Generalised anxiety disorder in children and adolescents

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Christopher K. Gale and Jane Millichamp

ABSTRACT

INTRODUCTION: Generalised anxiety disorder (GAD) in a child or adolescent is excessive worry and tension about everyday events that the child or adolescent cannot control and that is expressed on most days for at least 6 months, to the extent that there is distress or difficulty in performing day-to-day tasks. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of pharmacological treatments for generalised anxiety disorder in children and adolescents? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2014 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). RESULTS: At this update, searching of electronic databases retrieved 949 studies. After deduplication and removal of conference abstracts, 417 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 310 studies and the further review of 107 full publications. Of the 107 full articles evaluated, one systematic review was added at this update. We performed a GRADE evaluation for six PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for six interventions based on information about the effectiveness and safety of antidepressants, antipsychotics, benzodiazepines, buspirone, hydroxyzine, and pregabalin.

QUESTIONS

INTERVENTIONS

Key points

- Generalised anxiety disorder (GAD) is excessive worry and tension about everyday events that the child or adolescent cannot control and that is expressed on most days for at least 6 months, to the extent that there is distress or difficulty in performing day-to-day tasks.

  The most common anxieties in children relate to the health of others.

  GAD in children is highly comorbid, with only 14% of one survey not having a comorbid anxiety disorder.

  Among adolescents the lifetime prevalence is 3%: if one relaxes the duration criteria to the last 3 months, the lifetime prevalence increases to 5%.
- Cognitive behavioural therapy (CBT) is the best and most evidenced treatment for anxiety disorders. Please see our previous overview (see Generalised anxiety disorder) for further information on the evidence for CBT.
- For this update, we have decided to focus on examining the evidence from RCTs and systematic reviews of RCTs for medications that have been suggested for use in GAD, either in children or in adolescents.
- Most of the options that have been proposed have data suggesting that they may work in adults, but no such data are available for children.
- We found limited RCT evidence regarding the efficacy of antidepressants for childhood GAD. SSRIs (e.g., fluvoxamine, fluoxetine, sertraline) have shown some promise, but antidepressants are associated with abdominal pain and nausea, an increase in initial suicidal ideation, and other adverse effects.
- We found no RCT evidence on the effects of benzodiazepines, buspirone, hydroxyzine, pregabalin, or antipsychotics in children and adolescents.

Clinical context

GENERAL BACKGROUND

Generalized anxiety disorder (GAD) is overwhelming, chronic worry about many aspects of life. It affects about 1% of children and 3% of adolescents. In children, it often involves fears about the family and about performing well at school. Children with GAD often have difficulties coping in the home environment, with daily tasks and self-care.

FOCUS OF THE REVIEW

Cognitive behavioural therapy (CBT) is the best and most evidenced treatment for anxiety disorders. However, for this update, we have decided to focus instead on examining the evidence for medications that have been suggested for use in GAD, either in children or in adolescents. Please see our previous overview (see Generalised anxiety disorders), which included information on the evidence for CBT as well as evidence on interventions to treat GAD in adults.

COMMENTS ON EVIDENCE

There is some evidence that newer antidepressants such as serotonin re-uptake inhibitors (SSRIs) may help children and adolescents with GAD, but these have side effects. Most of the options that have been proposed have data suggesting that they may work in adults, but no such data are available for children.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, May 2011, to August 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 949 studies. After deduplication and removal of conference abstracts, 417 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 310 studies and the further review of 107 full publications. Of the 107 full articles evaluated, one systematic review was added at this update.

DEFINITION	Generalised anxiety disorder (GAD) is defined as excessive worry and tension about everyday events and problems that is not controllable and is expressed 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] In children, this worry frequently involves the health of others, but children with GAD are more likely to worry about performance at school and family matters than children with other anxiety disorders. [2] Only 14% of one survey did not have a comorbid anxiety disorder. [2] Children with GAD, either pure or comorbid, have little difference in adaptive functioning in school compared with healthy children without GAD, but show difficulties in adaptive functioning at home duties or self-care and in family relationships. [3]
INCIDENCE/ PREVALENCE	A survey of children and adolescents aged 5 to 16 years in the UK in 2004 estimated that 0.7% had GAD (boys: 0.6%; girls: 0.8%). [4] The US National Replication survey included participants aged 13 to 18, who had a lifetime prevalence of GAD of 3%. [5]
AETIOLOGY/ RISK FACTORS	Little is known about the aetiology of GAD alone in children and adolescents. The fluidity of the diagnosis and the high rate of comorbidity has led some researchers to question if this is a valid entity in this group, or a temperamental state. This has been challenged by the demonstration of significant decreased function both in pure GAD and in comorbid GAD. [3]
PROGNOSIS	There is a hypothesis that child and adolescent GAD either persists or is a risk factor for later anxiety disorders. The data for each condition, however, are lacking. It seems that having disorders or dysfunction in childhood predicts disorder in adolescents, and adolescent disorder increases risk for disorders in adults. The loading does not seem to be to any one disorder, but to either externalising or internalising factors, using a three- or two-item model [6] that seems to be robust into at least middle adulthood. [7] One has to approach this with caution: childhood GAD is much more comorbid, and may indeed be different from adult GAD.
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). 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 pre-treatment score; patient-rated improvement; failure to show a response. **Quality of life**; **adverse effects**.
METHODS	**Search strategy** *BMJ Clinical Evidence* search and appraisal date August 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to August 2014, Embase 1980 to August 2014, The Cochrane Database of Systematic Reviews 2014, issue 8 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this system-

atic overview were systematic reviews and RCTs published in English, at least double-blinded, and containing 20 or more individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the review. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported question: What are the effects of treatments for generalised anxiety disorder in adults? We have amended the question on children and adolescents to focus on pharmacological therapies. **Data and quality** To aid readability of the numerical data in our overviews, 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). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15). 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 pharmacological treatments for generalised anxiety disorder in children and adolescents?**

OPTION **ANTIDEPRESSANTS**

- For GRADE evaluation of interventions for Generalised anxiety disorder in children and adolescents, see table, p 15 .
- We found limited RCT evidence regarding the efficacy of antidepressants for childhood generalised anxiety disorder (GAD). Serotonin re-uptake inhibitors (SSRIs; e.g., 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.
- We only found one RCT comparing antidepressants with CBT in children and adolescents with GAD. This found that sertraline and CBT seemed to be equally effective at increasing response at 12 weeks in children and adolescents with generalised and other anxiety disorders.

Benefits and harms

Antidepressants versus placebo:

We found one systematic review (search date 2008, 9 RCTs), [8] which evaluated RCTs in children with any anxiety disorder, not exclusively GAD. We have reported the meta-analyses from the review, [8] but have supplemented reporting with results from the individual RCTs. [9] [10] [11] [12] See Comment section for additional information on general harms of antidepressants in children and adolescents.

Symptom severity

Antidepressants compared with placebo Antidepressants (sertraline, fluoxetine, fluvoxamine, paroxetine, venlafaxine) may be more effective than placebo 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					
[8] Systematic review	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 Significant heterogeneity: I^2 = 66%; P = 0.003 Heterogeneity not further discussed	●●○	antidepressants
[8] Systematic review	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 428 children in this analysis	SMD –0.82 95% CI –1.30 to –0.33 P <0.0001 Significant heterogeneity: I^2 = 78%; P = 0.003 Heterogeneity not further discussed	○○○	antidepressants

Quality of life

Antidepressants compared with placebo Sertraline and fluoxetine may be more effective than placebo 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					
[8] Systematic review	Children with anxiety disorders including GAD 4 RCTs in this analysis	**Quality of life as assessed by the Children's Global Assessment Scale , up to 16 weeks** with antidepressants (sertraline, fluoxetine) with placebo Absolute numbers not reported 390 children in this analysis	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					
[8] Systematic review	Children with anxiety disorders including GAD 2 RCTs in this analysis	**Adverse effects** with antidepressants (sertraline, fluoxetine) with placebo Absolute numbers not reported 95 children included in this analysis 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), [8] which identified one RCT. [10]

Symptom severity

Fluoxetine compared with placebo Fluoxetine may be more effective than placebo 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					
[10] RCT	74 children and adolescents aged 7–17 years with GAD, separation anxiety disorder, and/or social phobia (47/74 [64%] had GAD either with or without another disorder) In review [8]	**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
[10] RCT	46 children and adolescents aged 7–17 years with GAD, either with or without another disorder In review [8] Subgroup analysis	**Proportion of people with CGI-I score 2 or less** 67% with fluoxetine 36% with placebo Absolute results not reported	P = 0.04	○○○	fluoxetine

Quality of life

No data from the following reference on this outcome. [10]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[10] RCT	74 children and adolescents aged 7–17 years with GAD, separation anxiety disorder, and/or social phobia (47/74 [64%] had GAD either with or without another disorder) In review [8]	**Gastrointestinal adverse effects (abdominal pain and nausea) , 2 weeks** 16/35 (46%) with fluoxetine 7/32 (22%) with placebo	P = 0.04	○○○	placebo
[10] RCT	74 children and adolescents aged 7–17 years with GAD, separation anxiety disorder, and/or social phobia (47/74 [64%] had GAD either with or without another disorder) In review [8]	**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			
[10] RCT	74 children and adolescents aged 7–17 years with GAD, separation anxiety disorder, and/or social phobia (47/74 [64%] had GAD either with or without another disorder) In review [8]	**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 systematic review (search date 2008), [8] which identified one RCT. [11]

Symptom severity

Fluvoxamine compared with placebo Fluvoxamine may be more effective than placebo at improving symptoms of anxiety (as measured by HAM-A and 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					
[11] RCT	128 people aged 6–17 years, who previously received 3 weeks of psychological treatment without benefit (73/128 [57%] had GAD with or without another disorder) In review [8]	**Mean decrease in Pediatric Anxiety Rating Scale** 9.7 with fluvoxamine 3.1 with placebo	P <0.001	○○○	fluvoxamine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[11] RCT	128 people aged 6–17 years, who previously received 3 weeks of psychological treatment without benefit (73/128 [57%] had GAD with or without another disorder) In review [8]	**CGI-I Scale, response defined as score <4** 48/63 (76%) with fluvoxamine 19/65 (29%) with placebo	P <0.001	○○○	fluvoxamine

Quality of life

No data from the following reference on this outcome. [11]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] RCT	128 people aged 6–17 years, who previously received 3 weeks of psychological treatment without benefit (73/128 [57%] had GAD with or without another disorder) In review [8]	**Abdominal discomfort** 31/63 (49%) with fluvoxamine 18/65 (28%) with placebo	P = 0.02	○○○	placebo
[11] RCT	128 people aged 6–17 years, who previously received 3 weeks of psychological treatment without benefit (73/128 [57%] had GAD with or without another disorder) In review [8]	**Increased motor activity** 17/63 (27%) with fluvoxamine 8/65 (12%) with placebo	P = 0.06	⟷	Not significant

Sertraline versus placebo:

We found two systematic reviews (search dates 2002; [13] and 2008 [8]). Both reviews identified the same small RCT. [12] The second review [8] identified one further RCT. [9]

Symptom severity

Sertraline compared with placebo Sertraline seems more effective than placebo at improving symptoms of anxiety (as measured by HAM-A and 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					
[12] RCT	22 children and adolescents aged 5–17 years with childhood GAD In review [8] [13]	**Mean Hamilton Anxiety Scale (HAM-A) total score , week 9** 7.8 with sertraline 21.0 with placebo	P <0.001	○○○	sertraline
[12] RCT	22 children and adolescents aged 5–17 years with childhood GAD In review [8] [13]	**Mean CGI total score , week 9** 2.4 with sertraline 3.9 with placebo	P <0.001	○○○	sertraline
[9] RCT **4-armed trial**	488 children aged 7–17 years with GAD or other anxiety disorders In review [8]	**Proportion of children rated as very much improved or better on the CGI-I Scale , 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) The remaining arms assessed CBT plus sertraline and CBT alone	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. [8] [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] RCT	22 children and adolescents aged 5–17 years with childhood GAD In review [8]	**Adverse effects** with sertraline 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
[9] RCT **4-armed trial**	488 children aged 7–17 years with GAD or other anxiety disorders In review [8]	**Adverse effects** with sertraline with placebo Absolute numbers not reported	P = 0.23 for insomnia P = 0.75 for fatigue P = 0.43 for sedation P = 1.00 for restlessness P = 0.36 for suicidal ideation	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		209 children in this analysis (133 in sertraline arm and 76 in placebo arm) The RCT reported no significant difference for insomnia, fatigue, sedation, suicidal ideation/attempt, and restlessness with sertraline compared with placebo The remaining arms assessed CBT plus sertraline and CBT alone	P value not reported for suicidal attempt		

Antidepressants versus CBT:

We found one systematic review (search date 2012), [14] which identified one RCT. [9] We found a further report of this RCT analysing data at 24 and 36 weeks follow-up. [15] It did not meet *BMJ Clinical Evidence* inclusion criteria because this follow-up period was a maintenance phase of the trial, and only those considered as 'treatment responders' after the initial 12-week acute phase were considered as participants (see Further information on studies).

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					
[9] RCT **4-armed trial**	488 children aged 7–17 years with generalised or other anxiety disorders In review [14]	**Proportion of children rated as very much improved or better on the CGI-I Scale , 12 weeks** 55% with sertraline 60% with CBT Absolute numbers not reported 272 children in this analysis The remaining arms assessed CBT plus sertraline and placebo	P = 0.41	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [9]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[9] RCT **4-armed trial**	488 children aged 7–17 years with GAD or other anxiety disorders In review [14]	**Adverse effects** with sertraline with CBT Absolute results not reported	P = 0.01 for insomnia P = 0.003 for fatigue P = 0.01 for sedation P = 0.03 for restlessness	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		272 children in this analysis (133 in sertraline arm and 139 in CBT arm) The RCT reported significantly more insomnia, fatigue, sedation, and restlessness with sertraline compared with CBT The remaining arms assessed CBT plus sertraline and placebo			
[9] RCT **4-armed trial**	488 children aged 7–17 years with GAD or other anxiety disorders In review [14]	**Adverse effects** with sertraline with CBT Absolute results not reported 272 children in this analysis (133 in sertraline arm and 139 in CBT arm) The RCT reported no significant difference between the two groups for suicidal ideation The remaining arms assessed CBT plus sertraline and placebo	P = 0.06 for suicidal ideation	⟷	Not significant

Antidepressants versus other talking therapies:

We found no systematic review or RCTs.

Further information on studies

[14] Since running our literature search, the systematic review reported here has been edited and the findings reviewed. An update search was not carried out. No changes were made to the conclusions of the review. The amended version of the review will be evaluated at the next update.

[15] Similar to the 12-week results in the initial RCT, [9] the authors of this further study, in the subgroup of treatment responders, found sertraline to be indistinguishable from CBT at 24 and 36 weeks follow-up for all outcomes studied.

Comment:

Two additional RCTs [16] [17] add support to the results of the RCT comparing fluvoxamine with placebo [11] 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 pharmacological effects on childhood anxiety have included participants with comorbid disorders such as depression. This may restrict the generalisability of the results.

General harms

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. [18] 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. [19] There have been warnings about the risks associated with using antidepressants in children.

Clinical guide

The clinician needs to warn parents and the child about ideas of self-harm and suicide and monitor for these if the use of antidepressants is agreed to. In addition, the clinician needs to let the parents

and child know that, once SSRIs are started, there may be an initial period of time of increased agitation and restlessness before any improvement in anxiety symptoms may occur.

OPTION ANTIPSYCHOTICS

- For GRADE evaluation of interventions for Generalised anxiety disorder in children and adolescents, see table, p 15 .
- We found no RCT evidence on the effects of antipsychotics in children and adolescents with generalised anxiety disorder.

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.

Comment:

In the adult population, the atypical antipsychotics have been associated with significant weight gain, metabolic syndrome, and prolonged Q-Tc syndrome, while being less associated with movement disorders than older medications. Given that there are no data for children and adolescents, one must approach the use of these medications with considerable caution.

Clinical guide

There is no evidence that the antipsychotic group has efficacy in children. The risk profile for antipsychotics includes weight gain, metabolic syndrome, risk of arrhythmias, and acute dystonias. The use of these medications should be limited to therapeutic trials, including N = 1 trials, under appropriate ethical review.

OPTION BENZODIAZEPINES

- For GRADE evaluation of interventions for Generalised anxiety disorder in children and adolescents, see table, p 15 .
- We found no RCT evidence on the effects of benzodiazepines in children and adolescents with generalised anxiety disorder.

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]). [20] The diagnosis of overanxious disorder (OAD, DSM-III) predates the current classification of GAD (DSM-IV) and the question of how it correlates with GAD remains controversial.

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). [20] 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).

Clinical guide

In adults, the use of benzodiazepines has considerable risks not limited to cognitive impairment, increased risk of falls, impaired driving, and dependence. [21] Use of benzodiazepines in children should be approached with caution and a clear informed consent from parents and (preferably) the child, ideally in writing.

OPTION BUSPIRONE

- For GRADE evaluation of interventions for Generalised anxiety disorder in children and adolescents, see table, p 15 .
- We found no RCT evidence on the effects of buspirone in children and adolescents with generalised anxiety disorder.

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.

Comment: There is no evidence to indicate that buspirone may be of efficacy in children and adolescents with generalised anxiety disorder. Please see the previous version of this overview for evidence on the efficacy of buspirone in GAD in adults.

Clinical guide

In children and adolescents, the use of buspirone should be reserved for therapeutic trials, including N = 1 trials, under appropriate ethical review.

OPTION HYDROXYZINE

- For GRADE evaluation of interventions for Generalised anxiety disorder in children and adolescents, see table, p 15 .
- We found no RCT evidence on the effects of hydroxyzine in children and adolescents with generalised anxiety disorder.

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.

Comment: There is no evidence to indicate that hydroxine may be of efficacy in children and adolescents with generalised anxiety disorder.

Clinical guide

There is no evidence that hydroxyzine has efficacy in children, and its use should be limited to therapeutic trials, including N = 1 trials, under appropriate ethical review. Hydroxyzine has been associated with cardiac events in vulnerable people, and the European Medicines Agency (EMA) recommends that the doses are lowered. In children, the maximum dose depends on their weight, and the daily total should not be more than 2 mg per kg of body weight in children weighing up to 40 kg (children over 40 kg may be given the adult dose). [22]

OPTION PREGABALIN

- For GRADE evaluation of interventions for Generalised anxiety disorder in children and adolescents, see table, p 15 .
- We found no RCT evidence on the effects of pregabalin in children and adolescents with generalised anxiety disorder.

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.

Comment: In adults, pregabalin has been associated with cognitive impairment.

Clinical guide
The use of these medications should be limited to therapeutic trials, including N = 1 trials, under appropriate ethical review.

GLOSSARY

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.

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.

SUBSTANTIVE CHANGES

Antidepressants in children and adolescents One systematic review added. [14] Categorisation unchanged (trade-off between benefits and harms).

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Christopher K. Gale
Senior Lecturer
Department of Psychological Medicine
Dunedin School of Medicine, University of Otago
Dunedin
New Zealand

Jane Millichamp
Professional Practice Fellow
Department of Psychological Medicine
Dunedin School of Medicine, University of Otago
Dunedin
New Zealand

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Disclaimer

GRADE **Evaluation of interventions for Generalised anxiety disorder in children and adolescents.**

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 pharmacological treatments for generalised anxiety disorder in children and adolescents?									
9 (1448) [8]	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 anxiety disorders
4 (390) [8]	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 anxiety disorders
1 (74) [10]	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 anxiety disorders
1 (128) [11]	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 anxiety disorders
2 (231) [9] [12]	Symptom severity	Sertraline versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of children with other anxiety disorders
1 (272) [9]	Symptom severity	Antidepressants versus CBT	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of children with other anxiety 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.