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 pharmaceutical 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 pharmaceutical 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 SSRIs 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. These disorders include: separation anxiety disorder; selective mutism; specific phobias; social anxiety disorder; panic disorder; agoraphobia and generalised anxiety disorder. With overall prevalence estimated at 6.5%, anxiety disorders are the most common childhood mental disorders, making them a crucial public health concern. Because these disorders typically start early and persist, they also cause distress and impairment across the lifespan, making them a leading cause of disability worldwide.

Beyond the costs for children and families, 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).

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. Exacerbating this situation, access to psychosocial treatments for childhood anxiety is also limited in most jurisdictions. 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, showed increased usage ranging from 18% to 61% between 2005 and 2012.

To address these shortages 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 pharmaceutical 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 or only treatment. 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
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,
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.10–13 Coping and Promoting Strength also significantly reduced symptoms: on 2 measures with large effect sizes (Cohen’s 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 31 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 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 49 50 w51 As well, 3 RCTs compared different formats including individual child versus individual family delivery42 and psychologist versus counsellor delivery.46–48 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                               | 910 (Australia)       | Grade 4 (not applicable)   | Child group CBT‡   | 10 sessions over 2.5 months | 2.5 years         | • 1 of 1 symptom                         |
|                                                |                       |                            |                    |                             |                   | • Any AD diagnoses (3% vs 4%)            |
|                                                |                       |                            |                    |                             |                   |                                          |
| Targeted programmes—community-based           |                       |                            |                    |                             |                   |                                          |
| Cool Little Kids                              | 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                 | 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              | 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                                        | 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                                 | 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                                       | 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%) |
| Cognitive Bias Modification                   |                       |                            |                    |                             |                   | • 4 of 4 symptoms                        |
|                                                |                       |                            |                    |                             |                   | • 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.
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] (SPAD)††       | 37 (Australia)        | 6–14 years | Single dose | ↓ of 2 of 2 symptoms                       | Headache 39%; left study due to adverse events 0% |
| Fluoxetine [50–300 mg] (Sp, SpAD, GAD)‡‡ | 128 (USA)            | 6–17 years | 2 months  | ↓ of 2 of 2 symptoms                       | Abdominal discomfort 49%; headache 43%; left study due to adverse events 8% |
| Fluoxetine [40 mg] (SAD)‡‡        | 139 (USA)            | 7–17 years | 3 months  | ↓ of 4 of 8 symptoms                        | Nausea % NR; left study due to adverse events 0% |
| Fluoxetine II [10–20 mg] (GAD, Sp, SpAD)‡‡ | 74 (USA)             | 7–17 years | 3 months  | ↓ of 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] (Sp, GAD, SpAD)‡‡ | 62 (Australia)      | 11–16 years | 6 months  | • AD diagnoses (68% vs 77%)                 | Left study due to adverse events 5% |
| Imipramine I [100–200 mg] (NR)**‡‡ | 42 (USA)             | 6–14 years | 1.5 months | ↓ of 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)‡‡ | 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)‡‡     | 322 (USA, South Africa, Canada Belgium) | 8–17 years | 4 months  | ↓ of 6 of 6 symptoms                        | Insomnia 14%; left study due to adverse events 6% |
| Sertraline I [50 mg] (GAD)††       | 22 (USA)             | 5–17 years | 2.25 months | ↓ of 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, Sp)‡‡ | 488 (USA)          | 7–17 years | 3 months  | ↓ of 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)‡‡ | 293 (USA)            | 8–18 years | 4 months  | ↓ of 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% |

1 Denotes statistically-significant reductions in symptoms favouring medication over placebo.  
* Denotes medication did not show statistically-significant benefit over placebo.  
† Diagnostic rates for medication versus placebo.  
‡ Assessed 1 week after medication was administered.  
§ Adverse events 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 study favoured placebo over medication.  
‡‡ All adverse events 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; Sp, social phobia; SpAD, Separation anxiety disorder.  

measure (OR=3.29 and 2.56, respectively) in 1 trial. 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.43

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 Counselor-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 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 Counselor-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.

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).52–62 Venlafaxine was evaluated in 3 RCTs while imipramine and sertraline were each evaluated in 2.53–55,56–58,60–61 The other medications were evaluated in single RCTs.52,53,59–61 In addition to placebos, fluoxetine was compared with behaviour treatment in 1 RCT,54 and with CBT in another,55,56 while sertraline was compared with CBT in 1 RCT.57 All medications were assessed at post-test only, except D-cycloserine which was assessed at 1-week follow-up.62 Some studies included children with a variety of...
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.\textsuperscript{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.\textsuperscript{w55} 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).\textsuperscript{w56} Similarly, there was no difference among the 3 conditions on symptoms on 4 measures.\textsuperscript{w56} A third trial (fluoxetine II) did not assess diagnoses but reduced symptoms on 1 measure.\textsuperscript{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).\textsuperscript{w52} Fluvoxamine reduced symptoms on 2 measures.\textsuperscript{w53} The first imipramine RCT showed 8 symptom reductions, with a medium effect size for the 1 outcome where this was calculated (Cohen’s $d=0.73$). 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.\textsuperscript{w57} In contrast, the second imipramine RCT found the medication no better than placebo on 28 of 29 measures and worse on 1.\textsuperscript{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).\textsuperscript{w59} Sertraline also reduced symptoms in 2 RCTs. In the first, it reduced symptoms on 6 measures.\textsuperscript{w60} In the second, it reduced symptoms on 2 measures compared with placebo with moderate-to-large effect sizes (Hedges’ $g=0.45$; OR=3.9); however, outcomes were not significant when compared with CBT.\textsuperscript{w61} Meanwhile, venlafaxine reduced symptoms on 2 measures, with moderate effect sizes ($q=0.46$ and number needed to treat $=5$).\textsuperscript{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.\textsuperscript{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.\textsuperscript{w41 w42} 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.\textsuperscript{w24 w25} Specifically, we identified conflicts-of-interest for 6 of 11 medication RCTs—with author(s) declaring ties to pharmaceutical companies including receiving honouraria, owning stock and/or being company employees.\textsuperscript{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.\textsuperscript{w37}

### 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 post-test (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.)
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.\(^w6\) 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.\(^w6\) 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-blind (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.\(^w6\) 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.

Acknowledgements We are grateful to our reviewers, whose suggestions greatly strengthened the manuscript.

Contributors All authors played a role in developing the idea for this review and all approved the final version. CS interpreted the data and wrote the manuscript with extensive input from CW. JLH and DY conducted the literature searches, extracted relevant data and contributed to the manuscript. YZ led the meta-analyses and contributed to the manuscript. All authors approved the final version.

Funding The British Columbia Ministry of Children and Family Development supported this work (grant number SL00444501, dated 11 April 2011, modified 1 April 2019).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are available on reasonable request from the corresponding author until 31 March 2022.

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REFERENCES

1 American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. 5th edn. Washington, DC: APA, 2013.
2 Georgiades K, Duncan L, Wang L, et al. Six-month prevalence of mental disorders and service contacts among children and youth in Ontario: evidence from the 2014 Ontario Child Health Study. Can J Psychiatry 2015;60:452–56.
3 Polanczyk GV, Salum GA, Sugaya LS, et al. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry 2015;56:345–65.
4 Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602.
5 Bate C, Vos T, Scott KM, et al. The global burden of anxiety disorders in 2010. Psychol Med 2014;44:2363–74.
6 Senarathne R, Van Ameringen M, Mancini C, et al. The burden of anxiety disorders on the family. J Nerv Ment Dis 2010;198:876–80.
7 Olesen I, Gustavsson A, Svenson M, et al. The economic cost of brain disorders in Europe. Eur J Neurol 2012;19:155–62.
8 Office for National Statistics. UK Health Accounts: 2016. Apr 2018 www.onst.gov.uk/releases/ukhealthaccount2016 (Accessed Apr 2019).
9 Canadian Institute for Health Information (CIHI). National health expenditure trends, 1975 to 2018. Ottawa, ON: CIHI, 2018.
10 Waddell C, Georgiades K, Duncan L, et al. 2014 Ontario Child Health Study findings: policy implications for Canada. Can J Psychiatry 2019;64:227–31.
11 Waddell C, Shepherd C, Schwartz C, et al. Child and youth mental disorders: prevalence and evidence-based interventions. Vancouver, BC: Children’s Health Policy Centre, Faculty of Health Sciences, Simon Fraser University, 2014.
12 Craske MG, Stein MB. Anxiety. Lancer 2016;388:3048–59.
13 Bachmann CJ, Aagaard L, Burcu M, et al. Trends and patterns of antidepressant use in children and adolescents from five western countries, 2005-2012. Eur Neuropsychopharmacol 2016;26:411–9.
14 Fisak BJ, Richard D, Mann A. The prevention of child and adolescent anxiety: a meta-analytic review. Prev Sci 2011;12:255–68.
15 Teubert D, Pinquart M. A meta-analytic review on the prevention of symptoms of anxiety in children and adolescents. J Anxiety Disorders 2011;25:1046–59.
16 Waldron SM, Stallard P, Grist R, et al. The ‘long-term’ effects of universal school-based anxiety prevention trials: a systematic review. Ment Health Prev 2018;11:8–15.
17 Reynolds S, Wilson C, Austin J, et al. Effects of psychotherapy for anxiety in children and adolescents: a meta-analytic review. Clin Psychol Rev 2012;32:251–62.
18 James AC, James, G, Cowdrey FA, et al. Cognitive behavioural therapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev 2015;2:CD004690.
19 Higa-McMillan CK, Francis SE, Rith-Najarian L, et al. Evidence base update: 50 years of research on treatment for child and adolescent anxiety. J Clin Child Adolesc Psychol 2016;45:91–113.
20 Wang Z, Whiteside SP, Sim J, et al. Comparative effectiveness and safety of cognitive behavioral therapy and pharmacotherapy for childhood anxiety disorders: a systematic review and meta-analysis. JAMA Pediatr 2017;171:1049–56.
21 Zhou X, Zhang Y, Furukawa TA, et al. Different types and acceptability of psychotherapies for acute anxiety disorders in children and adolescents: a network meta-analysis. JAMA Psychiatry 2019;76:41–50.
22 Mohler D, Liberman A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.
23 World Health Organization (WHO). Mental health atlas 2017. Geneva: WHO, 2018.
24 Higgins JPT, Altman DG, Gattez PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
25 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions, version 5.1.0. Updated Mar 2011 www.cochrane.org (Accessed Feb 2019).
26 Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.
27 Rooney R, Hassan S, Kane R, et al. Reducing depression in 9-10 year old children in low SES schools: a longitudinal universal randomized controlled trial. Behav Res Ther 2013;51:845–54.
28 Rooney RM, Morrison D, Hassan S, et al. Prevention of internalizing disorders in 9–10 year old children: efficacy of the Aussie Optimism Positive Thinking Skills Program at 30-month follow-up. Front Psychol 2013;4:1–10.
29 Bayer JK, Beatson R, Bretherton L, et al. Translational delivery of Cool Little Kids’ intervention for prevent internalising problems: randomised controlled trial. Aust N Z J Psychiatry 2018;52:181–91.
30 Ginsburg GS. The child anxiety prevention study: intervention model and primary outcomes. J Consult Clin Psychol 2009;77:580–7.
31 Ginsburg GS, Drake KL, Tein JY, et al. Preventing onset of anxiety disorders in offspring of anxious parents: a randomized controlled trial of a family-based intervention. Am J Psychiatry 2015;172:1207–14.
32 Pella JE, Drake KL, Tein JY, et al. Child anxiety prevention study: impact on functional outcomes. Child Psychiatry Hum Dev 2017;48:400–10.
33 Schreider J, Weisz J. A single-session growth Mindset intervention for adolescent anxiety and depression: 9-month outcomes of a randomized trial. J Child Psychol Psychiatry 2018;59:160–70.
34 Manassis K, Williams-Traynor P, Farzan N, et al. The Feelings Club: randomized controlled evaluation of school-based CBT for anxious or depressive symptoms. Depress Anxiety 2010;27:945–52.
35 Hunt C, Andrews G, Crino R, et al. Randomized controlled trial of an early intervention programme for adolescent anxiety disorders. Aust N Z J Psychiatry 2009;43:300–4.
36 de Hullu E, Spontel BE, Nauta MH, et al. Cognitive bias modification and CBT as early interventions for adolescent social and test anxiety; two-year follow-up of a randomized controlled trial. J Behav Ther Exp Psychiatry 2017;55:81–9.
37 McGrath P, Lingley-Potter P, Thurston C, et al. Telephone-based mental health interventions for child disruptive behavior or anxiety disorders: randomized trials and overall analysis. J Am Acad Child Adolesc Psychiatry 2011;50:1162–72.
38 Lau EK, Raper RM, Coplan RJ. Combining child social skills training with a parent early intervention program for inhibited preschool children. J Anxiety Disorder 2017;31:32–8.
39 Raper RM, Kennedy SJ, Ingram M, et al. Altering the trajectory of anxiety in at-risk young children. Am J Psychiatry 2010;167:1518–25.
40 Cartwright-Hatton S, McNally D, Field AP, et al. A new parenting-based group intervention for young anxious children: results of a randomized controlled trial. J Am Acad Child Adolesc Psychiatry 2011;50:242–51.
41 Pergamin-Hight L, Pine DS, Fox NA, et al. Attention bias modification for youth with social anxiety disorder. J Child Psychiatry 2016;57:1317–25.
42 Kendall PC, Hudson JL, Gorsc E, et al. Cognitive-behavioral therapy for anxiety disorders: a randomized clinical trial evaluating child and family modalities. J Consult Clin Psychol 2008;76:282–97.
43 Hudson JL, Raper RM, Deveyre C, et al. Cognitive-behavioral treatment versus an active control for children and adolescents with anxiety disorders: a randomized trial. J Am Acad Child Adolesc Psychiatry 2009;48:533–44.
44 Ollendorck TH, Ost LG, Reuterskiöld L, et al. One-session treatment of specific phobias in youth: a randomized clinical trial in the United States and Sweden. J Consult Clin Psychol 2009;77:504–16.
45 Silk JS, Tan PZ, Ladouceur CD, et al. A randomized clinical trial comparing individual cognitive behavioral therapy and child-centered therapy for child anxiety disorders. J Clin Child Adolesc Psychol 2018;47:542–54.
46 Herbert JD, Gaudiano BA, Rheingold AA, et al. Cognitive behavior therapy for generalized social anxiety disorder in adolescents: a randomized controlled trial. J Anxiety Disorder 2009;23:167–77.
47 Bernstein GA, Bernat DH, Victor AM, et al. School-based interventions for anxious children: 3-, 6-, and 12-month follow-ups. J Am Acad Child Adolesc Psychiatry 2008;47:1039–47.
48 Lee SS, Victor AM, James MG, et al. School-based interventions for anxious children: long-term follow-up. Child Psychiatry Hum Dev 2016;47:183–93.
49 Dadds MR, Holland DE, Laurens KR, et al. Early intervention and prevention of anxiety disorders in children: results at 2-year follow-up. J Consult Clin Psychol 1999;67:145–50.
50 Masia-Warner C, Fisher PH, Shroot PE, et al. Treating adolescents with social anxiety disorder in school: an attention control trial. J Child Psychiatry Psychol 2007;48:676–86.