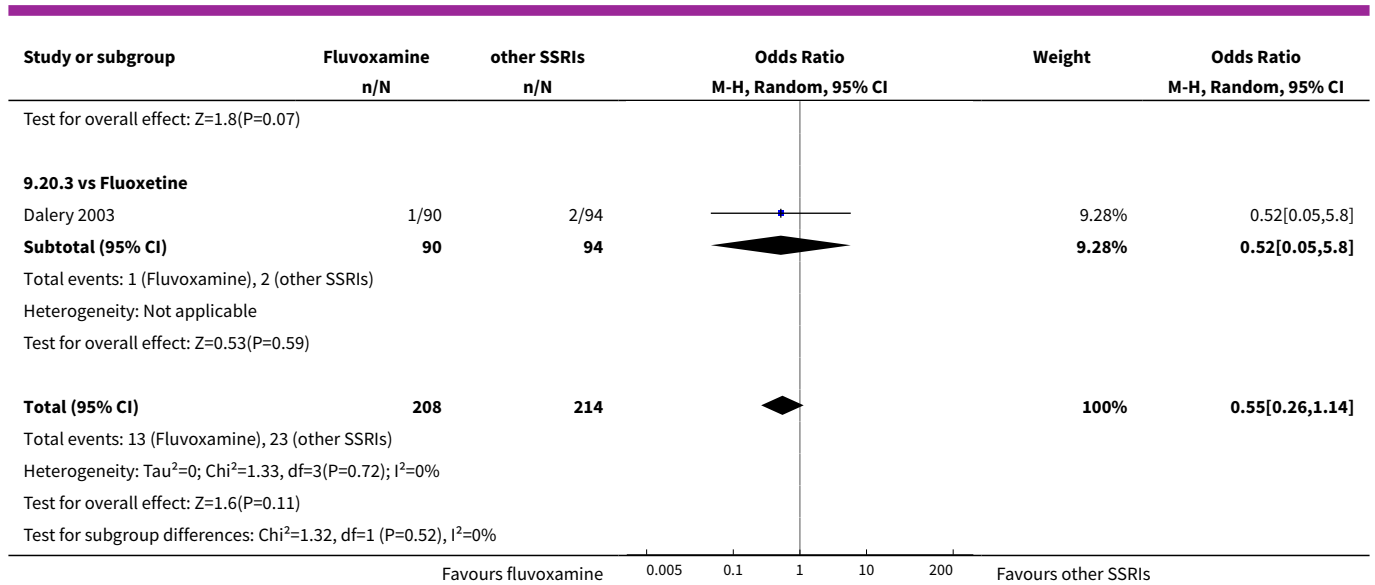


Analysis 9.19. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 19 Neuropsychiatric - Suicide wishes / gestures / attempts.



Analysis 9.20. Comparison 9 Side effect profile: Fluvoxamine vs other SSRIs, Outcome 20 Genitourinary - Sexual dysfunction.





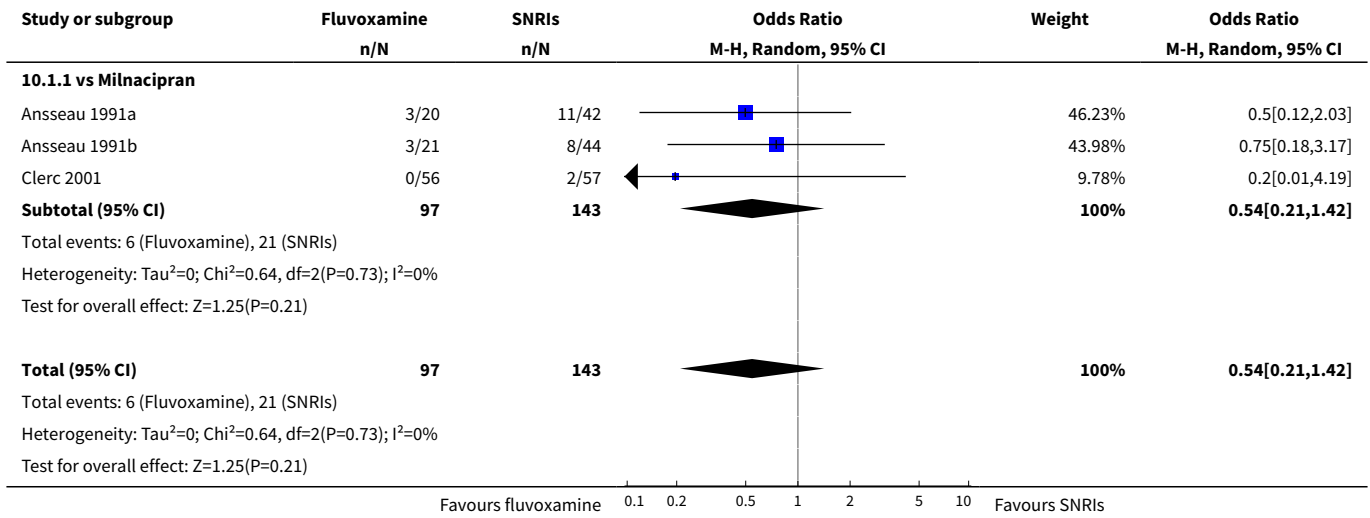
Comparison 10. Side effect profile: Fluvoxamine vs SNRIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular - Hypertension / tachycardia	3	240	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.21, 1.42]
1.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.21, 1.42]
2 Cardiovascular - Hypotension / bradycardia	2	127	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.28, 1.77]
2.1 vs Milnacipran	2	127	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.28, 1.77]
3 Dermatological - Dermatitis / rash	2	127	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.22, 9.16]
3.1 vs Milnacipran	2	127	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.22, 9.16]
4 Dermatological - Sweating	1	113	Odds Ratio (M-H, Random, 95% CI)	3.17 [0.32, 31.43]
4.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	3.17 [0.32, 31.43]
5 Gastrointestinal - Increased salivation	3	240	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.04, 3.38]
5.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.04, 3.38]

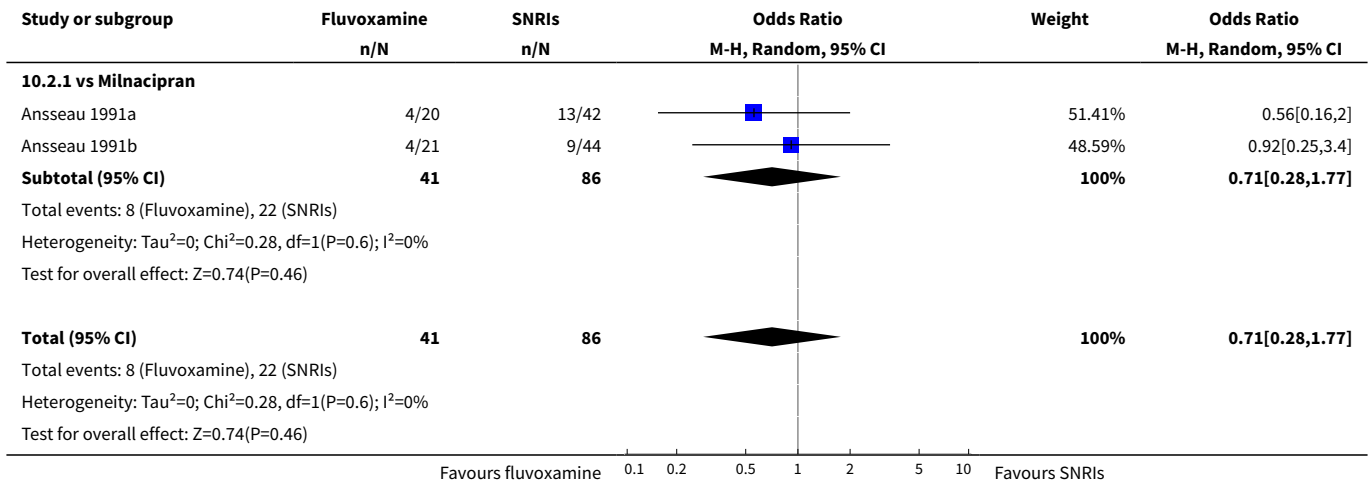
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Gastrointestinal - Dry mouth	3	240	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.56, 2.36]
6.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.56, 2.36]
7 Gastrointestinal - Oral discomfort / taste disturbance	1	113	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.36]
7.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.36]
8 Gastrointestinal - Vomiting / nausea	3	240	Odds Ratio (M-H, Random, 95% CI)	1.95 [1.09, 3.50]
8.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.95 [1.09, 3.50]
9 Gastrointestinal - Constipation	3	240	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.45, 2.76]
9.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.45, 2.76]
10 Gastrointestinal - Diarrhoea	3	240	Odds Ratio (M-H, Random, 95% CI)	1.52 [0.59, 3.89]
10.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.52 [0.59, 3.89]
11 Gastrointestinal - Weight gain	2	127	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.05, 4.76]
11.1 vs Milnacipran	2	127	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.05, 4.76]
12 Gastrointestinal - Weight loss	2	127	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.34, 2.16]
12.1 vs Milnacipran	2	127	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.34, 2.16]
13 Gastrointestinal - Anorexia	1	113	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.06, 16.69]
13.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.06, 16.69]
14 Neuropsychiatric - Blurred vision	2	127	Odds Ratio (M-H, Random, 95% CI)	1.66 [0.66, 4.14]
14.1 vs Milnacipran	2	127	Odds Ratio (M-H, Random, 95% CI)	1.66 [0.66, 4.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 Neuropsychiatric - Dizziness / vertigo / faintness	3	240	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.50, 2.52]
15.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.50, 2.52]
16 Neuropsychiatric - Fatigue / tiredness / asthenia	1	113	Odds Ratio (M-H, Random, 95% CI)	0.5 [0.04, 5.68]
16.1 vs Milnacipran	1	113	Odds Ratio (M-H, Random, 95% CI)	0.5 [0.04, 5.68]
17 Neuropsychiatric - Headache	3	240	Odds Ratio (M-H, Random, 95% CI)	1.33 [0.59, 3.01]
17.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.33 [0.59, 3.01]
18 Neuropsychiatric - Tremor	3	240	Odds Ratio (M-H, Random, 95% CI)	1.49 [0.56, 3.93]
18.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.49 [0.56, 3.93]
19 Neuropsychiatric - Involuntary movement other than tremor	3	240	Odds Ratio (M-H, Random, 95% CI)	2.82 [0.87, 9.10]
19.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	2.82 [0.87, 9.10]
20 Neuropsychiatric - Insomnia	3	240	Odds Ratio (M-H, Random, 95% CI)	1.60 [0.62, 4.10]
20.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.60 [0.62, 4.10]
21 Neuropsychiatric - Sleepiness / drowsiness	3	240	Odds Ratio (M-H, Random, 95% CI)	1.68 [0.62, 4.54]
21.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.68 [0.62, 4.54]
22 Neuropsychiatric - Agitation / anxiety	3	240	Odds Ratio (M-H, Random, 95% CI)	1.95 [0.72, 5.30]
22.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	1.95 [0.72, 5.30]
23 Genitourinary - Problems urinating	3	240	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.14, 2.55]
23.1 vs Milnacipran	3	240	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.14, 2.55]

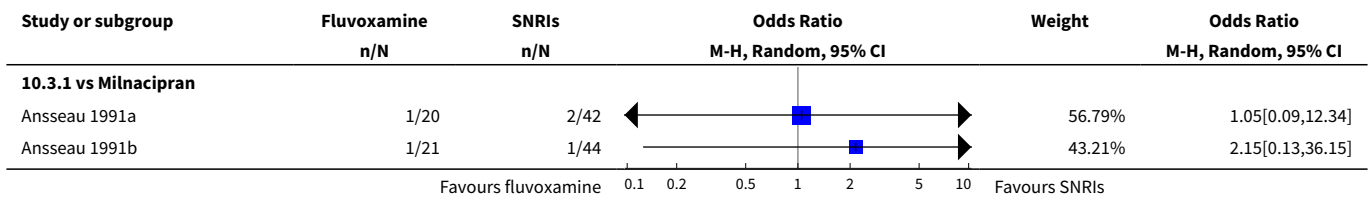
Analysis 10.1. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 1 Cardiovascular - Hypertension / tachycardia.

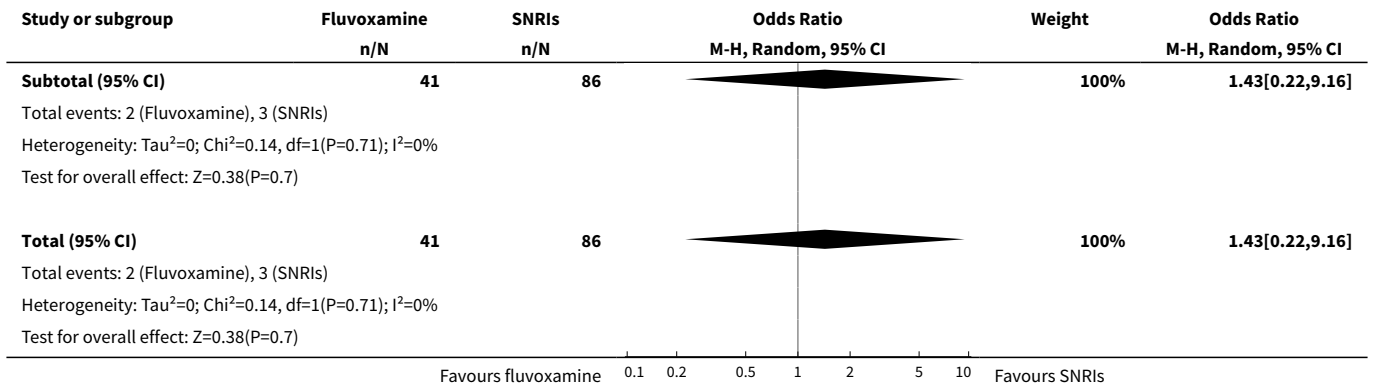


Analysis 10.2. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 2 Cardiovascular - Hypotension / bradycardia.

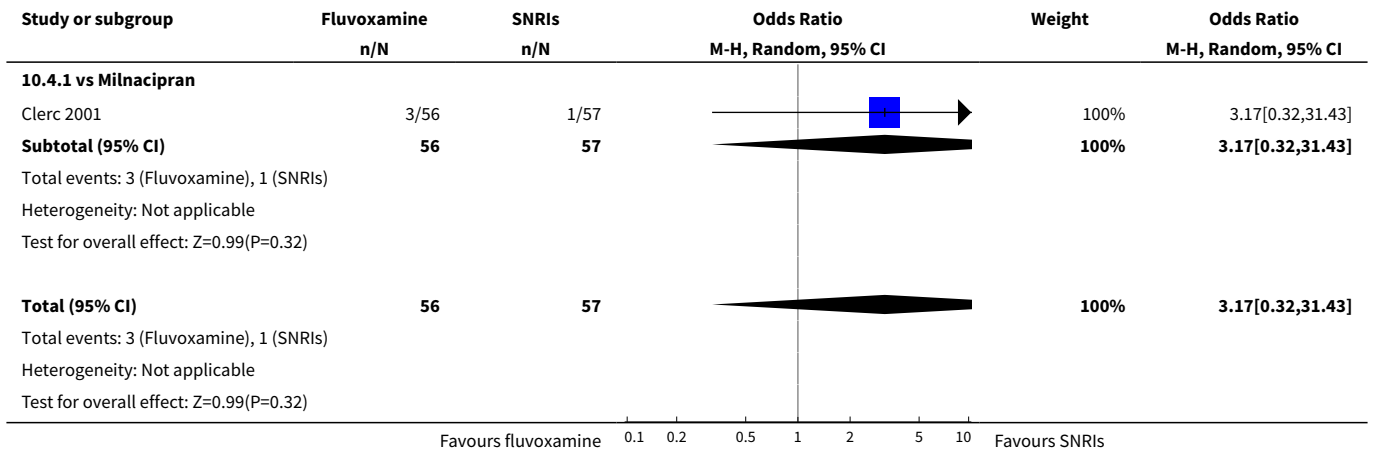


Analysis 10.3. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 3 Dermatological - Dermatitis / rash.

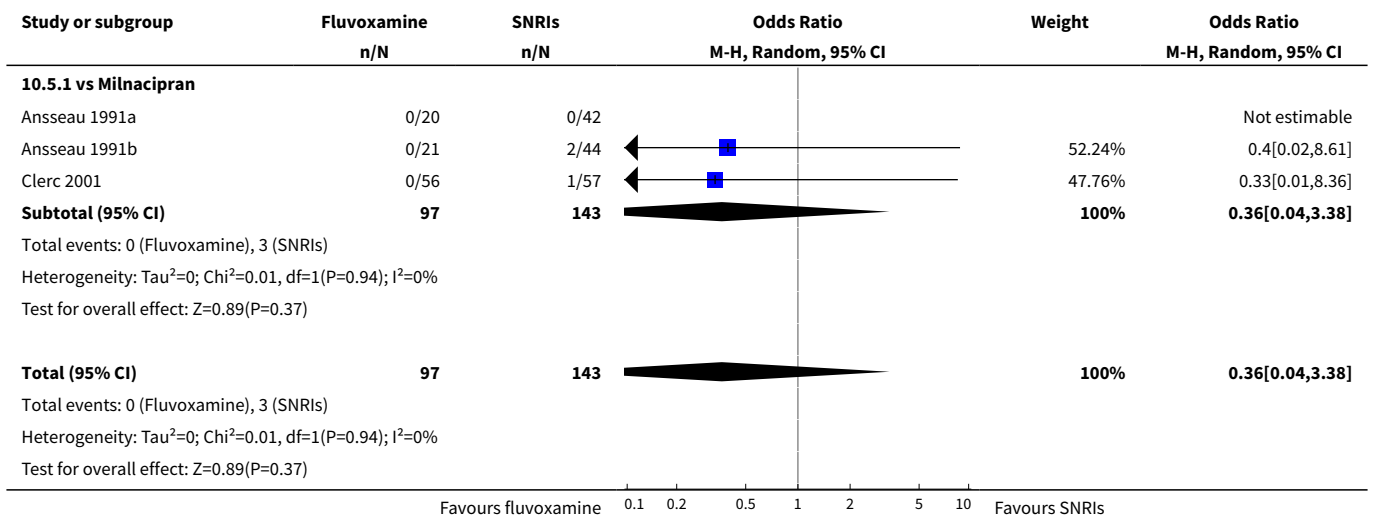




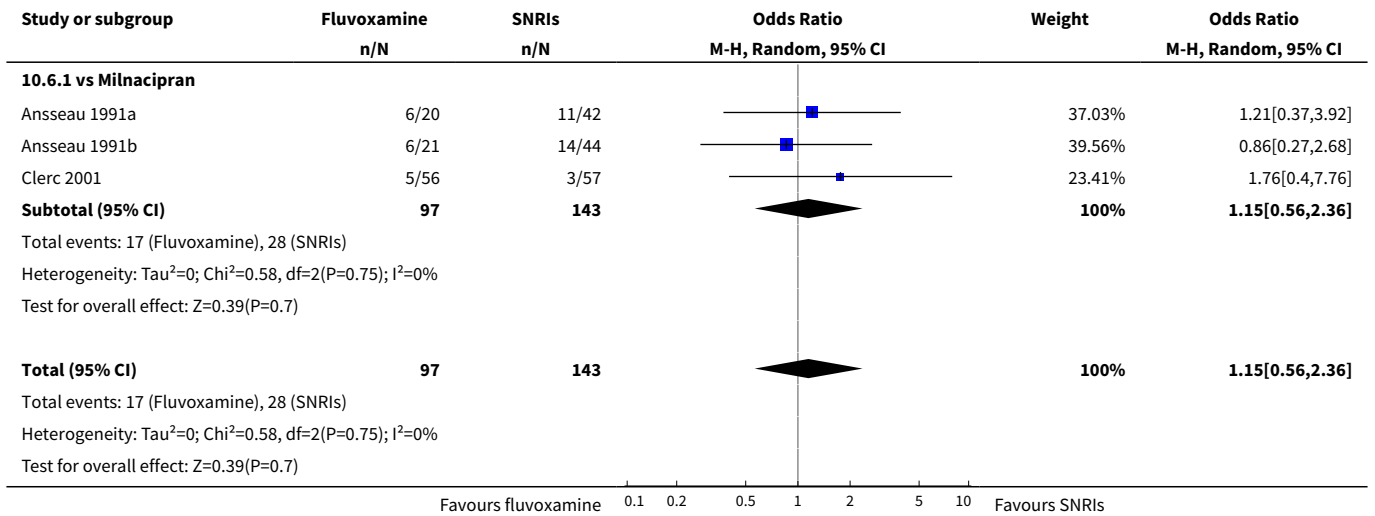
Analysis 10.4. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 4 Dermatological - Sweating.



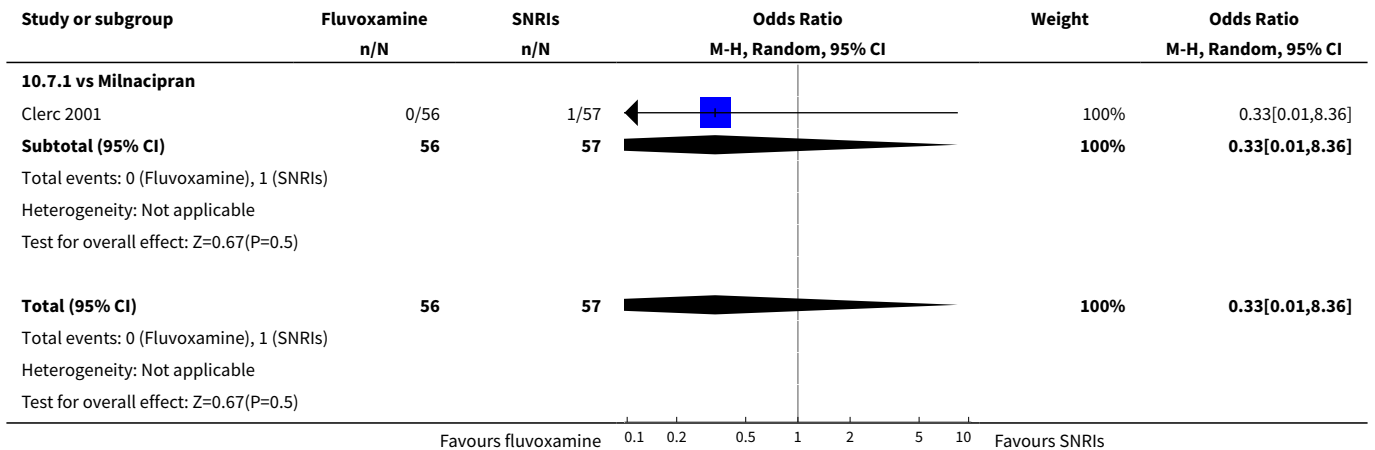
Analysis 10.5. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 5 Gastrointestinal - Increased salivation.



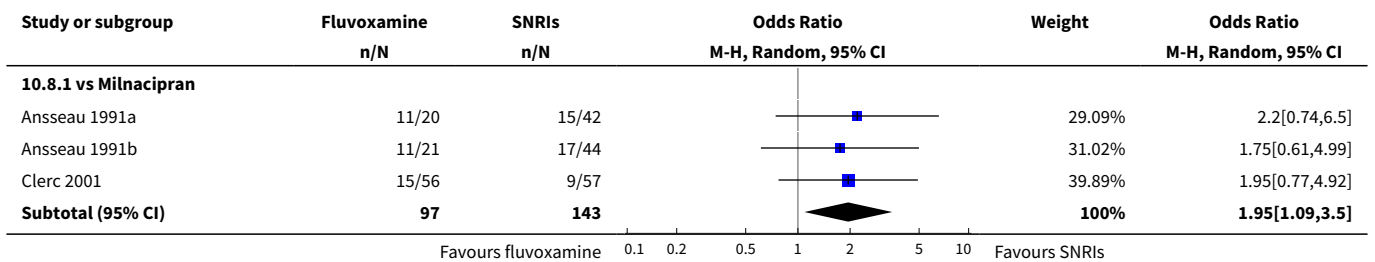
Analysis 10.6. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 6 Gastrointestinal - Dry mouth.

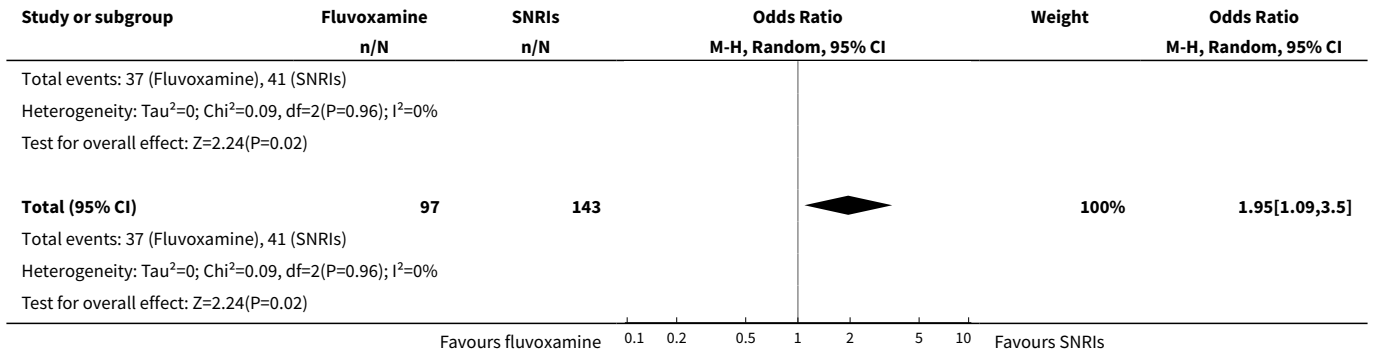


Analysis 10.7. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 7 Gastrointestinal - Oral discomfort / taste disturbance.

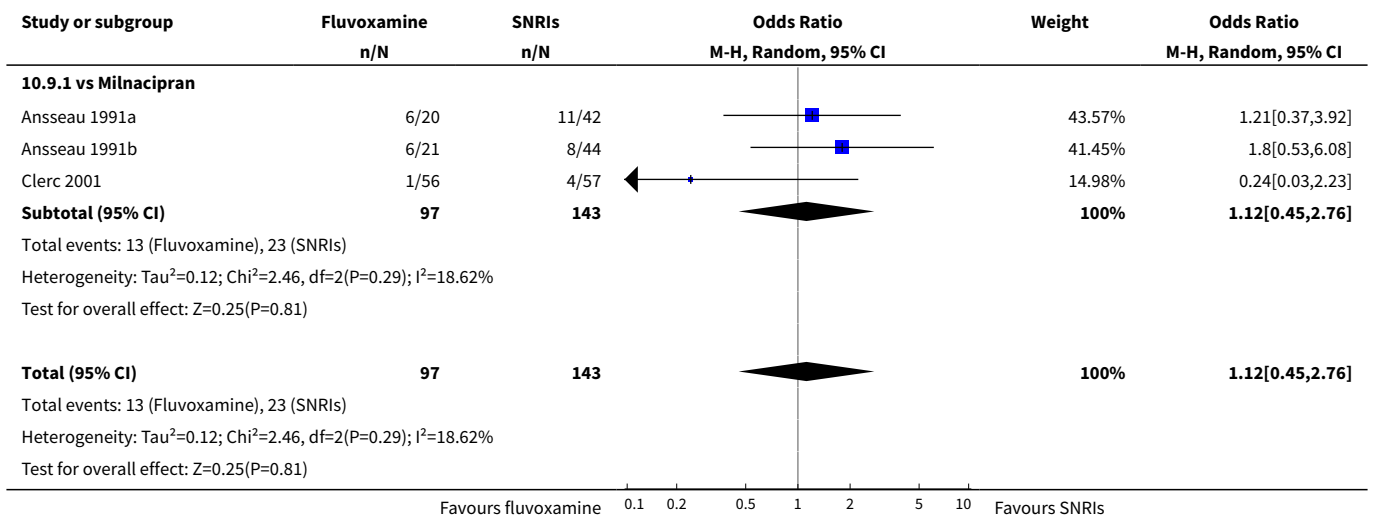


Analysis 10.8. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 8 Gastrointestinal - Vomiting / nausea.

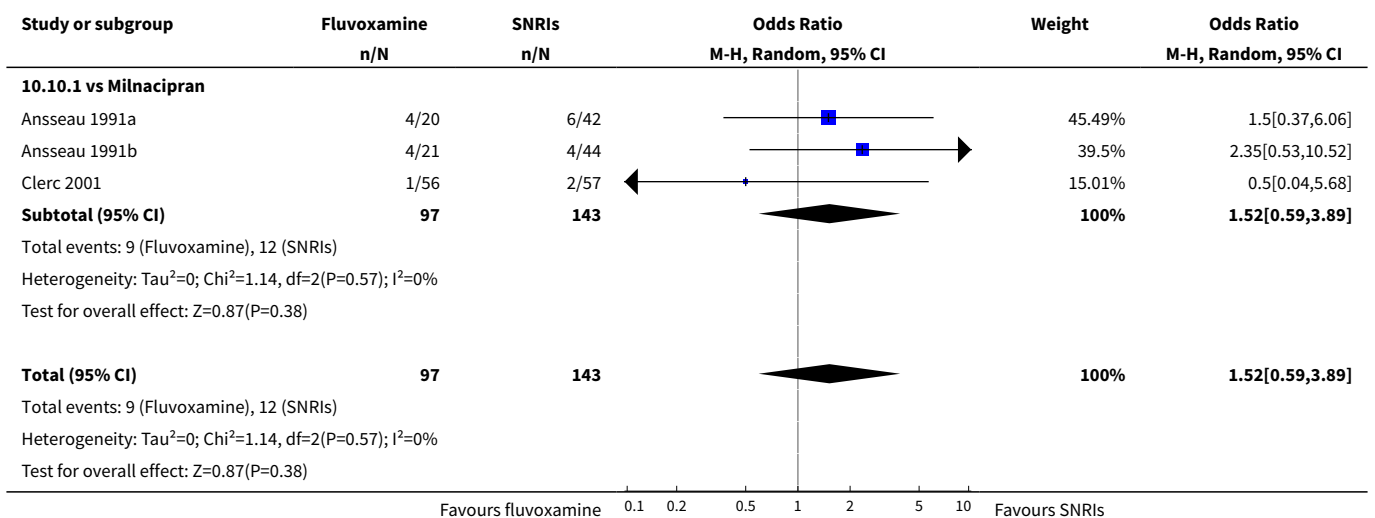




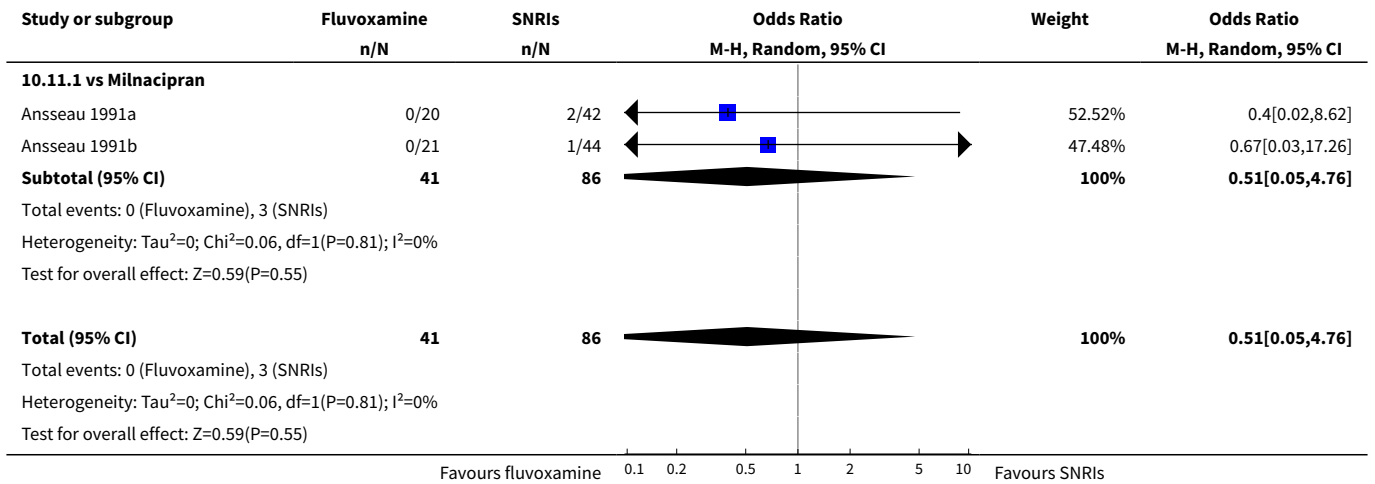
Analysis 10.9. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 9 Gastrointestinal - Constipation.



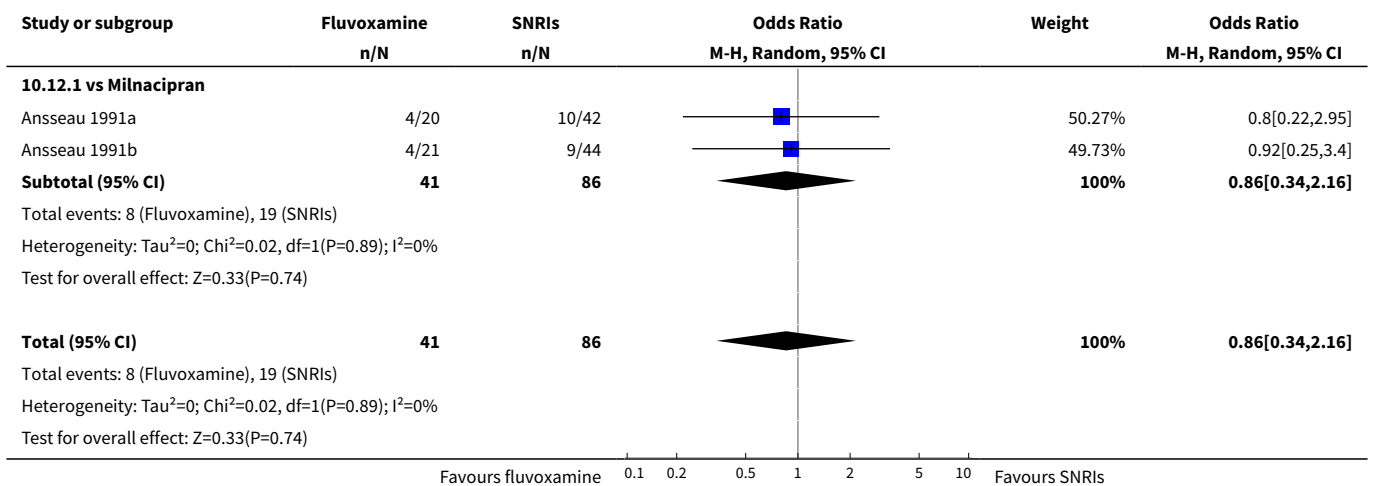
Analysis 10.10. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 10 Gastrointestinal - Diarrhoea.



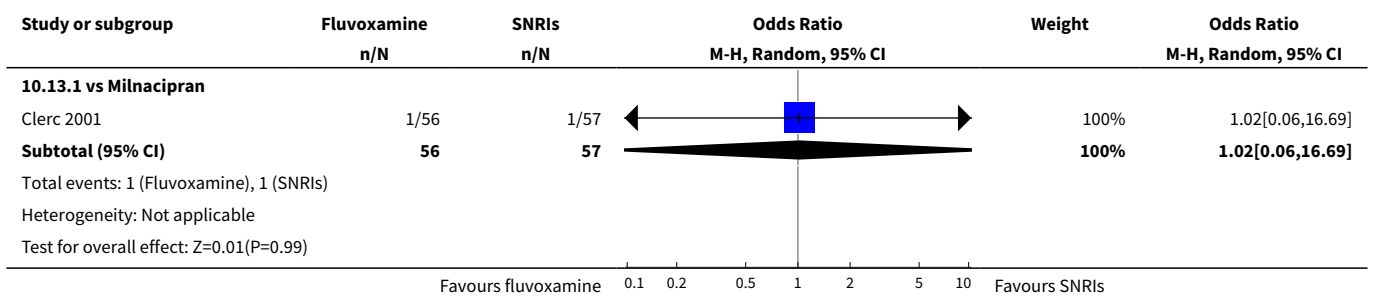
Analysis 10.11. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 11 Gastrointestinal - Weight gain.

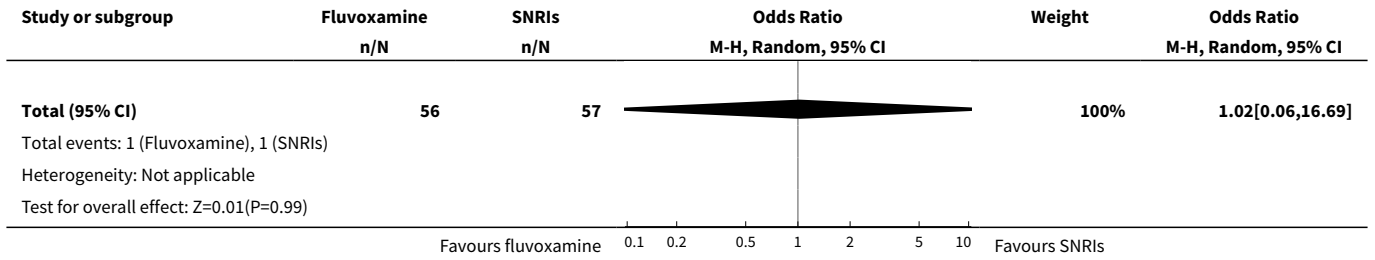


Analysis 10.12. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 12 Gastrointestinal - Weight loss.

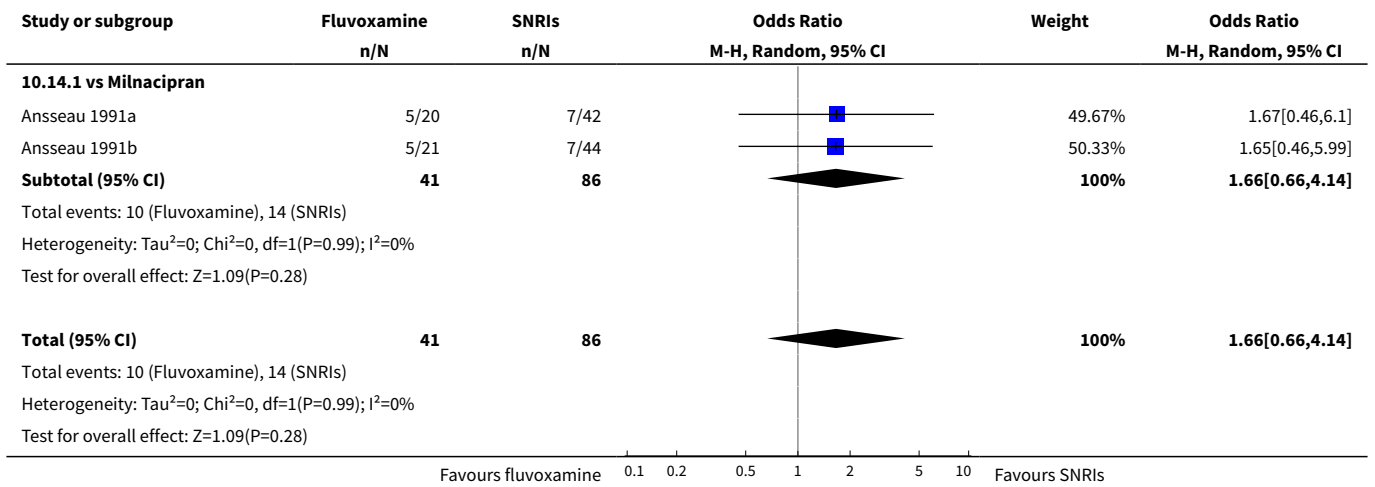


Analysis 10.13. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 13 Gastrointestinal - Anorexia.

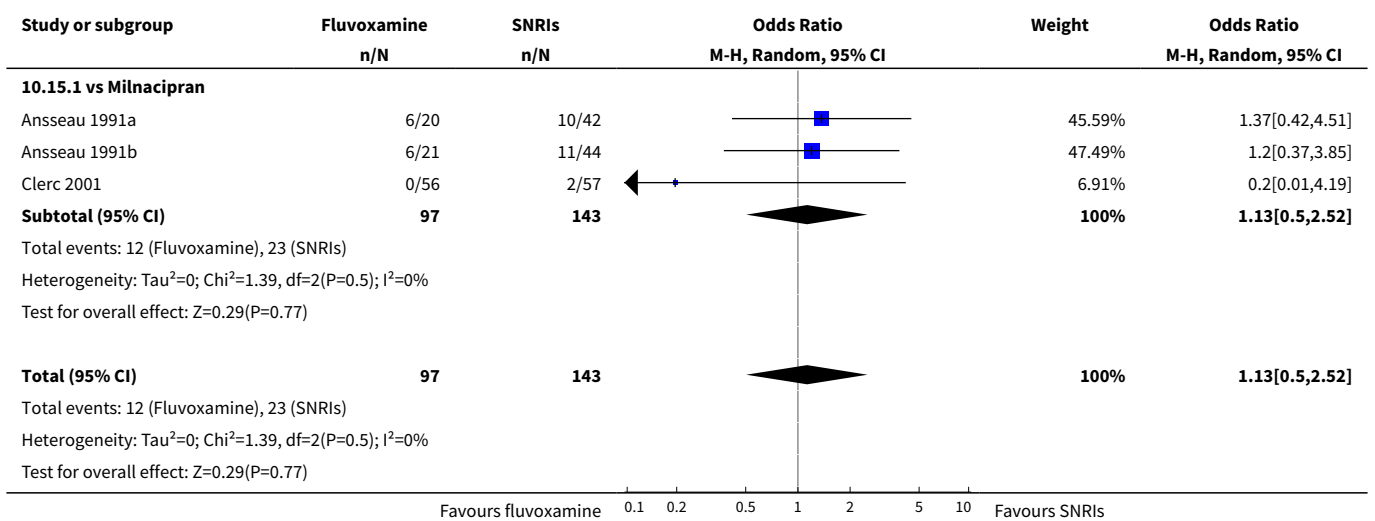




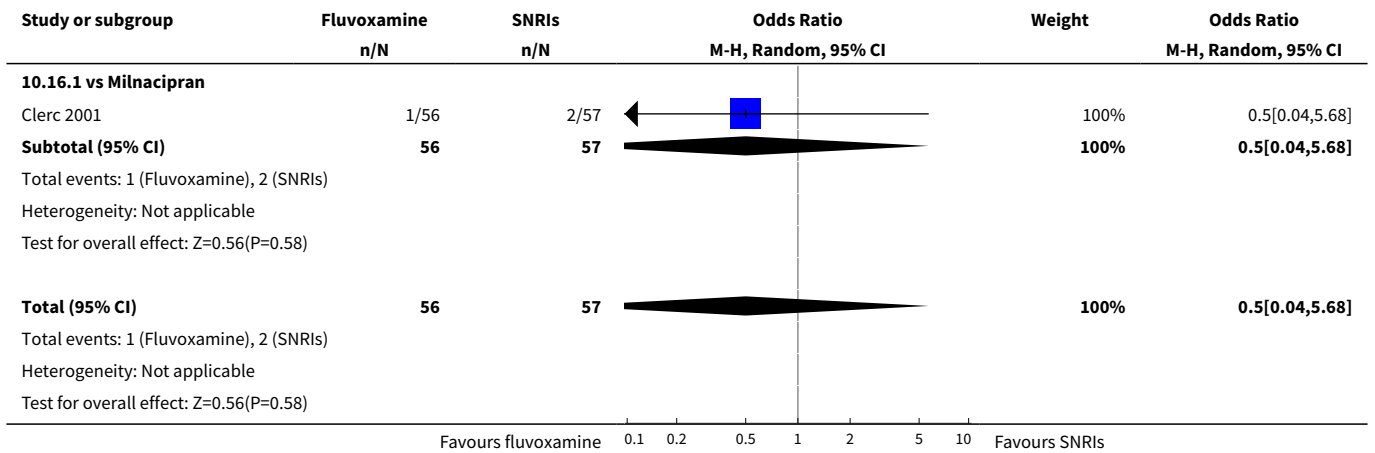
Analysis 10.14. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 14 Neuropsychiatric - Blurred vision.



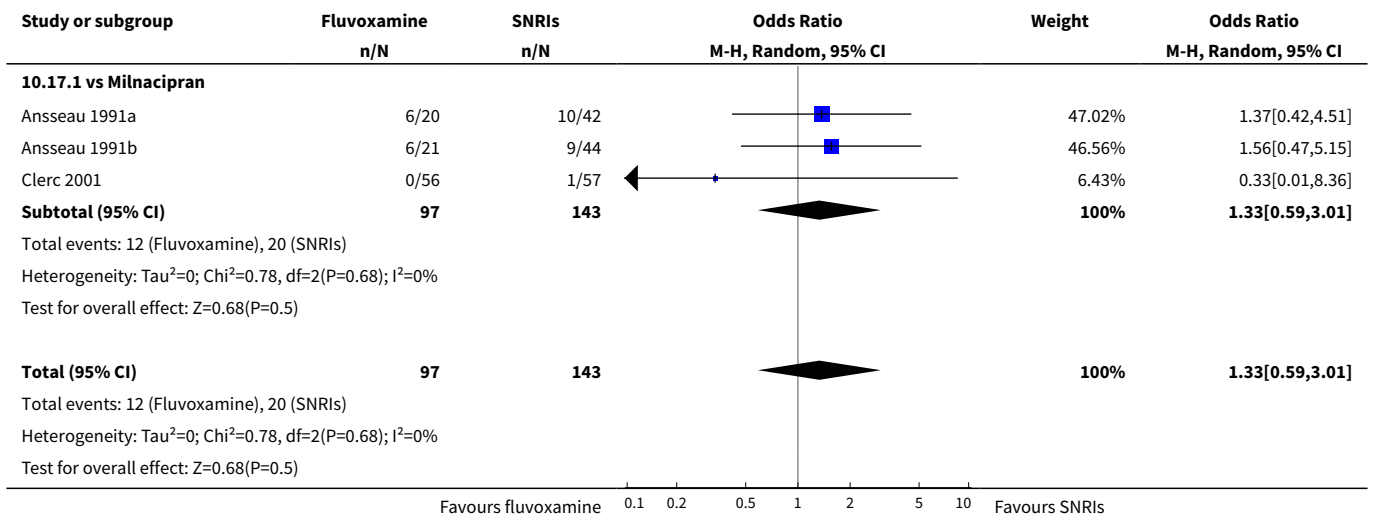
Analysis 10.15. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 15 Neuropsychiatric - Dizziness / vertigo / faintness.



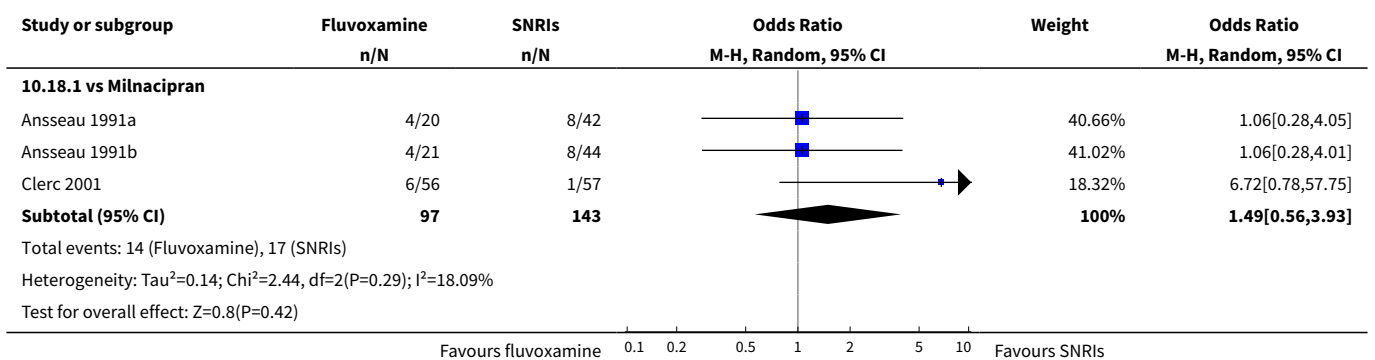
Analysis 10.16. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 16 Neuropsychiatric - Fatigue / tiredness / asthenia.

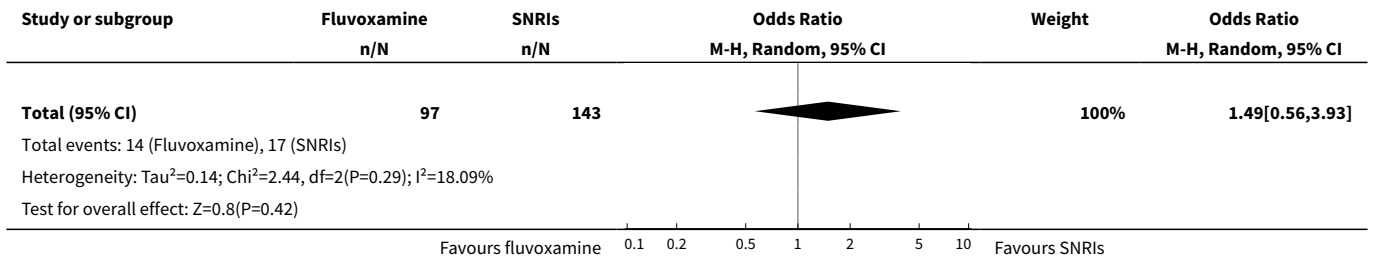


Analysis 10.17. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 17 Neuropsychiatric - Headache.

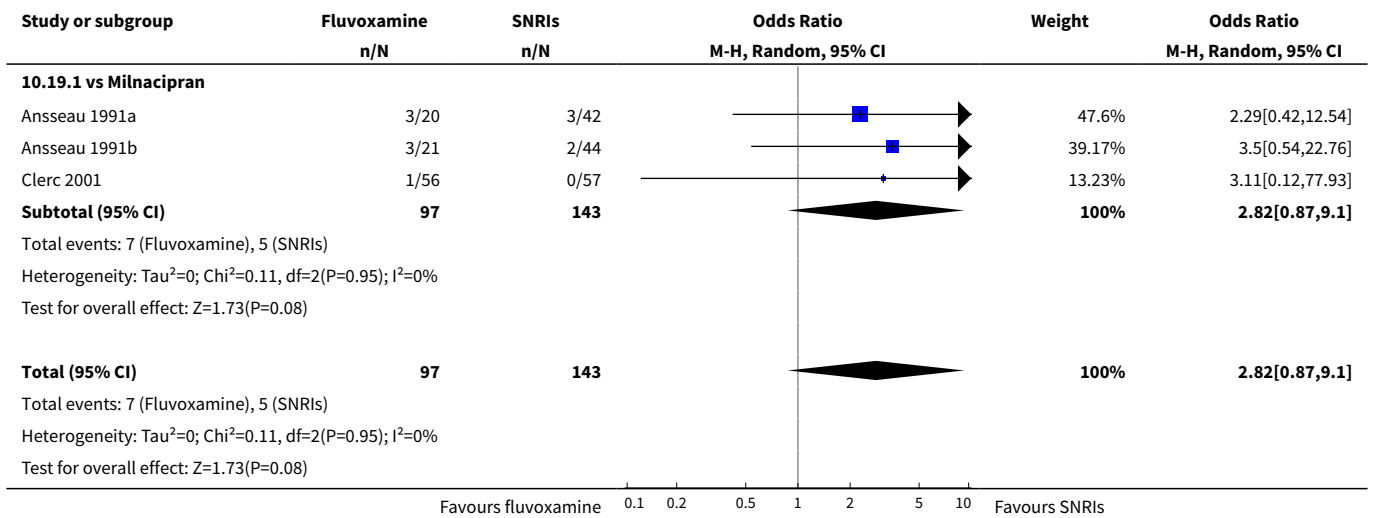


Analysis 10.18. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 18 Neuropsychiatric - Tremor.

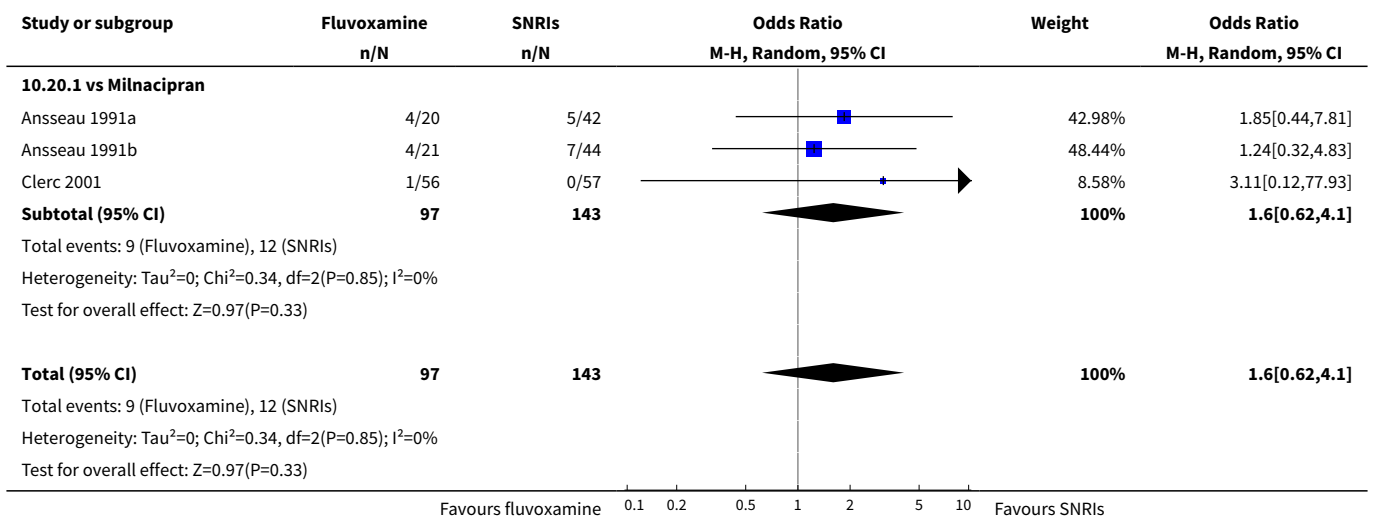




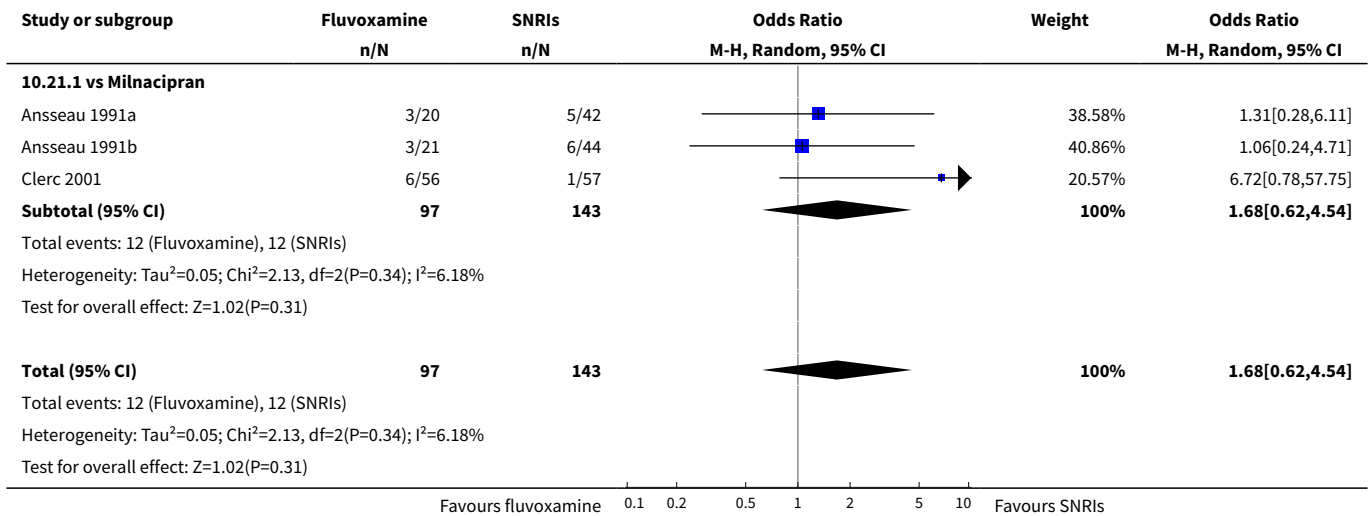
Analysis 10.19. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 19 Neuropsychiatric - Involuntary movement other than tremor.



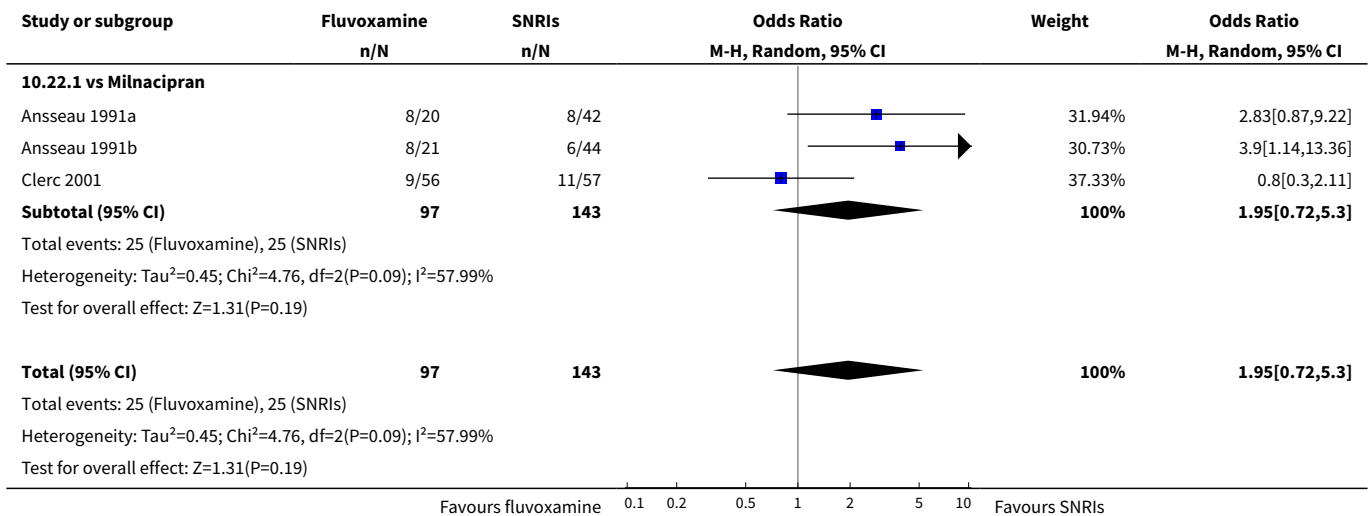
Analysis 10.20. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 20 Neuropsychiatric - Insomnia.



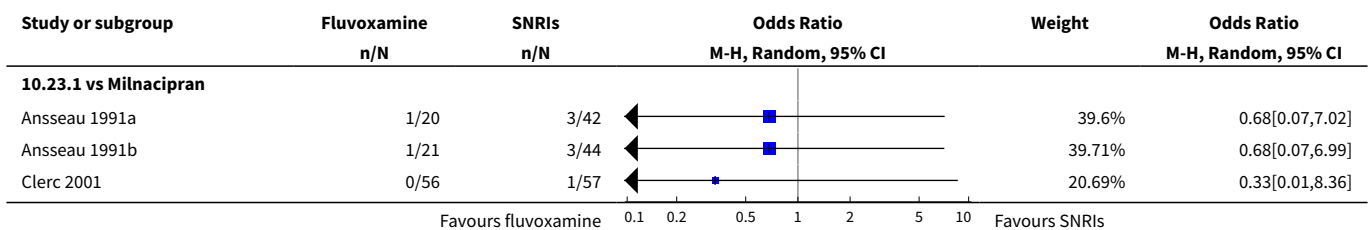
Analysis 10.21. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 21 Neuropsychiatric - Sleepiness / drowsiness.

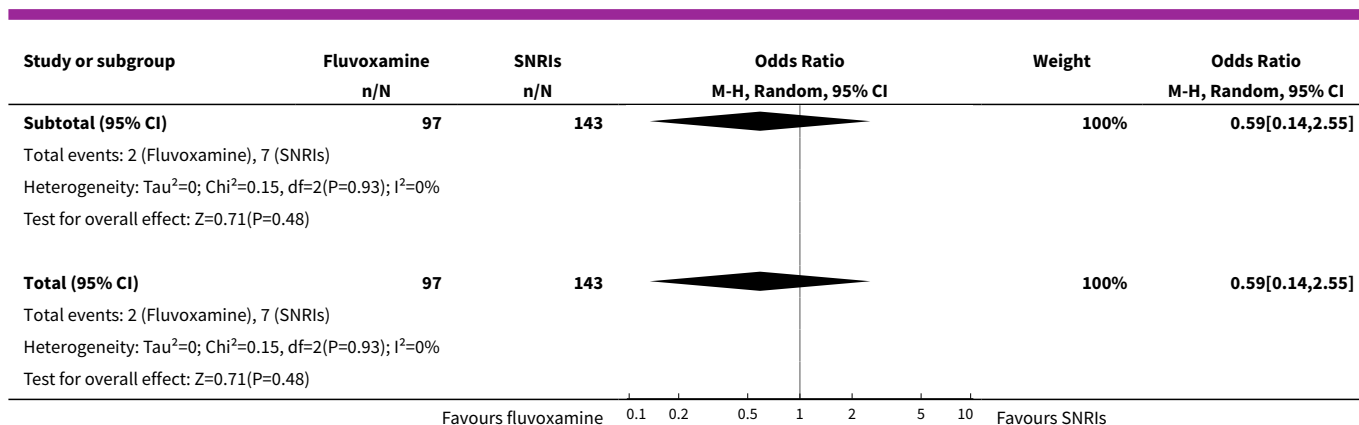


Analysis 10.22. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 22 Neuropsychiatric - Agitation / anxiety.



Analysis 10.23. Comparison 10 Side effect profile: Fluvoxamine vs SNRIs, Outcome 23 Genitourinary - Problems urinating.





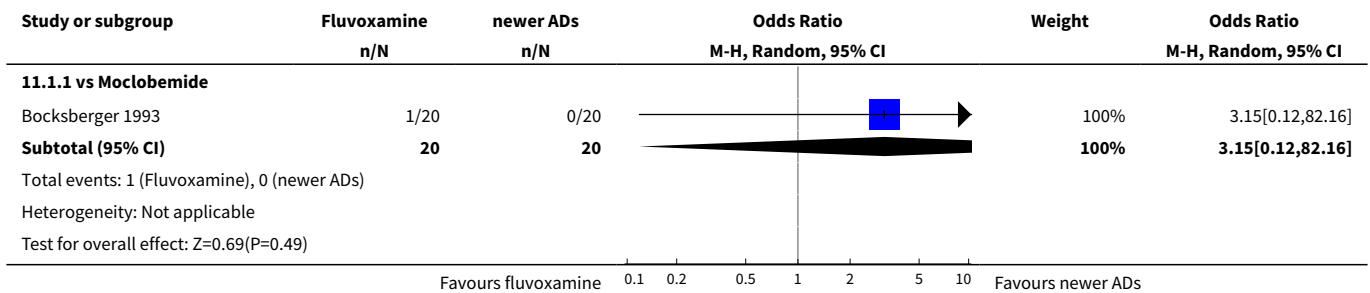
Comparison 11. Side effect profile: Fluvoxamine vs newer ADs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular - Hypotension / bradycardia	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 vs Moclobemide	1	40	Odds Ratio (M-H, Random, 95% CI)	3.15 [0.12, 82.16]
2 Dermatological - Sweating	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 vs Moclobemide	2	170	Odds Ratio (M-H, Random, 95% CI)	1.67 [0.41, 6.70]
3 Gastrointestinal - Dry mouth	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.37, 1.37]
3.2 vs Moclobemide	2	191	Odds Ratio (M-H, Random, 95% CI)	4.73 [1.14, 19.57]
4 Gastrointestinal - Vomiting / nausea	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	3.43 [1.90, 6.19]
4.2 vs Moclobemide	2	170	Odds Ratio (M-H, Random, 95% CI)	2.01 [1.03, 3.92]
5 Gastrointestinal - Constipation	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.47, 2.08]
6 Gastrointestinal - Diarrhoea	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.52, 2.15]
7 Gastrointestinal - Weight gain	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.17, 1.03]

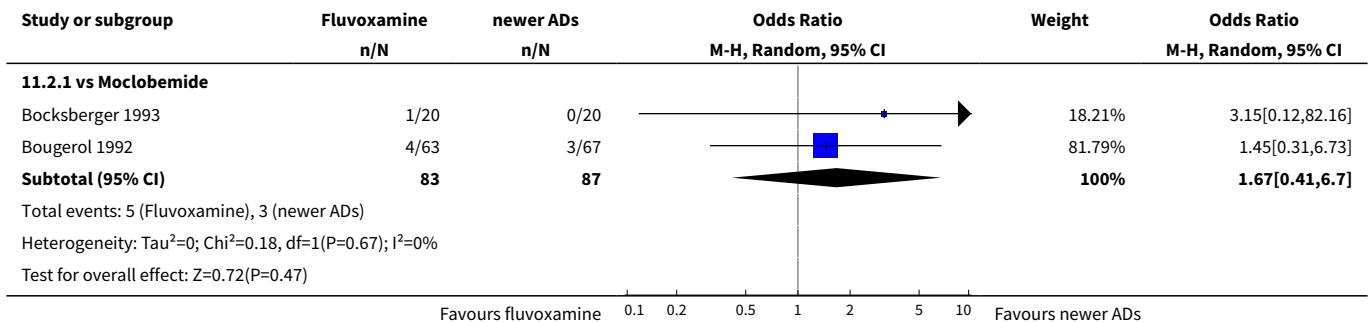
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Gastrointestinal - Increased appetite	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.14, 1.15]
9 Neuropsychiatric - Blurred vision	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 vs Moclobemide	1	130	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.11, 4.33]
10 Neuropsychiatric - Dizziness / vertigo / faintness	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.40, 1.44]
10.2 vs Moclobemide	2	101	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.04, 28.71]
11 Neuropsychiatric - Fatigue / tiredness / asthenia	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.50, 2.27]
11.2 vs Moclobemide	3	231	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.42, 3.67]
12 Neuropsychiatric - Headache	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.65, 2.19]
12.2 vs Moclobemide	3	231	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.23, 6.72]
13 Neuropsychiatric - Tremor	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 vs Moclobemide	3	231	Odds Ratio (M-H, Random, 95% CI)	2.64 [0.96, 7.27]
14 Neuropsychiatric - Insomnia	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 vs Moclobemide	2	191	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.26, 1.35]
15 Neuropsychiatric - Sleepiness / drowsiness	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.76]
16 Neuropsychiatric - Agitation / anxiety	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 vs Mirtazapine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.17 [0.05, 0.61]
16.2 vs Moclobemide	3	231	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.53, 2.39]
17 Neuropsychiatric - Manic symptom	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 vs Moclobemide	2	101	Odds Ratio (M-H, Random, 95% CI)	3.18 [0.32, 31.64]
18 Neuropsychiatric - Completed suicide	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 vs Moclobemide	1	61	Odds Ratio (M-H, Random, 95% CI)	3.20 [0.13, 81.78]

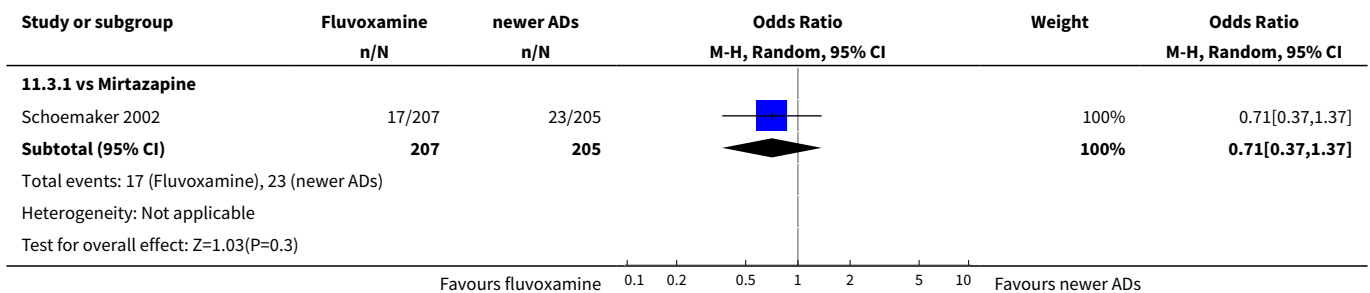
Analysis 11.1. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 1 Cardiovascular - Hypotension / bradycardia.

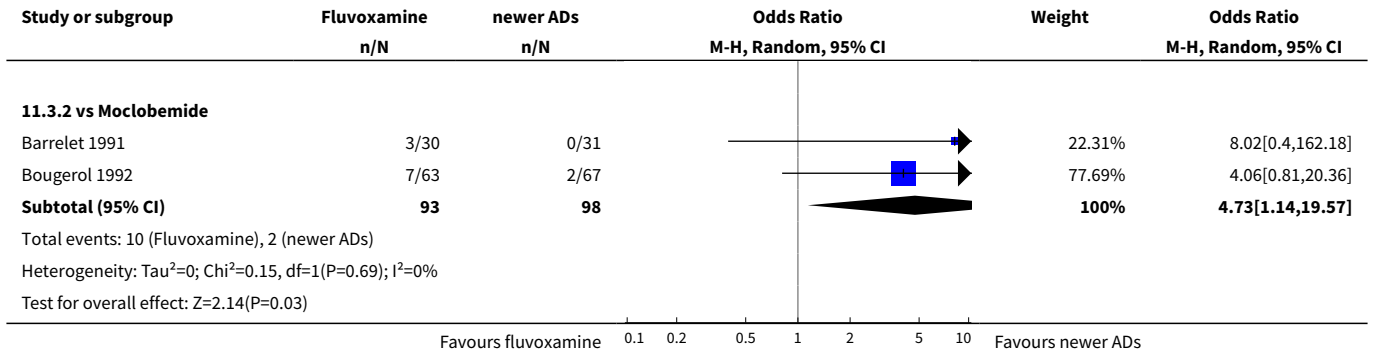


Analysis 11.2. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 2 Dermatological - Sweating.

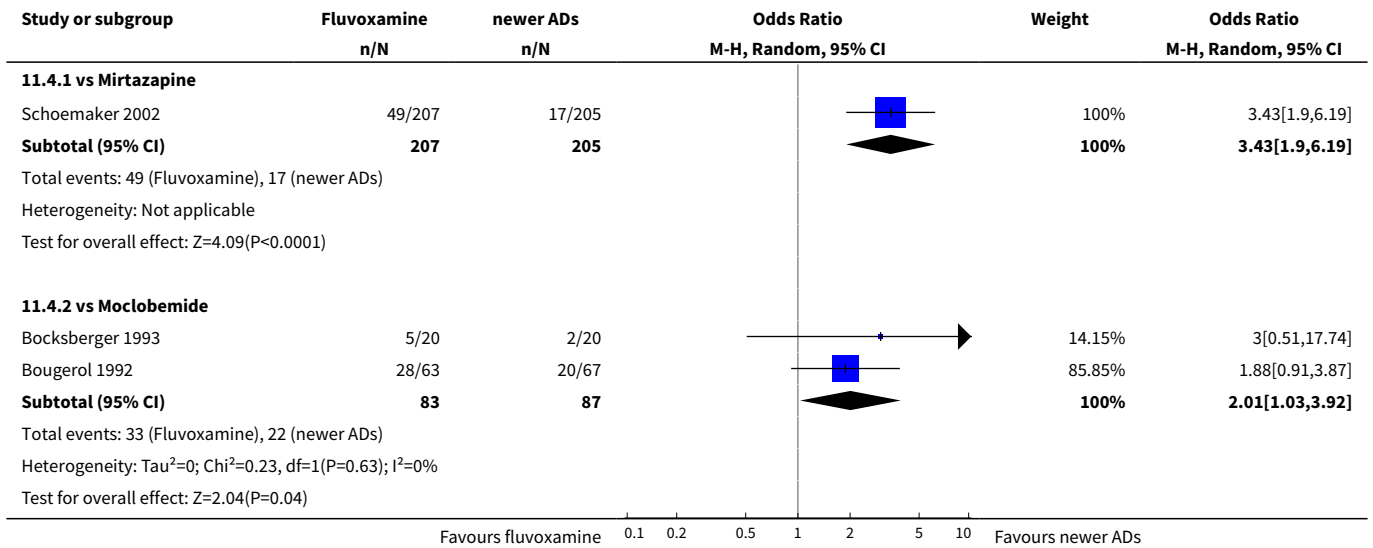


Analysis 11.3. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 3 Gastrointestinal - Dry mouth.

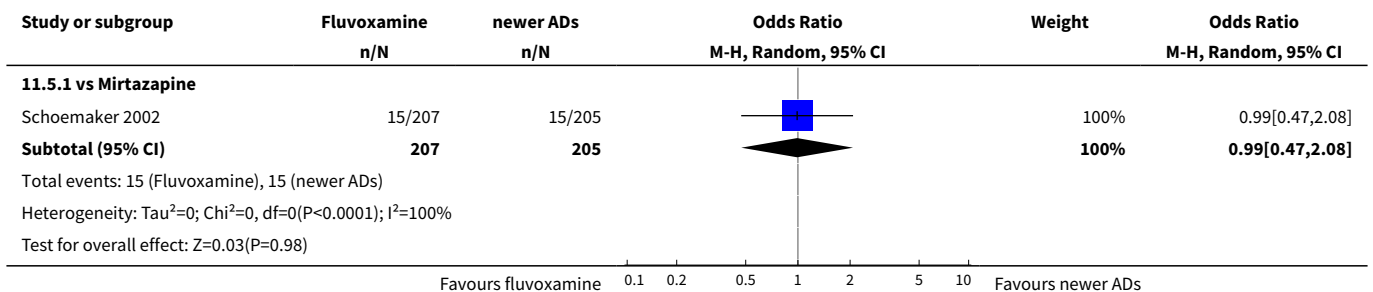




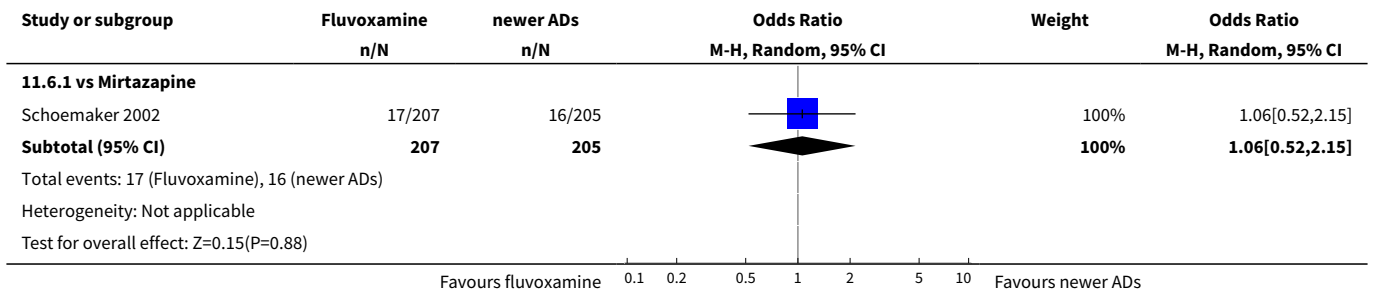
Analysis 11.4. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 4 Gastrointestinal - Vomiting / nausea.



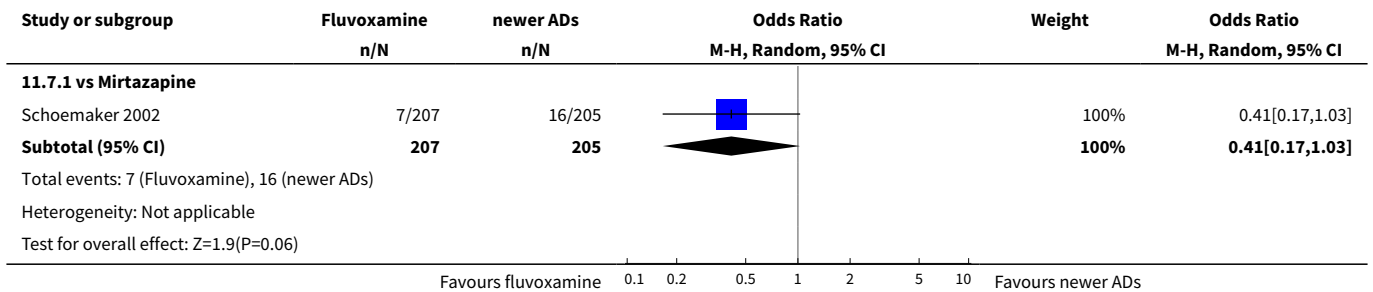
Analysis 11.5. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 5 Gastrointestinal - Constipation.



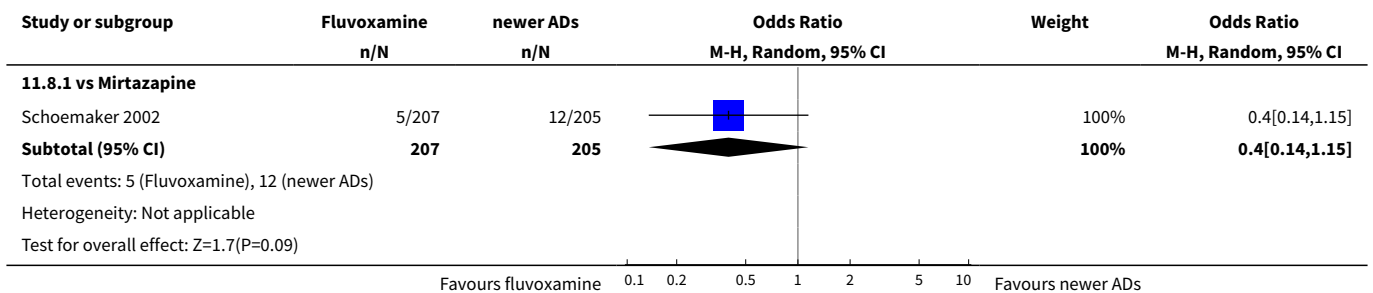
Analysis 11.6. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 6 Gastrointestinal - Diarrhoea.



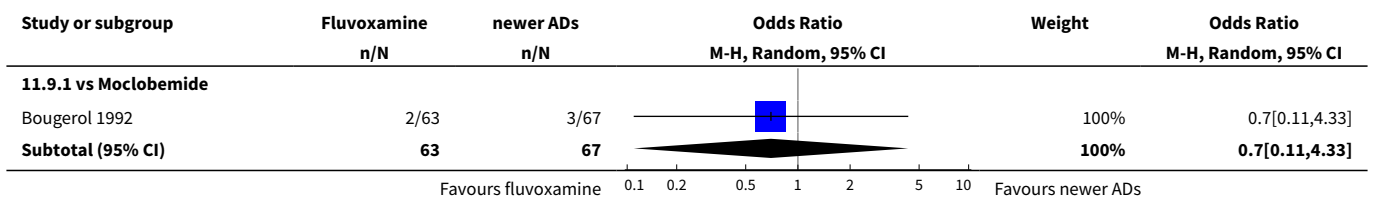
Analysis 11.7. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 7 Gastrointestinal - Weight gain.

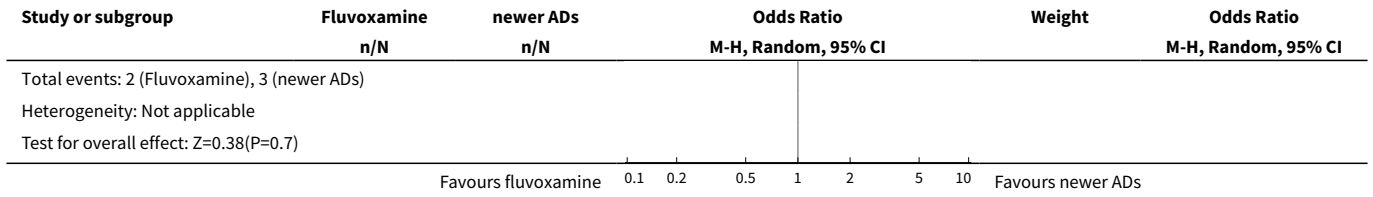


Analysis 11.8. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 8 Gastrointestinal - Increased appetite.

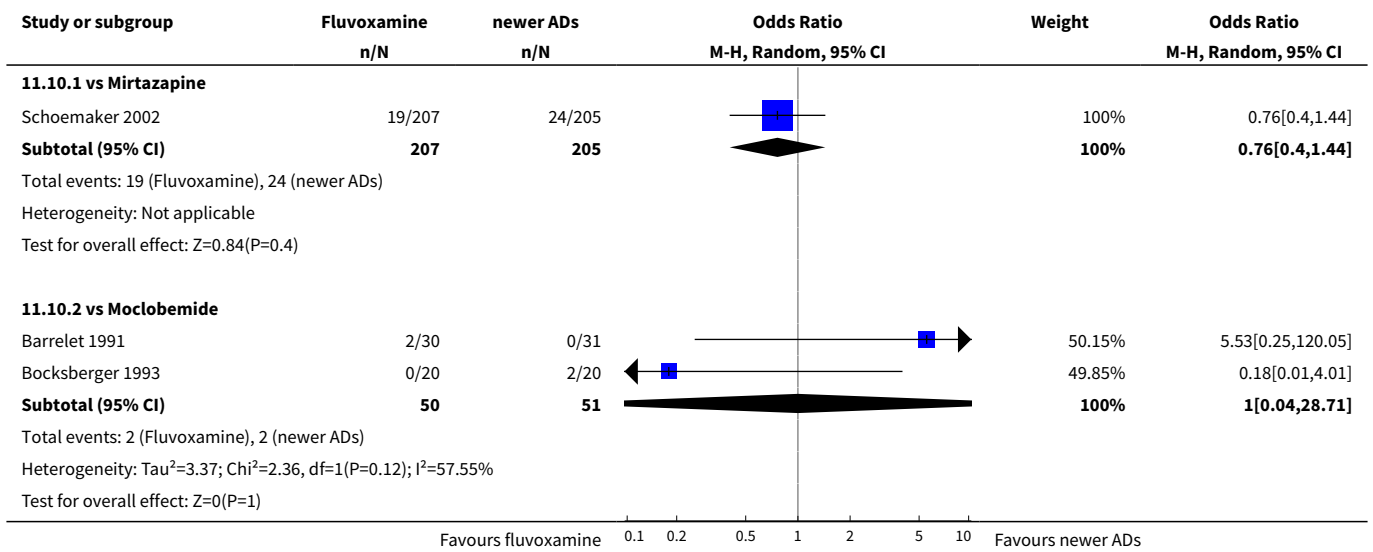


Analysis 11.9. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 9 Neuropsychiatric - Blurred vision.

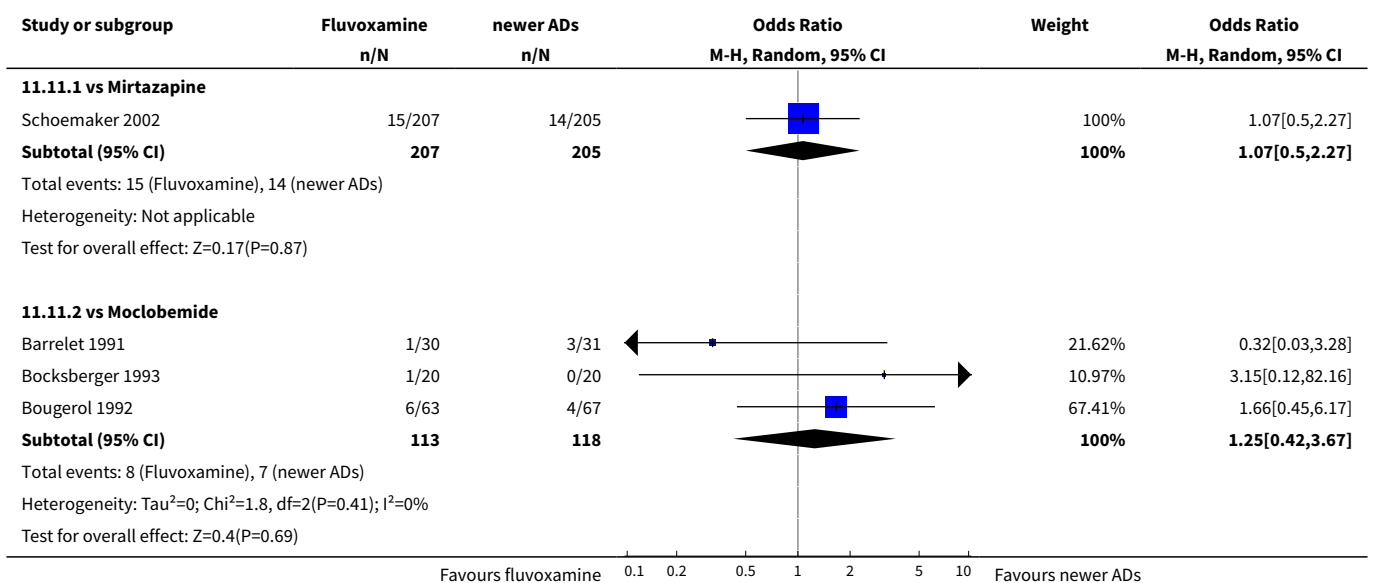




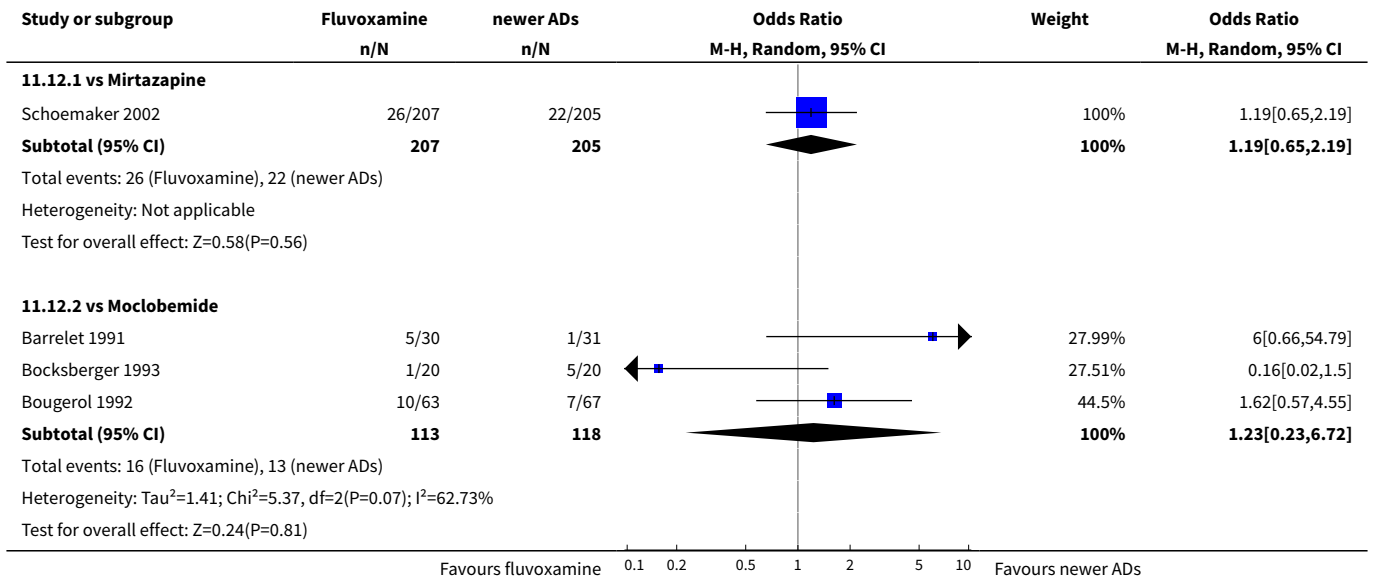
Analysis 11.10. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 10 Neuropsychiatric - Dizziness / vertigo / faintness.



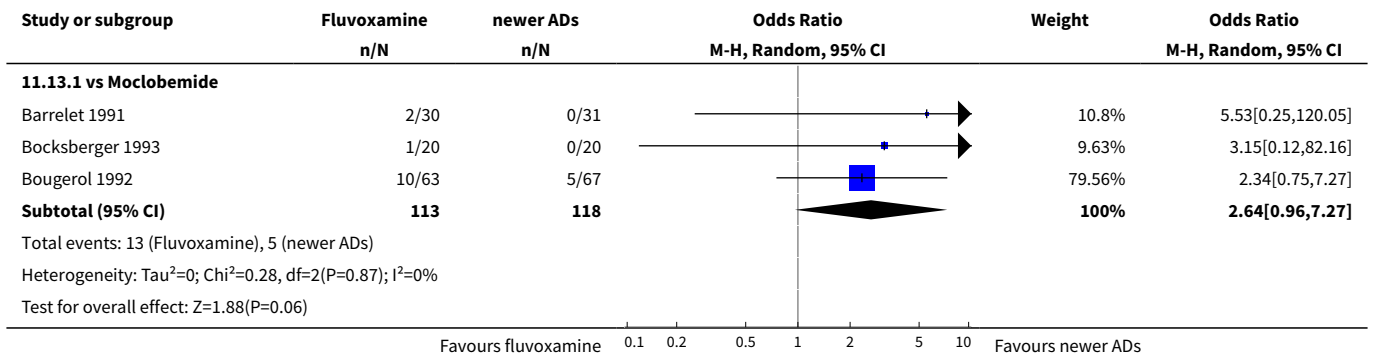
Analysis 11.11. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 11 Neuropsychiatric - Fatigue / tiredness / asthenia.



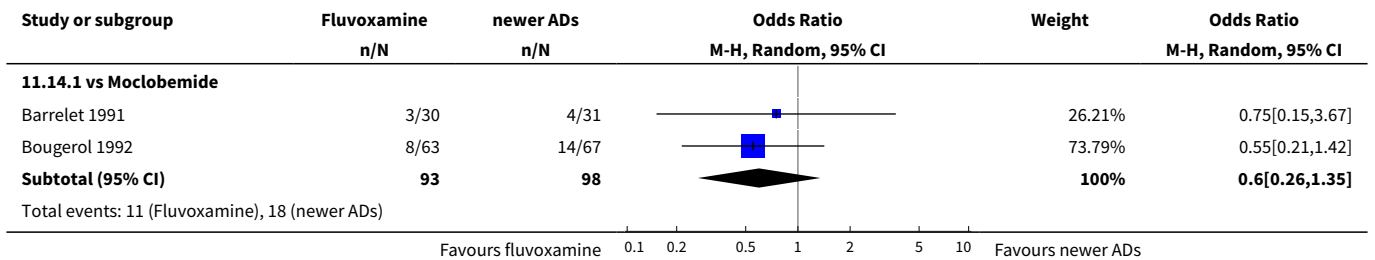
Analysis 11.12. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 12 Neuropsychiatric - Headache.

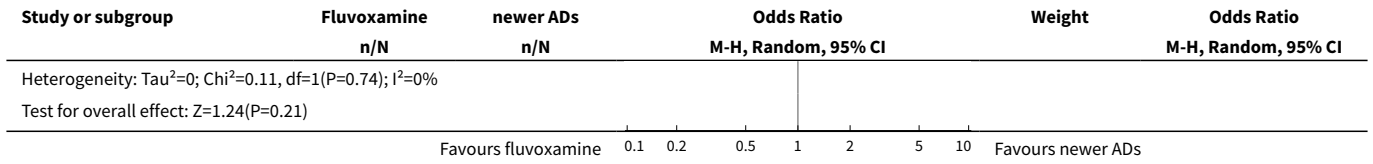


Analysis 11.13. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 13 Neuropsychiatric - Tremor.

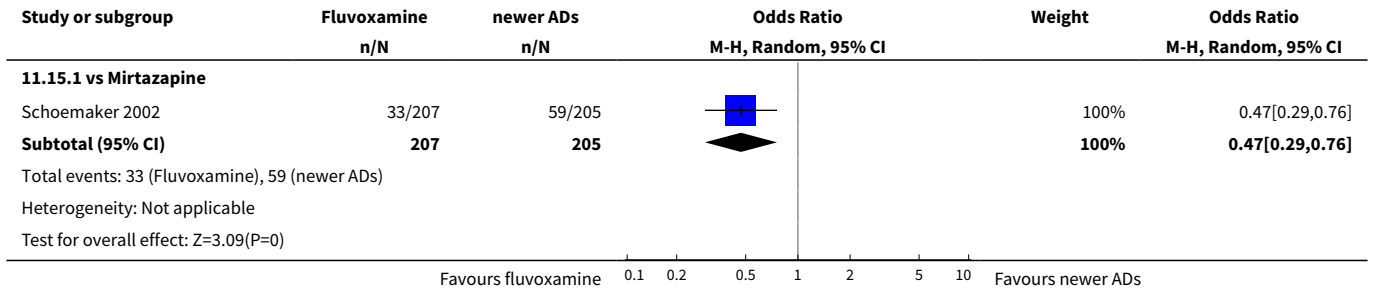


Analysis 11.14. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 14 Neuropsychiatric - Insomnia.

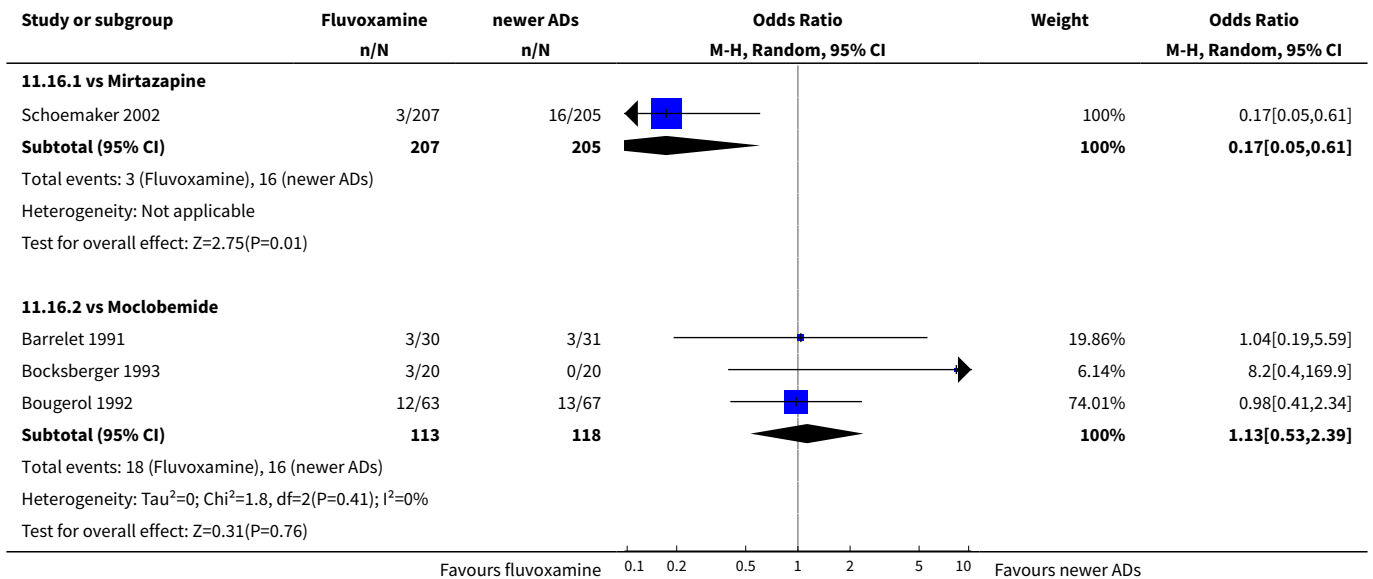




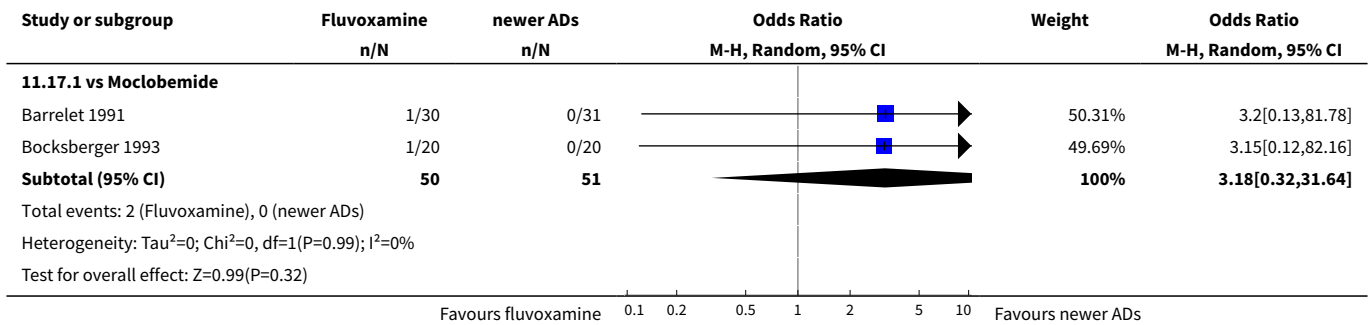
Analysis 11.15. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 15 Neuropsychiatric - Sleepiness / drowsiness.



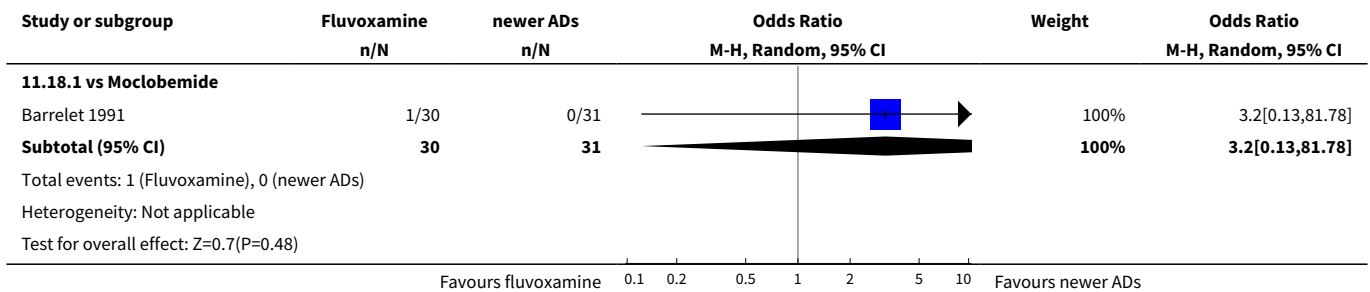
Analysis 11.16. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 16 Neuropsychiatric - Agitation / anxiety.



Analysis 11.17. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 17 Neuropsychiatric - Manic symptom.



Analysis 11.18. Comparison 11 Side effect profile: Fluvoxamine vs newer ADs, Outcome 18 Neuropsychiatric - Completed suicide.



ADDITIONAL TABLES

Table 1. Imputation methods and borrowed SD use to obtain response rate

Comparator	Study	Early phase		Acute phase		
		Imputation methods	borrowed SD	Imputation methods	borrowed SD	
TCAs	Imipramine	Cassano 1986	Yes	Yes	-	-
		Amore 1989	Yes	Yes	-	-
		Lydiard 1989	Yes	Yes	Yes	Yes
		Bramanti 1988	Yes	No	-	-
		Claghorn 1996	Yes	Yes	Yes	Yes
		Fabre 1992	Yes	Yes	No	Yes
		Feighner 1989	Yes	Yes	Yes	Yes
		Guy 1984	Yes	Yes	Yes	Yes

Table 1. Imputation methods and borrowed SD use to obtain response rate (Continued)

	Itil 1983	Yes	No	-	-	
	Koetsier 2002	Yes	No	-	-	
	March 1990	Yes	Yes	Yes	Yes	
	Miller 2001	-	-	-	-	
Clomipramine	Coleman 1982	Yes	Yes	-	-	
	de Wilde 1983	Yes	Yes	Yes	Yes	
	Dick 1983	No	No	-	-	
	Ottevanger 1995	Yes	No	-	-	
	Zohar 2003	Yes	Yes	No	Yes	
Amitriptyline	B-Schaapveld 1995	No	No	No	No	
	Harris 1991	Yes	Yes	Yes	Yes	
	Remick 1994	Yes	No	Yes	No	
	Kostiukova 2003	No	Yes	No	Yes	
	Murasaki 1998	No	No	-	-	
Nortriptyline	Otsubo 2005	Yes	No	No	No	
Dothiepin	Mullin 1988	Yes	Yes	Yes	Yes	
	Rahman 1991	Yes	Yes	Yes	Yes	
Desipramine	Nathan 1990	Yes	No	-	-	
	Tourigny Rivard 1996	-	-	Yes	Yes	
Hetero-cyclics	Amineptine	Brunner 1994	Yes	No	-	-
	Mianserin	Moon 1991	No	No	No	No
		Perez 1990	Yes	Yes	Yes	Yes
Maprotiline	Kasper 1989	Yes	No	-	-	
	Mendonca Lima 1997	Yes	Yes	-	-	
SSRIs	Paroxetine	Annseaa 1993	No	No	No	No
		Kato 2006	No	Yes	No	Yes
		Kiev 1997	Yes	Yes	Yes	No
Sertraline	Nemeroff 1995	Yes	Yes	Yes	No	

Table 1. Imputation methods and borrowed SD use to obtain response rate (Continued)

		Rossini 2002	Yes	No	Yes	No
Fluoxetine		Dalery 1998	No	Yes	No	Yes
		Rapaport 1995	Yes	Yes	Yes	Yes
Citalopram		Haffmans 1996	Yes	Yes	No	Yes
SNRI	Milnacipran	Clerc 2001	No	No	No	No
		Anseau 1991b	No	No	-	-
		Anseau 1991a	No	No	-	-
Venlafaxine		Hackett 1998a	Yes	No	Yes	No
		Hackett 1998b	Yes	No	Yes	No
Newer ADs	Mirtazapine	Schoemaker 2002	No	Yes	No	Yes
	Moclobemide	Barrelet 1991	Yes	No	-	-
		Bocksberger 1992	Yes	No	-	-
		Bougerol 1992	Yes	No	-	-
Other conventional	Sulpiride	Ueda 2002	Yes	No	-	-

Table 2. Imputation methods and borrowed SD use to obtain remission rate

Comparator	Study	Early phase		Acute phase		
		Imputation methods	borrowed SD	Imputation methods	borrowed SD	
TCAs	Imipramine	Cassano 1986	Yes	Yes	-	-
		Amore 1989	Yes	Yes	-	-
		Lydiard 1989	Yes	Yes	Yes	Yes
		Bramanti 1988	Yes	No	-	-
		Claghorn 1996	Yes	Yes	Yes	Yes
		Fabre 1992	Yes	Yes	Yes	Yes
		Feighner 1989	Yes	Yes	Yes	Yes
		Guy 1984	Yes	Yes	Yes	Yes
		Itil 1983	No	No	-	-

Table 2. Imputation methods and borrowed SD use to obtain remission rate (Continued)

		Koetsier 2002	Yes	No	-	-
		March 1990	Yes	Yes	Yes	Yes
		Miller 2001	-	-	-	-
Clomipramine		Coleman 1982	Yes	Yes	-	-
		de Wilde 1983	Yes	Yes	Yes	Yes
		Dick 1983	No	No	-	-
		Ottevanger 1995	Yes	No	-	-
		Zohar 2003	Yes	Yes	Yes	Yes
Amitriptyline		B-Schaapveld 1995	No	No	No	No
		Harris 1991	Yes	Yes	Yes	Yes
		Remick 1994	Yes	No	Yes	No
		Kostiukova 2003	Yes	Yes	Yes	Yes
		Murasaki 1998	Yes	No	-	-
Nortriptyline		Otsubo 2005	Yes	No	No	No
Dothiepin		Mullin 1988	Yes	Yes	Yes	Yes
		Rahman 1991	Yes	Yes	Yes	Yes
Desipramine		Nathan 1990	Yes	No	-	-
		Tourigny Rivard 1996	-	-	Yes	Yes
Hetero-cyclics	Amineptine	Brunner 1994	Yes	No	-	-
	Mianserin	Moon 1991	No	No	No	No
		Perez 1990	Yes	Yes	Yes	Yes
	Maprotoline	Kasper 1989	Yes	No	-	-
		Mendonca Lima 1997	Yes	Yes	-	-
SSRIs	Paroxetine	Annseaa 1993	Yes	No	Yes	No
		Kato 2006	Yes	Yes	Yes	Yes
		Kiev 1997	Yes	Yes	Yes	No
	Sertraline	Nemeroff 1995	Yes	Yes	Yes	No
		Rossini 2002	No	No	No	No

Table 2. Imputation methods and borrowed SD use to obtain remission rate (Continued)

	Fluoxetine	Dalery 1998	Yes	Yes	Yes	Yes
		Rapaport 1995	Yes	Yes	Yes	Yes
	Citalopram	Haffmans 1996	Yes	Yes	No	Yes
SNRI	Milnacipran	Clerc 2001	Yes	No	Yes	No
		Anseau 1991b	Yes	No	-	-
		Anseau 1991a	Yes	No	-	-
	Venlafaxine	Hackett 1998a	No	No	No	No
		Hackett 1998b	No	No	No	No
Newer ADs	Mirtazapine	Schoemaker 2002	Yes	Yes	Yes	Yes
	Moclobemide	Barrelet 1991	Yes	No	-	-
		Bocksberger 1992	Yes	No	-	-
		Bougerol 1992	Yes	No	-	-
Other conventional	Sulpiride	Ueda 2002	Yes	No	-	-

Table 3. Side effect profiles by body system

Control drug	Body system	Side effect	N of comparisons	N of participants	OR	95% CI	NNT	95% CI
versus TCAs								
Imipramine	Cardiovascular	Hypotension / bradycardia	4	560	0.24	0.10, 0.62	16	13, 33
	Dermatological	Sweating	7	972	0.32	0.16, 0.66	14	11, 28
	Gastrointestinal	Dry mouth	9	1055	0.24	0.16, 0.34	4	3, 5
		Vomiting / nausea	9	1055	2.23	1.59, 3.14	-9	-6, -17
		Constipation	8	1008	0.50	0.27, 0.93	11	8, 86
		Diarrhoea	2	136	6.38	1.27, 32.04	-8	-3, -133
	Neuropsychiatric	Dizziness / vertigo / faintness	9	1055	0.24	0.15, 0.38	7	6, 8
		Anxiety / agitation	5	644	2.24	1.01, 4.97	-17	-6, -1893
	Genitourinary	Problems urinating	2	409	0.18	0.04, 0.71	18	15, 51
Clomipramine	Gastrointestinal	Dry mouth	3	216	0.43	0.22, 0.81	5	4, 20
		Nausea / vomiting	3	216	2.13	1.06, 4.27	-9	-4, -138
	Neuropsychiatric	Dizziness / vertigo / faintness	1	86	0.21	0.05, 0.80	6	5, 25
Amitriptyline	Gastrointestinal	Vomiting / nausea	4	387	2.86	1.31, 6.23	-13	-6, -68
	Neuropsychiatric	Dizziness / vertigo / faintness	2	304	0.31	0.11, 0.83	7	5, 30
Nortriptyline	Neuropsychiatric	Dizziness / vertigo / faintness	1	74	0.22	0.07, 0.70	4	3, 12
Dothiepine	Gastrointestinal	Dry mouth	1	73	0.08	0.01, 0.70	5	5, 17
versus Heterocyclics								
Maptiline	Neuropsychiatric	Dizziness / vertigo / faintness	1	42	0.13	0.03, 0.56	3	2, 6

Table 3. Side effect profiles by body system (Continued)

Mianserin	Gastrointestinal	Nausea/vomiting	2	125	9.62	1.96, 47.30	-5	-2, -36
versus SSRIs								
Paroxetine	Dermatological	Sweating	1	60	0.22	0.05, 0.91	5	4, 49
versus SNRIs								
Milnacipran	Gastrointestinal	Vomiting / nausea	3	241	1.95	1.09, 3.50	-7	-4, -83
versus newer ADs								
Mirtazapine	Gastrointestinal	Vomiting / nausea	1	412	3.43	1.90, 6.19	-7	-4, -16
	Neuropsychiatric	Sleepiness / drowsiness	1	412	0.47	0.29, 0.76	8	6, 19
		Agitation / anxiety	1	412	0.17	0.05, 0.61	16	14, 35
Moclobemide	Gastrointestinal	Dry mouth	2	191	4.73	1.14, 19.57	-15	-4, -336
		Vomiting / nausea	2	170	2.01	1.03, 3.92	-7	-4, -178

Only results for statistically significant difference were shown. OR, odds ratio. OR < 1 favours fluvoxamine.

Table 4. Ratio of ORs from MTM and this review

Outcomes	OR (95%CI)		Ratio of ORs*
	MTM (direct + indirect comparisons) (Cipriani 2009)	Direct comparisons (This review)	
Response			
paroxetine	0.96 (0.76 to 1.23)	0.83 (0.51 to 1.34)	1.16
sertraline	0.79 (0.61 to 1.01)	1.21 (0.53 to 2.75)	0.65
fluoxetine	0.98 (0.77 to 1.23)	1.00 (0.62 to 1.61)	0.98
citalopram	0.88 (0.68 to 1.16)	0.90 (0.50 to 1.62)	0.98
milnacipran	0.97 (0.68 to 1.37)	0.57 (0.26 to 1.23)	1.70
venlafaxine	0.77 (0.59 to 0.99)	0.40 (0.18 to 0.92)	1.93
mirtazapine	0.71 (0.55 to 0.92)	0.88 (0.59 to 1.31)	0.81
Total dropout			
paroxetine	1.10 (0.84 to 1.47)	1.08 (0.63 to 1.85)**	1.02
sertraline	1.38 (1.03 to 1.89)	1.46 (0.19 to 11.16)**	0.95
fluoxetine	1.22 (0.93 to 1.61)	1.17 (0.66 to 2.09)**	1.04
citalopram	1.37 (1.01 to 1.85)	1.42 (0.75 to 2.67)	0.96
milnacipran	1.18 (0.76 to 1.75)	1.22 (0.54 to 2.77)**	0.97
venlafaxine	1.14 (0.86 to 1.54)	2.29 (0.97 to 5.43)	0.50
mirtazapine	1.18 (0.87 to 1.61)	0.83 (0.52 to 1.33)	1.42

MTM, multiple-treatments meta-analysis; OR, odds ratio; CI, confidence interval;

For response, ORs higher than 1 favor fluvoxamine. For total dropout, ORs lower than one favour fluvoxamine;

* ORs of this review as reference;

**Data from three comparisons (Ansseau 1991a, Ansseau 1991b, and Gonul 1999) were omitted because these 4-week trials were not included in MTM (Cipriani 2009).

WHAT'S NEW

Date	Event	Description
30 September 2013	Amended	Minor error in Additional Table 3 corrected.
1 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

IMO, AN, AC, CB, HM and RC have nothing to declare. NW has received a speaking fee from GlaxoSmithKline. TAF has received research funds and speaking fees from Dai Nippon Sumitomo, Eli Lilly, GSK, Meiji, Otsuka, and Pfizer. The Japanese Ministry of Education, Science, and Technology and the Japanese Ministry of Health Labor and Welfare have also funded TAF's research.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no substantive differences between protocol and review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents, Second-Generation [*therapeutic use]; Antidepressive Agents, Tricyclic [therapeutic use]; Depression [*drug therapy]; Fluvoxamine [*therapeutic use]; Randomized Controlled Trials as Topic; Selective Serotonin Reuptake Inhibitors [therapeutic use]

MeSH check words

Humans