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Antidepressants for generalised anxiety disorder (GAD) (Review)

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TABLE OF CONTENTS

[Intervention Review]

Antidepressants for generalised anxiety disorder (GAD)

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ABSTRACT

Background

Pharmacological treatments have been successfully used to treat Generalized Anxiety Disorder (GAD). Benzodiazepine and non benzodiazepine anxiolytics used to be the mainstay for the pharmacological treatment of GAD. However, data emerging over the last two decades have shown that antidepressants may be as effective as anxiolytics in this condition. The use of antidepressants may also be beneficial , because GAD often coexists with major depressive disorder (62% comorbidity) and dysthymia (37%).

Objectives

To assess the efficacy and acceptability of antidepressants for treating generalized anxiety disorder.

Search methods

Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register - CCDANCTR (up to May 2002), Anxiety Neurosis (up to May 2002) and Cochrane Controlled Trials Register (CENTRAL/CCTR) (up to May 2002), MEDLINE (1966 to May 2002), LILACS (1982 to May 2002); reference searching; personal communication; conference abstracts and book chapters on the treatment of generalized anxiety disorder.

Selection criteria

Randomized controlled trials were included. Non randomized studies and those that included patients with both GAD and another Axis I co-morbidity were excluded.

Data collection and analysis

The data from studies were extracted independently by two reviewers. Relative risks, weighted mean difference and number needed to treat were estimated. People who died or dropped out were regarded as having had no improvement.

Main results

Antidepressants (imipramine, venlafaxine and paroxetine) were found to be superior to placebo in treating GAD. The calculated NNT for antidepressants in GAD is 5.15. Dropout rates did not differ between antidepressants. Only one study presented data on imipramine and trazodone. Imipramine was chosen as the reference drug and, therefore, data on trazodone could not be included in the meta analysis. Only one study was conducted among children and adolescents (Rynn 2000). This showed very promising results of sertraline in children and adolescents with GAD, which warrants replication in larger samples.

Authors' conclusions

The available evidence suggests that antidepressants are superior to placebo in treating GAD. There is evidence from one trial suggesting that paroxetine and imipramine have a similar efficacy and tolerability. There is also evidence from placebo-controlled trials suggesting that these drugs are well tolerated by GAD patients. Further trials of antidepressants for GAD will help to demonstrate which antidepressants should be used for which patients.

PLAIN LANGUAGE SUMMARY

Antidepressants for generalized anxiety disorder (GAD)

In the past, people with generalized anxiety disorder (GAD) were usually treated with drugs designed to reduce anxiety (called anxiolytics). There is growing evidence that drugs used to treat depression (antidepressants) may also be helpful for people with GAD. We therefore reviewed clinical trials of the use of antidepressants in GAD . Fifteen published trials were included. Of these trials, eight used recognized methods for diagnosing GAD and gave useful data (Rickels 1993; Rocca 1997; Davidson 1999 a; Gelenberg 2000, Rickels 2000 b, Hackett 1999, Pollack 2001, Rynn 2000). Six trials were excluded: two trials were open studies, without a control group (Hedges 1996; Wingerson 1992); two included patients with GAD plus other types of mental illness (Johnstone 1980 a; Lipman 1986); one study included patients who were stopping long term benzodiazepine therapy (Rickels 2000 a). One study presented early data for an already included study (Hackett 1999). We are waiting for further data for one study (Hoehn-Saric 1988). One study involved children and adolescents with GAD (Rynn 2000) and its results were reviewed separately. Our review showed that antidepressants were better than placebo (dummy treament) for treating GAD and were well tolerated. We did not find evidence to conclude whether some types of antidepressant are better than others. Overall, about 5 people need to be treated in order for one person with GAD to benefit. The single study using antidepressants in children and adolescents with GAD also showed very promising results.

BACKGROUND

Generalized anxiety disorder (GAD) is characterized by excessive, pervasive and uncontrollable worry. Associated symptoms include irritability, restlessness and concentration problems. Somatic symptoms of GAD include muscle tension, sweating, dry mouth, nausea and diarrhea (APA 1994). GAD is a chronic and recurrent disorder with a low rate of remission (Yonkers 1996). GAD has a considerable impact on quality of life and is associated with increased reliance in public assistance, impaired social life and low ratings of life satisfaction (Massion 1993). The current and lifetime prevalence of GAD have been estimated to be 1.6% and 5.1% respectively (Wittchen 1994). The lifetime prevalence of psychiatric comorbidities in GAD patients can reach over 90 % (Wittchen 1994). The most common co-morbidities are major depressive disorder (62%) and dysthymia (39%) (Judd 1998). However, recent epidemiological data suggests that the impact of comorbidity in clinical outcomes is no greater in GAD than in other anxiety disorders (Hunt 2002). Moreover, comorbidities such as major depression do not appear to change the course of GAD (Hunt 2002).

Benzodiazepines and non benzodiazepine anxiolytics such as buspirone have been the mainstay for the treatment of GAD in the past (Brawman-Mintzer 2001). As GAD tends to be a chronic condition, long-term pharmacological treatment is often necessary. This raises concern about the use of benzodiazepines, since these compounds may be associated with risks of abuse and dependence. Buspirone is devoid of the dependence risks associated with benzodiazepines, however it has a more limited spectrum of efficacy and delayed onset of action compared to other treatments.

A variety of psychotherapeutic approaches have been used to treat GAD. To date, the most consistent data on the psychotherapy of GAD comes from the cognitive-behavioural therapy (CBT) approach. Results from well-conducted trials suggest that CBT can produce clinically relevant and long term therapeutic improvements compared with controls. Psychotherapeutic approaches also seem to be well tolerated by patients and the dropout rates in clinical trials are low (Borkovec 2001). There are also data supporting the notion that psychotherapy may have an additional impact in the comorbid conditions associated to GAD (Borkovec 2001).

The first trial assessing the effect of antidepressants in GAD, diagnosed according to DSM-III criteria, was conducted by Hoehn-Saric and his colleagues (Hoehn-Saric 1988). These authors com-

pared alprazolam and imipramine in a group of 52 GAD patients. They showed that both drugs were effective in treating GAD. However, imipramine was more effective in attenuating psychological symptoms such as dysphoria and anticipatory negative thinking, whereas alprazolam was more effective in somatic symptoms and in the hyperarousal associated with GAD. The same trend was detected by Rickels and his colleagues (Rickels 1993) in a comparison between imipramine, trazodone, diazepam and placebo. Rickels (Rickels 1993) showed that from week 3 through week 8, trazodone achieved similar anxiolytic efficacy to diazepam; the effect of imipramine was found to be somewhat better, and psychological symptoms such as apprehension and worry respondedbetter to the antidepressants than the anxiolytics. A study by Rocca and associates (Rocca 1997), within a sample of DSM-IV diagnosed GAD patients, supported the theory that antidepressants affect predominantly psychological symptoms whereas benzodiazepine affect predominantly somatic symptoms in GAD. A comparison between antidepressants and non benzodiazepine anxiolytics is available only for venlafaxine and buspirone (Davidson 1999 a). This study included 365 patients and showed that venlafaxine and buspirone were superior to placebo in the majority of outcomes considered. There is also evidence that the management of benzodiazepine discontinuation in GAD patients can be facilitated by co-prescribing imipramine but not buspirone (Rickels 2000 a).

In the light of the data presented, there are reasons to believe that antidepressants may offer a valuable alternative in the treatment of GAD patients. In the present review, RCT data on the use of antidepressants for treating GAD were assessed. The present review is part of a series of reviews on GAD treatment:

In the light of the data presented, there are reasons to believe that antidepressants may offer a valuable alternative in the treatment of GAD patients. In the present review, RCTs data on the use of antidepressants for treating GAD will be assessed. The present review is part of a series of reviews on GAD treatment. The other reviews in the series are:

(1) Antidepressants

(2) Buspirone and other azapirones

(3) Benzodiazepines

(4) Psychotherapy.

OBJECTIVES

To investigate the efficacy and acceptability of antidepressants in the treatment of generalized anxiety disorder.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials comparing antidepressants to placebo or to another active pharmacological treatment.

Types of participants

People with a diagnosis of generalized anxiety disorder irrespective of gender, race, age or nationality.
Exclusion criteria: patients with generalized anxiety disorder and another axis I co-morbidity.

Types of interventions

1) Any type of antidepressant
2) Control treatments (any active drug or placebo). Whenever a placebo arm was present in the study, the comparison included in the metanalysis was antidepressant vs placebo.

Types of outcome measures

Primary outcomes of interest were:
1) Generalized anxiety changes at the end of trial
(a) absence of treatment response as defined in the studies (treatment response is defined as absence of sufficient symptoms to meet diagnostic criteria for generalized anxiety disorder); scores of 1 or 2 in the Clinical Global impression Scale, which is a continuous scale of seven grades, where 1= very much improved, 2 = much improved... and 7 = very much worse
2) Acceptability of the treatment as measured by:
(a) the number of people dropping out during the trial, and post randomisation exclusions
(b) specific side-effects.

Search methods for identification of studies

1. Electronic databases:
The following electronic databases were searched:
- The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) up to May 2002;
- The Cochrane Central Register of Controlled Trials (CENTRAL) (previously CCTR);
- MEDLINE (1966-May2002)
- LILACS (1982-May 2002)
The MEDLINE and LILACS (up to May 2002) searches also acted as a quality assessment whereby the comprehensiveness and completeness of the two Cochrane registers were evaluated.
The terms used in the search were: anxiety or anxiety disorder and pharmacotherapy-5ht or pharmacotherapy-ad or pharmacotherapy-maoi or pharmacotherapy-nari or pharmacotherapy-

rima or pharmacotherapy-r-ssri or pharmacotherapy-r-tca or pharmacotherapy-snri or pharmacotherapy-ssri or pharmacotherapy-tca.
2. Conference abstracts were searched for references.
3. Personal communication: in order to ensure that as many as possible RCTs would be identified, the authors of the included studies were consulted to find out if they knew of any published or unpublished RCTs/ CCTs of pharmacological treatment of generalized anxiety disorder, and which were not yet identified. A list of all identified RCTs identified through consulting other sources was sent to the authors.
4. Attempts were made to obtain unpublished trials from the pharmaceutical industry.
5. Book chapters on treatment of generalized anxiety disorder were reviewed.

Data collection and analysis

Selection of trials
One reviewer (FK) screened the abstracts of all publications that were obtained by the search strategy. A distinction was made between:
1) eligible studies, in which antidepressants were compared to placebo or another drug
2) studies without any control element; studies of general treatment for GAD rather than pharmacological; studies of drug treatments other than antidepressants
For abstracts where the authors found any indication of a clinical trial, the full article was obtained and inspected to assess its relevance to this review.
Quality assessment
In order to ensure that variation was not caused by systematic errors in the design of a study, the methodological quality of the selected trials was assessed by two independent reviewers (FK and RS). The methodological quality was assessed using the criteria described in the Cochrane Handbook (Clarke 2000). It is based on the evidence of a strong relationship between the potential for bias in the results and the allocation concealment and is defined as below:
A. Low risk of bias (adequate allocation concealment)
B. Moderate risk of bias (unclear method of allocation concealment)
C. High risk of bias (inadequate allocation concealment)
For the purpose of the analysis in this review, trials were included if they met the criteria A or B as described in the Cochrane Handbook.
Data Management
Data were independently extracted by two reviewers (FK and RS). Any disagreement was discussed with a third reviewer (MSL), decisions were documented and, where necessary, the study authors contacted to resolve the issue. All exclusions/dropouts were identified. If no information was available (either from the report or the authors) it was assumed that dropouts were due to side effects/ treatment failure.
Analysis
In the statistical analysis, the relative risk and 95% confidence interval for dichotomous variables were calculated using the random effects model, as it takes into account of any between study differences (even if there is no statistically significant heterogeneity) and gives the same result as the fixed effects model when there is no between-study variance. Review Manager Software 4.1was used to analyse the results. In the efficacy analysis, the number needed to treat (NNT) was also calculated, using 95% confidence intervals. The NNT is defined as the inverse of differences of risk between groups. The NNT expresses the number of patients that have to be treated in order to achieve oneresponse, when compared to the control group.

RESULTS

Description of studies

Search
We retrieved 15 clinical trials in which antidepressants were used to treat GAD.
- Eight trials assessing antidepressants in adult GAD patients used diagnostic criteria for GAD and had data that could be included in this review (2058 patients in total). One trial was conducted among children, so these results were handled separately and not included in the "all antidepressants" (Rynn 2000). One additional report presented preliminary data for an already included study (Hackett 1999). We included the following trials in the meta analysis: Rickels 1993, Rocca 1997, Davidson 1999 a, Gelenberg 2000, Rickels 2000 b, Hackett 1999 and Pollack 2001. In one trial, just one variable (side-effects), was described in a way which permitted inclusion in the meta-analysis (Rickels 2000 b); further information from the authors is awaited in order to include other outcomes.
- Five trials were excluded: two studies were open trials (Hedges 1996; Wingerson 1992); two studies (Johnstone 1980 a; Lipman 1986) included patients who fulfilled criteria for more than one diagnostic category (depressive neurosis and hysterical or phobic neurosis); one study included patients who were discontinuing long term benzodiazepine therapy at the time the trial was conducted (Rickels 2000 a).
- One study is still awaiting assessment because the data required for this review were not available in the published version (Hoehn-Saric 1988).
Design
All the included studies were described as randomised and used a parallel group design. The duration of the trials ranged from 6 weeks (Hoehn-Saric 1988) to 28 weeks (Gelenberg 2000). Two

studies included a long term follow up after the acute phase of treatment (Gelenberg 2000, Hackett 1999) All studies used inactive placebo groups.

Setting

All included trials were conducted in the US, except Rocca 1997, conducted in Italy and Hackett 1999, conducted in several countries in Europe. All trials studied outpatients from psychiatric clinics or from the community.

Participants

All trials included for the main comparisons used DSM-III, DSM-III-R or DSM-IV criteria for the diagnosis of GAD. The study populations were reasonably comparable. The number of participants randomised in the trials ranged from 56 to 541.

Outcomes

All trials used symptom scales in assessing treatment effects. The Hamilton Anxiety Scale (HAM-A) was the most commonly used. However, some trials lacked data on standard deviations, and in other cases showed skewed data distribution. Continuous outcomes will be analysed in future versions of this review, when further information from the authors are obtained.

Three dichotomous outcomes were used in this review:

(1) absence of response: for most trials this equated to a Clinical Global Impression (CGI) score of 1 or 2;

(2) dropout rate;

(3) specific side effects.

Reason for excluding studies

Some of the excluded studies were not randomized and some were conducted using patients with an Axis I disorder in addition to GAD.

Risk of bias in included studies

All RCTs were classified as 'B', not giving information on allocation concealment. We are still awaiting further details from most of the authors.

All trials reported the randomization procedure without any information on allocation concealment. Although many trials reported an intention-to-treat analysis, some of them excluded patients after randomization because of protocol violations. The omission of standard deviations was also common

Effects of interventions

Efficacy

All antidepressants vs placebo:

The efficacy analysis included the following studies, where data could be extracted: Rickels 1993, Davidson 1999 a, Gelenberg 2000 and Pollack 2001. Other included studies were used in the analysis of number of dropouts and specific side effects.

In general, short-term treatment response was more likely in patients receiving antidepressants than placebo. One study (Rickels 1993) compared treatments (imipramine, trazodone, diazepam and placebo). As imipramine was considered a reference antidepressant, we used the 'imipramine vs placebo' comparison rather than 'trazodone vs placebo'. Considering all trials, the pooled RR for non treatment response was 0.70 (95% CI 0.62-0.79), favouring antidepressant treatment. The calculated NNT was 5.5 (95% CI 4.1-8.4) for a non-response rate of 62% in the placebo group.

- Imipramine (Rickels 1993): The calculated RR was 0.67 (95 % CI 0.50-0.91) and the NNT was 4.0 (95% CI 2.4-13.7).

- Venlafaxine (Davidson 1999 a, Gelenberg 2000): The calculated RR for non treatment response was 0.68 (95% CI 0.46-0.99), and the NNT was 5.0 (95% CI 3.58-8.62) for a non-response rate of 66% in the placebo group. The studies carried out by Rickels 2000 b and Hackett 1999could not be used for the efficacy analysis, as data could not be extracted as reported.

- Paroxetine (Pollack 2001): The calculated RR for non treatment response was 0.72 (95% CI 0.56-0.92), and the calculated NNT was 6.72 (95% CI 3.9-24.7)

- Paroxetine vs imipramine (Rocca 1997): The calculated RR was 1.73 (95% CI 0.31-9.57)

Sertraline vs placebo in children and adolescents:

- Sertraline (Rynn 2000): This study was not included in the meta analysis because it studied children and adolescents. The results obtained in this small trial (N = 22) were very compelling, showing a calculated NNT of 1.22 (0.90-1.7).

Acceptability

Dropouts:

No significant differences were found between antidepressants and placebo. The RR for any antidepressant was 0.95 (95% CI 0.84-1.09). Similarly, when individual antidepressants were considered, no differences were found between individual treatments and the placebo group:

-Imipramine: RR = 0.71 (95% CI 0.41-1.24);

- Venlafaxine: RR = 0.86 (95% CI 0.72-1.02);

- Sertraline: RR = 0.45 (95% CI 0.03-5.84)

- Paroxetine: RR = 1.15 (95% CI 0.74 - 1.78) and

- Paroxetine vs imipramine: RR = 1.62 (95% CI 0.58 - 4.48)

Common drug specific side effects:

Overall, side effects were more common in the drug treated than in the placebo treated groups. Data for more than one trial were available only for venlafaxine:

- Venlafaxine (Davidson 1999 a, Gelenberg 2000): those taking venlafaxine were more likely to report nausea, dry mouth, insomnia, constipation, somnolence, anorexia, sexual dysfunction and flatulence.

DISCUSSION

Efficacy

The present review showed the efficacy of antidepressants in the

treatment of GAD. These results were obtained when drugs with differential profiles such as imipramine and venlafaxine were compared to placebo. The calculated NNT for these antidepressants as a group, was 5.54. This means that about 6 patients have to be treated to cause one additional clinical improvement.

Imipramine showed a smaller NNT (4.07, 95% CI 2.39 to 13.74) than venlafaxine = 5.06 (95% CI 3.6 to 8.6) and paroxetine = 6.7 (95% CI 3.9 or 24.7). However, this does not allow for the conclusion that the effect size of imipramine is larger.Only one study compared an SSRI (paroxetine) to imipramine, and similar results were found for the efficacy assessment and acceptability. The available evidence clearly suggests that antidepressants are better than placebo. No study using active placebo groups was conducted in GAD patients. This leaves unanswered questions about whether patients may be aware that they are receiving an active drug, and whether it is this that might be responsible for beneficial effect in the treated groups. The idea that antidepressants may improve both symptoms of depression and anxiety is not a new one (Johnstone 1980 a). However, this review was conducted using studies which included patients with GAD without concurrent major depression or other Axis I comorbidities. This allows us to conclude that the anxiolytic effect of antidepressants in GAD is independent from its effect on major depression and dysthymia.

Only one study assessed the use of antidepressants among children and adolescents (Rynn 2000). This study included a small sample of patients (N=22) and, therefore, results should be viewed with caution. However, the effect size obtained was very robust, which suggests that younger patients may have a more favourable response than adults.

Acceptability

Overall, the number of patients dropping out of studies was similar in the antidepressant and placebo groups. Newer antidepressants such as venlafaxine and paroxetine usually have a better acceptability profile than tricyclics. However, there was no difference between the tricyclic imipramine and the new antidepressants (venlafaxine and paroxetine) in terms of dropouts, which is, perhaps, the most robust indicator of acceptability. Again, a direct comparison between venlafaxine and imipramine in terms of acceptability is lacking. Some insight into this question can be drawn from the study conducted by Rocca 1997, which allowed a direct comparison between imipramine and the selective serotonin reuptake inhibitor (SSRI) paroxetine. In the latter study, similar rates of dropouts were reported, adding to the notion that acceptability may not vary as much as one might expect when newer, and supposedly better tolerated drugs, are compared to the tricyclics. The study conducted by Rocca 1997cannot be used as a final argument in favour of an equal acceptability between tricyclics and SSRIs as the sample size of this study was rather small (25 patients allocated to paroxetine and 18 patients allocated to imipramine), resulting in the possibility of a type II error. However, the study conducted by Rocca 1997 is consistent with the side effect profile expected for these two classes of drugs. Paroxetine was associated with significantly more reports of nausea whereas imipramine was associated with more anti-cholinergic side effects such as dry mouth, constipation and drowsiness.

Generalisability of findings

The present review included only GAD patients without concurrent Axis I co-morbidities. This is a strength in terms of the generalisability of the findings for 'pure GAD' patients. However, if one considers that nearly all people (around 90%) with GAD also have psychiatric co-morbidities (Wittchen 1994), one should be cautious in translating findings obtained in such an specific (and unusual) population into clinical practice. However, the two major co-morbidities of GAD are major depression and dysthymia, both of which are known to be treatable with antidepressants.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence suggests that imipramine, venlafaxine and paroxetine are superior to placebo in treating GAD in adults. Sertraline has been shown to be superior to placebo in treating GAD in children and adolescents. It was not possible to assess differences in efficacy between imipramine and venlafaxine or venlafaxine and paroxetine, as no direct comparison between these drugs was carried out. There is evidence from one trial suggesting that paroxetine and imipramine are similar in terms of efficacy and tolerability. Dropout rates were not significantly different between antidepressant and placebo groups which suggests that antidepressants are well tolerated.

Implications for research

The efficacy of antidepressants such as imipramine, venlafaxine and paroxetine in treating GAD raises the question of whether other antidepressants would be equally useful. Data emerging from open trials suggest that nefazodone (Hedges 1996) and clomipramine (Wingerson 1992) may be useful choices in GAD patients. However, in one of the excluded trials, clomipramine showed a very high dropout rate within the first weeks of treatment (Wingerson 1992), which might indicate that potent serotonergic effects may be unacceptable to patients suffering from GAD. Further trials using antidepressants in the treatment of GAD will help to demonstrate which antidepressants could be a reasonable choice in the treatment of these patients. Another important research question is whether the long-term efficacy described for venlafaxine (Gelenberg 2000, Hackett 1999) also applies to other antidepressants. Finally, studies designed to compare efficacy and acceptability of different antidepressants; antidepressants versus

anxiolytics; antidepressants versus specific forms of psychotherapy; and the advantages and disadvantages of the combination of these treatments will help to better define the role of antidepressants in the treatment of GAD.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Davidson 1999 a

Methods	1. Randomized 2. Double blind 3. Four parallel groups (placebo, venlafaxine 75 mg/d, venlafaxine 150 mg/d, buspirone 30 mg/d) 4. Duration: 8 weeks 5. Analysis: LOCF
Participants	1. Diagnosis: GAD (DSM-IV) 2. N = 405 3. Age (mean and SD): placebo = 39 (11) venlafaxine 75 mg/d = 38(10) venlafaxine 150 mg/d = 37 (11) buspirone 30 mg/d = 37(10) Sex: 61,4% females Setting: outpatients History: excluded any significant psychiatric disorder other than GAD
Interventions	1. Placebo (N = 98) 2. Venlafaxine 75 mg/d (N = 87) 3. Venlafaxine 150 mg/d (N = 97)
Outcomes	1. dropout rates 2. CGI scores 3. HAM -A endpoint scores 4. Patient-rated hospital anxiety and depression scale 5. Covi Anxiety Scale 6. Raskin Depression Scale
Notes	Supported by Wyeth-Ayerst Research

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gelenberg 2000

Methods	1. Randomized 2. Double blind 3. Two parallel groups 4. Duration 28 weeks 5. Analysis: LOCF
Participants	1. Diagnosis: GAD (DSM-IV) 2. N = 251 3. Age: placebo = 38(11) venlafaxine = 41(12) 4. Sex: 59% females 5. Setting: outpatients 6. History: excluded major depression; any psychotic disorder; clinically significant psychiatric disorder other than GAD
Interventions	1. Placebo (N = 127) 2. Venlafaxine 75-150 mg/d (N = 124)
Outcomes	1. dropout rates 2. CGI scores 3. HAM -A scores
Notes	Supported by Wyeth-Ayerst Research

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hackett 1999

Methods	1. Randomized 2. Double blind 3. Four parallel groups (placebo, venlafaxine 37.5, 75 and 150 mg/d) 4. Duration: 24 weeks 5. Analysis: LOCF
Participants	1. Diagnosis: GAD (DSM-IV) 2. N = 541 3. Age (mean and SD): placebo = 46.1(range 18-86); velnafaxine 37.5 mg/d = 45.4 (range 19-79); venlafaxine 75 mg/d = 45.4(range 19-79); venlafaxine 150 mg/d = 45 (range 20-82); Sex: placebo = 58% females; venlafaxine 37.5 mg/d = 57 % females; venlafaxine 75 mg/d = 62 % females; venlafaxine 150 mg/d = 65 % females Setting: outpatients History:

Hackett 1999 (*Continued*)

	excluded psychiatric disorder other than GAD
Interventions	1. Placebo (N = 130) 2. Venlafaxine 37.5 mg/d (N = 140) 3. Venlafaxine 75 mg/d (N=134) 4. Venlafaxine 150 mg/d (N = 137)
Outcomes	1. dropout rates 2. CGI scores 3. HAM -A scores 4. Hospital anxiety and depression scale 5. The brief scale for anxiety 6. Self-rated social adjustment scale 7. Physician Withdrawal Checklist
Notes	Supported by Wyeth-Ayerst Research

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Pollack 2001

Methods	1. Randomized 2. Double blind 3. Two parallel groups 4. Duration: 8 weeks 5. Analysis: ITT
Participants	1. Diagnosis: GAD (DSM-IV) 2. N = 331 3. Age: placebo = 41.3(range 19-80) paroxetine = 39.7 (range 19-69) 4. Sex: 66% females 5. Setting: outpatients 6. History: DSM-IV criteria for GAD, MINI-International Neuropsychiatric Interview , Excluded any other Axis I disorder
Interventions	1. Placebo (N = 163) 2. Paroxetine (N = 161)
Outcomes	1. dropout rates 2. CGI scores 3. HAM -A scores 4. Sheehan disability scale scores

Pollack 2001 (*Continued*)

Notes	Supported by Wyeth-Ayerst Research	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Rickels 1993

Methods	1. Randomized 2. Double blind 3. Four parallel groups (placebo, imipramine, trazodone, diazepam) 4. Duration: 8 weeks 5. Analysis: LOCF	
Participants	1. Diagnosis: GAD (DSM-III) 2. N = 230 Age: 39(12) Sex: 61,4% females Setting: outpatients History: GAD without other significant axis I diagnoses	
Interventions	1. Placebo (N = 55) 2. Imipramine +/- 143 mg/d (N = 58) 3. trazodone +/- 225 mg/d (N = 61) 4. diazepam +/- 26 mg/d (N = 56)	
Outcomes	1. dropout rates 2. CGI scores 3. HAM -A scores	
Notes	Supported by an US Public Health Grant	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rickels 2000 b

Methods	1. Randomized 2. Double blind 3. Four parallel groups 4. Duration 8 weeks 5. Analysis: LOCF
Participants	1. Diagnosis: GAD (DSM-IV) 2. N = 377 3. Age: placebo = 40.9(11.3) venlafaxine 75 = 40.4(12.8) venlafaxine 150 = 39.6(11.9) venlafaxine 225 = 42.4(12.3) 4. Sex: 56% females 5. Setting: outpatients 6. History: DSM-IV criteria for GAD but not for Major Depressive Disorder
Interventions	1. Placebo (N = 96) 2. Venlafaxine 75 mg/d (N = 86) 3. Venlafaxine 150 mg/d (N = 81) 4. Venlafaxine 225 mg/d (N = 86)
Outcomes	1. dropout rates 2. CGI scores 3. HAM -A scores 4. Hospital Anxiety and Depression Scale anxiety subscale
Notes	Supported by Wyeth-Ayerst Laboratories

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rocca 1997

Methods	1. Randomized 2. Double blind 3. Duration: 8 weeks 4. Three parallel groups 5. Analysis: Repeated measures ANOVA (interaction drug X time)
Participants	1. Diagnosis: GAD (DSM-IV) 2. N = 81; 3. Age: imipramine group (mean and SD) = 37.6(9.1) paroxetine 20 mg/d group = 35.3(9.3) 4. Sex: 57 % females

Rocca 1997 (*Continued*)

	5. Setting: outpatients 6. History: DSM-IV GAD (other Axis I diagnosis were excluded)
Interventions	1. Imipramine 50-100 mg/d (N = 26) 2. Paroxetine 20 mg/d (N = 30) 3. Chlordesmethyldiazepam 4.2(1.1) mg/d (N = 25)
Outcomes	1. dropout rates 2. CGI scores 3. HAM-A scores
Notes	Funding not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rynn 2000

Methods	1. Randomized (random study assignments were made in groups of four patients) 2. Double blind 3. Duration: 9 weeks 4. Analysis: Repeated measures analysis of covariance (with baseline score on CGI as covariate)
Participants	1. Diagnosis: GAD (DSM-IV, according to the Anxiety Disorders Interview Schedule for children - Revised) 2. N = 22; 3. Age: 5 to 17 4. Sex: 33% female 5. Setting: outpatients 6. History: Included DSM-IV GAD patients; excluded ustable or acute medical conditions and additional axis I or II disorders (apart from subsyndromal symptoms of separation anxiety)
Interventions	1. Placebo (N = 11) 2. Sertraline (N = 11)
Outcomes	1. dropout rates 2. CGI scores 3. HAM-A scores
Notes	Supported by the mood and Anxiety Disorders Section, Department of Psychiatry, University of pennsylvannia, and by NIMH grants MH-14651 and MH-011819

Risk of bias

Rynn 2000 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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

Study	Reason for exclusion
Hedges 1996	Open trial, non randomized
Johnstone 1980 a	Included patients suffering from depressive and anxious neurosis
Lipman 1986	Included patients with anxiety neurosis as well as patients suffering from either hysterical or phobic neurosis
Rickels 2000 a	This trial was designed to assess the effectiveness of imipramine and buspirone in facilitating benzodiazepine discontinuation in patients suffering from GAD
Wingerson 1992	Open trial, non randomized

DATA AND ANALYSES

Comparison 1. Antidepressants vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No treatment response	4	1056	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.60, 0.82]
2 Number of people who dropped out	6	1951	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.73, 1.24]
3 Side effects	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Drowsiness	1	174	Risk Ratio (M-H, Random, 95% CI)	4.89 [2.41, 9.90]
3.2 Dizziness	5	1623	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.26, 2.69]
3.3 Confusion	1	174	Risk Ratio (M-H, Random, 95% CI)	12.02 [1.67, 86.30]
3.4 Tremors	1	174	Risk Ratio (M-H, Random, 95% CI)	14.47 [0.88, 237.48]
3.5 Dry mouth	5	1623	Risk Ratio (M-H, Random, 95% CI)	2.96 [2.19, 4.01]
3.6 Constipation	4	1290	Risk Ratio (M-H, Random, 95% CI)	3.48 [2.10, 5.78]
3.7 Nausea	5	1773	Risk Ratio (M-H, Random, 95% CI)	2.83 [2.16, 3.72]
3.8 Insomnia	1	350	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.15, 3.28]
3.9 Somnolence	3	922	Risk Ratio (M-H, Random, 95% CI)	2.59 [1.85, 3.64]
3.10 Asthenia	3	981	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.33, 2.70]
3.11 Anorexia	2	601	Risk Ratio (M-H, Random, 95% CI)	9.04 [2.57, 31.77]
3.12 Nervousness	1	350	Risk Ratio (M-H, Random, 95% CI)	1.92 [0.88, 4.17]
3.13 Flatulence	1	350	Risk Ratio (M-H, Random, 95% CI)	8.87 [0.53, 149.15]
3.14 Sexual dysfunction	3	925	Risk Ratio (M-H, Random, 95% CI)	5.66 [2.98, 10.73]
3.15 Sweating	2	792	Risk Ratio (M-H, Random, 95% CI)	2.92 [1.46, 5.86]
3.16 Infection	1	541	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.73, 5.78]
3.17 Paraesthesiae	1	541	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.47, 8.99]

Comparison 2. Imipramine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No treatment response	1	113	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.91]
2 Number of people who dropped out	1	113	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.41, 1.24]
3 Specific side effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Drowsiness	1	113	Risk Ratio (M-H, Random, 95% CI)	4.06 [1.95, 8.48]
3.2 Dizziness	1	113	Risk Ratio (M-H, Random, 95% CI)	3.48 [1.53, 7.93]
3.3 Confusion	1	113	Risk Ratio (M-H, Random, 95% CI)	7.59 [0.98, 58.69]
3.4 Tremors	1	113	Risk Ratio (M-H, Random, 95% CI)	18.03 [1.07, 302.62]
3.5 Dry mouth	1	113	Risk Ratio (M-H, Random, 95% CI)	40.78 [5.81, 286.03]
3.6 Constipation	1	113	Risk Ratio (M-H, Random, 95% CI)	3.22 [1.28, 8.14]

Comparison 3. Venlafaxine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No treatment response	2	558	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 0.99]
2 Number of people who dropped out	3	997	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.02]
3 Specific side effects	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Nausea	4	1449	Risk Ratio (M-H, Random, 95% CI)	2.66 [2.01, 3.52]
3.2 Dizziness	4	1449	Risk Ratio (M-H, Random, 95% CI)	1.88 [1.20, 2.95]
3.3 Asthenia	2	657	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.98, 2.38]
3.4 Dry mouth	4	1449	Risk Ratio (M-H, Random, 95% CI)	3.04 [2.07, 4.46]
3.5 Insomnia	1	350	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.15, 3.28]
3.6 Constipation	2	792	Risk Ratio (M-H, Random, 95% CI)	2.75 [1.37, 5.53]
3.7 Somnolence	2	601	Risk Ratio (M-H, Random, 95% CI)	2.64 [1.62, 4.31]
3.8 Anorexia	2	601	Risk Ratio (M-H, Random, 95% CI)	9.04 [2.57, 31.77]
3.9 Sexual dysfunction	2	601	Risk Ratio (M-H, Random, 95% CI)	4.19 [1.53, 11.51]
3.10 Nervousness	1	350	Risk Ratio (M-H, Random, 95% CI)	1.92 [0.88, 4.17]
3.11 Flatulence	1	350	Risk Ratio (M-H, Random, 95% CI)	8.87 [0.53, 149.15]
3.12 Infection	1	541	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.73, 5.78]
3.13 Paraesthesiae	1	541	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.47, 8.99]
3.14 Sweating	1	541	Risk Ratio (M-H, Random, 95% CI)	2.40 [0.97, 5.98]

Comparison 4. Paroxetine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No treatment response	1	324	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.92]
2 Number of people who dropped out	1	324	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.74, 1.78]
3 Specific side effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Asthenia	1	324	Risk Ratio (M-H, Random, 95% CI)	2.02 [1.18, 3.47]
3.2 Constipation	1	324	Risk Ratio (M-H, Random, 95% CI)	8.44 [2.60, 27.39]
3.3 Sexual dysfunction	1	324	Risk Ratio (M-H, Random, 95% CI)	6.92 [3.02, 15.84]
3.4 Nausea	1	324	Risk Ratio (M-H, Random, 95% CI)	4.15 [2.15, 8.00]
3.5 Somnolence	1	324	Risk Ratio (M-H, Random, 95% CI)	2.49 [1.28, 4.84]

Comparison 5. Sertraline vs placebo (in children and adolescents)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No treatment response	1	22	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.02, 0.65]
2 Number of people who dropped out	1	22	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 4.75]
3 Specific side effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Dry mouth	1	22	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.66, 6.04]
3.2 Drowsiness	1	22	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.71, 4.31]
3.3 Leg spasms	1	22	Risk Ratio (M-H, Random, 95% CI)	4.0 [0.53, 30.33]
3.4 Restlessness	1	22	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.66, 6.04]
3.5 Dizziness	1	22	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.08, 1.08]
3.6 Nausea	1	22	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.17]
3.7 Stomach pain	1	22	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.08, 1.08]

Comparison 6. Paroxetine vs imipramine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No treatment response	1	56	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.31, 9.57]
2 Number of people who dropped out	1	56	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.58, 4.48]
3 Specific side effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Constipation	1	56	Risk Ratio (M-H, Random, 95% CI)	5.77 [1.39, 23.97]
3.2 Dizziness	1	56	Risk Ratio (M-H, Random, 95% CI)	3.46 [0.76, 15.70]
3.3 Dry mouth	1	56	Risk Ratio (M-H, Random, 95% CI)	8.65 [2.18, 34.36]
3.4 Nausea	1	56	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.05, 0.78]
3.5 Nervousness	1	56	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.21, 3.52]
3.6 Drowsiness	1	56	Risk Ratio (M-H, Random, 95% CI)	11.54 [1.58, 84.19]
3.7 Tiredness	1	56	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.08, 1.74]

Analysis 1.1. Comparison 1 Antidepressants vs placebo, Outcome 1 No treatment response.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 1 Antidepressants vs placebo

Outcome: 1 No treatment response

Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Davidson 1999 a	105/203	66/104		29.1 %	0.82 [0.67, 0.99]
Gelenberg 2000	47/124	87/127		22.3 %	0.55 [0.43, 0.71]
Pollack 2001	61/161	86/163		23.3 %	0.72 [0.56, 0.92]
Rickels 1993	64/119	41/55		25.3 %	0.72 [0.57, 0.91]
Total (95% CI)	**607**	**449**		**100.0 %**	**0.70 [0.60, 0.82]**

Total events: 277 (Antidepressants), 280 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.67$, df = 3 (P = 0.13); $I^2 = 47\%$

Test for overall effect: Z = 4.36 (P = 0.000013)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Antidepressants vs placebo, Outcome 2 Number of people who dropped out.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 1 Antidepressants vs placebo

Outcome: 2 Number of people who dropped out

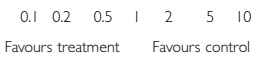
Study or subgroup	Antidepressant n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Davidson 1999 a	84/203	36/104		17.9 %	1.20 [0.88, 1.63]
Gelenberg 2000	73/124	87/127		21.3 %	0.86 [0.71, 1.04]
Hackett 1999	102/411	45/130		18.5 %	0.72 [0.54, 0.96]
Pollack 2001	34/161	30/163		14.3 %	1.15 [0.74, 1.78]
Rickels 1993	27/121	23/58		13.8 %	0.56 [0.36, 0.89]
Rickels 2000 b	83/253	19/96		14.3 %	1.66 [1.07, 2.57]
Total (95% CI)	**1273**	**678**		**100.0 %**	**0.95 [0.73, 1.24]**

Total events: 403 (Antidepressant), 240 (Placebo)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 18.75$, df = 5 (P = 0.002); $I^2 = 73\%$

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable

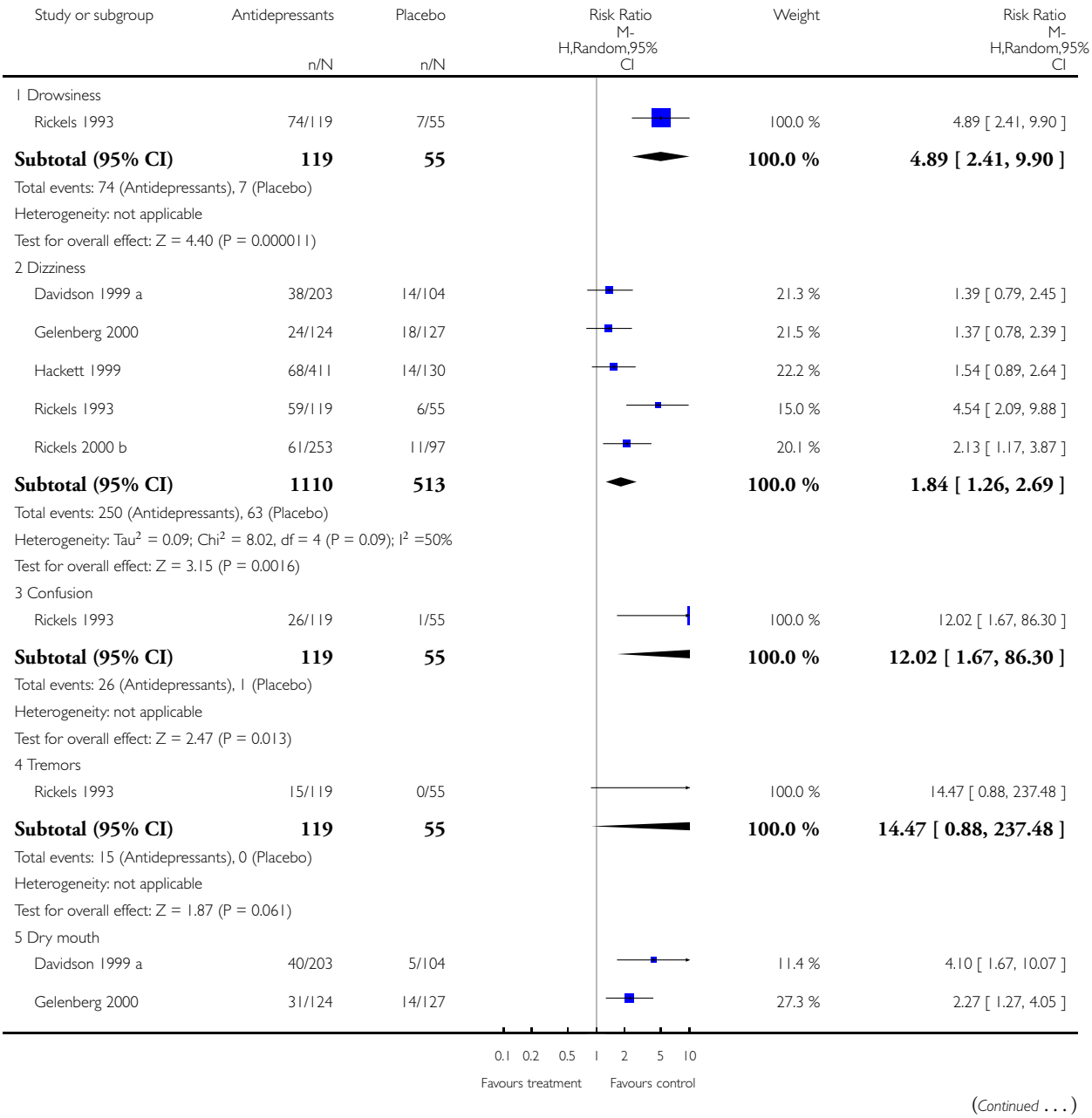


Analysis 1.3. Comparison 1 Antidepressants vs placebo, Outcome 3 Side effects.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 1 Antidepressants vs placebo

Outcome: 3 Side effects



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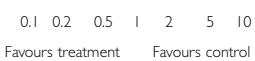
Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hackett 1999	36/411	4/130		8.9 %	2.85 [1.03, 7.85]
Rickels 1993	80/119	13/55		38.1 %	2.84 [1.74, 4.65]
Rickels 2000 b	68/253	6/97		14.3 %	4.35 [1.95, 9.68]
Subtotal (95% CI)	**1110**	**513**		**100.0 %**	**2.96 [2.19, 4.01]**
Total events: 255 (Antidepressants), 42 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.31, df = 4 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 7.02 (P < 0.00001)					
6 Constipation					
Gelenberg 2000	14/124	4/127		21.2 %	3.58 [1.21, 10.59]
Hackett 1999	36/411	5/130		29.4 %	2.28 [0.91, 5.68]
Pollack 2001	25/161	3/163		18.0 %	8.44 [2.60, 27.39]
Rickels 1993	33/119	5/55		31.3 %	3.05 [1.26, 7.39]
Subtotal (95% CI)	**815**	**475**		**100.0 %**	**3.48 [2.10, 5.78]**
Total events: 108 (Antidepressants), 17 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 3.12, df = 3 (P = 0.37); I^2 =4%					
Test for overall effect: Z = 4.82 (P < 0.00001)					
7 Nausea					
Davidson 1999 a	78/203	14/104		19.7 %	2.85 [1.70, 4.79]
Gelenberg 2000	58/124	27/127		28.9 %	2.20 [1.50, 3.23]
Hackett 1999	98/411	14/130		19.3 %	2.21 [1.31, 3.74]
Pollack 2001	41/161	10/163		13.7 %	4.15 [2.15, 8.00]
Rickels 2000 b	128/253	12/97		18.3 %	4.09 [2.37, 7.04]
Subtotal (95% CI)	**1152**	**621**		**100.0 %**	**2.83 [2.16, 3.72]**
Total events: 403 (Antidepressants), 77 (Placebo)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 5.67, df = 4 (P = 0.23); I^2 =29%					
Test for overall effect: Z = 7.50 (P < 0.00001)					
8 Insomnia					
Rickels 2000 b	71/253	14/97		100.0 %	1.94 [1.15, 3.28]
Subtotal (95% CI)	**253**	**97**		**100.0 %**	**1.94 [1.15, 3.28]**
Total events: 71 (Antidepressants), 14 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.49 (P = 0.013)					
9 Somnolence					
Gelenberg 2000	46/124	14/127		38.7 %	3.37 [1.95, 5.80]
Pollack 2001	27/161	11/161		25.9 %	2.45 [1.26, 4.78]
Rickels 2000 b	64/253	12/96		35.4 %	2.02 [1.14, 3.58]
Subtotal (95% CI)	**538**	**384**		**100.0 %**	**2.59 [1.85, 3.64]**



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Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 137 (Antidepressants), 37 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.63, df = 2 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 5.50 (P < 0.00001)					
10 Asthenia					
Davidson 1999 a	36/203	10/104		29.2 %	1.84 [0.95, 3.57]
Pollack 2001	34/161	17/163		43.6 %	2.02 [1.18, 3.47]
Rickels 2000 b	41/253	9/97		27.3 %	1.75 [0.88, 3.46]
Subtotal (95% CI)	**617**	**364**		**100.0 %**	**1.89 [1.33, 2.70]**
Total events: 111 (Antidepressants), 36 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.12, df = 2 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 3.51 (P = 0.00045)					
11 Anorexia					
Gelenberg 2000	14/124	0/127		20.0 %	29.70 [1.79, 492.46]
Rickels 2000 b	35/253	2/97		80.0 %	6.71 [1.65, 27.36]
Subtotal (95% CI)	**377**	**224**		**100.0 %**	**9.04 [2.57, 31.77]**
Total events: 49 (Antidepressants), 2 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.89, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 3.43 (P = 0.00060)					
12 Nervousness					
Rickels 2000 b	35/253	7/97		100.0 %	1.92 [0.88, 4.17]
Subtotal (95% CI)	**253**	**97**		**100.0 %**	**1.92 [0.88, 4.17]**
Total events: 35 (Antidepressants), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.64 (P = 0.10)					
13 Flatulence					
Rickels 2000 b	11/253	0/97		100.0 %	8.87 [0.53, 149.15]
Subtotal (95% CI)	**253**	**97**		**100.0 %**	**8.87 [0.53, 149.15]**
Total events: 11 (Antidepressants), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.52 (P = 0.13)					
14 Sexual dysfunction					
Gelenberg 2000	14/124	4/127		35.0 %	3.58 [1.21, 10.59]
Pollack 2001	41/161	6/163		59.8 %	6.92 [3.02, 15.84]
Rickels 2000 b	15/253	0/97		5.2 %	11.96 [0.72, 197.97]
Subtotal (95% CI)	**538**	**387**		**100.0 %**	**5.66 [2.98, 10.73]**
Total events: 70 (Antidepressants), 10 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.22, df = 2 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 5.30 (P < 0.00001)					

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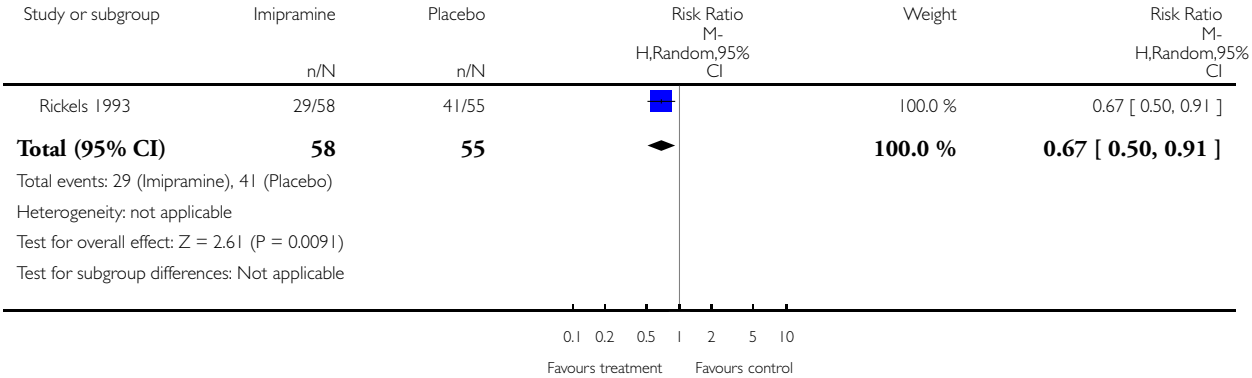
Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
15 Sweating					
Gelenberg 2000	15/124	4/127		41.8 %	3.84 [1.31, 11.25]
Hackett 1999	38/411	5/130		58.2 %	2.40 [0.97, 5.98]
Subtotal (95% CI)	**535**	**257**		**100.0 %**	**2.92 [1.46, 5.86]**
Total events: 53 (Antidepressants), 9 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.43$, df = 1 (P = 0.51); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.03 (P = 0.0025)					
16 Infection					
Hackett 1999	26/411	4/130		100.0 %	2.06 [0.73, 5.78]
Subtotal (95% CI)	**411**	**130**		**100.0 %**	**2.06 [0.73, 5.78]**
Total events: 26 (Antidepressants), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
17 Paraesthesiae					
Hackett 1999	13/411	2/130		100.0 %	2.06 [0.47, 8.99]
Subtotal (95% CI)	**411**	**130**		**100.0 %**	**2.06 [0.47, 8.99]**
Total events: 13 (Antidepressants), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.96 (P = 0.34)					

Analysis 2.1. Comparison 2 Imipramine vs placebo, Outcome 1 No treatment response.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 2 Imipramine vs placebo

Outcome: 1 No treatment response

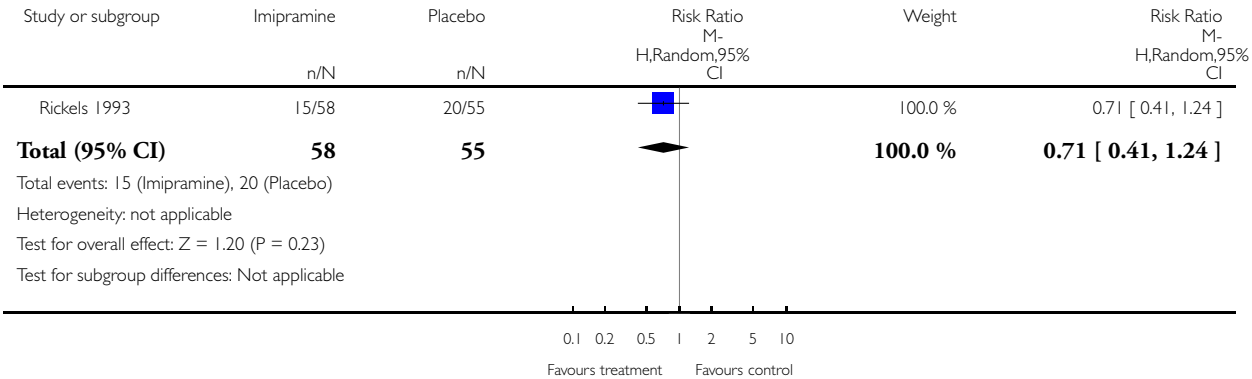


Analysis 2.2. Comparison 2 Imipramine vs placebo, Outcome 2 Number of people who dropped out.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 2 Imipramine vs placebo

Outcome: 2 Number of people who dropped out



Analysis 2.3. Comparison 2 Imipramine vs placebo, Outcome 3 Specific side effects.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 2 Imipramine vs placebo

Outcome: 3 Specific side effects

Study or subgroup	Imipramine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Drowsiness					
Rickels 1993	30/58	7/55		100.0 %	4.06 [1.95, 8.48]
Subtotal (95% CI)	**58**	**55**		**100.0 %**	**4.06 [1.95, 8.48]**
Total events: 30 (Imipramine), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.74 (P = 0.00019)					
2 Dizziness					
Rickels 1993	22/58	6/55		100.0 %	3.48 [1.53, 7.93]
Subtotal (95% CI)	**58**	**55**		**100.0 %**	**3.48 [1.53, 7.93]**
Total events: 22 (Imipramine), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.96 (P = 0.0030)					
3 Confusion					
Rickels 1993	8/58	1/55		100.0 %	7.59 [0.98, 58.69]
Subtotal (95% CI)	**58**	**55**		**100.0 %**	**7.59 [0.98, 58.69]**
Total events: 8 (Imipramine), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.052)					
4 Tremors					
Rickels 1993	9/58	0/55		100.0 %	18.03 [1.07, 302.62]
Subtotal (95% CI)	**58**	**55**		**100.0 %**	**18.03 [1.07, 302.62]**
Total events: 9 (Imipramine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.01 (P = 0.044)					
5 Dry mouth					
Rickels 1993	43/58	1/55		100.0 %	40.78 [5.81, 286.03]
Subtotal (95% CI)	**58**	**55**		**100.0 %**	**40.78 [5.81, 286.03]**
Total events: 43 (Imipramine), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.73 (P = 0.00019)					
6 Constipation					
Rickels 1993	17/58	5/55		100.0 %	3.22 [1.28, 8.14]
Subtotal (95% CI)	**58**	**55**		**100.0 %**	**3.22 [1.28, 8.14]**

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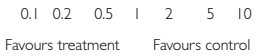
Study or subgroup	Imipramine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 17 (Imipramine), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.48 (P = 0.013)					



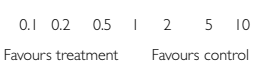
Analysis 3.1. Comparison 3 Venlafaxine vs placebo, Outcome 1 No treatment response.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 3 Venlafaxine vs placebo

Outcome: 1 No treatment response

Study or subgroup	Venlafaxine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Davidson 1999 a	105/203	66/104		52.2 %	0.82 [0.67, 0.99]
Gelenberg 2000	47/124	87/127		47.8 %	0.55 [0.43, 0.71]
Total (95% CI)	**327**	**231**		**100.0 %**	**0.68 [0.46, 0.99]**
Total events: 152 (Venlafaxine), 153 (Placebo)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 5.69, df = 1 (P = 0.02); I^2 =82%					
Test for overall effect: Z = 1.99 (P = 0.046)					
Test for subgroup differences: Not applicable					



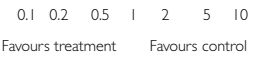
Analysis 3.2. Comparison 3 Venlafaxine vs placebo, Outcome 2 Number of people who dropped out.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 3 Venlafaxine vs placebo

Outcome: 2 Number of people who dropped out

Study or subgroup	Venlafaxine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Davidson 1999 a	46/101	46/104		25.3 %	1.03 [0.76, 1.39]
Gelenberg 2000	73/124	87/127		47.5 %	0.86 [0.71, 1.04]
Hackett 1999	102/411	45/130		27.1 %	0.72 [0.54, 0.96]
Total (95% CI)	**636**	**361**		**100.0 %**	**0.86 [0.72, 1.02]**
Total events: 221 (Venlafaxine), 178 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 2.87, df = 2 (P = 0.24); I^2 =30%					
Test for overall effect: Z = 1.73 (P = 0.083)					
Test for subgroup differences: Not applicable					

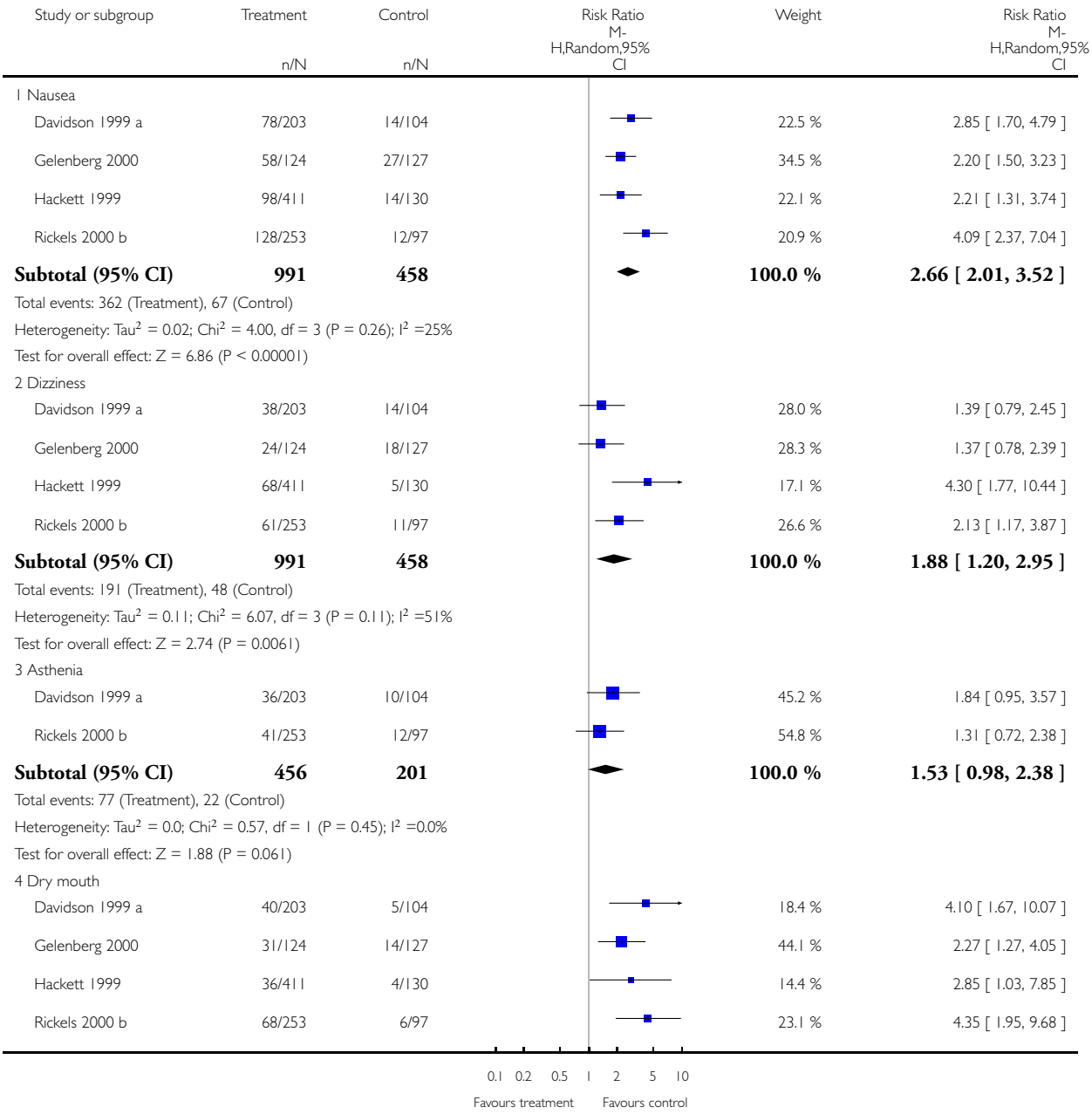


Analysis 3.3. Comparison 3 Venlafaxine vs placebo, Outcome 3 Specific side effects.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 3 Venlafaxine vs placebo

Outcome: 3 Specific side effects



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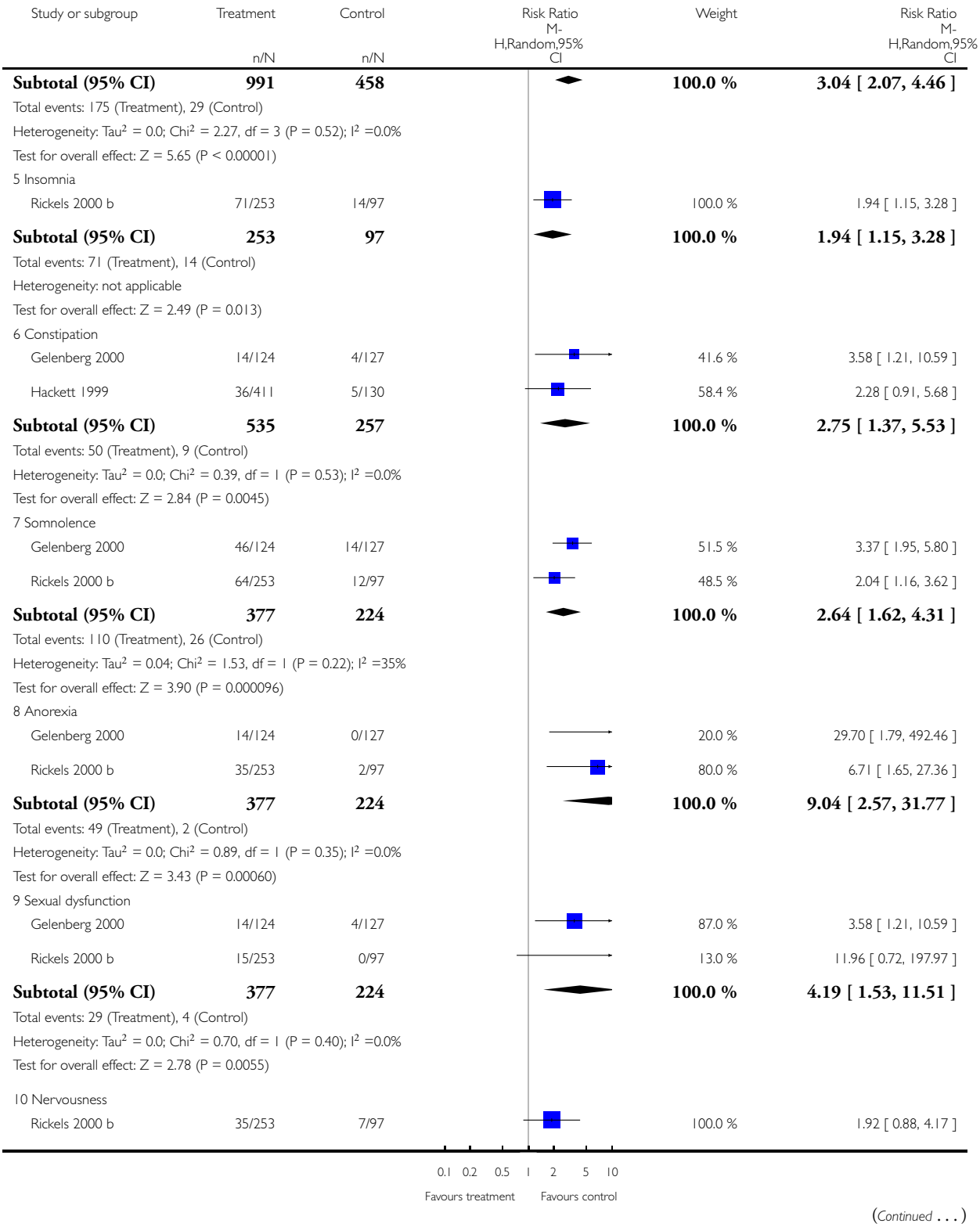

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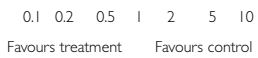
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**253**	**97**		**100.0 %**	**1.92 [0.88, 4.17]**
Total events: 35 (Treatment), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.64 (P = 0.10)					
11 Flatulence					
Rickels 2000 b	11/253	0/97		100.0 %	8.87 [0.53, 149.15]
Subtotal (95% CI)	**253**	**97**		**100.0 %**	**8.87 [0.53, 149.15]**
Total events: 11 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.52 (P = 0.13)					
12 Infection					
Hackett 1999	26/411	4/130		100.0 %	2.06 [0.73, 5.78]
Subtotal (95% CI)	**411**	**130**		**100.0 %**	**2.06 [0.73, 5.78]**
Total events: 26 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
13 Paraesthesiae					
Hackett 1999	13/411	2/130		100.0 %	2.06 [0.47, 8.99]
Subtotal (95% CI)	**411**	**130**		**100.0 %**	**2.06 [0.47, 8.99]**
Total events: 13 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.96 (P = 0.34)					
14 Sweating					
Hackett 1999	38/411	5/130		100.0 %	2.40 [0.97, 5.98]
Subtotal (95% CI)	**411**	**130**		**100.0 %**	**2.40 [0.97, 5.98]**
Total events: 38 (Treatment), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.89 (P = 0.059)					



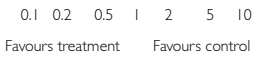
Analysis 4.1. Comparison 4 Paroxetine vs placebo, Outcome 1 No treatment response.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 4 Paroxetine vs placebo

Outcome: 1 No treatment response

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Pollack 2001	61/161	86/163		100.0 %	0.72 [0.56, 0.92]
Total (95% CI)	**161**	**163**		**100.0 %**	**0.72 [0.56, 0.92]**
Total events: 61 (Treatment), 86 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.64 (P = 0.0082)					
Test for subgroup differences: Not applicable					



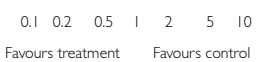
Analysis 4.2. Comparison 4 Paroxetine vs placebo, Outcome 2 Number of people who dropped out.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 4 Paroxetine vs placebo

Outcome: 2 Number of people who dropped out

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Pollack 2001	34/161	30/163		100.0 %	1.15 [0.74, 1.78]
Total (95% CI)	**161**	**163**		**100.0 %**	**1.15 [0.74, 1.78]**
Total events: 34 (Treatment), 30 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
Test for subgroup differences: Not applicable					

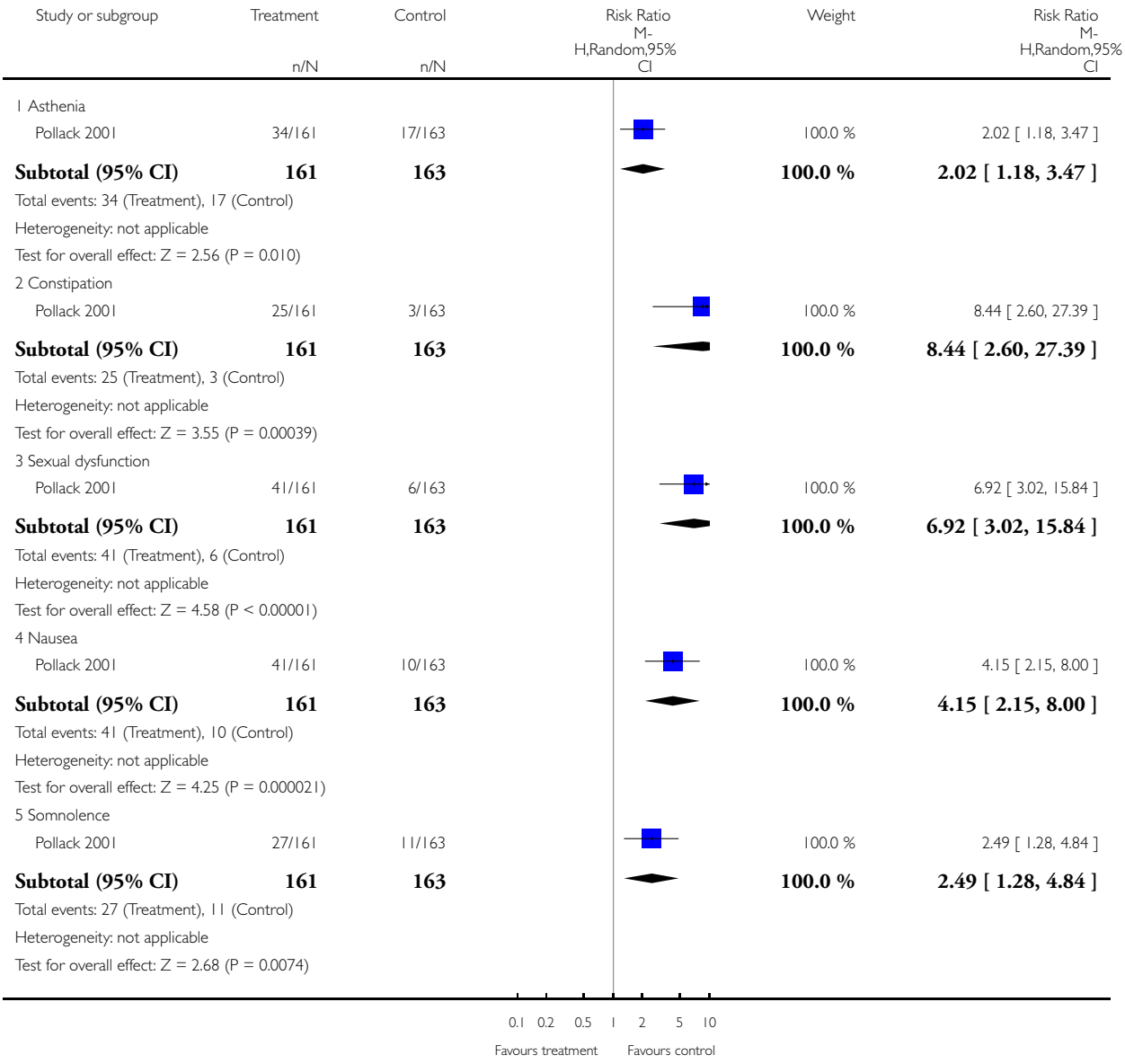


Analysis 4.3. Comparison 4 Paroxetine vs placebo, Outcome 3 Specific side effects.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 4 Paroxetine vs placebo

Outcome: 3 Specific side effects



Analysis 5.1. Comparison 5 Sertraline vs placebo (in children and adolescents), Outcome 1 No treatment response.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 5 Sertraline vs placebo (in children and adolescents)

Outcome: 1 No treatment response

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rynn 2000	1/11	10/11		100.0 %	0.10 [0.02, 0.65]
Total (95% CI)	**11**	**11**		**100.0 %**	**0.10 [0.02, 0.65]**
Total events: 1 (Treatment), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.40 (P = 0.016)					
Test for subgroup differences: Not applicable					

Analysis 5.2. Comparison 5 Sertraline vs placebo (in children and adolescents), Outcome 2 Number of people who dropped out.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 5 Sertraline vs placebo (in children and adolescents)

Outcome: 2 Number of people who dropped out

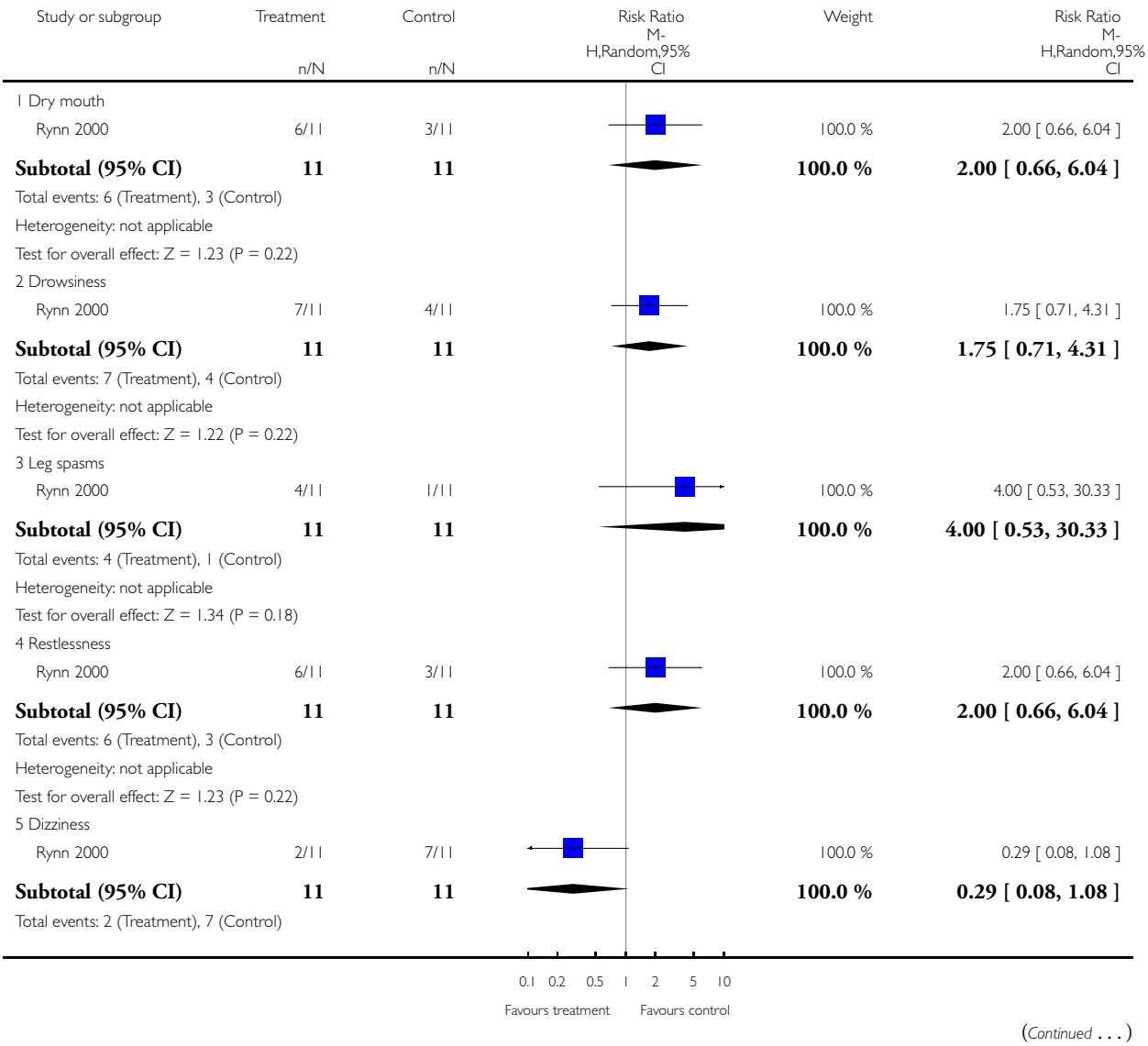
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rynn 2000	1/11	2/11		100.0 %	0.50 [0.05, 4.75]
Total (95% CI)	**11**	**11**		**100.0 %**	**0.50 [0.05, 4.75]**
Total events: 1 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
Test for subgroup differences: Not applicable					

Analysis 5.3. Comparison 5 Sertraline vs placebo (in children and adolescents), Outcome 3 Specific side effects.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 5 Sertraline vs placebo (in children and adolescents)

Outcome: 3 Specific side effects



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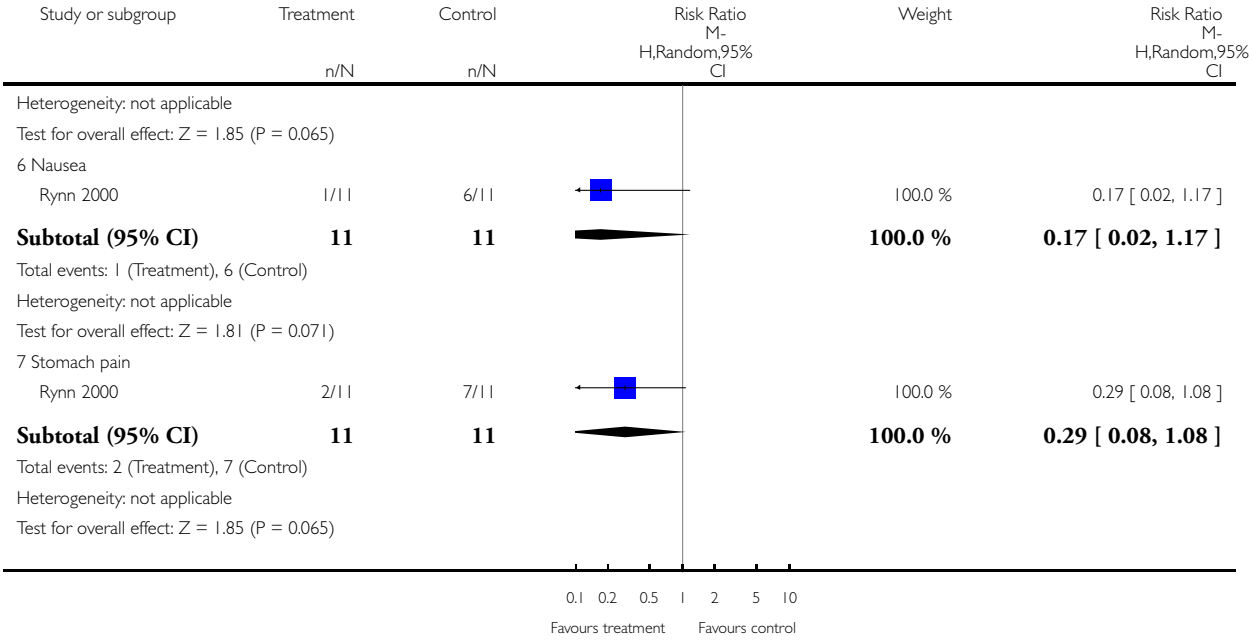
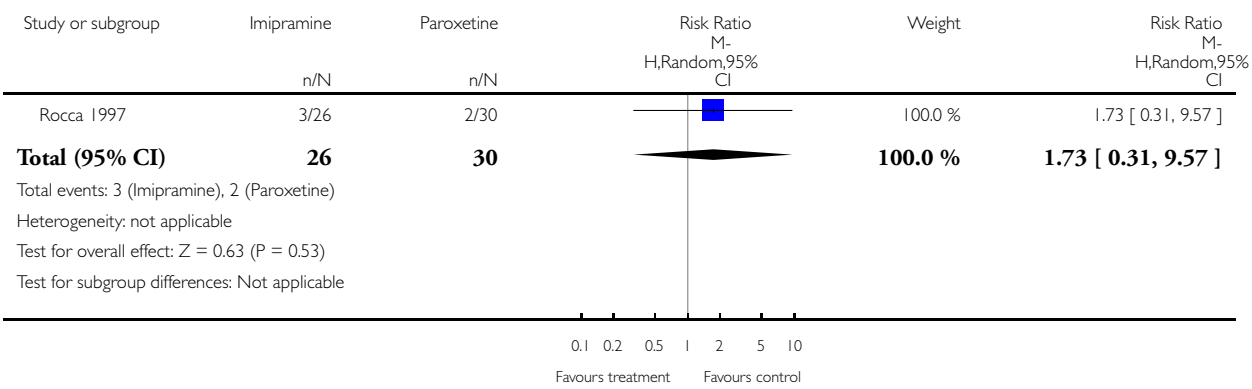


Analysis 6.1. Comparison 6 Paroxetine vs imipramine, Outcome 1 No treatment response.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 6 Paroxetine vs imipramine

Outcome: 1 No treatment response



Analysis 6.2. Comparison 6 Paroxetine vs imipramine, Outcome 2 Number of people who dropped out.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 6 Paroxetine vs imipramine

Outcome: 2 Number of people who dropped out

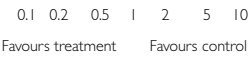
Study or subgroup	Imipramine n/N	Paroxetine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rocca 1997	7/26	5/30		100.0 %	1.62 [0.58, 4.48]
Total (95% CI)	**26**	**30**		**100.0 %**	**1.62 [0.58, 4.48]**

Total events: 7 (Imipramine), 5 (Paroxetine)

Heterogeneity: not applicable

Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable

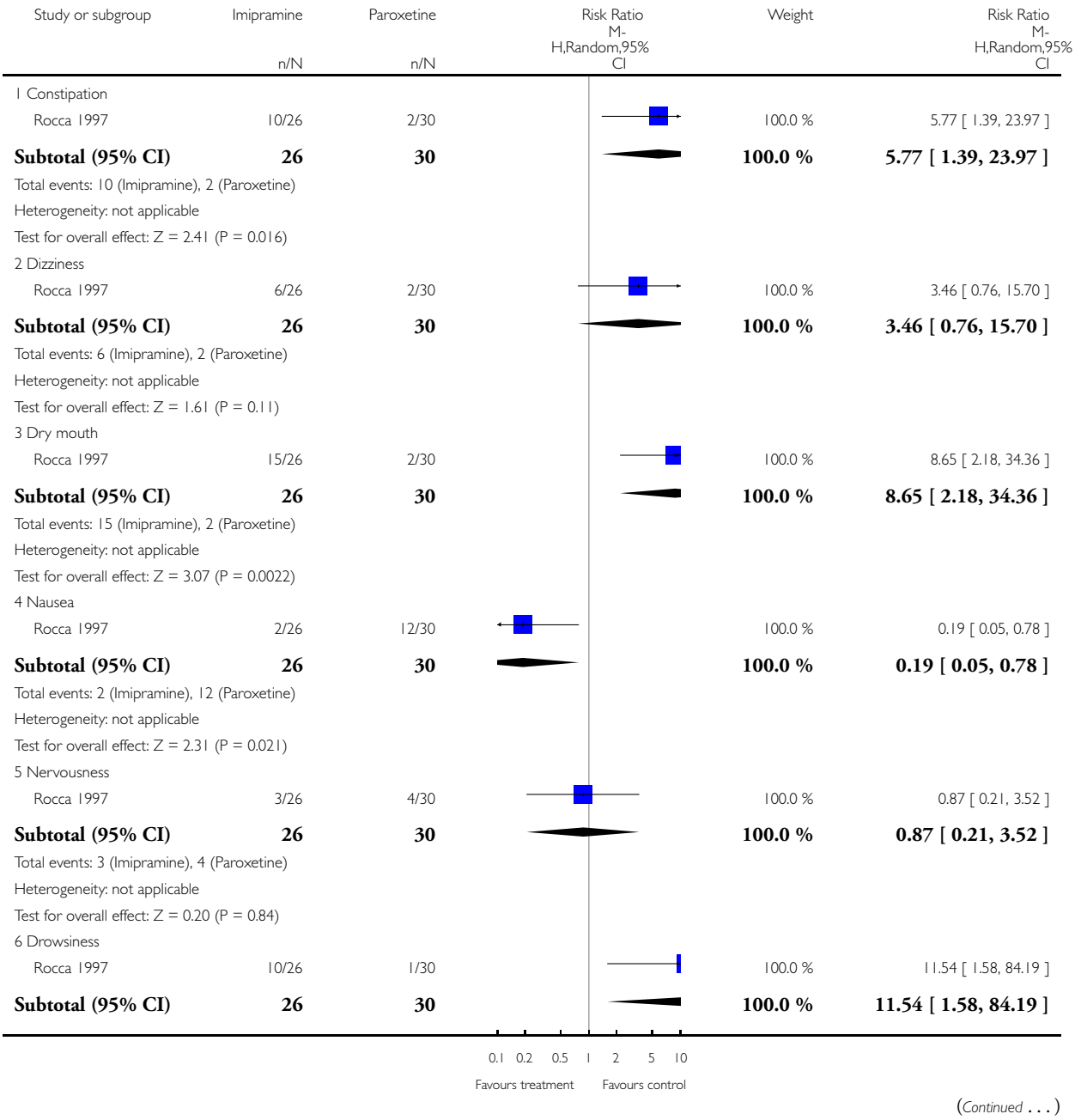


Analysis 6.3. Comparison 6 Paroxetine vs imipramine, Outcome 3 Specific side effects.

Review: Antidepressants for generalised anxiety disorder (GAD)

Comparison: 6 Paroxetine vs imipramine

Outcome: 3 Specific side effects



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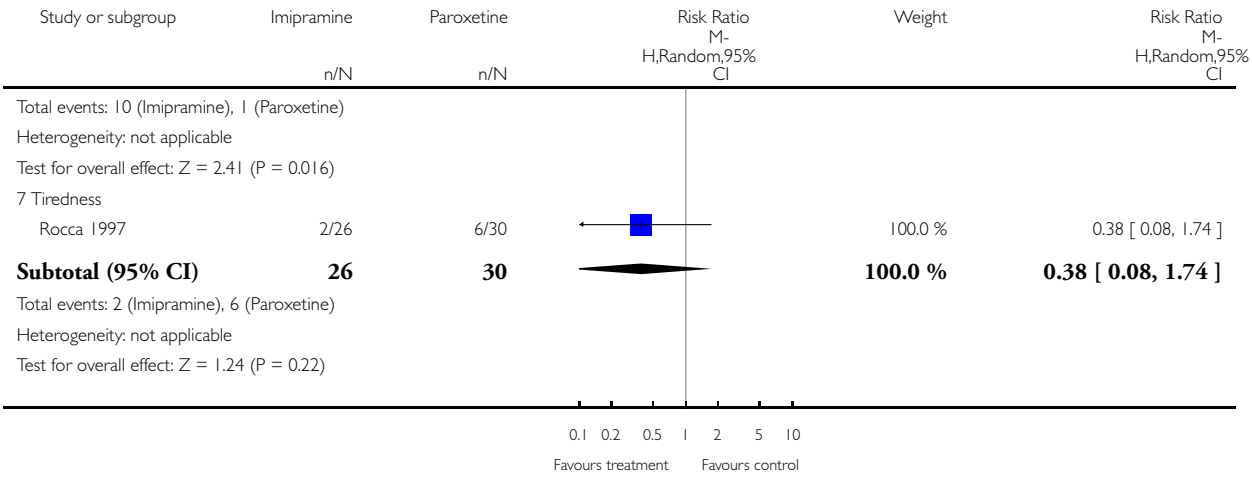

WHAT'S NEW

Last assessed as up-to-date: 20 January 2003.

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

HISTORY

Protocol first published: Issue 4, 1999

Review first published: Issue 2, 2002

Date	Event	Description
21 January 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

FK: Principal Investigator

MSL: Co-principal Investigator

ABC: Co-principal Investigator

JSS: Research Assistant

RS: Research Assistant

DECLARATIONS OF INTEREST

MSL took up a position with Eli Lilly in 2003.

Please note that the current version of this review contravenes Cochrane's commercial sponsorship policy (revised 2014). The protocol for this review is being re-written and publication of the new review is scheduled for 2016/17.

SOURCES OF SUPPORT

Internal sources

- CNPq, Brazil.

External sources

- No sources of support supplied

NOTES

This review is to be passed onto a new group of authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Anxiety Disorders [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans