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[Intervention Review]

Antidepressants versus placebo for people with bulimia nervosa

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ABSTRACT

Background

Bulimia Nervosa (BN) represents an important public health problem and is related to serious morbidity and even mortality. This review attempted to systematically evaluate the use of antidepressant medications compared with placebo for the treatment of bulimia nervosa.

Objectives

The primary objective of this review was to determine whether using antidepressant medications was clinically effective for the treatment of bulimia nervosa.

The secondary objectives were:
(i) to examine whether there was a differential effect for the various classes/types of antidepressants with regard to effectiveness and tolerability
(ii) to test the hypothesis that the effect of antidepressants on bulimic symptoms was independent of its effect on depressive symptoms

Search methods

(1) electronic searches of MEDLINE (1966 to December 2002), EMBASE (1980-December 2002) , PsycINFO (to December 2002), LILACS & SCISEARCH (to 2002)
(2) the Cochrane Register of Controlled Trials and the Cochrane Depression, Anxiety and Neurosis Group Register - ongoing
(3) inspection of the references of all identified trials
(4) contact with the pharmaceutical companies and the principal investigator of included trials
(5) inspection of the International Journal of Eating Disorders - ongoing

Selection criteria

Inclusion criteria: every randomised, placebo-controlled trial in which antidepressant medications were compared to placebo to reduce the symptoms of bulimia nervosa in patients of any age or gender.
Quality criteria: reports were considered adequate if they were classified as A or B according to the Cochrane Manual. The Jadad scale, with a cut off of 2 points, was applied to check the validity of the above referred criterion but was not used as an inclusion criterion.

Data collection and analysis

Data were extracted independently by two reviewers for each included trial. Dichotomous data were evaluated by the relative risk with 95% confidence intervals (CI) around this measure, based on the random effects model; continuous data were evaluated by the standardised mean difference with the 95% CI. NNT was calculated using the inverse of the absolute risk reduction.

Main results

Currently the review includes 19 trials comparing antidepressants with placebo: 6 trials with TCAs (imipramine, desipramine and amitriptyline), 5 with SSRIs (fluoxetine), 5 with MAOIs (phenelzine, isocarboxazid, moclobemide and brofaromine) and 3 with other classes of drugs (mianserin, trazodone and bupropion). Similar results were obtained in terms of efficacy for these different groups of drugs. The pooled RR for remission of binge episodes was 0.87 (95% CI 0.81-0.93; p<0,001) favouring drugs. The NNT for a mean treatment duration of 8 weeks, taking the non-remission rate in the placebo controls of 92% as a measure of the baseline risk was 9 (95% CI 6 - 16). The RR for clinical improvement, defined as a reduction of 50% or more in binge episodes was 0.63 (95% CI 0.55-0.74) and the NNT for a mean treatment duration of 9 weeks was 4 (95% CI 3 - 6), with a non-improvement rate of 67% in the placebo group. Patients treated with antidepressants were more likely to interrupt prematurely the treatment due to adverse events. Patients treated with TCAs dropped out due to any cause more frequently that patients treated with placebo. The opposite was found for those treated with fluoxetine, suggesting it may be a more acceptable treatment. Independence between antidepressant and anti-bulimic effects could not be evaluated due to incomplete published data.

Authors' conclusions

The use of a single antidepressant agent was clinically effective for the treatment of bulimia nervosa when compared to placebo, with an overall greater remission rate but a higher rate of dropouts. No differential effect regarding efficacy and tolerability among the various classes of antidepressants could be demonstrated.

PLAIN LANGUAGE SUMMARY

Antidepressants compared with placebo for bulimia nervosa

Individual antidepressants are effective for the treatment of bulimia nervosa when compared to placebo treatment, with an overall greater remission rate but a higher rate of dropouts.

BACKGROUND

Bulimia Nervosa is an eating disorder characterized by recurrent episodes binge eating (eating objectively large amounts of food over which the person has loss of control) followed by recurrent use of extreme compensatory behaviours in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas or other medications; fasting; or excessive exercise. In addition, body shape and weight have an undue influence on sufferers self-esteem and their self-evaluation (APA 1994). The Diagnostic and Statistical Manual of the APA (APA 1994) specify frequency criteria for both binge eating and extreme compensatory behaviours, namely they occur a minimum of twice weekly over the preceding three months at the time of assessment.

Bulimia nervosa as a syndrome is not the same as "bulimia", meaning overeating, which can be found as a symptom in different psychiatric, neurologic or medical conditions. The syndrome as it is recognized by today's clinicians was first described by Russell in 1979 (Russell 1979) and was virtually unknown until the latter half of the 20th century (Russell 1997). A period of confusion followed the definition for the so-called "bulimia" published in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (APA 1980). Bulimia was simply defined by recurrent episodes of binge eating, and the important criterion of morbid fear of fatness was omitted, and the criterion of attempted weight loss by self-induced vomiting or other purging and non purging compensatory behaviours was optional. This confusion was addressed in the revision of the DSM in 1987 (APA 1987). During these seven years, and to a smaller extent thereafter, researchers included patients in trials who did not present the full syndrome as it is now understood.

Surveys indicate that the disorder affects 1.3% to 10.1% of North American women, depending on the diagnostic criteria used in the epidemiological studies (DSM-III criteria being probably over inclusive). The prevalence among adolescent and young adult females is approximately 1% (APA 1994). Bulimia nervosa has been reported in all socio-economic classes even if it is most commonly reported in developed countries and higher socio-economic classes. At least 90% of individuals with bulimia nervosa are female. Bulimia nervosa may cause serious morbidity and even mortality (FBNCSG 1992) representing an important public health problem.

Two treatments have received the most support in controlled studies of bulimia nervosa: psychotherapeutic approaches, mainly cognitive behavior therapy, and antidepressant medication.

Binge eating is typically triggered by dysphoric mood stages and the episodes are often followed by depressed mood and self-criticism. Moreover, there is an increased frequency of depressive symptoms or underlying mood disorders in individuals with bulimia nervosa. Thus, the connection between bulimia nervosa and depression has received particular attention. Although it is not clear whether depression antedates, coexists with or is a consequence of the eating disorders, this association led to the investigation of antidepressants in the treatment of bulimia nervosa (Advokat 1995).

All types of antidepressants seem to be beneficial in relieving bulimic symptoms (Wolfe 1995). There is no clear evidence of a differential effect among the various drugs used. It is not known if any particular class of antidepressants is more effective although selective serotonin re uptake inhibitors have been thought to produce benefits relative to placebo. It is thought that antidepressants have specific anti-bulimic effects as they are both effective in bulimic patients who do and do not suffer depression.

Although antidepressants have been shown to be useful in the treatment of bulimia nervosa, results are far from optimal. Short-term abstinence rates (on average 8 weeks) are about 30%, and overall reductions in bulimic behaviours are about 70% (Agras 1992, Leitenberg 1994). A significant relapse rate (30-45%) is observed in patients followed for 4-6 months (Walsh 1991a). Pope 1983 also reported prompt relapse with discontinuation of antidepressant treatment, but good maintenance of effects when the drug was continued in a small 2-year follow-up of participants from a randomised controlled trial (RCT). In addition, two RCTs have specifically examined adverse effects of treatment. Walsh 1991a found significant increases in pulse rate, reclining systolic and diastolic blood pressures and orthostatic hypotension in young women with bulimia nervosa treated with desipramine. These effects appeared to be well-tolerated. Carruba 2001 found no changes in blood pressure in participants randomised to moclobemide despite food diaries documenting a high consumption of tyramine-containing foods. In addition, Wheadon 1992a in a meta-analysis of two double-blind RCTs of fluoxetine versus placebo found no significant difference in the incidence of suicidal acts or ideation. However, these were infrequent (suicide attempts 1.2%, none fatal; emergent suicidal ideation 3.1%). This review evaluated the use of antidepressants compared to placebo in the treatment of bulimia nervosa, both with regard to efficacy and acceptability.

OBJECTIVES

The primary objective of this review was to investigate whether the use of antidepressant medications is clinically effective for the treatment of bulimia nervosa when compared with placebo. Where possible, a meta-analytic synthesis of the studies was performed.

The secondary objectives were:
(i) to examine whether there was a differential effect for the various classes/types of antidepressants with regard to effectiveness and tolerability
(ii) to test the hypothesis that the effect of antidepressants on bulimic symptoms was independent of their effect on depressive symptoms

Usefulness of antidepressants for more than 8 weeks was also investigated.

METHODS

Criteria for considering studies for this review

Types of studies

We attempted to identify all relevant randomised placebo-controlled trials.

Types of participants

People with bulimia nervosa defined by clinical state description or diagnosed by Russell's, DSM-III, DSM-III-R, DSM-IV or ICD-10 criteria, irrespective of gender, age or treatment setting. Participants with both purging and non purging type bulimia nervosa, as defined

in DSM-IV (APA 1994), were included. As we intended to examine the influence of depression and obesity on clinical outcome, trials including patients with co morbid depression or obesity were also eligible.

Exclusion criteria: people with binge-eating/purging type anorexia nervosa or binge-eating disorder as defined in DSM-IV (APA 1994).

Types of interventions

Trials were included if they compared antidepressant medications of any class/type to placebo for at least 4 weeks. The following antidepressants were included:
a) tricyclic antidepressants (TCA):imipramine, amitriptyline, clomipramine, nortriptyline, desipramine;
b) selective serotonin re uptake inhibitors (SSRI): fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine;
c) monoamine oxidase inhibitors (MAOI): phenelzine, isocarboxazid, moclobemide, brofaromine, tranylcypromine;
d) other antidepressants: bupropion, trazodone, nefazodone, mianserin, mirtazapine, venlafaxine.

Trials with combined or augmentation drug therapies compared to placebo could also be included.

Types of outcome measures

Primary outcomes of interest were:

A. Changes in bulimic symptoms
(i) the number of people per treatment group who did not show a remission in the bulimic symptoms, defined as 100% reduction in binge-eating episodes from baseline at endpoint
(ii) the number of people per treatment group who did not show a clinical improvement in the bulimic symptoms, defined as more than 50% reduction in binge-eating episodes from baseline at endpoint
(iii) the difference in the mean number of bulimic episodes at the end of the trial

B. Comorbidity
(i) difference in the severity of depressive symptoms at the end of the trial

C. Acceptability of the treatment
(i) acceptability of the intervention to the participant group as measured by the number of people per treatment group dropping out during the trial for any cause
(ii) tolerability of the intervention as measured by the number of people per treatment group dropping out during the trial due to adverse events

Search methods for identification of studies

See: Collaborative Review Group search strategy

A. Electronic searching
Relevant randomised trials were identified by searching the following electronic databases by means of the Depression, Anxiety and Neurosis Group Strategy (see CCDAN module). A subsection of these trials was obtained by linking the CCDANCTR search with the following specific search for this review:

bulimia or bing* or overeat* or "compulsive eat*" or "compulsive vomit*" and pharmacotherapy*

(i) MEDLINE (January 1966 to December 2002).

(ii) EMBASE (January 1980 to December 2002)

(iii) LILACS (January 1982 to December 2002)

(iv) PsycINFO (January 1974 to December 2002)

This downloaded set of reports was searched for possible trials and re-searched, within the bibliographic package, ProCite, with the phrase:
[antidepressant* or tricyclic* or imipramine or amitriptyline or clomipramine or nortriptyline or desipramine or fluoxetine or sertraline or paroxetine or citalopram or fluvoxamine or bupropion or trazodone or nefazodone or phenelzine or isocarboxazid* or moclobemide or brofaromine or tranylcypromine or mianserin or mirtazapine]

(v) the Cochrane Depression, Anxiety and Neurosis Group Database of Trials

(vi) the Cochrane Central Register of Controlled Trials (CENTRAL)

(vii) SCISEARCH - Science Citation Index
Each of the included studies was sought as a citation on the SCISEARCH database. Reports of articles that had cited these studies were inspected in order to identify further trials.

Electronic search was performed by the DAN Group.

B. A second search was conducted with Clinical Evidence (Hay 2001) and comprised MEDLINE 1966-December 2002, EMBASE 1980-December 2002, PsycINFO 1989-December 2002 and The Cochrane Library 2002 Issue 4. The following terms were used: (bulimia or bulimia nervosa or eating disorders or binge eating) and (therapy or treatments or trials or psychotherapy or cognitive-behavioural therapy or pharmacotherapy or antidepressant or SSRI or MAOI)

C. Reference searching
The reference lists of all papers selected were inspected for further relevant studies.

D. Pharmaceutical companies
Companies carrying out comparative studies of their own products with placebo in the treatment of bulimia nervosa were contacted in order to obtain data on unpublished trials.

E. Personal contact
The first authors of all included studies were contacted for further information or information regarding unpublished trials.

F. An inspection from the first issue of the International Journal of Eating Disorders is ongoing.

Data collection and analysis

Selection of trials
The abstract of each reference identified by the search was evaluated by one reviewer (JB) in order to see if the study was likely to be relevant to this review. For this review all trials comparing drugs with placebo were eligible, regardless if other comparisons were made in the trial or not. Studies comparing two active drugs or drugs versus psychotherapy were not eligible for this review. For possible RCTs the full article was obtained and inspected to assess their relevance for this review based on the inclusion criteria.

Quality assessment
Once the full relevant articles were obtained, two reviewers (JB and PH), independently, decided whether they met criteria to be included. In order to ensure that variation in results was not caused by systematic errors in the design of a study, the methodological quality of the trials was assessed by the two independent reviewers using the criteria described in the Cochrane Handbook (Mulrow 1996) and the Jadad Scale (Jadad 1996). The Cochrane Collaboration Handbook criteria are based on the evidence of a strong relationship between potential for bias in the results and allocation concealment (Schultz 1995) and are defined as below:

A. Low risk of bias (adequate allocation concealment)
B. Moderate risk of bias (some doubt about the results)
C. High risk of bias (inadequate allocation concealment)

The Jadad Scale measures a wider range of factors that impact on the quality of a trial. The scale includes three items:

1. Was the study described as randomised?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and drop-outs?

Each item received 1 point if the answer was positive. In addition, a point was deducted if either the randomisation or the blinding/masking procedures described were inadequate.

For the purpose of the analysis in this review, trials were included if they met the criteria A or B according to the Cochrane quality criteria (Sackett 1997). Additionally, a cut-off of two points was used in the Jadad scale to check the assessment made by the Handbook criteria. However, the latter was not used to exclude trials in this review.

Reviewers were not blind to the names of the authors, institutions and journal of publication. Where disagreement could not be resolved by discussion and consensus, further information was sought contacting the authors for clarification. The articles were then added to the list of those awaiting assessment. The same methodology was used for the selection of trials identified by means of reference lists searched and for data on unpublished trials obtained through contacts with the pharmaceutical industry or with first authors. An inter-rater reliability study between reviewers for the Cochrane Collaboration Handbook criteria (Sackett 1997) was performed by means of the kappa.

Data Management
Data from the selected trials were extracted by the two reviewers. Again, any disagreement was discussed, decisions documented and, where necessary, the authors of the studies were contacted for clarification. Justification for excluding references from the review was documented. We anticipated that many trials would have inadequate reporting. Therefore, for studies that did not specify reasons for subjects who dropped out, we assumed that the subjects had no change in their bulimic symptoms. When insufficient data were provided to identify the original group size (prior to drop-outs) the authors were contacted and the trials were allocated to the "awaiting assessment" list for a period of up to 1 year. If no information from authors was obtained, the trial was excluded.

We also expected that some trials would have used a crossover design. In order to exclude the potential additive effect in the second or later stages on these trials, only data from the first stage were analysed. If information from this first period was not obtained from authors, the trial was excluded from the meta-analysis.

Analysis
Dichotomous outcomes (remission, clinical improvement, drop-outs) were analysed by the relative risk (RR) with 95% confidence intervals (CI) for each trial. The RR from the individual trials were combined using appropriate methods of meta-analysis. Additionally, when overall results were significant, the number needed to harm (NNH) or the number needed to treat (NNT) to prevent (or to produce) one outcome was calculated on the inverse of the absolute risk reduction, by combining the RR with an estimate of the prevalence of the event in the control groups of the trials. The estimates of RR were based on the random effects model as it takes into account any difference between studies (even if there is no statistically significant heterogeneity) and gives the same result as the fixed effects model when there is no between study variance (DerSimonian 1986).
For the analysis of continuous outcomes, the mean and standard deviation of bulimic symptoms and scores of depression scales for each trial were assessed, and the standardised mean difference with 95% CI calculated using the random effects method.
Heterogeneity in the results of the trials - i.e., whether differences were greater than would be expected by chance alone - was assessed both by inspection of graphical presentations and by a test of heterogeneity using a Q ("combinability") statistic. A p value < 0.05 indicated statistical heterogeneity.
The presence of publication bias from the tendency to publish only statistically significant results or results supporting the hypothesis was detected graphically in a "funnel plot" (Light 1984). When selective publication is present the distribution around the pooled RR of all studies is not homogeneous, indicating that small trials with non-significant results are not being published, the "file-drawer problem" (Rosenthal 1979).
Sensitivity analyses were performed for: quality of trials; length of treatment (up to 8 weeks of treatment and 8 or more weeks of treatment); diagnostic criteria (DSM-III bulimia versus DSM-III-R bulimia nervosa criteria); bulimic and purging symptoms; and class of drugs.

RESULTS

Description of studies

Nineteen trials fulfilled inclusion criteria and had available data which could be used in this review (1436 patients in total). These trials were used for at least one of the main comparisons.

Further information for four trials could not be obtained from authors, therefore the following trials were excluded from this review: Alger 1991 (separate data for bulimic patients not obtained); Barlow 1988 and Blouin 1988 (data for the first crossover period not obtained); and Hughes 1986a (no evaluable data available). The first authors of these four papers have been contacted by courier. Three of them (Alger 1991, Barlow 1988, Blouin 1988) changed their address and did not receive the letters and no information could be obtained from the fourth (Hughes 1986a).
Other twenty-six studies were excluded. Most (n=15) were subsets from other studies, including follow-up or interim analyses. Six

studies compared antidepressants and psychotherapy without a placebo controlled group and were analysed in other specific reviews (Bacaltchuk 2003) (Fichter 1991; Agras 1992; Leitenberg 1994; Russell 1995b; Goldbloom 1996; and Walsh 1997). One study was excluded because patients did not fulfil diagnostic criteria for bulimia or bulimia nervosa (Box 1983; patients described as "overweight compulsive eaters"); one study compared antidepressants with no intervention (Scrimali 1994; no placebo controlled group); and one study did not provide separate data for obese binge eaters and bulimic patients (Marcus 1990; author replied to contact, data not available).

When multiple publications of the same trial were found, all reports were checked and even if information of all trials was used only the main publication was referenced. In case of discrepancies among different publications of the same trial authors were contacted.

Design

All studies were described as randomised. One study (FBNCSG 1992) compared two fixed doses of fluoxetine (20 and 60 mg daily) to placebo. As the 20 mg group showed no significant difference over placebo, we considered only the 60 mg group for comparisons; one study (Mitchell 1990) compared imipramine to psychotherapy and placebo. For the purpose of this review we considered only the imipramine and placebo groups; another study (Mitchell 1999c) compared fluoxetine to either placebo, self help manual or a combination of both active treatments. Only the fluoxetine and placebo groups were considered. Finally, one study (Rothschild 1994) compared three groups of patients with atypical depression presenting comorbid bulimia randomised to receive either imipramine, phenelzine or placebo. Outcomes were analysed retrospectively. We included the phenelzine and placebo groups in the comparisons as more patients were randomised to these groups than for imipramine. All other studies used parallel group design comparing one antidepressant drug to placebo. One further study (Walsh 1999) randomised patients to fluoxetine or placebo following a poor response to psychotherapy. Duration of trials ranged from 6 weeks to 16 weeks. A subgroup analysis was performed comparing trials with a duration of up to weeks versus those with a duration of more than 8 weeks.

Settings

Two studies were multicenter, multinational (FBNCSG 1992; Wheadon 1992a), both comparing fluoxetine to placebo. Twelve trials were conducted in the United States of America (Agras 1987; Horne 1988; McCann 1990; Mitchell 1984, Mitchell 1990 and Mitchell 1999c; Pope 1983 and Pope 1989; Rothschild 1994; Walsh 1984a, Walsh 1991a and Walsh 1999), two in Canada (Kennedy 1988 and Kennedy 1993) one in the United Kingdom (Sabine 1983), one in Norway (Kanerva 1994) and one in Italy (Carruba 2001). Trials recruited outpatients either seeking treatment "spontaneously" from eating disorders clinics/programs (6 trials) or included also "volunteers" for research recruited through advertisement in local newspapers and media (13 trials).

Participants

Eight trials included in the main comparisons used DSM-III criteria for bulimia, 9 trials used DSM-III-R criteria for bulimia nervosa and one trial used DSM IV criteria. Sabine 1983 did not use a formal diagnostic criterion but described patients clinically as bulimics. As the DSM-III diagnostic criteria for "bulimia" omitted the important criterion of a morbid fear of fatness and even the criterion of attempted weight loss by self-induced vomiting was optional, we can not state that patients diagnosed as bulimics according to the DSM-III criteria are equivalent to those presenting the DSM-III-R criteria for bulimia nervosa. We then performed a sensitivity analysis comparing trials using bulimic patients diagnosed according to DSM-III with those diagnosed according to DSM-III-R or Russell's criteria.

The study population included in the trials had comparable demographic and behavioral features. All studies except one (McCann 1990) included purging type bulimics, according to the DSM-III-R definition ("the person regularly engages in self-induced vomiting or misuse laxatives, diuretics or enemas"). Patients were mostly adult and young adult females, few adolescents were included. The median mean number of binges at baseline was 10.1, ranging from 3.8 to 12.0. A constant inclusion criterion was that patients should be between 80 and 120% of the expected ideal weight or body mass index (BMI). Most patients were not depressed, and mean baseline scores in depression scales ranged from 12.2 to 16.9 for the studies assessing depression by means of the Hamilton Depression Rating Scale - 21 items and from 12.4 to 18.8 for those using the Beck Depression Inventory. Mean duration of symptoms ranged from 5.0 to 14.0 years. The number of participants randomised in the trials ranged from 18 to 398. No concomitant psychotherapy was performed.

Interventions

All comparisons were of a single antidepressant versus placebo. No trial compared two or more combined drugs or augmentation therapies with placebo. Six trials compared TCAs with placebo: imipramine (Agras 1987; Mitchell 1990; Pope 1983) desipramine (McCann 1990; Walsh 1991a) and amitriptyline (Mitchell 1984); five compared MAOIs with placebo: phenelzine (Rothschild 1994; Walsh 1984a) isocarboxazid (Kennedy 1988), brofaromine (Kennedy 1993) and moclobemide (Carruba 2001); five studies compared fluoxetine with placebo (FBNCSG 1992; Wheadon 1992a; Kanerva 1994; Mitchell 1999c; Walsh 1999); and three compared other antidepressants with placebo: mianserin (Sabine 1983) trazodone (Pope 1989) and bupropion (Horne 1988).

Outcomes

Four dichotomous outcomes were used in this review. Two concerned changes in bulimic symptoms, and were considered primary efficacy outcomes: remission and clinical improvement. Remission was described in 10 trials and clinical improvement in 8 studies. Remission in bulimic symptoms was considered the more stringent criteria for improvement and was defined as 100% reduction in binge-eating episodes from baseline to endpoint. Clinical improvement was defined as a reduction of 50% or more in binge-eating episodes.

As we could not assume beforehand that all patients included in the studies would be purging type bulimic individuals, binge-eating episodes were considered the main bulimic symptom. So, where binge eating and purging episodes were reported, only binge-eating episodes were considered. Where only purging episodes were reported, they were considered as binge-eating episodes. A sensitivity analysis was performed to verify if purging and bingeing could be conflated.

The other two dichotomous outcomes used concerned acceptability and tolerability of treatment. The first, 'number of drop-outs due to adverse events' was recorded where adverse experiences were so severe that patients stopped treatment prematurely. This was extracted from 13 trials. The second, 'drop-outs due to any cause', (causes included adverse events, lack

of improvement, protocol violations, patient choice) could be extracted from 15 trials.
Continuous outcomes analysed were the mean difference in bulimic symptoms (mean number of binges per treatment group) and mean difference in depressive symptoms (mean scores in depression scales per treatment group) at endpoint. Three trials reported only median scores with range for both bulimic and depressive symptoms (FBNCSG 1992; Wheadon 1992a and Walsh 1999) and data were not used in the pooled analysis. In some other cases data on standard deviations were lacking, so these trials could not be included in the analysis. For analysis of improvement in depressive symptoms, studies were pooled together, as far as all of the trials were comparable even if measures of depression were from different scales (according to Cucherat 1997, pp. 250).

Risk of bias in included studies

Methodological quality was assessed independently by two reviewers (JB and PH). Inter-rater agreement for the Cochrane Collaboration Handbook criteria between reviewers employed the kappa statistic as a measure of agreement. Kappa for this analysis was calculated by means of the ARCUS Quickstat software for windows (Buchan 1998) and the result (0.81) indicated a very good agreement beyond chance. Letters requesting additional information on allocation concealment for all trials were sent to authors. Only two trials (Wheadon 1992a and Sabine 1983) were graded as "A" according to the first quality assessment criteria (Mulrow 1996), thanks to further information provided by the authors to our inquiry. All other 14 trials were classified as "B" because no information on allocation concealment was given in the report.

In general, the quality of reporting was poor. All trials reported the randomisation procedure without adequate information on allocation concealment. Blinding procedures were also inadequately described in all trials. Some did not reported the number of drop-outs or did not specified reasons for drop-out. Several trials excluded patients after randomisation from analysis and did not perform an intention-to-treat analysis. Some trials also omitted the standard deviations of continuos outcomes. The most frequently reported outcome was mean percentage change in bulimic episodes, the omission of standard deviations being common again for this measure.

Effects of interventions

Publication bias
The dysymetric funnel plot histogram for the dichotomous outcomes "remission" and "clinical improvement" reflects the absence of smaller studies favouring placebo or showing lower RR in favour of antidepressants, consistent with possible publication bias. This bias was confirmed by the identification of at least two unpublished reports of a negative multicenter, multinational study comparing fluvoxamine with placebo (Corcos 1996), showing a lack of greater efficacy of fluvoxamine compared to placebo. Authors were contacted (Russell GFM in England and Jeammet PH in France) but we could not obtain their unpublished results.

Remission
This outcome was reported in ten trials (Agras 1987, McCann 1990, Walsh 1991a[TCAs]; Wheadon 1992a[SSRI]; Kennedy 1993, Walsh 1984a [MAOIs]; Horne 1988 [bupropion]; Pope 1989 [trazodone] and Walsh 1999 and Mitchell 1999c [SSRI]). In general, short-term remission of binge episodes was more likely on antidepressants than placebo.
TCAs (three studies, 66 patients per treatment group) showed a RR of 0.86 (95% CI 0.70-1.07). Concerning MAOIs (two trials, 50 patients in the antidepressant group and 48 patients in the placebo group), the RR was 0.81 (95% CI 0.68-0.96) and the NNT for a mean treatment duration of 8 weeks was 6 (95% CI 3 - 27), considering a non-remission rate of 94% in the placebo group. SSRIs (three trials, 335 treated with fluoxetine and 132 with placebo) showed a RR of 0.89 (95% CI 0.76-1.03). Two trials evaluating other drugs (trazodone and bupropion) reported remission rates.
As no evidence of heterogeneity in terms of non-remission was found considering all studies together by using a chi-square statistic (X2=10.63; df=9; p=0.3) it was possible to perform a further analysis: "any antidepressant" versus placebo. The pooled RR considering the eight studies reporting this outcome was 0.88 (95% CI 0.82-0.93; p<0.001) favouring drugs. The NNT for a mean treatment duration of 8 weeks (min-max=6-16), taking the non-remission rate in the placebo controls of 92% as a measure of the baseline risk, was 9 (95% CI 6 - 16).

Clinical improvement
This outcome was reported in eight trials (Agras 1987, Pope 1983 [TCAs]; FBNCSG 1992, Wheadon 1992a, Kanerva 1994 [SSRI]; Kennedy 1988 [MAOI]; Horne 1988 [bupropion] and Pope 1989 [trazodone]). Effects were much stronger than those observed for remission, specially for TCAs, but the two studies were small, including only 44 patients (21 for active drug and 23 for placebo) in total. The RR for these two trials was 0,29 (95% CI 0,13-0,63) and the NNT for a mean treatment duration of 11 weeks was 2 (95% CI 1 - 3), for a non-improvement rate in the placebo group of 83%. For fluoxetine, the only SSRI studied, the RR was 0,68 (95% CI 0.59-0.79). The three trials considered in the pooled analysis included 706 patients (449 and 257 for fluoxetine and placebo respectively), representing 78% of the total patients included in the analysis of this outcome. The NNT for a mean treatment duration of 10 weeks with fluoxetine was 6 (95% CI 4 - 10), for a non-improvement rate of 62% in the placebo group. Considering the effect of any drug, the RR was 0.63 (95% CI 0.55-0.74). This estimate was based on the random effects model and possible differences between studies (chi-square heterogeneity test: 9.22 (df=7; p=0.237) were taken into account. The NNT for a mean treatment duration of 9 weeks (min-max=6-16) with any drug for clinical improvement was 4 (95% CI 3 - 6), with a non-improvement rate of 67% in the placebo group.

Tolerability
No significant results among and within classes of drugs were found in the number of people per treatment group dropping out during the trial due to adverse events, the measure of tolerability used in this review, as reported in thirteen trials (Agras 1987, McCann 1990, Mitchell 1984, Pope 1983, Walsh 1991a[TCAs]; FBNCSG 1992, Wheadon 1992a, Kanerva 1994 [SSRI]; Kennedy 1993, Walsh 1984a and Carruba 2001[MAOIs]; Horne 1988[bupropion] and Pope 1989 [trazodone]). The RR for TCAs (five trials and 192 patients analysed) was 2.38 (95% CI 0.76-7.45; chi-square heterogeneity test: 3.69 (df=4; p= 0.45)). For fluoxetine (SSRI) the RR was 1.52 (95% CI 0.83-2.75 ; three trials and 706 patients analysed; chi-square heterogeneity test: 1.05 (df=2; p=0.59)) The pooled RR for MAOIs (three trials and 175 patients) was 2.06 (95% CI 0.45-9.53; X2 heterogeneity test: 4.30 (df=2; p=0.12)). Other drugs (bupropion: one trial, RR= 1.89 [95% CI 0,22-16,09] and trazodone: one trial, RR= 1.00 [95% CI 0.07-15.04]) reported similar results for drop-

outs. MAOIs presented the higher rates of drop-outs due to adverse events of all classes of antidepressants analysed (22% versus 4% for placebo). As no heterogeneity was found among classes of drugs, the comparison "any drug" versus placebo was performed. The pooled analysis of all trials reporting drop-outs due to adverse events showed a statistically significant result in favour of placebo: RR= 1.65 (95% CI 1.05-2.57); chi-square statistic for heterogeneity=9.50 (df=12); p=0.64. The NNH for a mean treatment duration of 9 weeks (min-max=6-16) was 19 (95% CI 12 - 46), given a prevalence of drop-outs of 5.1% in the placebo group.

Acceptability of treatment

TCAs and SSRIs showed statistically significant results for drop-outs due to any cause, but in opposite directions. The RR for TCAs (six trials and 277 patients [Agras 1987, McCann 1990, Mitchell 1984 and Mitchell 1990, Pope 1983 and Walsh 1991a]) was 1.93 (95% CI 1.15-3.25), drop-outs being more likely in the TCA group. No heterogeneity was found among TCA studies (X2=3,74[df=5]; p=0.577) and the NNH for a mean treatment duration of 10 weeks (min-max=6-16) was 7 (95% CI 4 - 18), given a prevalence of drop-outs due to adverse events of 14.4% in the placebo group. For fluoxetine (SSRI; three trials and 706 patients [FBNCSG 1992, Wheadon 1992a, Kanerva 1994]) the RR was 0.82 (95% CI 0.68-0.99) but the drop-outs were more likely in the placebo group. As no heterogeneity was found among these three trials the NNH was calculated (35 [95% CI 10 - infinity]). No statistically significant increase in drop-outs due to any cause was found for MAOIs (three trials and 175 patients [Kennedy 1993; Walsh 1984a and Carruba 2001]), bupropion (Horne 1988), trazodone (Pope 1989) or mianserin (Sabine 1983). As the test of heterogeneity for the comparison "any drug" versus placebo was not significant (chi-square heterogeneity test: 19.51 (df=14; p=0.15) this comparison was performed. No statistically significant difference in acceptability of treatment between antidepressants and placebo has been shown (RR= 0.98,95% CI 0.78-1.24).

Difference in bulimic symptoms

This analysis was based on the number of patients who reported the number of bulimic episodes at the end of the trial, and it was not an intention to treat analysis because of missing data. No difference was found among treatment groups in baseline mean rates of bulimic episodes, and all trials reporting this outcome were included in the analysis (Agras 1987, McCann 1990, Walsh 1991a [TCAs]; Kennedy 1993, Walsh 1984a and Carruba 2001[MAOIs]). As heterogeneity was found among these 6 trials, they were not pooled. When the outlier (Carruba 2001) identified through the graphic analysis of SMD results was excluded from the pooled studies no heterogeneity was found among the remaining 5 trials (X2= 4.67, df=4; p=0,323)). A possible reason for the heterogeneity was that this was the only study significantly favouring placebo. Pooled estimate of standardised effect size for the comparison "any antidepressant" versus placebo was -0.59 (approximate 95% CI = -0,87 to -0,31; p < 0,0001) in favour of active antidepressant drugs.

Difference in depressive symptoms

This analysis was based on the number of patients who reported depression scores at the end of the trial, and it was not an intention to treat analysis due to missing data. Eight trials reported mean and standard deviations for depressive symptoms at endpoint (Agras 1987, Carruba 2001, Kanerva 1994, Kennedy 1993, McCann 1990, Rothschild 1994, Walsh 1984a, Walsh 1999). No statistically significant difference was observed between classes of drugs. Baseline mean depression scores were low, except for one trial (Rothschild 1994) that analysed retrospectively atypical depressive patients with comorbid bulimia. Other trials usually did not include depressive patients. No heterogeneity in the results of these eight trials has been found (X2= 5.49 (df=7; p= 0.6).

Secondary methodological assessment

Trials were rated according to the Jadad Scale (see methods section for a description of the items). Scores for each trial are summarized in the table below:

STUDY	JADAD SCORE	STUDY	JADAD SCORE
AGRAS 1987	1	FBNCSG 1992	1
CARRUBA 2001	1	GOLDSTEIN 1995	5
HORNE 1988	2	McCANN 1990	1
KANERVA 1994	2	KENNEDY 1988	0
KENNEDY 1993	2	MITCHELL 1984	1
MITCHELL 1990	2	MITCHELL 2001	1
POPE 1983	2	POPE 1989	2
ROTHSCHILD 1994	0	SABINE 1983	2
WALSH 1988	2	WALSH 1991	1
WALSH 2000	0		

Sensitivity analyses

These analyses were defined a priori and subsidiary to the main review question, and were based on non-randomised comparisons. The comparison "any drug" versus placebo was used in order to evaluate the main efficacy outcomes (remission and clinical improvement) according to:

(i) Quality of the trial

As only two trials were classified as "A" according to the quality assessment criteria (Wheadon 1992a and Sabine 1983) this comparison was not performed.

(ii) Length of treatment

Remission: Six trials (Horne 1988, Kennedy 1993, Pope 1989, Walsh 1984a, Walsh 1991a and Walsh 1999) reporting this outcome had a duration of up to 8 weeks and four trials had a duration longer than 8 weeks (Agras 1987, Wheadon 1992a, McCann 1990 and). No statistical difference was found between RR and 95% confidence intervals for these two groups of trials (RR= 0.85 [0.78-0.94] versus 0,91 [0.84-0.99]).

Clinical improvement: six trials (Horne 1988, FBNCSG 1992, Kanerva 1994, Kennedy 1988, Pope 1983 and Pope 1989) reporting this outcome had a duration of 6 to 8 weeks and two trials had a duration longer than 8 weeks (Agras 1987 and Wheadon 1992a). No statistical difference was found between RR and 95% confidence intervals for these two groups of trials (RR= 0.6257 [0.5096-0.768] versus 0.5264 [0.2313-1.198]).

(iii) Diagnostic criteria (DSM-III bulimia versus DSM-III-R bulimia nervosa criteria)

Remission: three trials (Agras 1987, Horne 1988 and Walsh 1984a) reporting this outcome used DSM-III criteria and seven trials used DSM-III-R more strict criteria (Wheadon 1992a, Kennedy 1993, McCann 1990, Mitchell 1999c, Pope 1989 , Walsh 1991a and Walsh 1999). No statistical difference was found between RR and 95% confidence intervals for these two groups of trials (RR= 0.79 [0.71-0.88] versus 0.91 [0.86-0.97]). A non significant difference

favouring antidepressants in trials using the less restrictive criteria of DSM-III was observed.
Clinical improvement: four trials (Agras 1987, Horne 1988, Kennedy 1988 and Pope 1983) reporting this outcome used DSM-III criteria and four trials used DSM-III-R criteria (FBNCSG 1992, Wheadon 1992a,Kanerva 1994 and Pope 1989). No statistical difference was found between RR and 95% confidence intervals for these two groups of trials (RR= 0.4575 [0.3372-0.6208] versus 0.6876 [0.6056-0.7808]). A slightly more pronounced difference favouring antidepressants in trials using the less restrictive criteria of DSM-III was observed.

(iv) Bulimic versus purging episodes
Five studies reported remission of binge episodes (Horne 1988, McCann 1990, Pope 1989, Walsh 1984a, Walsh 1991a), one of purge episodes (Agras 1987) and three of both purging and bulimic episodes (Wheadon 1992a, Kennedy 1993 and Walsh 1999). The subgroup analysis confirmed that antidepressants remained superior to placebo when either bingeing or purging was considered the main bulimic symptom (RR =0.86; 95% CI= 0.79-0.94 for bingeing and RR= 0.80; 95% CI= 0.65-0.98 for purging).

(v) Class of drugs
When different classes of antidepressants were compared, approximate 95% confidence intervals for estimates of DL-RR for remission and clinical improvement of bulimic episodes overlapped (TCA= 0.86; 0.7-1.07; SSRI= 0.89; 0.76-1.03; MAOI= 0.81; 0.68-0.96 for remission; and TCA= 0.29; 0.13-0.63; SSRI= 0.68; 0.59-0.79; MAOI= 0.29; 0.07-1.10 for clinical improvement).Therefore, there is no conclusive evidence to support statistically significant differences in efficacy among these different classes of antidepressants.

DISCUSSION

BN is considered a complex and multi factorial clinical condition that may be difficult to treat, with a chronic course. Investigations of drug therapy with antidepressants for bulimia nervosa have been limited by several conceptual and methodological problems, including definition of cases, control of relevant variables and methods of assessment and strategies for treatment outcome trials (Shaw 1990). Many of the papers reviewed lacked important methodological information, such as details about adequacy of randomisation, blinding procedures and reasons for non-completion. Some trials were published more than once, reporting preliminary results and sub-samples with post-hoc analysis. Cross-over studies did not provide information for the first period and carry-over or withdrawn effects were not taken into account. The most frequently reported outcome for efficacy was the mean percent reduction in bulimic episodes, some trials lacking data on standard deviations of this measure. We did not consider this outcome helpful for clinical decision making as it does not translate benefits of treatment. A 70% reduction in binge episodes in the experimental group compared to a 50% reduction in the placebo control group does not help clinicians advise their patients regarding the probability for them of being free of bulimic symptoms or presenting a relevant clinical improvement with that specific drug. Remission and clinical improvement were considered more appropriate outcomes for efficacy. Nevertheless, data could not be obtained for a considerable number of trials. These methodological inconsistencies, added to a possible publication bias, may have altered the differences in efficacy between antidepressants and placebo and should be taken into account in the appraisal of results of the present review.

Concerning generalisation of main findings from this review, bulimia nervosa patients included in the trials seem similar to those seen in clinical settings in terms of age, duration of illness, settings and severity of symptoms. Most studies included strictly defined bulimic patients, according to the diagnostic criteria used at the time of study implementation. Most patients did not present severe depression or other concurrent DSM-IV axis I major disorder. Rates of patients with personality disorders or other conditions (e.g.. multi-impulsive patients, substance abuse) that may be more difficult to treat were not systematically reported. Few adolescents were included in the trials, due to restrictive inclusion criteria regarding age (in general, patients were over 18 years old). However, although the onset of symptoms in bulimia nervosa is during late adolescence, patients usually seek treatment in average five years later (Johnson 1987). Therefore, results of this review should be directed to young adult bulimic patients without severe co-morbidity.

Efficacy
This meta-analysis provides statistical evidence that, in general, a single antidepressant agent is clinically effective for the treatment of BN when compared to placebo, but the effect is modest. Although the differences in terms of definition of illness according to different diagnostic criteria, length of treatment, quality of trials, and classes of drugs, a homogeneous therapeutic effect was found. No statistically significant differential effect regarding efficacy among TCAs, SSRIs, MAOIs and other classes of antidepressants could be demonstrated. Remission rates were low and a considerable fraction of patients did not show a reduction of at least 50% in bulimic symptoms in a short-term. Clinical improvement was consistent for all classes of antidepressants, though most of the patients would still fulfil criteria for BN at the end of the trials.

Acceptability and tolerability
Medication studies without concurrent psychological approaches included in this review confirmed the high dropout rates observed in most trials evaluating single pharmacological treatments, in part because of side effects and in part because of patients' negative attitudes towards medication use. The better acceptability of SSRIs may be related to its short-term effects on appetite and weight (Advokat 1995).

Depression
Even if most patients included in the studies presented low scores in depression rating scales, it is possible that antidepressants have both a direct effect over bulimic symptoms and an effect over depressive symptoms, reducing indirectly the disturbed eating behaviours. However, as individual patient data for concurrent depression was not systematically provided, it was not possible to conclude how depression affected short-term efficacy of antidepressants on bulimic symptoms.

Dose
The doses used in TCAs and MAOIs trials have generally been similar to those employed in the treatment of depression. The only dose-response study conducted was the first multicenter fluoxetine study, which compared a high dose (60 mg) and a low dose (20 mg) of fluoxetine with placebo. The high dose regimen was clearly superior to both other treatments in this trial (FBNCSG 1992). The

other SSRI trials used doses of 60 mg of fluoxetine, which are higher than the usual 20 mg dose used in the treatment of depression.

Relapse and follow-up
Few trials followed patients after this short-term period of double-blind treatment. Two trials reported a significant relapse rate (30-45%) in improved patients followed for 4-6 months (Mitchell 1987a) following patients reported by Mitchell and colleagues (Mitchell 1990; Walsh 1991a). Only one published trial was designed to specifically evaluate prevention of relapse (Fichter 1996b). In this randomised, double-blind, placebo controlled trial, 72 inpatients successfully treated with psychotherapy were randomised to fluvoxamine (SSRI) or placebo for the following 15 weeks (12 as outpatients). Drop-out rates were high (33% or 27 patients, 19 out of 33 randomised to fluvoxamine). Relapse rates were significantly higher for placebo. It was not possible to include data from this maintenance study as it used a different randomisation scheme.

AUTHORS' CONCLUSIONS

Implications for practice

Antidepressants are part of the therapeutic armamentarium for the treatment of bulimia nervosa patients. However, their use as sole therapy does not seem sufficient to effectively treat these patients. Fluoxetine is the most systematically studied antidepressant agent. Even if it is not superior to other drugs in terms of efficacy, its' better acceptability may justify its' use as a first line antidepressant in bulimia nervosa. A daily dose of 60 mg is more effective than antidepressant doses of 20 mg. Eight weeks seems to be an appropriate period to obtain a relevant clinical improvement. If no or only partial response is noted, an alternative therapeutic approach is indicated.

Implications for research

It is of note that the number of studies is declining with time, with little new research since the inception of this review in 1996. There are likely to be several reasons for this, and include the possible greater acceptance of psychotherapy by clinicians and patients and the costs of further trials for the use of medication in areas other than that of their first indication.
The effect of other SSRIs than fluoxetine, as well as newer antidepressants (e.g. venlafaxine, mirtazepine and reboxetine) still need to be studied. Future research should systematically include bulimic patients with co-morbid major depression, personality disorders, substance abuse and other relevant clinical conditions. Other relevant dimensions of response, for example the modulation of the cognitive aspects of bulimia nervosa, namely extreme weight and shape concern, and less specific outcomes such as social functioning and quality of life, should be assessed in future trials. The impact of depression and other co-morbid disorders on prognosis should be evaluated, improving generalization of results. The option of trying a second antidepressant agent to reduce side effects or increase efficacy should also be evaluated. Given the chronic, frequently relapsing course of treated patients, short-term results are of limited clinical value and long-term studies as well as more studies evaluating maintenance of change are needed.
The relative low efficacy of antidepressants in both research and clinical setting has prompted investigators to assess some new and provocative pharmacological approaches, including the 5-HT3 inhibitor ondansetron and the antiepileptic drug topiramate.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agras 1987

Methods	RCT, 16 weeks, drop-outs replaced, standard interviews (15 min), physicians different from measurement team, participants self-monitoring

Agras 1987 *(Continued)*

Participants	DSM-III bulimia, > 18 years old. >= 2 bulimic episodes (binge + purge) 1 week prior the trial. Age: 30,9. Duration of BN: 8,7 years. BDI: 17,8. Purges /w: 11,8
Interventions	Imipramine: 50 mg/3days; 100 mg/4days; 150 mg for 1 week; 200 mg/1 week; 250 mg/1week; 300 mg for the rest of period. Mean: 167 mg versus placebo
Outcomes	Remission Clinical Improvement Change in bulimic symptoms Drop-outs for any cause and side effects Depression: BDI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Carruba 2001

Methods	RCT, 6 weeks, Multicenter in Italy
Participants	77 women aged 18-40 years (mean around 25) diagnosed according DSM IV criteria for Bulimia Nervosa, mean BMI around 20
Interventions	Moclobemide 600 mg/day versus placebo
Outcomes	Binge and vomiting episodes per week Depression: HAM-D Drop-outs for AE and any cause
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

FBNCSG 1992

Methods	Multicenter, multicountry, RCT, 8 weeks, single-blind placebo run in, weekly interviews,
Participants	BN DSM-III-R patients, 3 episodes/week/6 mo. > 18 years old, 85-130% of ideal body weight. Mean age: 27.7(pl);26.4(fl). Binges/w: 11. Purges/w: 11.Weight(kg): 60-61. BMI: 22.5; HDRS: 11.9
Interventions	Fluoxetine 20 and 60 mg (only 60 mg included) versus placebo
Outcomes	Clinical improvement Drop-out due to adverse effects and any cause

FBNCSG 1992 *(Continued)*

	Depr:HDRS
Notes	No psychotherapy but self-monitoring of eating behavior

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Horne 1988

Methods	RCT, D-B, 8 weeks, ITT possible for dichotomic outcomes
Participants	81 Bulimia DSM-III, 3 episodes/week/6 months, BN > 1year, not depressed, 18-55 years old, mean 26(b) and 27(PL), weight=80-130% desirable body weight, mean 57 (b), 60 (pl), duration of BN=6.5 years, binges/week= 12(b)/8.5(pl), HDRS baseline 10.6, patients seeking treatment and advertisement
Interventions	Bupropion 450mg versus placebo, no other concomitant ttt (no psychotherapy)
Outcomes	Remission Clinical improvement Drop-outs dus to adverse events and any cause
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kanerva 1994

Methods	RCT, D-B, 8 weeks, 1 week run-in placebo, self assessments (diaries)
Participants	BN DSM-III-R, > 15 years old, mean 25.2 years, BMI > 16, wight baseline 63 kg, 8 non-purging, duration of illness: 5.7 years, age of onset: 19.6 years old, binges/week baseline=10HDRS baseline: 12
Interventions	Fluoxetine 60 mg versus placebo
Outcomes	Clinical improvement Drop-outs due to adverse events and any cause Depression: HDRS 21 items
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kennedy 1988

Methods	RCT, D-B, 6 weeks, crossover
Participants	Bulimia DSM-III, >= 3 binges/week, BN > 1 year, 18-40 years old, mean 26.4, referred to hospital for ED ttt, 75-125% of ideal body weight, mean 95%, age at onset: 19
Interventions	Isocarboxazida 60 mg (increases of 10 mg, 60 mg by the end of 4 weeks) versus placebo
Outcomes	Clinical improvement
Notes	Lack data for 1st period of crossover.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kennedy 1993

Methods	RCT, D-B, 8 weeks, self-report (diary) and observer reted questionaires, 1 week placebo run-in.
Participants	BN DSM-III-R, women, 85-125% ideal body weight, mean 70.2kg(b)/62.8kg(pl), BMI 26.2(b)/24.2(pl), 18-40 years old, mean 27.6(b)/25.9(pl), referred consultations at the hospital, duration of illness 14 years, binges/week baseline=9, purges/week baseline 10.2(b)/7.5(pl)
Interventions	Brofaromine 175 mg versus placebo
Outcomes	Remission Change in bulimic symptoms Drop-outs due to adverse events and any cause Depression:HDRS 17 item
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

McCann 1990

Methods	RCT, D-B, 12 weeks, follow-up visit week 16. Food diaries. Not ITT
Participants	Non-purging BN DSM-III-R, 2 episode/week/1 years plus overconcern with body shape & weight, women, adverstisement in newspapers and TV. Binges/week baseline= 3.8(d)/2.5(pl), BDI baseline= 12.4; BMI= 31. Weight:90 kg.
Interventions	Desipramine 188mg versus placebo. 25 mg/day 2 days, increasind os 25 mg every 2 days during first week and 5o mg every 2 days second week till maximum tolerated dose up to 300 mg.

McCann 1990 *(Continued)*

Outcomes	Remission Change in bulimic symptoms Drp-outs due to adverse events and any cause Depression: BDI - not ITT
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mitchell 1984

Methods	RCT, D-B, 8 weeks, routine patients in eating disorder clinic
Participants	32 Bulimia, DSM III, > 6 months, age 18-45, median 26(a)/24.5(pl), duration of illness 5 years
Interventions	Amitriptyline versus Placebo. 50 mg 3 days, 100 mg 4 days and then 150 mg.
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mitchell 1990

Methods	RCT, 10 weeks, physicians responsible for medication management were blind to randomization.
Participants	Bulimia DSM-III, 3 episodes/week/6 months, patients being evaluated in ED clinic and advertise-ments. Age 18-40, mean 24, female, 80-120% ideal body weight, mean 107%, duration of illness 6.5 years,binges/week baseline=7,3(i)/ 8,0(pl)/ 9,2(pt)/ 8.4(comb).HDRS baseline=11
Interventions	Imipramine initial dose 50 mg, increments to 200 mg for 2 weeks, maintained for 2 weeks, if necessary 300 mg.CBT= 3 phases. 1= 2 hour sessions for each week 2 weeks: mael planning and CBT techniques. 2=arttempt to interrupt bulimic behaviors begin eating regular meals, use of CBT techniques,5 nights a week, 3 hour sessions, then 2 sessions/week (lecture+diner+psychotherapy). 3= last month: 1 and half hour sessions, exposure and relapse prevention
Outcomes	Relapse Drop-outs due to any cause
Notes	

Risk of bias

Mitchell 1990 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mitchell 1999c

Methods	RCT, 16 weeks, D-B, 4 comparison groups
Participants	DSM-III-R, 91 adult women, mean age: 26.6 years old
Interventions	Fluoxetine 60 mg, placebo
Outcomes	Remission
Notes	Data provide by author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pope 1983

Methods	RCT, D-B, 6 weeks
Participants	22 Bulimia DSM-III, 16-55 years old, mean 27.7. Inclusion criteria: 2 binges/week followed by purging, BN > 1 year. Recruitment from advertisements and referrals, weight between 80-115% normal weight.
Interventions	Imipramine 200mg versus placebo
Outcomes	Clinical improvement Deterioration Change in bulimic symptoms Drop-outs due to adverse events and any cause Depression: HDRS (difference or change from baseline to endpoint)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pope 1989

Methods	RCT, D-B, 6 weeks, 2 weeks wash out placebo run-in,

Pope 1989 *(Continued)*

Participants	BN DSM-III-R + 3 episodes/week/6 months, age 18-55, mean 26, weight 80-140% of ideal weight, mean 98.3%, purging type, from advertisements, baseline=12 binges/week, duration of BN=7.4 years
Interventions	Trazodone 355 mg (maximum 400 mg) versus placebo, increasing dose of 50 mg every 2 days
Outcomes	Remission Clinical improvement Drop-outs due to adverse events and any cause Depression (differene baseline-endpoint): HDRS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rothschild 1994

Methods	RCT, D-B, 6 weeks after 10 day placebo period, raters blind to ttt
Participants	Patients with atypic depression and BN diagnosed post-hoc according to DSM-III criteria. Age: 32.8. Binges/week baseline=5.2. HDRS baseline= 15.2
Interventions	Phenelzine 45mg versus imipramine 150mg versus placebo
Outcomes	Clinical improvement (not ITT) Depression: HDRS (21 items)
Notes	Retrospective data!!

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sabine 1983

Methods	RCT, D-B, 8 weeks
Participants	50 bulimic female patients referred to a hospital, 1-2 episodes/week+ preoccupation with food, fear of fatness, weight... Russell's criteria!! Age=16-65, mean 22.4(m) / 25(pl), weight in kg= 63.3(m) / 61 (pl)
Interventions	Mianserin 30-60 mg versus placebo
Outcomes	Drop-outs due to any cause
Notes	

Risk of bias

Sabine 1983 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Walsh 1984a

Methods	RCT, D-B, 8 weeks, single-blind plecebo phase of 2 weeks, diary, seen weekly
Participants	Bulimia DSM III + 3 episodes/week, 18-45 years old, mean 27, women, 80-120% ideal body weight, referral from therapists and advertisements. Duration of illness= 9.0-9.8 years, mean binges baseline= 11.9(ph) / 9.2 (pl), HDRS= 10.8 (ph) / 7.5 (pl) :significant difference
Interventions	Phenelzine 60-90 mg versus placebo. 30 mg first weeks, 60 mg 2nd week, 90 mg by week 6.
Outcomes	Remission Change in bulimic symptoms Drop-outs due to adverse events and any cause Depression: HDRS 17 items
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Walsh 1991a

Methods	RCT, D-B, 6 weeks, 2 week single blind wash out placebo, 30 min weekly sessions, diary
Participants	80 BN DSM-III-R for 1 year, 18-45 years old, mean 25, 85-120% ideal weight, mean 134 lb, BMI 22, trough advertisements, duration of illness=6.6 years, binges/week baseline=8, HDRS baseline 7.3(pl) / 8.3 (d), BDI 15(pl) / 10.4 (d): signifficant difference
Interventions	Desipramine 200-300 mg versus placebo. 200 mg till week 4, 300 if not better.
Outcomes	Remission Change in bulimic symptoms Drop-outs due to any cause and adverse events Depression: BDI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Walsh 1999

Methods	RCT, two sites in US, D-B 8 weeks, following poor response to psychotherapy
Participants	22 patients diagnosed according DSM-III-R criteria, purging type self-inducing vomiting at once a week over 1 month
Interventions	Fluoxetine 60 mg/day versus placebo
Outcomes	Remission, depression (BDI)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Wheadon 1992

Methods	RCT, D-B, 16 weeks, ITT, multicenter, run-in one week period, sample size calculation
Participants	BN DSM-III-R, >= 3 episodes of vomiting/week, BN for 6 months, > 18 years old, 96.2% women, 96.7% white, age: 27, weight: 58kg, vomiting/week baseline: 9, binges/week baseline: 9, median days /week binges:6
Interventions	Fluoxetine 60 mg versus placebo
Outcomes	Remission Clinical improvement Drop-outs due to adverse events and any cause
Notes	Median number of binges/purges and median scores of HDRS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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

Study	Reason for exclusion
Agras 1992	No placebo control group.
Agras 1994	No placebo control group
Alger 1991	Separate data for bulimic and BED patients not obtained
Barlow 1988	Data for first phase of crossover not obtained

Study	Reason for exclusion
Blouin 1988	Data for first phase of crossover not obtained
Box 1983	Not BN patients.
Fichter 1991	Antidepressants plus psychotherapy versus psychotherapy plus placebo. Absence of "drug versus placebo alone" comparisons.
Fichter 1996	Additional report of Fichter 1991.
Goldbloom 1996	No placebo control group. Ads versus psychotherapy.
Hahn 1989	Letter discussin Horne 1988 trial.
Hughes 1986a	No data for any outcome obtained
Kennedy 1986	Letter with subset data of Kennedy 1988.
Koran 1995	Not BN patients
Leitenberg 1994	No placebo control group. Control=CBT
Marcus 1990	Paper did not provide separate data for obese bulimic and non bulimic patients. Author contacted, did not provide data.
Margittai 1987	Subset of Barlow 1988. Evaluation of drop-outs of crossover study not providing data for first period.
Mitchell 1987a	Subset of Mitchell 1990. 6-month follow-up maintenance data.
Price 1987	Letter to the editor. Not described as RCT. Phenelzine study. No address from authors to contact.
Russell 1995b	No placebo control group. Ads versus psychotherapy.
Scrimali 1994	No placebo control group. Control=no drug, only diet
Walsh 1984	Subset of Walsh 1988. Partial data on phenelzine trial.
Walsh 1992	Subset of Walsh 1991. Pulse and blood pressure analysis from desipramine trial.
Walsh 1997	No placebo group. Controls= CBT & SPT

DATA AND ANALYSES

Comparison 1. Antidepressants versus placebo

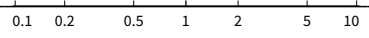
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	10	824	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.84, 0.94]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Tricyclics versus placebo	3	132	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.07]
1.2 SSRIs versus placebo	3	467	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.02]
1.3 MAOIs versus placebo	2	98	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.68, 0.96]
1.4 Other antidepressants versus placebo	2	127	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.76, 0.97]
2 Clinical improvement	8	901	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.54, 0.74]
2.1 Tricyclics versus placebo	2	44	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.13, 0.63]
2.2 SSRIs versus placebo	3	706	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.59, 0.79]
2.3 MAOIs versus placebo	1	24	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.07, 1.10]
2.4 Other antidepressants versus placebo	2	127	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.45, 0.83]
3 Difference in bulimic sypmtoms	6	259	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.94, 0.44]
3.1 Tricyclics versus placebo	3	121	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.12, -0.38]
3.2 SSRIs versus placebo	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 MAOIs versus placebo	3	138	Std. Mean Difference (IV, Random, 95% CI)	0.22 [-0.94, 1.37]
3.4 Other antidepressants versus placebo	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Drop-outs due to adverse events	13	1200	Risk Ratio (M-H, Random, 95% CI)	1.65 [1.05, 2.57]
4.1 Tricyclics versus placebo	5	192	Risk Ratio (M-H, Random, 95% CI)	2.38 [0.76, 7.45]
4.2 SSRIs versus placebo	3	706	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.83, 2.75]
4.3 MAOIs versus placebo	3	175	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.45, 9.53]
4.4 Other antidepressants versus placebo	2	127	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.28, 7.95]
5 Drop-outs due to any cause	15	1335	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.78, 1.24]
5.1 Tricyclics versus placebo	6	277	Risk Ratio (M-H, Random, 95% CI)	1.93 [1.15, 3.25]
5.2 SSRIs versus placebo	3	706	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.68, 0.99]
5.3 MAOIs versus placebo	3	175	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.61, 1.45]
5.4 Other antidepressants versus placebo	3	177	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.48, 1.83]

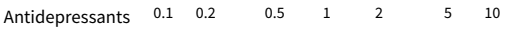
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6 Difference in depression	8	323	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.41, 0.03]
6.1 Tricyclics versus placebo	3	121	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.55, 0.17]
6.2 SSRIs versus placebo	1	46	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-1.03, 0.14]
6.3 MAOIs versus placebo	4	156	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.50, 0.22]

Analysis 1.1. Comparison 1 Antidepressants versus placebo, Outcome 1 Remission.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Tricyclics versus placebo					
Agras 1987	7/10	11/12		1.61%	0.76[0.49,1.19]
McCann 1990	9/15	13/15		1.48%	0.69[0.44,1.09]
Walsh 1991a	36/41	36/39		14.22%	0.95[0.82,1.1]
Subtotal (95% CI)	**66**	**66**		**17.31%**	**0.86[0.7,1.07]**
Total events: 52 (Treatment), 60 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=2.88, df=2(P=0.24); I^2=30.58%					
Test for overall effect: Z=1.35(P=0.18)					
1.1.2 SSRIs versus placebo					
Mitchell 1999c	22/26	19/21		6.66%	0.94[0.75,1.16]
Walsh 1999	8/13	9/9		1.57%	0.64[0.41,1]
Wheadon 1992	241/296	90/102		35.78%	0.92[0.84,1.01]
Subtotal (95% CI)	**335**	**132**		**44.02%**	**0.9[0.8,1.02]**
Total events: 271 (Treatment), 118 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.62, df=2(P=0.27); I^2=23.6%					
Test for overall effect: Z=1.66(P=0.1)					
1.1.3 MAOIs versus placebo					
Kennedy 1993	15/19	15/17		3.68%	0.89[0.67,1.2]
Walsh 1984a	23/31	30/31		6.51%	0.77[0.62,0.95]
Subtotal (95% CI)	**50**	**48**		**10.19%**	**0.81[0.68,0.96]**
Total events: 38 (Treatment), 45 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.7, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=2.37(P=0.02)					
1.1.4 Other antidepressants versus placebo					
Horne 1988	44/55	26/26		14.76%	0.81[0.7,0.93]
Pope 1989	21/23	23/23		13.72%	0.91[0.79,1.06]
Subtotal (95% CI)	**78**	**49**		**28.48%**	**0.86[0.76,0.97]**
Total events: 65 (Treatment), 49 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.38, df=1(P=0.24); I^2=27.48%					

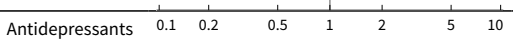


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=2.46(P=0.01)					
Total (95% CI)	**529**	**295**		**100%**	**0.89[0.84,0.94]**
Total events: 426 (Treatment), 272 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.2, df=9(P=0.42); I^2=2.16%					
Test for overall effect: Z=4.28(P<0.0001)					
Test for subgroup differences: Not applicable					

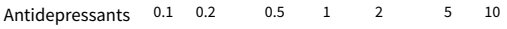


Analysis 1.2. Comparison 1 Antidepressants versus placebo, Outcome 2 Clinical improvement.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Tricyclics versus placebo					
Agras 1987	2/10	9/12		1.41%	0.27[0.07,0.96]
Pope 1983	3/11	10/11		2.35%	0.3[0.11,0.8]
Subtotal (95% CI)	**21**	**23**		**3.76%**	**0.29[0.13,0.63]**
Total events: 5 (Treatment), 19 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%					
Test for overall effect: Z=3.13(P=0)					
1.2.2 SSRIs versus placebo					
FBNCSG 1992	49/129	74/129		20.91%	0.66[0.51,0.86]
Kanerva 1994	12/24	15/26		7.63%	0.87[0.52,1.45]
Wheadon 1992	137/296	70/102		31.61%	0.67[0.56,0.81]
Subtotal (95% CI)	**449**	**257**		**60.16%**	**0.68[0.59,0.79]**
Total events: 198 (Treatment), 159 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.88, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=5.21(P<0.0001)					
1.2.3 MAOIs versus placebo					
Kennedy 1988	2/12	7/12		1.27%	0.29[0.07,1.1]
Subtotal (95% CI)	**12**	**12**		**1.27%**	**0.29[0.07,1.1]**
Total events: 2 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.82(P=0.07)					
1.2.4 Other antidepressants versus placebo					
Horne 1988	24/55	22/26		14.85%	0.52[0.37,0.73]
Pope 1989	16/23	23/23		19.96%	0.7[0.53,0.93]
Subtotal (95% CI)	**78**	**49**		**34.81%**	**0.61[0.45,0.83]**
Total events: 40 (Treatment), 45 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=2.02, df=1(P=0.16); I^2=50.53%					
Test for overall effect: Z=3.1(P=0)					
Total (95% CI)	**560**	**341**		**100%**	**0.64[0.54,0.74]**
Total events: 245 (Treatment), 230 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=9.28, df=7(P=0.23); I^2=24.56%					
Test for overall effect: Z=5.77(P<0.0001)					

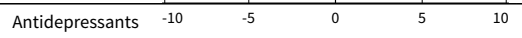


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Not applicable					



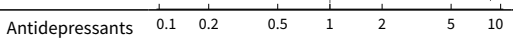
Analysis 1.3. Comparison 1 Antidepressants versus placebo, Outcome 3 Difference in bulimic sypmtoms.

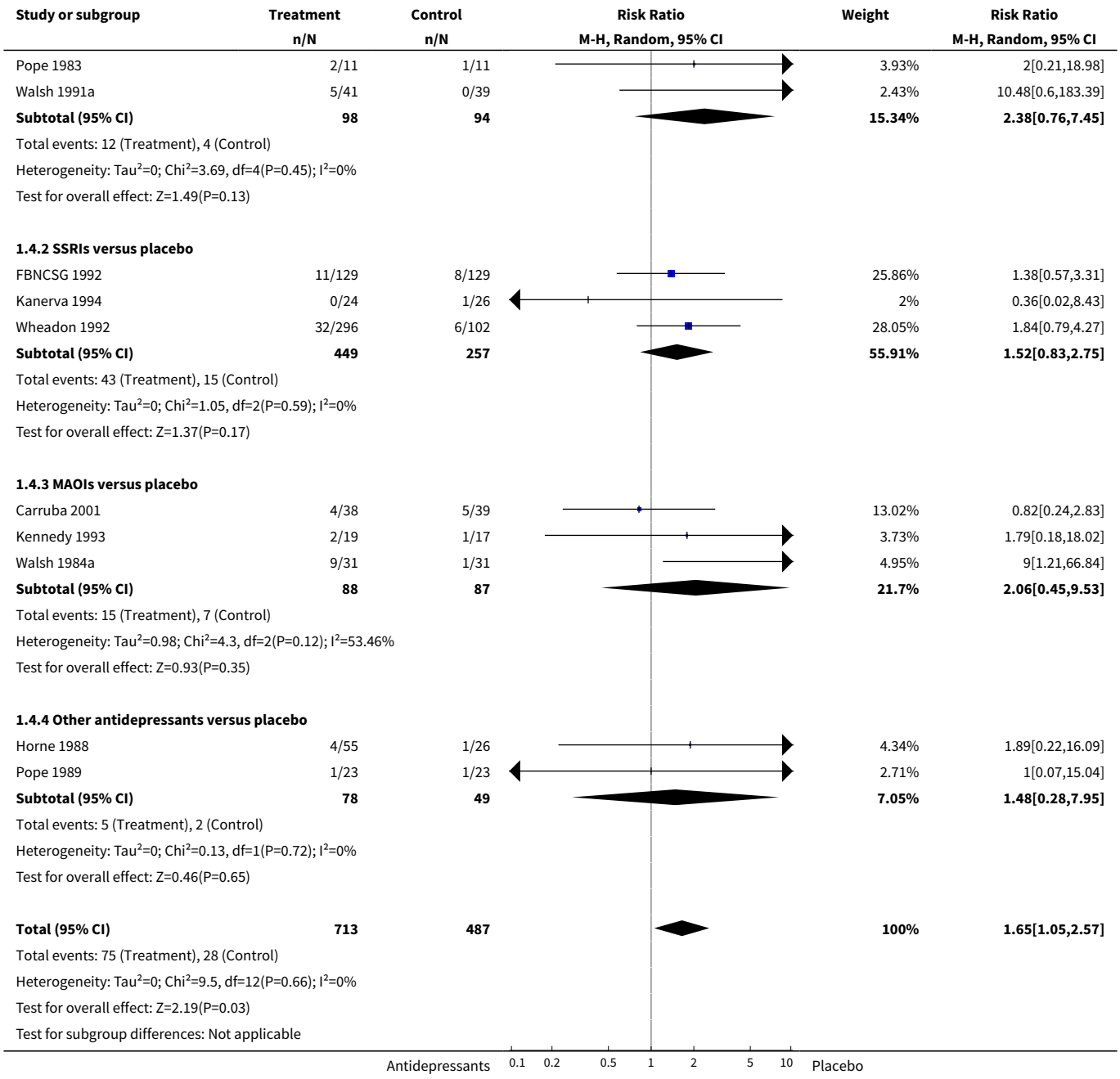
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.3.1 Tricyclics versus placebo							
Agras 1987	10	3 (4.1)	10	8.2 (8.3)		14.78%	-0.76[-1.67,0.16]
McCann 1990	10	1.4 (2.2)	13	3.7 (3.4)		15.25%	-0.75[-1.61,0.11]
Walsh 1991a	40	4.3 (3.9)	38	8.6 (7.2)		18.29%	-0.74[-1.2,-0.28]
Subtotal ***	**60**		**61**			**48.32%**	**-0.75[-1.12,-0.38]**
Heterogeneity: Tau^2=0; Chi^2=0, df=2(P=1); I^2=0%							
Test for overall effect: Z=3.94(P<0.0001)							
1.3.2 SSRIs versus placebo							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.3.3 MAOIs versus placebo							
Carruba 2001	28	4.8 (0.8)	24	3.6 (1)		17.23%	1.38[0.77,1.99]
Kennedy 1993	19	3.5 (3)	17	4.4 (3.9)		16.88%	-0.25[-0.91,0.4]
Walsh 1984a	23	5.4 (7.1)	27	8.4 (5.5)		17.57%	-0.47[-1.03,0.09]
Subtotal ***	**70**		**68**			**51.68%**	**0.22[-0.94,1.37]**
Heterogeneity: Tau^2=0.95; Chi^2=21.59, df=2(P<0.0001); I^2=90.74%							
Test for overall effect: Z=0.37(P=0.71)							
1.3.4 Other antidepressants versus placebo							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**130**		**129**			**100%**	**-0.25[-0.94,0.44]**
Heterogeneity: Tau^2=0.63; Chi^2=34.82, df=5(P<0.0001); I^2=85.64%							
Test for overall effect: Z=0.71(P=0.48)							
Test for subgroup differences: Chi^2=13.22, df=1 (P=0), I^2=92.44%							



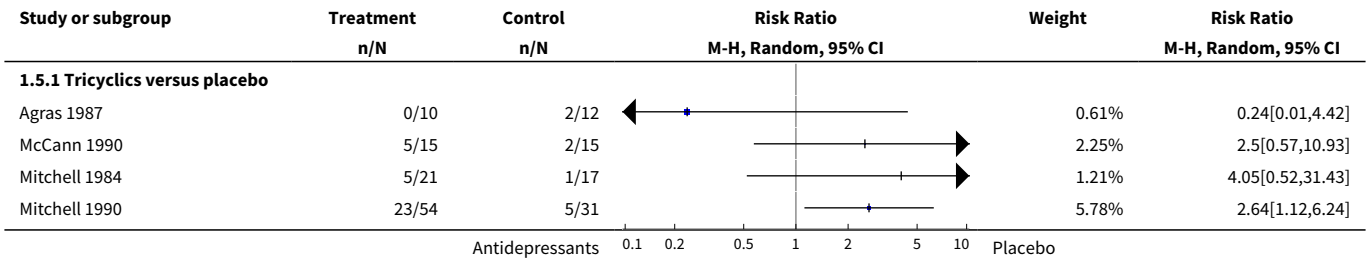
Analysis 1.4. Comparison 1 Antidepressants versus placebo, Outcome 4 Drop-outs due to adverse events.

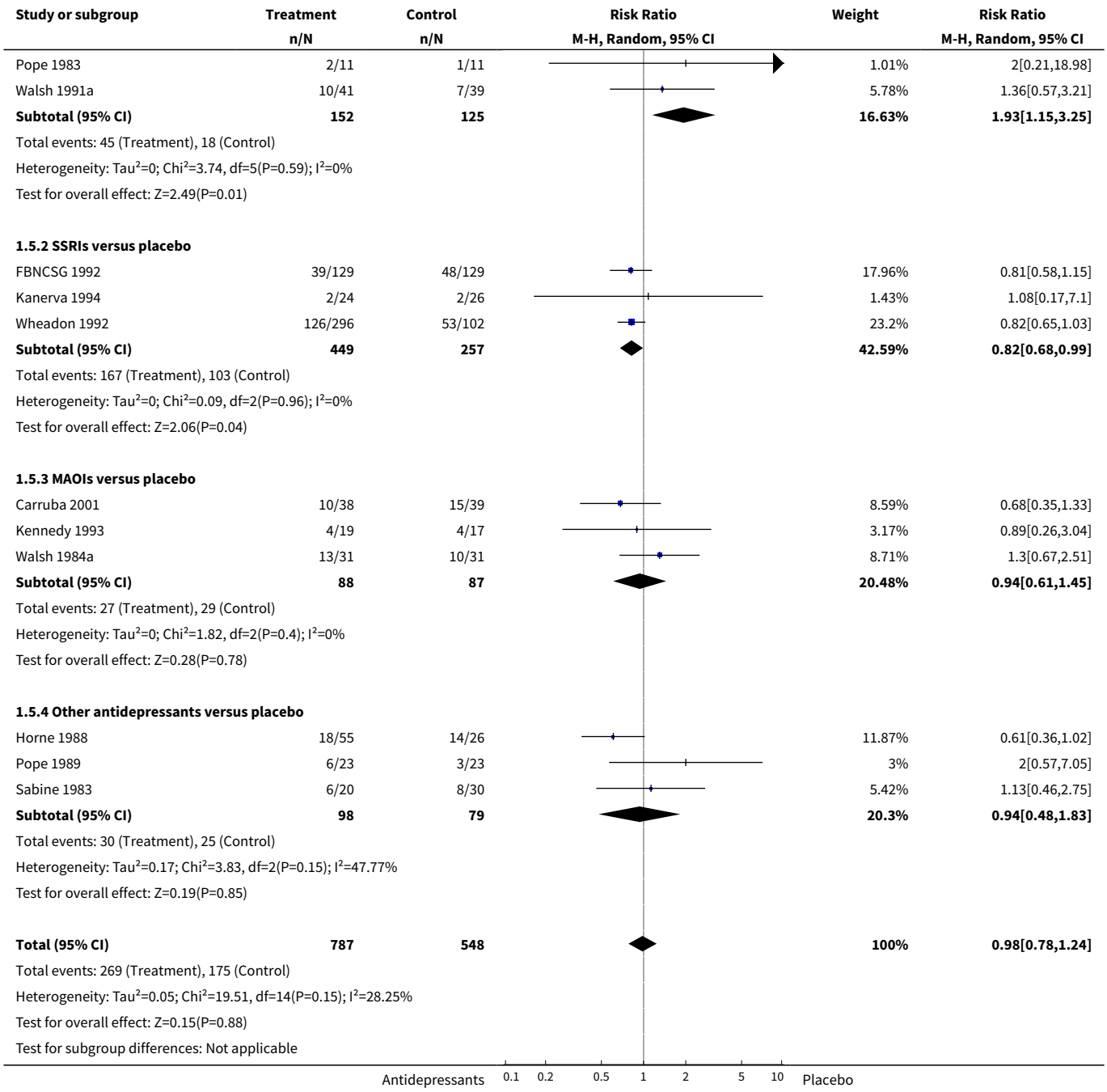
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Tricyclics versus placebo					
Agras 1987	0/10	2/12		2.32%	0.24[0.01,4.42]
McCann 1990	4/15	1/15		4.64%	4[0.5,31.74]
Mitchell 1984	1/21	0/17		2.02%	2.45[0.11,56.68]



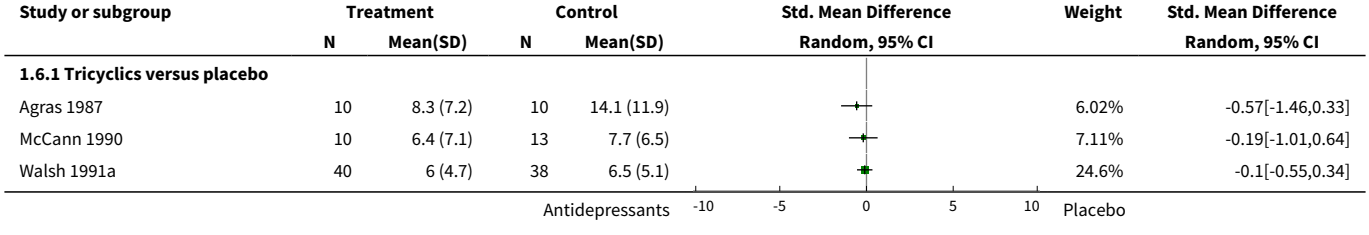


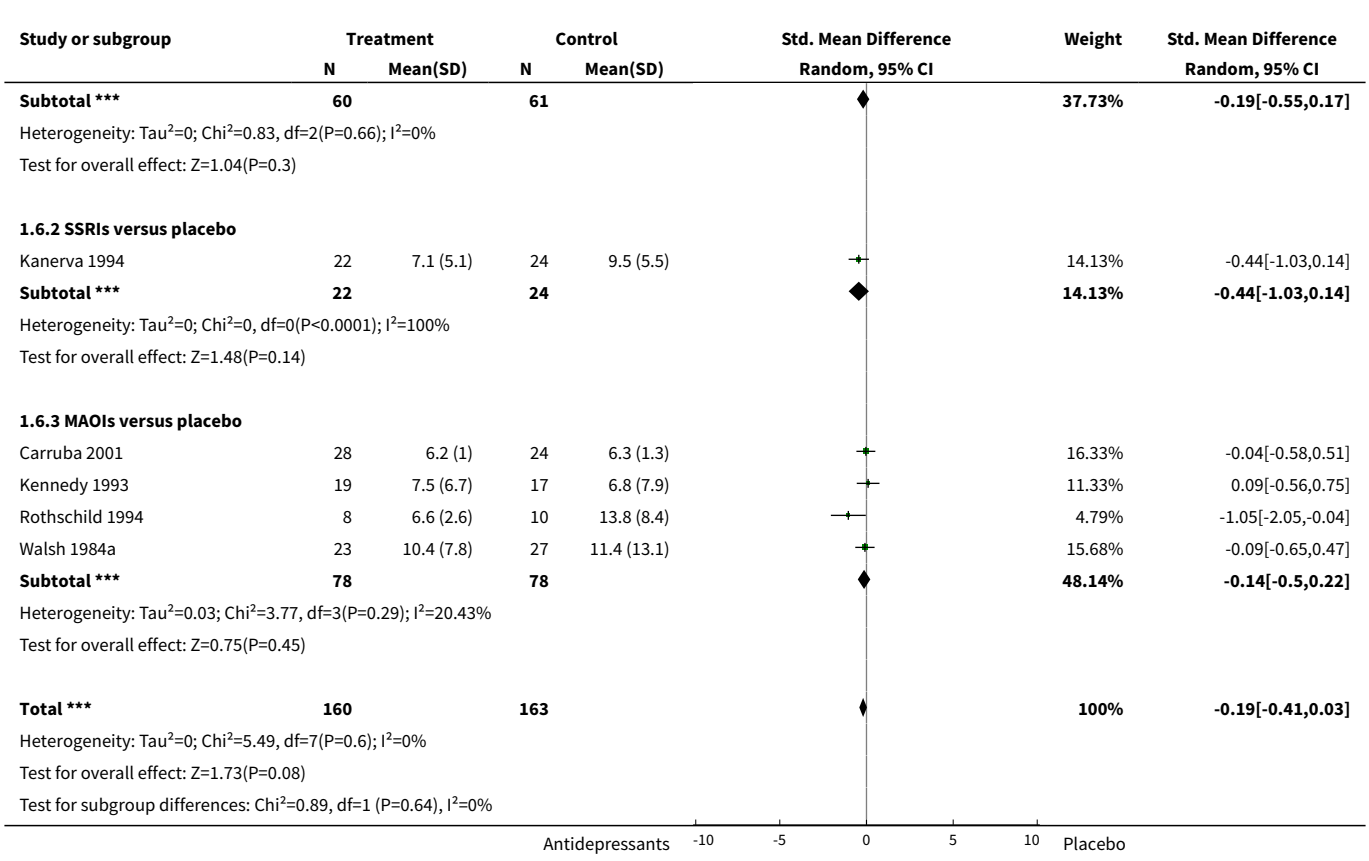
Analysis 1.5. Comparison 1 Antidepressants versus placebo, Outcome 5 Drop-outs due to any cause.





Analysis 1.6. Comparison 1 Antidepressants versus placebo, Outcome 6 Difference in depression.





Comparison 2. Length of treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 6 to 8 weeks	6	327	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.79, 0.94]
1.2 More than 8 weeks	4	497	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.84, 0.99]
2 Clinical Improvement	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 6 to 8 weeks	6	481	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.51, 0.77]
2.2 More than 8 weeks	2	420	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.23, 1.20]

Analysis 2.1. Comparison 2 Length of treatment, Outcome 1 Remission.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 6 to 8 weeks					
Horne 1988	44/55	26/26		27.1%	0.81[0.7,0.93]
Kennedy 1993	15/19	15/17		6.76%	0.89[0.67,1.2]
Pope 1989	21/23	23/23		25.19%	0.91[0.79,1.06]
Walsh 1984a	23/31	30/31		11.95%	0.77[0.62,0.95]
Walsh 1991a	36/41	36/39		26.1%	0.95[0.82,1.1]
Walsh 1999	8/13	9/9		2.89%	0.64[0.41,1]
Subtotal (95% CI)	**182**	**145**		**100%**	**0.86[0.79,0.94]**
Total events: 147 (Treatment), 139 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.31, df=5(P=0.28); I^2=20.77%					
Test for overall effect: Z=3.35(P=0)					
2.1.2 More than 8 weeks					
Agras 1987	7/10	11/12		3.53%	0.76[0.49,1.19]
McCann 1990	9/15	13/15		3.25%	0.69[0.44,1.09]
Mitchell 1999c	22/26	19/21		14.64%	0.94[0.75,1.16]
Wheadon 1992	241/296	90/102		78.58%	0.92[0.84,1.01]
Subtotal (95% CI)	**347**	**150**		**100%**	**0.91[0.84,0.99]**
Total events: 279 (Treatment), 133 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.24, df=3(P=0.52); I^2=0%					
Test for overall effect: Z=2.29(P=0.02)					

Analysis 2.2. Comparison 2 Length of treatment, Outcome 2 Clinical Improvement.

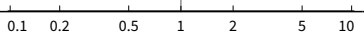
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 6 to 8 weeks					
FBNCSG 1992	49/129	74/129		31.22%	0.66[0.51,0.86]
Horne 1988	24/55	22/26		22.18%	0.52[0.37,0.73]
Kanerva 1994	12/24	15/26		11.4%	0.87[0.52,1.45]
Kennedy 1988	2/12	7/12		1.89%	0.29[0.07,1.1]
Pope 1983	3/11	10/11		3.52%	0.3[0.11,0.8]
Pope 1989	16/23	23/23		29.8%	0.7[0.53,0.93]
Subtotal (95% CI)	**254**	**227**		**100%**	**0.63[0.51,0.77]**
Total events: 106 (Treatment), 151 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=7.09, df=5(P=0.21); I^2=29.52%					
Test for overall effect: Z=4.48(P<0.0001)					
2.2.2 More than 8 weeks					
Agras 1987	2/10	9/12		4.27%	0.27[0.07,0.96]
Wheadon 1992	137/296	70/102		95.73%	0.67[0.56,0.81]
Subtotal (95% CI)	**306**	**114**		**100%**	**0.53[0.23,1.2]**
Total events: 139 (Treatment), 79 (Control)					
Heterogeneity: Tau^2=0.23; Chi^2=2.06, df=1(P=0.15); I^2=51.54%					
Test for overall effect: Z=1.53(P=0.13)					

Comparison 3. Diagnostic criteria applied in trials: DSM-III vs DSM-III-R

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 DSM-III	3	165	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.71, 0.89]
1.2 DSM-III-R	7	659	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.86, 0.97]
2 Clinical improvement	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 DSM-III	4	149	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.34, 0.62]
2.2 DSM-III-R	4	752	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.61, 0.78]

Analysis 3.1. Comparison 3 Diagnostic criteria applied in trials: DSM-III vs DSM-III-R, Outcome 1 Remission.

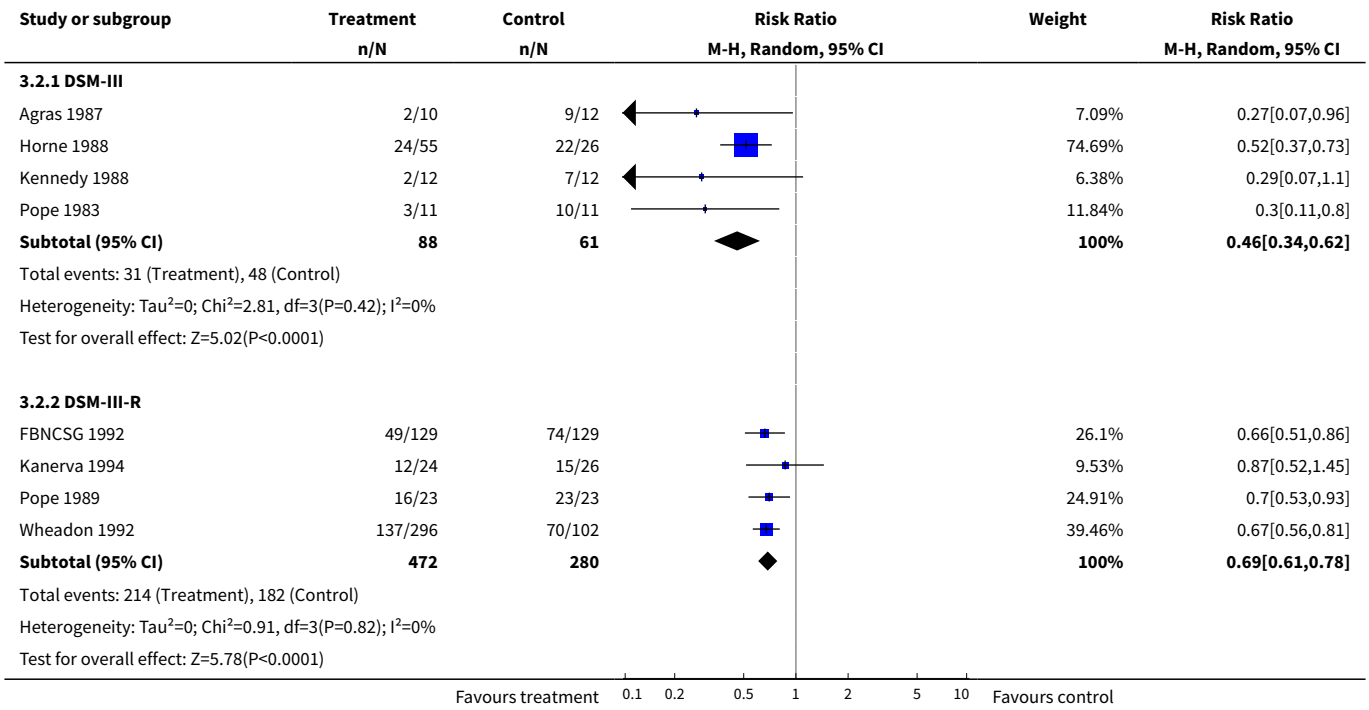
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 DSM-III					
Agras 1987	7/10	11/12		7.02%	0.76[0.49,1.19]
Horne 1988	44/55	26/26		64.53%	0.81[0.7,0.93]
Walsh 1984a	23/31	30/31		28.45%	0.77[0.62,0.95]
Subtotal (95% CI)	**96**	**69**		**100%**	**0.79[0.71,0.89]**
Total events: 74 (Treatment), 67 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.23, df=2(P=0.89); I^2=0%					
Test for overall effect: Z=3.92(P<0.0001)					
3.1.2 DSM-III-R					
Kennedy 1993	15/19	15/17		4.78%	0.89[0.67,1.2]
McCann 1990	9/15	13/15		1.92%	0.69[0.44,1.09]
Mitchell 1999c	22/26	19/21		8.64%	0.94[0.75,1.16]
Pope 1989	21/23	23/23		17.79%	0.91[0.79,1.06]
Walsh 1991a	36/41	36/39		18.44%	0.95[0.82,1.1]
Walsh 1999	8/13	9/9		2.04%	0.64[0.41,1]
Wheadon 1992	241/296	90/102		46.39%	0.92[0.84,1.01]
Subtotal (95% CI)	**433**	**226**		**100%**	**0.91[0.86,0.97]**
Total events: 352 (Treatment), 205 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.51, df=6(P=0.61); I^2=0%					
Test for overall effect: Z=2.82(P=0)					



Favours treatment

Favours control

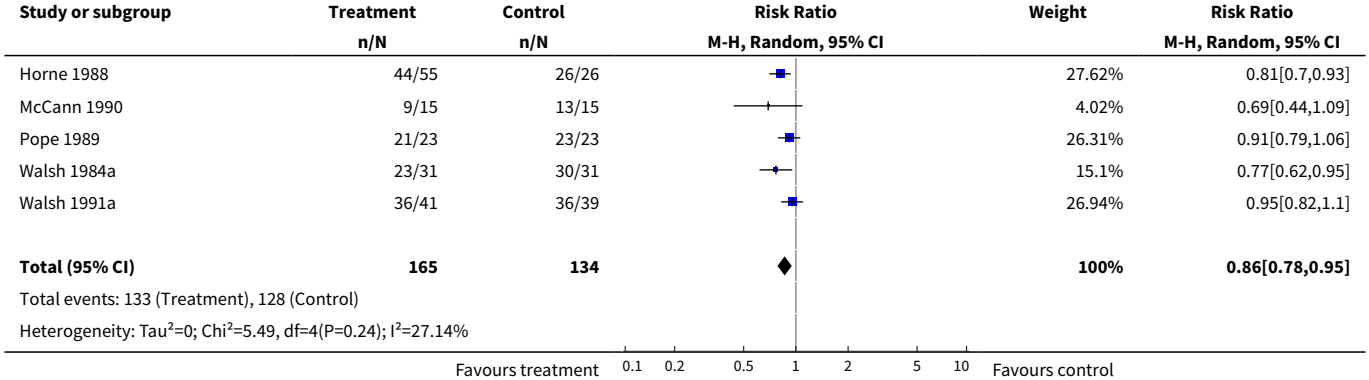
Analysis 3.2. Comparison 3 Diagnostic criteria applied in trials: DSM-III vs DSM-III-R, Outcome 2 Clinical improvement.

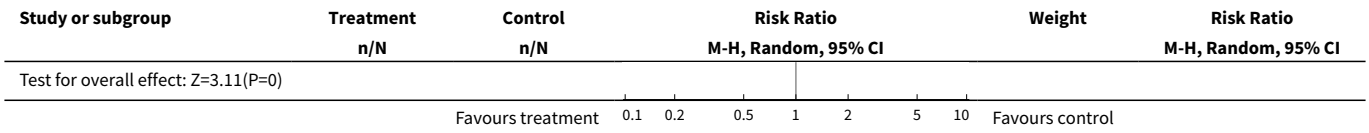


Comparison 4. Binge-eating versus Purging episodes reported as a measure of recovery

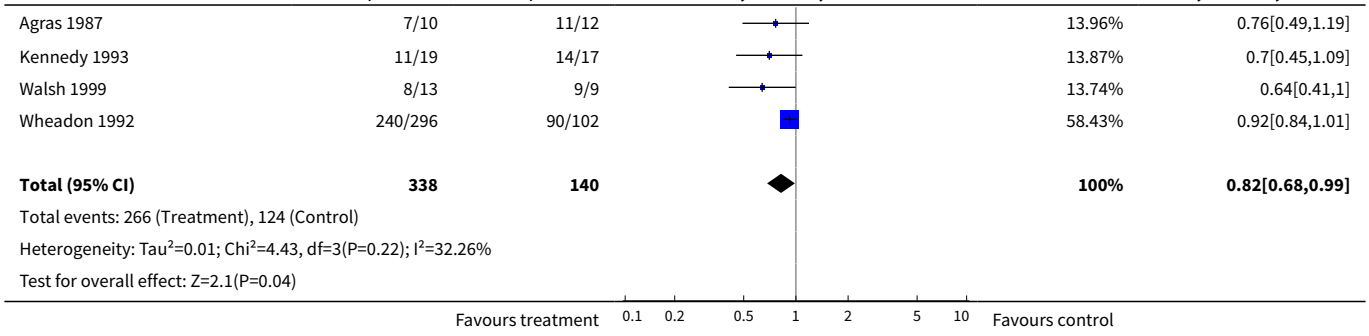
Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 Binge	5	299	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.78, 0.95]
2 Purge	4	478	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.68, 0.99]

Analysis 4.1. Comparison 4 Binge-eating versus Purging episodes reported as a measure of recovery, Outcome 1 Binge.





Analysis 4.2. Comparison 4 Binge-eating versus Purging episodes reported as a measure of recovery, Outcome 2 Purge.



WHAT'S NEW

Date	Event	Description
1 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1999
Review first published: Issue 4, 2001

Date	Event	Description
11 August 2003	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None

JB has received fees from Janssen-Cilag Farmaceutica, Brazil. PH has received support to attend conferences and meetings from Pfizer PTY Ltd, Solvay Pharmaceuticals and Bristol-Myers Squibb Pharmaceuticals.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Bulimia [*drug therapy]; Placebo Effect; Randomized Controlled Trials as Topic

MeSH check words

Humans