Antidepressants for anorexia nervosa (Review)

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[Intervention Review]

Antidepressants for anorexia nervosa

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ABSTRACT

Background

Anorexia Nervosa (AN) is an illness characterised by extreme concern about body weight and shape, severe self-imposed weight loss, and endocrine dysfunction. In spite of its high mortality, morbidity and chronicity, there are few intervention studies on the subject.

Objectives

The aim of this review was to evaluate the efficacy and acceptability of antidepressant drugs in the treatment of acute AN.

Search methods

The strategy comprised of database searches of the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register, MEDLINE (1966 to April 28th, 2005), EMBASE (1980 to week 36, 2004), PsycINFO (1969 to August week 5, 2004), handsearching the International Journal of Eating Disorders and searching the reference lists of all papers selected. Personal letters were sent to researchers in the field requesting information on unpublished or in-progress trials.

Selection criteria

All randomised controlled trials of antidepressant treatment for AN patients, as defined by the Diagnostic and Statistical Manual, fourth edition (DSM-IV) or similar international criteria, were selected.

Data collection and analysis

Quality ratings were made giving consideration to the strong relationship between allocation concealment and potential for bias in the results; studies meeting criteria A and B were included. Trials were excluded if non-completion rates were above 50%. The standardised mean difference and relative risk were used for continuous data and dichotomous data comparisons, respectively. Whenever possible, analyses were performed according to intention-to-treat principles. Heterogeneity was tested with the I-squared statistic. Weight change was the primary outcome. Secondary outcomes were severity of eating disorder, depression and anxiety symptoms, and global clinical state. Acceptability of treatment was evaluated by considering non-completion rates.

Main results

Only seven studies were included. Major methodological limitations such as small trial size and large confidence intervals decreased the power of the studies to detect differences between treatments, and meta-analysis of data was not possible for the majority of outcomes. Four placebo-controlled trials did not find evidence that antidepressants improved weight gain, eating disorder or associated psychopathology. Isolated findings, favouring amineptine and nortriptyline, emerged from the antidepressant versus antidepressant comparisons, but cannot be conceived as evidence of efficacy of a specific drug or class of antidepressant in light of the findings from the placebo comparisons. Non-completion rates were similar between the compared groups.

Authors' conclusions

A lack of quality information precludes us from drawing definite conclusions or recommendations on the use of antidepressants in acute AN. Future studies testing safer and more tolerable antidepressants in larger, well designed trials are needed to provide guidance for clinical practice.

PLAIN LANGUAGE SUMMARY

Antidepressants for anorexia nervosa

The aim of the present review was to evaluate the evidence from randomised controlled trials for the efficacy and acceptability of antidepressant treatment in acute AN. Seven small studies were identified; four placebo-controlled trials did not find evidence of efficacy of antidepressants in improving weight gain, eating disorder or associated symptoms, as well as differences in completion rates. Meta-analysis of data was not possible for most outcomes. However, major methodological limitations of these studies (e.g. insufficient power to detect differences) prevent from drawing definite conclusions or recommendations for antidepressant use in acute AN. Further studies testing safer antidepressants in larger and well designed trials are needed to guide clinical practice.

BACKGROUND

Anorexia nervosa (AN) is an illness characterised by extreme concern about body weight, with serious disturbances in eating behaviour leading to a self-imposed starvation state with severe weight loss. The current psychiatric classification manuals, Diagnostic and Statistical Manual, fourth edition (DSM-IV-TR) (APA 2000) and International Classification of Diseases, revision 10 (ICD-10) (WHO 1992), have based their criteria for AN diagnosis on the following aspects: (a) refusal to maintain weight within the normal range for height and age; (b) fear of weight gain; (c) body image disturbance and (d) absence of menstrual cycles or amenorrhoea in women (and loss of sexual interest in men). Body image becomes the predominant measure of self-worth, with concomitant denial of the seriousness of the illness. In DSM-IV-TR, two types of AN are described: the restricting type (in which the main feature is severe restriction of food intake and often excessive exercise), and the binge-purge type (in which patients regularly eat large amounts of food in a short period of time and/or engage in compensatory behaviours such as vomiting). As well as the impact on psychological wellbeing, AN has notable and sometimes fatal medical consequences from the effects of starvation and purging behaviours. In particular, growth and development are often delayed when AN occurs in childhood or early adolescence (Wiseman 1998).

Although AN is not a common condition in the population as a whole, its morbidity and mortality are amongst the highest of all functional psychiatric disorders due to malnutrition, purging behaviour and suicide. In outcome reviews, a mean crude mortality rate of 5% (Steinhausen 2002; Sullivan 1995) and standardised mortality rates between 1.36% and 17.80% (indicating a slight to an almost 18-fold increase in mortality in patients with AN) have been reported (Nielsen 1998). AN affects mainly adolescent girls and young women and is up to ten times more common in women than in men. It has a point prevalence of no more than 0.5% within this group (Aalto-Setala 2001; Verhulst 1997). A systematic review of 12 cumulative incidence studies reported an estimated mean yearly incidence in the general population of 18.5/100.000 (standard deviation (SD) = 21.01) in women and 2.25/100.000 (SD = 2.63) in men (Pawluck 1998). Increases in incidence of AN in young women over the second half of the 20th century have been reported (Lucas 1991; Pawluck 1998).

The aetiology of AN is thought to be multi-factorial (Jacobi 2004; Schmidt 2003; Collier 2004) and involves environmental factors (social and cultural factors), psychological and developmental aspects, and biological/genetic vulnerabilities. As yet it is not known how these factors interact in the development of eating disorders. Great emphasis has been given to sociocultural explanations in the last decades, such as pressure to be slim, with slenderness as a measure of beauty (Stice 2002), and modernisation processes in cultures in transition associated with confused gender roles and identities (Nasser 2000). The advent of new biotechnologies (neuroimaging, molecular biology) has led to a growing interest in putative biological components of the aetiology of eating disorders (Schmidt 2003), especially to the genetic contribution (Bulik 2000; Wade 2000).

It is known that AN and bulimia nervosa (BN) cluster in families. One controlled family study found that female relatives of probands with AN or BN had, respectively, approximately elevenfold and twelve-fold greater lifetime risks of full syndrome AN than relatives of unaffected controls (Strober 2000), suggesting a common or shared familial diathesis for eating disorders. Population-based twin studies have estimated mean heritabilities for a broad anorexia-like phenotype of 58% to 74% (Wade 2000; Klump 2001; Kortegaard 2001). The low prevalence of the disorder, low sample sizes and many common methodological problems of the studies make it hard to produce more precise estimates of genetic effects in the aetiology of AN.

The findings of common association (comorbidity) of eating disorders and certain psychiatric symptoms and disorders have led to the hypothesis that a predisposition to a particular personality type, to affective, anxiety or obsessive-compulsive disorder (OCD), or a physiological vulnerability may all play a role in the genetic contribution to the aetiology of AN (Klump 2001). Family and twin studies have found that there are shared as well as unique genetic influences on major depression and AN (Wade 2000; Strober 2000). In one controlled family study (Lilenfeld 1998) there was an increased risk of obsessive-compulsive personality disorder (OCPD) in relatives of AN probands and the rate of OCPD was similar in the relatives, whether or not the person with anorexia nervosa was comorbid for OCPD. This suggests linked transmission for AN and OCPD.

From the developmental perspective, features that precede the onset of the eating disorder and are present in childhood, such as traits reflecting obsessive-compulsive personality (perfectionism, rigidity, harm-avoidance, obsession with symmetry, negative affect and over-control), can act as risk factors for developing eating disorders and represent markers for a broader phenotype of a subgroup of AN patients possibly associated with serotonergic dysfunction (PRCG 2001; Anderluh 2003; Connan 2003a; Steiger 2004). One recent systematic review classified risk factors for both anorexia nervosa and bulimia nervosa according to their potency and specificity (Jacobi 2004). The only two high potency risk factors for AN were being female and exercising before onset. Feeding difficulties, gastrointestinal problems, problems with sleeping and over involved parenting were medium potency risk factors for AN, as were childhood perfectionism, obsessive-compulsive personality disorder and negative evaluation of self. Preterm birth, perinatal complications and birth trauma were specific risk factors for AN, as were OCD, perfectionism and negative self-evaluation.

An increasing number of molecular genetics studies in eating disorders have focused on candidate genes that could be involved in neurotransmitter pathways regulating behaviour or implicated in the control of weight, feeding and energy expenditure (Gorwood 1998). Studies have targeted mainly serotonin-linked genes (Collier 1997; Enoch 1998; Kaye 2001a; Devlin 2002) based on the involvement of the serotonin system in the control of appetite and satiety, and its possible association with some of the personality traits underlying restricting-type AN. Other genes, such as the brain-derived neurotrophic factor gene have also been studied and found to be associated with susceptibility to eating disorders, possibly through its involvement in affective symptoms (Ribases 2004).

With regard to the neurobiological contribution to the development of eating disorders, many questions remain unanswered. A number of abnormalities in neurotransmitters (serotonin, dopamine, norepinephrine), neuropeptides and neuroendocrine hormones have been described in AN during the acute phase of the illness (Kaye 1998; Connan 2003b), most of them considered to be changes due to the starvation state and to the pathological eating behaviours (Gendall 1999; Mantzoros 1997; Connan 2003b), but others also seeming to persist after weight restoration (Kaye 1998; Kaye 1999a). Perceptions of hunger and satiety seem to reflect the complex integration of cognitive sets and internal physiology. Energy intake is clearly reduced in AN, but it is controversial whether appetite is affected: a tight cognitive control of normal appetite has been suggested for some (Palmer 2000) while others consider appetite to be impaired (Pinel 2000).

Research on changes in neurotransmitter systems is of considerable interest, not only because of their potential role in the pathophysiology of eating disorders, but for improving pharmacological approaches in the treatment of these disorders. Brain neurotransmitters play an important role in the modulation of appetite behaviours, post-prandial satiety, neuroendocrine function, mood and many behaviours associated with AN. Attempts have been made to identify putative predisposing factors that either pre-date the weight loss or that may have a predisposition to recurrence or maintenance of low-weight. Functional activity of central serotonin systems has been found to be diminished during low-weight, but may be abnormally increased in long-term weight-recovered AN patients (Kaye 1991a; Kaye 1998), leading to the hypothesis that some individuals who develop AN possibly had high levels of serotonin activity "before the onset of the illness", i.e. a brain serotonergic dysfunction that might contribute to the pathophysi-

ology of AN. However, it cannot be ruled out that decreased levels of cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) in acute AN patients are related to reduced intake of tryptophan and increased levels of CSF 5-HIAA are a physiological consequence of chronic malnutrition (de Zwann 2003b). Additional findings of reduced noradrenergic and dopaminergic activity have been described in ill AN patients (Kaye 1984; Pirke 1996) with persistent low levels of CSF homovanillic acid (HVA) reported in the subgroup of restricting-type AN after recovery and also hypothesised as another trait-related vulnerability related to altered reward, novelty seeking and motor activity (Kaye 1999a).

Moreover, enhanced satiety has been proposed to be associated with elevated cholecystokinin (CCK) release in AN, and tends to normalise with weight gain, but can be reduced by the serotonergic dysfunction (Stallone 1989). Mantzoros 1997 found leptin levels to be lowered in acute AN, but the CSF to plasma ratio was higher in patients compared to controls; at post-treatment, however, both leptin levels normalised even before weight was fully restored, possibly "contributing to resistance to weight gain and to incomplete weight recovery", according to the authors. Additional findings of altered response of cortisol and insulin to a meal following recovery may represent sequelae of AN or a vulnerability factor for the disorder. Hypothalamic function seems to be more implicated in the appetite imbalance than peripheral signals of energy homeostasis, with an aberrant response to chronic stress (demonstrated by persistent elevated corticotropin-releasing hormone (CRH)) being a possible pathophysiological factor in AN (Connan 2003b).

Structural neuroimaging studies in AN have also reported alterations, such as increased cerebrospinal fluid and ventricles, and decreased brain tissue, most of which are apparently linked to endocrine and metabolic consequences of starvation and are reversible with weight restoration (Katzman 2003; de Zwann 2003b). However, some recent evidence that emerged from functional neuroimaging studies in patients with early-onset AN raised the possibility of a predisposing biological substrate involved in the pathogenesis of AN for some patients. Results from these studies suggest temporal lobe abnormality (Gordon 1997; Lask 2005) and limbic system dysfunction (Chowdhury 2003; Lask 2005). Lask 2005 found that unilateral reduction of blood flow in the temporal region was associated with impaired cognitive function, such as impaired visuospatial ability, impaired visual memory and enhanced information processing. The authors considered that the "hypoperfusion could be a primary phenomenon or a result of starvation that either reversed slowly or was irreversible".

Treatment goals in AN include stabilisation of medical and nutritional status (restoration of weight and normal menstrual cycles), re-establishment of healthy patterns of eating (including cessation of restriction and purging), improvement of body image and amelioration of the morbid pre-occupation with weight and shape. Non-specific aims of the treatment include improvement in functioning and quality of life. The treatment of AN is frequently long-term and challenging. Prognostic studies have shown that AN is often a chronic illness, with only half of the patients achieving full recovery in long-term follow-up studies (Hsu 1986; Steinhausen 2002). Currently, recommended treatments for AN rely on a multidisciplinary approach, due to the multidimensional nature of the illness (APA 2000; NCCMH 2004), but there is limited empirical support for the range of treatments used (Fairburn 2005; Agras 2004). Patients can be treated in an inpatient or outpatient/day care setting depending on their clinical and psychiatric condition. Because of the severe and potentially irreversible effects of starvation, restoration of weight is considered an important initial treatment focus. Combinations of individual and family psychotherapies, nutritional rehabilitation and pharmacotherapy are usual.

The rationale for pharmacological treatment of AN is based on neurobiological research into the control of appetite and food intake, and on biological models of AN as discussed earlier (Connan 2003b; de Zwann 2003b; Kaye 1991a) on clinical observations and uncontrolled studies (De Zwann 2003a). Pharmacotherapy is a frequent adjunctive intervention. Different classes of drugs (e.g. neuroleptic medication or cyproheptadine, a weight-inducing drug) have been tried with the aim of reducing the core symptoms of AN and associated psychopathology (Bosanac 2005), or to stimulate appetite (Halmi 1986), but there is little current evidence of their efficacy or effectiveness (Treasure 2004). For that reason, recent mental health guidelines (APA 2000; NCCMH 2004) do not recommend medications as first-line treatment for AN.

Antidepressants are the first-line agents for treatment of depression, obsessive-compulsive disorder and bulimia nervosa (Geddes 2002; Soomro 2002; Fineberg 2004; Bacaltchuk 2005). Researchers have attempted to link these disorders to eating disorders based on their common underlying neurobiological abnormalities in catecholamine metabolism, especially the serotonergic dysfunction (Jimerson 1990; Kaye 1991a; Chamberlain 2005), on findings of frequent comorbidity (Braun 1994), their shared genetic risk and personality traits (Lilenfeld 1998; Wade 2000; Strober 2000; Anderluh 2003; Steiger 2004; Graybiel 2005). Additionally, many patients with AN also suffer from symptoms that are commonly targeted with antidepressants, such as depressive symptoms (e.g. low mood, loss of interest, social isolation) and obsessive-compulsive symptoms (related to eating/food and other behaviour) (Mayer 1998). Finally, antidepressant drugs have also been considered of interest in the treatment of AN due to their weight gain inducing properties (as a side effect), especially the tricyclics (Fernstrom 1995).

De Zwann 2003a reviewed studies on drug treatment of AN and found some evidence from uncontrolled studies that antidepressants could help in weight gain (Gwirtsman 1990; Pallanti 1997; Frank 2001a). They noted, however, that confounding variables (e.g. other adjunctive treatments) limited the confidence in the findings. Non-randomised trials comparing selective serotonin re-

uptake inhibitor (SSRI) treatment (combined to other interventions) to no drug treatment report mixed results (Strober 1999; Ferguson 1999; Santonastaso 2001; Ruggiero 2003). For example, Ruggiero 2003 found a significantly higher weight gain in AN outpatients treated with nutritional management and fluoxetine compared to patients treated only with nutritional management. In contrast, Strober 1999 did not find any advantage of adding fluoxetine to inpatient treatment in terms of weight gain or AN symptoms compared to matched historical controls, who received the same interventions without adjunctive pharmacotherapy. Randomised controlled trials testing antidepressant drugs are considered a better level of evidence in treatment studies, but unfortunately are scarce in AN (Treasure 2004).

The aim of this systematic review was to evaluate the efficacy and acceptability of antidepressant drugs for the treatment of acute AN. Data from several studies in meta-analysis might help increase the knowledge of the effects of these drugs.

OBJECTIVES

The primary objective of this review was to determine the clinical efficacy and acceptability of antidepressants when compared to placebo in patients with anorexia nervosa (acute phase).

Secondary objectives were:

(i) to investigate the efficacy and acceptability of different classes of antidepressant drugs;

(ii) to evaluate the efficacy of antidepressants with respect to general psychiatric symptoms usually associated with anorexia nervosa and global clinical improvement.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Patients diagnosed with anorexia nervosa by any criteria such as Russell's, ICD-9 or ICD-10, DSM-III, DSM-III-R or DSM-IV (including both subtypes) or by "clinical judgement", independent of gender or age.

Types of interventions

RCTs lasting at least four weeks and comparing any antidepressant drug to:
(i) placebo;
(ii) other antidepressant drug.
Treatment could be conducted on an out or inpatient basis (primary, secondary or tertiary sectors), as monotherapy, or as adjunctive therapy to other non-pharmacological treatment.

Types of outcome measures

Primary outcome measures
1. Efficacy at the end of treatment, measured through weight gain or weight restoration as follows:
(a) end-of-treatment mean absolute weight or body mass index (BMI) (where groups were not significantly different in mean weight/BMI at start of treatment);
(b) number of patients achieving target weight or weight within a normal range (e.g. BMI >18 or weight >85% of average for age, gender and height; data were entered in tables as number or patients not achieving target weight);
(c) mean rate of weight gain;
(d) number of days to achieve ideal weight;
(e) any other consistent measure of change in weight.
Secondary outcome measures
1. Efficacy at the end of treatment, through the following outcome measures:
(a) eating disorder symptoms: measured by mean scores on any recognised and validated eating disorder questionnaire or interview e.g. Eating Attitudes Test (EAT), Eating Disorders Inventory (EDI), Bulimic Investigatory Test Edinburgh (BITE), Yale-Brown-Cornell Eating Disorder Scale (Y-Brown-Cornell EDS);
(b) recovery evaluated through scales such as:
(i) Morgan and Russell (Morgan 1975) narrow criteria of:
1. good outcome, namely normal body weight (>85% of average for age, gender and height) with normal menstruation
2. intermediate outcome, namely normal body weight (>85% of average for age, gender and height) with no menstruation
3. poor outcome, neither obtaining normal menses or weight
(ii) Morgan and Russell (Morgan 1988) broader criteria for average outcome;
(c) level of depression symptoms: as measured by mean scores on any recognised and validated depressive rating scale e.g. Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Schedule for Affective Disorders and Schizophrenia - Change (SADS -C);
(d) level of anxiety symptoms (including obsessive-compulsive ones): as measured by mean scores on any recognised and validated obsessive-compulsive rating scale e.g. Hamilton Depression Anxiety Scale (HDAS), Hopkins Symptom Checklist (HSCL), Yale-Brown Obsessive Compulsive Scale (Y-BOCS);

(e) clinical improvement: as measured by any scale (e.g. Clinical Global Impression (CGI) - score of "much improved" or "improved" (dichotomous) or mean scores; Global Severity Scale and Global Improvement Scale ratings - categories of improvement (dichotomous).
2. Acceptability of the treatment measured by:
(a) proportion of non-completers (drop-outs) due to any reason or post-randomisation exclusions;
(b) proportion of non-completers due to adverse effects;
(c) number of subjects reporting side effects.

Search methods for identification of studies

Electronic searches:

The Cochrane Depression, Anxiety and Neurosis Review Group Register (CCDANCTR-Studies) were searched using the following terms:
Diagnosis = "Anorexia Nervosa" or "Eating Disorders"
and
Intervention = "Antidepressive Agents" or "Monoamine Oxidase Inhibitors" or "Selective Serotonin Reuptake Inhibitors" or "Tricyclic Drugs" or Acetylcarnitine or Alaproclate or Amersergide or Amiflamine or Amineptine or Amisulpride or Amitriptyline or Amoxapine or Befloxatone or Benactyzine or Brofaromine or Bupropion or Butriptyline or Caroxazone or Chlorpoxiten or Cilosamine or Cimoxatone or Citalopram or Clomipramine or Clorgyline or Clorimipramine or Clovoxamine or Deanol or Demexiptiline or Deprenyl or Desipramine or Dibenzipin or Diclofensine or Dothiepin or Doxepin or Duloxetine or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluparoxan or Fluvoxamine or Idazoxan or Imipramine or Iprindole or Iproniazid or isocarboxazid or Litoxetine or Lofepramine or Maprotiline or Medifoxamine or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nomifensine or Nortriptyline or Noxiptiline or Opipramol or Oxaflozane or Oxaprotiline or Pargyline or Paroxetine or Phenelzine or Piribedil or Pirlindole or Pivagabine or Prosulpride or Protriptyline or Quinupramine or Reboxetine or Rolipram or Sertraline or Setiptiline or Sulpiride or Teniloxine or Tetrindole or Thiazesim or Thozalinone or Tianeptine or Toloxatone or Tomoxetine or Tranylcypromine or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Viqualine or Zimeldine
In order to test the sensitivity of the CCDAN database, searches were also performed in the following databases, using the standard search phrase for controlled clinical trials (Dickersin 1994), associated to the previous anorexia and antidepressants phrases: MEDLINE (1966 to April 28th, 2005), EMBASE (1980 to week 36, 2004), PsycINFO (1969 to August week 5, 2004).
Social Sciences and the Science Citation Index were searched for all selected papers.
The searches were conducted with the assistance of the Depression, Anxiety and Neurosis Cochrane Group.
Handsearches:
The International Journal of Eating Disorders since its first issue.
The reference lists of relevant articles and book chapters on treatment or pharmacological treatment of AN were searched.
Personal communication:
Personal letters to experts in the area of anorexia nervosa treatment in the US, UK, Europe, NZ and Australia were sent requesting information for unpublished or ongoing trials.

Data collection and analysis

Selection of trials

The first author (AMC) selected the articles that met criteria for this systematic review by scrutinising abstracts of all the papers that came out of the searches and that met the criteria for inclusion.
Quality assessment
Two reviewers (AMC and JB) independently assessed the methodological quality of the included studies giving consideration to the strong relationship between quality of allocation concealment and potential for bias in the results, using the following criteria (based on the guidelines proposed by Mulrow 1999):
A. Low risk of bias (adequate allocation concealment): i.e. patients were randomised by researchers who were not responsible for recruiting participants, and precautions were taken to prevent manipulation of randomisation codes (for example using numbered or coded bottles and serially numbered, sealed, opaque envelopes).
B. Moderate risk of bias (some doubt about the results): i.e. when trials do not report any concealment approach, but state that patients were randomly allocated.
C. High risk of bias (inadequate allocation concealment): i.e. inadequate approaches to concealment allocation, such as alternation, reference to case record numbers, dates of birth, day of the week or any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers.
Trials were included if they met criteria A or B.
Because of the rarity of trials in this area and methodological problems associated with conducting trials in AN, trials were only excluded if the non-completion rates were >50%.

A further quality assessment was also performed using the 23 item criteria from the Cochrane Collaboration Depression, Anxiety and Neurosis Group Quality Rating Scale (QRS) (Moncrieff 2001). The QRS consists of 23 items, including items on sample size, allocation, use of diagnostic criteria, compliance, attrition and statistical analysis. Total scores can range from 0-46. Exclusions of trials were not made based on these criteria.
In addition, a criterion evaluating "information on baseline nutritional status" was also evaluated as this was considered an important issue for this review.

Data extraction

Two reviewers (AMC, JB) independently extracted the data using a standardised data extraction sheet in order to ensure reliability. Any disagreement was discussed and the decisions documented. Authorship was not concealed at the point of data collection.
First authors of the studies were contacted through letters and emails to ask for information about the methodology used (for quality evaluation) or results that were not available in the published trial(s). In cases where there was no reply after four weeks, only published data were considered. All additional information obtained were included in the review. Data from unpublished trials were not included.

Analysis

Data were entered into Review Manager (RevMan) 4.2.6 software for analysis.
1. Dichotomous data:
Relative risk (RR) analyses were conducted for dichotomous outcome data (RR was preferred to the odds ratio as it is a more conservative statistic and appropriate where the outcome is not a rare event). Whenever possible, analyses were performed according to intention-to-treat (ITT) principles (e.g. number of improved patients out of the number of patients randomised to experimental and control groups). If no information was available (either from the report or from the authors) for dichotomous missing data, assumptions were made based on the worst result for the outcome (a negative outcome), such as "patient did not achieve target weight or weight within normal range", "drop-out was due to side-effects or treatment failure".
2. Continuous data:
Standardised mean difference (SMD) analyses were conducted for continuous outcome data. The SMD was chosen as different scales are often used to assess psychopathology. Continuous data were analysed as provided by authors in original studies, i.e. endpoint scores for groups or change in scores from baseline to endpoint. The method adopted by authors for analysing continuous outcomes was described when provided (for instance, last observation carried forward (LOCF)), as they could vary and have implications for the assessment of the results. Data on the number of patients evaluated for each variable at the end of treatment were presented when available.
95% confidence intervals (CI) were reported for both dichotomous (RR) and continuous (SMD) variables, based on the random effects model (DerSimonian 1986), as this takes into account any differences between studies even if heterogeneity is not statistically significant.
3. Heterogeneity:
I-squared tests (I^2) for homogeneity were done. I^2 test describes the percentage of total variation across studies that is due to heterogeneity rather than chance alone, and a value greater than 50% is considered substantial heterogeneity (Higgins 2003). If significant heterogeneity was found (through graphical inspection or by I^2 tests), trials contributing most to heterogeneity were removed in sensitivity analyses and reasons for heterogeneity discussed.
4. Sensitivity analyses:
Sensitivity analyses were planned as follows:
(i) where diagnosis of AN was not defined according to rigorous criteria (DSM, ICD) but through other forms of evaluation (e.g. described as "clinical");
(ii) if completion rates of less than 70% were obtained in any arm of the trial (post hoc sub-group analysis);
(iii) to test if assumptions made from reviewers based on "intention to treat principles" caused any substantial change in results;
(iv) if heterogeneity among studies was found (to verify which trials were contributing most to heterogeneity).
5. Addressing publication bias:
Wherever the number of trials allowed, funnel plots were planned to be done to assess the possibility of publication bias.
6. Subgroup analyses:
Two subgroup analyses were planned to compare:
(i) efficacy across different classes of antidepressants;
(ii) efficacy across setting of treatment (in or outpatient treatment).

RESULTS

Description of studies

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

1. Search

A total of 1303 citations, including papers and abstracts, on antidepressants for patients with anorexia nervosa or eating disorders were identified from the searches (based on strategies described in the Search Strategy section):

211 from MEDLINE (1966 until April 28, 2005)
593 from EMBASE (1980 until end of week 36, 2004)
175 from psycINFO (1969 until end of August, 2004)
04 from the International Journal of Eating Disorders (from the first issue up to March 2005 issue)
18 from CCDANCTR (until Feb 14, 2005)
302 from SOCIAL SCIENCES (from 1956 to April 28th 2005) and SCIENCE CITATION INDEX (from 1945 to April 28th 2005) of articles included in the review.
One hundred and sixty four citations were selected for examination of abstracts. From these, 40 studies were fully examined. Seven trials fulfilled the inclusion criteria and 33 studies were excluded (see table of excluded studies for details). No ongoing or unpublished RCT related to the objectives of this review was identified in searches in Current Contents database or from experts in the field.

Funnel plots to verify possible publication biases were not conducted as the paucity of trials did not allow this.

2. Excluded studies

Studies excluded from the searches were mainly review articles on pharmacological treatment of eating disorders, trials of treatment of other eating disorders, bulimia nervosa and binge-eating disorder, or drug trials of other psychiatric disorders (e.g. depression). Within the selected articles (number (N) = 40), seven studies fulfilled inclusion criteria and 33 studies did not (see table of excluded studies for details). Thirteen of the excluded studies were RCTs:
three tested other drug classes (zinc, lithium carbohidrate, pimozide) in AN;
one tested additional nutritional supplements to fluoxetine in AN;
three evaluated aspects in AN patients receiving antidepressant treatment that were not pertinent to the questions of this review;
one tested a non-pharmacological intervention for AN;
one tested citalopram versus a no-drug control group in AN;
two (Halmi 1982; Halmi 1983) were partial data of one of the included studies (Halmi 1986), and
two were relapse prevention studies in AN.
The remaining excluded studies were not randomised trials (N = 20):
one study was a quasi-randomised comparison of venlafaxine versus fluoxetine in atypical AN patients;
two were non-randomised, open controlled trials: one tested adjunct fluoxetine to nutritional management versus nutritional management only (control group) and the other tested adjunctive sertraline to cognitive behaviour therapy (CBT) and nutritional counselling versus CBT and nutritional counselling only (control group);
one was a non-randomised, open label trial of drug treatments (lithium, carbamazepine, antidepressants) in AN;
one was an open label trial of fluoxetine compared to a matched historic control group;
five were retrospective observational studies;
two studies evaluated relapse prevention in AN;
four were uncontrolled open trials in AN;
one was a single-case study of interaction of antidepressant to psychotherapy and
three were case reports of drug treatment in AN.
Comparisons of pharmacological therapy (including antidepressant drugs) with individual psychotherapy, or combination of pharmacological therapy and individual psychotherapy versus either drug therapy or psychotherapy alone have been included in another systematic review - "Individual psychotherapy in the outpatient treatment of adults with anorexia nervosa" (Hay 2003).

3. Included studies

Seven published studies were selected for inclusion in this review: four of them compared antidepressants to placebo (Lacey 1980; Biederman 1985; Halmi 1986; Attia 1998) and three compared antidepressant drugs (Brambilla 1995a; Brambilla 1995b; Ruggiero 2001).
One author replied to the letters and gave information concerning two studies (Brambilla 1995a; Brambilla 1995b). Two other authors also replied to the letters but did not have additional information over and above what was published in the articles (Halmi 1986; Biederman 1985).

Summary of the characteristics of the included studies

Size of the samples

The size of samples ranged from 16 to 48 patients in the placebo controlled trials and from 13 to 35 patients in the antidepressants comparisons trials. Halmi 1986 had the biggest sample of the studies included (23 drug arm by 25 placebo) and Brambilla 1995b the smallest group sizes (6 fluoxetine by 7 amineptine).

Setting

Most of the placebo controlled studies involved only inpatient treatment (three of four studies); one trial (Biederman 1985) involved mainly inpatients (20/25) and only five subjects were treated as outpatients. Of the comparisons between antidepressants, two RCTs studied outpatients (Brambilla 1995a; Brambilla 1995b) and the other was conducted with inpatients (Ruggiero 2001). Two of the RCTs were multi-centre studies (Biederman 1985; Halmi 1986).

Duration of trials

The planned duration of the trials ranged from five weeks (Biederman 1985) to four months (Brambilla 1995a; Brambilla 1995b). All studies (except Lacey 1980) did not have follow-up periods.

Participants

A total of 178 patients were randomised in total, 120 in the placebo controlled trials and 58 in the antidepressants comparisons' trials. All trials but one (Lacey 1980) used operational criteria for diagnosis (mainly DSM-III, DSM-IIIR or DSM-IV). Lacey 1980 did not provide criteria for diagnosis of AN but stated that patients were "admitted to anorectic unit at Atkinson's Morley Hospital". Three studies included both types of AN patients (Lacey 1980; Halmi 1986; Attia 1998), two included only restrictive type AN (Brambilla 1995a; Ruggiero 2001), one included only bulimic/purging type AN (Brambilla 1995b) and the last one did not specify type of AN (Biederman 1985). Two trials did not report gender and the rest involved only females. Patients were mainly young adults with mean ages between 20 and 30 years in six studies, and only one study presented a younger group of patients of mean age around 17 years (Biederman 1985). Duration of illness varied among studies with means that ranged from around two years to eight years in six studies (which provided that information), including patients with a duration of illness that as brief as three months or as long as 14 years.

Interventions

In all studies the drug was added to other kinds of interventions (psychotherapies, nutritional therapy), including intensive re-feeding programmes for hospitalised patients.
Low to modest doses of drugs were used in four trials (Lacey 1980;

Biederman 1985; Halmi 1986; Ruggiero 2001) while the other studies used higher doses (e.g. fluoxetine 60mg in Attia 1998; Brambilla 1995a; Brambilla 1995b).

Outcomes

All studies provided data concerning the primary outcome weight gain (with varied types of measure) and all (except Lacey 1980) also evaluated eating disorders and/or general psychopathology. Specific information concerning the main characteristics of each study is provided in the Table of Included Studies.

Risk of bias in included studies

As there were so few trials, the levels of agreement on quality of trials and data extraction were not tested statistically. All data related to quality ratings and outcomes were extracted by two reviewers, who then reached consensus on final ratings.

The reviewers added the criteria "information on baseline nutritional status" to the CCDAN quality-criteria items, as this was considered an important issue for this review.

Randomisation

All studies were described as randomised but no details about the concealment of allocation were given in any of the articles. Thus there was uncertainty about whether allocation was adequately concealed; for that reason five studies were graded as "B" (Attia 1998; Halmi 1986; Biederman 1985; Lacey 1980; Ruggiero 2001). One author (Brambilla 1995a; Brambilla 1995b) answered queries and reported that randomisation codes were protected by sealed opaque envelopes; these two studies were therefore graded as "A".

Blinding and test of integrity

All four placebo controlled studies were double-blind, but no study reported testing the integrity of blindness. One of the studies comparing different antidepressants (Ruggiero 2001) was single-blind (outcome assessor) but no test of the integrity was reported, and the two remaining trials in this group (Brambilla 1995a; Brambilla 1995b) were open label.

Objectives and main outcome

Three studies provided clear objectives (Attia 1998; Biederman 1985; Ruggiero 2001); three objectives were clear but the main outcomes were not specified a priori (Brambilla 1995a; Brambilla 1995b; Halmi 1986) and in one early study the objectives were unclear (Lacey 1980).

Sample size per group

All studies involved less than 50 patients per group. Indeed in all, fewer than 50 patients were randomised (considering only the arms used for comparisons of this review); thus overall sample sizes were small.

Planned duration of trial and follow-up

Four studies (Attia 1998; Biederman 1985; Halmi 1986; Ruggiero 2001) were planned to be of short duration (maximum three months), with no follow-up period. One trial did not report a planned duration (duration variable, maximum time not established), and its mean duration was around 10 weeks (Lacey 1980); nevertheless this is the only trial that presented follow-up data (partial) at one year and at four years. Brambilla's trials (Brambilla 1995a; Brambilla 1995b) had a moderate duration of four months.

Power calculation

The only trial that mentioned conducting a power calculation, albeit without giving details on this, was Attia 1998; all the others did not report a power calculation.

Description of treatment

All studies presented details of drug treatment and adjunctive treatments.

Source of subjects

Most studies described the source of subjects and representative samples were taken. Ruggiero 2001 excluded patients younger than 17 years old.

Diagnostic criteria

All trials used diagnostic criteria and/or inclusion criteria (mainly DSM-III, DSM-IIIR or DSM-IV) except for one trial (Lacey 1980) in which patients were "admissions to a specialist eating disorders unit" with no further information on the diagnostic criteria. Biederman 1985 included one patient who had a weight loss of 19% of the body weight (BMI not stated), less than asked for by DSM-III criterion of weight used in the trial, but all other criteria were fulfilled. In Attia's study (Attia 1998), three patients had irregular menses, but were included because they were substantially underweight. In one of Brambilla's studies (Brambilla 1995b) only three patients were amenorrheic and the rest had irregular menses or oligomenorrhoea. The absence of amenorrhoea could technically put these patients outside diagnostic criteria for anorexia nervosa, but the reviewers decided to accept and include these trials because amenorrhoea is considered a controversial diagnostic criteria in AN (Garfinkel 1996).

Exclusion criteria and number of exclusions and refusals

Only one study did not specify any exclusion criteria (Lacey 1980). Except for Biederman 1985, who reported the number of suitable patients who refused to participate (18 patients), only Ruggiero 2001 reported that patients were selected from a sample of 164 AN patients; this study presented data from 35 patients who finished the re-feeding programme but did not differentiate between eligible patients who refused to participate, the number of exclusions (due to meeting exclusion criteria) before randomisation, and the number of exclusions after randomisation (for the 129 patients excluded).

Description of sample demographics

Three studies (Biederman 1985; Lacey 1980; Halmi 1986) gave full details of sample demographics. The remaining studies gave little or basic information.

Assessment of compliance with experimental treatment

Only two trials assessed drug compliance by measuring plasma levels (Attia 1998; Biederman 1985; Brambilla 1995a; Brambilla 1995b) noted that in her study compliance with drug treatment was ensured through family support. None of the other trials made

any reference to assessment of compliance.

Details on side-effects

Three studies provided information on side-effects per group (Attia 1998; Biederman 1985; Halmi 1986) but the details were inadequate (Halmi 1986). Two authors gave no details on side-effects (Lacey 1980; Ruggiero 2001) and (Brambilla 1995a; Brambilla 1995b) reported that there were no side-effects in her trials.

Description of completion rates

Three studies reported on withdrawals before the end of the trial both detailing and breaking down the reasons for this (Attia 1998; Halmi 1986; Lacey 1980); two did not refer to drop-outs but the data imply, and the present reviewers assumed, that there were no people lost at follow-up (Biederman 1985; Ruggiero 2001); the two remaining studies (Brambilla 1995a; Brambilla 1995b) did not report on drop-outs in the published data, and when the authors were contacted they informed us that there were no withdrawals.

Outcomes description and use of validated instruments

Outcomes were clearly described in four studies (Halmi 1986; Attia 1998; Brambilla 1995a; Brambilla 1995b). Lacey 1980; Biederman 1985 provided some outcomes in graphical form, from which it was not possible to acquire raw data for synthesis. Most studies presented data from primary and secondary outcomes as continuous data, but some means were provided without standard deviations (Lacey 1980; Ruggiero 2001). Most studies used validated instruments (e.g. EAT, BITE, EDI, SCL90, HRS-D, HRS-A, BDI, SADS-C) to evaluate eating disorder symptoms and associated psychopathology. Evaluations that were not related to the scope of this review or that were not based on validated instruments were not considered (Lacey 1980; Halmi 1986; Ruggiero 2001). The only unvalidated scales considered in this review were scales of improvement in the global state (Attia 1998; Biederman 1985).

Information on baseline nutritional status

Information on baseline nutritional status was provided by three main measures in studies (for the whole sample or by group): BMI, percentage of ideal body weight or just weight. The mean BMI at baseline was reported in only three studies (Attia 1998; Brambilla 1995a; Brambilla 1995b) and ranged from 14.7 to 16.7 kg/m^2. Data on mean percentage of ideal body weight at baseline was given in three studies (Attia 1998; Biederman 1985; Halmi 1986) and ranged from 69.0% to 82.4% among studies.

Although it is not a good measure of "adequacy" of weight, mean baseline weight was provided in four studies (Attia 1998; Biederman 1985; Lacey 1980; Ruggiero 2001) and varied from 35.5 kg to 41.7 kg. These data suggest that overall patients were substantially underweight at baseline, but the level of severity of weight loss cannot be precisely compared between trials in light of the different measures provided.

Information on comparability of groups and adjustment for differences in analysis

All studies had comparable groups in weight or initial BMI, although this information was not always provided (Halmi 1986; Lacey 1980; Ruggiero 2001). Where provision of initial data allowed this, comparability of groups at baseline was tested by the reviewers. Four studies did not provide information on the comparability of groups in terms of their demographics or clinical histories (Brambilla 1995a; Brambilla 1995b; Halmi 1986; Ruggiero 2001); two studies reported on comparability of their study groups in all variables (Biederman 1985; Lacey 1980). Attia 1998 found no differences apart from a small difference in mean age, which was not found to be related to clinical outcome.

Inclusion of withdrawals in analysis

The majority of studies provided no information on the use of ITT analyses or otherwise. Two studies (Brambilla 1995a; Brambilla 1995b) had no withdrawals (author information) and seemed to have included all patients in analyses. Ruggiero 2001analysed data from the whole group selected for the trial (N = 35), but commented that patients who did not complete the re-feeding programme were excluded (apparently post-randomisation exclusions). Attia 1998 reported two post-randomisation exclusions that were not considered in the analyses and an additional patient who was included in the analysis whose self-report data were not analysed (as she was considered to be unreliable in terms of reporting her symptoms). However, in this study results were presented for all outcomes in the whole sample and it is unclear how much of the data from this last patient were included. Biederman 1985 did not report on withdrawals (apparently none) and analysed data from all patients for some outcomes. Halmi 1986 had withdrawals and exclusions, and did not include all patients in all analyses (e.g. scores on Hamilton Depression Scale). Lacey 1980 had drop-outs but seem to have followed-up all patients and analysed their weight gain outcomes.

Statistical analysis

Most studies had appropriate statistical analysis and two (Attia 1998; Halmi 1986) had appropriate and comprehensive statistical analysis.

Conclusions

Conclusions were judged to be justified in all studies.

Conflict of interest

Three trials acknowledged support and/or declared interests (Attia 1998; Biederman 1985; Halmi 1986).

Effects of interventions

The following results show that major methodological limitations of trials such as small size of samples and large confidence intervals decreased the power of studies to detect differences between treatments. Additionally, meta-analysis of data was not possible for the majority of outcomes.

Two included studies were investigated in sensitivity analysis as they were insufficient to differ from the other trials and presented lower quality information: Lacey 1980 did not provide criteria for diagnosis of AN (the sample was "patients admitted to anorectic

unit at Atkinson's Morley Hospital"); Halmi 1986 presented a completion rate of 64% in the placebo arm; however, there was a "minimal early weight gain exclusion criterion" in this trial, and most of the non-completers were post-randomisation exclusions due to this criterion (13% in the drug group and 20% in the placebo group). If only later drop-outs were considered in Halmi 1986, the study had completion rates of 87% in the drug group and 88% in the placebo group.

1. Comparison antidepressants versus placebo

Four trials compared an antidepressant drug to placebo: Attia 1998; Biederman 1985; Halmi 1986; Lacey 1980.

Primary outcome: weight gain

No evidence of any effect on weight gain was found for antidepressants combined with other interventions (mainly inpatient treatment) when compared to placebo.

Data on the main outcome, weight gain, were provided in many different forms and, for that reason, with the exception of the outcome number of patients achieving target weight, aggregation of data in meta-analysis was not possible. Data from individual studies were presented in graphs.

(a) End-of-treatment mean absolute weight gain or body mass index

Lacey 1980 compared clomipramine to placebo and did not find a statistically significant difference in mean weight gain (absolute weight increase in kilograms) at the end of the treatment (SMD = 0.64 95% CI -0.37 to 1.65). Although the placebo group seemed to do better during the treatment phase, at one year follow-up patients in the clomipramine group were maintaining their weight at a higher percentage of ideal weight than patients in the placebo group (even though medication had been discontinued soon after their target weights had been attained), but again the difference between groups did not reach statistical significance (SMD = -0.74 95% CI -1.77 to 0.28). Reviewers assumed that the data referred to all patients (N = 16) on both outcomes.

Attia 1998 compared fluoxetine to placebo and found no significant difference between groups (SMD = 0.14 95% CI -0.56 to 0.85) in mean percentage of ideal weight at the end of treatment.

(b) Number of patients achieving target weight or weight within the normal range

(presented in negative form in the graphs: number of patients NOT achieving target weight)

Information on the number of patients who achieved target weight could be extracted from three studies (Attia 1998; Halmi 1986; Lacey 1980). However, the reviewers considered that differences in characteristics of the studies precluded us from grouping data of one of the studies (Lacey 1980) with the other two (Attia 1998; Halmi 1986) for this outcome measure. Lacey 1980 did not establish a time to achieve normal weight, while the other two studies determined a maximum duration of treatment (90 days in the Halmi 1986 study and seven weeks in the Attia 1998 trial) and reported the number of patients who were able to reach the target during this time period. Lacey 1980 reported a mean time of 10 weeks for all patients of the study to achieve weight within normal range, including the drop-outs. In the other two trials (Attia 1998; Halmi 1986), those who did not drop out or were excluded took a mean time of five weeks to reach target weight. Thus, it did not seem appropriate for us to combine data from studies that applied different methods to estimate improvement in weight gain and had different time scales for reaching target weight.

Meta-analysis of data on the number of patients not achieving target weight (N = 79) from the two studies (Attia 1998; Halmi 1986) with a more similar design did not show a significant difference in efficacy between antidepressant treatment and placebo (RR = 0.83 95% CI 0.41 to 1.67; Z = 0.53, P = 0.60) in helping patients to achieve a weight within the normal range (target weight) during the brief time period of the trials. Sensitivity analysis was planned for any meta-analysis that included the Halmi 1986 trial (as stated earlier) but this meta-analysis had only two trials and heterogeneity was not identified between studies (I^2 = 0%).

As stated above, all patients in the third study (Lacey 1980) reached target weight (including drop-outs) and thus, no difference in efficacy was evident from use of antidepressants.

(c) Mean rate of weight gain

Two studies investigated the rate of weight gain, measuring the increase in kilograms per day of treatment with antidepressants (tricyclics) compared to placebo (Halmi 1986; Lacey 1980). The estimates of effect were in opposite directions in these two trials and as considerable heterogeneity was found when meta-analysis of data was tried (I^2 = 83.4%) reviewers considered that the data would be better presented independently.

The possible explanations raised for the heterogeneity found between these studies are:

(i) differences in treatment due to its mean duration (as discussed in the previous item), the antidepressant doses used (higher in the Halmi 1986 trial, amitriptyline 160mg per day versus clomipramine 50mg per day in the Lacey 1980 trial), the combined inpatient treatments offered;

(ii) data on the Halmi trial were relative only to those who gained minimal weight at the beginning of treatment and managed to remain in trial: these patients could be at a higher baseline weight for example (information not available for comparison) and with greater chances of having an antidepressant effect;

(iii) very small sample size in the Lacey 1980 trial (N = 16);

(iv) differences in patient selection, as diagnosis of AN was not based on rigorous criteria in the Lacey 1980 trial.

Halmi 1986 found that the daily rate of weight increase was higher in the drug group (amitriptyline) but the difference was not statistically significant (SMD = -0.53 95% CI -1.22 to 0.17). These data referred only to patients that achieved target weight (33/48), excluding non-completers for any reason (and those who failed to achieve minimal weight gain in the first six weeks of trial). In the Lacey 1980 trial, the daily rate of weight gain tended to be greater in the placebo group (SMD = 1.07 95% CI 0.00 to 2.14)

when the total number of the randomised patients (N = 16) in the study were considered (although information relative to number of patients for this data was not available and was inferred by the reviewers). In the paper, the authors (Lacey 1980) stated that the difference in body weight gained each day was not statistically significant.

Attia 1998 also analysed rate of weight gain reflected by the change in percent of ideal body weight per day, but no differences were found between fluoxetine and placebo (SMD = 0.48 95% CI -0.24 to 1.20).

(d) Time to achieve target weight (ideal, weight within normal range)

Again, data from the two studies (Halmi 1986; Lacey 1980) that reported on mean days to achieve target weight were not aggregated for the reasons stated above (differences in studies characteristics discussed in the two earlier items). Neither trial found any significant difference between antidepressants and placebo in time to achieve target weight.

Halmi 1986 considered only patients who achieved their target weight (33/48) and found a SMD of -0.70 (95% CI - 1.40 to 0.01). The Lacey 1980 trial found a SMD of 0.15 (95% CI -0.84 to 1.13). This calculation was made on the total number of randomised patients (N = 16).

(e) Any other measure of change in weight

In the Biederman 1985 trial there was no significant difference (RR = 1.08 95% CI 0.93 to 1.25) in the number of patients who did not manage to increase more than 30% of their baseline weight during treatment with amitriptyline compared to placebo (five weeks).

Secondary outcomes

1. Efficacy in reducing eating disorders symptoms, associated psychopathology and improving clinical global state.

Antidepressants did not differ from placebo in terms of reducing eating disorder and associated psychopathology, nor in improving global clinical state.

(a) Eating disorder symptomatology

In the Attia 1998 trial we found no evidence for efficacy of fluoxetine in reducing eating disorders symptoms as measured by end-of-treatment mean scores on either of the following scales:

Anorectic Behaviour Scale (SMD = -0.11 95% CI -0.82 to 0.59); Yale-Brown-Cornell Eating Disorder Scale (SMD = 0.17 95% CI -0.54 to 0.87); Eating Attitudes Test (SMD = 0.33 95% CI -0.38 to 1.04) and Body Shape Questionnaire (SMD = -0.28 95% CI -0.98 to 0.43).

(b) Recovery

No study provided this data except for Lacey 1980; however authors provided mean scores without reporting standard deviations and it was not possible to use the data.

(c) Level of depressive symptoms

Biederman 1985 reported on the number of patients not presenting greater than 50% improvement in depressive symptoms evaluated with the antidepressant scale of the SADS-C: RR of 1.27 (95% CI 0.97 to 1.67) no significant difference between antipressant (amitriptyline) and placebo.

As there were missing data in this outcome, the reviewers adopted ITT principles and considered these patients as unimproved, and data are presented including them. Sensitivity analysis comparing ITT analysis, and analysis based on the number of analysed patients showed similar results (both not significant).

A meta-analysis of data from two studies (Attia 1998; Halmi 1986) (N = 79) evaluating reduction in depressive symptoms through end-point mean scores in Beck Depression Scale (where groups were comparable at baseline in both studies, tested by reviewers) did not find an advantage for antidepressant treatment (SMD = 0.01 95% CI -0.43 to 0.45; overall effect Z = 0.05, P = 0.96). Sensitivity analysis (as planned) was not performed as there were only two trials but no heterogeneity was found between studies (I^2 = 0%).

Attia 1998 evaluated improvement in depressive symptoms using end-point mean scores in the depression subscale of the SCL-90, and did not find any differences (SMD = 0.11 95% CI -0.60 to 0.81) between groups. Halmi 1986 analysed depressive symptoms comparing end-point mean scores of Hamilton Depression Scale, but also did not find a statistically significant difference (SMD = -0.45 95% CI -1.12 to 0.22); moreover data in this outcome did not refer to all randomised patients (36/48) and reviewers were not able to apply ITT principles as no additional information could be obtained from the authors.

(d) Level of anxiety symptoms (including obsessive-compulsive symptoms)

Biederman 1985 did not find any difference in the number of patients failing to present greater than 50% improvement in obsessional symptoms evaluated with the HSCL (RR = 1.08 95% CI 0.93 to 1.25), and in anxiety symptoms evaluated with the SADS-C (RR = 1.17 95% CI 0.94 to 1.44). ITT principles were applied to missing data in both outcome measures, in that patients with missing data were assumed not to have improved. Sensitivity analysis comparing ITT analysis and analysis based on the number of evaluated patients showed no difference in results (both not significant).

Attia 1998 also reported on improvement in obsessional symptoms based on end-point mean scores in the obsessive-compulsive subscale of the SCL-90 (comparable baseline scores between groups) but did not detect any effect of fluoxetine (SMD = 0.25 95% CI -0.46 to 0.96).

(e) Clinical Global Improvement

Biederman 1985 compared clinical global effect of amytriptyline versus placebo, but found no difference between groups as measured by number of patients not reporting greater than 50% improvement on the Clinical Global Scale (RR = 0.98 95% CI 0.77 to 1.24).

One study (Attia 1998) provided end-point mean scores in Clinical Global Improvement. Statistical analysis did not identify any effect of antidepressant (fluoxetine) in improving clinical global

state (SMD = -0.20 95% CI -0.91 to 0.51).

2. Acceptability of treatment

This review did not find any evidence of differential acceptability of antidepressants when compared to placebo as measured by the following outcomes:

(a) Proportion of non-completers (drop-outs) due to any reason

Meta-analysis of drop-outs for any reason was performed and no difference was found in overall non-completion rates in groups receiving antidepressant treatment compared to those receiving placebo. Four studies were considered (Attia 1998; Biederman 1985; Halmi 1986; Lacey 1980) (N = 120), and 12 out of 57 patients in the antidepressants group did not complete the trials, compared to 14 out of 63 patients in the placebo group who left the study before its end (RR = 0.90 95% CI 0.46 to 1.75; overall effect Z = 0.32, P = 0.75).

Reviewers assumed there were no drop-outs in the Biederman 1985 study.

ITT analysis was not performed by reviewers as it was not possible to identify group assignment of one of the two patients excluded post-randomisation in the Attia 1998 trial.

(b) Proportion of non-completers due to adverse effects

Aggregation of data of all placebo-controlled trials (Attia 1998; Biederman 1985; Halmi 1986; Lacey 1980) in meta-analysis (N = 120) found no significant difference in the numbers of patients leaving the treatment because of side-effects, thus no difference in acceptability of treatment due to adverse effects could be demonstrated in this review (RR = 0.66 95% CI 0.09 to 4.82; overall effect Z = 0.42, P = 0.68). Again reviewers assumed that no drop-outs for side effects occurred in the Biederman 1985 (the authors reported on side-effects but not on drop-outs for that reason). Again, ITT analysis was not performed by reviewers as it was not possible to identify group assignment of one of the two patients excluded post-randomisation in the Attia 1998 study.

(c) Number of subjects reporting side effects

This information could only be extracted from one study (Attia 1998), which found no difference between the number of patients reporting side-effects on antidepressant treatment or placebo (RR = 2.13 95% CI 0.22 to 21.17).

2. Comparison antidepressant versus antidepressant

Three studies were included in this comparison (Brambilla 1995a; Brambilla 1995b; Ruggiero 2001).

Primary Outcome : weight gain

(a) End-of-treatment mean absolute weight gain or body mass index

No evidence was found of greater efficacy for any antidepressant compared to another antidepressant, when used in combination with other types of interventions.

Brambilla 1995a and Brambilla 1995b compared fluoxetine to nortriptyline and to amineptine. In both studies no statistical difference was found in end-of-treatment mean BMI between different antidepressants; the SMD found for the fluoxetine versus amineptine comparison was -0.68 (95% CI -1.81to 0.46) and for the fluoxetine versus nortriptyline comparison was 0.81 (95% CI -0.12 to 1.75).

Ruggiero 2001 tested the efficacy of fluoxetine against clomipramine but did not find greater efficacy for either drug in improving weight gain as measured by end-of-treatment mean absolute weight (SMD = -0.45 95% CI -1.28 to 0.39) or mean percent of weight increase (SMD = -0.19 95% CI -1.02 to 0.63).

(b) Other measures of weight gain: not available for this group of studies.

Secondary outcomes

(a) Eating disorder symptoms: one study found amineptine had a greater effect on eating disorder symptoms compared to fluoxetine (Brambilla 1995b).

Two studies (Brambilla 1995a; Brambilla 1995b) used the Eating Disorders Inventory scores to evaluate improvement in eating disorders symptoms in the trials: in one of the studies (Brambilla 1995b) amineptine was superior to fluoxetine in reducing eating disorder symptoms (SMD = 1.70 95% CI 0.36 to 3.04; overall effect Z = 2.48, P = 0.01); the second study, comparing fluoxetine versus nortriptyline (Brambilla 1995a) did not identify differences between antidepressants in relation to eating disorder symptoms (SMD = 0.09 95% CI -0.81to 0.99).

(b) Level of depression: no difference between tested antidepressant drugs.

Depressive symptoms were evaluated in Brambilla 1995a and Brambilla 1995b using end-point mean scores on the Hamilton Depression Scale. No difference was found between the comparisons in terms of reduction of depressive symptoms: fluoxetine versus nortriptyline (SMD = 0.86 95% CI -0.08 to 1.80) and fluoxetine versus amineptine (SMD = 0.00 95% CI -1.09 to 1.09).

(c) Level of anxiety: one study found a greater efficacy of nortriptyline compared to fluoxetine in reducing anxiety (Brambilla 1995a).

Anxiety symptoms were also evaluated in two studies (Brambilla 1995a; Brambilla 1995b) through end-point mean scores on the Hamilton Anxiety Scale. Nortriptyline showed greater efficacy compared to fluoxetine in reducing anxiety symptoms (Brambilla 1995a), with a SMD of 1.28 (95% CI 0.29 to 2.27; overall effect Z = 2.53, P = 0.01). The comparison of fluoxetine versus amineptine did not identify any difference (SMD = 0.38 95% CI - 0.72 to 1.48).

Finally, subgroup analysis comparing different classes of antidepressants or setting of treatment were not performed due to the small number of trials and methodological limitations to aggregation of data.

DISCUSSION

This systematic review aimed to evaluate the existing evidence on the efficacy and acceptability of antidepressant treatment in the acute phase of AN. It is clear from the review that there is a lack

of quality of information in this field that severely compromises interpretation of results.

Methodological considerations

The numerous methodological limitations of the trials included might have accounted for the findings of this review. To start, a very small number of studies have been performed to date comparing antidepressants to placebo, limiting the available data. Considering the quality of assessment, none of the studies gave details on concealment of randomisation allocation and none reported on testing for the integrity of blinding. Nevertheless, as no evidence of efficacy of drug treatment has been found, bias due to inadequate allocation concealment and/or blinding does not seem to have occurred or to have affected results in terms of increasing the chance of overestimation of drug effect.

The greatest limitation of the studies was the very small sample size of all trials (e.g. eight patients in each arm of one trial), as it led to decreased power to detect differences in effects, shown in the results by the large confidence intervals found in most analyses. As expected, no trial of the placebo comparisons investigated antidepressants as the sole treatment, which would be outside current clinical practice guidelines (APA 2000; NCCMH 2004). However, this might have been another important limitation of the studies, the combination of antidepressants with multiple psychological and nutritional inpatient interventions (including behavioural programmes devoted to weight gain) i.e. an intensive care that usually promotes weight restoration by itself. In such a condition, the effect that a drug added to this whole "package" of treatment is able to contribute, for instance in terms of increase in the rate of weight gain, is likely to be small and difficult to demonstrate; if we also take into account the small sizes of trials, the power of these studies to detect even large differences in effects is definitely compromised.

Another important methodological flaw of the placebo-controlled trials included here were their short length, some with planned or mean duration of around five weeks and no follow-up period; this period is too short to evaluate the effect of an antidepressant in a disorder with psychopathological disturbances of enduring nature and a typically slow course of recovery. Additionally, some trials used low or moderate doses of antidepressants and some did not refer to testing compliance with drug treatment, a possible problem with patients with AN, who are usually reluctant to take medicines.

Other methodological shortcomings of trials involved the outcome measures and reporting of outcomes. The primary outcome in this review was improvement in weight gain, as it is considered a first and essential step in recovering from AN, as is a reliable outcome measure. Most of the trials had weight gain as the primary outcome; however, the way this was reported varied between studies, preventing aggregation of the results. It would be useful if trials systematically reported the number of patients achieving normal weight at the end of the trial, as weight restoration to normal seems to be associated with better outcomes (Baran 1995; Agras 2004), and can be easily reported and further aggregated. The same problem occurred with secondary outcome measures: different scales were used or different ways of reporting data prevented us from performing meta-analysis of data. The use of dichotomous data, such as the number of patients presenting end-of-treatment scores below the scale cut-off point, or the use of categories of levels of improvement in symptoms would facilitate further aggregation of results.

Additionally, other problems identified in studies were that the presentation of data on completion rates and on numbers of patients evaluated for each outcome variable were not always available. Authors also rarely performed ITT analyses.

Heterogeneity was found between studies. Two main reasons for this could be that studies were found to be pursuing similar objectives (improvement in the treatment of acute AN) but with possible differences in goals and in expected actions of the antidepressants. Differences in definition of an adequate time scale for weight rehabilitation (or no definition at all) may have led to different results, as observed in terms of the mean duration of treatments (in Lacey 1980 the mean duration of treatment was twice that of the mean durations in the Attia 1998 and Halmi 1986 studies); secondly, different "packages" of treatment combined with drugs may result in poorly comparable interventions.

Finally, another aspect that can impact on treatment outcome (but was not evaluated in this review) is patient variability (such as age and illness factors). Biederman 1985 had a younger sample than other placebo-controlled trials; as in other disorders, presentation at early onset of the disorder (before 18 years of age) may have a better outcome (Strober 1997b), but longer periods of follow-up are required to evaluate this. Case-mix in terms of sub-type of AN (binge-purge or restrictor) is another aspect that may have an impact when evaluating a drug, as biological differences may lead to different effects (Kaye 1999a; Kaye 1999b); however, samples of the placebo comparisons had mixed types of AN patients, and only one trial investigated efficacy of drugs by AN sub-type (Halmi 1986).

Main findings

A comprehensive search of the literature was conducted in order to identify RCTs that tested antidepressants in the treatment of acute AN, but only seven studies were found to fulfill criteria for this review, four of them comparing antidepressant treatment to placebo. Although patients showed improvement during treatments in most studies, usually with significant changes in weight compared to baseline, the RCTs included here were not able to demonstrate any effect of antidepressant drugs compared to placebo in the majority of the outcomes considered in this review. The only positive findings in this review were a greater effect of amineptine compared to fluoxetine in reduction of eating dis-

order symptoms evaluated through end-of-treatment Eating Disorders Inventory mean scores, and greater effect of nortriptyline compared to fluoxetine in reducing anxiety symptoms measured through Hamilton Anxiety Scale mean scores. However, these were isolated findings, of unclear significance in light of the findings from the placebo comparisons; for that reason, they should not be conceived as evidence of efficacy of a specific drug or class of antidepressant. The authors of the present review expected that aggregation of data from trials would increase the power to detect differences in efficacy between tested drugs (or placebo), as pharmacotherapy trials in AN were few and of small sizes; however, aggregation of data in meta-analysis was not possible for the majority of outcomes in this review. The only efficacy outcome in which meta-analysis (with data from two trials) was done was with the number of patients not achieving target weight, but evidence of effect of antidepressants could not be demonstrated.

In the trials included in this review, drugs with different profiles of pharmacological action have been tested: amitriptiline (both noradrenergic and serotonergic), clomipramine (mainly serotonergic), fluoxetine (selective serotonergic), nortriptiline (mainly noradrenergic) and amineptine (mainly dopaminergic). Researchers seem to have tried to target different goals through different expected action of drugs. As mentioned earlier, serotonergic deregulation has been demonstrated in AN (Kaye 1991a; Kaye 1998; Frank 2001b; Attia 2005) and considered a predisposing factor for developing the illness. It has been postulated that serotonin modulates the balance between dopamine, noradrenaline and GABA (the aminobutyric acid), which mediate, respectively, thought processes, anxiety and mood; the homeostasis of these neurotransmitters are thought to be disturbed in the illness, and serotonergic drugs are expected to reinstate the homeostasis (Vaswani 2004). Moreover, the neurotransmitter systems are all involved in the complex neurobiological control of weight and food intake (Appolinario 2004). Reduced serotonergic neurotransmission and compensatory receptor activation (functional supersensitivity of 5-HT2c receptors) due to dieting have been associated with increased food consumption and weight gain (Kaye 1991c; Cowan 1996). Other authors considered that a decrease in hypothalamic noradrenergic activity could be involved in AN and that tricyclic antidepressants could enhace food intake/appetite through stimulation of alpha-noradrenergic receptors within the medial hyphotalamus (Pirke 1996; Appolinario 2004; Leibowitz 1986). Brambilla 1995b however, tested amineptine to inhibit hunger in binge-purge AN patients through its dopaminergic-stimulating effect, in contrast with the current, renewed interest in antipsychotic drugs (the atypicals) to treat acute AN, that is based on the dopaminergic deregulation hypothesis and the appetite-stimulating side-effect of these drugs (through blockade of dopamine receptors in the ventromedial nucleus) (Bosanac 2005).

It has been suggested that the neurochemical abnormalities of the malnourished state may partially explain the clinical non-response to drugs, especially SSRIs, observed in the acute phase of AN (Attia 1998; Kaye 1998; Attia 2005). In fact, decreased levels of CSF 5-HIAA, noradrenaline (NE) and 3-methoxy-4-hydroxy-phenylglycol (MHPG), and HVA have all been reported in studies (Kaye 1984; Pirke 1996; Kaye 1998). The low levels of CSF 5-HIAA detected in AN underweight patients may be possibly related to the poor dietary intake of tryptophan (the precursor of serotonin). Moreover, low values of oestrogen during the malnourished state and low intake of other nutrients (essential fatty acids, zinc, pyridoxine) that are believed to influence serotonin pathway function may also impair neuronal release of 5-HT in the brain, downregulate its receptor, and thus, reduce the antidepressant action. Attia 2005 measured plasma tryptophan (TRP) and the ratio TRP/LNAA (large neutral amino acids) in AN during re-feeding, and found levels to be low at baseline, but to increase gradually towards normalisation with weight restoration. In a recent RCT, however, this finding of lack of response to SSRI medication due to inadequate supply of nutrients has been contested as nutritional supplementation (including tryptophan) or placebo nutritional supplements were added to fluoxetine and it was found that nutritional supplements did not increase efficacy of fluoxetine treatment in underweight AN patients (Barbarich 2004); however, a small sample size and high attrition rate limit the interpretation of results.

Although limited by the poor quality of evidence available, the findings of antidepressant trials in acute AN have raised the discussion of whether research testing these drugs during the starvation state should go on. The use of antidepressant drugs have then been considered in weight-restored patients, when the effects of malnutrition are beign resolved. In this stage, medications could be used to treat remaining depressive and obsessive-compulsive symptoms, and to prevent relapse (weight loss). Preliminary positive findings in this field support the indication of SSRIs (fluoxetine) to prevent relapse in AN (Kaye 1991b; Kaye 2001b), but negative findings have all been reported (Strober 1997a). This is certainly an area that should be further explored.

Apart from the unproven efficacy of antidepressants, issues of safety and acceptability of drug treatment in AN also have to be considered. Previous studies in bulimia nervosa from our group (Bacaltchuk 2005) have found relatively high rates of treatment drop-out with antidepressant therapy compared to low rates with psychotherapy. In this review, it was possible to perform meta-analysis of non-completion rates in trials. Despite the reported side-effects by patients treated with antidepressant drugs (especially tricyclics) in some trials (Biederman 1985; Halmi 1986), no significant difference in drop-outs from studies (for any reason or for side-effects) was detected of tested antidepressants compared to placebo. While still widely used in developing countries (for economic reasons), tricyclics are associated with uncomfortable adverse effects and increased cardiac risks as prolongation of the QT interval (and arrhythmias) can occur. As some AN patients (especially those who purge and develop hypokalaemia) may also

present with a prolonged QT interval, tricyclics are likely to be contra-indicated in underweight AN patients (Ackerman 1998; Reilly 2000) and new trials testing them are not expected to be developed. Newer drugs, with safer and better side-effect profiles such as SSRIs, are considered a better options, though they could not prove to be of benefit until the moment. However, results from open label studies (Pallanti 1997; Fassino 2002; Santonastaso 2001; Ruggiero 2003) have suggested improvement with SSRIs, and the methodological limitations (discussed below) of the trials presented in this review compromise the clear understanding of the role of these drugs in acute AN. It is expected that an improved knowledge of the neurochemical alterations of the starvation state of AN can give clues to pharmacological research in this phase of the illness.

AUTHORS' CONCLUSIONS

Implications for practice

Anorexia nervosa is a complex disorder that challenges clinicians and researchers who wish to improve its treatment. In line with what is commonly reported in the literature in the field (Treasure 2004; De Zwann 2003a) this systematic review could not find evidence of efficacy of antidepressants in the acute phase of AN. A lack of quality information precludes us from drawing definite conclusions or recommendations on the use of these drugs in this phase of the illness. It is likely that short term treatment of underweight patients with antidepressants does not confer added benefit over and above specialised inpatient treatment, as most patients responded to complex inpatient programmes that targeted weight gain in trials. However, it needs to be noted that many patients with AN are treated as outpatients, with less intensive input, or outside specialised services, and antidepressants have not been tested in such conditions.

Moreover, although improved, many patients remain clinically symptomatic following re-feeding in hospital (Attia 1998), and are highly vulnerable to relapse. Unlike the findings in this review, promising initial results have been achieved by studies that investigated fluoxetine for relapse prevention in weight restored AN patients (Kaye 1991a; Kaye 2001a). Although these findings need replication, it suggests that the use of antidepressants could be considered after weight has been at least partially restored, aiming at improvement of residual symptoms and prevention of weight loss at follow-up.

Nevertheless, the regulatory agencies in United Kingdom (MHRA) and United States (FDA) have not approved any medication for the treatment of AN. Additionally, they have recently examined the controversial issue of the existence of a possible link between suicidality and use of antidepressants in children and adults, and they found that there was no, or insufficient, evidence from clinical trials to demonstrate that benefits of treating depressive illness in patients under 18 years of age with SSRIs outweighs the risks of side-effects, with the exception of fluoxetine, that was identified to have a positive balance. Thus, fluoxetine is the only approved drug in UK and US for treatment of depression in children (although recently it has been shown to be also associated with increased suicidal behaviour). In a critical appraisal of the subject, Licinio 2005 states that "most people who commit suicide suffer from major depression disorder, and in the vast majority of cases their suicide is the result of untreated or inadequately treated depression". Authors also state that "warnings from the agencies are not intended to prohibit the use of antidepressants, but to encourage prescribers to balance this risk versus the clinical need and the long-term consequences of not treating depression or other psychiatric disorders in children and adolescents". It is advisable, of course, to take all possible safety measures when antidepressants are used.

Implications for research

Although considerable research has been devoted to understanding AN, little progress has been made in developing effective treatments for this disorder and there is currently no single leading treatment for AN (NCCMH 2004; Agras 2004; Fairburn 2005). As seen in this review, the trials that investigated antidepressants in acute AN had major limitations that were mainly due to the small sample sizes (insufficient power to detect differences, large confidence intervals), and setting of treatment (inpatient complex programmes).

Thus, a randomised trial with a naturalistic design, comparing drug plus routine clinical practice (e.g. psychotherapy that includes nutritional advice) and routine clinical practice without medication in outpatient settings, could address the methodological pitfalls raised so far if the following aspects are also considered: (a) as inadequate sample sizes may have precluded finding meaningful differences between treatment groups, it is therefore paramount to have multi-centre trials with a large number of participants; (b) patients with AN need individualised interventions. The impact of treatment variations should be evaluated in analysis; (c) the study should have a long duration so as to assess the full spectrum of consequences and outcomes of these treatments; (d) the primary outcome should focus on the proportion of patients achieving normal BMI, and (e) as pointed out by the NIH report on "Overcoming barriers to treatment research in AN", secondary outcomes should include both measures of core and associated symptoms as well as measures of quality of life, social adaptation and resource utilization (Agras 2004). The blinding of the outcome assessments could be done by masking the research interviewers to the aims of the study. This study design may lead to numbers participating, fewer drop-outs and improved compliance.

Despite the existing controversy with utility of pharmacological agents during the starvation state of AN, drug trials are still needed as definitive conclusions on efficacy cannot yet be made. More-

over, specialist treatment is expensive and not widely available. Given the clinical problems and cardiac risks associated with tricyclic antidepressants, it is advisable that further trials test safer and more tolerable antidepressants such a SSRIs, noradrenergic specific agents and non tricyclic dual reuptake antidepressants to help inform clinical practice. It is also expected that increased knowledge on the neurobiology of AN might favour the development of more specific pharmacological targets in the treatment.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Attia 1998

Methods	RCT; placebo controlled; double-blind; duration variable: maximum 7 weeks or until reached 90% of ideal body weight plus one week (approximately 5 to 6 weeks); plasma levels of drug measured at week 4 and end of treatment; It is not certain that ITT analysis was conducted: of 33 patients initially randomised, data from only 31 were considered for analysis
Participants	AN Diagnosis: DSM-IV (criteria A, B and C) and weight less then 80% of ideal body weight ; 31 female inpatients: 12 AN-restrictive and 19 AN-binge/purge; significant difference in mean age between groups: fluoxetine 29.1ys (SD=7.2) and placebo 23.4 ys (SD=6.4)
Interventions	Fluoxetine 60 mg (mean dose 56mg/d SD=11.2) X placebo; all patients also attended individual psychotherapy (supportive and cognitive-behav), group sessions, family sessions (if available) and a structured behavioral treatment aimed at normalizing eating behavior and weight
Outcomes	Weight gain: end of treatment mean percent of ideal body weight, mean change in percent of ideal body weight per day; improvement in eating disorders symptoms (Anorexic Behvaior Scale, BSQ, EAT, Y-Brown-Cornell Eating Disorder Scale); improvement in depression and obsessive-compulsive symptoms (mean scores of SCL-90) and clinical improvement (mean scores in CGI); proportion of drop-outs for any reason and for side effects reported per group, and number of subjects reporting side effects also
Notes	Allocation concealment not mentioned; although groups differed in mean age, age was not related to clinical outcome on any clinical outcome measure; mean duration of treatment not different between groups (fluoxetine = 36.1 days SD 14.1 and placebo = 37.4 days SD 13.8); self -report data from one patient not analyzed (unreliable)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Biederman 1985

Methods	RCT; placebo controlled; double-blind; multi-centre (2); 3 arms (parallel); amitriptiline x placebo x control group (no drug); 5 weeks duration; compliance assessed (plasma levels measured weekly); ITT analysis apparently not realized (some outcomes do not consider all patients)
Participants	AN Diagnosis: Feighner + DSMIII criteria; 25 in and outpatients; amitriptyline n=11, mean age 18.4ys (SD=4.9); placebo n=14, 17.2ys (SD=4.3); gender not specified, nor anorexia type.
Interventions	Amitriptyline (mean daily dose 115 mg SD= 31) X placebo; all patients received medical and psychiatric treatment including suportive measures, nutritional counseling, individual psychotherapy and family intervention. Inpatients also received Behavior Modification Programme
Outcomes	Weight gain: mean weekly weight gain (kg/week) and number of patients responding to categories of percentage of weight gain; improvement in eating disorders, depression, anxiety, and obsessive-compulsive symptoms, and global clinical effect measured by weekly changes in scores in scales (EAT-40, SADS-C, HSCL, Global Severity and Global Improvement Scales); outcomes in overall symptomatology offered through number of patients per categories of percentages of response. Drop-outs not informed (apparently none as total number of patients were evaluated in some outcomes); number of patients reporting specific side-effects in each group referred but total number of patients with adverse events not described
Notes	Allocation concealment not mentioned; drug plasma levels available for 8 patients showed wide variation at the same dose (2 at the lower limit of assay sensitivity suggesting compliance problems); high refusal rate to study: 18 patients, who formed a control (no drug) group, not considered in this review

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Brambilla 1995a

Methods	RCT; two arms (not placebo controlled); open study; one center; 4 months duration; although authors informed that ITT analysis were not performed, they also informed that there were no drop-outs
Participants	AN - Restrictive Type Diagnosis: DSMIII-R + IV criteria; 22 female outpatients: nortriptyline n=7, fluoxetine n=15; overall sample mean age was 21 years (SD=5); groups comparable in BMI (no information on demographic and clinical factors comparisons)
Interventions	Nortriptyline 75mg/d X fluoxetine 60mg/d; all patients also attended CBT and nutritional therapy sessions

Brambilla 1995a (*Continued*)

Outcomes	Weight gain: evaluated through BMI; evaluation of eating disorders symptomatology (EDI and BITE), depression and anxiety symptomatology (HRS-D and HRS-A)
Notes	Allocation concealment based on use of sealed opaque envelopes; assesment of compliance only based in family support (no plasma levels of drug); no drop-outs. Information provided by first author

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Brambilla 1995b

Methods	RCT; two arms (not placebo controlled); open study; one center; 4 months duration ; although authors informed that ITT analysis were not performed, they also informed that there were no drop-outs
Participants	AN- Binge-Eating / Purging Type Diagnosis: DSMIII-R + IV criteria ; 13 female outpatients: amineptine n=7, fluoxetine n=6; overall sample mean age was 23.1 (SD=6.8); groups comparable in BMI (no information on clinical factors comparisons)
Interventions	Amineptine 300mg/d X fluoxetine 60mg/d; all patients also attended CBT and nutritional therapy sessions
Outcomes	Weight gain: evaluated through BMI; evaluation of eating disorders symptomatology (EDI and BITE), depression and anxiety symptomatology (HRS-D and HRS-A)
Notes	Allocation concealment based on use of sealed opaque envelopes; assesment of compliance only based in family support (no plasma levels of drug); no drop-outs. Information provided by first author

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Halmi 1986

Methods	RCT; placebo controlled; double-blind; duration variable (until reached target weight or maximum of 90 days) but mean duration was 4 to 5 weeks; multi-centre (2); 3 arms (parallel) (amitriptiline x cyproheptadine x placebo); ITT analysis not specifically reported and different number of patients were evaluated in outcomes

Halmi 1986 (*Continued*)

Participants	AN Diagnosis: DSM III + amenorrhea; 48 female inpatients (72 randomised considering cyproheptadine group) with 33 bulimic type and 39 restrictors; amitriptyline n=23 and placebo n=25; Overall mean age was 20.56ys SD=5.1. No information on comparability of groups
Interventions	Amitriptyline (maximum dose 160mg) X placebo, added to inpatient interventions not specified, except for a refeeding programme
Outcomes	Weight gain: number of patients achieving target weight (within 5% of normal range), average daily weight gain (kg/day) and time to achieve target weight (in those who achieved it); improvement in eating disorders symptoms (Anorectic Behavior Scale, and Anorectic Atittude Scale); improvement in depression (HRS-D, HSCL-90, BDI); drop-outs for any reason (treatment failures) and for side-effects stated
Notes	Allocation concealment not mentioned. No reference to measurement of drug plasma levels; statistical significant difference (greater achievement of target weight) in patients using maximum dose; placebo group presented a drop-out rate of 36%.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lacey 1980

Methods	RCT; placebo controlled; double-blind; duration variable: drug treatment until reached target weight (around 10-11 weeks); follow-up at one year and four years after weight gain; ITT analysis not clear (withdrawals were followed up and seems to have been included in analyses)
Participants	AN Diagnosis: criteria not described, authors refer to consecutive admissions to anorectic unit at hospital; 16 female inpatients: clomipramine n=8, mean age 20.9 yrs and placebo n=8, mean age 21.4 yrs (no SD informed); groups comparable (sex,age, weight, clinical history and social class). 7 AN-Restrictive and 1AN-Bulimic -type patient in each group.
Interventions	Clomipramine 50mg X placebo added to inpatient refeeding behavioural programme (bed-rest + planned meal), and individual and family psychotherapies; outpatient follow-up monitored weight and related behaviour coupled with

Lacey 1980 (*Continued*)

	psychotherapy (no drug)
Outcomes	Weight gain: absolute mean weight gain (kg) , mean daily rate of weight gain (kg/day), mean number of days to achieve target weight and mean % of ideal weight at one year follow-up; aspects of mood (sadness, anxiety, irritability) and appetite behaviour measured through analogue scales (developed by authors); drop -outs for any reason and for side-effects stated
Notes	Allocation concealment not mentioned. Low dose of clomipramine used; no reference to assessment of compliance (drug levels); number of evaluated patients not stated for some outcome measures (data probably refers to the complete sample as authors inform that all patients reached target weight (including drop-outs) and offer data of 1-year follow-up

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ruggiero 2001

Methods	RCT; 3 arms (not placebo controlled); single-blind (outcome assessor); three months duration; ITT analysis not clear (number of before and post - randomisation exclusions not clearly informed and outcomes refers to 35 patients who finished the re-feeding phase)
Participants	AN Restrictive Type Diagnosis: DSM-IV criteria; 35 inpatients (gender not specified): clomipramine n= 13, mean age 23.69 (SD 4.57); fluoxetine n=10, mean age 24.50 (SD 5.06) ; groups comparable in age and weight, but no information in other clinical or demographic aspects)
Interventions	Clomipramine mean daily dose 57.69 mg SD = 25.79; fluoxetine mean daily dose 28.00mg SD = 10.32; all patients received a nutritional and psychoeducation-al treatment
Outcomes	Weight gain: end of treatment mean weight and percentual of weight increase; improvement in eating disorders symptoms evaluated through Eating Disorder Interview based on Long Interval Follow-up (LIFE II BEI)
Notes	Allocation concealment not mentioned; data from one of the arms (amisulpride) was not considered: no reference to assesment of compliance (drug blood measurement); drop-outs not referred

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Study	Reason for exclusion
Barbarich 2004	RCT of additional nutritional supplements to potentiate the effects of fluoxetine in underweight AN subjects, which was not pertinent to the questions in this review
Bergh 1996	Retrospective observational study (clinical records) of citalopram in AN, which was not pertinent to the questions in this review
Bergh 2002	RCT of training of eating behavior and saciety by computer support, reduction of physical hyperactivity, supply or warmth and restoration of social function in eating disorders patients, which was not pertinent to the questions in this review
Birmingham 1994	RCT of zinc treatment AN, which was not pertinent to the questions in this review
Brambilla 1995c	RCT of T-lymphocite cholecystokinin-8 and beta-endorphin concentrations in AN patients, which was not pertinent to the questions in this review
Calandra 1999	Uncontrolled open trial of citalopram in eating disorders patients,which was not pertinent to the questions in this review
Corwin 1995	Retrospective observational study (chart review) of TCA versus fluoxetine in AN, which was not pertinent to the questions in this review
Eckert 1987	RCT investigates psychological aspects of subgroups of AN patients participating in a drug treatment, which was not pertinent to the questions in this review
Falk 1985	RCT investigates activity measures of AN patients in a drug treatment, which was not pertinent to the questions in this review
Fassino 2002	RCT of citalopram for AN compared to no-drug controls, which was not pertinent to the questions in this review
Ferguson 1987	Single-case report of AN treated with fluoxetine, which was not pertinent to the questions in this review
Ferguson 1999	Retrospective observational study (chart review) of SSRI versus no drug group AN patients, which was not pertinent to the questions in this review
Frank 2001a	Case reports of sertraline in underweight binge/eating purging type eating disorders, which was not pertinent to the questions in this review
Gross 1981	RCT of litium carbonate for AN, which was not pertinent to the questions in this review
Gwirtsman 1990	Uncontrolled open clinical trial of fluoxetine in AN, which was not pertinent to the questions in this review
Halmi 1982	RCT of cyproheptadine and amitriptyline for AN (partial data of included study: Halmi et al, 1986)
Halmi 1983	RCT of cyproheptadine and amitriptyline for AN (partial data of included study: Halmi et al, 1986)

(*Continued*)

Halmi 1999	RCT of fluoxetine versus CBT for relapse prevention of AN (ongoing trial - abstract published in APA Conference Annals), which was not pertinent to the questions in this review
Holtkamp 2005	Retrospective observational study (chart review) of SSRIs versus no drug treatment of child and adolescent AN, which was not pertinent to the questions in this review
Hudson 1985	Open clinical trial, not randomized, of drug treatment (AD, litium carbonate, carbamazepine) in AN patients, which was not pertinent to the questions in this review
Kaye 1991b	Open label clinical trial of fluoxetine for relapse prevention of AN, which was not pertinent to the questions in this review
Kaye 2001b	RCT of fluoxetine for relapse prevention of AN, which was not pertinent to the questions in this review
Moore 1977	Case report of amitriptyline in AN patient, which was not pertinent to the questions in this review
Mumford 1984	Single-case study of interaction of imipramine and CBT in the treatment of AN,which was not pertinent to the questions in this review
Pallanti 1997	Uncontrolled open trial of citalopram in AN, which was not pertinent to the questions in this review
Ricca 1999	Quasi-randomised study of venlafaxine versus fluoxetine in atypical anorectic patients, which was not pertinent to the questions in this review
Ruggiero 2003	Not-randomised, open controlled trial of nutritional management with and without fluoxetine in AN, which was not pertinent to the questions in this review
Sanchez 1993	Uncontrolled, open trial of fluvoxamine in AN patients, which was not pertinent to the questions in this review
Santonastaso 2001	Not randomised, open controlled trial of sertraline versus a no-drug group of AN patients, which was not pertinent to the questions in this review
Strobel 2004	Retrospective observational study (clinical reports) of paroxetine versus clomipramine for AN (abstract information), which was not pertinent to the questions in this review
Strober 1997a	Naturalistic prospective longitudinal follow-up study of relapse prevention for AN (matched historical controls) , which was not pertinent to the questions in this review
Strober 1999	Open label clinical trial of adjunctive fluoxetine for AN compared to matched historical controls, which was not pertinent to the questions in this review
Vandereycken 1984	RCT of neuroleptic treatment, which was not pertinent to the questions in this review

DATA AND ANALYSES

Comparison 1. ANTIDEPRESSANTS VS. PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean weight gain (kg) (high is better)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Mean percentage of target weight at 1y. follow-up (high is better)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
3 End of treatment mean percentage of ideal body weight (high is better)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Number of patients not achieving target weight	2	79	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.67]
5 Rate of weight gain (kg/day) (high is better)	2		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Rate of weight gain (change in % of ideal body weight /day) (high is better)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Time to achieve target weight (days)	2		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Absence of greater than 30% increase in weight (weight gain of 30% or less)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 End-point mean scores in Eating Disorder Scales	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
9.1 Anorectic Behaviour Scale	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
9.2 Yale-Brown-Cornell Eating Disorder Scale	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
9.3 Eating Attitudes Test (EAT)	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
9.4 Body Shape Questionnaire (BSQ)	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
10 Absence of greater than 50% response in antidepressant effect (50% response or less in SADS-C)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 End-point mean scores in Depression Scales	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 Beck Depression Scale	2	79	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.43, 0.45]
11.2 SCL-90 Depression Subscale	1	31	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.60, 0.81]
11.3 Hamilton Depression Scale	1	36	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-1.12, 0.22]

12 Absence of greater than 50% response in antiobsessional effect (50% response or less in HSCL)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 End-point mean scores in Obsessive Subscale (SCL-90)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
14 Absence of greater than 50% response in antianxiety effect (50% response or less in SADS-C)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15 Absence of greater than 50% response in clinical global effect (50% response or less in G. Improv. Scale)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16 End-point mean scores in clinical global improvement scale (CGI)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
17 Rates of non-completers	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 for any reason	4	120	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.46, 1.75]
17.2 drop-outs for side effects	4	120	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.09, 4.82]
18 Number of patients reporting side effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 2. ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 End of treatment mean BMI (high is better)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 fluoxetine versus nortriptyline	1	22	Std. Mean Difference (IV, Random, 95% CI)	0.81 [-0.12, 1.75]
1.2 fluoxetine versus amineptine	1	13	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-1.81, 0.46]
2 End of treatment mean absolute weight (high is better)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 fluoxetine versus clomipramine	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
3 Mean percentage of weight increase (high is better)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 fluoxetine versus clomipramine	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
4 End-point mean scores in Eating Disorders Inventory (EDI)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 fluoxetine versus nortriptyline	1	22	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.81, 0.99]
4.2 fluoxetine versus amineptine	1	13	Std. Mean Difference (IV, Random, 95% CI)	1.70 [0.36, 3.04]

5 End-point mean scores in Hamilton Depression Scale (HRS-D)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 fluoxetine versus nortriptyline	1	22	Std. Mean Difference (IV, Random, 95% CI)	0.86 [-0.08, 1.80]
5.2 fluoxetine versus amineptine	1	13	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
6 End-point mean scores in Hamilton Anxiety Scale (HRS-A)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 fluoxetine versus nortriptyline	1	22	Std. Mean Difference (IV, Random, 95% CI)	1.28 [0.29, 2.27]
6.2 fluoxetine versus amineptine	1	13	Std. Mean Difference (IV, Random, 95% CI)	0.38 [-0.72, 1.48]

Analysis 1.1. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 1 Mean weight gain (kg) (high is better).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 1 Mean weight gain (kg) (high is better)

Study or subgroup	placebo N	Mean(SD)	clomipramine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Lacey 1980	8	14.7 (4.6)	8	11.33 (5.32)		0.64 [-0.37, 1.65]

Analysis 1.2. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 2 Mean percentage of target weight at 1y. follow-up (high is better).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 2 Mean percentage of target weight at 1y. follow-up (high is better)

Study or subgroup	placebo		clomipramine		Std. Mean Difference	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Lacey 1980	8	89.89 (8.38)	8	95.63 (6.04)		-0.74 [-1.77, 0.28]

Analysis 1.3. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 3 End of treatment mean percentage of ideal body weight (high is better).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 3 End of treatment mean percentage of ideal body weight (high is better)

Study or subgroup	placebo		fluoxetine		Std. Mean Difference	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Attia 1998	16	87.4 (4.7)	15	86.6 (6.3)		0.14 [-0.56, 0.85]

Analysis 1.4. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 4 Number of patients not achieving target weight.

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 4 Number of patients not achieving target weight

Study or subgroup	treatment n/N	placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Attia 1998	4/15	4/16		34.4 %	1.07 [0.32, 3.52]
Halmi 1986	6/23	9/25		65.6 %	0.72 [0.31, 1.72]
Total (95% CI)	**38**	**41**		**100.0 %**	**0.83 [0.41, 1.67]**

Total events: 10 (treatment), 13 (placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.26$, df = 1 (P = 0.61); $I^2 = 0.0\%$

Test for overall effect: Z = 0.53 (P = 0.60)

Analysis 1.5. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 5 Rate of weight gain (kg/day) (high is better).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 5 Rate of weight gain (kg/day) (high is better)

Study or subgroup	placebo N	Mean(SD)	treatment N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Halmi 1986	16	0.23 (0.12)	17	0.31 (0.17)		-0.53 [-1.22, 0.17]
Lacey 1980	8	0.21 (0.03)	8	0.17 (0.04)		1.07 [0.00, 2.14]

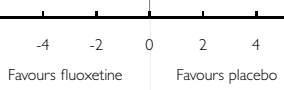
Analysis 1.6. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 6 Rate of weight gain (change in % of ideal body weight /day) (high is better).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 6 Rate of weight gain (change in % of ideal body weight /day) (high is better)

Study or subgroup	placebo N	Mean(SD)	fluoxetine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Attia 1998	16	0.42 (0.11)	15	0.35 (0.17)		0.48 [-0.24, 1.20]



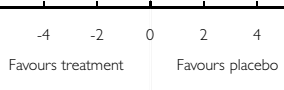
Analysis 1.7. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 7 Time to achieve target weight (days).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 7 Time to achieve target weight (days)

Study or subgroup	treatment N	Mean(SD)	placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Halmi 1986	17	32.24 (17.37)	16	45 (18.34)		-0.70 [-1.40, 0.01]
Lacey 1980	8	76 (24)	8	72 (28)		0.15 [-0.84, 1.13]

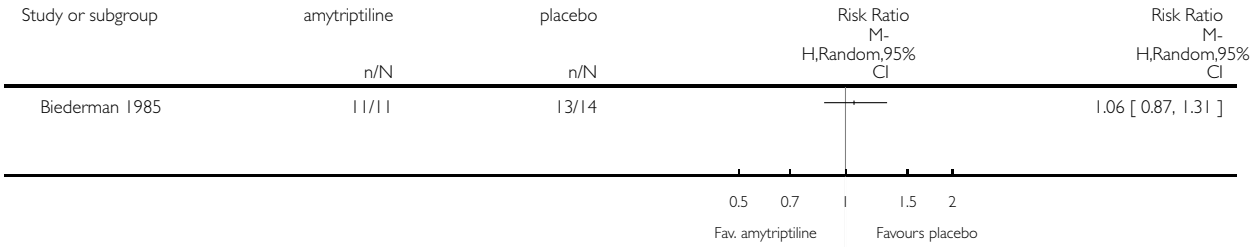


Analysis 1.8. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 8 Absence of greater than 30% increase in weight (weight gain of 30% or less).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 8 Absence of greater than 30% increase in weight (weight gain of 30% or less)

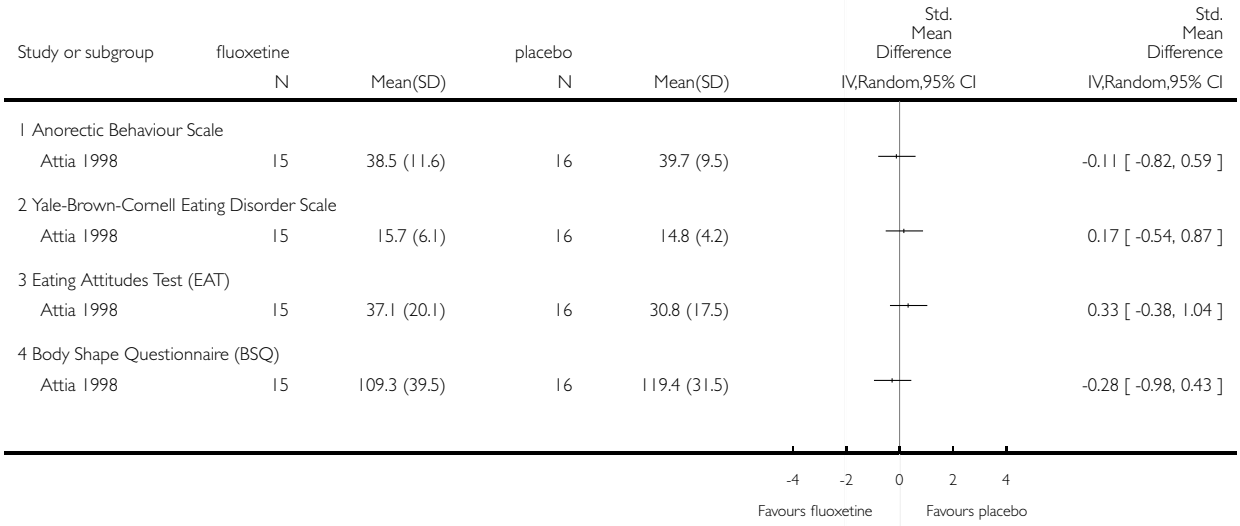


Analysis 1.9. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 9 End-point mean scores in Eating Disorder Scales.

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 9 End-point mean scores in Eating Disorder Scales

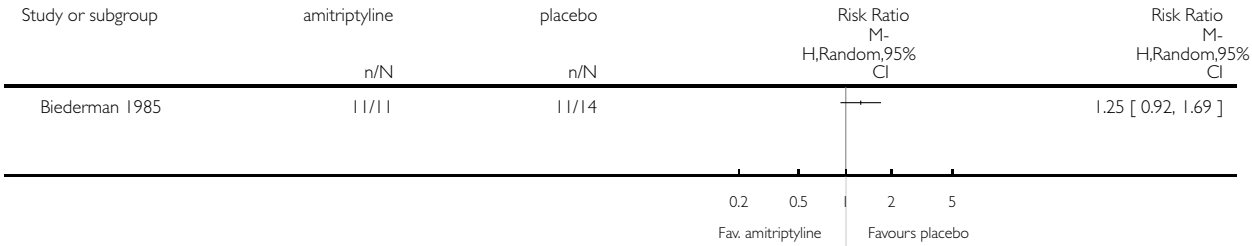


Analysis 1.10. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 10 Absence of greater than 50% response in antidepressant effect (50% response or less in SADS-C).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 10 Absence of greater than 50% response in antidepressant effect (50% response or less in SADS-C)

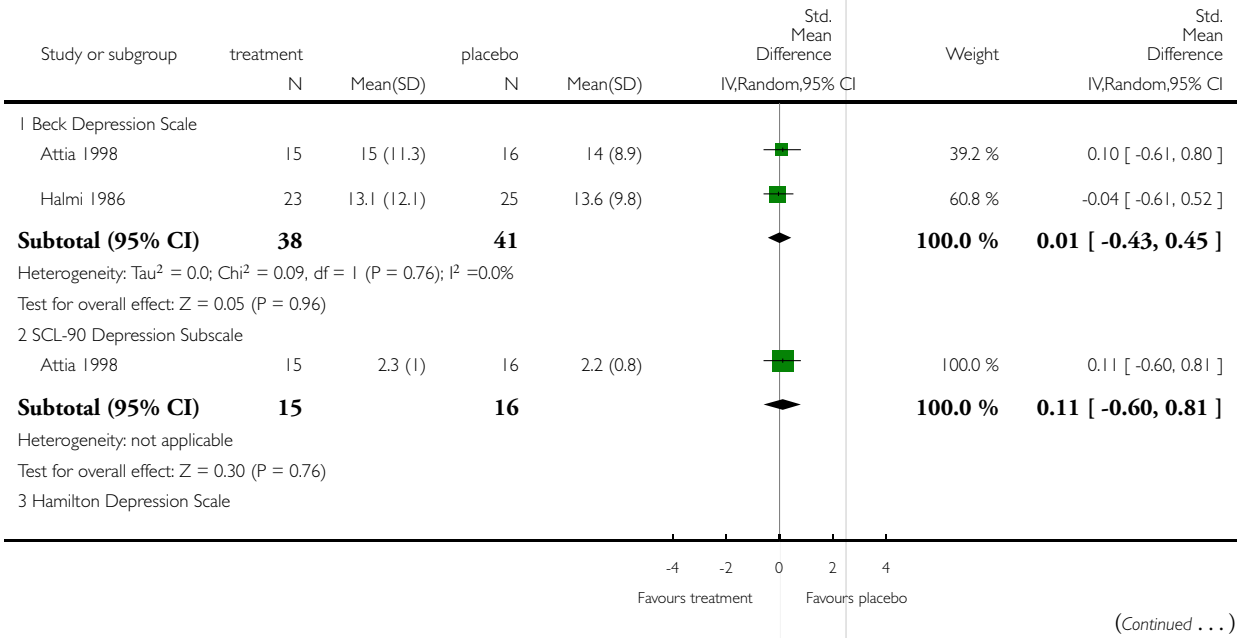


Analysis 1.11. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 11 End-point mean scores in Depression Scales.

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 11 End-point mean scores in Depression Scales



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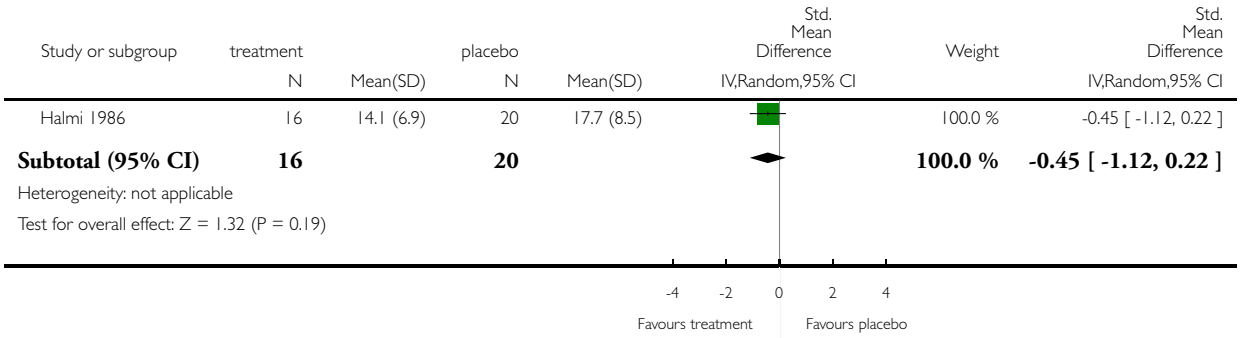
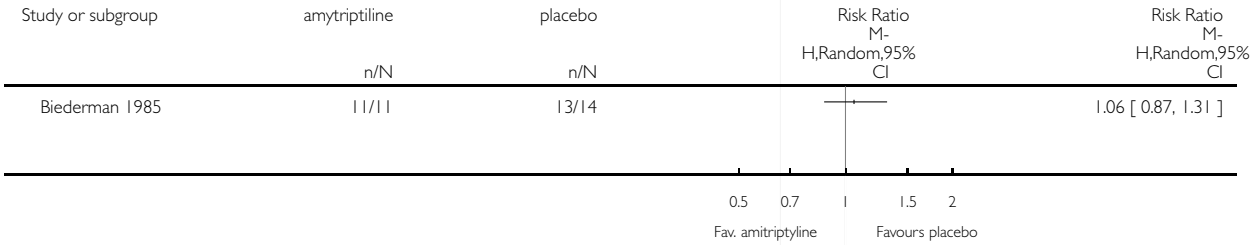


Analysis 1.12. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 12 Absence of greater than 50% response in antiobsessional effect (50% response or less in HSCL).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 12 Absence of greater than 50% response in antiobsessional effect (50% response or less in HSCL)



Analysis 1.13. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 13 End-point mean scores in Obsessive Subscale (SCL-90).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

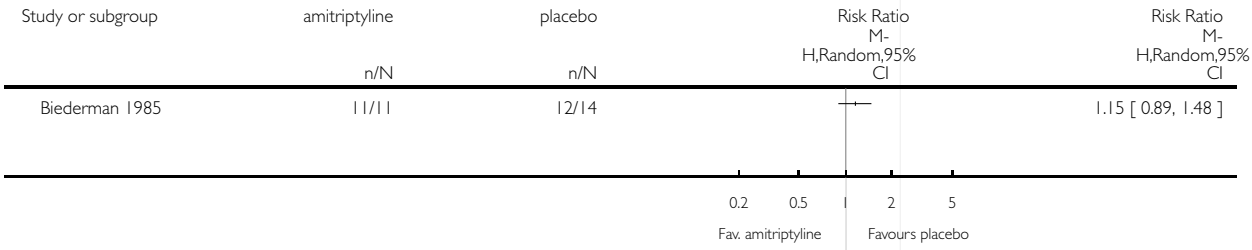
Outcome: 13 End-point mean scores in Obsessive Subscale (SCL-90)

Analysis 1.14. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 14 Absence of greater than 50% response in antianxiety effect (50% response or less in SADS-C).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 14 Absence of greater than 50% response in antianxiety effect (50% response or less in SADS-C)



Analysis 1.15. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 15 Absence of greater than 50% response in clinical global effect (50% response or less in G. Improv. Scale).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 15 Absence of greater than 50% response in clinical global effect (50% response or less in G. Improv. Scale)

Study or subgroup	amitriptyline n/N	placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Biederman 1985	10/11	13/14		0.98 [0.77, 1.24]

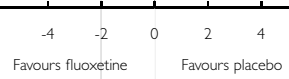
Analysis 1.16. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 16 End-point mean scores in clinical global improvement scale (CGI).

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 16 End-point mean scores in clinical global improvement scale (CGI)

Study or subgroup	fluoxetine N	Mean(SD)	placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
Attia 1998	15	2.5 (1.4)	16	2.8 (1.5)		-0.20 [-0.91, 0.51]

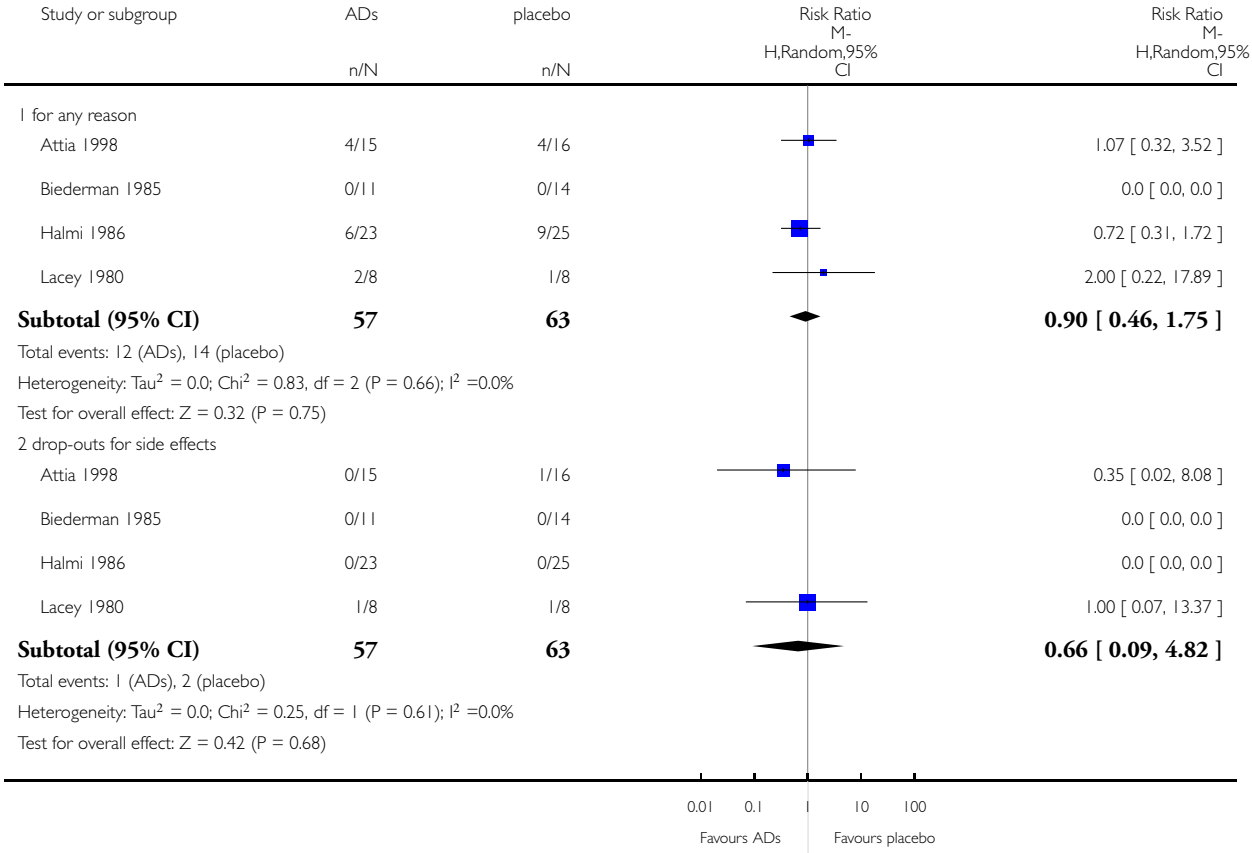


Analysis 1.17. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 17 Rates of non-completers.

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 17 Rates of non-completers



Analysis 1.18. Comparison 1 ANTIDEPRESSANTS VS. PLACEBO, Outcome 18 Number of patients reporting side effects.

Review: Antidepressants for anorexia nervosa

Comparison: 1 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 18 Number of patients reporting side effects

Study or subgroup	fluoxetine n/N	placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Attia 1998	2/15	1/16		2.13 [0.22, 21.17]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 2 (fluoxetine), 1 (placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

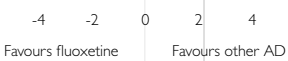
Analysis 2.1. Comparison 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 1 End of treatment mean BMI (high is better).

Review: Antidepressants for anorexia nervosa

Comparison: 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 1 End of treatment mean BMI (high is better)

Study or subgroup	other AD N	Mean(SD)	fluoxetine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 fluoxetine versus nortriptyline							
Brambilla 1995a	7	18.3 (1.7)	15	16.3 (2.6)		100.0 %	0.81 [-0.12, 1.75]
Subtotal (95% CI)	**7**		**15**			**100.0 %**	**0.81 [-0.12, 1.75]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.70 (P = 0.088)							
2 fluoxetine versus amineptine							
Brambilla 1995b	7	17.7 (2.6)	6	21.1 (6.3)		100.0 %	-0.68 [-1.81, 0.46]
Subtotal (95% CI)	**7**		**6**			**100.0 %**	**-0.68 [-1.81, 0.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.17 (P = 0.24)							



Analysis 2.2. Comparison 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 2 End of treatment mean absolute weight (high is better).

Review: Antidepressants for anorexia nervosa

Comparison: 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 2 End of treatment mean absolute weight (high is better)

Study or subgroup	clomipramine N	Mean(SD)	fluoxetine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
1 fluoxetine versus clomipramine						
Ruggiero 2001	13	38.69 (9.38)	10	42.7 (7.54)		-0.45 [-1.28, 0.39]

Analysis 2.3. Comparison 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 3 Mean percentage of weight increase (high is better).

Review: Antidepressants for anorexia nervosa

Comparison: 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 3 Mean percentage of weight increase (high is better)

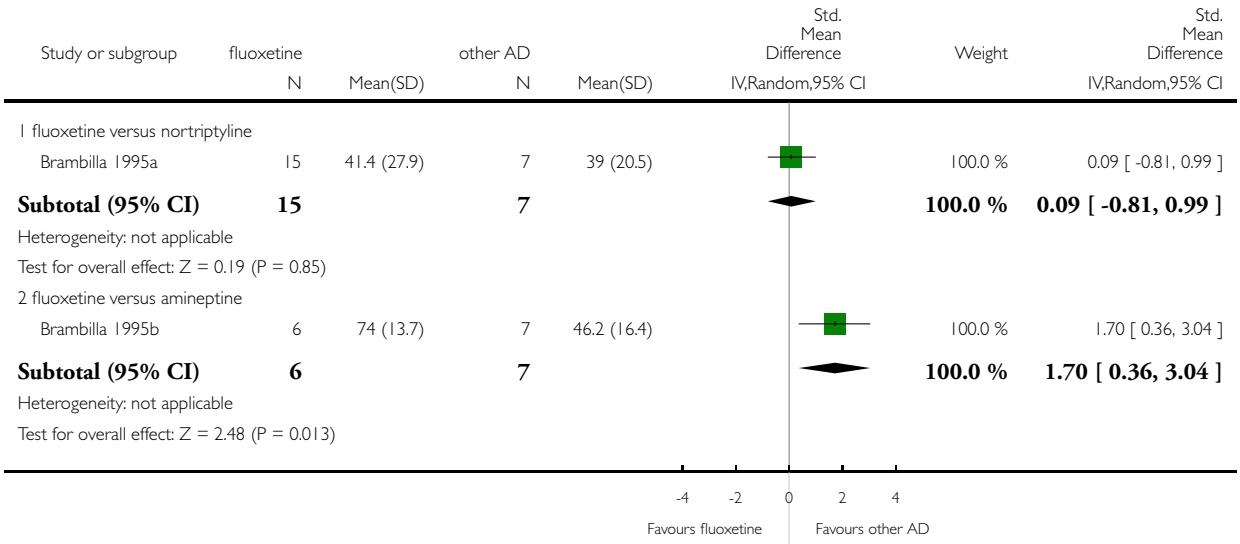
Study or subgroup	clomipramine N	Mean(SD)	fluoxetine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Std. Mean Difference IV,Random,95% CI
1 fluoxetine versus clomipramine						
Ruggiero 2001	13	3.26 (6.48)	10	4.52 (5.89)		-0.19 [-1.02, 0.63]

Analysis 2.4. Comparison 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 4 End-point mean scores in Eating Disorders Inventory (EDI).

Review: Antidepressants for anorexia nervosa

Comparison: 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 4 End-point mean scores in Eating Disorders Inventory (EDI)



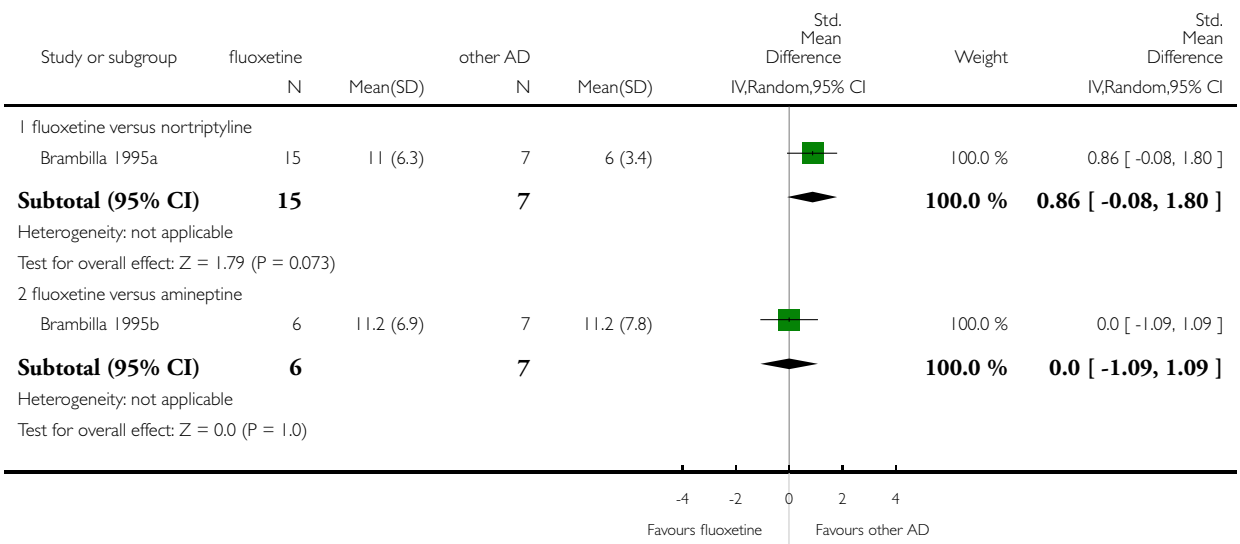
Analysis 2.5. Comparison 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 5 End-point mean scores in Hamilton Depression Scale (HRS-D).

Review: Antidepressants for anorexia nervosa

Comparison: 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 5 End-point mean scores in Hamilton Depression Scale (HRS-D)

Study or subgroup	fluoxetine N	Mean(SD)	other AD N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 fluoxetine versus nortriptyline							
Brambilla 1995a	15	11 (6.3)	7	6 (3.4)		100.0 %	0.86 [-0.08, 1.80]
Subtotal (95% CI)	**15**		**7**			**100.0 %**	**0.86 [-0.08, 1.80]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.79 (P = 0.073)							
2 fluoxetine versus amineptine							
Brambilla 1995b	6	11.2 (6.9)	7	11.2 (7.8)		100.0 %	0.0 [-1.09, 1.09]
Subtotal (95% CI)	**6**		**7**			**100.0 %**	**0.0 [-1.09, 1.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							

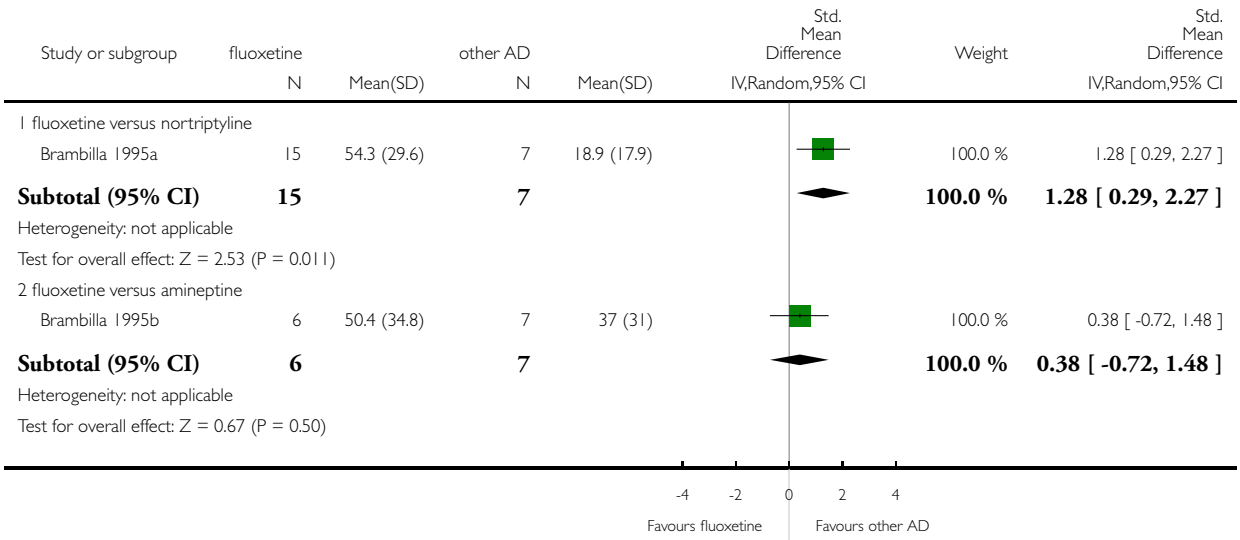


Analysis 2.6. Comparison 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 6 End-point mean scores in Hamilton Anxiety Scale (HRS-A).

Review: Antidepressants for anorexia nervosa

Comparison: 2 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 6 End-point mean scores in Hamilton Anxiety Scale (HRS-A)



WHAT'S NEW

Last assessed as up-to-date: 3 November 2005.

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

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 1, 2006

Date	Event	Description
4 November 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AMC - protocol writing, data searches, quality assessment, data extraction and entering, review writting

MSL - protocol writing, quality checking of data extraction and entering, statistical advice and commentary on findings and conclusions

JB - - protocol writing, quality assessment and data extraction, commentary on findings and conclusions

PH - protocol and revision commentaries

JT - protocol and revision commentaries

US - protocol and revision commentaries

DECLARATIONS OF INTEREST

JB is Medical Director of Janssen-Cilag in São Paulo, Brazil. MSL is Senior Clinical Research Physician in Eli Lilly Brazil, São Paulo.

SOURCES OF SUPPORT

Internal sources

- Universidade Federal de São Paulo (UNIFESP / EPM), Brazil.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Anorexia Nervosa [*drug therapy]; Antidepressive Agents [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans