ClinicalEvidence

Generalised anxiety disorder

Search date May 2011

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ABSTRACT

INTRODUCTION: Up to one in five people may have generalised anxiety disorder (GAD) at some point, and most have other health problems. Less than half of people have full remission after 5 years. GAD may have a genetic component, and has also been linked to previous psychological or other trauma. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for GAD? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2011 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 74 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: abecarnil, antidepressants (duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, opipramol, paroxetine, sertraline, and venlafaxine), antipsychotic drugs (trifluoperazine), applied relaxation, benzodiazepines, buspirone, cognitive behavioural therapy, hydroxyzine, and pregabalin.

QUESTIONS

INTERVENTIONS

Key points

- Generalised anxiety disorder (GAD) is excessive worry and tension about everyday events, on most days, for at least 6 months, to the extent that there is distress or difficulty in performing day-to-day tasks. However, diagnosing GAD accurately can be difficult.

  Up to 1 in 20 people may have GAD at any one time, and most have other health problems. Less than half of people have full remission after 5 years.

  GAD may have a genetic component, and has also been linked to previous psychological or other trauma.

- **In adults:**

- CBT (including exposure, relaxation, and cognitive restructuring) improves anxiety compared with waiting list control, treatment as usual, or enhanced usual care.

  It is unclear whether CBT is more effective than supportive therapy.

- Applied relaxation may be as effective as CBT, but we found insufficient RCT evidence about applied relaxation compared with no treatment.

- Various drug treatments, such as benzodiazepines, buspirone, hydroxyzine, antidepressants, and pregabalin may all reduce symptoms of anxiety in people with GAD, but they can have unpleasant adverse effects, and most trials have been short term.

  Benzodiazepines increase the risk of dependence, sedation, and accidents, and can cause adverse effects in neonates if used during pregnancy.

  Buspirone may be less effective if used in people who have recently been taking benzodiazepines.

  Antidepressants (imipramine, paroxetine, sertraline, escitalopram, venlafaxine, and opipramol) have been shown to reduce symptoms compared with placebo, but antidepressants can cause a variety of adverse effects including sedation, dizziness, falls, nausea, and sexual dysfunction.

  In general, comparisons between different antidepressants have shown similar effectiveness in reducing anxiety, although one RCT found limited evidence of an increased benefit with escitalopram compared with paroxetine.

- Antipsychotic drugs may reduce anxiety in people who have not responded to other treatments, but these drugs may have adverse effects including drowsiness, and movement disorders.
- We don't know whether abecarnil reduces anxiety as the RCTs we found reported inconsistent results.
- **In children and adolescents:**
- CBT improves symptoms compared with waiting list control or active control.

  Most RCTs of CBT in children and adolescents have included other anxiety disorders.

- We found limited RCT evidence regarding the efficacy of antidepressants for childhood GAD. SSRIs (fluvoxamine, fluoxetine, sertraline) have shown some promise, but antidepressants are associated with abdominal pain and nausea, and other well documented adverse effects.
- We found no RCT evidence on the effects of applied relaxation, benzodiazepines, buspirone, hydroxyzine, abecarnil, pregabalin, or antipsychotics in children and adolescents.

DEFINITION

Generalised anxiety disorder (GAD) is defined as excessive worry and tension about everyday events and problems, on most days, for at least 6 months, to the point where the person experiences distress or has marked difficulty in performing day-to-day tasks. [1] It may be characterised by the following symptoms and signs: increased motor tension (fatigability, trembling, restlessness, and muscle tension); autonomic hyperactivity (shortness of breath, rapid heart rate, dry mouth, cold hands, and dizziness); and increased vigilance and scanning (feeling keyed up, increased startling, and impaired concentration), but not by panic attacks. [1] One non-systematic review of epidemiological and clinical studies found marked reduction in quality of life and psychosocial functioning in people with anxiety disorders, including GAD. [2] It also found that people with GAD had low overall life satisfaction, and some impairment in ability to fulfil roles, social tasks, or both. [2]

INCIDENCE/ PREVALENCE

The most recent community surveys have used a newer version of the Composite International Diagnostic Interview (CIDI), which allows direct comparisons between different surveys. One observational survey in Europe completed in 2003, which included people from Belgium, France, Germany, Italy, the Netherlands, and Spain, estimated the 12-month prevalence of GAD at 1.0% (0.5% males, 1.3% females). [3] An observational survey in New Zealand (12,800 people) estimated the 12-month prevalence of GAD at 2.0%, 95% CI 1.7% to 2.3% (men: 1.4%, 95% CI 1.1% to 1.8%; women: 2.6%, 95% CI 2.2% to 3.1%). [4] In this survey, people aged >65 years had a markedly lower 12-month prevalence of GAD (1.0%, 95% CI 0.6% to 1.5%). The lifetime prevalence of GAD was estimated to be 6.0%, 95% CI 5.5% to 6.6%. [4] An observational survey in the UK in 2000 of people aged 16 to 74 years used the Clinical Interview Schedule-Revised (CIS-R), followed by a Schedules for Clinical Assessment in Neuropsychiatry [SCAN] interview of a stratified sample. [5] The survey estimated that 4.7% of people had GAD (men: 4.6%; women: 4.8%). A survey of children and adolescents aged 5 to 16 years in the UK in 2004, which used a similar methodology, estimated that 0.7% had GAD (boys: 0.6%; girls: 0.8%). [6] In the European survey of adults, 76% of those people who had more than one mental disorder for 12 months had GAD. [3] Those people who had GAD were significantly more likely to have other mental disorders which included (odds ratio to have the disorder): major depression (OR 37.1, 95% CI 23.2 to 59.1), social phobia (OR 13.5, 95% CI 7.8 to 23.6), specific phobia (OR 7.4, 95% CI 4.6 to 12.0), post-traumatic stress disorder (OR 16.4, 95% CI 9.1 to 29.8), agoraphobia (OR 26.6, 95% CI 10.8 to 65.1), panic disorder (OR 21.8, 95% CI 11.5 to 41.2), and alcohol dependence (OR 18.9, 95% CI 4.8 to 74.4). [3] Another observational survey in 2004 found that people with GAD were also more likely to have physical health problems. [7] In one systematic review (search date 2006), people with GAD had a significantly decreased quality of life (effect size [6 studies, 248 people, P <0.01). [8] A non-systematic review (20 observational studies in younger and older adults) suggested that autonomic arousal to stressful tasks was decreased in older people, and that older people became accustomed to stressful tasks more quickly than younger people. [9]

AETIOLOGY/ RISK FACTORS

GAD is believed to be associated with an increase in the number of minor life events, independent of demographic factors; [10] however, this finding is also common in people with other diagnoses. [11] One non-systematic review (5 case-control studies) of psychological sequelae to civilian trauma found that rates of GAD reported in 4 of the 5 studies were significantly increased compared with a control population (RR 3.3, 95% CI 2.0 to 5.5). [12] One systematic review (search date 1997) of cross-sectional studies found that bullying (or peer victimisation) was associated with a significant increase in the incidence of GAD (effect size 0.21, CI not reported). [13] One systematic review (search date not reported, 2 family studies, 45 index cases, 225 first-degree relatives) found a significant association between GAD in the index cases and in their first-degree relatives (OR 6.1, 95% CI 2.5 to 14.9). [14] One systematic review of twin and family studies (search date 2003, 23 twin studies, 12 family studies) found an association between GAD, other anxiety disorders, and depression, and postulated that a common genetic factor was implicated. [15]

PROGNOSIS

One systematic review found that 25% of adults with GAD will be in full remission after 2 years, and 38% will have a remission after 5 years. [16] The Harvard–Brown anxiety research programme reported 5-year follow-up of 167 people with GAD. [17] During this period, the weighted probability for full remission was 38% and for at least partial remission was 47%; the probability of relapse from full remission was 27%, and of relapse from partial remission was 39%.

AIMS OF INTERVENTION

To reduce symptoms of anxiety; to minimise disruption of day-to-day functioning; and to improve quality of life, with minimum adverse effects.

OUTCOMES

Symptom severity: as measured by symptom scores on continuous rating scales. Frequently used rating scales include the Hamilton Anxiety Scale (HAM-A), Spielberger State-Trait Anxiety Inventory (STAI), and Clinical Global Impressions Scale (CGI). Other continuous scales for symptom assessment include the Penn State Worry Questionnaire (PSWQ), Anxiety Status Inventory (ASI), and the GAD Severity Scale. Where numbers needed to treat are given, these represent the number of people requiring treatment within a given time period (usually 6–12 weeks) for one additional person to achieve a certain improvement in symptom score. The method for obtaining numbers needed to treat was not standardised across studies. Some RCTs defined a reduction by, for example, 20 points in the HAM-A as a clinical response; others defined a clinical response as a reduction by, for example, 50% of the pretreatment score. The authors have not attempted to standardise methods, but instead have used the response rates reported in each study to calculate numbers needed to treat. **Quality of life**. **Adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal May 2011. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2011, Embase 1980 to May 2011, and The Cochrane Database of Systematic Reviews, 2011, Issue 2 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. Recent changes in diagnostic classification make it difficult to compare older studies versus more recent ones. In the earlier classification system (DSM-III-R), the diagnosis was made only in the absence of other psychiatric disorders. In current systems (DSM-IV and *International Classification of Diseases 10* [ICD-10]), GAD can be diagnosed in the presence of any comorbid condition. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 71). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for generalised anxiety disorder in adults?

OPTION CBT IN ADULTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- CBT (including exposure, relaxation, and cognitive restructuring) improves anxiety compared with waiting list control, treatment as usual, or enhanced usual care.
- CBT and applied relaxation may be equally effective at improving anxiety.
- It is unclear whether CBT is more effective than supportive therapy.

Benefits and harms

CBT versus waiting list control or non-specific therapies:

We found 6 systematic reviews (search dates 1996, [18] not reported, [19] 2006, [20] [21] [22] and 2007 [23]) comparing CBT versus waiting list control (no treatment) or versus other psychotherapies in people with generalised anxiety disorder (GAD). Many of the RCTs were small and were not analysed on an intention-to-treat basis. Owing to crossover reporting between reviews, we report meta-analyses only from the more recent reviews. We found two subsequent RCTs. [24] [25]

Symptom severity

Compared with waiting list control or non-specific therapies CBT (using a combination of interventions, such as exposure, relaxation, systematic desensitisation, and cognitive restructuring) may be more effective than waiting list control or usual treatments (anxiety management, relaxation, supportive therapy, and non-directive psychotherapy) at improving symptoms of anxiety and at increasing clinical responses (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Anxiety					
[23] Systematic review	95 people 2 RCTs in this analysis	**Change in anxiety scale , treatment duration not reported** with CBT with non-directive therapy or supportive therapy Absolute numbers not reported	P = 0.03	○○○	CBT
[22] Systematic review	146 people aged >60 years 4 RCTs in this analysis	**Change in anxiety scale , treatment duration not specified** with CBT with waiting list control Absolute numbers not reported The review reported that there was poor follow-up in studies (78%), 1 study included patients with mixed anxiety disorders, and that all analyses were completer based	SMD –0.44 95% CI –0.84 to –0.04 P = 0.03	○○○	CBT
[22] Systematic review	243 people aged >60 years 5 RCTs in this analysis	**Change in anxiety scale , treatment duration not specified** with CBT with active control Absolute numbers not reported The active control condition involved minimal contact including weekly telephone calls and consultation on demand, supportive psychotherapy, and a discussion group	SMD –0.51 95% CI –0.81 to –0.21 P = 0.0009	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The review reported that there was poor follow-up in studies (75%), 1 study included patients with mixed anxiety disorders, and that all analyses were completer based			
[21] Systematic review	Total number of people not reported 7 RCTs in this analysis Included 6 RCTs identified by review [19]	**Anxiety symptoms: all trials used Penn State Worry Questionnaire (PSWQ)** with CBT with waiting list control or non-specific therapies (supportive therapy) Absolute results not reported	Pooled effect size (CBT *v* control) 1.15 CI not reported P <0.05 Measure of effect size not reported	○○○	CBT
[24] RCT	134 older people (mean age 67 years)	**Mean change in worry severity (PSWQ) , 3 months** 7.7 with CBT 3.2 with enhanced usual care PSWQ is a 16-item self-report scale, range 16 to 80	P <0.001	○○○	CBT
[24] RCT	134 older people (mean age 67 years)	**Mean change in anxiety (GAD Severity Scale [GADSS]) , 3 months** 2.8 with CBT 1.4 with enhanced usual care GADSS is a 6-item clinician-rated scale	P = 0.19	⟷	Not significant
[24] RCT	134 older people (mean age 67 years)	**Mean change in anxiety severity (SIGH-A) , 3 months** 4.3 with CBT 3.0 with enhanced usual care SIGH-A: Structured Interview Guidelines for the Hamilton Anxiety Rating Scale	P = 0.23	⟷	Not significant
[24] RCT	134 older people (mean age 67 years)	**Mean change in general mental health (short-form [SF]-12 mental component scale) , 3 months** 7.2 with CBT 3.6 with enhanced usual care	P = 0.008	○○○	CBT
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed applied relaxation	**Change in Clinician Severity Rating , 12 weeks** From 5.78 to 1.61 with CBT From 5.90 to 4.78 with waiting list control 43 people in this analysis	P <0.001	○○○	CBT
[25] RCT	65 people in whom GAD was the primary diagnosis	**Change in PSWQ , 12 weeks** From 61.65 to 51.13 with CBT	P <0.001	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed applied relaxation	From 57.34 to 58.80 with waiting list control 45 people in this analysis			
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed applied relaxation	**Change in Worry and Anxiety Questionnaire, Somatic Scale , 12 weeks** From 21.13 to 17.74 with CBT From 22.42 to 21.45 with waiting list control 45 people in this analysis	P <0.005	○○○	CBT
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed applied relaxation	**Change in State Trait Anxiety Inventory, trait version , 12 weeks** From 53.04 to 46.35 with CBT From 52.06 to 48.98 with waiting list control 45 people in this analysis	P <0.001	○○○	CBT
Clinical response					
[20] Systematic review	334 people 8 RCTs in this analysis	**Proportion of non-responders measured by clinician-rated composite measure or structured diagnostic interviews** 54% with CBT 86% with waiting list control or treatment as usual	RR 0.64 95% CI 0.55 to 0.74	●○○	CBT

Quality of life

No data from the following reference on this outcome. [20] [21] [22] [23] [24] [25]

Adverse effects

No data from the following reference on this outcome. [20] [21] [22] [23] [24] [25]

CBT versus psychodynamic therapy:

We found one systematic review (search date 2006), which included one RCT comparing cognitive therapy plus anxiety management versus psychodynamic therapy. [20] We found one subsequent RCT. [26]

Symptom severity

Compared with psychodynamic therapy We don't know how CBT and psychodynamic therapy compare at improving symptoms of generalised anxiety disorder (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[20] Systematic review	110 people Data from 1 RCT	**Response rate defined from State-Trait Anxiety Inventory (STAI-I) , after therapy** 28% with CBT plus anxiety management 7% with psychodynamic therapy	RR 0.77 95% CI 0.65 to 0.92	●○○	CBT plus anxiety management
[20] Systematic review	110 people Data from 1 RCT	**Response rate defined from STAI-I , 6 months** 39% with CBT plus anxiety management 23% with psychodynamic therapy	RR 0.79 95% CI 0.62 to 1.01	⟷	Not significant
[26] RCT	57 people	**Hamilton Anxiety Rating Scale (HAM-A) score , 30 weeks** 8.99 with CBT 9.15 with short-term psychodynamic therapy	P = 0.51	⟷	Not significant
[26] RCT	57 people	**Penn State Worry Questionnaire score , 30 weeks** 7.32 with CBT 4.23 with short-term psychodynamic therapy	P = 0.03	○○○	CBT
[26] RCT	57 people	**Beck Anxiety Inventory score , 30 weeks** 6.35 with CBT 6.20 with short-term psychodynamic therapy	P = 0.89	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [20] [26]

Adverse effects

No data from the following reference on this outcome. [20] [26]

CBT versus supportive therapy:

We found one systematic review (search date 2006, 7 RCTs) comparing CBT versus supportive therapy. [20] Many of the RCTs were small and were not analysed on an intention-to-treat basis.

Symptom severity

Compared with supportive therapy CBT and supportive therapy seem equally effective at improving clinical responses, but CBT seems more effective at improving anxiety symptoms at 6 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[20] Systematic review	332 people 6 RCTs in this analysis	**Response rate assessed through composite measure of anxiety severity (3 RCTs) and Hamilton Anxiety Rating Scale (HAM-A) (3 RCTs) , post treatment** 42% with cognitive therapy 28% with supportive therapy Absolute numbers not reported	RR 0.86 95% CI 0.70 to 1.06	⟷	Not significant
[20] Systematic review	332 people 6 RCTs in this analysis	**Response rate assessed through composite measure of anxiety severity (3 RCTs) and HAM-A (3 RCTs) , 6 months** with cognitive therapy with supportive therapy Absolute numbers not reported	RR 0.79 95% CI 0.59 to 1.06	⟷	Not significant
[20] Systematic review	235 people 6 RCTs in this analysis	**Anxiety symptoms , post treatment** with cognitive therapy with supportive therapy Absolute numbers not reported	SMD –0.40 95% CI –0.66 to –0.14	○○○	CBT
[20] Systematic review	97 people 3 RCTs in this analysis	**Anxiety symptoms , 6 months** with cognitive therapy with supportive therapy Absolute numbers not reported	SMD –0.42 95% CI –0.83 to –0.02	○○○	CBT

Quality of life

No data from the following reference on this outcome. [20]

Adverse effects

No data from the following reference on this outcome. [20]

Cognitive therapy versus behavioural therapy (including applied relaxation):

We found one systematic review (search date 2006, 5 RCTs), which pooled data. [20] Three included RCTs compared cognitive therapy versus applied relaxation; one included RCT compared combined relaxation plus cognitive restructuring, cognitive restructuring, and applied progressive muscle relaxation; and one included RCT compared cognitive

therapy, analytic psychotherapy, and anxiety management training. We found one additional [27] and one subsequent RCT. [25]

Symptom severity

Compared with behavioural therapy (including applied relaxation) Cognitive therapy may be more effective than behavioural therapy at improving response rates but not anxiety scores at 6 months. Cognitive therapy may be no more effective than applied relaxation at improving response rates or symptoms of anxiety (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[20] Systematic review	220 people 5 RCTs in this analysis	**Clinical response rates , end of treatment** 50% with cognitive therapy 31% with behavioural therapy Absolute numbers not reported	RR 0.70 95% CI 0.56 to 0.87	●○○	cognitive therapy
[20] Systematic review	105 people 2 RCTs in this analysis	**Clinical response rates , 6 months** 58% with cognitive therapy 29% with behavioural therapy Absolute numbers not reported	RR 0.56 95% CI 0.40 to 0.79	●○○	cognitive therapy
[20] Systematic review	131 people 4 RCTs in this analysis	**Mean anxiety symptom scores , post treatment** with cognitive therapy with behavioural therapy Absolute numbers not reported	SMD –0.11 95% CI –0.59 to +0.30	⟷	Not significant
[20] Systematic review	67 people 2 RCTs in this analysis	**Mean anxiety symptom scores , 6 months** with cognitive therapy with behavioural therapy Absolute numbers not reported	SMD –0.11 95% CI –0.59 to +0.37	⟷	Not significant
[20] Systematic review	36 people Data from 1 RCT	**Clinical response , post treatment** with cognitive therapy with applied relaxation Absolute numbers not reported	RR 0.60 95% CI 0.28 to 1.30 The review did not pool data on this comparison	⟷	Not significant
[20] Systematic review	45 people Data from 1 RCT	**Clinical response , post treatment** with cognitive therapy with applied relaxation Absolute numbers not reported	RR 0.80 95% CI 0.51 to 1.26 The review did not pool data on this comparison	⟷	Not significant
[20] Systematic review	40 people Data from 1 RCT	**Clinical response , post treatment** with cognitive therapy with applied relaxation Absolute numbers not reported	RR 0.29 95% CI 0.11 to 0.72 The review did not pool data on this comparison	●●○	cognitive therapy
[20] Systematic review	40 people Data from 1 RCT	**Clinical response , 6 months** with cognitive therapy with applied relaxation Absolute numbers not reported	RR 0.55 95% CI 0.25 to 1.19 The review did not pool data on this comparison	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[27] RCT **3-armed trial**	76 people	**Proportion of people no longer meeting criteria for GAD , immediately after treatment** with cognitive therapy (with a behavioural component) with cognitive therapy (without a behavioural component) with applied relaxation with visualisation Absolute numbers not reported	Reported no significant difference among groups	⟷	Not significant
[27] RCT **3-armed trial**	76 people	**Proportion of people no longer meeting criteria for GAD , 24 months** with cognitive therapy (with a behavioural component) with cognitive therapy (without a behavioural component) with applied relaxation with visualisation Absolute numbers not reported	Reported no significant difference among groups	⟷	Not significant
[27] RCT **3-armed trial**	76 people	**Anxiety measures (6) and depression measures (2) , 24 months** with cognitive therapy (with a behavioural component) with cognitive therapy (without a behavioural component) with applied relaxation with visualisation Absolute numbers not reported	Reported no significant difference among groups	⟷	Not significant
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed waiting list control	**Change in Clinician Severity Rating , 12 weeks** From 5.78 to 1.61 with CBT From 5.36 to 2.55 with applied relaxation 45 people in this analysis	P value not reported Reported as not significant	⟷	Not significant
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed waiting list control	**Change in Penn State Worry Questionnaire score , 12 weeks** From 61.65 to 51.13 with CBT From 58.01 to 52.16 with applied relaxation 45 people in this analysis	P value not reported Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed waiting list control	**Change in Worry and Anxiety Questionnaire, Somatic Scale , 12 weeks** From 21.13 to 17.74 with CBT From 20.82 to 17.91 with applied relaxation 45 people in this analysis	P value not reported Reported as not significant	⟷	Not significant
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed waiting list control	**Change in State Trait Anxiety Inventory, trait version , 12 weeks** From 53.04 to 46.35 with CBT From 52.23 to 46.95 with applied relaxation 45 people in this analysis	P value not reported Reported as not significant	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [20] [25] [27]

Adverse effects

No data from the following reference on this outcome. [20] [25] [27]

CBT versus non-specific therapy in benzodiazepine discontinuation:

We found one RCT comparing CBT plus medication tapering for benzodiazepine discontinuation versus non-specific psychological therapy (based on active listening) plus medication tapering. [28] Both groups had twelve 90-minute sessions of therapy.

Symptom severity

CBT plus medication tapering compared with non-specific therapy in benzodiazepine discontinuation CBT plus medication tapering may be more effective at increasing the proportion of people who discontinue benzodiazepines (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[28] RCT	61 people with GAD who had used benzodiazepines for at least 12 months	**Proportion of people who had stopped benzodiazepines , at the end of the treatment** 74% with CBT plus medication tapering 37% with non-specific psychological therapy plus medication tapering Absolute numbers not reported	P = 0.003	○○○	CBT plus medication tapering
[28] RCT	61 people with GAD who had used benzodiazepines for at least 12 months	**Proportion of people who had stopped benzodiazepines , 12 months** 65% with CBT plus medication tapering 30% with non-specific psychological therapy plus medication tapering Absolute numbers not reported	P = 0.007	○○○	CBT plus medication tapering

Quality of life

No data from the following reference on this outcome. [28]

Adverse effects

No data from the following reference on this outcome. [28]

CBT versus drug treatment:

See option on benzodiazepines, p 14 .

Further information on studies

[21] The review noted that the RCTs were heterogeneous (age was a confounding factor), and reanalysed the data for younger (mean age 38 years) and older (mean age 68 years) adults (age range in each group not further defined). The pooled effect size was still significant for CBT compared with supportive or no therapy for both age groups (1.69 for younger adults and 0.82 for older adults; P <0.05 for either comparison).

Comment: None.

OPTION APPLIED RELAXATION IN ADULTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .

- Applied relaxation may be as effective as CBT at reducing anxiety, but we found RCT insufficient evidence about applied relaxation compared with no treatment.

Benefits and harms

Applied relaxation versus placebo or no treatment:

We found one RCT. [25] See also cognitive therapy versus behavioural therapy (including applied relaxation) in CBT option, p 4 .

Symptom severity

Compared with no treatment We don't know whether applied relaxation is more effective at improving symptoms of anxiety (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed CBT	**Change in Clinician Severity Rating , 12 weeks** From 5.36 to 2.55 with applied relaxation From 5.90 to 4.78 with waiting list control 42 people in this analysis	P = 0.006	○○○	applied relaxation
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed CBT	**Change in Penn State Worry Questionnaire score , 12 weeks** From 58.01 to 52.16 with applied relaxation From 57.34 to 58.80 with waiting list control 42 people in this analysis	P value not reported Reported as not significant	⟷	Not significant
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder, major depressive disorder, and OCD The remaining arm assessed CBT	**Change in Worry and Anxiety Questionnaire, Somatic Scale , 12 weeks** From 20.82 to 17.91 with applied relaxation From 22.42 to 21.45 with waiting list control 42 people in this analysis	P value not reported Reported as not significant	⟷	Not significant
[25] RCT **3-armed trial**	65 people in whom GAD was the primary diagnosis 58% of people had comorbid conditions, including panic disorder, specific phobia, dysthymic disorder,	**Change in State Trait Anxiety Inventory, trait version , 12 weeks** From 52.23 to 46.95 with applied relaxation From 52.06 to 48.98 with waiting list control 45 people in this analysis	P value not reported Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	major depressive disorder, and OCD The remaining arm assessed CBT				

Quality of life

No data from the following reference on this outcome. [25]

Adverse effects

No data from the following reference on this outcome. [25]

Applied relaxation versus CBT:

See option on CBT, p 4 .

Applied relaxation versus other psychological treatments:

See option on CBT, p 4 .

Further information on studies

Comment: We found one systematic review (search date 1998, 6 RCTs, 404 people) comparing applied relaxation versus a variety of other psychological treatments, which did not compare treatments directly (see comment on CBT, p 4). [29]

OPTION BENZODIAZEPINES IN ADULTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- Benzodiazepines may reduce symptoms of anxiety in people with GAD, but can have unpleasant adverse effects, and most trials have been short term.
- Benzodiazepines increase the risk of dependence, sedation, and accidents, and can cause adverse effects in neonates if used during pregnancy.

Benefits and harms

Benzodiazepines versus placebo:

We found two systematic reviews (search date 1996, 17 RCTs; [18] and search date 2002, 37 RCTs [30]). For further information on harms of benzodiazepines from observational studies, see comment.

Symptom severity

Compared with placebo Benzodiazepines seem more effective at reducing symptoms of anxiety at 2 to 9 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[18] Systematic review	2044 people 17 RCTs in this analysis	**Symptoms , 2 to 9 weeks** with benzodiazepines with placebo	Reported as significant Pooled mean effect size 0.70 CI not reported Measure of effect size not reported	○○○	benzodiazepines
[30] Systematic review	People with anxiety disorders (total number of people not reported) 37 RCTs in this analysis	**Anxiety** with benzodiazepines with placebo	Reported as significant P value not reported	○○○	benzodiazepines

Quality of life

No data from the following reference on this outcome. [18] [30]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[31] RCT **3-armed trial**	310 people In review [30] The remaining arm evaluated abecarnil	**Drowsiness** 52% with diazepam (15–35 mg/day) 14% with placebo Absolute numbers not reported	P <0.05 for diazepam *v* placebo	○○○	placebo
[31] RCT **3-armed trial**	310 people In review [30] The remaining arm evaluated abecarnil	**Dizziness** 11% with diazepam (15–35 mg/day) 3% with placebo Absolute numbers not reported	P <0.05 for diazepam *v* placebo	○○○	placebo
[18] Systematic review	People with anxiety disorders Data from 1 RCT	**Drowsiness** 71% with diazepam 13% with placebo Absolute numbers not reported	P = 0.001	○○○	placebo
[18] Systematic review	People with anxiety disorders Data from 1 RCT	**Dizziness** 29% with diazepam 11% with placebo Absolute numbers not reported	P = 0.001	○○○	placebo

Benzodiazepines versus each other:

We found two RCTs. [32] [33]

Symptom severity

Benzodiazepines compared with each other We don't know whether one benzodiazepine is more effective than the others at 3 to 5 weeks at improving Hamilton Anxiety Scale (HAM-A) or Clinical Global Impressions Scale (CGI) scores (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[32] RCT	121 people	**Hamilton Anxiety Scale (HAM-A) scores , over 5 weeks** with sustained-release alprazolam with bromazepam Absolute results reported graphically	Reported as not significant	⟷	Not significant
[32] RCT	121 people	**Clinical Global Impressions Scale (CGI) scores , over 5 weeks** with sustained-release alprazolam with bromazepam Absolute results reported graphically	Reported as not significant	⟷	Not significant
[33] RCT	64 people	**Proportion of people who had "highly improved" or "moderately improved" CGIS scores , 3 weeks** with mexazolam with alprazolam Absolute results reported graphically	98% "highly improved"; 87% "moderately improved" P >0.05	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [32] [33]

Adverse effects

No data from the following reference on this outcome. [32] [33]

Benzodiazepines versus CBT:

We found one systematic review (search date not reported, 2 small RCTs). [34] The review did not perform a meta-analysis.

Symptom severity

Lorazepam compared with CBT We don't know how lorazepam and CBT compare at improving symptoms of generalised anxiety disorder (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[34] Systematic review	20 people Data from 1 RCT	**Patient-rated improvement , 4 weeks** with lorazepam with CBT Absolute numbers not reported The review reported that the effect size was greater for CBT than for lorazepam. However, the review also stated that, because of the study's low statistical power, it did not calculate mean effect size	Significance not assessed		
[34] Systematic review	41 people Data from 1 RCT	**Patient-rated improvement , 10 weeks** with lorazepam with CBT Absolute numbers not reported The review reported that the effect size was greater for CBT than for diazepam. However, the review also stated that, because of the study's low statistical power, it did not calculate mean effect size	Significance not assessed		
[34] Systematic review	41 people Data from 1 RCT	**Clinician-rated improvement , 10 weeks** with lorazepam with CBT Absolute numbers not reported The review reported that the effect size was greater for CBT than for diazepam. However, the review also stated that, because of the study's low statistical power, it did not calculate mean effect size	Significance not assessed		

Quality of life

No data from the following reference on this outcome. [34]

Adverse effects

No data from the following reference on this outcome. [34]

Long-term treatment with benzodiazepines:

We found one systematic review (search date 1998, 8 RCTs, any benzodiazepine medication, >2 months' duration). [35] It found that the weak methods of the RCTs prevented firm conclusions being drawn.

Benzodiazepines versus buspirone:
See option on buspirone, p 19 .

Benzodiazepines versus hydroxyzine:
See option on hydroxyzine, p 23 .

Benzodiazepines versus abecarnil:
See option on abecarnil, p 25 .

Benzodiazepines versus antidepressants:
See option on antidepressants, p 28 .

Benzodiazepines versus pregabalin:
See option on pregabalin, p 50 .

Further information on studies

[18] [31] [32] All of the RCTs assessing benzodiazepines were short term (at most 12 weeks).

Comment:

Dependence and sedation: One non-systematic review of the harms of benzodiazepines found that rebound anxiety on withdrawal was reported in 15% to 30% of people. [36] It also found a high risk of substance abuse and dependence with benzodiazepines.

Memory: Thirty-one people with agoraphobia/panic disorder in an RCT comparing alprazolam versus placebo for 8 weeks were reviewed after 3.5 years. [37] Five people were still taking benzodiazepines and had significant impairment in memory tasks. There was no clear difference in memory performance between those who had been in the placebo group and those who had been given alprazolam but were no longer taking the drug.

Road traffic accidents: We found one systematic review (search date 1997) examining the relationship between benzodiazepines and road traffic accidents. [38] In the case-control studies, the odds ratio for death or emergency medical treatment in those who had taken benzodiazepines compared with those who had not taken them was 1.45 to 2.40. The odds ratio increased with higher doses and more recent intake. In the police and emergency-ward studies, benzodiazepine use was a factor in 1% to 65% of accidents (usually 5–10%). In two studies in which people had blood alcohol concentrations under the legal limit, benzodiazepines were found in 43% and 65% of people. For drivers aged >65 years, the risk of being involved in reported road traffic accidents was higher if they had taken longer-acting and larger quantities of benzodiazepines.These results are from case-control studies and, consequently, subject to confounding.

Pregnancy and breast feeding: One systematic review (search date 1997) of 23 case series and reports found no association between cleft lip and palate and benzodiazepines during the first trimester of pregnancy. [39] However, case reports in one non-systematic review suggested that benzodiazepines taken in late pregnancy may be associated with neonatal hypotonia and withdrawal

syndrome. [40] Benzodiazepines are secreted in breast milk, and there have been reports of sedation and hypothermia in infants. [40]

Other precautions: One non-systematic industry-funded review (8 RCTs) comparing benzodiazepines versus placebo or buspirone found that recent use of benzodiazepines limited the effectiveness of buspirone in people with generalised anxiety disorder. [41]

OPTION BUSPIRONE IN ADULTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- Buspirone may reduce symptoms of anxiety in people with GAD, but can have unpleasant adverse effects, and most trials have been short term.
- Buspirone may be less effective if used in people who have recently been taking benzodiazepines.

Benefits and harms

Buspirone versus placebo:

We found three systematic reviews (search date 1996, 9 RCTs; [18] search date 2002, 12 RCTs; [30] and search date 2005). [42]

Symptom severity

Compared with placebo Buspirone seems more effective at improving symptoms based on the Hamilton Anxiety Scale (HAM-A) or Clinical Global Impressions Scale (CGI) scores (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[18] Systematic review	People with anxiety disorders 9 RCTs in this analysis	**Symptoms , 4 to 9 weeks** with buspirone with placebo Absolute results not reported Withdrawal rate 17%	Reported as significant CI and P value not reported	○○○	buspirone
[30] Systematic review	People with anxiety disorders 12 RCTs in this analysis	**Symptoms** with buspirone with placebo Absolute results not reported	Reported as significant Pooled mean effect size 0.39 CI not reported	○○○	buspirone
[42] Systematic review	21 people Data from 1 RCT	**Hamilton Anxiety Scale (HAM-A) score** with buspirone with placebo Absolute results not reported	WMD +0.4 95% CI –5.62 to +6.42	⟷	Not significant
[42] Systematic review	38 people Data from 1 RCT	**HAM-A score** with buspirone with placebo Absolute results not reported	WMD –7.52 95% CI –9.89 to –5.15	○○○	buspirone
[42] Systematic review	52 people Data from 1 RCT	**HAM-A score** with buspirone with placebo Absolute results not reported	WMD –3.73 95% CI –4.01 to –3.45	○○○	buspirone
[42] Systematic review	162 people Data from 1 RCT	**Clinical Global Impressions scale (CGI) much or very improved** with buspirone with placebo	RR 1.48 95% CI 1.01 to 2.17 P = 0.04	●○○	buspirone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			

Quality of life

No data from the following reference on this outcome. [18] [30] [42]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[43] RCT	240 people In review [30]	**Proportion of people with nausea** 27/80 (34%) with buspirone 11/82 (13%) with placebo	RR 2.5 95% CI 1.3 to 4.7 NNH 5 95% CI 4 to 14	●●○	placebo
[43] RCT	240 people In review [30]	**Proportion of people with dizziness** 51/80 (64%) with buspirone 10/82 (12%) with placebo	RR 5.2 95% CI 2.9 to 9.6 NNH 2 95% CI 2 to 3	●●●	placebo
[43] RCT	240 people In review [30]	**Proportion of people with somnolence** 15/80 (19%) with buspirone 6/82 (7%) with placebo	RR 2.6 95% CI 1.0 to 6.3 NNH 9 95% CI 5 to 104	●●○	placebo
[42] Systematic review	635 people Data from 1 RCT	**Dizziness** with buspirone with placebo Absolute results not reported	RR 3.18 95% CI 1.82 to 5.56	●●○	placebo
[42] Systematic review	429 people Data from 1 RCT	**Nausea** with buspirone with placebo Absolute results not reported	RR 2.16 95% CI 1.14 to 4.10	●●○	placebo

No data from the following reference on this outcome. [18]

Buspirone versus benzodiazepines:

We found two systematic reviews (search dates 1996 [18] and 2005 [42]). The first systematic review [18] found one RCT, which compared three interventions: buspirone, diazepam, and placebo. [43] The other systematic review excluded the large RCT identified by the first review on methods (lack of a formal diagnosis of generalised anxiety disorder [GAD]) and reported data on two other RCTs. [42]

Symptom severity

Compared with benzodiazepines We don't know whether buspirone is more effective at improving symptoms at 6 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[43] RCT **3-armed trial**	240 people In review [18] The remaining arm evaluated placebo	**Proportion of people who responded (at least 40% reduction in Hamilton Anxiety Scale [HAM-A] score) , 6 weeks** 54% with buspirone 61% with diazepam Absolute numbers not reported	P value not reported		
[42] Systematic review **3-armed trial**	60 people Data from 1 RCT The remaining arm evaluated lorazepam	**HAM-A score** with buspirone with alprazolam Absolute results not reported	WMD (alprazolam *v* buspirone) 1.1 95% CI 0.28 to 1.92	○○○	alprazolam
[42] Systematic review **3-armed trial**	60 people Data from 1 RCT The remaining arm evaluated alprazolam	**HAM-A score** with lorazepam with buspirone Absolute results not reported	WMD (lorazepam *v* buspirone) 1.1 95% CI 0.29 to 1.91	○○○	lorazepam

Quality of life

No data from the following reference on this outcome. [18] [42] [43]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[43] RCT **3-armed trial**	240 people In review [18] The remaining arm evaluated placebo	**Adverse effects** with buspirone with diazepam Absolute numbers not reported Diazepam was associated with more fatigue and weakness compared with buspirone, but less headache and dizziness	Significance not assessed		
[42] Systematic review	People with anxiety disorders Number of people or RCTs in analysis not clear	**Drowsiness** with buspirone with benzodiazepines Absolute results not reported	RR 0.29 95% CI 0.21 to 0.41	●●○	buspirone
[42] Systematic review	People with anxiety disorders Number of people or RCTs in analysis not clear	**Fatigue** with buspirone with benzodiazepines Absolute results not reported	RR 0.24 95% CI 0.13 to 0.45	●●○	buspirone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[42] Systematic review	People with anxiety disorders Number of people or RCTs in analysis not clear	**Nervousness** with buspirone with benzodiazepines Absolute results not reported	RR 0.17 95% CI 0.06 to 0.47	●●●	buspirone
[42] Systematic review	People with anxiety disorders Number of people or RCTs in analysis not clear	**Depression** with buspirone with benzodiazepines Absolute results not reported	RR 0.22 95% CI 0.12 to 0.39	●●○	buspirone
[42] Systematic review	People with anxiety disorders Number of people or RCTs in analysis not clear	**Insomnia** with buspirone with benzodiazepines Absolute results not reported	RR 0.14 95% CI 0.03 to 0.63	●●●	buspirone
[42] Systematic review	People with anxiety disorders Number of people or RCTs in analysis not clear	**Sleep problems** with buspirone with benzodiazepines Absolute results not reported	RR 0.25 95% CI 0.08 to 0.81	●●○	buspirone
[42] Systematic review	People with anxiety disorders Number of people or RCTs in analysis not clear	**Nausea** with buspirone with benzodiazepines Absolute results not reported	RR 2.84 95% CI 1.14 to 7.09	●●○	benzodiazepines
[42] Systematic review	People with anxiety disorders Number of people or RCTs in analysis not clear	**Dizziness** with buspirone with benzodiazepines Absolute results not reported	RR 2.28 95% CI 1.15 to 4.54	●●○	benzodiazepines

Buspirone versus antidepressants:
See option on antidepressants, p 28 .

Buspirone versus hydroxyzine:
See option on hydroxyzine, p 23 .

Further information on studies

Comment:

Benzodiazepines versus placebo or buspirone:
A re-analysis of pooled drug company data from 8 RCTs comparing benzodiazepines versus placebo or buspirone suggested that recent use of benzodiazepines limited the effectiveness of buspirone in people with generalised anxiety disorder (GAD). [41] **Adverse effects** One systematic

review of jitteriness/anxiety syndrome (search date 2006) [44] identified a case report of anxiety/jitteriness syndrome in a patient with GAD taking buspirone.

OPTION HYDROXYZINE IN ADULTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- Hydroxyzine may reduce symptoms of anxiety in people with GAD, but it can have unpleasant adverse effects, and most trials have been short term.

Benefits and harms

Hydroxyzine versus placebo:

We found one systematic review (search date 2010, 5 RCTs). [45]

Symptom severity

Compared with placebo Hydroxyzine seems more effective at improving symptoms and response rates (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[45] Systematic review	417 people 4 RCTs in this analysis	**Proportion of people who did not show a response** 83/219 (38%) with hydroxyzine 123/198 (62%) with placebo See further information on studies for definition of response	OR 0.30 95% CI 0.15 to 0.58 P <0.0004	○○○	hydroxyzine
[45] Systematic review	381 people 2 RCTs in this analysis	**Difference in efficacy scale** with hydroxyzine with placebo Absolute numbers not reported See further information on studies for details of scales used	SMD –0.42 95% CI –0.62 to –0.21 P <0.00006	○○○	hydroxyzine

Quality of life

No data from the following reference on this outcome. [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] Systematic review	584 people 4 RCTs in this analysis	**Proportion of people reporting adverse effects** 127/301 (42%) with hydroxyzine 99/283 (35%) with placebo	OR 1.49 95% CI 0.92 to 2.40 P = 0.1	⟷	Not significant
[45] Systematic review	218 people Data from 1 RCT	**Withdrawal symptoms** 42% with hydroxyzine 35% with placebo Absolute results not reported	OR 1.43 95% CI 0.62 to 3.30	⟷	Not significant

Hydroxyzine versus benzodiazepines:

We found one systematic review (search date 2010, 5 RCTs). [45]

Symptom severity

Compared with benzodiazepines Hydroxyzine and benzodiazepines may be equally effective at improving response and reducing symptom severity (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[45] Systematic review	106 people Data from 1 RCT	**Proportion of people who did not show a response** 22/55 (40%) with hydroxyzine 24/51 (47%) with chlordiazepoxide See further information on studies for definition of response	OR 0.75 95% CI 0.35 to 1.62	⟷	Not significant
[45] Systematic review	221 people Data from 1 RCT	**Difference in efficacy scale** with hydroxyzine with bromazepam Absolute numbers not reported See further information on studies for details of scales used	SMD –0.01 95% CI –0.27 to +0.26	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] Systematic review	327 people 2 RCTs in this analysis	**Proportion of people reporting adverse effects** 34/160 (21%) with hydroxyzine 30/167 (18%) with benzodiazepines	OR 1.20 95% CI 0.69 to 2.09 P = 0.52	⟷	Not significant
[45] Systematic review	221 people Data from 1 RCT	**Proportion of people reporting withdrawal symptoms** with hydroxyzine with benzodiazepines Absolute numbers not reported	OR 0.84 95% CI 0.39 to 1.78	⟷	Not significant

Hydroxyzine versus buspirone:

We found one systematic review (search date 2010, 1 RCT). [45]

Symptom severity

Hydroxyzine compared with buspirone Hydroxyzine and buspirone seem equally effective at improving response (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[45] Systematic review	163 people Data from 1 RCT	**Proportion of people who failed to show a response** 47/81 (58%) with hydroxyzine 53/82 (65%) with buspirone See further information on studies for definition of response	OR 0.76 95% CI 0.40 to 1.42	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] Systematic review	163 people Data from 1 RCT	**Proportion of people reporting adverse effects** 32/81 (40%) with hydroxyzine 31/82 (38%) with buspirone	OR 1.07 95% CI 0.57 to 2.02	⟷	Not significant

Further information on studies

[45] The review defined response as a reduction of at least 50% on the Hamilton Anxiety Scale (HAM-A) at follow-up. When HAM-A and other scales were not available, the review considered as response a Clinical Global Impressions Scale (CGI)-S (severity) criteria score of 1, 2, or 3, and CGI-I (improvement) criteria score of 1 or 2. If no scale was provided, the review accepted any definition of outcome from the authors. **Adverse effects** The review found an association between hydroxyzine and increased sleepiness and drowsiness (OR 1.74, 95% CI 0.86 to 3.53).

Comment: There have been case reports of cutaneous drug eruptions [46] and supraventricular tachycardia in a child associated with use of hydroxyzine. [47] In overdose, catatonia has been reported. [48] A neonatal withdrawal syndrome involving seizures has been described in one case report. [49]

OPTION ABECARNIL IN ADULTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- We don't know whether abecarnil reduces anxiety as the RCTs we found reported inconsistent results.

Benefits and harms

Abecarnil versus placebo:

We found one systematic review (search date 2002, 4 RCTs) [30] and two multicentre RCTs of abecarnil. [50] [31] The review did not report results for abecarnil versus placebo separately. [30] The first RCT compared 3 weeks of treatment with abecarnil in three separate dose regimens (3–9 mg/day, 7.5–15 mg/day, and 15–30 mg/day) versus placebo. [50] Within each group the dose was escalated from the minimum to the maximum over the length of the trial. The second RCT compared three interventions: abecarnil 7.5 mg to 17.5 mg daily, diazepam 15 mg to 35 mg daily, and placebo. [31]

Symptom severity

Compared with placebo We don't know whether abecarnil is more effective at reducing Hamilton Anxiety Scale (HAM-A) scores by 50% (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[50] RCT **4-armed trial**	129 people The remaining arms evaluated higher doses of abecarnil (7.5–15 mg/day and 15–30 mg/day)	**50% reduction in Hamilton Anxiety Scale (HAM-A) score** 19/31 (61%) with abecarnil (3–9 mg/day) 8/26 (31%) with placebo Results were not calculated by intention to treat	RR 1.99 95% CI 1.05 to 3.78	●○○	abecarnil
[50] RCT **4-armed trial**	129 people The remaining arm evaluated lower doses of abecarnil (3–9 mg/day)	**50% reduction in HAM-A score** with abecarnil (7.5–15 mg/day and 15–30 mg/day) with placebo Results were not calculated by intention to treat	Reported no significant difference between higher doses of abecarnil and placebo	⟷	Not significant
[31] RCT **3-armed trial**	310 people The remaining arm evaluated di-azepam (15–35 mg/day)	**Proportion of people with moderate improvement on the Clinical Global Impressions Scale (CGI) scores , at 6 weeks** 62% with abecarnil (7.5–17.5 mg/day) 56% with placebo	Reported no significant difference between abecarnil and placebo P value not reported	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [31] [50]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[50] RCT **4-armed trial**	129 people The remaining arms evaluated higher doses of abecarnil (7.5–15 mg/day and 15–30 mg/day)	**Fatigue** 4/32 (13%) with abecarnil (3–9 mg/day) 0/28 (0%) with placebo	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[50] RCT **4-armed trial**	129 people The remaining arms evaluated higher doses of abecarnil (7.5–15 mg/day and 15–30 mg/day)	**Equilibrium loss** 2/32 (6%) with abecarnil (3–9 mg/day) 0/28 (0%) with placebo	Significance not assessed		
[50] RCT **4-armed trial**	129 people The remaining arms evaluated higher doses of abecarnil (7.5–15 mg/day and 15–30 mg/day)	**Drowsiness** 10/32 (31%) with abecarnil (3–9 mg/day) 4/28 (14%) with placebo	Significance not assessed		
[50] RCT **4-armed trial**	129 people	**Proportion of people experiencing at least 1 adverse effect** 62% with abecarnil (15–30 mg/day) 51% with abecarnil (7.5–15 mg/day) 22% with abecarnil (3–9 mg/day) 21% with placebo Absolute numbers not reported	Significance not assessed		
[50] RCT **4-armed trial**	129 people 12/34 (35%) people	**Proportion of people who withdrew from treatment** 12/34 (35%) with abecarnil (15–30 mg/day) 4/35 (11%) with abecarnil (7.5–15 mg/day) 1/32 (3%) with abecarnil (3–9 mg/day) 2/28 (7%) with placebo	Significance not assessed		

No data from the following reference on this outcome. [31]

Abecarnil versus benzodiazepines:

We found one RCT (310 people) comparing three interventions: abecarnil 7.5 mg to 17.5 mg daily, diazepam 15 mg to 35 mg daily, and placebo. [31]

Symptom severity

Compared with benzodiazepines Abecarnil and benzodiazepines seem equally effective at 6 weeks at increasing the number of people with a moderate improvement on Clinical Global Impressions Scale (CGI) scores (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[31] RCT **3-armed trial**	310 people The remaining arm evaluated placebo	**Proportion of people with moderate improvement on the Clinical Global Impressions Scale (CGI) scores , at 6 weeks**	Reported no significant difference between abecarnil and diazepam P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		62% with abecarnil (7.5–17.5 mg/day) 73% with diazepam (15–35 mg/day)			

Quality of life

No data from the following reference on this outcome. [31]

Adverse effects

No data from the following reference on this outcome. [31]

Further information on studies

Comment: None.

OPTION ANTIDEPRESSANTS IN ADULTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- Antidepressants (imipramine, duloxetine, paroxetine, sertraline, escitalopram, venlafaxine, and opipramol) have been shown to reduce symptoms compared with placebo, but antidepressants can cause a variety of adverse effects including sedation, dizziness, falls, nausea, and sexual dysfunction.
- In general, comparisons between different antidepressants have shown similar effectiveness in reducing anxiety, although one RCT found limited evidence of an increased benefit with escitalopram compared with paroxetine.

Benefits and harms

Any antidepressant versus placebo:

We found two systematic reviews (search dates 2002 [51] and 2008 [52]). The second review assessed relapse prevention. [52] See also comment section for further information from observational studies and comments on adverse effects of antidepressants.

Symptom severity

Any antidepressant compared with placebo Antidepressants (imipramine, paroxetine, and venlafaxine) seem more effective at 4 to 28 weeks at increasing response rates and at reducing relapse in people who have responded to treatment (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[51] Systematic review	1056 people 4 RCTs in this analysis	**Non-response rate , 8 to 28 weeks** 277/606 (46%) with antidepressants (imipramine, paroxetine, and venlafaxine) 280/449 (62%) with placebo	RR of not responding 0.70 95% CI 0.62 to 0.79 NNT 6 95% CI 5 to 9	●○○	antidepressants
[53] RCT	230 people In review [51]	**Proportion of people with participant-assessed global improvement , 8 weeks** 73% with imipramine 67% with trazodone 66% with diazepam 39% with placebo	P <0.026 for any drug *v* placebo Results not analysed by intention to treat	○○○	antidepressants
[52] Systematic review	1342 people 3 RCTs in this analysis	**Proportion of people who relapsed after responding to treatment , 6 months** 93/664 (14%) with continuation of antidepressants 304/678 (45%) with placebo 2 RCTs assessed selective serotonin-reuptake inhibitors (SSRIs) and the other RCT assessed a serotonin-norepinephrine reuptake inhibitor (SNRI) Relapse defined as an increase in Clinical Global Impressions Scale (severity) (CGI-S) score to at least 4, Hamilton Anxiety Scale (HAM-A) score of at least 15, and/or clinical judgement	OR 0.2 95% CI 0.15 to 0.26 NNT 3 95% CI 2.86 to 3.85	●●○	antidepressants

Quality of life

No data from the following reference on this outcome. [51] [52] [53]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[53] RCT	People with anxiety disorders In review [51]	**Adverse effects** with antidepressants with placebo Sedation, confusion, dry mouth, and constipation were reported with both imipramine and trazodone			

No data from the following reference on this outcome. [52]

Duloxetine versus placebo:

We found one systematic review (search date 2009, 5 RCTs). [54] We also report additional data separately from one RCT identified by the review, which was not included in the meta-analysis. [55]

Symptom severity

Compared with placebo Duloxetine seems more effective at reducing symptom severity (Sheehan Disability Scale) at 9 to 10 weeks and at reducing the proportion of people who relapse after responding to treatment (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[54] Systematic review	Number of people not reported 3 RCTs in this analysis	**Proportion of people with normalised Sheehan Disability Scale score , 9 to 10 weeks** 47% with duloxetine 28% with placebo Absolute numbers not reported	P <0.001	○○○	duloxetine
[55] RCT	419 people who had responded to duloxetine in the first phase of a trial In review [54]	**Proportion of people who relapsed after response , 26 weeks** 28/204 (14%) with duloxetine (60–120 mg/day) 84/201 (42%) with placebo Study population consisted of people who completed an initial, open-label phase of the trial and were treatment responders; they were then randomised to duloxetine or placebo for a further 26 weeks' treatment	P <0.001	○○○	duloxetine 60 mg to 120 mg

Quality of life

No data from the following reference on this outcome. [54] [55]

Adverse effects

No data from the following reference on this outcome. [54] [55]

Escitalopram versus placebo:

We found 5 RCTs [56] [57] [58] [59] [60] and one report of pooled data from three RCTs comparing escitalopram versus placebo. [61] See also comment section for further information from observational studies and comments on adverse effects of antidepressants.

Symptom severity

Compared with placebo Escitalopram may be more effective at increasing remission and response rates at 8 to 12 weeks, and at reducing relapses and increasing time to relapse (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[56] RCT	315 people	**Remission (defined as a score of 7 or less on Hamilton Anxiety Scale [HAM-A]) , 8 weeks** 36% with escitalopram (10–20 mg/day) 16% with placebo Absolute numbers not reported	P <0.01 Mean difference 3.9 95% CI 1.7 to 6.0	○○○	escitalopram
[56] RCT	315 people	**Response rate (Clinical Global Impressions Scale [CGI] score of 1 or 2) , 8 weeks** 58% with escitalopram (10–20 mg/day) 38% with placebo Absolute numbers not reported	P = 0.01	○○○	escitalopram
[57] RCT **5-armed trial**	681 people The remaining arms evaluated escitalopram (10 mg/day and 20 mg/day) and paroxetine	**Mean HAM-A scores , 12 weeks** –15.49 with escitalopram (5 mg/day) –14.2 with placebo	P = 0.165 for escitalopram 5 mg *v* placebo	⟷	Not significant
[57] RCT **5-armed trial**	681 people The remaining arms evaluated escitalopram (5 mg/day and 20 mg/day) and paroxetine	**Mean HAM-A scores , 12 weeks** –16.8 with escitalopram (10 mg/day) –14.2 with placebo	P = 0.006 for escitalopram 10 mg *v* placebo	○○○	escitalopram
[57] RCT **5-armed trial**	681 people The remaining arms evaluated escitalopram (5 mg/day and 10 mg/day) and paroxetine	**Mean HAM-A scores , 12 weeks** –16.4 with escitalopram (20 mg/day) –14.2 with placebo	P = 0.022 for escitalopram 20 mg *v* placebo	○○○	escitalopram
[57] RCT **5-armed trial**	681 people The remaining arm evaluated paroxetine	**Remission (defined as a HAM-A score <7) , 12 weeks** with escitalopram (5 mg/day) with escitalopram (10 mg/day) with escitalopram (20 mg/day) with placebo Absolute numbers not reported	P <0.05 (all doses of escitalopram *v* placebo)	○○○	escitalopram
[61] Non-systematic review	856 people 3 RCTs in this analysis	**Remission (defined as a HAM-A score <7) , 8 weeks** 5.8 with escitalopram 3.9 with placebo	P <0.001	○○○	escitalopram
[61] Non-systematic review	856 people 3 RCTs in this analysis	**Mean improvement in HAM-A somatic anxiety subscale from baseline , 8 weeks** 4.3 with escitalopram 3.7 with placebo	P = 0.02	○○○	escitalopram

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[61] Non-systematic review	856 people 3 RCTs in this analysis	**Rates of HAM-A response (defined as at least 50% improvement in mean HAM-A score) , 8 weeks** 48% with escitalopram 29% with placebo Absolute numbers not reported	P <0.001	○○○	escitalopram
[61] Non-systematic review	856 people 3 RCTs in this analysis	**Rates of CGI response (defined as CGI score of 1 or 2 [much or very much improved] plus remission [HAM-A score of 7 or less]) , 8 weeks** 52% with escitalopram 37% with placebo Absolute numbers not reported	P <0.001	○○○	escitalopram
[59] RCT **3-armed trial**	392 people The remaining arm assessed venlafaxine extended release	**Mean difference in HAM-A , 8 weeks** with escitalopram with placebo Absolute numbers not reported 263 people in this analysis Analysis by last observation carried forward 78% of people in this comparison completed treatment	Mean difference –1.52 P = 0.09	⟷	Not significant
[58] RCT	375 people who had responded to escitalopram and had a HAM-A score of 10 or less Initially, 491 people had been treated with 12 weeks of open-label escitalopram; see further information on studies for details	**Proportion of people who had relapsed (defined as a HAM-A score of 15 or above) , 24 weeks** 34/187 (18%) with continued escitalopram (20 mg/day) 98/188 (52%) with placebo	P <0.001	○○○	escitalopram
[58] RCT	375 people who had responded to escitalopram and had a HAM-A score of 10 or less Initially, 491 people had been treated with 12 weeks of open-label escitalopram; see further information about studies for details	**Time to relapse (defined as a HAM-A score of 15 or above)** with continued escitalopram (20 mg/day) with placebo Absolute results reported graphically Kaplan-Meier analysis	P <0.001	○○○	escitalopram
[60] RCT	177 people aged >60 years The RCT stated that people with comorbid unipolar depression or anxiety disorders were included if GAD was the principal diagnosis, as were patients with a his-	**Proportion of people responding (CGI) , 12 weeks** 57% with escitalopram 45% with placebo Absolute numbers not reported Analysis by intention to treat	P = 0.11	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	tory of alcohol or substance abuse that was in full remission for at least 3 months				

Quality of life

No data from the following reference on this outcome. [56] [57] [58] [59] [60] [61]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[56] RCT	315 people	**Headache** 23% with escitalopram 18% with placebo Absolute numbers not reported			
[56] RCT	315 people	**Nausea** 19% with escitalopram 9% with placebo Absolute numbers not reported			
[56] RCT	315 people	**Somnolence** 12% with escitalopram 6% with placebo Absolute numbers not reported			
[56] RCT	315 people	**Upper respiratory tract infection** 11% with escitalopram 7% with placebo Absolute numbers not reported			
[57] RCT **5-armed trial**	681 people The remaining arms evaluated escitalopram (5 mg/day) and paroxetine	**Anorgasmia , over 12 weeks** 9/139 (7%) with escitalopram (20 mg/day) 6/136 (4%) with escitalopram (10 mg/day) 0/139 (0%) with placebo	P <0.05 escitalopram *v* placebo	○○○	placebo
[57] RCT **5-armed trial**	681 people The 5 arms evaluated escitalopram (5 mg/day, 10 mg/day, and 20 mg/day), paroxetine (20 mg/day), and placebo	**Insomnia** 10% with escitalopram or paroxetine 2% with placebo Absolute numbers not reported			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[57] RCT **5-armed trial**	681 people The remaining arms evaluated paroxetine (20 mg/day) and escitalopram (5 mg/day)	**Proportion of people reporting fatigue** 10% with escitalopram (10 mg/day) 17% with escitalopram (20 mg/day) 3% with placebo Absolute numbers not reported	P <0.05 escitalopram *v* placebo	○○○	placebo
[57] RCT **5-armed trial**	681 people The remaining arm evaluated paroxetine (20 mg/day)	**Diarrhoea** 9.7% with escitalopram (5 mg/day) 9.6% with escitalopram (10 mg/day) 9.8% with escitalopram (20 mg/day) 2.9% with placebo Absolute numbers not reported	P <0.05 escitalopram *v* placebo	○○○	placebo
[59] RCT **3-armed trial**	392 people The remaining arm assessed venlafaxine extended release	**Adverse effects , 8 weeks** with escitalopram with placebo Absolute numbers not reported 263 people in this analysis The RCT reported significant increases in nausea, ejaculation disorder, and erectile dysfunction compared with placebo	P <0.05	○○○	placebo

No data from the following reference on this outcome. [58] [60] [61]

Opipramol versus placebo:

We found one systematic review [30] (search date 2002), which found one RCT. [62] See also comment section for further information from observational studies and comments on adverse effects of antidepressants.

Symptom severity

Compared with placebo Opipramol is more effective at increasing response rates at 28 days (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Response rate					
[62] RCT **3-armed trial**	318 people The remaining arm evaluated alprazolam	**Response rate (defined as Clinical Global Impressions Scale [CGI] score of <2) , 28 days** 63/100 (63%) with opipramol 50/107 (47%) with placebo 207 people in this analysis	RR 1.35 95% CI 1.05 to 1.69 NNT 7 95% CI 1 to 26	●○○	opipramol

Quality of life

No data from the following reference on this outcome. [62]

Adverse effects

No data from the following reference on this outcome. [62]

Paroxetine versus placebo:

We found one systematic review [51] (search date 2002, 8 RCTs), which identified one RCT. We also found one additional RCT [63] and one subsequent multi-arm RCT. [57] See also comment section for further information from observational studies and comments on adverse effects of antidepressants.

Symptom severity

Paroxetine compared with placebo Paroxetine seems more effective than placebo at improving responses (measured as lower Clinical Global Impressions Scale [CGI] scores) at 4 to 10 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[51] Systematic review	324 people Data from 1 RCT	**Non-treatment response (measured using Clinical Global Impressions Scale [CGI] scores, Hamilton Anxiety Scale [HAM-A] scores, and Sheehan Disability Scale scores) , 8 weeks** with paroxetine with placebo Absolute results not reported	RR 0.72 95% CI 0.56 to 0.92 NNT 7 95% CI 4 to 25	●○○	paroxetine
[63] RCT **3-armed trial**	565 people The remaining arm assessed paroxetine 40 mg	**Response (defined as CGI scores 2 or less) , 8 weeks** 116/188 (62%) with paroxetine (20 mg/day) 82/180 (45%) with placebo	RR 1.36 95% CI 1.11 to 1.64 NNT 6 95% CI 4 to 13	●○○	paroxetine (20 mg/day)
[63] RCT **3-armed trial**	565 people The remaining arm assessed paroxetine 20 mg	**Response (defined as CGI scores 2 or less) , 8 weeks** 134/197 (68%) with paroxetine (40 mg/day) 82/180 (45%) with placebo	RR 1.49 95% CI 1.24 to 1.679 NNT 4 95% CI 3 to 6	●○○	paroxetine (40 mg/day)
[57] RCT **5-armed trial**	681 people, 274 people in this analysis The remaining arms evaluated escitalopram (5, 10, 20 mg)	**Mean change in HAM-A total score , 12 weeks** with paroxetine (20 mg/day) with placebo Absolute numbers not reported	Difference between groups –0.51 95% CI –2.33 to +1.32 P = 0.585	⟷	Not significant
[57] RCT **5-armed trial**	274 people The remaining arms evaluated escitalopram (5, 10, 20 mg)	**Mean CGI-Improvement (CGI-I) scores , weeks 4, 8, and 10** with paroxetine (20 mg/day) with placebo Absolute results reported graphically	P <0.05	○○○	paroxetine

Quality of life

No data from the following reference on this outcome. [51] [63] [57]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[63] RCT **3-armed trial**	565 people	**People with at least one adverse event , 8 weeks** 88% with paroxetine (20 mg/day) 86% with paroxetine (40 mg/day) 74% with placebo Adverse effects included: asthenia, constipation, dry mouth, abnormal ejaculation, decreased libido, nausea, somnolence, decreased appetite, sweating, yawning, and female genital disorders	P <0.002	○○○	placebo
[57] RCT **5-armed trial**	681 people The remaining arms evaluated escitalopram (5 mg/day and 20 mg/day)	**Anorgasmia , over 12 weeks** 9/139 (6.5%) with paroxetine (20 mg/day) 6/136 (4.4%) with escitalopram (10 mg/day) 0/139 (0%) with placebo	P <0.05	○○○	placebo
[57] RCT **5-armed trial**	681 people The 5 arms evaluated escitalopram (5, 10, and 20 mg/day), paroxetine (20 mg/day), and placebo	**Insomnia** 10% with escitalopram or paroxetine 2% with placebo Absolute numbers not reported			

No data from the following reference on this outcome. [51]

Sertraline versus placebo:

We found three RCTs. [64] [65] [66]

Symptom severity

Compared with placebo Sertraline seems more effective at 12 weeks at improving Hamilton Anxiety Scale (HAM-A) and Clinical Global Impressions Scale (CGI) scores (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[64] RCT	373 people	**Hamilton Anxiety Scale (HAM-A) score (mean change from baseline) , 12 weeks**	P <0.0001	○○○	sertraline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		11.7 with sertraline (dose titrated from 25 mg/day in the first week to 50–150 mg/day by week 12) –8.0 with placebo			
[64] RCT	373 people	**Anxiety component of Hospital Anxiety and Depression (HAD) scale (mean change from baseline) , 12 weeks** –4.5 with sertraline (dose titrated from 25 mg/day in the first week to 50–150 mg/day by week 12) –2.6 with placebo	P <0.0001	○○○	sertraline
[64] RCT	373 people	**Clinical Global Impressions Scale (CGI) (mean change from baseline at end point) , 12 weeks** 1.56 with sertraline (dose titrated from 25 mg/day in the first week to 50–150 mg/day by week 12) –0.90 with placebo	P <0.0001	○○○	sertraline
[65] RCT	373 people	**HAM-A score improvement , 12 weeks** with sertraline with placebo Absolute numbers not reported	Mean ratio 1.5 95% CI 1.3 to 1.6 Mean difference 3.7 95% CI 3.5 to 3.9	○○○	sertraline
[65] RCT	373 people	**CGI score improvement , 12 weeks** with sertraline with placebo Absolute numbers not reported	Mean ratio 1.33 95% CI 1.27 to 1.3 Mean difference 0.40 95% CI 0.34 to 0.46	○○○	sertraline
[65] RCT	373 people	**Response rates (30% reduction in HAM-A) , 12 weeks** 73% with sertraline 40% with placebo Absolute numbers not reported	P = 0.001	○○○	sertraline
[65] RCT	373 people	**Response rates (50% reduction in HAM-A) , 12 weeks** 55% with sertraline 32% with placebo Absolute numbers not reported	P = 0.001	○○○	sertraline
[66] RCT	326 people	**Reduction in HAM-A total score from baseline , 10 weeks** –12.71 with sertraline (50–200 mg/day) –11.5 with placebo	P = 0.032	○○○	sertraline

Quality of life

Compared with placebo Sertraline seems more effective at improving quality of life at 12 weeks as assessed by the Quality-of-Life Enjoyment and Satisfaction Questionnaire (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[64] RCT	373 people	**Quality of Life Enjoyment and Satisfaction Questionnaire (mean change from baseline) , 12 weeks** 9% with sertraline (dose titrated from 25 mg/day in the first week to 50–150 mg/day by week 12) 2% with placebo Absolute numbers not reported	P <0.0001	○○○	sertraline

No data from the following reference on this outcome. [65] [66]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[66] RCT	328 people	**Mean change in diastolic blood pressure , over 10 weeks** +1.59 mmHg with sertraline –0.63 mmHg with placebo	P = 0.02	○○○	placebo
[66] RCT	328 people	**Mean weight loss , over 10 weeks** –1.94 lbs with sertraline +1.07 lbs with placebo	P = 0.0002	○○○	placebo
[66] RCT	328 people	**Proportion of people with decrease in libido , over 10 weeks** 29/165 (18%) with sertraline 4/163 (2%) with placebo	P <0.01	○○○	placebo
[66] RCT	Men with anxiety disorder	**Sexual dysfunction , over 10 weeks** with sertraline with placebo Among men, 12/67 (18%) with sertraline had sexual dysfunction, most commonly abnormal orgasm (7/67 [10%]) and ejaculation failure (4/67 [6%]). No one in the placebo arm reported abnormal orgasm or ejaculation failure	Significance not assessed		

No data from the following reference on this outcome. [64] [65]

Venlafaxine versus placebo:

We found two systematic reviews (search date 2002, 8 RCTs; [51] and search date 2002, 7 RCTs [30]), one additional RCT, [67] and three subsequent RCTs. [68] [69] [59] See also comment section for further information from observational studies and comments on adverse effects of antidepressants.

Symptom severity

Compared with placebo Venlafaxine may be more effective at increasing response and remission rates (measured as reduction in Hamilton Anxiety Scale [HAM-A] and Clinical Global Impressions Scale [CGI] scores) at 8 to 28 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[70] RCT **4-armed trial**	365 people In review [51] The remaining arms evaluated venlafaxine (150 mg/day) and buspirone (30 mg/day)	**Response rates (response defined as Clinical Global Impressions Scale [CGI] score of 1 or 2) , 8 weeks** 54/87 (62%) with venlafaxine (75 mg/day) 38/98 (39%) with placebo	P = 0.002 venlafaxine 75 mg *v* placebo	○○○	venlafaxine (75 mg/day)
[70] RCT **4-armed trial**	365 people In review [51] The remaining arms evaluated venlafaxine (75 mg/day) and buspirone (30 mg/day)	**Response rates (response defined as CGI score of 1 or 2) , 8 weeks** 44/87 (49%) with venlafaxine (150 mg/day) 38/98 (39%) with placebo	P value not reported for venlafaxine 150 mg *v* placebo		
[51] Systematic review	558 people 2 RCTs in this analysis	**Non-treatment response , 8 to 28 weeks** with venlafaxine with placebo Absolute numbers not reported	RR 0.68 95% CI 0.46 to 0.99 NNT 5 95% CI 4 to 9	●○○	venlafaxine
[30] Systematic review	1626 people 5 RCTs in this analysis	**Symptoms** with venlafaxine with placebo Absolute results not reported	Reported as improved with venlafaxine P value not reported		
[68] RCT	244 people with GAD and depression, recruited from general practice	**Response rates (50% reduction in Hamilton Anxiety Scale [HAM-A]) , 24 weeks** 52% with venlafaxine (sustained release 75–150 mg/day) 48% with placebo Absolute numbers not reported	P = 0.68	⟷	Not significant
[59] RCT **3-armed trial**	392 people The remaining arm assessed escitalopram	**Mean difference in HAM-A , 8 weeks** with venlafaxine extended release with placebo Absolute numbers not reported 265 people in this analysis Analysis by last observation carried forward 75% of people in this comparison completed treatment	Mean difference –2.27 P = 0.01	○○○	venlafaxine
[68] RCT	244 people with GAD and depression, recruited from general practice	**Remission rate (defined as HAM-A score of >7) , 24 weeks** 28% with venlafaxine (sustained release 75–150 mg/day) 19% with placebo	P = 0.11	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported			
[68] RCT	244 people with GAD and depression, recruited from general practice	**CGI score of 1 or 2 (meaning "much" or "very" improved) , 24 weeks** 65% with venlafaxine (sustained release 75–150 mg/day) 46% with placebo Absolute numbers not reported	P = 0.003	○○○	venlafaxine
[67] RCT	46 people	**Remission rates (defined as a score of 7 or less in HAM-A) , 8 weeks** 15/24 (63%) with venlafaxine (75 mg/day) 2/22 (9%) with placebo	P = 0.0006	○○○	venlafaxine
[67] RCT	46 people	**HAM-A (mean change from baseline) , 8 weeks** –19.2 with venlafaxine (75 mg/day) –10.8 with placebo	P <0.001	○○○	venlafaxine
[67] RCT	42 people	**CGI-Severity (mean change from baseline) , 8 weeks** –2.4 with venlafaxine (75 mg/day) –1.2 with placebo	P = 0.002	○○○	venlafaxine
[67] RCT	42 people	**CGI-Improvement (mean change from baseline) , 8 weeks** –1.8 with venlafaxine (75 mg/day) –0.6 with placebo	P = 0.012	○○○	venlafaxine
[67] RCT	42 people	**Covi Anxiety Scale (mean change from baseline) , 8 weeks** –4.8 with venlafaxine (75 mg/day) –3.3 with placebo	P = 0.056	⟷	Not significant
[69] RCT **4-armed trial**	421 people The remaining arms assessed pregabalin (400 mg/day and 600 mg/day)	**Mean change in HAM-A , 6 weeks** –14.1 with venlafaxine (75 mg/day) –11.6 with placebo 214 people in this analysis 79/113 (70%) people in the venlafaxine arm and 81/101 (80%) in the placebo arm completed treatment	P = 0.03	○○○	venlafaxine

Quality of life

Compared with placebo Venlafaxine is more effective at 6 months at decreasing the proportion of people with moderately impaired social function (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[71] RCT	544 people Further report of reference [51]	**Proportion of people with no/minimal social impairment following treatment , 6 months** 78/125 (62%) with venlafaxine (37.5 mg/day) 83/115 (72%) with venlafaxine (75 mg/day) 94/118 (80%) with venlafaxine (150 mg/day) 63/111 (56%) with placebo	Significance not assessed		

No data from the following reference on this outcome. [30] [59] [67] [68] [69]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[51] Systematic review	People with anxiety disorders Number of people and RCTs in this analysis not clear	**Adverse effects** with venlafaxine with placebo Nausea, dry mouth, insomnia, constipation, flatulence, anorexia, somnolence, and sexual dysfunction were more likely to be reported in people taking venlafaxine	Significance not assessed		
[67] RCT	42 people	**Adverse events** 41.7% with venlafaxine 40.9% with placebo Nausea, sweating, constipation, and dry mouth reported	Significance not assessed		
[68] RCT	244 people with GAD and depression, recruited from general practice	**Adverse effects** with venlafaxine (sustained release 75–150 mg/day) with placebo Absolute numbers not reported Nausea, somnolence, dry mouth, sweating, constipation, anorexia, and sexual dysfunction were reported with venlafaxine. Most (apart from dizziness and sexual dysfunction) decreased over 6 months in those who continued taking the medication	Significance not assessed		
[68] RCT	244 people with GAD and depression, recruited from general practice	**Nausea** 31% with venlafaxine 10% with placebo Absolute numbers not reported Nausea, somnolence, dry mouth, sweating, constipation, anorexia, and sexual dysfunction were reported with venlafaxine. Most	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		(apart from dizziness and sexual dysfunction) decreased over 6 months in those who continued taking the medication			
[68] RCT	244 people with GAD and depression, recruited from general practice	**Sweating** 13% with venlafaxine 2% with placebo Absolute numbers not reported Nausea, somnolence, dry mouth, sweating, constipation, anorexia, and sexual dysfunction were reported with venlafaxine. Most (apart from dizziness and sexual dysfunction) decreased over 6 months in those who continued taking the medication	P value not reported		
[59] RCT **3-armed trial**	392 people The remaining arm assessed escitalopram	**Adverse effects , 8 weeks** with venlafaxine extended release with placebo Absolute numbers not reported 265 people in this analysis The RCT reported significant increases in nausea, dry mouth, somnolence, fatigue, and ejaculation disorder compared with placebo	P <0.05	○○○	placebo

No data from the following reference on this outcome. [69]

Antidepressants versus each other:

We found one systematic review (search date 2002, 8 RCTs), [51] and three subsequent RCTs. [72] [73] [57] See also comment section for further information from observational studies and comments on adverse effects of antidepressants.

Symptom severity

Antidepressants compared with each other We don't know whether one antidepressant is more effective than another at improving response rates (measured as reduction in Hamilton Anxiety Scale [HAM-A] and Clinical Global Impressions Scale [CGI] scores) at 8 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[74] RCT	81 people In review [51]	**Proportion of people who failed to respond , 8 weeks** 3/36 (8%) with paroxetine 2/30 (7%) with imipramine	RR of failing to respond 1.73 95% CI 0.31 to 9.57	⟷	Not significant
[73] RCT	55 people	**Rate of response (defined as 50% reduction in Hamilton Anxiety Scale [HAM-A]) , 8 weeks** 17/25 (68%) with paroxetine 17/28 (61%) with sertraline	RR 1.1 95% CI 0.7 to 1.6	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[73] RCT	55 people	**Rate of remission (defined as HAM-A <7) , 8 weeks** 10/25 (40%) with paroxetine 14/28 (50%) with sertraline	RR 0.8 95% CI 0.4 to 1.4	⟷	Not significant
[73] RCT	55 people	**Clinical Global Impressions Scale [CGI] rating "normal" , 8 weeks** 10/25 (40%) with paroxetine 13/28 (46%) with sertraline	RR 0.8 95% CI 0.5 to 1.5	⟷	Not significant
[72] RCT	121 people Method of randomisation not reported	**Response (defined as CGI of 1 or 2) , 24 weeks** with escitalopram with paroxetine Absolute numbers not reported	RR 1.25 95% CI 0.99 to 1.59 Results should be interpreted with caution, as there were differences in withdrawal rates between groups, and discontinuation syndrome	⟷	Not significant
[72] RCT	121 people Method of randomisation not reported	**HAM-A scale , 24 weeks** with escitalopram with paroxetine Absolute numbers not reported	Mean difference: 2.0 95% CI 0.63 to 4.63 Results should be interpreted with caution as there were differences in withdrawal rates between groups, and discontinuation syndrome	○○○	paroxetine
[72] RCT	121 people Method of randomisation not reported	**CGI scale , 24 weeks** with escitalopram with paroxetine Absolute numbers not reported	Mean difference: +0.3 95% CI –0.77 to +1.37 Results should be interpreted with caution as there were differences in withdrawal rates between groups, and discontinuation syndrome	⟷	Not significant
[57] RCT **5-armed trial**	270 people The remaining arms evaluated placebo and escitalopram (5 mg/day and 20 mg/day)	**Mean change in HAM-A scores , 12 weeks** with escitalopram (10 mg/day) with paroxetine (20 mg/day) Absolute numbers not reported Intention-to-treat analysis using last observation carried forward (LOCF)	Mean difference: –2.06 95% CI –3.90 to –0.21	○○○	escitalopram (10 mg/day)
[57] RCT **5-armed trial**	270 people The remaining arms evaluated placebo and escitalopram (5 mg/day and 20 mg/day)	**Response (defined as at least a 50% decrease in HAM-A score) , 12 weeks** 72% with escitalopram (10 mg/day) 60% with paroxetine (20 mg/day) Absolute numbers not reported Intention-to-treat analysis using LOCF	P <0.05	○○○	escitalopram (10 mg/day)
[57] RCT **5-armed trial**	270 people The remaining arms evaluated placebo and escitalopram (5 mg/day and 20 mg/day)	**Remission (defined as HAM-A score <7) , 12 weeks** 48% with escitalopram (10 mg/day) 33% with paroxetine (20 mg/day) Absolute numbers not reported	P <0.05	○○○	escitalopram (10 mg/day)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Intention-to-treat analysis using LOCF			

Quality of life

No data from the following reference on this outcome. [57] [72] [73] [74]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[72] RCT	121 people	**Overall adverse effects** 77% with escitalopram 89% with paroxetine Absolute numbers not reported			
[72] RCT	121 men and women	**Ejaculation disorder** 30% of men with escitalopram 14% of men with paroxetine Absolute numbers not reported	Reported as significant P value not reported	○○○	paroxetine
[72] RCT	121 men and women	**Decreased libido** 26% with escitalopram 5% with paroxetine Absolute numbers not reported Some analyses are 1 sex only	Reported as significant P value not reported	○○○	paroxetine
[72] RCT	121 men and women	**Anorgasmia** 26% with escitalopram 7% with paroxetine Absolute numbers not reported Some analyses are 1 sex only	Reported as significant P value not reported	○○○	paroxetine
[57] RCT **5-armed trial**	681 people The remaining arms evaluated escitalopram (5 mg/day and 20 mg/day) and placebo	**Anorgasmia , over 12 weeks** 6/136 (5%) with escitalopram (10 mg/day) 9/139 (7%) with paroxetine (20 mg/day)			

No data from the following reference on this outcome. [73] [74]

Antidepressants versus benzodiazepines:

We found two reviews (search dates 2002) [51] [30] and one subsequent RCT. [75] The first review [51] included two RCTs, [53] [74] and the second review [30] included one RCT. [62] The first RCT [53] identified by the first review [51] found similar improvements with imipramine, trazodone, diazepam, and placebo, but did not directly compare the

significance of differences between groups. See also comment section for further information from observational studies and comments on adverse effects of antidepressants.

Symptom severity

Antidepressants compared with benzodiazepines Antidepressants and benzodiazepines seem equally effective at 8 weeks at improving anxiety (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[74] RCT **3-armed trial**	81 people In review [51] The remaining arm evaluated paroxetine	**Anxiety (mean Hamilton Anxiety Scale [HAM-A] score) , 8 weeks** 10.8 with imipramine 12.9 with 2'-chlordesmethyldiazepam	P = 0.05	⟷	Not significant
[74] RCT **3-armed trial**	81 people In review [51] The remaining arm evaluated imipramine	**Anxiety (mean HAM-A score) , 8 weeks** 11.1 with paroxetine 12.9 with 2'-chlordesmethyldiazepam	P = 0.05	⟷	Not significant
[62] RCT **3-armed trial**	318 people In review [30] The remaining arm evaluated placebo	**Response (defined as Clinical Global Impressions Scale [CGI] of <2) , 28 days** 63% with opipramol 64% with alprazolam Absolute numbers not reported			
[75] RCT	80 people	**HAM-A improvement , 6 weeks** 13.7 with paroxetine 10.8 with lorazepam	P >0.05	⟷	Not significant
[75] RCT	80 people	**Self-rating Anxiety Scale (SAS)** 16.5 with paroxetine 14.4 with lorazepam	P >0.05	⟷	Not significant
[75] RCT	80 people	**Recovery , 6 weeks** 18/40 (45%) with paroxetine 16/40 (40%) with lorazepam	P >0.05	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [53] [62] [74] [75]

Adverse effects

No data from the following reference on this outcome. [53] [62] [74] [75]

Antidepressants versus buspirone:

We found one systematic review (search date 2002, 8 RCTs), [51] which identified one RCT. [70] See also comment section for further information from observational studies and comments on adverse effects of antidepressants.

Symptom severity

Antidepressants compared with buspirone The antidepressant venlafaxine and buspirone seem equally effective at improving response rates at 8 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[70] RCT **3-armed trial**	365 people In review [51]	**Rates of response (defined as Clinical Global Impressions Scale [CGI] of 1 or 2) , 8 weeks** 54/87 (62%) with venlafaxine (75 mg) 44/89 (49%) with venlafaxine (150 mg) 52/95 (55%) with buspirone	Significance not assessed		

Quality of life

No data from the following reference on this outcome. [70]

Adverse effects

No data from the following reference on this outcome. [70]

Further information on studies

[58] The RCT compared continued escitalopram 20 mg daily over 24 to 76 weeks versus placebo in 375 people. Initially, 491 people had been treated with 12 weeks of open-label escitalopram. The RCT population was 375 (77%) people who had responded to escitalopram and had a HAM-A score of 10 or less. These people were then randomised to continued escitalopram or placebo.

[61] A re-analysis of the same trials found a pooled effect size of 0.3 compared with placebo. [76]

Comment: The more-recent RCTs comparing one antidepressant with another are better powered to detect any difference between antidepressants.

We found one systematic review that used a Bayesian approach to perform a mixed-treatment meta-analysis of 9 medications including 6 antidepressants (duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine). [77] A probabilistic analysis was used to rank the treatments. The order of ranking differed by outcome: for response, the rank order of antidepressants was: fluoxetine, duloxetine, sertraline, paroxetine, venlafaxine, and escitalopram. For remission (final Hamilton Anxiety Scale [HAM-A] score 7 or less), the rank order was: fluoxetine, escitalopram, venlafaxine, paroxetine, sertraline, and duloxetine. The rank order for withdrawing from the trial owing to adverse effects (most withdrawals first) was: sertraline, fluoxetine, paroxetine, venlafaxine, escitalopram, and duloxetine. [77]

Nausea: There have been case reports of nausea in people taking paroxetine. [74]
Adverse effects when discontinuing treatment: Abrupt discontinuation of SSRIs has been associated with adverse effects including dizziness, headache, nausea, vomiting, diarrhoea, movement disorders, insomnia, irritability, visual disturbance, lethargy, anorexia, and lowered mood. One RCT (120 people receiving maintenance SSRIs for depression) found that significantly more people had adverse effects when discontinuing paroxetine or sertraline compared with people discontinuing fluoxetine (60% with paroxetine *v* 66% with sertraline *v* 16% with fluoxetine; P <0.01 for paroxetine or sertraline *v* fluoxetine). [78] In a 12-week trial of escitalopram, paroxetine, and placebo, there was a significant increase in scores with paroxetine on the Discontinuation Emergent Signs and Symptoms (DESS) scale at day 7 compared with placebo (4.2 with paroxetine *v* 0.4 with placebo; P <0.001). [57]
Overdose: In a series of 239 coroner-directed necropsies from 1970 to 1989, tricyclic antidepressants (TCAs) were considered a causal factor in 12% of deaths, and hypnosedatives (primarily benzodiazepines and excluding barbiturates) in 8%. [79]
Accidental poisoning: TCAs are a major cause of accidental poisoning. [80] A study estimated that there was one death for every 44 children admitted to hospital after ingestion of TCAs. [81]
Hyponatraemia: One case series reported 736 incidents of hyponatraemia in people taking SSRIs; 83% of episodes were in hospital inpatients aged >65 years. [82] It is not possible to establish causation from this type of data.
Falls: One retrospective cohort study (2428 elderly residents of nursing homes) found an increased risk of falls in new users of antidepressants (665 people taking TCAs: adjusted RR 2.0, 95% CI 1.8 to 2.2; 612 people taking SSRIs: adjusted RR 1.8, 95% CI 1.6 to 2.0; and 304 people taking trazodone: adjusted RR 1.2, 95% CI 1.0 to 1.4). [83] The increased rate of falls persisted through the first 180 days of treatment and beyond. One case-control study (8239 people aged at least 66 years, treated in hospital for hip fracture) found an increased risk of hip fracture in those taking antidepressants (SSRIs: adjusted OR 2.4, 95% CI 2.0 to 2.7; secondary amine TCAs such as nortriptyline: adjusted OR 2.2, 95% CI 1.8 to 2.8; and tertiary amine TCAs such as amitriptyline: adjusted OR 1.5, 95% CI 1.3 to 1.7). [84] This study could not control for confounding factors; people taking antidepressants may be at increased risk of hip fracture for other reasons.
In pregnancy: We found no reports of harmful effects in pregnancy. One case-control study found no evidence that imipramine or fluoxetine increased the rate of malformations in pregnancy. [85] The FDA issued a public health advisory in response to new research about a potential risk of congenital malformations after maternal use of paroxetine (Seroxat) during the first trimester. However, other epidemiological studies did not support such an increased risk, and data are being actively investigated by the Commission on Human Medicines (CHM) and MHRA. [86]
Sexual dysfunction: A survey (1022 people mostly suffering from depression; 610 women) of people using antidepressants with acceptable sexual function before antidepressant treatment reported the incidence of sexual dysfunction (decreased desire, delayed ejaculation, and anorgasmia) to be 71% with paroxetine, 67% with venlafaxine, and 63% with fluvoxamine. [87]
Suicide:
See option on prescription antidepressant drugs for mild, moderate, or severe depression in review on depression in adults (drug and other physical treatments).

OPTION ANTIPSYCHOTICS IN ADULTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- Antipsychotic drugs may reduce anxiety in people who have not responded to other treatments, but these drugs may have adverse effects including drowsiness and movement disorders.

Benefits and harms

Antipsychotics versus placebo:

We found two systematic reviews (search dates 2005 [88] and 2010 [89]). The first review included three RCTs of older antipsychotics. [88] It did not pool data. Of the included RCTs, two were in people with generalised anxiety disorder (GAD). (See *Clinical Evidence* review on schizophrenia for additional information about adverse effects of antipsychotics.)

Symptom severity

Compared with placebo Antipsychotics (trifluoperazine, chlorprothixene, and quetiapine) may be more effective at improving Hamilton Anxiety Scale (HAM-A) scores, and quetiapine may be more effective at reducing relapse and at increasing response over the longer term; but antipsychotics also cause more adverse effects (such as drowsiness, extrapyramidal reactions, weight gain, and movement disorders) compared with placebo (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[88] Systematic review	413 people Data from 1 RCT	**Hamilton Anxiety Scale (HAM-A) score** with trifluoperazine (2–6 mg/day) with placebo Absolute results not reported	P <0.001	○○○	trifluoperazine
[88] Systematic review	31 people Data from 1 RCT	**"Outcomes" (not further specified)** with flupentixol with placebo Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[88] Systematic review	139 people Data from 1 RCT	**Median reductions in HAM-A scores , 2 weeks** 10.3 with chlorprothixene 7.3 with placebo	Statistical analysis between groups not reported The RCT was short (2 weeks), which may not have allowed differences in outcomes to become apparent		
[89] Systematic review	2262 people 4 RCTs in this analysis	**Proportion of people responding to treatment** 811/1369 (59%) with quetiapine 379/893 (42%) with placebo	RR 2.21 95% CI 1.10 to 4.45 P = 0.026	●●○	quetiapine
[89] Systematic review	433 people Data from 1 RCT	**Proportion of people relapsing after responding to treatment** 22/216 (10%) with quetiapine 85/217 (39%) with placebo	RR 0.18 95% CI 0.10 to 0.30 P <0.00001	●●●	quetiapine
[89] Systematic review	2256 people 4 RCTs in this analysis	**Mean change in HAM-A (short-term trials)** with quetiapine with placebo Absolute numbers not reported	Mean difference –2.58 95% CI –4.00 to –1.16 P <0.0004	○○○	quetiapine
[89] Systematic review	432 people Data from 1 RCT	**Mean change in HAM-A (long-term trials)** with quetiapine with placebo Absolute numbers not reported	Mean difference –2.04 95% CI –3.25 to –0.83 P <0.001	○○○	quetiapine
[89] Systematic review	2256 people 4 RCTs in this analysis	**Proportion of people with a clinically significant change in Clinical Global Impressions Scale [CGI]** 869/1369 (63%) with quetiapine 412/893 (46%) with placebo	OR 2.28 95% CI 1.01 to 5.14 P = 0.046	●●○	quetiapine

Quality of life

No data from the following reference on this outcome. [88] [89]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[90] RCT	413 people In review [88]	**Drowsiness** 43% with trifluoperazine 25% with placebo Absolute numbers not reported	Significance not assessed		
[90] RCT	413 people In review [88] 11 RCTs in this analysis The review did not separately report harms in people with GAD	**Extrapyramidal reactions and movement disorders** 17% with trifluoperazine 8% with placebo Absolute numbers not reported The most common adverse effect with antipsychotics was sedation/somnolence (20% of people). Other adverse effects commonly reported: weight gain, nausea, dizziness, dry mouth, gastrointestinal distress, and increased appetite	Significance not assessed		
[89] Systematic review	450 people Data from 1 RCT	**Proportion of people with at least 1 adverse effect** 145/223 (65%) with quetiapine 114/227 (50%) with placebo	OR 1.84 95% CI 1.26 to 2.69 P <0.002	●○○	placebo
[89] Systematic review	2262 people 4 RCTs in this analysis	**Proportion of people with extrapyramidal adverse effects** 63/1369 (5%) with quetiapine 25/893 (3%) with placebo	OR 1.80 95% CI 1.12 to 2.90 P <0.016	●○○	placebo
[89] Systematic review	2201 people 4 RCTs in this analysis	**Mean change in weight (kg)** with quetiapine with placebo Absolute numbers not reported	Mean difference 0.63 kg 95% CI 0.40 kg to 0.86 kg P <0.00001	○○○	placebo
[89] Systematic review	437 people Data from 1 RCT	**Increase in prolactin (ng/mL)** with quetiapine with placebo Absolute numbers not reported	Mean difference +0.70 ng/mL 95% CI –1.09 ng/mL to +2.49 ng/mL P = 0.44	⟷	Not significant

Further information on studies

Comment:

Clinical guide:
Any benefits of antipsychotic treatment must be weighed against the risks of movement disorders, parkinsonian adverse effects (including depressed mood and poor concentration), and endocrine dysfunction associated with weight gain. We note that the most recent systematic review is (appropriately) only reviewing trials in people where other approaches have failed.

OPTION PREGABALIN IN ADULTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- Pregabalin may reduce symptoms of anxiety in people with GAD, but can have unpleasant adverse effects, and most trials have been short term.

Benefits and harms

Pregabalin versus placebo:

We found one narrative systematic review (search date 2006), [91] which did not perform a meta-analysis. The review identified 4 RCTs, including 2 RCTs already reported in detail here. [92] [93] As the review [91] did not perform a meta-analysis, we continue to report those individual RCTs here. [92] [93] We found two subsequent RCTs. [69] [94]

Symptom severity

Compared with placebo Pregabalin may be more effective at 4 weeks at improving Hamilton Anxiety Scale (HAM-A) and Clinical Global Impressions Scale (CGI) scores (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[91] Systematic review **4-armed trial**	276 people Data from 1 RCT The remaining arms assessed pregabalin (600 mg/day) and lorazepam	**Reduction in Hamilton Anxiety Scale (HAM-A) scores , 4 weeks** with pregabalin (150 mg/day) with placebo Absolute numbers not reported Number of people in this analysis not reported	P value not reported Reported as not significant	⟷	Not significant
[91] Systematic review **4-armed trial**	276 people Data from 1 RCT The remaining arms assessed pregabalin (150 mg/day) and lorazepam	**Reduction in HAM-A scores , 4 weeks** with pregabalin (600 mg/day) with placebo Absolute numbers not reported Number of people in this analysis not reported	P <0.01 No further data reported	○○○	pregabalin (600 mg/day)
[91] Systematic review **4-armed trial**	341 people Data from 1 RCT The remaining arms assessed pregabalin (400 mg/day and 450 mg/day)	**Reduction in HAM-A scores , 4 weeks** with pregabalin (200 mg/day) with placebo Absolute numbers not reported Number of people in this analysis not reported	P = 0.006 No further data reported	○○○	pregabalin (200 mg/day)
[91] Systematic review **4-armed trial**	341 people Data from 1 RCT The remaining arms assessed pregabalin (200 mg/day and 450 mg/day)	**Reduction in HAM-A scores , 4 weeks** with pregabalin (400 mg/day) with placebo Absolute numbers not reported Number of people in this analysis not reported	P = 0.001 No further data reported	○○○	pregabalin (400 mg/day)
[91] Systematic review **4-armed trial**	341 people Data from 1 RCT The remaining arms assessed pregabalin (200 mg/day and 400 mg/day)	**Reduction in HAM-A scores , 4 weeks** with pregabalin (450 mg/day) with placebo Absolute results not reported	P = 0.005 No further data reported	○○○	pregabalin (450 mg/day)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Number of people in this analysis not reported			
[92] RCT **4-armed trial**	271 people In review [91] The remaining arms evaluated lorazepam (2 mg/day) and pregabalin (200 mg/day)	**HAM-A total scores , 4 weeks** with pregabalin (50 mg/day) with placebo Absolute results not reported	Mean difference –1.62 (pregabalin 50 mg *v* placebo) 95% CI –3.90 to +0.67 P >0.16	⟷	Not significant
[92] RCT **4-armed trial**	271 people In review [91] The remaining arms evaluated lorazepam (2 mg/day) and pregabalin (50 mg/day)	**HAM-A total scores , 4 weeks** with pregabalin (200 mg/day) with placebo Absolute results not reported	Mean difference –3.90 (pregabalin 200 mg *v* placebo) 95% CI –6.26 to –1.54 P = 0.0013	○○○	pregabalin (200 mg/day)
[92] RCT **4-armed trial**	271 people In review [91] The remaining arm evaluated lorazepam (2 mg/day)	**Rates of response** 36/62 (59%) with pregabalin (200 mg/day) 36/69 (52%) with pregabalin (50 mg/day) 29/66 (44%) with placebo Rates of response defined as at least 50% improvement in HAM-A score or Clinical Global Impressions Scale (CGI) rating of "very much improved" or "much improved"	P >0.34 (pregabalin 50 mg/day *v* placebo) P >0.09 (pregabalin 200 mg/day *v* placebo)	⟷	Not significant
[93] RCT **5-armed trial**	454 people, randomised in blocks of 10 In review [91] The remaining arms evaluated alprazolam (1.5 mg/day), pregabalin (450 mg/day), and pregabalin (600 mg/day)	**HAM-A scores from baseline , at 4 weeks** with pregabalin (300 mg/day) with placebo Absolute results not reported	Mean difference from placebo in reduction in HAM-A score −3.89 95% CI −6.05 to −1.73 P <0.001	○○○	pregabalin (300 mg/day)
[93] RCT **5-armed trial**	454 people, randomised in blocks of 10 In review [91] The remaining arms evaluated alprazolam (1.5 mg/day), pregabalin (300 mg/day), and pregabalin (600 mg/day)	**HAM-A scores from baseline , at 4 weeks** with pregabalin (450 mg/day) with placebo Absolute results not reported	Mean difference from placebo in reduction in HAM-A score −2.65 95% CI −4.82 to −0.48 P = 0.2	⟷	Not significant
[93] RCT **5-armed trial**	454 people, randomised in blocks of 10 In review [91] The remaining arms evaluated al-	**HAM-A scores from baseline , at 4 weeks** with pregabalin (600 mg/day) with placebo Absolute results not reported	Mean difference from placebo in reduction in HAM-A score −3.43 95% CI −5.62 to −1.25 P = 0.02	○○○	pregabalin (600 mg/day)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	prazolam (1.5 mg/day), pregabalin (300 mg/day), and pregabalin (450 mg/day)				
[69] RCT **4-armed trial**	421 people The remaining arms assessed pregabalin (600 mg/day) and venlafaxine	**Mean change in HAM-A , 6 weeks** –14.7 with pregabalin (400 mg/day) –11.6 with placebo 194 people in this analysis Last observation carried forward (LOCF) analysis	P = 0.008	○○○	pregabalin (400 mg/day)
[69] RCT **4-armed trial**	421 people The remaining arms assessed pregabalin (400 mg/day) and venlafaxine	**Mean change in HAM-A , 6 weeks** –14.1 with pregabalin (600 mg/day) –11.6 with placebo 204 people in this analysis LOCF analysis	P = 0.03	○○○	pregabalin (600 mg/day)
[94] RCT	273 older people (mean age 72 years)	**Mean change from baseline in HAM-A , 8 weeks** –15.4 with pregabalin (150–600 mg/day) –12.7 with placebo	P = 0.096	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [92] [93] [91] [69] [94]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[92] RCT **4-armed trial**	271 people In review [91] The remaining arm evaluated lorazepam (2 mg/day)	**Proportion of people with adverse events** 59 (89%) with pregabalin (200 mg/day) 51 (73%) with pregabalin (50 mg/day) 45 (67%) with placebo Most common adverse events were somnolence, dizziness, headache, and dry mouth			

No data from the following reference on this outcome. [93] [69] [94]

Pregabalin versus benzodiazepines:

We found two RCTs. [92] [93]

Symptom severity

Compared with benzodiazepines We don't know whether pregabalin is more effective than benzodiazepines at 4 weeks at improving Hamilton Anxiety Scale (HAM-A) or Clinical Global Impressions Scale (CGI) scores (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[92] RCT **4-armed trial**	271 people In review [91] The remaining arms evaluated placebo and pregabalin (50 mg/day)	**Hamilton Anxiety Scale (HAM-A) total scores , 4 weeks** with pregabalin (200 mg/day) with lorazepam (2 mg/day) Absolute results not reported Secondary analysis	P >0.1 for lorazepam (2 mg/day) *v* pregabalin (200 mg/day)	⟷	Not significant
[92] RCT **4-armed trial**	271 people In review [91] The remaining arms evaluated placebo and pregabalin (200 mg/day)	**HAM-A total scores , 4 weeks** with pregabalin (50 mg/day) with lorazepam (2 mg/day) Absolute results not reported Secondary analysis	P >0.5 for lorazepam (2 mg/day) *v* pregabalin (50 mg/day)	⟷	Not significant
[93] RCT **5-armed trial**	454 people, randomised in blocks of 10 In review [91] The remaining arms evaluated pregabalin (450 mg/day), pregabalin (600 mg/day), and placebo	**Response rates (at least 50% improvement in HAM-A score or Clinical Global Impressions Scale (CGI) rating of "very much improved" or "much improved") , 4 weeks** 61% with pregabalin (300 mg/day) 43% with alprazolam (1.5 mg/day) Absolute results reported graphically	P <0.05	○○○	pregabalin (300 mg/day)

Quality of life

No data from the following reference on this outcome. [92] [93]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[92] RCT **4-armed trial**	271 people In review [91] The remaining arm evaluated placebo	**Proportion of people with adverse events** 59/66 (89%) with pregabalin (200 mg/day) 51/70 (73%) with pregabalin (50 mg/day)			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		62/68 (91%) with lorazepam (2 mg/day) Most common adverse effects were somnolence, dizziness, headache, and dry mouth. Somnolence was most common with lorazepam, dizziness with pregabalin 200 mg daily, and headache and dry mouth with any dose of pregabalin than with lorazepam			

No data from the following reference on this outcome. [93]

Further information on studies

Comment: None.

QUESTION **What are the effects of treatments for generalised anxiety disorder in children and adolescents?**

OPTION **CBT IN CHILDREN AND ADOLESCENTS**

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- CBT improves symptoms compared with waiting list control or active control. Most RCTs of CBT in children and adolescents have included other anxiety disorders. We found no trials in participants with GAD alone.

Benefits and harms

CBT versus waiting list control or active control:

We found 4 systematic reviews (search dates 2003, [95] 2002, [96] 2004, [97] and 2008 [98]). In the systematic reviews, no included RCT examined the effects of CBT in children or adolescents with generalised anxiety disorder (GAD) alone (see further information on studies and comment, below). None of the reviews performed a meta-analysis. We found two RCTs [99] [100] included in the first three reviews that satisfied *Clinical Evidence* inclusion criteria and two RCTs [101] [102] in the most recent review. We found 8 subsequent RCTs. [103] [104] [105] [106] [107] [108] [109] [110]

Symptom severity

Compared with waiting list control or active control CBT may be more effective at improving remission rates and at reducing symptoms in children and adolescents with generalised and other anxiety disorders (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[97] Systematic review	45 participants aged 8 to 14 years, 21 (47%) with GAD, 11 (24%) with separation anxiety disorder (SAD), 5 (11%) with social anxiety disorder (SOP) Data from 1 RCT	**Proportion of people with anxiety diagnosis** 17/31 (55%) with CBT (individual or group) 14/14 (100%) with waiting list control Intention-to-treat (ITT) analysis	RR 0.55 95% CI 0.40 to 0.75	●○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[97] Systematic review	71 people aged 7 to 14 years, 42 (59%) with GAD, 19 (27%) with SAD, 10 (14%) with SOP Data from 1 RCT	**Proportion of people with anxiety diagnosis** 21/54 (39%) with group-based CBT 15/17 (88%) with waiting list control ITT analysis	RR 0.44 95% CI 0.30 to 0.64	●●○	CBT
[103] RCT **3-armed trial**	61 children aged 7 to 11 years, 20 (33%) with primary diagnosis of GAD, 17 (28%) with GAD in conjunction with other anxiety disorder	**Improvement in clinician severity rating score** with group CBT with group CBT plus parent training with no treatment Absolute numbers not reported Children were from 3 schools; treatments were randomly allocated by school to avoid cross-contamination with >1 intervention being given at the same school	P = 0.03 for both CBT groups combined *v* no treatment group Some additional benefit was noted with the use of parent training	○○○	CBT
[104] RCT **4-armed trial**	100 children aged 6 to 12 years, 40% with GAD as the principal diagnosis, 32% with GAD in conjunction with another anxiety disorder	**Percentage of children no longer meeting criteria for anxiety disorder** 79% with therapist-initiated telephone support plus CBT 33% with therapist-initiated email support plus CBT 31% with client-initiated support plus CBT 1% with waiting list control Absolute numbers not reported CBT involved parent-implemented CBT (bibliotherapy format)	P <0.01 (all active treatments *v* waiting list control) P <0.01 (any individual active treatment *v* waiting list control)	○○○	support plus CBT
[105] RCT **3-armed trial**	267 children aged 6 to 12 years, 103 (39%) with GAD	**Percentage of children free from anxiety disorder after treatment** 49% with group CBT 18% with parent bibliotherapy (including self-help anxiety-management books, workbooks, and worksheets used by the CBT group) 6% with waiting list control Absolute numbers not reported	P <0.05 (bibliotherapy *v* waiting list control) P <0.001 (bibliotherapy *v* group CBT)	○○○	group CBT
[107] RCT **4-armed trial**	488 children aged 7 to 17 years with anxiety disorders; 79% had GAD The remaining arms assessed CBT plus sertraline and sertraline alone	**Response (proportion of children much improved or better) , 12 weeks** 60% with CBT 24% with placebo Absolute numbers not reported 215 children in this analysis	OR 4.8 95% CI 2.6 to 9.0 P <0.001	●●○	CBT
[108] RCT	112 children aged 7 to 16 years with anxiety disorders; 53% had GAD	**Proportion of children who did not meet diagnostic criteria for their principal anxiety diagnosis , after 3 months' treatment** 23/51 (45%) with CBT	P <0.1	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		13/44 (30%) with group support and attention Completer analysis			
[108] RCT	112 children aged 7 to 16 years with anxiety disorders; 53% had GAD	**Proportion of children who did not meet diagnostic criteria for their principal anxiety diagnosis , 6 months post treatment** 35/51 (69%) with CBT 20/44 (45%) with group support and attention Completer analysis	P <0.05	○○○	CBT
[109] RCT	64 children aged 4 to 7 years with anxiety disorders; 38% had GAD	**Response (proportion of children much improved or better) , post treatment** 20/34 (59%) with CBT 9/30 (30%) with waiting list control ITT analysis	P = 0.016	○○○	CBT
[110] RCT	45 children aged 6 to 11 years; 38% had GAD	**Proportion of children who did not meet criteria for an anxiety disorder , 13 weeks** 13/20 (65%) with CBT 0/21 (0%) with waiting list control	P <0.01	○○○	CBT
[101] RCT **3-armed trial**	72 children aged 7 to 14 years with an anxiety disorder; 28% had GAD In review [98] The remaining arm assessed group CBT partially delivered via the internet (CLIN-NET)	**Proportion of children free of anxiety disorder diagnosis , 10 weeks** 11/20 (55%) with clinic-based group CBT 2/23 (7%) with waiting list control Children were stratified into 2 age groups: 7 to 10 years and 11 to 14 years 43 children in this analysis	P = 0.002	○○○	clinic-based group CBT
[101] RCT **3-armed trial**	72 children aged 7 to 14 years with an anxiety disorder; 28% had GAD In review [98] The remaining arm assessed clinic-based group CBT	**Proportion of children free of anxiety disorder diagnosis , 10 weeks** 11/25 (45%) with group CBT partially delivered via the internet (CLIN-NET) 2/23 (7%) with waiting list control Children were stratified into 2 age groups: 7 to 10 years and 11 to 14 years 48 children in this analysis	P = 0.006	○○○	CLIN-NET
[101] RCT **3-armed trial**	72 children aged 7 to 14 years with an anxiety disorder; 28% had GAD In review [98] The remaining arm assessed group CBT partially delivered via the internet (CLIN-NET)	**Mean change in Children's Depression Inventory , 10 weeks** From 48.45 to 42.50 with clinic-based group CBT From 53.48 to 50.00 with waiting list control Children were stratified into 2 age groups: 7 to 10 years and 11 to 14 years 43 children in this analysis	P value not reported Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[101] RCT **3-armed trial**	72 children aged 7 to 14 years with an anxiety disorder; 28% had GAD In review [98] The remaining arm assessed clinic-based group CBT	**Mean change in Children's Depression Inventory (CDI) , 10 weeks** From 55.07 to 46.96 with group CBT partially delivered via the internet (CLIN-NET) From 53.48 to 50.00 with waiting list control Children were stratified into 2 age groups: 7 to 10 years and 11 to 14 years 48 children in this analysis	P = 0.017	○○○	CLIN-NET
[102] RCT	73 children aged 7 to 12 years with anxiety disorders; 23% had primary diagnosis of GAD In review [98]	**Mean change in Children's Global Assessment Scale , 10 weeks** From 50.87 to 61.73 with internet-based CBT From 51.72 to 54.93 with waiting list control	P = 0.065	⟷	Not significant

No data from the following reference on this outcome. [106]

Quality of life

No data from the following reference on this outcome. [97] [101] [102] [103] [104] [105] [106] [107] [108] [109] [110]

Adverse effects

No data from the following reference on this outcome. [97] [101] [102] [103] [104] [105] [106] [107] [108] [109] [110]

Individual versus family or group CBT:

We found no systematic review. We found two RCTs comparing individual versus family CBT [106] [111] and one RCT comparing individual versus group CBT. [112]

Symptom severity

Individual compared with family or group CBT Individual, family, and group CBT may be equally effective at improving symptoms and increasing remission in children and adolescents with generalised and other anxiety disorders (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[106] RCT **3-armed trial**	161 children aged 7 to 14 years with anxiety disorders; 55% had GAD The remaining arm assessed FESA (family-based edu-	**Proportion of children for whom the principal diagnosis is no longer the main reason for treatment , 12 months** 67% with individual CBT (ICBT) 64% with family CBT (FCBT)	P value not reported Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	cation/support/attention)	Absolute numbers not reported 111 children in this analysis; analysis by intention to treat 43/55 (78%) in the ICBT group and 40/56 (71%) in the FCBT group completed treatment			
[111] RCT	119 children aged 7 to 16 years with anxiety disorders; 42% had GAD; 20% had GAD as primary diagnosis	**Proportion of children who no longer had primary diagnosis , post treatment** 78% with CBT 78% with CBT with active parental involvement (CBT/P) Absolute numbers not reported 48/60 (80%) children in the CBT group and 40/59 (68%) in the CBT/P group completed treatment Per-protocol analysis	P value not reported Reported as not significant	⟷	Not significant
[112] RCT	127 children aged 8 to 12 years with anxiety disorders; 29% had GAD	**Mean change in Multidimensional Anxiety Scale for Children (MASC) , 11 weeks** From 50.85 to 36.94 with ICBT From 51.43 to 37.00 with group CBT (GCBT)	P value not reported Reported as not significant	⟷	Not significant
[112] RCT	127 children aged 8 to 12 years with anxiety disorders; 29% had GAD	**Mean change in Children's Depression Inventory (CDI) , 11 weeks** From 10.28 to 5.65 with ICBT From 8.73 to 4.68 with group CBT (GCBT)	P value not reported Reported as not significant	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [106] [111] [112]

Adverse effects

No data from the following reference on this outcome. [106] [111] [112]

CBT versus drug treatments:

See option on antidepressants in children and adolescents, p 61 .

Further information on studies

[95] The systematic review pooled data for all included RCTs (age range 7–16 years) including participants with GAD, SAD, SOP, and overanxious disorder. It found that CBT significantly increased remission rate compared with control (10 RCTs; remission rate: 57% with CBT *v* 35% with control; OR 3.27, 95% CI 1.9 to 5.6).

[97] The third review pooled data on included RCTs (age range 7–17 years) including participants with SAD, SOP, overanxious disorder, GAD, any DSM-IV diagnosis, and avoidant disorder. It found similar results to the first review, in that CBT significantly improved response compared with control (12 RCTs, 765 people; response rate for remission: 56% with CBT *v* 28% with control; RR 0.58, 95% CI 0.50 to 0.67).

Comment: No included RCT examined the effects of CBT in children or adolescents with generalised anxiety disorder (GAD) alone. Two systematic reviews noted that, while reviews in adults were able to examine the role of CBT separately with regard to GAD or other specific anxiety disorders, the majority of trials in children and adolescents had treated anxiety disorders (e.g., social anxiety disorder [SOP], GAD, separation anxiety disorder [SAD]) as a group together.

It is noted that studies assessing the effects of anxiety treatments on younger children (e.g., [109]) are much needed if we are to understand the most effective interventions for this group and early intervention and prevention efforts are to be maximised. However, it is also acknowledged that differential diagnosis of GAD versus other anxiety disorders is difficult in very young participants; therefore, the use of participants with mixed anxiety disorders is warranted.

OPTION APPLIED RELAXATION IN CHILDREN AND ADOLESCENTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- We found no RCT evidence on the effects of applied relaxation in children and adolescents.

Benefits and harms

Applied relaxation in children and adolescents:

We found no systematic review or RCTs on the effects of applied relaxation in children or adolescents with generalised anxiety disorder.

Further information on studies

Comment: None.

OPTION BENZODIAZEPINES IN CHILDREN AND ADOLESCENTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- We found no RCT evidence on the effects of benzodiazepines in children and adolescents.

Benefits and harms

Benzodiazepines in children and adolescents:

We found no systematic review or RCTs on the effects of benzodiazepines in children or adolescents with generalised anxiety disorder (GAD). We found one small RCT (mean age 12 years; 30 participants with DSM-III overanxious disorder [OAD]). [113] The diagnosis of overanxious disorder (OAD, DSM-III) predates the current classification of GAD (DSM-IV). See comment for further information on this study.

Further information on studies

Comment: The RCT published in 1992 found no significant difference in clinical efficacy measured by clinical global ratings between alprazolam and placebo at 4 weeks (reported as not significant, P value not reported). [113] The study may have been underpowered to detect differences between groups. The RCT reported that adverse effects were mild, and were reported equally by the alprazolam and placebo groups (absolute numbers not reported).

OPTION BUSPIRONE IN CHILDREN AND ADOLESCENTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- We found no RCT evidence on the effects of buspirone in children and adolescents.

Benefits and harms

Buspirone in children and adolescents:

We found no systematic review or RCTs on the effects of buspirone in children or adolescents with generalised anxiety disorder.

Further information on studies

Comment: None.

OPTION HYDROXYZINE IN CHILDREN AND ADOLESCENTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- We found no RCT evidence on the effects of hydroxyzine in children and adolescents.

Benefits and harms

Hydroxyzine in children and adolescents:

We found no systematic review or RCTs on the effects of hydroxyzine in children or adolescents with generalised anxiety disorder.

Further information on studies

Comment: None.

OPTION ABECARNIL IN CHILDREN AND ADOLESCENTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- We found no RCT evidence on the effects of abecarnil in children and adolescents.

Benefits and harms

Abecarnil in children and adolescents:

We found no systematic review or RCTs on the effects of abecarnil on children or adolescents with generalised anxiety disorder.

Further information on studies

Comment: None.

OPTION ANTIDEPRESSANTS IN CHILDREN AND ADOLESCENTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- We found limited RCT evidence regarding the efficacy of antidepressants for childhood GAD. SSRIs (fluvoxamine, fluoxetine, sertraline) have shown some promise, but antidepressants are associated with abdominal pain and nausea, and other well documented adverse effects. The general use of antidepressants in children and adolescents has been the subject of adverse events warnings regarding self-harm and other potential serious adverse effects.

Benefits and harms

Antidepressants versus placebo:

We found one systematic review (search date 2008, 9 RCTs). [114] See comment section for additional information on general harms of antidepressants in children and adolescents.

Symptom severity

Compared with placebo Antidepressants (sertraline, fluoxetine, fluvoxamine, paroxetine, venlafaxine) may be more effective at increasing response and reducing anxiety at up to 16 weeks in children and adolescents with generalised and other anxiety disorders (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[114] Systematic review	1448 children with anxiety disorders including GAD 9 RCTs in this analysis	**Response rate , up to 16 weeks** 478/748 (64%) with antidepressants (sertraline, fluoxetine, fluvoxamine, paroxetine, venlafaxine) 237/700 (34%) with placebo	RR 2.01 95% CI 1.59 to 2.55 P <0.00001	●●○	antidepressants
[114] Systematic review	428 children with anxiety disorders including GAD 4 RCTs in this analysis	**Change in anxiety scores , up to 16 weeks** with antidepressants (sertraline, fluoxetine, fluvoxamine, paroxetine, venlafaxine) with placebo Absolute numbers not reported	SMD –0.82 95% CI –1.30 to –0.33 P <0.0001	●●○	antidepressants

Quality of life

Antidepressants compared with placebo Sertraline and fluoxetine may be more effective at improving quality-of-life measures at up to 16 weeks in children and adolescents with generalised and other anxiety disorders (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[114] Systematic review	390 children with anxiety disorders including GAD 4 RCTs in this analysis	**Response rate , up to 16 weeks** with antidepressants (sertraline, fluoxetine) with placebo Absolute numbers not reported	SMD 0.55 95% CI 0.34 to 0.76 P <0.00001	●●○	antidepressants

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[114] Systematic review	95 children with anxiety disorders including GAD 2 RCTs in this analysis	**Adverse effects** with antidepressants (sertraline, fluoxetine) with placebo Absolute numbers not reported The review reported that, in 2 RCTs that reported on adverse effects in children with anxiety disorders including GAD, fluoxetine was associated with abdominal pain and sertraline with anorexia	Significance not assessed		

Fluoxetine versus placebo:

We found one systematic review (search date 2008), [114] which identified one RCT. [115]

Symptom severity

Compared with placebo Fluoxetine may be more effective at improving symptoms of anxiety (as measured by Hamilton Anxiety Scale [HAM-A] and Clinical Global Impressions Scale [CGI] scores) in children and adolescents with generalised and other anxiety disorders (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[115] RCT	74 children and adolescents aged 7 to 17 years with GAD, separation anxiety disorder, and/or social phobia (47/74 [64%] had GAD either with or without another disorder) In review [114]	**Proportion of people who were much or very much improved (defined as Clinical Global Impression-Improvement [CGI-I] score 2 or less)** 22/36 (61%) with fluoxetine 13/37 (35%) with placebo	P = 0.03	○○○	fluoxetine
[115] RCT	46 children and adolescents aged 7 to 17 years with GAD, either with or without another disorder	**Proportion of people with CGI-I score 2 or less** 61% with fluoxetine (20 mg/day) 36% with placebo Absolute results not reported	P = 0.04	○○○	fluoxetine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [114]				

Quality of life

No data from the following reference on this outcome. [115]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[115] RCT	74 children and adolescents aged 7 to 17 years with GAD, separation anxiety disorder, and/or social phobia (47/74 [64%] had GAD either with or without another disorder) In review [114]	**Gastrointestinal adverse effects (abdominal pain and nausea) , 2 weeks** 16/35 (46%) with fluoxetine 7/37 (19%) with placebo	P = 0.04	○○○	placebo
[115] RCT	74 children and adolescents aged 7 to 17 years with GAD, separation anxiety disorder, and/or social phobia (47/74 [64%] had GAD either with or without another disorder) In review [114]	**Withdrawal from trial** with fluoxetine with placebo 5 children receiving fluoxetine were removed from the trial because of (not significant) incidences of excitement, giddiness, or disinhibition			
[115] RCT	74 children and adolescents aged 7 to 17 years with GAD, separation anxiety disorder, and/or social phobia (47/74 [64%] had GAD either with or without another disorder) In review [114]	**Neurological complaints (drowsiness and headaches) , 2 weeks** 16/36 (44%) with fluoxetine 5/36 (14%) with placebo	P = 0.004	○○○	placebo

Fluvoxamine versus placebo:
We found one RCT. [116]

Symptom severity

Compared with placebo Fluvoxamine may be more effective at improving symptoms of anxiety (as measured by Hamilton Anxiety Scale [HAM-A] and Clinical Global Impressions Scale [CGI] scores) in children and adolescents with generalised and other anxiety disorders (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[116] RCT	128 people aged 6 to 17 years, who previously received 3 weeks of psychological treatment without benefit (73/128 [57%] had GAD with or without another disorder)	**Mean decrease in Pediatric Anxiety Rating Scale** 9.7 with fluvoxamine (300 mg/day, maximum) 3.1 with placebo	P <0.001	○○○	fluvoxamine
[116] RCT	128 people aged 6 to 17 years, who previously received 3 weeks of psychological treatment without benefit (73/128 [57%] had GAD with or without another disorder)	**Clinical Global Impression-Improvement [CGI-I] scale, response defined as score <4** 48/63 (76%) with fluvoxamine (300 mg/day, maximum) 19/65 (29%) with placebo	P <0.001	○○○	fluvoxamine

Quality of life

No data from the following reference on this outcome. [116]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[116] RCT	128 people aged 6 to 17 years, who previously received 3 weeks of psychological treatment without benefit (73/128 [57%] had GAD with or without another disorder)	**Abdominal discomfort** 49% with fluvoxamine 28% with placebo Absolute numbers not reported	P = 0.02	○○○	placebo
[116] RCT	128 people aged 6 to 17 years, who previously received 3 weeks of psychological treatment without benefit (73/128 [57%] had GAD with or without another disorder)	**Increased motor activity** 27% with fluvoxamine 8% with placebo Absolute numbers not reported	P = 0.06	⟷	Not significant

Sertraline versus placebo:

We found two systematic reviews (search dates 2002 [51] and 2008 [114]). Both reviews identified the same small RCT. [117] The second review [114] identified one further RCT. [107]

Symptom severity

Compared with placebo Sertraline seems more effective at improving symptoms of anxiety (as measured by Hamilton Anxiety Scale [HAM-A] and Clinical Global Impressions Scale [CGI] scores) and response in children and adolescents with generalised and other anxiety disorders (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[117] RCT	22 children and adolescents aged 5 to 17 years with childhood GAD In review [51] [114]	**Mean Hamilton Anxiety Scale (HAM-A) total score , week 9** 7.8 with sertraline (50 mg/day maximum) 2.1 with placebo	P <0.001	○○○	sertraline
[117] RCT	22 children and adolescents aged 5 to 17 years with childhood GAD In review [51] [114]	**Mean Clinical Global Impressions Scale [CGI] total score , week 9** 2.4 with sertraline (50 mg/day maximum) 3.9 with placebo	P <0.001	○○○	sertraline
[107] RCT **4-armed trial**	488 children aged 7 to 17 years with GAD or other anxiety disorders In review [114] The remaining arms assessed CBT plus sertraline and CBT alone	**Response (proportion of children very much improved or better) , 12 weeks** 55% with sertraline 24% with placebo Absolute numbers not reported 209 children in this analysis (133 in sertraline arm and 76 in placebo arm)	OR 3.9 95% CI 2.1 to 7.4 P <0.001	●●○	sertraline

Quality of life

No data from the following reference on this outcome. [117] [114]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[117] RCT	22 children and adolescents aged 5 to 17 years with childhood GAD In review [114]	**Adverse effects** with sertraline (50 mg/day maximum) with placebo Non-significant trend for children receiving sertraline to report less dizziness, nausea, and stomach pain compared with placebo. Participants receiving sertraline reported numerically (but not significantly) more incidences of dry mouth, drowsiness, leg spasms, and restlessness		⟷	Not significant
[107] RCT	488 children aged 7 to 17 years with GAD or other anxiety disorders	**Adverse effects** with sertraline	P = 0.01 for insomnia P = 0.003 for fatigue	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial	In review [114] The remaining arms assessed CBT plus sertraline and CBT alone	with placebo Absolute numbers not reported 209 children in this analysis (133 in sertraline arm and 76 in placebo arm) The RCT reported significantly more insomnia, fatigue, sedation, and restlessness with sertraline compared with placebo	P = 0.01 for sedation P = 0.03 for restlessness		

Antidepressants versus CBT:

We found one RCT. [107]

Symptom severity

Sertraline compared with CBT Sertraline and CBT seem equally effective at increasing response at 12 weeks in children and adolescents with generalised and other anxiety disorders (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[107] RCT **4-armed trial**	488 children aged 7 to 17 years with generalised or other anxiety disorders The remaining arms assessed CBT plus sertraline and placebo	**Response (proportion of children very much improved or better) , 12 weeks** 55% with sertraline 60% with CBT Absolute numbers not reported 272 children in this analysis	P = 0.41	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [107]

Adverse effects

No data from the following reference on this outcome. [107]

Further information on studies

Comment: Two additional RCTs [118] [119] add support to the results of the RCT comparing fluvoxamine versus placebo, [116] with the findings that fluvoxamine reduced somatic symptoms (e.g., muscle tension and stomach aches), and sleep-related problems in children with anxiety disorders. Despite the positive findings with SSRIs to date, it is important to note that most studies investigating pharma-

cological effects on childhood anxiety have included participants with comorbid disorders such as depression. This may restrict the generalisability of the results.

General harms: See review on depression in adults (drug and other physical treatments). One review of suicidality and antidepressant use in paediatric patients (most of whom were diagnosed with major depression) found a modest increase in suicide risk associated with antidepressants. [120] However, one meta-analysis of RCTs of second-generation antidepressants in the treatment of paediatric depressive and anxiety disorders found no completed suicides reported in the RCTs reviewed. [121] There have been warnings about the risks associated with using antidepressants in children. See review on depression in children and adolescents.

OPTION ANTIPSYCHOTICS IN CHILDREN AND ADOLESCENTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- We found no RCT evidence on the effects of antipsychotics in children and adolescents.

Benefits and harms

Antipsychotics in children and adolescents:

We found no systematic review or RCTs on the effects of antipsychotics in children or adolescents with generalised anxiety disorder.

Further information on studies

Comment: None.

OPTION PREGABALIN IN CHILDREN AND ADOLESCENTS

- For GRADE evaluation of interventions for Generalised anxiety disorder, see table, p 71 .
- We found no RCT evidence on the effects of pregabalin in children and adolescents.

Benefits and harms

Pregabalin in children and adolescents:

We found no systematic review or RCTs on the effects of pregabalin in children or adolescents with generalised anxiety disorder.

Further information on studies

Comment: None.

GLOSSARY

Applied relaxation A technique involving training in relaxation techniques and self-monitoring of symptoms without challenging beliefs.

Clinical Global Impressions Scale (CGI or CGIS) A clinician-rated scale, usually from 0 to 4, with descriptions of severity at each point: 0 = no symptoms; 1 = very mild, subclinical symptoms; 2 = mild but clinical symptoms; 3 = moderate severity; and 4 = severe symptoms.

Hamilton Anxiety Scale (HAM-A) The HAM-A is a validated instrument consisting of 14 items scored on a 5-point scale, ranging from 0 (not present) to 4 (severe), to give a total score of between 0 and 56.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antidepressants in children and adolescents New evidence added. [107] [114] Categorisation unchanged (Trade-off between benefits and harms).

Antipsychotics in adults New evidence added. [89] Categorisation unchanged (Trade-off between benefits and harms).

Applied relaxation in adults New evidence added. [25] Categorisation unchanged (Likely to be beneficial).

Benzodiazepines in adults New evidence added. [34] Categorisation unchanged (Trade-off between benefits and harms).

CBT in adults New evidence added. [22] [23] [24] [25] [26] Categorisation unchanged (Beneficial).

CBT in children and adolescents New evidence added. [98] [101] [102] [106] [107] [108] [109] [110] [111] [112] Categorisation unchanged (Beneficial).

Hydroxyzine in adults New evidence added. [45] Categorisation unchanged (Likely to be beneficial).

Pregabalin in adults New evidence added. [69] [91] [94]

Antidepressants in adults New evidence added. [52] [54] [55] [59] [60] [69] Categorisation changed from Likely to be beneficial to Beneficial.

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Competing interests: CKG has received reimbursement for attending conferences from Lilly and Janssen-Cilag, and has been reimbursed for speaking by Lilly, Janssen-Cilag, and AstraZeneca. JM declares that she has no competing interests.

We would like to acknowledge the previous contributor to this review: Mark Oakley-Browne.

Disclaimer

GRADE **Evaluation of interventions for Generalised anxiety disorder.**

Important outcomes			Quality of life, Symptom severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for generalised anxiety disorder in adults?									
at least 23 (at least 871) [20] [21] [22] [23] [24] [25]	Symptom severity	CBT versus waiting list control or non-specific therapies	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for poor-quality RCTs in systematic reviews (poor follow-up, mixed populations, no intention-to-treat analyses in some RCTs)
2 (167) [20] [26]	Symptom severity	CBT versus psychodynamic therapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
7 (332) [20]	Symptom severity	CBT versus supportive therapy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (at least 341) [20] [27] [25]	Symptom severity	Cognitive therapy versus behavioural therapy (including applied relaxation)	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (61) [28]	Symptom severity	CBT versus non-specific therapy in benzodiazepine discontinuation	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (42) [25]	Symptom severity	Applied relaxation versus placebo or no treatment	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for population with comorbid conditions
54 (at least 2044) [18] [30]	Symptom severity	Benzodiazepines versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (185) [32] [33]	Symptom severity	Benzodiazepines versus each other	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (61) [34]	Symptom severity	Benzodiazepines versus CBT	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and no significance assessments
24 (at least 273) [18] [30] [42]	Symptom severity	Buspirone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
4 (338) [18] [43] [42]	Symptom severity	Buspirone versus benzodiazepines	4	–2	–1	0	0	Very low	Quality points deducted for incomplete reporting of results and methodological flaws (uncertainty about diagnosis). Consistency point deducted for conflicting results
at least 4 (at least 417) [45]	Symptom severity	Hydroxyzine versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (327) [45]	Symptom severity	Hydroxyzine versus benzodiazepines	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and no intention-to-treat analysis in the larger RCT
1 (163) [45]	Symptom severity	Hydroxyzine versus buspirone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes			Quality of life, Symptom severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (439) [31] [50]	Symptom severity	Abecarnil versus placebo	4	–2	0	0	0	Low	Quality points deducted for no intention-to-treat analysis and incomplete reporting of results
1 (310) [31]	Symptom severity	Abecarnil versus benzodiazepines	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (2418) [51] [53] [52]	Symptom severity	Any antidepressant versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for no intention-to-treat analysis in some trials
4 (at least 419) [54] [55]	Symptom severity	Duloxetine versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
8 (2667) [56] [57] [58] [59] [60] [61]	Symptom severity	Escitalopram versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (207) [62]	Symptom severity	Opipramol versus placebo	4	0	0	0	0	High	
3 (1163) [51] [63] [57]	Symptom severity	Paroxetine versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (1084) [64] [65] [66]	Symptom severity	Sertraline versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for not describing method of randomisation in 1 RCT
1 (373) [64]	Quality of life	Sertraline versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
11 (at least 2949) [51] [30] [67] [68] [69] [59]	Symptom severity	Venlafaxine versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (544) [71]	Quality of life	Venlafaxine versus placebo	4	–1	+1	0	0	High	Quality point deducted for lack of significance assessment. Consistency point added for dose response
5 (583) [74] [73] [72] [57]	Symptom severity	Antidepressants versus each other	4	–1	–1	0	0	Low	Quality point deducted for methodological weaknesses (not reporting method of randomisation, and short follow-up). Consistency point deducted for conflicting results
3 (479) [53] [74] [62] [75]	Symptom severity	Antidepressants versus benzodiazepines	4	0	0	–1	0	Moderate	Directness point deducted for no direct comparison between groups in 1 RCT
1 (365) [70]	Symptom severity	Antidepressants versus buspirone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 6 (at least 2845) [88] [89]	Symptom severity	Antipsychotics versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
5 (at least 1260) [92] [93] [91] [69] [94]	Symptom severity	Pregabalin versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results with different doses

Important outcomes			Quality of life, Symptom severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (725) [92] [93]	Symptom severity	Pregabalin versus benzodiazepines	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
What are the effects of treatments for generalised anxiety disorder in children and adolescents?									
11 (1125) [97] [101] [102] [103] [104] [105] [107] [108] [109] [110]	Symptom severity	CBT versus waiting list control or active control	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of children with other disorders
3 (357) [106] [111] [112]	Symptom severity	Individual versus family or group CBT	4	–1	0	–1	0	Low	Quality point deducted for low follow-up. Directness point deducted for inclusion of children with other disorders
9 (1448) [114]	Symptom severity	Antidepressants versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of children with other disorders
4 (390) [114]	Quality of life	Antidepressants versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of children with other disorders
1 (74) [115]	Symptom severity	Fluoxetine versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of children with other disorders
1 (128) [116]	Symptom severity	Fluvoxamine versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of children with other disorders
2 (231) [117] [107]	Symptom severity	Sertraline versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of children with other disorders
1 (272) [107]	Symptom severity	Antidepressants versus CBT	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of children with other disorders

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.