# Six decades of preventing and treating childhood anxiety disorders: a systematic review and meta-analysis to inform policy and practice

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## ABSTRACT

**Question** Anxiety disorders are the most prevalent childhood mental disorders. They also start early and persist, causing high individual and collective costs. To inform policy and practice, we therefore asked: What is the best available research evidence on preventing and treating these disorders?

**Methods** We sought randomised controlled trials (RCTs) evaluating interventions addressing anxiety problems in young people. We identified RCTs by searching CINAHL, ERIC, MEDLINE, PsycINFO and Web of Science. Thirty-three RCTs met inclusion criteria— evaluating 8 prevention programmes, 12 psychosocial treatments and 7 pharmacological treatments. We then conducted meta-analyses by intervention type.

**Findings** For prevention, the cognitive-behavioural therapy (CBT) programme *Coping and Promoting Strength* stood out for reducing anxiety diagnoses. For psychosocial treatment, 9 CBT interventions also reduced diagnoses: *Cool Kids*; *Cool Little Kids Plus Social Skills*; *Coping Cat*; *Coping Koala*; *One-Session Treatment*; *Parent Education Program*; *Skills for Academic and Social Success*; *Strongest Families* and *Timid to Tiger*. Successful CBT interventions were used with children ranging from pre-schoolers to teens in homes, communities/schools and clinics. For pharmacological treatment, selective-serotonergic-reuptake-inhibitors (SSRIs) significantly improved symptoms. Fluoxetine stood out for also reducing post-test diagnoses, but caused adverse events. Meta-analyses indicated strongest effects for CBT (Log OR=0.95; 95% CI, 0.69 to 1.21) and SSRI treatments (1.57; 1.09 to 2.06).

**Conclusions** CBT is effective for preventing and treating childhood anxiety—across a range of ages and formats. Fluoxetine is also an effective treatment but side effects must be managed. CBT prevention and treatment interventions should be made widely available, adding fluoxetine in severe cases.

## BACKGROUND

Anxiety disorders are characterised by excessive fear and behavioural disturbances that cause clinically significant distress and/or impairment in functioning.[1] These disorders include: separation anxiety disorder; selective mutism; specific phobias; social anxiety disorder; panic disorder; agoraphobia and generalised anxiety disorder.[1] With overall prevalence estimated at 6.5%, anxiety disorders are the most common childhood mental disorders, making them a crucial public health concern.[2 3] Because these disorders typically start early and persist, they also cause distress and impairment across the lifespan,[4] making them a leading cause of disability worldwide.[5] Beyond the costs for children and families,[6] anxiety disorders also lead to collective burdens. Considering direct and indirect healthcare and related expenditures, these disorders are estimated to cost up to €1200 (US$1300) per person annually—or €83.2B in total for Europe annually (2019 equivalency).[7]

Given these high burdens, prevention should be a priority. However, prevention investments are meagre, even in high-income jurisdictions. For example, in the UK and Canada, less than 6% of health spending goes towards public health including prevention, with even less allocated for preventing childhood mental disorders such as anxiety.[8–10] Exacerbating this situation, access to psychosocial treatments for childhood anxiety is also limited in most jurisdictions.[2 11] In contrast, psychiatric prescribing for these disorders is rising. For example, in Europe and the USA, paediatric prescriptions for antidepressants, commonly used to treat anxiety disorders,[12] showed increases ranging from 18% to 61% between 2005 and 2012.[13]

To address these shortfalls and imbalances, policymakers need robust research evidence on effective interventions across the prevention-through-treatment spectrum to inform public priorities. Practitioners also need this information to guide the implementation of effective approaches.

## OBJECTIVES

To inform policy and practice, we asked: What is the best available research evidence on preventing and treating childhood anxiety disorders? To provide comprehensive data, we included prevention programmes, psychosocial treatments and pharmacological treatments. To our knowledge, this is the first systematic review and meta-analysis covering this full intervention continuum for childhood anxiety. Past reviews/meta-analyses have examined only prevention[14–16] or only treatment.[17–21] This review also includes recent studies not covered in prior reviews.

## METHODS

We searched CINAHL, ERIC, MEDLINE and PsycINFO databases using the terms: *anxiety disorder*, *anxiety*, *agoraphobia*, *generalised anxiety disorder*, *panic disorder*, *phobic disorder*, *separation anxiety disorder*, *specific phobia*, *social anxiety disorder*, *social phobia*, OR *selective mutism* AND *prevention*, *intervention* OR *treatment*. Our search dates were January 1950 through May 2018. We

**Table 1** Randomised controlled trial inclusion criteria*

| | |
|---|---|
| 1 | Children ≤18 years of age were the main focus or were clearly reported on separately if part of an adult study. |
| 2 | Interventions aimed to prevent or treat anxiety disorders. |
| | a. For prevention, at enrolment/pretest, <50% had a primary anxiety disorder diagnosis. |
| | b. For treatment, at enrolment/pretest, ≥50% had a primary anxiety disorder diagnosis. |
| 3 | Clear descriptions were provided of participant characteristics, study settings and interventions. |
| 4 | Participants (or clusters) were randomly assigned to intervention and either control (no-intervention) or comparison (minimal intervention) groups at study outset. |
| 5 | Outcome measures pertained to anxiety, for example, scales had established reliability and validity or ≥50% of items addressed anxiety symptoms. |
| 6 | Anxiety indicators included either 1 diagnostic measure where the diagnostician was blinded or 2 symptom measures evaluated by 2 or more informant sources, for example, child, parent or teacher, at least one of whom was blinded. |
| 7 | Maximum attrition was 20% at post-test (medication studies) or at follow-up (prevention or psychosocial treatment studies) or authors used intention-to-treat analyses. |
| 8 | For prevention and psychosocial treatment studies, postintervention follow-up was 3 months or more. |
| 9 | For medication studies, double-blinding and placebo controls were used, and side effects were comprehensively assessed. |
| 10 | Statistical significance (using $p<0.05$) was reported for relevant outcome measures at post-test (medication studies) or at follow-up (prevention and psychosocial treatment studies). |
| 11 | Interventions were evaluated in high-income countries (by World Bank standards). |
| 12 | Studies focused on populations and settings with applicability to most children who may be at risk of or who may have anxiety, rather than specialised subpopulations. |

*For inclusion, all criteria had to be met.

applied limiters, seeking only randomised controlled trials (RCTs) that evaluated interventions addressing anxiety in individuals aged 18 years or younger. We also limited our searches to English-language articles due to most research being published in this language and due to translation capacity not being available within the team. We then searched *Evidence-Based Mental Health* and the Cochrane and Campbell Collaboration databases to identify relevant systematic reviews that we subsequently hand-searched. After title screening, 2 authors independently assessed all relevant abstracts. Relevant studies were then retrieved and independently assessed by 2 authors who identified those that met all inclusion criteria (see table 1). We next identified supplemental publications for accepted RCTs in Web of Science using intervention and author names and article titles. Figure 1 shows our search process.[22]

We limited our review to RCTs because this design is the most rigorous way of evaluating interventions. We applied additional quality indicators including requiring reliable and valid measures. To minimise risk of bias, after title screening at least 2 authors independently completed each step of the review process, resolving disagreements by consensus. To maximise policy and practice applicability, we also focused on studies in high-income countries because most low-income countries have yet to mobilise children's mental health services on a large scale.[23] This approach yielded 33 RCTs meeting all inclusion criteria—reporting on 8 prevention programmes, 12 psychosocial treatments and 7 pharmacotherapies. We then assessed risk-of-bias for each RCT using the Cochrane tool, based on data provided in the RCTs; this tool assesses biases across 5 domains which can lead to inaccurate estimates of intervention effects.[24 25] We augmented this process by also assessing conflicts of interest.

For all interventions, we extracted diagnostic findings for all follow-ups and symptom findings for longest follow-ups. We also identified common adverse events, where reported. We then conducted random-effects meta-analyses. Due to heterogeneity regarding participants, interventions, comparators and outcome measures across the 3 intervention groups, we conducted separate meta-analyses for: 1) diagnoses prevented for cognitive-behavioural therapy (CBT) prevention programmes versus comparison groups; 2) diagnoses remitted for CBT treatments versus comparison groups; and 3) symptom improvements for selective-serotoninergic-reuptake-inhibitors (SSRIs) (fluoxetine, fluvoxamine, paroxetine and sertraline) versus placebo. We extracted or calculated odds ratios (OR) for diagnostic and/or symptom improvement, then calculated Cochran's Q to evaluate heterogeneity. Publication bias was evaluated by inspecting asymmetry of funnel plots and performing an Egger's test. All statistical analyses were conducted using the Meta-Analysis Package for R.[26] This review was registered with PROSPERO (registration number CRD42016052643; see www.crd.york.ac.uk/PROSPERO/).

## FINDINGS
### Prevention programmes
Eight RCTs met inclusion criteria, evaluating 8 prevention programmes: 5 delivered in schools and 3 in other community settings.[27–36] One programme—*Coping and Promoting Strength*—was evaluated in 2 RCTs while the others were evaluated in single RCTs. One RCT also evaluated 2 interventions: *Cognitive Bias Modification* and a CBT programme. One programme was universal while 7 focused on at-risk children,
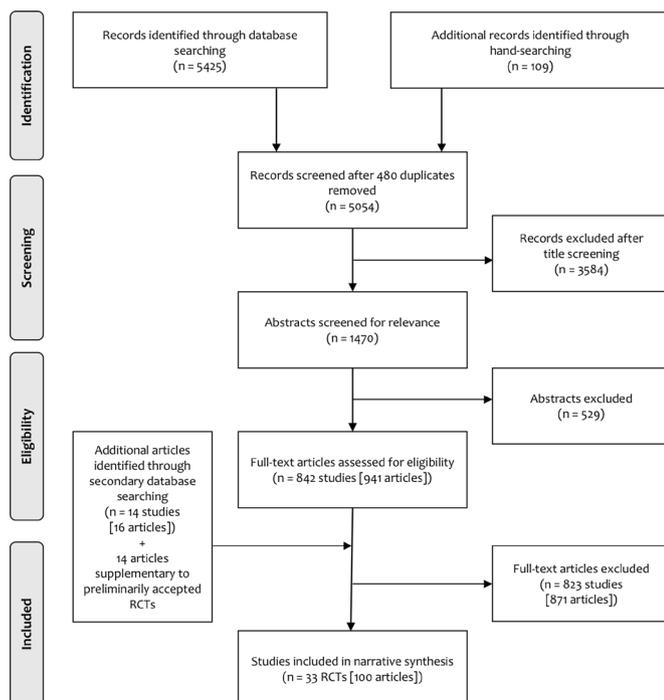
**Figure 1** Search process

that is, with temperamental inhibition, anxiety symptoms or a parent with an anxiety disorder.

Six programmes used CBT techniques including psychoeducation, relaxation, cognitive restructuring and exposure exercises.[28–30 34–36] Four CBT programmes were delivered to groups of children in schools, with 2 also providing parent sessions.[28 34–36] The 2 other CBT programmes focused on parents; 1 was delivered to individual families and 1 trained parents to provide CBT to their young children.[29 30] The 2 non-CBT programmes used computer delivery. *Cognitive Bias Modification* aimed to reduce negative assumptions in noticing and interpreting social situations.[36] Meanwhile, *Mindset* taught teens to cope with stress by viewing personality traits as being modifiable.[33] All 8 programmes were relatively brief, ranging from 30 min to 5.5 months.

Three prevention programmes—all using CBT and all focusing on at-risk children—significantly reduced anxiety diagnoses and/or symptoms. *Coping and Promoting Strength* was notable for reducing anxiety diagnoses across 2 RCTs, with a large effect size for the second (OR=8.54).[30 31] This included only 0%–5% of intervention children developing disorders between post-test and 9-month follow-up, compared with 30%–31% of controls.[30–32] *Coping and Promoting Strength* also significantly reduced symptoms: on 2 measures with large effect sizes (Cohen's *d* [*d*]=0.82 and 1.99) in the first RCT and on 3 measures with medium effect sizes (*d*=0.54–0.74) in the second.[30 31] *Cool Little Kids* and *Friends* also significantly reduced symptoms on one measure but did not reduce diagnoses.[29 35]

Five prevention programmes failed to show benefits pertaining to anxiety, including 3 CBT programmes (*Aussie Optimism*, *Feelings Club* and *Generic CBT*) and both non-CBT programmes (*Cognitive Bias Modification* and *Mindset*).[27 28 33 34 36] Adverse events were only assessed for *Feelings Club*; none were reported by children or parents.[34] Table 2 summarises the 8 prevention evaluations.

## Psychosocial treatments

Fourteen RCTs met inclusion criteria, evaluating 12 psychosocial treatments: 1 delivered in homes, 8 in clinics and 3 in schools.[37–50 w51] Two treatments—*Coping Cat* and *Skills for Academic and Social Success (SASS)*—were evaluated in 2 RCTs while the others were evaluated in single RCTs.[42 45 50 w51] As well, 3 RCTs compared different formats including individual child versus individual family delivery[42] and psychologist versus counsellor delivery.[w51] Most studies included children with a variety of anxiety disorders.

Eleven treatments used CBT, delivered to children and parents individually and in groups in a variety of settings. The only non-CBT treatment, *Attention Bias Modification Training (ABMT)*, used computers to teach children to reduce their focus on socially threatening situations.[41] All treatments were relatively brief, ranging from 3 hours to 6 months.

**Table 2** Prevention programme descriptions and evaluation findings

| Programme | Sample size (country) | Ages/Grades (risk factors) | Programme elements | Session number and duration | Follow-up period* | Child anxiety outcomes (diagnostic rates)† |
|---|---|---|---|---|---|---|
| **Universal programmes—school-based** | | | | | | |
| Aussie Optimism[27 28] | 910 (Australia) | Grade 4 (not applicable) | Child group CBT‡ | 10 sessions over 2.5 months | 2.5 years / 1.5 years | • 1 of 1 symptom / • Any AD diagnoses (3% vs 4%) |
| **Targeted programmes—community-based** | | | | | | |
| Cool Little Kids[29] | 545 (Australia) | 4 years (temperamental inhibition) | Parent group CBT training | 6 sessions over 3 months | 9 months | • SAD, SP, SpAD + GAD diagnoses (44% vs 50%) ↓ 1 of 1 symptom |
| Coping and Promoting Strength I[30] | 40 (USA) | 7–12 years (parent with an anxiety disorder) | Family CBT | 9–11 sessions over 5 months | 9 months | ↓ Any AD diagnoses§ (0% vs 30%) ↓ 2 of 3 symptoms |
| Coping and Promoting Strength II[31 32] | 136 (USA) | 6–13 years (parent with an anxiety disorder) | Family CBT | 11 sessions over 5 months | 9 months | ↓ Any AD diagnoses§ (5% vs 31%) ↓ 3 of 4 symptoms |
| Mindset[33] | 96 (USA) | 12–15 years (anxiety/depressive symptoms) | Child individual training on trait modifiability via computer | 1 30-min session | 9 months | • 2 of 2 symptoms |
| **Targeted programmes—school-based** | | | | | | |
| Feelings Club[34] | 148 (Canada) | Grades 3–6 (anxiety/depressive symptoms) | Child group CBT + parent group education | 12 child + 3 parent sessions over 3 months | 1 year | • Any AD diagnoses (7% vs 10% by parent report; 8% vs 17% by child report) • 1 of 1 symptom |
| Friends[35] | 260 (Australia) | Grade 7 (anxiety symptoms) | Child group CBT + parent group education | 12 child + 1–2 parent sessions over 5.5 months | 3.75 years | • Any AD diagnoses¶ (23% vs 24%) ↓ 1 of 2 symptoms |
| Generic Cognitive Behavioural Therapy | 240 (Netherlands) | 12–16 years (anxiety symptoms) | Child group CBT | 10 sessions over 2.5 months | 2 years | • SAD diagnoses (2% vs 6%) • 4 of 4 symptoms |
| Cognitive Bias Modification[36] | | | Child individual cognitive bias training via computer | 20 sessions over 2.5 months | 2 years | • SAD diagnoses (10% vs 6%) • 4 of 4 symptoms |

• Denotes no significant differences between intervention and comparison group.
↓ Denotes statistically-significant reductions in diagnoses/symptoms favouring intervention over comparison group.
* Follow-up period counted from end of intervention including booster sessions, where applicable.
† Diagnostic rates for intervention versus comparison children.
‡ Programme addressed both anxiety and depression.
§ Included children with AD diagnosis from post-test to final follow-up.
¶ Included children with AD diagnosis at any point in year prior to the final follow-up.
AD, anxiety disorder; CBT, cognitive behavioural therapy; GAD, generalised anxiety disorder; SAD, social anxiety disorder; SP, specific phobia; SpAD, separation anxiety disorder.

**Table 3** Psychosocial treatment descriptions and evaluation findings

| Programme (diagnoses) | Sample size (country) | Ages/Grades | Programme elements | Session number and duration | Follow-up period* | Child anxiety outcomes (diagnostic rates)† |
|---|---|---|---|---|---|---|
| **Home-based** | | | | | | |
| Strongest Families (GAD, SpAD, SAD, SP)[37] | 91 (Canada) | 6–12 years | Self-directed family CBT with coaching | 13 sessions over 6.5 months | 5.5 months | ↓ Any AD diagnoses (25% vs 50%)‡ |
| **Clinic-based** | | | | | | |
| Cool Little Kids Plus Social Skills (SAD, GAD, SpAD, SP)[38] | 72 (Australia) | 2–5 years | Parent group CBT training + child group SST | 6 parent + 6 child sessions over 2.5 months | 3 months | ↓ Any AD diagnoses (66% vs 100%)<br>↓ # of AD diagnoses<br>↓ 3 of 5 symptoms |
| Parent Education Program (SoP, SP, SpAD, GAD)§[39] | 146 (Australia) | 3–4 years | Parent group CBT training | 6 sessions over 2.5 months | 3 years | ↓ Any AD diagnoses (40% vs 69%)<br>↓ 2 of 3 symptoms |
| Timid to Tiger (SpAD, SAD, SP, PD, GAD)[40] | 74 (England) | 2–9 years | Parent group CBT training | 10 sessions over 2.5 months | 1 year | ↓ Primary AD diagnoses (46% vs 76%)<br>↓ Any AD diagnoses (54% vs 91%)<br>• 3 of 3 symptoms |
| Attention Bias Modification Treatment (SAD)[41] | 67 (Israel) | 6–18 years | Child individual attention bias training via computer | 8 sessions over 1 month | 3 months | • 2 of 2 symptoms |
| Coping Cat Individual<br><br>Coping Cat Family (GAD, SoP, SpAD)[42] | 161 (USA) | 7–14 years | Child individual CBT¶<br><br>Family CBT | 16 sessions over 4 months | 1 year | • Primary AD diagnoses (39% vs 56%)<br>↓ 1 of 8 symptoms<br>• Primary AD diagnoses (42% vs 56%)<br>• 8 of 8 symptoms |
| Cool Kids (GAD, SoP, SpAD, PD, SP)[43] | 112 (Australia) | 7–16 years | Child group CBT + parent group CBT training | 10 sessions over 2.5 months | 3 months | ↓ Primary AD diagnoses (31% vs 55%)<br>↓ Any AD diagnoses (51% vs 70%)<br>↓ 3 of 6 symptoms |
| One-Session Treatment (SP)[44] | 196 (Sweden + USA) | 7–16 years | Child individual CBT | 1 session over 3 hours | 6 months | ↓ SP diagnoses (51% vs 65%)<br>↓ 1 of 6 symptoms |
| Coping Cat (GAD, SpAD, SAD)[45] | 133 (USA) | 9–14 years | Child individual CBT¶ | 14 sessions over unnamed period | 1 year | ↓ Any AD diagnoses (18% vs 35%)<br>↓ 1 of 3 symptoms |
| Generic CBT (SAD)[46] | 73 (USA) | 12–17 years | Child individual or group CBT | 12 sessions over 3 months | 6 months | • 5 of 5 symptoms |
| **School-based** | | | | | | |
| Friends (with or without parent involvement)** (SAD, GAD, SoP)†† [47 48] | 61 (USA) | Grades 2–5 | Child group CBT ± parent group CBT training | 11 child + 9 parent sessions over 5 months | 2.75 years | ↓ 1 of 5 symptoms |
| | | | | | 3 months | • Primary AD diagnoses (14%–25% vs 40%)<br>• New AD diagnoses (15%–29% vs 29%) |
| Coping Koala (SoP, SP, GAD, SpAD)†† [49] | 128 (Australia) | Grades 3–7 | Child group CBT + parent group CBT training | 10 child + 3 parent sessions over 2.5 months | 2 years | ↓ Any AD diagnoses (20% vs 39%)<br>↓ 2 of 6 symptoms |
| Skills for Academic and Social Success (SASS) (SAD)[50] | 36 (USA) | Grades 9–11 | Child group CBT + parent + teacher education | 20 child + 2 parent/teacher sessions over 5 months | 4 months | ↓ SAD diagnoses (27% vs 93%)<br>↓ 2 of 5 symptoms |
| SASS Psychologist-Delivered<br><br>SASS Counsellor-Delivered (SAD)[w51] | 138 (USA) | Grades 9–11 | Child group CBT + parent + teacher education | 20 child + 2 parent/teacher sessions over 5 months | 3 months | • SAD diagnoses (72% vs 88%)<br>↓ 4 of 5 symptoms<br>↓ SAD diagnoses (61% vs 88%)<br>↓ 3 of 5 symptoms |

↓ Denotes statistically-significant reductions in diagnoses/symptoms favouring treatment over comparison group.
• Denotes no significant differences between treatment and comparison groups.
* Follow-up period counted from end of treatment including booster sessions, where applicable.
† Diagnostic rates for intervention versus comparison.
‡ Rates are approximate.
§ Approximately 93% met criteria for anxiety disorder; remainder had temperamental inhibition.
¶ Parent involvement in 2 sessions including psychoeducation and coaching on responding to anxious behaviours.
** Because there was no difference in outcomes for *Friends* with and without parent involvement combined results from 2 treatment groups are reported.
†† Approximately 75% met criteria for anxiety disorder; remainder were symptomatic.
AD, anxiety disorder; CBT, cognitive behavioural therapy; GAD, generalised anxiety disorder; PD, panic disorder; SAD, social anxiety disorder; SoP, social phobia; SP, specific phobia; SpAD, separation anxiety disorder; SST, social skills training.

Ten psychosocial treatments—all CBT—significantly reduced anxiety diagnoses and/or symptoms by final follow-ups. The home-based *Strongest Families* reduced diagnoses (approximately 25% for intervention children vs 50% for controls) with a large effect size (OR=2.51).[37] Of the clinic-based treatments, *Cool Little Kids Plus Social Skills* reduced diagnoses (66% vs 100%) and number of disorders per child (d=1.76); it also reduced symptoms on 3 measures, with large effect sizes (d=0.89–2.11).[38] *Cool Kids* also reduced primary diagnoses (31%

vs 55%), any anxiety diagnoses (51% vs 70%) and symptoms on 3 measures.[43] *Parent Education Program* reduced diagnoses (40% vs 69%) and symptoms on 2 measures.[39] *Timid to Tiger* reduced primary diagnoses (46% vs 76%) and any anxiety diagnoses (54% vs 91%), both with large effect sizes (OR=3.68 and 8.50, respectively), but had no impact on symptoms.[40] *One-Session Treatment* reduced specific phobia diagnoses (51% vs 65%) as well as symptoms on 1 measure.[44] Meanwhile, *Coping Cat* reduced anxiety diagnoses (18% vs 35%) and symptoms on 1

**Table 4** Pharmacological treatment descriptions and evaluation findings

| Medication [daily dose]* (diagnoses) | Sample size (country) | Ages | Duration | Child anxiety outcomes (diagnostic rates)† | Child adverse events |
|---|---|---|---|---|---|
| D-cycloserine [50 mg] (SP)[w52] | 37 (Australia) | 6–14 years | Single dose | ↓ 2 of 2 symptoms‡ | Headache 39%; left study due to adverse events 0% |
| Fluvoxamine [50–300 mg] (SoP, SpAD, GAD)[w53] | 128 (USA) | 6–17 years | 2 months | ↓ 2 of 2 symptoms | Abdominal discomfort 49%§; headache 43%; left study due to adverse events 8% |
| Fluoxetine I¶ [40 mg] (SAD)[w54] | 139 (USA) | 7–17 years | 3 months | ↓ SAD diagnoses (79% vs 97%) ↓ 4 of 8 symptoms | Nausea % NR§; left study due to adverse events 0% |
| Fluoxetine II [10–20 mg] (GAD, SoP, SpAD)[w55] | 74 (USA) | 7–17 years | 3 months | ↓ 1 of 6 symptoms | Abdominal pain or nausea 46%§; drowsiness 44%§; headaches 14%§; left study due to adverse events 14% |
| Fluoxetine III¶ [10–60 mg] (SoP, GAD, SpAD)[w56] | 62 (Australia) | 11–16 years | 6 months | • AD diagnoses (68% vs 77%) • 4 of 4 symptoms | Left study due to adverse events 5% |
| Imipramine I [100–200 mg] (NR)** [w57] | 42 (USA) | 6–14 years | 1.5 months | ↓ 8 of 8 symptoms | Drowsiness 62%; dry mouth 50%§; constipation 31%; dizziness 25%; left study due to adverse events % NR |
| Imipramine II [75–275 mg] (SpAD)[w58] | 21 (USA) | 6–15 years | 1.5 months | • 29 of 29 symptoms†† | Dry mouth 46%; irritability 27%; changes in ECG % NR§; left study due to adverse events 0% |
| Paroxetine [10–50 mg] (SAD)[w59] | 322 (USA, South Africa, Canada Belgium) | 8–17 years | 4 months | ↓ 6 of 6 symptoms | Insomnia 14%§; left study due to adverse events 6% |
| Sertraline I [50 mg] (GAD)[w60] | 22 (USA) | 5–17 years | 2.25 months | ↓ 6 of 7 symptoms | Drowsiness 73%; dry mouth 55%; restlessness 55%; leg spasms 36%; left study due to adverse events 0% |
| Sertraline II¶ [25–200 mg] (SpAD, GAD, SoP)[w61] | 488 (USA) | 7–17 years | 3 months | ↓ 2 of 4 symptoms NR 2 of 4 symptoms | Insomnia 8%; fatigue 6%; sedation 5%; restlessness 4%; fever 1%‡‡; left study due to adverse events 6% |
| Venlafaxine [37.5–225 mg] (SAD)[w62] | 293 (USA) | 8–18 years | 4 months | ↓ 2 of 2 symptoms | Nausea 23%§; anorexia 22%§; weakness or loss of energy 20%§; sore throat 19%§; weight loss 11%§; dilated pupils 4%§; abnormal behaviour 4%§; heart rate increase % NR§; PR interval decrease % NR§; pulse rate increase % NR§; blood pressure increase % NR§; left study due to adverse events 4% |

↓ Denotes statistically-significant reductions in symptoms favouring medication over placebo.
• Denotes medication did not show statistically-significant benefit over placebo.
* Reported doses include widest range that children received at point therapeutic dose achieved; dosing is not equivalent across medications.
† Diagnostic rates for medication versus placebo.
‡ Assessed 1 week after medication was administered.
§ Adverse event(s) experienced by significantly more children on medication than placebo.
¶ Medication was also compared with a psychosocial treatment, as described in text
** All participating children were refusing to attend school or were doing so with marked distress.
†† One outcome favoured placebo over medication.
‡‡ All adverse events were experienced by significantly more children on sertraline than children participating in cognitive-behavioural therapy.
AD, anxiety disorder; ECG, electrocardiogram; GAD, generalised anxiety disorder; NR, not reported; PD, panic disorder; SAD, social anxiety disorder; SoP, social phobia; SP, specific phobia; SpAD, Separation anxiety disorder.

measure (OR=3.29 and 2.56, respectively) in 1 trial.[45] In the other *Coping Cat* trial, primary anxiety diagnoses were not significantly reduced for either child or family formats; however, the child version did reduce symptoms on 1 measure.[42]

For school-based treatments, *Coping Koala* reduced diagnoses (20% vs 39%) and symptoms on 2 measures.[49] *SASS* (delivered by psychologists and psychology graduate students) and *Counsellor-Delivered SASS* both reduced social anxiety diagnoses (27% vs 93% and 61% vs 88% [OR=4.89], respectively, although *Psychologist-Delivered SASS* did not).[50–w51] All *SASS* versions also reduced symptoms on 2-to-4 measures, with moderate-to-large effect sizes for 2 versions (OR=16.21 and $d$=0.38–0.93 for *Counsellor-Delivered* and OR=7.61 and $d$=0.34–0.83 for *Psychologist-Delivered*). In contrast, *Friends* improved 1 symptom measure but failed to reduce diagnoses.[47 48]

The remaining 2 treatments—both clinic-based—showed no benefits: *Generic CBT* and *ABMT* (the only non-CBT treatment).[41 46] Adverse events were assessed for 2 treatments. *Strongest Families* participants reported no adverse events,

and none were observed for *One-Session Treatment* participants.[37 44] Table 3 summarises the 14 psychosocial treatment evaluations.

## Pharmacological treatments

Eleven RCTs met inclusion criteria, evaluating 7 medications: SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline); a tricyclic (imipramine); a selective-noradrenergic-reuptake-inhibitor (venlafaxine); and an N-methyl-D-aspartate-partial-agonist (D-cycloserine).[w52–w62] Fluoxetine was evaluated in 3 RCTs while imipramine and sertraline were each evaluated in 2.[w54–w58 w60–w61] The other medications were evaluated in single RCTs.[w52 w53 w59 w62] In addition to placebos, fluoxetine was compared with behaviour treatment in 1 RCT[w54] and with CBT in another,[w56] while sertraline was compared with CBT in 1 RCT.[w61] All medications were assessed at posttest only, except D-cycloserine which was assessed at 1-week follow-up.[w52] Some studies included children with a variety of

anxiety disorders,[w53 w55 w56 w61] while others focused on single disorders.[w52 w54 w58–w60 w62]

For fluoxetine, 2 RCTs assessed diagnoses and symptoms. In 1 trial (fluoxetine I; see table 4), the medication significantly reduced social anxiety diagnoses (79% for intervention children vs 97% for placebo controls) and reduced symptoms on 4 measures.[w54] However, when compared with a 12-week behaviour treatment, fluoxetine was *less* effective at reducing social anxiety diagnoses (79% for fluoxetine vs 47% for behaviour treatment) as well as at reducing symptoms on 4 measures.[w54] In another trial (fluoxetine III), the medication was given with CBT but failed to reduce anxiety diagnoses compared with CBT alone or compared with CBT plus placebo (68% for fluoxetine plus CBT vs 65% for CBT alone vs 77% for CBT plus placebo).[w56] Similarly, there was no difference among the 3 conditions on symptoms on 4 measures.[w56] A third trial (fluoxetine II) did not assess diagnoses but reduced symptoms on 1 measure.[w55]

For the other 6 medications, RCTs assessed anxiety symptoms but not diagnoses. D-cycloserine reduced symptoms with medium effect sizes on 2 measures ($r=0.35$ and $0.37$).[w52] Fluvoxamine reduced symptoms on 2 measures.[w53] The first imipramine RCT showed 8 symptom reductions, with a medium effect size for the 1 outcome where this was calculated (Cohen's $h=0.73$).[w57] As well, despite initially refusing to attend school or only attending with marked distress, by the end of the trial, 81% of intervention children were regularly attending compared with only 47% of controls.[w57] In contrast, the second imipramine RCT found the medication no better than placebo on 28 of 29 measures and worse on 1.[w58] Paroxetine reduced symptoms on 6 social anxiety measures, with large effect sizes for the 2 outcomes where these were calculated ($OR=5.44$ and $6.05$).[w59] Sertraline also reduced symptoms in 2 RCTs. In the first, it reduced symptoms on 6 measures.[w60] In the second, it reduced symptoms on 2 measures compared with placebo with moderate-to-large effect sizes (Hedges' $g$ $[g]=0.45$; $OR=3.9$); however, outcomes were not significant when compared with CBT.[w61] Meanwhile, venlafaxine reduced symptoms on 2 measures, with moderate effect sizes ($g=0.46$ and number needed to treat=5).[w62]

Adverse events were common for most medications. These included more than 25% of children experiencing: abdominal pain/nausea and drowsiness with fluoxetine; headaches with D-cycloserine; abdominal discomfort and headaches with fluvoxamine; drowsiness, dry mouth, constipation, irritability and dizziness with imipramine; and drowsiness, dry mouth, restlessness and leg spasms with sertraline.[w52 w53 w55 w57 w58 w60] Table 4 summarises the 11 medication evaluations, including adverse events. (We reported adverse events where at least 25% of children were affected or where significantly more children on medication versus placebo were affected; however, not all studies tested the statistical significance of adverse events.)

### Risk of bias in included studies

Based on data provided in each RCT, we evaluated 5 risk indicators using the Cochrane risk-of-bias tool.[24 25] For most prevention studies, bias risks were low, with the exception of performance bias. For most psychosocial treatment studies, selection bias was unclear, while performance and detection biases were high; however, attrition and reporting biases were all low. For most medication studies, bias risks were low. Overall risk-of-bias profiles favoured medication over psychosocial studies. (Online supplementary appendix B gives individual RCT risk-of-bias assessments; online supplementary appendix C gives aggregated risk-of-bias by intervention category.) We also augmented our

risk-of-bias assessment to address concerns not covered in the Cochrane tool.[24 25] Specifically, we identified conflicts-of-interests for 6 of 11 medication RCTs—with author(s) declaring ties to pharmaceutical companies including receiving honouraria, owning stock and/or being company employees.[w52 w54 w59 w60 w62] In contrast, conflict-of-interest was reported for only 1 psychosocial study, with an author declaring the intervention may be commercialised.[37]

### Meta-analysis

Beyond identifying specific interventions for preventing and treating childhood anxiety to guide policy and practice, we undertook meta-analyses to determine the common effects of similar interventions where there were sufficient RCTs. This included CBT prevention programmes, CBT treatment programmes and SSRIs. For CBT prevention and treatment programmes, ORs for diagnoses prevented or remitted were either extracted or calculated. Because diagnostic outcomes were not available for most SSRI RCTs, we used ORs for symptom improvement.

CBT prevention programmes did not significantly outperform comparison conditions for preventing diagnoses (Log $OR=0.50$; 95% CI, $-0.14$ to $1.13$). However, study populations showed significant heterogeneity (Cochran's $Q=16.1$, $p=0.01$). In contrast, the CBT treatment programmes significantly outperformed comparison conditions for reducing diagnoses (Log $OR=0.95$; 95% CI, $0.69$ to $1.21$) with acceptable levels of heterogeneity (Cochran's $Q=15.5$, $p=0.16$). SSRIs resulted in significantly more symptom improvement than placebos at posttest (Log $OR=1.57$; 95% CI, $1.09$ to $2.06$), also with acceptable levels of heterogeneity (Cochran's $Q=10.56$, $p=0.06$). While the Log OR was greater for SSRIs than CBT treatment programmes, the latter used a more robust outcome measure—diagnostic versus symptom improvement. As well, CBT treatments were assessed at follow-ups averaging 10 months, while SSRIs were assessed at post-test. (Online supplementary appendices D and E summarise the meta-analyses.)

Regarding publication bias, Egger's tests showed asymmetry in CBT prevention and CBT treatment studies ($p<0.01$ for both) and symmetry in SSRI studies ($p=0.21$). However, the publication bias found for CBT treatment studies had minimal impact on our main findings. When we limited the analysis to studies with sample sizes greater than 100, asymmetry disappeared ($p=0.38$) and CBT treatment programmes still effectively reduced diagnoses (Log $OR=0.92$; 95% CI, $0.63$ to $1.22$). (Online supplementary appendix F gives funnel plots assessing publication bias.)

### CONCLUSION AND IMPLICATIONS

Childhood anxiety disorders come with high costs due, in part, to effective prevention and psychosocial treatment interventions not being readily available.[2 11] To assist policymakers and practitioners in improving this situation, we aimed to identify effective interventions—particularly those that were noteworthy for reducing childhood anxiety diagnoses. For prevention, the CBT programme *Coping and Promoting Strength* stood out. It reduced diagnoses in 6–13-year-olds whose parents had anxiety disorders in 2 RCTs. No other prevention programme showed comparable success. For psychosocial treatment, 9 CBT programmes stood out: *Cool Kids*, *Cool Little Kids Plus Social Skills*, *Coping Cat*, *Coping Koala*, *One-Session Treatment*, *Parent Education Program*, *SASS*, *Strongest Families* and *Timid to Tiger*. These treatments reduced diagnoses using CBT with children and families—helping children from early pre-school through

the late teen years. For medications, the SSRI fluoxetine successfully reduced diagnoses at post-test in 1 RCT with 7–17-year-old children. No other medication showed comparable success. Most medications, including fluoxetine, caused adverse events.

Based on this review, there is good evidence for making targeted prevention investments using CBT programmes such as *Coping and Promoting Strength*. Consequently, this intervention should be made readily available for all at-risk children. Prevention has unique potential—to reduce the incidence of anxiety disorders early in life, and to reduce the number of children going on to develop more severe disorders—and so should be prioritised by policymakers, practitioners and researchers, alongside treatment.[w63] Given the relatively limited benefits found for many of the prevention programmes, however, more research should be conducted to add to the options.

As well, based on this review, the case for CBT for treating childhood anxiety disorders is particularly strong. Nine CBT treatments showed diagnostic reductions—over a range of child ages, delivery formats and settings. Beyond clinical benefits, recent cost analyses (including 4 RCTs covered here) found that CBT produced net gains of €9500 (US$10,600; 2019 equivalency) per person.[w64] Therefore, CBT should be made readily available for all children with anxiety disorders, with a focus on the 9 successful interventions. That said, future psychosocial research should assess potential adverse events—which were seldom evaluated.

Based on this review, there is also evidence that the SSRI fluoxetine is effective in reducing childhood anxiety diagnoses. Therefore, when medication is being considered, fluoxetine should be considered first. Yet overall, the data suggest that effective prevention programming should be offered to all at-risk children and CBT should be offered to all children with anxiety disorders as first-line treatment, while fluoxetine should be considered for children who do not improve with CBT alone. As well, close monitoring is needed with any medication so adverse events can be managed. Nevertheless, more medication RCTs are needed—that examine diagnostic outcomes and that are conducted independently of pharmaceutical companies.

Our review also has limitations. Our inclusion criteria for blinding differed between psychosocial and medication studies, which may introduce bias favouring psychosocial studies. We took this approach to allow us to include a reasonable number of these studies, where double-blinding (and placebo controls) are often not feasible. We also noted that in the psychosocial studies, more blinded outcomes were statistically significant compared with non-blinded (62% vs 19%), suggesting that our criteria did not favour these studies. To balance our approach, we only required post-test follow-up for medication studies while requiring 3-month follow-up for psychosocial studies, in turn allowing us to include a reasonable number of medication studies given that most did not continue beyond post-test. Another limitation pertains to the high thresholds we set for study inclusion, meaning that we likely excluded many interventions that are being implemented. Yet our approach can serve as a model for guiding policy and practice decisions. Namely, when RCT evidence of effectiveness is lacking, interventions should only be used if there is commitment to evaluating outcomes to ensure that children benefit.

On balance, for preventing and treating childhood anxiety, the research evidence favours psychosocial interventions in general and CBT in particular. To implement this evidence, shifts in policy and practice will need to occur. These shifts include allocating more funding towards prevention and psychosocial treatments. Australia, for example, doubled the proportion of children with mental disorders receiving services—from one-third in 1998 to two-thirds in 2014—by making significant new public investments.[w65] Other countries could follow suit. It is also crucial to reach more children using efficient models such as group or online delivery. For example, anxiety prevention and treatment programmes can be delivered in schools, with the potential to reach many more children than individually-delivered interventions. Shifts in policy and practice regarding psychiatric medications are also needed, in particular, encouraging the use of CBT before considering medications for most children with anxiety.

Making new policy investments can be highly challenging given intense competing demands on public budgets. Changing practices can also be challenging given longstanding patterns of providing care. Yet children's mental health needs greater public investments, and children's mental health services need to evolve as new research evidence becomes available. Given how common anxiety disorders are, policymakers and practitioners have the opportunity to make a profound difference in the lives of many thousands of children. They can do this by investing in and delivering effective anxiety interventions across the prevention-through-treatment continuum—so that all children in need are reached.

Additional references are provided in online supplementary web references.

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