Evidence-based Clinical Practice Guidelines for Anxiety in Children and Young People 2023

Technical Evidence Report

Melbourne Children's
A world leader in child and adolescent health

The Royal Children's Hospital Melbourne

murdoch children's research institute

The University of Melbourne

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1. Evidence Report: Screening, diagnosis and assessment for anxiety in children and young people

1.1 Questions addressed:

Should children and young people in the general population be screened for anxiety? (Narrative review informed by indirect evidence in diagnostic accuracy and treatment evidence reviews)

Are there high-risk groups of children and young people that should be screened for anxiety?

What is the diagnostic accuracy of methods/tools/scales/ instruments, compared to gold standard diagnosis based on DSM or ICD criteria, for diagnosis of anxiety in children and young people? (Systematic evidence review)

What is the diagnostic accuracy of methods/tools/ instruments, compared to gold standard diagnosis based on DSM or ICD criteria, to determine severity/level (?) of anxiety in children and young people? (Systematic evidence review)

1.2 Evidence summary

1.2.1 Should children and young people in the general population be screened for anxiety?

The USPSTF search did not identify any studies that directly assessing the benefits or harms of screening for anxiety disorders in children and adolescents and relied on indirect evidence about the accuracy of screening and the benefits of treatment. Evidence for screening is outlined below and treatment evidence is outlined in ***the accompanying evidence statement of the USPSTF guideline.***

It was concluded that screening for anxiety in children and adolescents aged 8 to 18 years has a moderate net benefit (moderate certainty[1]) and the resulting recommendation to offer this service was graded B – The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

[1] USPSTF definition of moderate certainty - the available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

An evidence statement was made to reflect the finding that the evidence is insufficient on screening for anxiety in children 7 years or younger. A statement is made when the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. Refer to the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

1.2.2 Are there high-risk groups of children and young people that should be screened for anxiety?

Based on a scoping review of potential pre-existing conditions that may increase the risk of anxiety in children and young people (Appendix II), thirteen studies addressed predictive accuracy of the potential risk factors with high prevalence (>50%).

Meta-analyses based on moderate certainty evidence suggests that CYP of parents with anxiety were at statistically significantly higher risk of panic disorder (p=0.02) [1, 2] and potential for higher risk of generalised anxiety disorder (p=0.06) [1, 3]; however, parents with anxiety was not a statistically significant risk factor for separation anxiety disorder[1, 3], social phobia[1, 3], and phobic disorder [1, 3].

Very low certainty evidence, based on three studies, suggests that parents with anxiety is a statistically significant risk factor for overall anxiety (p=0.04) [1, 4, 5].

High certainty evidence, based on two studies, suggests that parents with depression is a statistically significant risk factor for overall anxiety (p=0.004) [2, 3].

A study of moderate certainty suggests that CYP of parents with OCD have a higher risk of anxiety (p=0.019), particularly overanxious disorder (p=0.02) and separation anxiety (p=0.002) [6].

A study of moderate certainty suggests that it is unclear whether CYP of parents with substance disorder have a higher risk of anxiety [1].

Evidence from single studies with a control group suggest higher risk of anxiety in CYP with:

- ASD, particularly GAD (low certainty) [7];
- Insomnia (low certainty) [8];
- Sleep terrors and/or sleep walking (moderate certainty) [9];

A small study of very low certainty suggests that CYP with cystic fibrosis may have higher risk of anxiety disorder (p=0.007) and specific phobia (p=0.005); however there was no statistically significant difference between CYP with and without cystic fibrosis for separation anxiety (p=0.054), social anxiety (p=0.303) or GAD (p=0.427) [10].

1.2.3 What is the diagnostic accuracy of methods/tools/scales/ instruments, compared to gold standard diagnosis based on DSM or ICD criteria, for diagnosis of anxiety or to determine severity/level of anxiety in children and young people?

Evidence summary from USPSTF guideline statement [11]:

"Ten fair-quality[2] studies (n = 3260) evaluated accuracy of [index test] screening instruments [against the gold standard reference test DSM interview]. Most studies included primarily adolescents (aged 12 to 18 years; mean age, 14.8 years); 4 studies included children as young as 7 years (mean age, 10.5 years). There were no studies that included children younger than 7 years, and there is limited evidence available on screening accuracy for the anxiety conditions that are more common in younger children. One study of children and adolescents with social anxiety disorder provided data separately for children aged 8 to 12 years and adolescents aged 13 to 17 years, with similar results in both age groups. In studies that reported sex, the percentage of female participants ranged from 43% to 63%. Four studies reported race or ethnicity, with the percentage of youth from underrepresented groups ranging from 1% to 58%.

Studies used 12 screening instruments to screen for 6 anxiety conditions (global anxiety, GAD, panic disorder, separation anxiety, social anxiety disorder, and any anxiety disorder). Some screening instruments with subscales screened for more than 1 anxiety disorder. Only 1 or 2 studies used each screening instrument for a given disorder. Although a variety of different screening instruments were assessed, 2 are widely used in practice for detecting anxiety: SCARED and the Social Phobia Inventory. The reference standard was a structured clinical interview for anxiety diagnosis.

Screening accuracy varied by condition screened for and specific screening test and threshold used. For example, sensitivity for detection of GAD ranged from 0.50 to 0.88 and specificity ranged from 0.63 to 0.98 (based on 3 studies). For social anxiety disorder, the ranges were narrower, with a sensitivity ranging from 0.67 to 0.93 and specificity ranging from 0.69 to 0.94; 4 of 5 studies found a sensitivity of 0.78 or greater and a specificity of 0.74 or greater. Across all of the screening instruments and subscales and thresholds for a positive test evaluated, sensitivity ranged between 0.34 and 1.00; specificity ranged between 0.47 and 0.99. Confidence intervals were wide and imprecise. The number of false-positive results also varied. For example, false-positive results per 1000 persons screened ranged from 17 to 361 for GAD and from 104 to 254 for social anxiety disorder. No additional analyses were available on populations by age, sex, or race or ethnicity."

[2] USPSTF definition of fair-quality: Generally comparable groups are assembled initially, but some question remains on whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is lacking for RCTs.

Table 1. Accuracy of Screening Instruments for Screening for Anxiety

Condition	Screener	Age range, y	No. of studies	Sensitivity	Specificity
Generalized anxiety disorder	PHQ-A	13-18	1[24]	0.50	0.98
	SCARED-GAD subscale	7-14	1[25]	0.64	0.63
	PI-ED-anxiety subscale	8-17	1[26]	0.88	0.85
Panic disorder	ANSQ (various thresholds)	12-18	1[27]	1.00	0.47-0.65
	PHQ-A	13-18	1[24]	0.42	0.99
Separation anxiety disorder	SCARED-SAD subscale	7-14	1[25]	0.88	0.73
Social anxiety disorder	SCARED-social phobia scale (various thresholds)	8-16	1[21]	0.78-0.83	0.69-0.81
	SAS (various thresholds)	8-18	2[21,23]	0.75-0.93	0.74-0.80
	SAS-A	12-18	1[23]	0.93	0.79
	SPAI-Brief	12-18	1[23]	0.86	0.88
	SPIN/Mini-SPIN (various thresholds)	12-17	3[28-30]	0.80-0.86	0.77-0.85
	SWQ (various thresholds)	13-17	1[21]	0.67-0.83	0.84-0.94
Any anxiety disorder	SCARED	7-18	2[24,25]	0.50-0.88	0.56-0.98

Abbreviations: ANSQ, Autonomic Nervous System Questionnaire; PHQ-A, Patient Health Questionnaire for Adolescents; PI-ED, Paediatric Index of Emotional Distress; SAS, Social Anxiety Scale; SAS-A, Social Anxiety Scale for Adolescents; SCARED, Screen for Child Anxiety Related Disorders; SCARED-GAD, Screen for Child Anxiety Related Disorders–Generalized Anxiety Disorder; SCARED-SAD, Screen for Child Anxiety Related Disorders–Separation Anxiety Disorder; SPAI, Social Phobia and Anxiety Inventory; SPIN, Social Phobia Inventory; SWQ, Social Worries Questionnaire.

USPSTF concluded that anxiety screening instruments addressed in the systematic review are heterogeneous; and upon detailed inspection of the systematic review, we agree that the data for the instruments is insufficient and heterogenous to combine statistically and to conduct a GRADE assessment.

While the USPSTF have not provided a recommendation about screening tests, they concluded that anxiety screening tools alone are not sufficient to diagnose anxiety, which requires diagnostic assessment and follow up.

Assessment of severity was not addressed.

The additional cross-sectional study (low risk of bias) identified by the search assessed the diagnostic accuracy of the Generalised Anxiety Disorder-7 scale (GAD-7) in adolescents aged 12 - 19 years compared to gold standard diagnosis with the Portuguese version of the MINI International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). At a cut off of 5 on the GAD-7, the sensitivity and specificity were 0.78 and 0.80, respectively, and the AUC was 0.84 (0.79–0.89). The SDQ Internalizing Subscale – anxiety was analysed at a cut off of 10 and resulted in sensitivity and specificity of 0.74 and 0.72, respectively and an AUC of 0.78 (0.73–0.84) [12].

1.3 Diagnostic accuracy

1.3.1 Methods

1.3.1.1 Selection criteria and definitions

What is the diagnostic accuracy of methods/tools/scales/ instruments, compared to gold standard diagnosis based on DSM or ICD criteria, for diagnosis of anxiety or to determine severity/level of anxiety in children and young people?

Population	
We will include studies in groups of children and young people (0-18) in any setting or geographical location that are representative of the general population.	**We will not** include studies in adults (18+) or that are not representative of the general population ie. have been diagnosed with an existing DSM condition. Studies that discriminate by using data from general group v clinical group.
Index test	
We will include studies that assess the diagnostic accuracy of methods/tools/ instruments to diagnose anxiety.	
Gold standard reference test	
We will include studies that assess ALL participants using the following as the gold standard reference test: Diagnosis of anxiety by healthcare professional or trained lay interviewer on the basis of universally screening the whole study population. Diagnostic interview using DSM (DSM III, III-R, IV and IV-TR) (APA 1980; APA 1987; APA 1994; APA 2000) or of ICD9 and ICD10 (WHO 1978, WHO 1992) for anxiety disorder, including one or more disorders of GAD, over-anxious disorder, SAD, SOP or PD.	**We will not** include studies in which anxiety diagnosis is based purely on self-report/questionnaire or where the anxiety diagnosis is based on previously noted diagnoses and the whole study population groups are not formally assessed.
Outcome measures to determine diagnostic accuracy	
We will include data for AUC or ROC curves, sensitivity and specificity.	**We will not** include any other type of data.
Study design	
We will include cohort or cross-sectional studies.	**We will not** include case control or case series studies, editorials, letters, commentaries.
Limits	
Studies reported in English language. No date limit unless a current high quality systematic review is identified by the search.	

1.3.1.2 Search strategy

Date of search: 23rd January 2023

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to January 20, 2023>

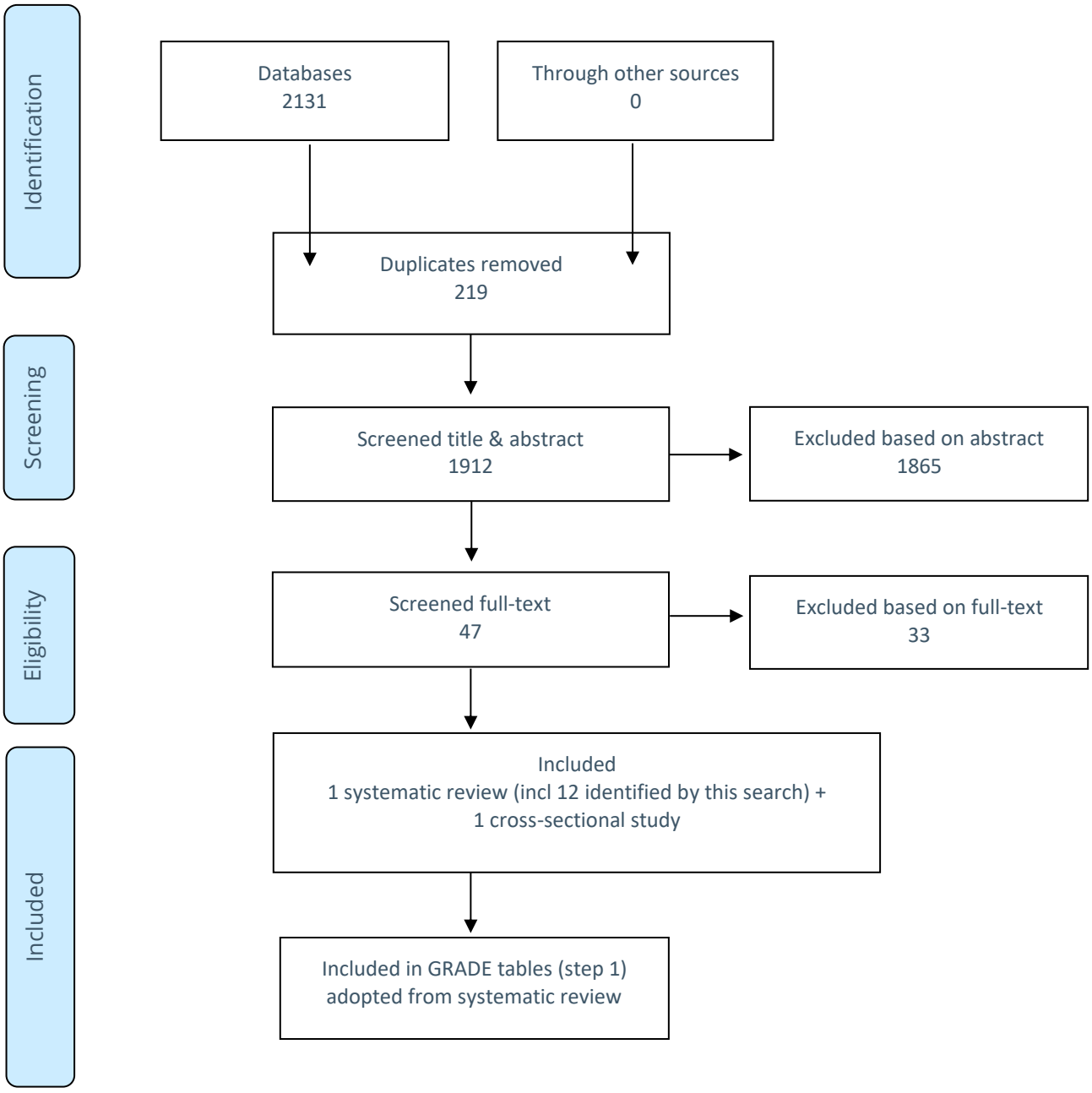
1 checklist/ or interview/ or interview, psychological/ or needs assessment/ or nursing assessment/ or "outcome and process assessment (health care)"/ or "outcome assessment (health care)"/ or exp personality assessment/ or "predictive value of tests"/ or exp psychiatric status rating scales/ or exp psychological tests/ or questionnaires/ or risk assessment/ or screening test/
2 (index or instrument$ or interview$ or inventor$ or item$ or measure$1 or questionnaire$ or scale$ or score$ or screen$ or self report$ or subscale$ or survey$ or tool$ or test form$).ti,ab.
3 1 or 2
4 di.fs. or exp diagnosis/ or mass screening/ or nursing diagnosis/
5 (detect$ or diagnos$ or identif$ or psychodiagnos$ or recogni$ or screen$).ti,ab.
6 4 or 5
7 (3 and 6) or (casefind$ or ((case or tool$) adj (find$ or identif$))).ti,ab.
8 "area under curve"/ or "predictive value of tests"/ or "reproducibility of results"/ or roc curve/ or "sensitivity and specificity"/ or validation studies/
9 (accurac$ or accurat$ or area under curve or auc value$ or (likelihood adj3 ratio$) or (diagnostic adj2 odds ratio$) or ((pretest or pre test or posttest or post test) adj2 probabilit$) or (predict$ adj3 value$) or receiver operating characteristic or (roc adj2 curv$) or reliabil$ or sensititiv$ or specificit$ or valid$).tw.
10 8 or 9
11 exp case control studies/ or exp cohort studies/ or cross-sectional studies/ or epidemiologic studies/
12 ((epidemiologic$ or observational) adj (study or studies)).ti,ab.
13 (cohort$1 or cross section$ or crosssection$ or followup$ or follow up$ or followed or longitudinal$ or prospective$ or retrospective$).ti,ab.
14 (case adj2 (control or series)).ti,ab.
15 or/11-14
16 3 and 7 and 10 and 15
17 exp Anxiety/
18 exp Anxiety Disorders/
19 (anxiety or anxious or panic or phobi$).ti,ab.
20 17 or 18 or 19
21 16 and 20
22 limit 21 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)")
23 limit 22 to "diagnosis (best balance of sensitivity and specificity)"
24 limit 23 to english language

Notes:

Translated searches for Embase, PsycInfo and All EBM on request.

This search was reviewed in October 2023, finding no new evidence to change recommendations.

1.3.2 Search results - PRISMA flowchart



1.3.3 Included studies

Of the 2131 articles retrieved from the multiple database search for screening and case identification studies, 234 duplicates were removed. Upon screening of the 1897 titles and abstracts, a current (searched June 2022) and comprehensive systematic review, commissioned to inform the US Preventive Services Task Force (USPSTF) evidence-based guideline, was identified [11]. The systematic review addressed screening, diagnosis, and treatment. Therefore, 196 titles and abstracts were screened to the beginning of 2021 and no later in an effort to avoid duplication of evidence synthesis completed in the systematic review. Of these, 31 full text articles were reviewed of which two articles met the selection criteria (one systematic review outlined above and one recent study).

The systematic review taken together with the corresponding evidence-based guideline provides sufficient detail about the methods, included studies, analysis, methodological quality, and certainty aligned with GRADE. Their findings and assessments have been adopted and summarised below. ***It is critical that this RCH guideline development group are familiar with the accompanying evidence statement of the USP GL***. The full evidence reviews are also available, and tables of quality assessments and results are in Appendix I of this document.

One recent study article has been assessed for quality and summarised narratively here.

1.3.4 Characteristics and risk of bias of included articles

Viswanathan 2022 (Systematic review to inform USPSTF guideline)

Study citation	Viswanathan, M., et al. (2022). "Screening for Anxiety in Children and Adolescents: Evidence Report and Systematic Review for the US Preventive Services Task Force." JAMA 328(14): 1445-1455.
External validity – selection criteria and characteristics of the systematic review	
Population, n=	Children and adolescents 18 years or younger 10 studies, n=3260
Selection criteria	Unselected primary care population, Primary care patients without known depression, anxiety disorders, or increased risk of suicide (including deliberate self-harm), or Comparable community-based population. “Screening interventions with or without additional provider or patient-facing elements such as referral support, treatment guidelines, symptoms monitoring, and standardized treatment. Screening tools must be brief standardized instruments designed to identify persons with major depressive disorder, anxiety disorders, or an increased risk of suicide; self-report with or without parental report), clinician administered, or electronically delivered (<5 minutes if clinician administered, <15 minutes if self-administered) instruments are eligible.” Sensitivity, specificity, or data to calculate one or both; or negative predictive value, positive predictive value, area under the curve/ area under the receiver operating characteristic/receiver operating characteristic, diagnostic odds/ likelihood ratios, Youden's index. Studies of diagnostic test accuracy.
Internal validity – risk of bias in systematic review methods	
Selection bias	Two independent reviewers screened articles but not known whether reviewers were blind to authors, institutions and affiliations in screening. The review does report detailed selection criteria.
Sampling & publication bias	A comprehensive search strategy is documented and includes gray literature.

Outcome bias	"For each included study, 1 reviewer abstracted relevant study characteristics and outcomes into a structured form. A second reviewer checked all data for completeness and accuracy. Methodological quality ratings for included studies from a prior AHRQ evidence review on anxiety treatment in youth were spot-checked and carried forward. All other studies were rated dually and independently using predefined criteria.	
Reporting bias	There is a detailed characteristics of included studies table and results of individual studies are summarised. The strengths and limitations of included studies and potential impact on the results were discussed and appropriate conclusions were made.	
Funding bias	Financial disclosures were reported.	
Comments	***The systematic review is sufficient to adopt the meta-analyses, GRADE and detailed risk of bias assessments.***	
Overall risk of bias of the systematic review	Low	Important criteria have been fulfilled and where criteria have not been fulfilled it is unlikely the conclusions of the study would be affected.

Lovero 2022 (Cross-sectional study)

Study citation	Lovero, K. L., et al. (2022). "Validation of brief screening instruments for internalizing and externalizing disorders in Mozambican adolescents." BMC Psychiatry 22(1): 549.	
External validity – selection criteria and characteristics of the study		
Patient/population/ participants	Adolescents aged 12 - 19 years.	
N	485	
Setting	Two secondary schools from lower and higher socioeconomic urban areas in peripheral and central regions of Maputo City, Mozambique.	
Index test	Generalised Anxiety Disorder-7 (GAD-7), Strengths and Difficulties Questionnaire (SDQ) Internalizing Subscale – anxiety.	
Reference standard	Diagnostic interviews for anxiety using the Portuguese version of the MINI International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), a structured diagnostic interview for DSM-IV and ICD-10 disorders.	
Outcomes	Criterion validity of GAD-7 and SDQ subscale – anxiety by ROC analysis. Outcomes not relevant to this evidence review were also measured.	
Internal validity – risk of bias (Based on QUADAS-2 TOOL and Cochrane diagnostic accuracy)		
Selection/spectrum bias	The spectrum of patients was representative of the patients who will receive the test in practice in Mozambique, and selection adopted a random sampling method of 2–3 classes (~ 100 students) per grade per school (two schools). There were apparently no exclusions as long as participants met the selection criteria.	
Classification/ verification bias	All participants were assessed with both index test and gold standard reference standard for diagnosis of anxiety, of which all received the same reference standard. All participants responded to the socio-demographics questionnaire first and were randomized to respond to either the screening battery or the MINI-KID next. Immediately following completion, a different interviewer administered the remaining measure.	
Detection bias	It is not clear whether the reference standard results were interpreted without knowledge of the results of the index test nor whether the index test results were interpreted without knowledge of the results of the reference standard test. The optimal cut-off score was determined by the highest Youden index. The index test and reference test were conducted on the same day.	
Attrition bias	493 eligible - 8 excluded due to incomplete consent form (1), incomplete interview (4) and because they were >19 (3).	
Report bias	All test results are reported.	
Other issues - applicability/ comparability / variation	Execution of all tests were described in sufficient detail to permit replication of the tests. Those undertaking the tests are similarly qualified, trained and experienced as would be the clinicians likely to undertake the tests in practice. Funding was declared. Appropriate statistical analysis was undertaken and reported.	
Overall risk of bias	Low	Most criteria have been fulfilled and the conclusions of the study are unlikely to be affected.

1.3.5 Findings

Please see below Appendix I: USPSTF systematic review/guideline key evidence review information. The results from the additional study identified by the search align with the USPSTF systematic review.

Study ID	Threshold	With anxiety	Without anxiety	Sensitivity	Specificity	AUC	Precision
Lovero 2022	GAD-7: 5	85	400	0.78	0.80	0.84	(0.79–0.89)
	SDQ Internalizing Subscale – anxiety: 10	As above		0.74	0.72	0.78	(0.73–0.84)

With and without anxiety based on MINI-KID

1.4 Risk factor predictive accuracy

1.4.1 Methods

1.4.1.1 Selection criteria and definitions

Are there high-risk groups of children and young people that should be screened for anxiety?

Population	
We will include studies in children and young people (0-18) in any setting or geographical location with and without the risk factor of interest.	**We will not** include studies in those with an existing diagnosis of anxiety; or in adults (18+).
Risk factors	
We will include studies that identify anxiety in groups of people with and without the following risk factors: *Comorbidities/personal medical history:* Neurodevelopmental disorders Intellectual disability Autism spectrum disorder (ASD) Mental health disorders Preterm children Family history of anxiety *Social/environmental factors:* Looked after children Secure estate Children not in mainstream schooling	**We will not** include studies that identify anxiety in groups of people with and without the following risk factors: Exposures such as paternal or maternal alcohol intake or pollutants Age of parent Birth weight
Outcome measures to determine high risk groups	
We will include studies that report raw effect sizes only – no data/confounders to be adjusted. Diagnosis of anxiety by healthcare professional or trained lay interviewer on the basis of universally screening the whole study population. Diagnostic interview using DSM (DSM III, III-R, IV and IV-TR) (APA 1980; APA 1987; APA 1994; APA 2000) or of ICD9 and ICD10 (WHO 1978, WHO 1992) for anxiety disorder.	We will not include studies in which anxiety diagnosis is based purely on self-report/questionnaire or where the anxiety diagnosis is based on previously noted diagnoses and the whole study population groups are not formally assessed.
Study design	
We will include cohort, case control and cross-sectional prevalence studies in which participants are divided into two groups by the presence/ absence of a specified risk factor and all participants are formally assessed for a diagnosis of anxiety.	We will not include cross-sectional prevalence studies that includes a population that is selected so as not to be generally representative of the risk factor population.
Limits	
Studies reported in English language. No date limit unless a current high quality systematic review is identified by the search.	

1.4.1.2 Risk factor predictive accuracy search strategy

Date of search: 9th February 2023

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to February 07, 2023>

1 ANXIETY DISORDERS/
2 *ANXIETY/di, pc, px, th
3 AGORAPHOBIA/ or PANIC DISORDER/ or ANXIETY, SEPARATION/
4 PHOBIC DISORDERS/ or PHOBIA, SOCIAL/
5 (agoraphobi* or generali#ed anxiety or GAD or separation anxiety or (social* adj2 (anxi* or fear*)) or phobi* or school refusal).ti,ab,kf.
6 anxiety.ab. /freq=3
7 panic.mp.
8 (anxiety adj5 (autism or autistic)).ti,ab,kf.
9 anxiety.mp. and (child development disorders, pervasive/px or autism spectrum disorder/px or autistic disorder/px
10 or/1-9
11 CHILD/ or CHILD, PRESCHOOL/
12 (infant? or child* or adolesc* or paediatr* or pediatr*).ti,ab.
13 (infant* or child* or boy* or girl* or kids or juvenil* or minors or paediatric* or pediatric* or adolesc* or preadolesc* or pubert* or pubescen* or prepube* or teen* or (young adj (survivor* or offender* or minorit*)) or youth* or school? or preschool* or nurser* or kindergarten).ti,ab.
14 (infant? or child* or adolesc* or paediatr* or pediatr*).ab. /freq=3
15 or/11-14
16 ((infant? or child* or adolesc* or p?ediatric* or teen* or young* or youth or school? or preschool*) adj2 anxi*).ti,ab.
17 15 or 16
18 incidence/ or prevalence/
19 Epidemiology/
20 (prevalen* or incidence* or epidemiolog*).ti,ab.
21 or/18-20
22 10 and 17 and 21
23 letter/
24 editorial/
25 news/
26 exp historical article/
27 Anecdotes as Topic/
28 comment/
29 case report/
30 (letter or comment*).ti.
31 or/23-30
32 randomized controlled trial/ or random*.ti,ab.
33 31 not 32
34 animals/ not humans/
35 Animals, Laboratory/
36 exp animal experiment/
37 exp animal model/
38 exp Rodentia/
39 (rat or rats or mouse or mice).ti.

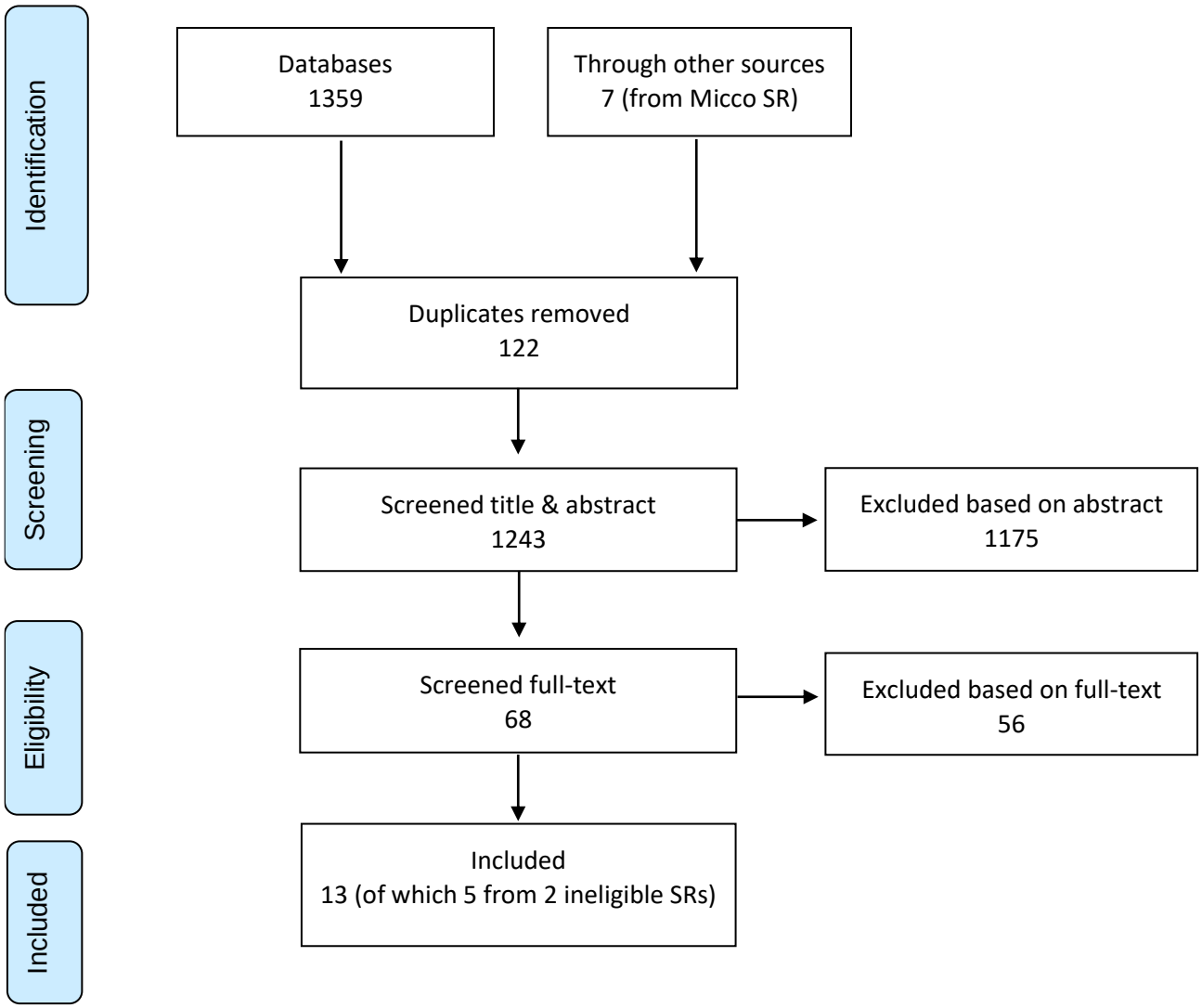
40 or/33-39
41 22 not 40
42 limit 41 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)")
43 limit 42 to (english language and humans)
44 exp COVID-19/
45 43 not 44
46 exp Risk Factors/
47 (risk adj2 anxi*).ti,ab.
48 ((comorbid or cooccurring) adj2 anxi*).ti,ab.
49 exp Comorbidity/
50 or/46-49
51 45 and 50
52 limit 51 to (address or autobiography or bibliography or biography or case reports or clinical conference or clinical trial, veterinary or comment or congress or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or interview or lecture or legal case or legislation or letter or news or newspaper article or observational study, veterinary or overall or patient education handout or periodical index or personal narrative or portrait or randomized controlled trial, veterinary or "research support, american recovery and reinvestment act" or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs or "scientific integrity review" or twin study or video-audio media or webcast)
53 51 not 52

Notes:

Translated searches for Embase, PsycInfo and All EBM on request.

This search was reviewed in October 2023, finding no new evidence to change recommendations.

1.4.2 Search results - PRISMA flowchart



1.4.3 Included studies

Prioritised risk factors were based on a narrative review of prevalence of anxiety >50% in non-control/potential high risk populations (see Appendix II).

Of the 1359 articles retrieved from the multiple database search for predictive accuracy studies, 122 duplicates were removed. Upon screening of the 1243 titles and abstracts, two systematic reviews with were identified however not all included studies met the selection criteria for this evidence review and risk of bias of included studies was not performed. The studies in the meta-analysis that met the selection criteria for this evidence review (5 articles) were assessed and synthesised with articles identified by the current search. Sixty-eight full text articles from the current search were reviewed of which eight articles met the selection criteria. A total of 13 articles are described and synthesised below.

1.4.4 Characteristics, risk of bias, data and GRADE of included studies

Study	Population	Reference test: anxiety diagnosis	Index test and threshold for risk factor	Number of CYP with anxiety		Risk factor effect size [95% CI] where reported for single studies	Risk of bias (ROB) and GRADE certainty
				With risk factor	Without risk factor		
Bitsika 2015 Cross-sectional prevalence **ASD**	Young males with and without ASD recruited from a local parent support group and schools on the Gold Coast, Queensland, Australia Mean age = 11.2±3.3yrs, range 6 -18 yrs, plus one of their parents for ASD group only (15 fathers, 125 mothers)	Clinical interview: KIDSCID and CASI	Clinical interview: DSM-5 criteria for ASD, plus family history.	ASD n=140	No ASD n=50	Not reported	Moderate ROB ⊕⊕◯◯ LOW A study of low certainty suggests that CYP with ASD may have a higher percentage of anxiety, particularly GAD, than those without ASD. [7]
		GAD		20.9%	0%		
		Specific phobia		16.8%	1%		
		Panic disorder		0%	0%		
		Social phobia		7.3%	1%		
		Separation anxiety disorder		5.8%	1.6%		
Blank 2015 Cross-sectional prevalence **Insomnia**	Population-based representative sample of adolescents (13-18yrs) across United States	Interview: DSM-IV using WHOCIDI – 1188 with separation, panic, phobias, GAD & *posttraumatic stress disorder*	Interview: DSM-IV - difficulty initiating sleep (DIS), maintaining sleep (DMS), early morning awakening (EMA)	Insomnia n=4,359 33.4%	No Insomnia n=2,124 NR	OR 3.44 [2.63–4.50]	Moderate ROB ⊕⊕◯◯ LOW A study of low certainty suggests that CYP with insomnia may have a higher risk of anxiety than those without insomnia. [8]
Gau 1999 Case control **Sleep terrors and sleep walking**	Junior high school students (13-15yrs) in Taipei City, Taiwan Mean age =14 yrs, 4.1 m ± 11m	Psychiatric interview: Chinese-version of the Kiddie- SADS-E	Psychiatric interview: DSM-III-R – sleep symptoms in previous year	Sleep terrors/ walking n=21	No sleep terrors/ walking n=30		Low ROB ⊕⊕⊕◯ MODERATE A small study of moderate certainty suggests CYP who

		GAD	1	0	OR 4.46 [0.22–91.53]	experience sleep terrors and/or sleep walking may have an increased risk of anxiety than those without sleep issues. [9]
		Separation anxiety disorder	2	0	OR 7.82 [0.53–115.06]	
		Panic disorder	3	0	OR 11.54 [0.95–139.59]	
		Social phobia	2	3	OR 0.95 [0.14–6.34]	
		Simple phobia	7	0	OR 31.55 [3.87–257.31]	
		Overanxious disorder	11	2	OR 15.40 [3.55–66.85]	
Gundogdu 2019 Cross-sectional prevalence **Cystic fibrosis**	CYP with cystic fibrosis (CF) and matched controls without any chronic disease (8-16 years) from Marmara university outpatient clinic, Turkey.	Clinical interview using K-SADS Clinical interview with questions specific to CF and FEV from medical records.	CF n=32	No CF n=33	Not reported	High ROB ⊕◯◯◯ VERY LOW A small study of very low certainty suggests that CYP with cystic fibrosis may have higher risk of anxiety disorder (p=0.007) and specific phobia (p=0.005). There was no statistically significant difference between CYP with and without cystic fibrosis for separation anxiety (p=0.054), social anxiety (p=0.303) or GAD (p=0.427). [10]
		Anxiety disorder p=0.007 Preadolescents p=0.038 Adolescents p=0.097	15 (46.9%) 9 (45.0) 6 (50.0)	5 (15.2) 3 (15.0) 2 (15.4)		
		Separation anxiety disorder p=0.054 Preadolescents p=0.342 Adolescents p=0.220	6 (18.8) 4 (20.0) 2 (16.7)	1 (3.0) 1 (5.0) 0 (0.0)		
		Social anxiety disorder p=0.303 Preadolescents p=1.000 Adolescents p=0.322	6 (18.8) 3 (15.0) 3 (25.0)	3 (9.1) 2 (10.0) 1 (7.7)		
		Specific phobia p=0.005 Preadolescents p=0.047 Adolescents p=0.220	7 (21.9) 5 (15.0) 2 (16.7)	0 (0.0) 0 (0.0) 0 (0.0)		
		Generalized anxiety disorder p=0.427 Preadolescents p=1.000 Adolescents p=0.593	4 (12.5) 2 (10.0) 2 (16.7)	2 (6.1) 1 (5.0) 1 (7.7)		

Vardar 2011 Cross-sectional **Eating disorders (ED)**	Stratified random sampling of 10th and 11th grade high school students from Edirne, Turkey. Mean age: ED 17.04 ± 0.8 years Control 16.9 ± 0.7 years	Clinical interview: SCID-OP Controls SCID-NP	Clinical interview: EAT + DSM-IV Controls only EAT	ED n=68	No ED n=68	Not reported	Moderate ROB ⊕⊕◯◯ LOW A study of low certainty suggests that it is unclear whether CYP with eating disorders have a higher risk of anxiety. [13]
		Generalized Anxiety Disorder		6 (8.8)	1 (1.5)		
		Social Phobia		4 (5.9)	-		
		Panic Disorder		1 (1.5)	-		
Beidel 1997 Cross-section of longitudi-nal study **Parents with anxiety disorder and/or depression**	Parents (of 7-12 y/o) with anxiety from anxiety clinics in South Carolina and controls (and a minority of patients with a disorder) from newspaper ads, United States *2 parents had OCD*	Interview: K-SADS	Interview: SCID – DSM-III-R	Anxiety	No anxiety n=48	Not reported for depression, data for anxiety alone and depression alone has been used in meta-analyses.	Low ROB Depression: ⊕⊕⊕◯ MODERATE A small study of moderate certainty suggests that it is unclear whether CYP of parents with depression or CYP of parents with depression and anxiety have a higher risk of anxiety. [3]
		Offspring of parents with anxiety n=28					
		Specific phobia		1 (4)	2 (4)		
		Social phobia		-	1 (2)		
		Overanxious disorder/GAD		6 (21)	1 (2)		
		Separation anxiety		1 (4)	-		
		Avoidant disorder		1 (4)	-		
		Offspring of parents with depression n=24					
		Specific phobia		1 (4)	2 (4)		
		Social phobia		3 (13)	1 (2)		
		Overanxious disorder/GAD		-	1 (2)		
		Separation anxiety		1 (4)	-		
		Avoidant disorder		-	-		
		Offspring of parents with anxiety and depression n=29					
		Specific phobia		1 (3)	2 (4)		
		Social phobia		2 (7)	1 (2)		
		Overanxious disorder/GAD		1 (3)	1 (2)		
		Separation anxiety		-	-		
		Avoidant disorder		1 (3)	-		
Capps 1996 Cross sectional **Parents with**	Parents (of 8-14 y/o) with agoraphobia from Anxiety Disorders Treatment	Interview: DISC-2.1	Interview: ADIS-R	Anxiety n=16 11 (68)	No anxiety n=16	Not reported, data has been used in meta-	Moderate ROB

agoraphobia	Program at UCLA and controls from a private school in SoCal, United States			(one or more types of anxiety)	0 (anxiety, one did have ODD)	analysis.	
McClellan 1990 Cross-sectional **Parents with panic disorder** or **depression**	Parents with and without DSM III disorders -panic disorder and depression at University Washington, and school parents, United States	Interview: DICA and DICA-P (overanxious or separation anxiety disorder)	Interview: DIS	PD n=60 Depression n=56	No DSM n=47	Not reported for depression, data for panic disorder has been used in meta-analyses.	Low ROB Depression: ⊕⊕⊕◯ MODERATE A study of moderate certainty suggests that CYP of parents with depression have a higher risk of anxiety. [2]
		Offspring of parents with panic disorder p<0.05		14 (23)	3 (06)		
		Offspring of parents with depression p<0.05		15 (27)	3 (06)		
Turner 1987 Cross-sectional **Parents with anxiety disorder - agoraphobia or OCD**	Parents (of 7-12 y/o) with agoraphobia or OCD from Anxiety Disorders Clinic and without solicited through advertisements in Pittsburgh, United States	Interview: CAS	Interview: ADIS	Anxiety n=16 7 (44)	No anxiety n=13 0	Not reported, data has been used in meta-analysis.	Low ROB
Diaz 2008 Cross-sectional **Parents with alcohol dependence (AD)**	Parents (of 6-17 y/o) who have alcohol dependence recruited from alcohol treatment centres and controls through schools from same localities, Spain	Clinical interview: DSM-IV	Clinical interview: DSM-IV	AD n=	No AD n=		Moderate ROB ⊕⊕◯◯ LOW A small study of low certainty suggests that it is unlikely that CYP of parents with alcohol dependence have a higher risk of anxiety. [14]
		Separation anxiety p=0.943		14 (4.2)	2 (1.5)	OR 0.9 [0.184–4.818]	
		Panic disorder p=0.853		1 (0.3)	-	OR 61.9 [0.00–5.3E+20]	
		Phobias (phobic disorder) p=0.624		7 (2.1)	-	OR 455,3[0.00–1.9E+13]	
		GAD (overanxious) p=0.614		16 (4.8)	-	OR 2020.1[0–1.5E+ 16]	
Merikangas	Parents (of 7-18 y/o) who	Interview: K-SADS-	Interview: SADS -	SD	No SD or	Not reported for	Low ROB

1998 Cross-sectional **Parents with substance disorder (SD)** or **anxiety disorder**	have used alcohol or substances recruited from several alcohol, drug, anxiety, and general treatment settings and controls through random digit dialling in Greater New Haven, United States	E	DSM-III and DSM-III-R	n=77 Anxiety n=58	anxiety n=57	SD, data for anxiety has been used in meta-analyses.	Substance disorder: ⊕⊕⊕◯ MODERATE A study of moderate certainty suggests that it is unclear that CYP of parents with substance disorder have a higher risk of anxiety.[1]
		Offspring of parents with substance disorder - alcoholism, drug use (anxiolytic, sedative, benzodiazepine), marijuana abuse/dependence					
		Anxiety disorders (not simple phobia)		10.4%	10.5%		
		GAD/Overanxious disorder		7.8%	5.3%		
		Panic disorder		0.0%	0.0%		
		Separation anxiety		2.6%	7.0%		
		Social phobia		1.3%	0.0%		
		Simple phobia		1.3%	3.5%		
		Offspring of parents with anxiety disorder - panic with or without agoraphobia, social phobia, GAD					
		Anxiety disorders (not simple phobia)		22.4% *13	10.5% *6		
		GAD/Overanxious disorder		12.1% *7	5.3% *3		
		Panic disorder		1.7% *1	0.0%		
		Separation anxiety		12.1% *7	7.0% *4		
		Social phobia		6.9% *4	0.0%		
		Simple phobia		6.9% *4	3.5% *2		
Black 2003 Cross-section of longitudi-nal study **Parents with OCD**	Parents with DSM-IV OCD from University of Iowa psychiatric out-patient and control parents via hospital newsletter, United States	Interview: DICA	Interview: SCID-IV (DSM-III-R)	OCD n=43	No OCD n=35	Not reported	Low ROB ⊕⊕⊕◯ MODERATE A study of moderate certainty suggests that CYP of parents with OCD have a higher risk of anxiety (p=0.019), particularly overanxious disorder (p=0.02) and separation anxiety (p=0.002). [6]
		Overanxious disorder p=0.02		13 (32)	3 (9)		
		Phobia p=NS		9 (21)	3 (9)		
		Separation anxiety disorder p=0.002		7 (17)	2 (6)		
		Any anxiety disorder p=0.019		22 (51)	9 (26)		
		Generalized Anxiety Disorder		6 (8.8)	1 (1.5)		
		Social Phobia		4 (5.9)	-		
		Panic Disorder		1 (1.5)	-		

1.4.5 Meta-analyses of risk of anxiety in CYP of parents with anxiety

Type of anxiety	No. studies	Risk factor cases	Controls	Odds ratio [95% CI]	P value	Heterogeneity I^2	Certainty
Anxiety not specified [1]	3 [4] [5]	31/90	6/86	10.87 [1.12, 105.54]	0.04	66%	⊕◯◯◯ VERY LOW
Generalised anxiety disorder	2 [1] [3]	15/86	4/105	4.53 [0.95, 21.67]	0.06	36%	⊕⊕⊕◯ MODERATE
Separation anxiety disorder	2 [1] [3]	8/86	4/105	2.10 [0.64, 6.96]	0.22	0%	⊕⊕⊕◯ MODERATE
Panic disorder	2 [1, 2]	15/118	3/104	2.10 [0.64, 6.96]	0.02	0%	⊕⊕⊕◯ MODERATE
Social phobia	2 [1] [3]	4/86	1/105	2.49 [0.15, 41.20]	0.52	39%	⊕⊕⊕◯ MODERATE
Phobic disorder	2 [1] [3]	5/86	4/105	1.52 [0.37, 6.27]	0.56	0%	⊕⊕⊕◯ MODERATE
Avoidant disorder	1 [3]	1/28	0/48	5.29 [0.21, 134.37]	0.31	NA	⊕⊕◯◯ LOW

1.4.6 Meta-analyses of risk of anxiety in CYP of parents with depression

Type of anxiety	No. studies	Risk factor cases	Controls	Odds ratio [95% CI]	P value	Heterogeneity I^2	Certainty
Anxiety not specified	2 [2] [3]	20/80	7/95	4.04 [1.54, 10.59]	0.004	0%	⊕⊕⊕⊕ HIGH

1.4.7 Excluded studies based on full text

Article	Reason for exclusion
Amiri S, Shafiee-Kandjani AR, Fakhari A, Abdi S, Golmirzaei J, Akbari Rafi Z, et al. Psychiatric comorbidities in ADHD children: an Iranian study among primary school students. Arch Iran Med. 2013;16(9):513-7.	No control group (for risk factor review)
Bentley, K. H., et al. (2021). "Validation of brief screening measures for depression and anxiety in young people with substance use disorders." Journal of Affective Disorders 282: 1021-1029.	Not general population and no control (for risk factor review)
Buss, K. A., et al. (2021). "Toddler dysregulated fear predicts continued risk for social anxiety symptoms in early adolescence." Development and Psychopathology 33(1): 252-263.	Not diagnostic accuracy
Cancilliere, M. K., et al. (2022). "Psychiatric Outcomes of Childhood Maltreatment: A Retrospective Chart Review from a Children's Psychiatric Inpatient Program." Child Psychiatry & Human Development 53(6): 1281-1292.	No useable data for anxiety
Capriola-Hall, N. N., et al. (2021). "Caution When Screening for Autism among Socially Anxious Youth." Journal of Autism & Developmental Disorders 51(5): 1540-1549.	No useable data for anxiety
Carlton, C. N., et al. (2022). "Screening for adolescent social anxiety: Psychometric properties of the Severity Measure for Social Anxiety Disorder." Child Psychiatry and Human Development 53(2): 237-243.	Not diagnostic accuracy
Carvajal-Velez, L., et al. (2023). "Validation of the Kriol and Belizean English Adaptation of the Revised Children's Anxiety and Depression Scale for Use With Adolescents in Belize." Journal of Adolescent Health 72(1S): S40-S51.	Not general population
Charlot, L. R., et al. (2022). "Psychiatric diagnostic dilemmas among people with intellectual and developmental disabilities." Journal of Intellectual Disability Research 66(10): 805-816.	Not diagnostic accuracy of an instrument
Chen LP, Murad MH, Paras ML, Colbenson KM, Sattler AL, Goranson EN, et al. Sexual abuse and lifetime diagnosis of psychiatric disorders: systematic review and meta-analysis. Mayo Clin Proc. 2010;85(7):618-29.	Insufficient diagnosis in included studies (for risk factor review)
Cheng J, Sun Y. Depression and anxiety among left-behind children in China: A systematic review. Child: Care, Health and Development. 2015;41(4):515-23.	Insufficient diagnosis (for risk factor review)
Chrisman SP, Whelan BM, Zatzick DF, Hilt RJ, Wang J, Marcynyszyn LA, et al. Prevalence and risk factors for depression, anxiety and suicidal ideation in youth with persistent post-concussive symptoms (PPCS). Brain Injury. 2021;35(12-13):1637-44.	No control group (for risk factor review)
Coffey BJ, Biederman J, Smoller JW, Geller DA, Sarin P, Schwartz S, et al. Anxiety disorders and tic severity in juveniles with Tourette's disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2000;39(5):562-8.	No control group (for risk factor review)
Dagar A, Falcone T. Psychiatric Comorbidities in Pediatric Epilepsy. Curr Psychiatry Rep. 2020;22(12):77.	Not a systematic review (for risk factor review)
Davidsen KA, Munk-Laursen T, Foli-Andersen P, Ranning A, Harder S, Nordentoft M, et al. Mental and pediatric disorders among children 0-6 years of parents with severe mental illness. Acta Psychiatrica Scandinavica. 2022;145(3):244-54.	Retrospective medical files (for risk factor review)
Derin, S., et al. (2022). "The role of adverse childhood experiences and attachment styles in social anxiety disorder in adolescents." Clinical Child Psychology & Psychiatry 27(3): 644-657.	Inappropriate diagnosis
Ding, X., et al. (2021). "Individual, Prenatal, Perinatal, and Family Factors for Anxiety Symptoms Among Preschool Children." Frontiers in Psychiatry 12 (no	Not diagnostic accuracy

pagination).	
Driessen J, Blom JD, Muris P, Blashfield RK, Molendijk ML. Anxiety in Children with Selective Mutism: A Meta-analysis. Child Psychiatry Hum Dev. 2020;51(2):330-41.	Not all studies had a control group or sufficient diagnosis (for risk factor review)
Eliacik K, Kanik A, Bolat N, Mertek H, Guven B, Karadas U, et al. Anxiety, depression, suicidal ideation, and stressful life events in non-cardiac adolescent chest pain: a comparative study about the hidden part of the iceberg. Cardiol Young. 2017;27(6):1098-103.	Insufficient diagnosis (for risk factor review)
Foley DL, Pickles A, Simonoff E, Maes HH, Silberg JL, Hewitt JK, et al. Parental concordance and comorbidity for psychiatric disorder and associate risks for current psychiatric symptoms and disorders in a community sample of juvenile twins. Journal of Child Psychology and Psychiatry. 2001;42(3):381-94.	No control group (for risk factor review)
Grant, M., et al. (2022). "Accuracy of a community mental health education and detection (CMED) tool for common mental disorders in KwaZulu-Natal, South Africa." International Journal of Mental Health Systems 16(1) (no pagination).	Inappropriate diagnosis
Helverschou, S. B., et al. (2021). "Psychometric properties of the Psychopathology in Autism Checklist (PAC)." International Journal of Developmental Disabilities 67(5): 318-326.	Inappropriate diagnosis
Hang., et al. (2022). "Assessing anxiety among adolescents in Hong Kong: Psychometric properties and validity of the Generalised Anxiety Disorder-7 (GAD-7) in an epidemiological community sample." BMC Psychiatry Vol 22 2022	Inappropriate age analysis
Jafferany M, Osuagwu FC, Khalid Z, Oberbarnscheidt T, Roy N. Prevalence and clinical characteristics of body dysmorphic disorder in adolescent inpatient psychiatric patients-a pilot study. Nordic Journal of Psychiatry. 2019;73(4-5):244-7.	Insufficient diagnosis (for risk factor review)
Jandac T, Stastna L. The prevalence of dual diagnoses in children and adolescents with substance use disorders, systematic review. Journal of Substance Use. 2023.	No useable data (for risk factor review)
Kemper, A. R., et al. (2021). "Screening for Anxiety in Pediatric Primary Care: A Systematic Review." Pediatrics 148(4): 10.	Systematic narrative review/no ROB
Kim JA, Szatmari P, Bryson SE, Streiner DL, Wilson FJ. The prevalence of anxiety and mood problems among children with autism and Asperger syndrome. Autism. 2000;4(2):117-32.	Insufficient diagnosis (for risk factor review)
Kovalenko PA, Hoven CW, Wu P, Wicks J, Mandell DJ, Tiet Q. Association between allergy and anxiety disorders in youth. Australian and New Zealand Journal of Psychiatry. 2001;35(6):815-21.	No useable data (for risk factor review)
Loades, M. E., et al. (2021). "How common are depression and anxiety in adolescents with chronic fatigue syndrome (CFS) and how should we screen for these mental health co-morbidities? A clinical cohort study." European Child & Adolescent Psychiatry 30(11): 1733-1743.	Not general population and no control (for risk factor review)
Marlow, M., et al. (2023). "Detecting Depression and Anxiety Among Adolescents in South Africa: Validity of the isiXhosa Patient Health Questionnaire-9 and Generalized Anxiety Disorder-7." Journal of Adolescent Health 72(1S): S52-S60.	Not general population
Martinez-Gonzalez, A. E., et al. (2022). "30-item version of the Revised Child Anxiety and Depression Scale in Chilean adolescents: Psychometric properties." Current Psychology: A Journal for Diverse Perspectives on Diverse Psychological Issues 41(7): 4231-4241.	Inappropriate diagnosis
Masi G, Millepiedi S, Mucci M, Poli P, Bertini N, Milantoni L. Generalized anxiety disorder in referred children and adolescents. Journal of the American Academy of Child & Adolescent Psychiatry. 2004;43(6):752-60.	No control group (for risk factor review)

Mathyssek CM, Olino TM, Verhulst FC, van Oort FV. Childhood internalizing and externalizing problems predict the onset of clinical panic attacks over adolescence: The TRAILS study. PLoS ONE Vol 7(12), 2012, ArtID e51564. 2012;7(12).	Insufficient diagnosis (for risk factor review)
Melegari MG, Sacco R, Manzi B, Vittori E, Persico AM. Deficient emotional self-regulation in preschoolers with ADHD: Identification, comorbidity, and interpersonal functioning. Journal of Attention Disorders. 2019;23(8):887-99.	Insufficient diagnosis (for risk factor review)
McLellan, L. F., et al. (2021). "The Youth Online Diagnostic Assessment (YODA): Validity of a new tool to assess anxiety disorders in youth." Child Psychiatry and Human Development 52(2): 270-280.	Not general population (based on interest in treatment trial)
Micco JA, Henin A, Mick E, Kim S, Hopkins CA, Biederman J, et al. Anxiety and depressive disorders in offspring at high risk for anxiety: a meta-analysis. Journal of Anxiety Disorders. 2009;23(8):1158-64.	No risk of bias, insufficient diagnosis in some studies (for risk factor review)
Moore SE, Scott JG, Ferrari AJ, Mills R, Dunne MP, Erskine HE, et al. Burden attributable to child maltreatment in Australia. Child Abuse & Neglect. 2015;48:208-20.	Modelling data (for risk factor review)
Orgiles, M., et al. (2022). "The Child Anxiety Life Interference Scale for Parents ((CALIS-P): Psychometric properties of the Spanish version." Current Psychology: A Journal for Diverse Perspectives on Diverse Psychological Issues 41(5): 3156-3164.	Not diagnostic accuracy
Park KJ, Lee JS, Kim HW. Medical and psychiatric comorbidities in Korean children and adolescents with attention-deficit/hyperactivity disorder. Psychiatry Investigation. 2017;14(6):817-24.	Retrospective medical files (for risk factor review)
Pilowsky DJ, Wickramaratne PJ, Rush AJ, Hughes CW, Garber J, Malloy E, et al. Children of currently depressed mothers: a STAR*D ancillary study. Journal of clinical psychiatry. 2006;Vol.67(1):126-36p.	No control group (for risk factor review)
Pontillo M, De Luca M, Pucciarini ML, Vicari S, Armando M. All that glitters is not gold: prevalence and relevance of psychotic-like experiences in clinical sample of children and adolescents aged 8-17 years old. Early Interv Psychiatry. 2018;12(4):702-7.	Inappropriate population group (for risk factor review)
Radez, J., et al. (2021). "Using the 11-item Version of the RCADS to Identify Anxiety and Depressive Disorders in Adolescents." Research on Child and Adolescent Psychopathology 49(9): 1241-1257.	Not general population and control group not diagnosed (for risk factor review)
Radtke, S., et al. (2022). "Increasing the Efficiency of Diagnostic Interviews for Childhood Anxiety Disorders Through Joint Child-Parent Administration." Journal of Psychopathology and Behavioral Assessment.	Inappropriate diagnosis
Rapee, R. M., et al. (2022). "Risk for social anxiety in early adolescence: Longitudinal impact of pubertal development, appearance comparisons, and peer connections." Behaviour Research and Therapy 154: 1-10.	Not diagnostic accuracy
Rapp, A. M., et al. (2022). "Psychometrics of the Multidimensional Anxiety Scale for Children in Latinx adolescents." Journal of Latinx Psychology 10(1): 71-79.	Not diagnostic accuracy
Reich W, Earls F, Frankel O, Shayka JJ. Psychopathology in children of alcoholics. Journal of the American Academy of Child & Adolescent Psychiatry. 1993;32(5):995-1002.	Insufficient diagnosis for risk factor review)
Reilly C, Kent E, Neville BG. Review: Psychopathology in childhood epilepsy. Child and Adolescent Mental Health. 2013;18(2):65-75.	No risk of bias (for risk factor review)
Robe, A., et al. (2022). "Factor structure and measurement invariance across age, gender, and clinical status of the screen for children anxiety related emotional disorders." European Journal of Psychological Assessment: No Pagination Specified.	Not diagnostic accuracy
Robinson C, Lao F, Chanchlani R, Gayowsky A, Darling E, Batthish M. Long-term hearing and neurodevelopmental outcomes following Kawasaki disease: A	Retrospective medical files (for risk factor review)

population-based cohort study. Brain & Development. 2021;43(7):735-44.	
Rodriguez-Menchon, M., et al. (2022). "Validation of the brief version of the Spence Children's Anxiety Scale for Spanish children (SCAS-C-8)." Journal of Clinical Psychology 78(6): 1093-1102.	Not diagnostic accuracy
Romano, I., et al. (2022). "Measurement invariance of the GAD-7 and CESD-R-10 among adolescents in Canada." Journal of Pediatric Psychology 47(5): 585-594.	Not diagnostic accuracy
Scott AJ, Sharpe L, Loomes M, Gandy M. Systematic review and meta-analysis of anxiety and depression in youth with epilepsy. Journal of Pediatric Psychology. 2020;45(2):133-44.	Insufficient diagnosis for control group (for risk factor review)
Shen M, Gao J, Liang Z, Wang Y, Du Y, Stallones L. Parental migration patterns and risk of depression and anxiety disorder among rural children aged 10-18 years in China: A cross-sectional study. BMJ Open. 2015;5(12) (no pagination).	Insufficient diagnosis (for risk factor review)
Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. Journal of the American Academy of Child & Adolescent Psychiatry. 2008;47(8):921-9.	No control group (for risk factor review)
Skarphedinsson, G., et al. (2021). "Diagnostic efficiency and validity of the DSM-oriented Child Behavior Checklist and Youth Self-Report scales in a clinical sample of Swedish youth." PLoS ONE [Electronic Resource] 16(7): e0254953.	Not general population (based on interest in treatment trial)
Skokauskas N, Gallagher L. Psychosis, affective disorders and anxiety in autistic spectrum disorder: prevalence and nosological considerations. Psychopathology. 2010;43(1):8-16.	No control group in any of the included studies (for risk factor review)
Soh, C. P., et al. (2021). "Caregiver- and child-reported anxiety using an autism-specific measure: Measurement properties and correlates of the anxiety scale for children with autism spectrum disorder (ASC-ASD) in verbal young people with ASD." Journal of Autism and Developmental Disorders 51(8): 2646-2662.	Not general population and no control (for risk factor review)
Somhovd MJ, Hansen BM, Brok J, Esbjorn BH, Greisen G. Anxiety in adolescents born preterm or with very low birthweight: A meta-analysis of case-control studies. Developmental Medicine & Child Neurology. 2012;54(11):988-94.	Insufficient diagnosis (for risk factor review)
Spence, S. H. and R. M. Rapee (2022). "The development and preliminary validation of a brief scale of emotional distress in young people using combined classical test theory and item response theory approaches: The Brief Emotional Distress Scale for Youth (BEDSY)." Journal of Anxiety Disorders 85: 102495.	Inappropriate diagnosis
Stahlberg T, Khanal P, Chudal R, Luntamo T, Kronstrom K, Sourander A. Prenatal and perinatal risk factors for anxiety disorders among children and adolescents: A systematic review. Journal of Affective Disorders. 2020;277:85-93.	Retrospective medical files and questionnaire (for risk factor review)
Sun CF, Mansuri Z, Trivedi C, Vadukapuram R, Reddy A. Homicidal ideation and psychiatric comorbidities in the inpatient adolescents aged 12-17. Frontiers in Psychiatry. 2022;13 (no pagination).	Retrospective medical files (for risk factor review)
Tangjittiporn, T., et al. (2022). "Psychometric properties of the Screen for Child Anxiety Related Disorders Thai version." Pediatrics International 64(1): e15093.	Not general population and no control (for risk factor review)
Tonmyr L, Williams G, Hovdestad WE, Draca J. Anxiety and/or depression in 10-15-year-olds investigated by child welfare in Canada. Journal of Adolescent Health. 2011;48(5):493-8.	No control group (for risk factor review)
van Steensel FJ, Bogels SM, Perrin S. Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis. Clin Child Fam Psychol Rev. 2011;14(3):302-17.	Not all studies have a control group or sufficient diagnosis (for risk factor review)
Vila G, Nollet-Clemencon C, de Blic J, Mouren-Simeoni M, Scheinmann P. Prevalence of DSM IV anxiety and affective disorders in a pediatric population	No diagnosis for controls (for risk factor review)

of asthmatic children and adolescents. Journal of Affective Disorders. 2000;58(3):223-31.	
Whitney DG, Peterson MD, Warschausky SA. Mental health disorders, participation, and bullying in children with cerebral palsy. Developmental Medicine & Child Neurology. 2019;61(8):937-42.	Insufficient diagnosis (for risk factor review)
Whitney DG, Warschausky SA, Peterson MD. Mental health disorders and physical risk factors in children with cerebral palsy: A cross-sectional study. Developmental Medicine & Child Neurology. 2019;61(5):579-85.	Insufficient diagnosis (for risk factor review)
Xiong, H., et al. (2021). "Prediction of anxiety disorders using a feature ensemble based bayesian neural network." Journal of Biomedical Informatics 123: 103921.	Not diagnostic accuracy
Yapici Eser H, Taskiran AS, Ertinmaz B, Mutluer T, Kilic O, Ozcan Morey A, et al. Anxiety disorders comorbidity in pediatric bipolar disorder: a meta-analysis and meta-regression study. Acta Psychiatrica Scandinavica. 2020;141(4):327-39.	Not all studies have a control group (for risk factor review)
Young, J., et al. (2021). "Psychometric properties of the Spanish Revised Child Anxiety and Depression Scale 25-item version in El Salvador." Journal of Psychopathology and Behavioral Assessment 43(2): 271-280.	Not diagnostic accuracy
Zemestani, M., et al. (2022). "Psychometric evaluation of the Intolerance of Uncertainty Scale for Children (IUSC): Findings from clinical and community samples in Iran." Assessment 29(5): 993-1004.	Not general population and no control (for risk factor review)
Zsido, A. N., et al. (2021). "Psychometric properties of the Social Interaction Anxiety Scale and the Social Phobia Scale in Hungarian adults and adolescents." BMC Psychiatry Vol 21 2021, ArtID 171 21.	Not diagnostic accuracy

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1.5 APPENDIX I – USPSTF systematic review/guideline key evidence review information

Diagnostic test accuracy screening instruments/index tests used in the studies

Instrument	Full Name	Description	Scoring, Range	Studies Using Instrument
ANS[77]	Autonomic Nervous System Questionnaire	5-item self-report measuring panic symptoms in the past 6 months. The first two items directly ask whether in the past 6 months the respondent has ever had a sudden spell or an attack of feeling frightened, anxious, or very uneasy and/or a spell or an attack with the heart racing, feeling faint, or an inability to catch one's breath. A "no" response to both questions is considered a negative screen. Items 3–5 for those who answered yes to one or two of the first questions ask about spontaneity, frequency, and anticipatory worry about panic attacks.	Each item on a 3-point scale (not at all worried, somewhat worried, or very worried). The total score range is 0 to 5.	Queen et al, 2012[73]
EDAS[78]	Escala para la Deteccion de Ansiedad Socia	A 26-item youth report that measures social anxiety. Items assess fear of speaking or acting in ways that would be embarrassing, youths' social avoidance, distress, and interference. Administration time is 16 minutes.	Two items are dichotomous, and the remaining items are on a 5-point scale (0 to 4). The nondichotomous items are summed for the total score ranging from 24 to 120.	Garcia-Lopez et al, 2015[67]
LSAS-CA[79]	The Liebowitz Social Anxiety Scale for Children and Adolescents	A youth-reported 24-item scale to measure social anxiety appropriate for children and adolescents. The screener assesses total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and performance avoidance. Administration time is 12 minutes.	The screener uses a 4-point Likert scale (0 to 3). Total scores range from 0 to 72.	Garcia-Lopez et al, 2015[67]
PHQ-A[80]	Patient Health Questionnaire-Adolescents	Derived from the original PRIME-MD screening questionnaire and clinical interview; PHQ-A is a 67-item self-administered questionnaire that can be administered in 5 minutes or less to assess anxiety and depressive disorders. Clinicians quickly review completed questionnaires and apply diagnostic algorithms, which appear at the bottom of the page of the printed page. The instrument is used to screen for panic disorder and GAD among other psychiatric disorders including depression and substance use.	NR	Johnson et al, 2002[69]
PI-ED	Paediatric Index of Emotional Distress – Total Scale; Anxiety Subscale; Depression Subscale	A brief, self-report screening tool based on HADS to measure 16 anxiety and depression symptoms that is suitable for children and adolescents ages 8 to 16 years. Items are scored on a 4-point scale from 3 to 0 (always, a lot of the time, sometimes, not at all).	Items are scored on a 4-point scale, 0 to 3 from "always" to "not at all." Total score ranges between 0 to 21.	O'Connor et al, 2016[72]

Instrument	Full Name	Description	Scoring, Range	Studies Using Instrument
		Includes a total score, an anxiety subscale and a depression subscale.		
SCARED[81-83]	Screen for Anxiety Related Emotional Disorders	41-item parent and child self-report measure used to screen for anxiety disorders in children ages 8 to 18 years. A total score is available as well as for the following scales: GAD, separation anxiety disorder, panic disorder, and social anxiety disorder. Administration time is 10 minutes. A 10-item short form is also available.	Each item is rated on a 3-point scale ranging from 0 to 2 ("almost never," "sometimes," "often"). Score ranges from 0 to 82. Total score > 25 may indicate anxiety disorder; subscale scores also available (panic: score of 7 or more; GAD: score of 9 or more; social anxiety: score of 8 or more; separation anxiety: score of 5 or more).	Bailey et al, 2006[64] Canals et al, 2012[65] Muris et al, 2001[71]
SAS[84,85]	Social Anxiety Scale	An 18-item screener plus four filler items used to assess social anxiety in children in relation to peers. It includes three scales: Fear of Negative Evaluation, Social Avoidance and Distress-Specific to New Peers and New Situations, and General Social Avoidance and Distress. Includes both a child and adult report version. The SAS for Adolescents (SAS-A) is a revision of the SAS to make it developmentally appropriate for adolescents. SAS-A includes 18 items and same three scales with both an adolescent and parent version.	Each item on a 5-point scale ("not at all" to "all the time"). Total score ranges from 18 to 90.	Bailey et al, 2006[64] Garcia-Lopez et al, 2015[67]
SASA[86]	Social Anxiety Scale for Adolescents (Slovenian measure)	28-item instrument measuring social anxiety with two scales: one measuring fears, worries, and anticipation of a negative peer evaluation and the second assessing social tension/relaxation, speech or behavior inhibition, and readiness to exposure in social situations. Administration time is 12 minutes.	All items are on a 5-point scale. The total score ranges from 28 to 140.	Garcia-Lopez et al, 2015[67]
SoPhI[87]	Social Phobia Inventory	A 21-item scale to assess social anxiety using DSM-IV criteria including an item assessing duration of symptoms (social anxiety must be present for at least 6 months). Administration time is 10 minutes.	All items are rated on a 5-point scale, with the total score ranging from 21 to 105.	Garcia-Lopez et al, 2015[67]
SPAI-B[88]	Social Phobia and Anxiety Inventory - Brief	16-item scale measuring social anxiety in adolescents. The screener assesses cognitive, somatic, and behavioral symptom. Administration time is 9 minutes.	Each item is rated on a 5-point Likert scale. The total ranges from 0 to 64.	Garcia-Lopez et al, 2015[67]
SPIN[89] Mini-SPIN[90,91]	Social Phobia Inventory/Mini Social Phobia Inventory	17 items measuring behavioral, physiological, and cognitive symptomatology associated with social anxiety; fear in social situations; avoidance of	Each item is rated on a 5-point 0 to 4 scale ("not at all" to " extremely"), with	Garcia-Lopez et al, 2015[67]

Instrument	Full Name	Description	Scoring, Range	Studies Using Instrument
		performing in social situations; and physiological discomfort in social situations. Time to administer is 8 minutes. The MiniSPIN is a 3-item version of the scale measuring avoidance and fear of embarrassment.	a total score ranging from 0-68 for the full instrument and from 0 to 12 for the Mini SPIN.	Ranta et al, 2007[74] Ranta et al, 2012[75] Tsai et al, 2009[76]
SWQ[92]	Social Worries Questionnaire	10-item parent-report screener to assess social anxiety symptomatology in youth ages 8 to 17 years. It measures the degree to which the youth avoids or worries about particular social situations.	Each item on a 3-point scale (not true to mostly true). Total scores range from 0 to 20.	Bailey et al, 2006[64]

Abbreviations: DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; GAD=generalized anxiety disorder; KQ=key question; MiniSPIN= Mini-Social Phobia Inventory; NR=not reported; PRIME-MD=Primary Care Evaluation of Mental Disorders.

Diagnostic test accuracy gold reference standard instruments used in the studies

Reference Measure	Description	Studies Using Reference Measure
Anxiety Disorders Interview Schedule for DSM: Child and Parent Version (ADIS C/P)	A semi-structured interview designed to diagnosis anxiety disorders as well as depression and behavioral disorders based on DSM criteria for children and adolescents.	Bailey et al, 2006;[64] Garcia-Lopez et al, 2015;[67] Queen et al, 2012;[73]
Computerized Diagnostic Schedule for Children (C-DISC)	A structured diagnostic instrument that can be self-completed. It covers diagnoses for anxiety disorders, mood disorders, disruptive disorders, and miscellaneous disorders.	O'Connor et al, 2016[72]
Diagnostic clinical interview	Diagnostic clinical interview with mental health professional that includes items from the Structured Clinical Interview for DSM-III-R, PRIME-MD Clinical Evaluation Guide, and DSM-IV Global Assessment of Functioning.	Johnson et al, 2002[69]
Mini-Neuropsychiatric Interview for Kids (MINI-Kid)	A structured diagnostic interview for children and adolescents based on DSM and ICD-10 criteria that is used to diagnose 23 Axis 1 disorders.	Canals et al, 2012;[65] Tsai et al, 2009[76]
Schedule for affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (K-SADs-PL)	A semi-structured clinical interview that covers 32 DSM child and adolescent diagnoses including both MDD and anxiety disorders such as panic disorder, SepAD, SocAD, and GAD.	Ranta et al, 2007;[74] Ranta et al, 2012;[75]
Structured Clinical Interview for DSM-IV for Children (K-SCID)	K-SCID for DSM-IV generates DSM-IV diagnoses on children, with probe questions to facilitate assessing whether diagnostic criteria are met.	Muris et al, 2001[71]

Abbreviations: DSM=Diagnostic and Statistical Manual of Mental Disorders; GAD=generalized anxiety disorder; ICD-10=International Classification of Diseases, Tenth Revision; KQ=key question; PRIME-MD= Primary Care Evaluation of Mental Disorders; SepAD=separation anxiety disorder; SocAD=social anxiety disorder.

Results of diagnostic test accuracy of screening index tests for anxiety compared with gold standard reference structured clinical interview

Author, Year Quality	Age Range; Mean Age (SD), Years	Total N (% Female)	Index Test Cutoff[a]	Respondent	Prevalence %	Sensitivity (95% CI)	Specificity (95% CI)	Per 1,000 Screens Across a Prevalence From 3% to 13%	
								No. False-Negatives	No. False-Positives
Anxiety (Global, that is positive on total anxiety score)									
Screen for Child Anxiety Related Emotional Disorders (SCARED)									
Canals et al, 2012[65] Fair	11 (1.0) 9 to 13	562 (55)	SCARED-C Cutoff ≥ 25)	Youth	24	0.76 (0.68 to 0.92)	0.68 (0.63 to 0.72)	6 to 31	278 to 312
			SCARED-P Cutoff ≥ 17	Parents	24	0.63 (0.54 to 0.74)	0.70 (0.65 to 0.74)	9 to 48	261 to 293
			SCARED-C Short Cutoff ≥ 3	Youth	24	0.67 (0.59 to 0.74)	0.74 (0.70 to 0.78)	8 to 43	226 to 254
			SCARED-P Short Cutoff ≥ 3	Parents	24	0.34 (0.26 to 0.42)	0.86 (0.82 to 0.89)	17 to 86	122 to 137
GAD									
Patient Health Questionnaire—Adolescent (PHQ-A)									
Johnson et al, 2002[69] Fair	16 (1.2) 13 to 18	403 (63)	PHQ-A Cutoff NR	Youth	2.5	0.50 (0.24 to 0.76)	0.98 (0.86 to 0.99)	13 to 65	17 to 20
SCARED—GAD Scale									
Muris et al, 2001[71] Fair	10 (1.4) 7 to 14	82 (61)	SCARED-C Male cutoff ≥ 10 Female cutoff ≥ 13	Youth	13	0.64 (0.35 to 0.85)	0.63 (0.52 to 0.74)	9 to 47	322 to 361
Paediatric Index of Emotional Distress (PI-ED)—Anxiety Scale									
O'Connor et al, 2016[72] Fair	12 (2.5) 8 to 17	100 (48)[1]	PI-ED Cutoff >=9)	Youth	6	0.88[b] (0.53 to 98)	0.85 (0.78 to 0.90)	3 to 16	130 to 146
Panic Disorder									
Autonomic Nervous System Questionnaire (ANS)									
Queen et al, 2012[73] Fair	14 (1.8) 12 to 17	45 (43)[†]	ANS 2 questions (cutoff ≥ 1)	Youth	NR	1.00 (NR)	0.47 (NR)	0 to 0	461 to 517
			ANS 3 questions (cutoff ≥ 2)	Youth	NR	1.00 (NR)	0.57 (NR)	0 to 0	374 to 419
			ANS 5 questions (cutoff ≥ 3)	Youth	NR	1.00 (NR)	0.65 (NR)	0 to 0	304 to 341
Patient Health Questionnaire—Adolescent (PHQ-A)									
Johnson et al, 2002[69]	16 (1.2)	403	PHQ – A	Youth	3	0.42	0.99	15 to 75	9 to 10

Author, Year Quality	Age Range; Mean Age (SD), Years	Total N (% Female)	Index Test Cutoff[c]	Respondent	Prevalence %	Sensitivity (95% CI)	Specificity (95% CI)	Per 1,000 Screens Across a Prevalence From 3% to 13%	
								No. False-Negatives	No. False-Positives
Fair	13 to 18	(63)	Cutoff NR			(0.19 to 0.68)	(0.97 to 1.0)		
Separation Anxiety Disorder									
Screen for Child Anxiety Related Emotional Disorders (SCARED)-Separation Anxiety Disorder Scale									
Muris et al, 2001[71] Fair	10 (1.4) 7 to 14	82 (61)	SCARED-C Male cutoff ≥ 10 Female cutoff ≥ 12	Youth	10	0.88 (0.52 to 0.98)	0.73 (0.62 to 0.82)	3 to 16	235 to 263
Social Anxiety Disorder									
Screen for Child Anxiety Related Emotional Disorders (SCARED)—Social Phobia Scale									
Bailey et al, 2006[64] Fair	Children Mean: NR 8 to 12 Adolescents 14 (1.3) 13 to 16	101 89 (49)[a]	SCARED-SP cutoff ≥5 SCARED-SP Cutoff ≥ 6	Parents Parents	9 13	0.78 (0.45 to 0.94) 0.83 (0.55 to 0.95)	0.69 (0.59 to 0.78) 0.81 (0. 71 to 0.88)	6 to 29 4 to 22	226 to 254 165 to 185
Social Anxiety Scale (SAS) Children/Adolescents									
Bailey et al, 2006[64] Fair	Children Mean: NR 8 to 12 Adolescents 14 (1.3 13 to 17	101 89 (49)[a]	SAS-C Cutoff ≥ 45 SAS-A Cutoff ≥ 47	Parents Parents	9 13	0.78 (0.45 to 0.94) 0.75 (0.47 to 0.91)	0.74 (0.65 to 0.82) 0.80 (0.69 to 0.87)	6 to 29 6 to 32	148 to 166 174 to 195
Garcia-Lopez et al, 2015[67] Fair	15 (1.3) 12 to 18	1,034 (54)	SAS-A Cutoff ≥ 48	Youth	41	0.93 (0.91 to 0.96)	0.78 (0.74 to 81)	2 to 9	189 to 215
Social Anxiety Scale for Adolescents (SASA)									
Garcia-Lopez et al, 2015[67] Fair	15 (1.3) 12 to 18	1,034 54	SASA Cutoff ≥ 73	Youth	41	0.93 (0.85 to 0.98)	0.79 (0.70 to 87)	2 to 9	183 to 205
Social Phobia and Anxiety Inventory-Brief (SPAI-B)									
Garcia-Lopez et al, 2015[67] Fair	15 (1.3) 12 to 18	1034 (54)	SPAI-B Ctoff ≥26.4	Youth	41	0.86 (0.83 to 0.89)	0.88 (0.85 to 0.91)	4 to 18	104 to 117

Author, Year Quality	Age Range; Mean Age (SD), Years	Total N (% Female)	Index Test Cutoff[b]	Respondent	Prevalence %	Sensitivity (95% CI)	Specificity (95% CI)	Per 1,000 Screens Across a Prevalence From 3% to 13%	
								No. False-Negatives	No. False-Positives
Social Phobia Inventory (SPIN)/Mini Social Phobia Inventory (Mini-SPIN)									
Ranta et al, 2007[74] Fair	14.7 (1.1) 12 to 17	350 (49)	SPIN Cutoff ≥ 24	Youth	6	0.82 (0.61 to 0.93)	0.85 (0.81 to 0.89)	5 to 23	130 to 146
Tsai et al, 2009[76] Fair	Mean NR 13 to 15	144 (50)[†]	SPIN Cutoff ≥25	Yourh	10	0.80 (0.55 to 0.93)	0.77 (0.69 to 0.83)	5 to 26	200 to 224
Ranta et al, 2012[75] Fair	14.7 (1.1)* 12 to 17	350 (49)	Mini-SPIN Cutoff ≥ 6	Youth	6	0.86 (0.67 to 0.92)	0.84 (0.79 to 0.87)	4 to 18	139 to 156
Social Worries Questionnaire (SWQ)									
Bailey et al, 2006[64]	Children Mean NR 8 to 12 Adolescents 14 (1.3) 13 to 17	101 89 (49)[a]	SWQ Cutoff ≥ 10 SWQ Cutoff ≥ 5.3	Parents Parents	9 13	0.67 (0.35 to 0.88) 0.83 (0.55 to 0.95)	0.94 (0.88 to 0.98) 0.84 (0.74 to 0.90)	8 to 43 4 to 22	52 to 58 139 to 156
Any Anxiety Disorder (at least one specific anxiety disorder)									
Screen for Child Anxiety Related Emotional Disorders (SCARED)									
Johnson et al, 2002[69] Fair	16 (1.2) 13 to 18	403 (63)	PHQ-A Cutoff NR	Youth	5	0.50 (0.30 to 0.70)	0.98 (0.96 to 0.99)	12 to 65	17 to 20
Screen for Child Anxiety Related Emotional Disorders (SCARED)									
Muris et al, 2001[71] Fair	10 (1.4) 7 to 14	82 (61)	SCARED-C NA	Youth	20	0.88 (0.63 to 0.96)	0.56 (0.44 to 0.67)	3 to 16	383 to 429

[a] Percentage of females in Bailey is for entire sample.
[b] Study calculated value.

Abbreviations: ANS, Autonomic Nervous System Questionnaire; CI, confidence interval; GAD, general anxiety disorder; KQ, key question; NA, not applicable; NR, not reported; PHQ, Patient Health Questionnaire; PHQ-A, Patient Health Questionnaire-Adolescent; PI-ED, Pediatric Index of Emotional Distress; SAS, Social Anxiety Scale; SAS-A (SASA), Social Anxiety Scale-Adolescents; SAS-C, Social Anxiety Scale-Children; SCARED, Screen for Child Anxiety Related Emotional Disorders; SCARED-C, Screen for Child Anxiety Related Emotional Disorders-Child version; SCARED-P, Screen for Child Anxiety Related Emotional Disorders-Parent version; SCARED-SP, Screen for Child Anxiety Related Emotional Disorders-Social Phobia; SD, standard deviation; SPAI-B, Social Phobia and Anxiety Inventory-Brief; SPIN, Social Phobia Inventory; SWQ, Social Worries Questionnaire.

Quality assessment of diagnostic test accuracy studies based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool

Author, Year	Did the study adequately describe methods of patient selection?	Did the study describe the index test and describe how it was conducted and interpreted?	Did the study describe the reference standard and how it was conducted and interpreted?	Did the study describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table?	Did the study describe included patients (prior testing, presentation, use of index test and setting)?	Did the study describe the time interval and any interventions between index test(s) and reference standard?
Bailey et al, 2006[64]	Yes	Yes	Yes	Yes	Yes	No
Canals et al, 2012[65]	Yes	Yes	Yes	Yes	Yes	Yes
Cunha et al, 2008[66]	Yes	Yes	Yes	Yes	Yes	Unclear
Garcia-Lopez et al, 2015[67]	Yes	Yes	Yes	Yes	Yes	No
Gardner et al, 2007[68]	Yes	Yes	Yes	Unclear	Yes	Yes
Johnson et al, 2002[69]	Yes	Yes	Yes	Yes	Yes	Yes
Katon et al, 2008[70]	Yes	Yes	Yes	Yes	Yes	Yes
Muris et al, 2001[71]	Yes	Yes	Yes	No	Yes	Yes
O'Connor et al, 2016[72]	Yes	Yes	Yes	No	Yes	Yes
Queen et al, 2012[73]	Yes	Yes	Yes	Yes	Yes	Yes
Ranta et al, 2007[74]	Yes	Yes	Yes	Unclear	Yes	Yes
Ranta et al, 2012[75]	Yes	Yes	Yes	Yes	Yes	Yes
Tsai et al, 2009[76]	Yes	Yes	Yes	Yes	Yes	Yes

Author, Year	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?	Was a case-control design avoided?	If a threshold was used, was it pre-specified?
Bailey et al, 2006[64]	Yes	Unclear	Yes	Unclear	Yes	No
Canals et al, 2012[65]	No	Yes	Yes	Yes	Unclear	Yes
Cunha et al, 2008[66]	Unclear	Yes	Yes	Unclear	Yes	No
Garcia-Lopez et al, 2015[67]	No	Unclear	Yes	Unclear	Yes	No
Gardner et al, 2007[68]	No	Yes	Yes	Yes	Yes	Yes
Johnson et al, 2002[69]	Yes	No	Yes	Yes	Yes	No
Katon et al, 2008[70]	Yes	Yes	Yes	Yes	Yes	Yes
Muris et al, 2001[71]	No	Unclear	Yes	Yes	Yes	Yes
O'Connor et al, 2016[72]	Yes	No	Unclear	Yes	Yes	No
Queen et al, 2012[73]	Yes	Unclear	Yes	Yes	Yes	No
Ranta et al, 2007[74]	Yes	Yes	Yes	Yes	Yes	Yes
Ranta et al, 2012[75]	Yes	Unclear	Yes	Yes	Yes	Yes
Tsai et al, 2009[76]	Yes	Unclear	Yes	Yes	Yes	Unclear

Author, Year	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?	Did the study avoid inappropriate exclusions?	Did all patients receive the same reference standard?	Were all patients included in the analysis?
Bailey et al, 2006[64]	Unclear	Yes	Yes	Yes	Yes
Canals et al, 2012[65]	Yes	Yes	Unclear	Yes	Yes
Cunha et al, 2008[66]	Yes	Yes	No	Yes	Yes
Garcia-Lopez et al, 2015[67]	Unclear	Yes	Yes	Yes	Yes
Gardner et al, 2007[68]	Yes	No	No	Yes	No
Johnson et al, 2002[69]	No	Yes	Yes	Yes	No
Katon et al, 2008[70]	Yes	Yes	Yes	Yes	No
Muris et al, 2001[71]	Unclear	Yes	No	Yes	Yes
O'Connor et al, 2016[72]	No	Yes	Yes	Yes	Yes
Queen et al, 2012[73]	Unclear	Yes	Yes	Yes	Yes
Ranta et al, 2007[74]	Yes	No	Yes	Yes	No
Ranta et al, 2012[75]	Unclear	Yes	Yes	Yes	Yes
Tsai et al, 2009[76]	Unclear	Yes	Yes	Yes	Yes

Author, Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or interpretation have introduced bias?	Could the patient flow have introduced bias?	Are there concerns that the included patients do not match the review question?
Bailey et al, 2006[64]	Unclear	Unclear	Unclear	Unclear	Unclear
Canals et al, 2012[65]	Yes	No	No	No	Yes
Cunha et al, 2008[66]	Yes	Unclear	No	Unclear	Unclear
Garcia-Lopez et al, 2015[67]	Unclear	Unclear	Unclear	Unclear	No
Gardner et al, 2007[68]	Yes	No	No	Yes	Yes
Johnson et al, 2002[69]	Unclear	Yes	Yes	Yes	No
Katon et al, 2008[70]	No	No	No	Unclear	No
Muris et al, 2001[71]	Yes	Unclear	Unclear	No	No
O'Connor et al, 2016[72]	No	Yes	Yes	No	Unclear
Queen et al, 2012[73]	Unclear	Yes	Unclear	No	No
Ranta et al, 2007[74]	No	No	No	Unclear	No
Ranta et al, 2012[75]	No	Unclear	Unclear	No	No
Tsai et al, 2009[76]	No	Unclear	Unclear	Unclear	Yes

Author, Year	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	Overall Study Quality	Rationale for Overall Rating
Bailey et al, 2006[64]	No	No	Fair	Only 99 participants (from the 1,470 that were randomly selected to participate) completed the full study so applicability uncertain. Blinding of index test and reference test results not reported, interval between testing NR, index test thresholds not prespecified
Canals et al, 2012[65]	No	No	Fair	Spectrum bias possible given the way the sample was selected (high and low scorers on the SCARED instrument administered the prior year)
Cunha et al, 2008[66]	No	No	Poor	Selection into this analysis based on results of prior tests/evaluations as part of a larger study, participants with and without diagnoses were selected, this analysis excluded all participants with a diagnosis of ADHD or other mood disorder, index test thresholds not prespecified, interval between index and reference test not specified
Garcia-Lopez et al, 2015[67]	No	No	Fair	Sample assembled based on scoring above a threshold on index test and then a random sample of those who scored below threshold; blinding of index test and referent tests not reported, interval of administration between index and reference test not reported, thresholds not prespecified
Gardner et al, 2007[68]	No	No	Poor	Sample was derived from a separate study that screened persons for entry into a study of anxiety and abdominal pain and mood disorders and mental health service use; thus, only children who screened positive on the SMFQ or SCARED were included thus high likelihood of spectrum bias. Children who did not screen positive did not receive a reference test, so Sn and Sp in an unselected primary care population cannot be determined

Author, Year	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	Overall Study Quality	Rationale for Overall Rating
Johnson et al, 2002[69]	No	No	Poor	Only a small proportion of those eligible actually participated in the study so although recruitment was consecutive, potential for selection bias. Several thresholds evaluated for index text, unclear timing between index screening test and clinical interview. Interviewers not masked to results of index text. Of 373 who agreed to participate, only 294 were included (78.9%), and no information is provided on those who were missing from the sample. The information on the index and reference standard were collected by the same interviewer during the telephone call, so the interviewer had knowledge of the index test and reference standard results
Katon et al, 2008[70]	No	No	Fair	Participants with an interval between index and reference test of more than 18 days were excluded from the analysis
Muris et al, 2001[71]	No	No	Poor	Inappropriate exclusions of patients for the analysis; recruitment methods NR; whether results of index and reference tests were masked was NR.
O'Connor et al, 2016[72]	No	No	Poor	Same interviewer administered the index test and reference standard so results not masked, thresholds for index test no prespecified, unclear that lay administers of reference standard with high school degree and 12 hours of training is equivalent to a clinician interview and diagnosis. Study specifically recruited children with asthma in addition to healthy children, so applicability to general population is uncertain.
Queen et al, 2012[73]	No	No	Fair	Thresholds for index test were not prespecified, unclear whether results of index and referent test were blinded, sample was enriched with some persons from specialty mental health settings.
Ranta et al, 2007[74]	No	No	Fair	Not all screened persons received the reference test; all those who screened positive received reference test plus 2 participants who screened negative were selected randomly for the reference test for each person that screened positive.
Ranta et al, 2012[75]	No	No	Fair	Blinding of index and reference test not reported, index test thresholds not prespecified.
Tsai et al, 2009[76]	No	No	Fair	Index test did not have prespecified thresholds used, unclear whether index test was blinded to results of reference test

1.6 APPENDIX II - Narrative outline of prevalence rates of anxiety in potential high-risk groups

High risk group	Prevalence of anxiety (%)	Source
ASD	42%-79%	Kent, R., & Simonoff, E. (2017). Prevalence of anxiety in autism spectrum disorders. *Anxiety in children and adolescents with autism spectrum disorder*, 5-32.
ADHD	42%-51%	Multiple sources- Tsang, T. W., Kohn, M. R., Efron, D., Clarke, S. D., Clark, C. R., Lamb, C., & Williams, L. M. (2015). Anxiety in young people with ADHD: Clinical and self-report outcomes. Journal of attention disorders, 19(1), 18-26.- Schatz, D. B., & Rostain, A. L. (2006). ADHD with comorbid anxiety: a review of the current literature. Journal of Attention disorders, 10(2), 141-149. - Lavigne, J. V., LeBailly, S. A., Hopkins, J., Gouze, K. R., & Binns, H. J. (2009). The prevalence of ADHD, ODD, depression, and anxiety in a community sample of 4-year-olds. Journal of Clinical Child & Adolescent Psychology, 38(3), 315-328.
Sleep difficulties – insomnia, sleep terrors and sleep walking	High correlation, 90-98% of Children and adolescents (6-18) with anxiety have at least one sleep related problem	Fehr, K. K., Chambers, D. E., & Ramasami, J. (2021). The impact of anxiety on behavioral sleep difficulties and treatment in young children: A Review of the Literature. *Journal of Clinical Psychology in Medical Settings*, *28*, 102-112.
Cystic fibrosis	28-47%	Kimball, H., Douglas, T., Sanders, M., & Cobham, V. E. (2021). Anxiety in children with cystic fibrosis and their parents: a systematic review. *Clinical Child and Family Psychology Review*, *24*, 370-390.
Eating disorder	20-55% of girls with AN also had an anxiety disorder, 31-75% of girls with BN also had an anxiety disorder, NA men	Pearlstein, T. (2002). Eating disorders and comorbidity. *Archives of Women's mental Health*, *4*, 67-78.
Family history of anxiety	53%	McLaughlin, K. A., Behar, E., & Borkovec, T. D. (2008). Family history of psychological problems in generalized anxiety disorder. *Journal of clinical psychology*, *64*(7), 905–918. https://doi.org/10.1002/jclp.20497
Suicidal ideation and behaviours/self-harm	46-50% of children and youth (m=11.92 yrs)with anxiety disorder had suicidal ideation.	O'Neil Rodriguez, K. A., & Kendall, P. C. (2014). Suicidal ideation in anxiety-disordered youth: Identifying predictors of risk. *Journal of Clinical Child & Adolescent Psychology*, *43*(1), 51-62.

Hearing impairment	33.70%	Gharashi, K., Moheb, N., & Abdi, R. (2019). Effects of acceptance and commitment therapy on decreasing anxiety and depression symptoms in mothers of hearing-impaired or deaf children. *Auditory and Vestibular Research*.
Asthma	33%	Lu, Y., Mak, K. K., Van Bever, H. P., Ng, T. P., Mak, A., & Ho, R. C. M. (2012). Prevalence of anxiety and depressive symptoms in adolescents with asthma: A meta-analysis and meta-regression. *Pediatric allergy and immunology*, *23*(8), 707-715.
Immune-mediated diseases	pIBD 33%/RD 13%	Jansson, S., Malham, M., Wewer, V., & Rask, C. U. (2022). Psychiatric comorbidity in childhood onset immune-mediated diseases—A systematic review and meta-analysis. *Acta Paediatrica*, *111*(3), 490-499.
Precocious puberty	31%	Temelturk, R. D., Ekici, G. I., Beberoglu, M., Siklar, Z., & Kilic, B. G. (2021). Managing precocious puberty: a necessity for psychiatric evaluation. *Asian Journal of Psychiatry*, *58*, 102617.
Epilepsy	23.30%	LaGrant, B., Marquis, B. O., Berg, A. T., & Grinspan, Z. M. (2020). Depression and anxiety in children with epilepsy and other chronic health conditions: National estimates of prevalence and risk factors. *Epilepsy & Behavior*, *103*, 106828.
Alcoholic parents	15%	Omkarappa, D. B., & Rentala, S. (2019). Anxiety, depression, self-esteem among children of alcoholic and nonalcoholic parents. *Journal of family medicine and primary care*, *8*(2), 604.
Looked after children	11.10%	Ford, T., Vostanis, P., Meltzer, H., & Goodman, R. (2007). Psychiatric disorder among British children looked after by local authorities: comparison with children living in private households. *The British Journal of Psychiatry*, *190*(4), 319-325.
Preterm birth	6.88% /OR 2.20	Fitzallen, G. C., Sagar, Y. K., Taylor, H. G., & Bora, S. (2021). Anxiety and depressive disorders in children born preterm: a meta-analysis. *Journal of Developmental & Behavioral Pediatrics*, *42*(2), 154-162.
Children not in mainstream schooling	na	Many studies focus on ASD/anxitey in school, the effects of COVID-19 homeschoo, or homeschooling as treatment for anxiety.
Detained/imprisoned/incarcerated	na	very little research in this area in Aus

2 Evidence report: Psychological therapy

Abbreviations

Bib-CBT	bibliotherapy cognitive behavioral therapy	I/P-BT	individual BT with parental involvement
G-BT	group BT without cognitive restructuring	I/P-CBT	individual CBT with parental involvement
G-CBT	group CBT	NT	no treatment
G/P-CBT	group CBT with parental involvement	PBO	psychological placebo
I-CBT	individual CBT	P-CBT	parent-only CBT
I/G-BT	individual and group BT	TAU	treatment as usual
I/G-CBT	individual and group CBT	WL	wait list
Int-CBT	Internet-assisted CBT		

GRADE certainty definitions

High	Further research is very unlikely to change our confidence in the results.
Moderate	Further research is likely to have an important impact on our confidence in the results and may change the results.
Low	Further research is very likely to have an important impact on our confidence in the results and is likely to change the results.
Very low	We are very uncertain about the results.

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2.1 Summary of evidence

Of the 7919 articles retrieved from the multiple database search for intervention studies, 1180 duplicates were removed, and 6739 titles and abstracts were screened. Of these, 42 articles were retained for full text review, of which 17 were excluded and 2 articles were unable to retrieved in full text. Therefore, this evidence review includes 23 articles - 9 systematic reviews [1-9] and 14 randomised controlled trials (RCTs) that meet the selection criteria and provide relevant outcome data for reduction in anxiety symptoms, treatment response, acceptability, and/or remission. The search did not identify any studies measuring the effectiveness of serotonin antagonist and reuptake inhibitors (SARIs), beta-blockers or MAOIs in children and young people with anxiety.

Six of the systematic reviews were either older or did not add [1-5, 7] to three current and comprehensive systematic reviews [6, 8, 9]. These three systematic reviews conducted network meta-analyses comparing up to 7 medication classes to each other, as well as each medication within each class (specific medication comparisons are not in the selection criteria for this evidence review but detailed data can be found in the systematic reviews). One of these systematic reviews additionally ranked the medication classes (and specific medications) to inform which of the medications are better than others, including placebo [6]. Thirteen of the RCTs were included, and their evidence reviewed, in the three systematic reviews. See 6.3.2 for map of included studies and 1.3.3 for characteristics and risk of bias of included systematic reviews and additional RCT published after the systematic reviews [10].

Two of the systematic reviews assessed the risk of bias (quality of the study methods) of each RCT and a third systematic review additionally prepared the GRADE step 1 [9]. These three systematic reviews have been appraised for quality and deemed of sufficient quality (1.3.3) to adopt their data analysis into GRADE step 1 tables (6.3.4) for this evidence review. The findings from GRADE step 1 tables are summarised immediately below.

2.1.1 Cognitive behavioural therapy (CBT)

(Evidence from James 2020 [1] unless otherwise noted and cited)

A Cochrane systematic review (highest level of evidence) by James et al 2020 [1] reported meta-analyses of RCTs that addressed the effect of various forms of CBT in comparison with waitlist/no treatment, treatment as usual (TAU) or attention control. The search identified RCTs from multiple databases published up to October 2019; and 87 studies with 5964 young people under 19 years of age with an anxiety diagnosis were included. Relevant analysis included sample sizes ranging from 12 to 206 participants with social anxiety disorder, specific phobia, separation anxiety disorder, GAD, and/or panic disorder with/without agoraphobia.

CBT is defined by James 2020 as "...administered according to standard principles as a psychological model of treatment involving helping the child to recognise anxious feelings and somatic reactions to anxiety; identify cognitions in anxiety-provoking situations; modify these anxiety-provoking cognitions; and respond to behavioural training strategies with exposure in vivo or by imagination."

Meta-analyses demonstrated that CBT was better than waitlist/no treatment for remission of primary anxiety diagnosis [moderate certainty), remission of all anxiety diagnoses [moderate certainty], anxiety symptoms (child report and parent report) [low certainty], depressive symptoms [moderate certainty] and global functioning [low certainty]; but there was no statistically significant difference for acceptability, reported as loss to follow up [low certainty].

There was no statistically significant difference between CBT and treatment as usual (TAU) for primary anxiety disorder remission [low certainty], acceptability [low certainty], anxiety symptoms (child report and parent report) [low certainty]; but CBT was better than TAU for remission from all anxiety disorders [low certainty]. There was insufficient data for depressive symptoms or global functioning.

CBT was better than attention control (defined as "attention only, e.g. support or education, but with no elements of CBT") for remission of primary anxiety disorders [low certainty], all anxiety disorders [low certainty], anxiety symptoms (child report) [moderate certainty]; but there was no statistically significant difference for anxiety symptoms (parent report) [low certainty], acceptability [low certainty] or depressive symptoms [low certainty]. There was insufficient data for global functioning.

There was no statistically significant difference between CBT and alternative treatment (defined as "one specific non-pharmacological intervention for the treatment of anxiety that followed a documented protocol and did not include CBT elements") for acceptability [low certainty], remission of all anxiety disorders [low certainty], anxiety symptoms (child report and parent report) [low certainty]. There was insufficient data to compare CBT to alternative treatments for remission of primary anxiety disorders, depressive symptoms or global functioning.

Recent RCTs comparing various forms of CBT reported varying results. There was no statistically significant difference in anxiety symptoms between CBT and targeted behavioural therapy (sleep and anxiety) in 20 6-12 year old participants with GAD for 16 weeks [2].

GRADE summary

	Outcome	GRADE certainty/confidence in results from meta-analysis
CBT better than waitlist/no treatment	remission of primary anxiety diagnosis OR 5.45, 95% confidence interval (CI) 3.90 to 7.60; n = 2697, 39 studies	⊕⊕⊕◯ MODERATE
	remission of all anxiety diagnoses	⊕⊕⊕◯ MODERATE
	anxiety symptoms (child report and parent report)	⊕⊕◯◯ LOW
	depressive symptoms	⊕⊕⊕◯ MODERATE
	and global functioning	⊕⊕◯◯ LOW
No difference bw CBT and waitlist/no treatment	acceptability, reported as loss to follow up	⊕⊕◯◯ LOW
No difference between CBT and treatment as usual (TAU)	primary anxiety disorder remission	⊕⊕◯◯ LOW
	acceptability	⊕⊕◯◯ LOW
	anxiety symptoms (child report and parent report)	⊕⊕◯◯ LOW
CBT better than TAU	remission from all anxiety disorders	⊕⊕◯◯ LOW
CBT better than	remission of primary anxiety disorders	⊕⊕◯◯ LOW
	all anxiety disorders	⊕⊕◯◯ LOW
	anxiety symptoms (child report)	⊕⊕⊕◯ MODERATE

No difference between CBT and attention control	anxiety symptoms (parent report)	⊕⊕◯◯ LOW
	acceptability	⊕⊕◯◯ LOW
	depressive symptoms	⊕⊕◯◯ LOW

2.1.2 Cognitive behavioural therapy (CBT) formats

(Evidence from Zhou 2019 [3] unless otherwise noted and cited)

A comprehensive systematic review (highest level of evidence) by Zhou et al 2019 [3] reported network meta-analyses of RCTs to compare and rank the effect of various formats of CBT. The search identified RCTs from multiple databases published up to November 2017, and 101 studies with 6625 young people with a mean age of 10.8 (3.0) years with an anxiety diagnosis were included. Relevant analysis included sample sizes ranging from 11 to 267 participants (median 54) with social anxiety disorder, specific phobia, separation anxiety disorder, GAD, and/or panic disorder with/without agoraphobia. Duration of treatment ranged from 6-32 weeks (median 12).

CBT is defined by Zhou 2019 as "… a combination of BT and CT. It therefore should include cognitive restructuring. Additional CBT skill-building techniques are used in many programs by teaching relaxation techniques to cope with environmental stressors, providing social skills and resolution training, and teaching general problem problem-solving."

Group CBT (G-CBT)

For anxiety symptoms, the network meta-analyses demonstrated that G-CBT was better than placebo [low certainty]; and was better than I-CBT, G/P-CBT, I/P-CBT, P-CBT, BiB-CBT, Int-CBT/iCBT, TAU, no treatment and waitlist. There was no statistically significant difference between G-CBT and G-BT, I/P-BT, I/G-BT and I/G-CBT for anxiety symptoms.

For acceptability, reported as all cause discontinuation, G-CBT was better than BiB-CBT; but there was no statistically significant difference between G-CBT and all other interventions or controls.

For QoL and functional improvement, G-CBT was better than placebo and waitlist; but there was no statistically significant difference between G-CBT and all other interventions or controls.

In a recent RCT, there was no statistically significant difference for diagnosis remission, anxiety symptoms or functional impairment between G-CBT and I/P-CBT in 183 7-16 year old participants with different types of anxiety for 12-14 weeks [4].

Group CBT with parent involvement (G/P-CBT)

For anxiety symptoms, there was no statistically significant difference between G/P-CBT and placebo [very low certainty]. G/P-CBT was better than waitlist but there was no statistically significant difference between G/P-CBT and all other interventions and controls for anxiety symptoms.

For acceptability, reported as all cause discontinuation, G/P-CBT was better than BiB-CBT; but there was no statistically significant difference between G/P-CBT and all other interventions or controls.

For QoL and functional improvement, G/P-CBT was better than placebo and waitlist; but there was no statistically significant difference between G/P-CBT and all other interventions or controls.

In a recent RCT, there was no statistically significant difference in diagnosis remission, treatment response or anxiety symptoms between child-focused CBT and mother-child-focused CBT in 142 7-12 year old participants with different types of anxiety for 8-10 weeks [5].

Individual CBT (I-CBT)

For anxiety symptoms, there was no statistically significant difference between I-CBT and placebo [very low certainty]. I-CBT was better than waitlist but there was no statistically significant difference between I-CBT and all other interventions and controls for anxiety symptoms.

For acceptability, reported as all cause discontinuation, I-CBT was better than BiB-CBT; but there was no statistically significant difference between I-CBT and all other interventions or controls.

For QoL and functional improvement, I-CBT was better than placebo and waitlist; but there was no statistically significant difference between I-CBT and all other interventions or controls.

Individual CBT with parent involvement (I/P-CBT)

For anxiety symptoms, there was no statistically significant difference between I/P-CBT and placebo [low certainty]. I/P-CBT was better than waitlist but there was no statistically significant difference between I/P-CBT and all other interventions and controls for anxiety symptoms.

For acceptability, reported as all cause discontinuation, there was no statistically significant difference between I/P-CBT and all other interventions or controls.

For QoL and functional improvement, I/P-CBT was better than placebo and waitlist; but there was no statistically significant difference between I/P-CBT and all other interventions or controls.

Parent-only CBT (P-CBT)

For anxiety symptoms, there was no statistically significant difference between P-CBT and placebo [low certainty]. P-CBT was better than waitlist but there was no statistically significant difference between P-CBT and all other interventions and controls for anxiety symptoms.

For acceptability, reported as all cause discontinuation, there was no statistically significant difference between P-CBT and all other interventions or controls.

For QoL and functional improvement, P-CBT was better than treatment as usual, placebo and waitlist; but there was no statistically significant difference between P-CBT and all other interventions or controls.

In a recent RCT, 8 weeks of Triple P-parent-focused CBT was better than waitlist in 55 parents of 8-12 year old participants with different types of anxiety for anxiety symptoms and global functioning [6].

Individual and group CBT (I/G-CBT)

For anxiety symptoms, there was no statistically significant difference between I/G-CBT and placebo [low certainty] or any other intervention or control.

For acceptability and for QoL and functional improvement, there was no statistically significant difference between I/G-CBT and any other intervention or control.

Bibliography CBT (BiB-CBT)

For anxiety symptoms, there was no statistically significant difference between BiB-CBT and placebo [low certainty]. BiB-CBT was better than waitlist but there was no statistically significant difference between BiB-CBT and all other interventions and controls for anxiety symptoms.

For acceptability and for QoL and functional improvement, there was no statistically significant difference between BiB-CBT and any other intervention or control.

Internet CBT (Int-CBT/iCBT)

For anxiety symptoms, there was no statistically significant difference between iCBT and placebo [very low certainty]. iCBT was better than waitlist for anxiety symptoms but there was no statistically significant difference between iCBT and all other interventions and controls.

In a recent RCT, iCBT was better than waitlist for diagnostic remission in 91 12-17 year old participants with different types of anxiety for 8 weeks [7].

In another two recent RCTs, there was no statistically significant difference in anxiety symptoms or global functioning between iCBT and internet-delivered supportive therapy (iSUPPORT) in 103 10-17 year old participants with social anxiety disorder for 10 weeks [8]; nor for diagnostic severity, anxiety symptoms, life interference, wellbeing or self-efficacy when iCBT was compared with waitlist in 70 13-17 year old participants with difference types of anxiety for 14 weeks [9].

For acceptability, reported as all cause discontinuation, there was no statistically significant difference between iCBT and all other interventions or controls.

For QoL and functional improvement, iCBT was better than placebo and waitlist; but there was no statistically significant difference between iCBT and all other interventions or controls.

Technology-delivered CBT (tCBT)

A systematic review (highest level of evidence) by Cervin and Lundgren 2022 [10] reported meta-analyses of RCTs assessing the effect of technology-delivered CBT in participants <18 years of age with an anxiety diagnosis. The search identified RCTs from multiple databases published up to January 2022, and 9 studies with 711 participants were included. Relevant analysis included sample sizes ranging from 32 to 131 participants with social anxiety disorder, specific phobia, separation anxiety disorder, GAD, and/or panic disorder with/without agoraphobia.

tCBT is defined by Cervin 2022 as "CBT delivered predominantly via internet/app/cell phone/tablet computer".

Meta-analyses demonstrated that tCBT was better than control (waitlist/TAU/placebo) for remission of primary anxiety disorder [moderate certainty] and remission for all anxiety disorders [moderate certainty] but there was no statistically significant difference for youth-reported anxiety [low certainty], caregiver-reported anxiety [low certainty] or clinician-rated functioning [low certainty].

Exposure-focused CBT

Two recent RCTs assessed exposure-focused CBT. One RCT assessed a SAD-specific exposure-based CBT intervention for 16 weeks in 67 9-13 year old participants with SAD and reported no difference when compared to waitlist [11]; the second RCT for 12 weeks in 102 8-15 year old participants with different types of anxiety reported a benefit over relaxation-based control for anxiety symptoms [12].

GRADE summary

Zhou et al 2019		
Outcome		GRADE certainty/confidence in results from meta-analysis
anxiety symptoms	Group CBT better than placebo, waitlist, no treatment, TAU, I-CBT, G/P-CBT, I/P-CBT, P-CBT, BiB-CBT	⊕⊕◯◯ LOW
	No difference bw G-CBT and all others	⊕⊕◯◯ LOW
	G/P-CBT, I-CBT, P-CBT, I/P-CBT, iCBT were all better than waitlist	⊕⊕◯◯ LOW to ⊕◯◯◯ VERY LOW
	No difference bw G/P-CBT and all others; I-CBT and all others; or I/P-CBT and all others; or P-CBT and all others; or iCBT and all others	⊕⊕◯◯ LOW to ⊕◯◯◯ VERY LOW

anxiety symptoms	G-BT and I/P-BT were both better than waitlist	⊕⊕◯◯ LOW to ⊕◯◯◯ VERY LOW

Cervin and Lundgren 2022		
Outcome		GRADE certainty/confidence in results from meta-analysis
Remission form primary anxiety disorder	tCBT better than control	⊕⊕⊕◯ MODERATE
remission from all anxiety disorders	tCBT better than control	⊕⊕⊕◯ MODERATE
youth anxiety symptoms	No difference bw tCBT and control	⊕⊕◯◯ LOW
care giver anxiety symptoms	No difference bw tCBT and control	⊕⊕◯◯ LOW
functioning	tCBT better than control	⊕⊕◯◯ LOW

2.1.3 Individual CBT (I-CBT) v group CBT (G-CBT)

A systematic review (highest level of evidence) by Guo et al 2021 [13] reported meta-analyses of RCTs to compare the effect of individual CBT (I-CBT) and group CBT (G-CBT). The search identified RCTs from multiple databases published up to October 2019, and 9 studies with 871 young people with a mean age of 11.49 (2.19) years with an anxiety diagnosis were included. Relevant analysis included sample sizes ranging from 29 to 182 participants (mean/SD 96.78 ± 56.41) with social anxiety disorder, specific phobia, separation anxiety disorder, GAD, and/or panic disorder. Duration of treatment ranged from 6-18 weeks (median 12).

Meta-analyses demonstrated that there was no statistically significant difference between I-CBT and G-CBT for anxiety symptoms, acceptability and remission. In subgroup analyses by age, I-CBT was better than G-CBT for anxiety symptoms in adolescents (13-17 years old), but not in children (7-12 years old).

GRADE summary

Guo 2021		
Outcome		GRADE certainty/confidence in results from meta-analysis
anxiety symptoms	No difference bw I-CBT and G-CBT	⊕⊕⊕◯ MODERATE
age 7-12 anxiety symptoms	No difference bw I-CBT and G-CBT	⊕⊕◯◯ LOW
age 13-17 anxiety symptoms	I-CBT better than G-CBT	⊕⊕◯◯ LOW
acceptability	No difference bw I-CBT and G-CBT	⊕◯◯◯ VERY LOW

remission	No difference bw I-CBT and G-CBT	⊕⊕◯◯ LOW

2.1.4 Behavioural therapy (BT)

BT is defined by Zhou 2019 as using "…some kind of behavioral training and psychoeducation. BT programs provide parents and youths information about the condition and interventions; teach youths to monitor their mood, thoughts and behaviors; proposed pleasant activity scheduling and behavioral activation. It should not include cognitive restructuring."

Group BT (G-BT)

For anxiety symptoms, there was no statistically significant difference between G-BT and placebo [low certainty]. G-BT was better than waitlist but there was no statistically significant difference between G-BT and all other interventions and controls for anxiety symptoms.

For acceptability, reported as all cause discontinuation, there was no statistically significant difference between G-BT and all other interventions or controls.

No evidence was identified for QoL and functional improvement.

Individual and group BT (I/G-BT)

For anxiety symptoms, there was no statistically significant difference between I/G-BT and placebo [very low certainty]. There was no statistically significant difference between I/G-BT and any other intervention or control for anxiety symptoms, acceptability and for QoL and functional improvement.

Individual BT with parent involvement (I/P-BT)

For anxiety symptoms, there was no statistically significant difference between I/P-BT and placebo [very low certainty]. I/P-BT was better than waitlist but there was no statistically significant difference between I/P-BT and all other interventions and controls for anxiety symptoms.

For acceptability, reported as all cause discontinuation, there was no statistically significant difference between I/P-BT and all other interventions or controls.

No evidence was identified for QoL and functional improvement.

See 2.1.2 for GRADE summary.

2.1.5 Ranking of CBT and BT interventions and controls in network meta-analyses

The tables below are adopted directly from Zhou 2019 outlining intervention ranking resulting from the network meta-analyses. Interventions listed at the top of each table are more effective than interventions lower in the table. GRADE for ranking: Very low (Downgrade by three levels due to study limitations, imprecision, and heterogeneity).

Mean overall change in anxiety symptoms Larger SUCRAs = more effective interventions		**All-cause discontinuation** Larger SUCRAs = more tolerable interventions		**Mean overall change in QoL & functional improvement** Larger SUCRAs = less effective interventions	
Intervention by rank	**Rank – SUCRA (%)**	**Intervention by rank**	**Rank – SUCRA (%)**	**Intervention by rank**	**Rank – SUCRA (%)**

G-CBT	93.4%	NT	85.2%	P-CBT	4.4%
G-BT	86.1%	I+G-CBT	69.3%	I-CBT	23.5%
I-BT+P	69.9%	TAU	66.4%	I-CBT+P	38.6%
I-CBT	69.5%	I-BT+P	66.0%	G-CBT+P	42.7%
G-CBT+P	69.3%	G-CBT	59.5%	Int-CBT	44.2%
I-CBT+P	54.8%	WL	57.5%	G-CBT	44.8%
I+G-BT	45.7%	G-CBT+P	56.0%	BIB-CBT	44.9%
P-CBT	42.2%	I-CBT	53.1%	I+G-BT	48.2%
BIB-CBT	42.0%	I+G-BT	49.4%	I+G-CBT	55.0%
I+G-CBT	40.8%	Int-CBT	47.8%	TAU	73.5%
PBO	37.9%	PBO	42.0%	WL	88.5%
TAU	33.5%	I-CBT+P	35.7%	PBO	91.8%
Int-CBT	33.4%	G-BT	27.6%		
NT	29.3%	P-CBT	27.5%		
WL	2.4%	BIB-CBT	7.1%		
Mean overall change in anxiety symptoms at follow-up Larger SUCRAs = more effective interventions		**Mean overall change in anxiety symptoms at short-term follow-up** Larger SUCRAs = more effective interventions		**Mean overall change in anxiety symptoms at long-term follow-up** Larger SUCRAs = more effective interventions	
Intervention by rank	**Rank – SUCRA (%)**	**Intervention by rank**	**Rank – SUCRA (%)**	**Intervention**	**SUCRA (%)**
P-CBT	67.9%	G-CBT	89.3%	G-CBT+P	81.0%
I-BT+P	66.1%	TAU	73.7%	P-CBT	77.0%
Int-CBT	65.6%	G-BT	71.1%	I-BT+P	58.3%
TAU	62.6%	Int-CBT	64.5%	I-CBT	57.8%
G-CBT	61.5%	P-CBT	58.8%	I-CBT+P	55.5%
BIB-CBT	60.1%	I-CBT	56.9%	TAU	54.5%
G-CBT+P	59.7%	I-CBT+P	54.1%	G-CBT	51.6%
I-CBT	58.7%	BIB-CBT	51.8%	G-BT	38.7%
I-CBT+P	57.6%	I-BT+P	43.7%	PBO	25.2%
G-BT	45.4%	G-CBT+P	39.7%	WL	0.6%
PBO	35.5%	PBO	36.9%		
WL	7.8%	WL	6.4%		
NT	1.5%	NT	3.1%		

2.1.6 Acceptance and commitment therapy (ACT)

No articles met the selection criteria to assess the effectiveness of this intervention in children and young people with anxiety.

2.1.7 Psychoeducation

No articles met the selection criteria to assess the effectiveness of this intervention in children and young people with anxiety.

There is evidence for the benefits of psychoeducation for a broad range of mental health conditions and settings. A systematic review of twenty studies about the effectiveness of brief psychoeducation

(programmes of 10 sessions or less) in people with severe mental illness found that it appeared to reduce relapse and promote medication compliance (noting low to very low quality evidence).

2.1.8 Family therapy

Three RCTs met the selection criteria to assess the effectiveness of this intervention in children and young people with anxiety.

2.1.9 Play therapy

One RCT met the selection criteria to assess the effectiveness of this intervention in children and young people with anxiety.

2.2 Methods

2.2.1 Selection criteria and definitions

Question: What is the clinical effectiveness of psychological therapy for anxiety in children and young people?

High priority interventions:

- *Acceptance and commitment therapy (ACT)*
- *CBT (individual, group)*
- *Psychoeducation*
- *Family therapy*
- *Play therapy*

Question: What is the clinical effectiveness of individual and group psychological therapy for anxiety in children and young people?

Population	
We will include studies in groups of children and young people (0-18) in any setting or geographical location with anxiety. Diagnosis of anxiety by healthcare professional or trained lay interviewer on the basis of universally screening the population in question as opposed to incidental diagnoses from health care contacts. Diagnostic criteria of the DSM (DSM III, III-R, IV, IV-TR and V) (APA 1980; APA 1987; APA 1994; APA 2000) or of ICD9 and ICD10 (WHO 1978, WHO 1992) for anxiety disorder, including one or more disorders of GAD, over-anxious disorder, SAD, SOP or PD. **We will** include studies that have included those with anxiety AND other co-occurring disorders. Including: Generalised anxiety and other anxiety conditions (e.g. OCD), other mental health conditions (PTSD, MDD), ASD, ADHD. Subgroups of those with only anxiety will be analysed separately to those with co-occurring disorders.	**We will not** include studies in people without anxiety or in adults (18+).
Intervention	
We will include studies that measure effectiveness of the following high priority psychological	

therapies:

- Acceptance and commitment therapy (ACT)
- CBT (individual, group)
- Psychoeducation
- Family therapy
- Play therapy

For all interventions, we will subgroup study data that compares delivery of the intervention by group to delivery of the intervention to an individual.

Comparison

We will include studies that have compared the intervention to:	**We will not** include studies that have compared the intervention to medication
• Waiting list and no treatment for anxiety during that period. • Other psychological treatment that did not include elements of the intervention (where relevant, specific details of comparison details will be described (e.g. support but with no elements of CBT). • Treatment as usual (TAU)/usual care. • Active control • Other psychological intervention	

Outcome measures to determine effectiveness

We will include studies that measure:

Reduction in anxiety symptoms using psychometrically robust measures of anxiety symptoms (Myers 2002) that yield symptom scores on continuous scales, and are completed as self-report or by a parent or guardian or an independent rater, such as:

- Revised Children's Manifest Anxiety Scale (RCMAS) (Reynolds 1985).
- Fear Survey for Children—Revised (FSSC-R) (Ollendick 1998).
- Social Phobia and Anxiety Inventory for Children (SPAI-C) (Beidel 1995).
- Child Behaviour Checklist (CBCL) (Achenbach 1991).
- Social Anxiety Scale for Adolescents (SAS-A) (La Greca 1998).
- State-Trait Anxiety Inventory for Children (STAI-C) (Spielberger 1973).
- Screen for Child Anxiety Related Emotional Disorders (SCARED) (Birmaher 1999).
- SCAS (Spence Child Anxiety Scale, Child and Parent Versions) (Spence 1997).

Treatment response using the Clinical Global Impression scale (CGI-I) (Guy 1976) - a score of 1 (very much improved) or 2 (much improved) on the CGI-I.

Acceptability, as determined by the numbers of participants who were lost to follow-up.

Impairment or distress.

Remission - the absence of a diagnosis of an anxiety disorder, as diagnosed by reliable and valid structured interviews for DSM or ICD child and adolescent anxiety disorders, including: Anxiety Disorder Interview Schedule for Parents (ADIS-P) (Silverman 1987); Anxiety Disorder Interview Schedule for Children (ADIS-C) (Silverman 1987); Diagnostic Interview Schedule for Children, Adolescents and Parents (DISCAP) (Holland 1995). The diagnostic interviews must be carried out independently of the study treatment team.

Where multiple measures are reported for the same outcome within a study, the most validated, best recognised, or most frequently used measures will be included in the analysis.

Studies were excluded if they only reported data from follow up assessments.

Study design	
We will include RCTs.	We will not include cohort, cross-sectional, case control or case series studies, editorials, letters, commentaries.
Limits	
Studies reported in English language and studies published since 1978 (introduction of ICD 9).	

2.2.2 Search Strategy

Date of search: 20th July 2022

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to July 18, 2022>

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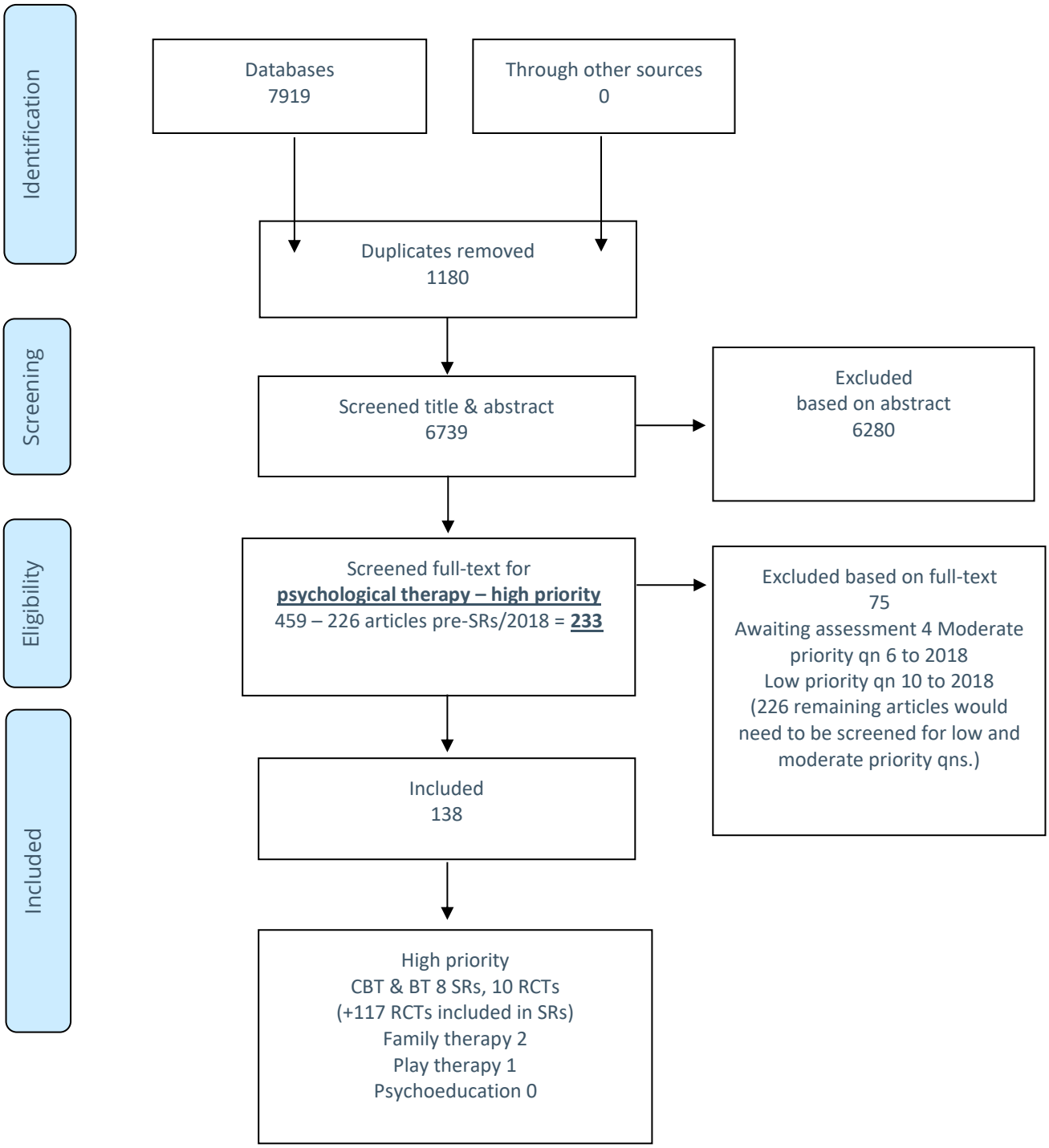
1 ANXIETY DISORDERS/
2 *ANXIETY/di, pc, px, th
3 AGORAPHOBIA/ or PANIC DISORDER/ or ANXIETY, SEPARATION/
4 PHOBIC DISORDERS/ or PHOBIA, SOCIAL/
5 (agoraphobi* or generali#ed anxiety or GAD or separation anxiety or (social* adj2 (anxi* or fear*)) or phobi* or school refusal).ti,ab,kf.
6 ((infant? or child* or adolesc* or p?ediatric* or teen* or young* or youth or school? or preschool*) adj2 anxi*).ti,ab,kf.
7 anxiety.ab. /freq=3
8 panic.mp.
9 (anxiety adj5 (autism or autistic)).ti,ab,kf.
10 anxiety.mp. and (child development disorders, pervasive/px or autism spectrum disorder/px or autistic disorder/px)
11 or/1-10
12 ADOLESCENT/ or CHILD/ or CHILD, PRESCHOOL/
13 (infant? or child* or adolesc* or paediatr* or pediatr*).hw,jn.
14 (infant* or child* or boy* or girl* or kids or juvenil* or minors or paediatric* or pediatric* or adolesc* or preadolesc* or pubert* or pubescen* or prepube* or teen* or (young adj (survivor* or offender* or minorit*)) or youth* or school? or preschool* or nurser* or kindergarten).ti,kf.
15 (infant? or child* or adolesc* or paediatr* or pediatr*).ab. /freq=3
16 or/12-15
17 ((anxi* or phobi* or panic) and (effectiveness or efficacy or evaluat* or intervention or program* or train* or treat* or prevent* or therapy or psychotherapy or trial or study) and (infant? or child* or adolesc* or paediatric* or pediatric* or teen* or young* or youth or school? or preschool*)).ti.
18 controlled clinical trial.pt.
19 randomized controlled trial.pt.
20 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf.
21 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,kf.
22 (placebo or ((attention or active) adj control*)).ti,ab,kf.
23 trial.ab,ti,kf.
24 ((control* or group* or compar*) adj5 (((care or treatment*) adj2 (usual or standard or routine)) or TAU or CAU)).ab.
25 ((control* or group* or compar*) adj5 (waitlist* or wait* list* or waiting or WLC)).ab.
26 or/18-25
27 11 and 16 and 26
28 17 and 26
29 27 or 28
30 ((OCD or obsessive compulsive or PTSD or posttraumatic stress disorder*) not (anxi* or phobi* or agoraphobi* or panic)).ti.
31 29 not 30
32 limit 31 to yr="1978 -Current"
33 limit 32 to (english language and humans)

Notes: Translated searches for Embase, PsycInfo and All EBM on request.
This search was reviewed in October 2023, finding no new evidence to change recommendations.

2.3 Results

2.3.1 Search results - PRISMA flowchart



2.3.2 Included studies

Following initial screening of the search results, there were 500+ articles that included information in the abstract to suggest that the article met the selection criteria for this evidence review about psychological interventions for treatment of anxiety in children and young people.

On review of the full article of 300+ of these, a handful of current systematic reviews were identified that analysed a large number of the randomised controlled trials identified by the search. Many of the systematic reviews included the same or similar sets of analysed RCTs, therefore four systematic reviews with the most recent search and the most comprehensive set of RCTs have been used here to address the questions and interventions of interest. James et al 2020 addressed effectiveness of CBT; Zhou et al 2019 addressed effectiveness of various formats of CBT and BT; Cervin and Lundgren 2022 addressed effectiveness of technology-delivered CBT; and Guo 2021 compared individual CBT to group CBT.

Please see APPENDIX I for a map of included systematic reviews and their included studies.

Recent RCTs that were identified by our search but not included in the systematic reviews (because they were published after the systematic review's search) have been assessed for risk of bias but have not been incorporated into analyses and are therefore not allocated a level of GRADE certainty. Please see below for Characteristics and risk of bias of these RCTs.

For detailed risk of bias assessments of RCTs and systematic reviews, please see below section 2.3.5

2.3.3 Characteristics and findings of included SRs

Please see below section 2.3.5 for detailed risk of bias assessments.

Study	Population	N	Search	Comparison	Duration	Findings	Risk of bias
James 2020	< 19 years of age with an anxiety diagnosis - social anxiety disorder, specific phobia, separation anxiety disorder, GAD, and/or panic disorder with/without agoraphobia. Note: subgroups by co-occurring disorders; individual v group, ITT	87 RCTs n=5964 sample ranging from 12 to 206	October 2019	CBT v waitlist/no treatment, treatment as usual (TAU) or attention control.	Therapist contact time < 10 hours to >20 hours.	*CBT v waitlist/no treatment* Remission of primary anxiety diagnosis OR 5.45 95% CI 3.90 to 7.60 Remission of all anxiety diagnoses OR 4.43 95% CI 2.89 to 6.78 Reduction in anxiety symptoms (child report and parent report) SMD -0.67 95% CI -0.88 to -0.47 Improvement in global functioning SMD 1.03 95% CI 0.68 to 1.38 Acceptability/loss to follow up OR 1.09 95% CI 0.85 to 1.41 *CBT v treatment as usual (TAU)* Remission of primary anxiety diagnosis OR 3.19 95% CI 0.90 to 11.29 Remission of all anxiety disorders OR 2.74 95% CI 1.16 to 6.46 Reduction in anxiety symptoms (child) SMD -0.15 95% CI -0.78 to 0.48 Reduction in anxiety symptoms (parent)	Low

						SMD -0.32 95% CI -0.70 to 0.06 Acceptability OR 1.37 95% CI 0.73 to 2.56	
						CBT v attention control Remission of primary anxiety disorders OR 2.28 95% CI 1.33 to 3.89 Remission of all anxiety disorders OR 2.75 95% CI 1.22 to 6.17 Reduction in anxiety symptoms (child) SMD -0.31 95% CI -0.51 to -0.11 Reduction in anxiety symptoms (parent) SMD -0.25 95% CI -0.61 to 0.11 Acceptability OR 1.00 95% CI 0.68 to 1.49	
Zhou 2019	Children and adolescents (≤18) with a primary diagnosis of anxiety - social anxiety disorder, specific phobia, separation anxiety disorder, GAD, and/or panic disorder with/ without agoraphobia.	101 RCTs n=6625 sample ranging from 11 to 267	November 2017	Structured psychotherapy v Other psychotherapy, psychological placebo, treatment as usual, waitlist, no treatment.	6-32 weeks	See Appendix II for data summary and network meta-analysis tables – anxiety symptoms, acceptability/ discontinuation, functional improvement and quality of life.	Low
Cervin 2022	<18 years of age with a confirmed primary anxiety disorder - social	9 RCTs, n=711 sample	January 2022	CBT delivered via internet/app/cell phone/tablet	Not reported – "accounts of	Remission from primary AD OR 4.73 95% CI 3.11 to 7.29 Remission from all AD	Moderate

	anxiety disorder, specific phobia, separation anxiety disorder, GAD, and/or panic disorder with/without agoraphobia.	ranging from 32 to 131		computer v TAU, placebo (pill or psychological), or waitlist.	therapist involvement were seldom provided"	OR 3.32 95% CI 1.95 to 5.66 Youth-reported anxiety SMD 0.13 95% CI -0.03 to 0.28 Care giver-reported anxiety SMD 0.27 95% CI 0.04 to 0.51 Clinician-rated functioning MD -4.38 95% CI -6.65 to -2.10	
Guo 2021	<17 years of age with an anxiety diagnosis - social anxiety disorder, specific phobia, separation anxiety disorder, GAD, and/or panic disorder.	9 studies n= 871 sample ranging from 29 to 182	October 2019	Individual CBT (I-CBT) v group CBT (G-CBT).	6-18 weeks	Anxiety symptoms SMD −0.14 95% CI −0.37 to 0.09 *Subgroup analysis by age* 13-17 SMD −0.77 95% CI −1.51 to −0.02 7-12 SMD 0.00 95% CI −0.02 to 0.20 Acceptability OR 1.30 95% CI 0.61–2.77 Remission OR 1.15 95% CI 0.79–1.66	Low

2.3.4 Characteristics and findings of included RCTs

The following studies were identified by our search and were published after the systematic review search dates. Please see below section 5.3.5 for detailed risk of bias assessments.

Study	Anxiety	Comparison	Age	N	Duration	Findings	Risk of bias
Asbrand 2020 Germany	SAD	Exposure-based SAD-specific group CBT v WL	9-13	67 CBT 30 WL 36	16 weeks	State anxiety CBT 6.7 (2.82) WL 5.5 (3.68) p = .189	Moderate
Bilek 2022 USA	Mixed – GAD, SoAD, SpAD, other	Exposure-focused CBT v relaxation-based control	CBT 11.86 ± 3.1 RMT 12.03 ± 3.1	CBT 70 RMT 32	12 sessions over 12 weeks	Anxiety severity - PARS CBT 12.9 [11.7, 14.0] RMT 16.5 [14.7, 18.3] p<0.001 CGI % responders CBT 57.3% (42.4–71.0) RMT 19.2% (6.2–46.2) p NR	High
Clementi 2020 USA	GAD	Targeted behavioural therapy (TBT) for sleep and anxiety v CBT	6-12	20 TBT 10 CBT 10	16 sessions over 16 weeks including 4 sleep sessions	Anxiety symptoms SCARED-P TBT 19.8 (11.27) CBT 20.60 (11.88) SCARED-C TBT 20.80 (11.08) CBT 24.10 (11.94)	Moderate
Creswell 2020 UK	Mixed – SAD, SoAD, GAD, SpAD, PD, Other, SM (1) + mother with current anxiety diagnosis -	Child-focused CBT with nonspecific control interventions (CCBT+Con) (b) CCBT with CBT for the maternal anxiety disorder (CCBT+MCBT), or v (c) CCBT with an intervention targeting the mother–child	7-12	CCBT+Con 71 CCBT+MCI 71	8 weekly 1hr sessions 10 sessions over 8 weeks	n (%) free of primary diagnosis CCBT+Con 27 (48.21) CCBT+MCI 37 (59.68) n (%) free of all anxiety diagnoses CCBT+Con 16 (28.57) CCBT+MCI 25 (40.32) n (%) CGI-I 'much'/'very much' improved CCBT+Con 36 (64.29)	Moderate

	mixed	interaction (CCBT+MCI)				CCBT+MCI 47 (75.81) No statistical significance for all three outcomes. No statistically significant difference for: anxiety symptoms (SCAS-c), Child Anxiety Impact Scale (CAIS-c), Conduct problems (SDQ-c), Child Adjustment to School (CAS-t). Maybe for Depression symptoms (SMFQ-c) but stats unclear.	
Kishida 2021 Japan [14]	Mixed – SAD, SoAD, GAD, SP, dysthymia	Streamlined Transdiagnostic Intervention for Anxiety and Depression (STREAM) v WL	9-12	STREAM 8 WL 8 ITT	8 sessions over 2 months? STREAM ~19 weeks WL ~11 weeks	Anxiety severity CSR STREAM 4.38 (3.25) WL 6.13 (1.64) Number of diagnoses STREAM 1.00 (0.76) WL 2.63 (1.19) *Due to considerable methodological flaws and insufficient data, this study has not been incorporated into the summary of evidence.*	High
Nordh 2021 Sweden	SoAD	Therapist-guided internet-delivered CBT (iCBT) v internet-delivered supportive therapy (ISUPPORT) Pot-treatment data from supplementary document.	10-17	iCBT 51 iSUPPORT 52	10 weeks - 10 online modules, 5 separate parent modules, and 3 video call sessions with a	Anxiety severity CSR iCBT 4.27 (1.24) iSUPPORT 4.62 (1.22) SoAD symptoms LSAS -C iCBT 66.25 (26.40) iSUPPORT 76.11 (28.77) SoAD symptoms LSAS -P iCBT 74.09 (30.01) iSUPPORT 81.69 (35.14) Depressive symptoms RCADS-C-dep	Low

					therapist.	iCBT 3.05 (2.79) iSUPPORT 3.56 (3.35) Anxiety & depressive symptoms RCADS-P iCBT 32.82 (17.16) iSUPPORT 39.65 (20.10) Global functioning CGAS – assessor rated iCBT 58.22 (9.17) iSUPPORT 57.50 (9.29) General functioning WSAS-P iCBT 11.71 (8.34) iSUPPORT 11.41 (7.66) QoL CHU9D – C iCBT 9.03 (5.91) iSUPPORT 10.67 (7.25) Unclear if effect sizes/CIs are pre/post or post interventions	
Özyurt 2019 Turkey	Mixed – SoAD, SP, SeAD, GAD, combinations, PD, other	Triple P - positive parenting programme - parent-focused CBT v WL	8-12	Triple P 26 WL 29	5 2hr group sessions and 3 15–30min individual tele sessions delivered to parents over 8 weeks	Strengths and Difficulties SDQ Triple P 11.73 ± 4.19 WL 14.86 ± 4.50 p=.008 Global functioning CGAS Triple P 65.30 ± 6.16 WL 52.13 ± 9.04 p <.001 Global functioning -Severity CGI-S Triple P 2.5 ± 0.64 WL 3.44 ± 0.9 p <.001 Anxiety symptoms SCARED-C Triple P 20.46 ± 9.27 WL 30.34 ± 11.17 p <.001 Anxiety symptoms SCARED-P	Moderate

						Triple P 21.19 ± 10.43 WL 32.13 ± 10.29 p <.001 General Health GHQ-28 Triple P 2.30 ± 3.46 WL 3.48 ± 4.58 p= .567 Trait anxiety STAI-T Triple P 38.69 ± 6.67 WL 41.75 ± 10.57 p= .38 State anxiety STAI-S Triple P 32.30 ± 6.76 WL 34.86 ± 11.49 p=.261	
Schniering 2022 Australia	Mixed – SeAD, SoAD, GAD, other PLUS some (~ half) with MDD, PDD or none	The Internet based Chilled Plus Program (CP) - iCBT v WL	12-17	iCBT 45 WL 46	8-module, online program + 8, 30-min tele sessions with a therapist, of which the caregiver participated in 4.	Number of anxiety diagnoses iCBT 1.10 (1.29) WL 1.99 (1.19) Anxiety symptoms SCAS-Y iCBT 28.60 (20.12) WL 39.70 (21.50) Anxiety symptoms SCAS-P iCBT 24.63 (36.43) WL 41.72 (33.17) Mood and feelings SMFQ-Y iCBT 8.59 (11.20) WL 14.51 (10.44) Mood and feelings SMFQ-P iCBT 6.92 (6.47) WL 9.10 (7.12) Adolescent life interference - Y iCBT 48.04 (27.64) WL 54.39 (27.60) Adolescent life interference - P iCBT 52.20 (29.31) WL 56.82 (26.65)	Moderate

						Diagnostic remission iCBT 43.8% WL 20.9% p=.030	
Silverman 2019 USA	Mixed – SeAD, SP, GAD, other	Peer group CBT (GCBT) v CBT involving parents (PCBT)	7-16	GCBT 83 PCBT 100	12-14 weekly 60min sessions using in- and out of-session exposures & CBT strategies	Anxiety symptom severity RCMAS GCBT 7.56 (5.85) PCBT 7.33 (5.85) Diagnostic remission ADIS C/P GCBT 67.9% PCBT 74.7% Functional impairment C-GAS GCBT 63.6% PCBT 72.5%	Moderate
Stjerneklar 2019 Denmark	Mixed – SoP, SpP, OCD, GAD, SeAD, PD+/- agoraphobia	Therapist-guided internet-based CBT – ChilledOut Online (iCBT) v WL	13-17	iCBT 35 WL 35 ITT	8 30min modules over 14 weeks	Diagnostic severity ADIS (primary diagnosis) iCBT 3.83 (2.65) WL 5.09 (2.29) Diagnostic severity ADIS (all diagnoses) iCBT 6.89 (4.56) WL 9.28 (4.13) Anxiety symptoms SCAS-C iCBT 31.88 (16.06) WL 40.19 (19.90) Anxiety life interference CALIS - adolescent iCBT 10.59 (7.65) WL 12.42 (8.65) Wellbeing WHO-5 iCBT 49.50 (21.69) WL 54.06 (20.39)	Moderate

						Moods and feelings S-MFQ - adolescent iCBT 8.06 (7.77) WL 7.77 (7.14) Self-efficacy SEQ-C total iCBT 75.25 (16.55) WL 74.00 (16.27) P values reported for between groups are for mean change from pre to post, not for means and SDs above. Also reported mother and father-rated anxiety symptoms SCAS-P, anxiety life interference CALIS	

2.3.5 Risk of bias: internal and external validity of included articles

James 2020 (Systematic review)

Study citation	James, A.C., et al., Cognitive behavioural therapy for anxiety disorders in children and adolescents. Cochrane Database of Systematic Reviews, 2020. 11: p. CD013162.	
External validity – selection criteria and characteristics of the systematic review		
Population, n=	Younger than age 19 with an anxiety disorder diagnosis. 87 RCTs, n=5964	
Intervention	CBT that involved direct contact with the child, parent, or both.	
Comparison	Waitlist/no treatment, treatment as usual (TAU), attention control, alternative treatment, and medication (not relevant to this evidence review).	
Outcome measures	Remission of primary anxiety diagnosis post-treatment, acceptability (number of participants lost to post-treatment assessment), remission of all anxiety diagnoses, reduction in anxiety symptoms, reduction in depressive symptoms, improvement in global functioning, adverse effects, and longer-term effects.	
Internal validity – risk of bias in systematic review methods		
Selection bias	Two independent reviewers screened articles but it is not known whether reviewers were blind to authors, institutions and affiliations. The review details specified selection criteria.	
Sampling & publication bias	A comprehensive search strategy is documented, including unpublished studies.	
Outcome bias	Two independent reviewers assessed risk of bias using the Cochrane risk of bias criteria. Data were extracted and checked by two reviewers but unclear if done independently.	
Reporting bias	There are detailed characteristics of included studies tables and results of individual studies are reported in forest plots. The strengths and limitations of the analysis and potential impact on the results were discussed and appropriate conclusions were made based on appropriately performed meta-analyses.	
Funding bias	Financial disclosures were reported.	
Comments	Publication bias is addressed. ***The systematic review is sufficient to adopt the meta-analyses, detailed risk of bias assessments of individual studies and the GRADE tables (Appendix II).***	
Overall risk of bias of the systematic review	Low	Most of the criteria have been fulfilled and where criteria have not been fulfilled it is unlikely the conclusions of the study would be affected.

Zhou 2019 (Systematic review)

Study citation	Zhou, X., et al., Different Types and Acceptability of Psychotherapies for Acute Anxiety Disorders in Children and Adolescents: A Network Meta-analysis. JAMA Psychiatry, 2019. 76(1): p. 41-50.	
External validity – selection criteria and characteristics of the systematic review		
Population, n=	Children and adolescents (≤18) with a primary diagnosis of anxiety disorders according to standardized diagnostic criteria assessed by trained staff via clinical interview. 101 RCTs, n=6625	
Intervention	Psychotherapy was considered structured when it was accompanied by an explicit manual for therapists to follow and/or laid out in a manual for the participants.	
Comparison	Other psychotherapy, psychological placebo, treatment as usual, waitlist, no treatment.	
Outcome measures	Symptoms, acceptability/discontinuation, functional improvement and quality of life.	
Internal validity – risk of bias in systematic review methods		
Selection bias	Four independent reviewers screened articles but it is not known whether reviewers were blind to authors, institutions and affiliations. The review details specified selection criteria.	
Sampling & publication bias	A comprehensive search strategy is documented, including unpublished studies.	
Outcome bias	Four independent reviewers extracted data and assessed risk of bias. The Cochrane risk of bias criteria was used.	
Reporting bias	There is a detailed characteristics of included studies table but results of individual studies are not reported or summarised. The strengths and limitations of included studies and potential impact on the results were discussed and appropriate conclusions were made based on appropriately performed meta-analyses and network meta-analyses.	
Funding bias	Financial disclosures were reported.	
Comments	Data and/or effect sizes for each study are not presented. Funnel plots indicated potential publication bias for efficacy/symptoms. ***The systematic review is sufficient to adopt the meta-analyses, detailed risk of bias assessments of individual studies and the GRADE tables (Appendix III).***	
Overall risk of bias of the systematic review	Low	Most of the criteria have been fulfilled and where criteria have not been fulfilled it is unlikely the conclusions of the study would be affected.

Cervin 2022 (Systematic review)

Study citation	Cervin, M. and T. Lundgren, Technology-delivered cognitive-behavioral therapy for pediatric anxiety disorders: a meta-analysis of remission, posttreatment anxiety, and functioning. Journal of Child Psychology & Psychiatry & Allied Disciplines, 2022. 63(1): p. 7-18.	
External validity – selection criteria and characteristics of the systematic review		
Population, n=	<18 years of age with a confirmed primary anxiety disorder according to a structured diagnostic interview. 9 RCTs, n=711	
Intervention	CBT delivered predominantly via internet/app/cell phone/tablet computer.	
Comparison	Treatment-as-usual (TAU), placebo (pill or psychological), or waitlist.	
Outcome measures	Remission for the primary AD according to a structured diagnostic interview, youth- and caregiver-reported anxiety.	
Internal validity – risk of bias in systematic review methods		
Selection bias	Two independent reviewers screened articles but it is not known whether reviewers were blind to authors, institutions and affiliations. The review details specified selection criteria.	
Sampling & publication bias	A comprehensive search strategy is documented. It is implied that unpublished studies were not searched for, however authors were contacted for additional data.	
Outcome bias	Two independent reviewers extracted data and assessed risk of bias. The Cochrane risk of bias criteria was used.	
Reporting bias	There is a detailed characteristics of included studies table but results of individual studies are not reported or summarised. The strengths and limitations of included studies and potential impact on the results were discussed and mostly appropriate conclusions were made based on appropriately performed meta-analyses. Minor discrepancies between abstract and results/conclusions. Have presented funnel plots but no mention of the results or impact on publication bias.	
Funding bias	Financial disclosures were not specifically reported, however the authors stated that there were no conflicts or competing interests to declare.	
Comments	Data and/or effect sizes for each study are not presented. Insufficient detail in forest plots re labelling direction of effect and individual study results. ***The systematic review is sufficiently reported to adopt the meta-analyses, detailed risk of bias assessments of individual studies, and body of evidence GRADE ratings into the summary of evidence (Appendix IV).***	
Overall risk of bias of the systematic review	Moderate	Some of the criteria have been fulfilled and where criteria have not been fulfilled it is possible that the conclusions of the study may be affected.

Guo 2021 (Systematic review)

Study citation	Guo, T., et al., Individual vs. Group Cognitive Behavior Therapy for Anxiety Disorder in Children and Adolescents: A Meta-Analysis of Randomized Controlled Trials. Frontiers in Psychiatry, 2021. 12 (no pagination).	
External validity – selection criteria and characteristics of the systematic review		
Population, n=	<17 years of age with an anxiety diagnosis according to standardized diagnostic criteria by structured interview. 9 RCTs n= 871	
Intervention	Individual CBT (I-CBT)	
Comparison	Group CBT (G-CBT)	
Outcome measures	Anxiety symptoms, acceptability (discontinuation for any reason), remission ("the proportion of participants who achieved a reduction of 50% or more in anxiety rating score or who scored much or very much improved on the anxiety rating scales (e.g., SPAI-C total score <18 and ADIS-IV-C/P total score <4").	
Internal validity – risk of bias in systematic review methods		
Selection bias	Two independent reviewers screened articles but it is not known whether reviewers were blind to authors, institutions and affiliations. The review details specified selection criteria.	
Sampling & publication bias	A comprehensive search strategy is documented and includes unpublished studies; and authors were contacted for additional data.	
Outcome bias	Two independent reviewers extracted data and assessed risk of bias. The Cochrane risk of bias criteria was used.	
Reporting bias	There is a detailed characteristics of included studies table but results of individual studies are not reported or summarised. The strengths and limitations of included studies and potential impact on the results were discussed and appropriate conclusions were made based on appropriately performed meta-analyses. Have presented funnel plots in supplementary info and the potential for publication bias in the results.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	Data and/or effect sizes for each study are presented in forest plots. ***The systematic review is sufficiently reported to adopt the meta-analyses and detailed risk of bias assessments of individual studies into GRADE (Appendix V).***	
Overall risk of bias of the systematic review	Low	Most of the criteria have been fulfilled and where criteria have not been fulfilled it is unlikely the conclusions of the study would be affected.

Asbrand 2020 (RCT)

Study citation	Asbrand, J., et al., Experience Versus Report: Where Are Changes Seen After Exposure-Based Cognitive-Behavioral Therapy? A Randomized Controlled Group Treatment of Childhood Social Anxiety Disorder. Child Psychiatry & Human Development, 2020. 51(3): p. 427-441.	
External validity – selection criteria and characteristics of the RCT		
Population	9-13 years who met DSM-IV criteria for social anxiety disorder (SAD) using Diagnostic Interview for Mental Disorders in Children and Adolescents (Kinder- DIPS). n=67	
Setting	Two German universities.	
Intervention	12-sessions/16 weeks of exposure-based SAD-specific group cognitive behavioral therapy (CBT) n = 31, dropout=1	
Comparison	Waitlist control (WLC) n = 36, dropout during waiting =5, dropout during intervention = 5	
Outcomes	Post treatment state anxiety was the relevant outcome for this review. 3 and 6 month follow up was assessed, however it is unclear if participants are still randomised.	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation and allocation - "block randomization, in which about half of the participants were allocated by drawing from a hat to an experimental condition receiving immediate treatment and half to a WLC condition receiving treatment about 16 weeks later. Randomization for each of two research centers was conducted in a concealed fashion by the other center, based on subject codes, as soon as there were enough participants for one experimental and one WLC allocation."	
Performance bias	Binding not reported and unlikely given the intervention. It is implied that the groups were likely to have been treated the same.	
Detection/outcome bias	Limitations noted that diagnostic interviews were not blinded. No further information provided about blinding of outcome assessors.	
Attrition bias	31/36 participants were allocated to intervention and placebo, respectively. 1/10 participants in intervention and WLC groups, respectively, dropped out. The number of participants' data analysed for the outcome relevant here is not reported.	
Reporting bias	The study briefly reports inclusion/exclusion criteria which are appropriate. It is unclear whether the article is free of selective outcome reporting. The unit of state anxiety data is unclear ie. whether meanSD	
Funding bias	Conflicts of interest and funding were declared.	
Comments	Sample size for state anxiety was calculated (n=54) and met, however diagnostic data sample size was n=62.	
Overall risk of bias of the RCT	Moderate	Some of the criteria have been fulfilled and where criteria have not been fulfilled the conclusions of the study may be affected.

Bilek 2022 (RCT)

Study citation	Bilek, E., et al., Exposure-Focused CBT Outperforms Relaxation-Based Control in an RCT of Treatment for Child and Adolescent Anxiety. Journal of Clinical Child & Adolescent Psychology, 2022. 51(4): p. 410-418	
External validity – selection criteria and characteristics of the RCT		
Population	7-17 years with child anxiety disorders (CADs) diagnosed based on structured clinical interview (mean age = 11.91) n=102 "Study inclusion criteria required anxiety to be the primary source of interference and distress, although comorbidities, such as attention-deficit/ hyperactivity, obsessive–compulsive, and oppositional–defiant disorders were allowed to increase generalizability." Persistent depressive disorder and other/ unspecified depressive disorders were also allowed.	
Setting	Academic medical center in the Midwest, United States	
Intervention	12 sessions of Exposure-Focused Cognitive Behavioral Therapy (EF-CBT) n = 70, 45-60 mins each session	
Comparison	12 sessions of Relaxation Mentorship Training (RMT) n = 32, 45-60 mins each session. Authors noted that only three sessions were completed.	
Outcomes	Measured at week 12 - clinical improvement with Clinical Global Impression – Improvement scale (CGI-I) and anxiety severity was measured with Pediatric Anxiety Rating Scale (PARS). Treatment completion was defined as completing >7 sessions.	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation (ratio 2:1), however allocation not reported.	
Performance bias	Blinding not reported. It is possible that aside from the experimental intervention, the groups were not treated the same, since RMT participants only received three sessions versus 9 sessions in the CBT group.	
Detection/outcome bias	Outcome measures were completed by an independent evaluator unaware of condition.	
Attrition bias	6/7 participants in intervention and comparison groups, respectively, dropped out. ITT. "Fourteen participants did not have CGI-I values at week 12 (CBT: n = 8, 11.4%; RMT: n = 6, 18.8%). Week 12 CGI scores were multiply imputed (10-fold imputation) using the "mice" package in R (R Core Team, 2018) to avoid dropping incomplete cases entirely." No imputation for anxiety symptoms.	
Reporting bias	The study reports specified inclusion/exclusion criteria which are appropriate. It is unknown whether the article is free of selective outcome reporting.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	Authors note that "the sample size while large, was not sufficient to examine a number of treatment predictors."	
Overall risk of bias of the RCT	High	Few of the criteria have been fulfilled and where criteria have not been fulfilled it is likely the conclusions of the study would be affected.

Clementi 2020 (RCT)

Study citation	Clementi, M.A. and C.A. Alfano, An integrated sleep and anxiety intervention for anxious children: A pilot randomized controlled trial. Clinical Child Psychology & Psychiatry, 2020. 25(4): p. 945-957.	
External validity – selection criteria and characteristics of the RCT		
Population	6-12 years who met DSM-IV criteria for primary generalised anxiety disorder (GAD) using ADIS-C/P diagnostic interview (n=20 – doesn't match with other numbers in article) might be 21.	
Setting	Academic, United States	
Intervention	16 weekly 1hr sessions of Targeted Behavioral Therapy (TBT), developed for co-morbid sleep and anxiety problems, n = 15	
Comparison	16 weekly 1hr sessions of "gold standard" cognitive-behavioral therapy (CBT) - The Coping Cat program, n = 15	
Outcomes	Anxiety symptoms with Screen for Child Anxiety-Related Emotional Disorders—Child and Parent Versions (SCARED-C/P).	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation and allocation - "Randomization was conducted using a computerized random number generator…A project coordinator obtained treatment allocation and notified the assigned study therapist."	
Performance bias	"Baseline interviewers and study therapists were naive to the randomization protocol. Interviewers were blind to the child's treatment condition at all assessment points." It is likely that aside from the experimental intervention, the groups were treated the same.	
Detection/outcome bias	Blinding of outcome assessors not reported.	
Attrition bias	4/5 participants in intervention and comparison groups, respectively, dropped out. ITT. 6/7 no longer met criteria for GAD at post treatment.	
Reporting bias	The study reports specified inclusion/exclusion criteria which are appropriate. It is unknown whether the article is free of selective outcome reporting.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	The authors note that the study was underpowered to detect small to moderate effects.	
Overall risk of bias of the RCT	Moderate	Some of the criteria have been fulfilled and where criteria have not been fulfilled it is likely the conclusions of the study may be affected.

Creswell 2020 (RCT)

Study citation	Creswell, C., et al., A randomised controlled trial of treatments of childhood anxiety disorder in the context of maternal anxiety disorder: clinical and cost-effectiveness outcomes. Journal of Child Psychology & Psychiatry & Allied Disciplines, 2020. 61(1): p. 62-76.	
External validity – selection criteria and characteristics of the RCT		
Population	7-12 years who met DSM-IV criteria for a primary anxiety disorder diagnosed based on structured clinical interview using ADIS-C/P, whose mothers also had a current anxiety disorder, n=211	
Setting	University research clinic in Oxford, United Kingdom	
Intervention	8 weekly one-hour sessions of child-focused CBT with nonspecific control interventions (CCBT+Con) n = 71	
Comparison	10 sessions delivered over 8 weeks of CCBT with an intervention targeting the mother–child interaction (CCBT+MCI) n = 71	
Outcomes	Measured post-treatment – remission, clinical improvement with Clinical Global Impression – Improvement scale (CGI-I) and anxiety symptoms was measured with anxiety symptoms (SCAS-c), Child Anxiety Impact Scale (CAIS-c), Conduct problems (SDQ-c), Child Adjustment to School (CAS-t).	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation, however allocation not reported – "Randomisation was performed externally at the Centre for Statistics in Medicine (University of Oxford) on receipt of anonymised participant information by fax. Patients were randomised with a 1:1:1 ratio, with minimisation for child age and gender, type of child anxiety disorder, and baseline severity of both child and maternal primary anxiety disorder."	
Performance bias	All those who collected measurement data were blind to treatment allocation. It is likely that aside from the experimental intervention, the groups were treated the same.	
Detection/outcome bias	Blinding of outcome assessors not reported.	
Attrition bias	15/9 participants in intervention and comparison groups, respectively, dropped out. ITT.	
Reporting bias	The study reports specified inclusion/exclusion criteria which are appropriate. It is unknown whether the article is free of selective outcome reporting.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	"The study was powered to provide 90% power at the 5% (two-sided) significance level to detect a 30% difference in the primary outcome… The required sample size of 56 children per group was increased to allow for an estimated 20% loss to follow-up." A third arm that was not relevant to this review - CCBT with CBT for the maternal anxiety disorder (CCBT+MCBT)	
Overall risk of bias of the RCT	Moderate	Some of the criteria have been fulfilled and where criteria have not been fulfilled it is likely the conclusions of the study may be affected.

Kishida 2021 (RCT)

Study citation	Kishida, K., et al., Transdiagnostic Behavioural Intervention for Children with Anxiety and Depressive Disorders: A Feasibility Study. Behaviour Change., 2021.	
External validity – selection criteria and characteristics of the RCT		
Population	9-12 years who met DSM-IV criteria for anxiety or depressive disorder (but none had depressive) diagnosed based on diagnostic interview, using ADIS (mean age = 9.81) n=16	
Setting	University clinical centre in the Kansai area, Japan	
Intervention	Streamlined Transdiagnostic Intervention for Anxiety and Depression (STREAM) n = 70, 8 sessions over 2 months? ~19 weeks	
Comparison	Waitlist ~11 weeks	
Outcomes	Anxiety severity with Clinician Severity Rating of Principle Diagnosis (CSR), remission.	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation, however allocation method not reported - "independent researcher (HA) randomly assigned them to the STREAM or WLC condition using stratified blocking randomisation based on gender (male or female) and PD (anxiety or depressive disorder)."	
Performance bias	Blinding not reported. It is possible that aside from the experimental intervention, the groups were not treated the same. The therapist for the STREAM condition was a qualified clinical psychologist, whereas the therapists for the WLC condition were doctoral students.	
Detection/outcome bias	"The independent assessors, who were blind to the assignment, were two doctoral students (AU and NA)."	
Attrition bias	None dropped out. ITT.	
Reporting bias	The study reports specified inclusion/exclusion criteria which are appropriate. It is unknown whether the article is free of selective outcome reporting but there seems to be multiple instances of unclear reporting – intervention and comparison conditions and duration.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	No sample size calculation. Due to considerable methodological flaws an insufficient data, this study has not been incorporated into the summary of evidence.	
Overall risk of bias of the RCT	High	Few of the criteria have been fulfilled and where criteria have not been fulfilled it is likely the conclusions of the study would be affected.

Nordh 2021 (RCT)

Study citation	Nordh, M., et al., Therapist-Guided Internet-Delivered Cognitive Behavioral Therapy vs Internet-Delivered Supportive Therapy for Children and Adolescents With Social Anxiety Disorder: A Randomized Clinical Trial. JAMA Psychiatry, 2021. 78(7): p. 705-713.	
External validity – selection criteria and characteristics of the RCT		
Population	10-17 years who met DSM-V criteria for social anxiety disorder (SAD) diagnosed based on structured clinical interview using ADIS-C (mean [SD] age, 14.1 [2.1] years) n=103 "…if taking psychotropic medication, having been taking a stable dose for 6 weeks or more before enrollment."	
Setting	Clinical research unit integrated within the child and adolescent mental health services in Stockholm, Sweden.	
Intervention	10 weeks of therapist-guided ICBT (n = 51) 10 online modules, 5 separate parental modules, and 3 video call sessions with a therapist.	
Comparison	10 weeks of an active comparator, internet-delivered therapist-guided ISUPPORT (n = 52). 10 online modules, 5 separate parental modules, and 3 video call sessions with a therapist.	
Outcomes	Clinician Severity Rating (CSR), derived from the Anxiety Disorder Interview Schedule, diagnostic status of SAD, global functioning, anxiety symptoms, and health-related costs.	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation and allocation concealment – "The random allocation sequence was generated by an independent clinical trials unit, the Karolinska Trial Alliance, in blocks of 4 or 6 and placed in opaque and sealed envelopes. The envelopes were managed by an independent administrator not otherwise involved in the study. An external observer from the Karolinska Trial Alliance also monitored the trial regularly."	
Performance bias	See above regarding blinding. It is likely that aside from the experimental intervention, the groups were treated the same.	
Detection/outcome bias	See above regarding blinding.	
Attrition bias	2/0 participants in intervention and comparison groups, respectively, dropped out. ITT.	
Reporting bias	The study reports specified inclusion/exclusion criteria which are appropriate. It is unknown whether the article is free of selective outcome reporting.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	Adequately powered.	
Overall risk of bias of the RCT	Low	Most of the criteria have been fulfilled and where criteria have not been fulfilled it is unlikely the conclusions of the study would be affected.

Ozyurt 2019 (RCT)

Study citation	Ozyurt, G., et al., Is Triple P effective in childhood anxiety disorder? A randomized controlled study. Psychiatry and Clinical Psychopharmacology, 2019. 29(4): p. 570-578.	
External validity – selection criteria and characteristics of the RCT		
Population	8-12 years who met DSM-IV-TR criteria for anxiety disorders diagnosed based on structured clinical interview using Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Life-time Kiddie (K-SADSPL) n=74	
Setting	Department of Child and Adolescent Psychiatry of Dokuz Eylül University Hospital, Turkey	
Intervention	Triple P - five 2-hour group sessions that educate and actively train skills, and three (15–30 minutes) individual telephone consultations n = 37	
Comparison	Waitlist – no therapy. Children in WL group were in usual order to have visits in Child and Adolescent Psychiatry Department.	
Outcomes	The Screen for Anxiety-Related Emotional Disorders (SCARED), Global Functioning and Severity – The Children's Global Assessment Scale (CGAS), functioning with The Clinical Global Impression-Severity Scale (CGIS), The Strengths and Difficulties Questionnaire (SDQ), The General Health Questionnaire (GHQ), The State-Trait Anxiety Inventory (STAI)	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation, however allocation method not reported – "They were randomized with Random Sequence Generator application in the web site of www.random.org"	
Performance bias	The clinician who assessed and diagnosed the children and parents was blind to intervention and WL group. It is likely that aside from the experimental intervention, the groups were treated the same.	
Detection/outcome bias	As above.	
Attrition bias	11/8 participants in intervention and comparison groups, respectively, dropped out. Per protocol.	
Reporting bias	The study reports specified inclusion/exclusion criteria which are appropriate. It is unknown whether the article is free of selective outcome reporting.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	Adequately powered.	
Overall risk of bias of the RCT	Moderate	Some of the criteria have been fulfilled and where criteria have not been fulfilled it is likely the conclusions of the study may be affected.

Schniering 2022 (RCT)

Study citation	Schniering, C.A., et al., Online treatment of adolescents with comorbid anxiety and depression: A randomized controlled trial. Journal of Affective Disorders, 2022. 311: p. 88-94.	
External validity – selection criteria and characteristics of the RCT		
Population	12-17 years who met DSM-V criteria for anxiety disorder and depressive disorder diagnosed based on structured clinical interview using Anxiety Disorders Interview Schedule for Children and Parents (ADIS-CP) n=91	
Setting	Centre for Emotional Health at Macquarie University, Australia	
Intervention	The Internet based Chilled Plus Program (CP) iCBT - 8-module, online program + 8, 30-min tele sessions with a therapist, of which the caregiver participated in 4 n = 45	
Comparison	Waitlist n = 46	
Outcomes	Number of diagnoses, clinician severity rating: CSR, remission, anxiety symptoms, depression, life interference.	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation, however allocation not reported - "Randomization was created using an internet random number generator and held by the last author, who remained blind to all participant data."	
Performance bias	No further detail about blinding reported. It is likely that aside from the experimental intervention, the groups were treated the same.	
Detection/outcome bias	Not reported.	
Attrition bias	5/5 participants in intervention and comparison groups, respectively, dropped out. ITT. "Because missing data were relatively minor at post-treatment and we were unable to conclude that the data were not missing completely at random (see below), missing data were imputed using the SPSS imputation function with 10 iterations, following which they were subjected to repeated measures analyses of variance (ANOVA)."	
Reporting bias	The study reports specified inclusion/exclusion criteria which are appropriate. It is unknown whether the article is free of selective outcome reporting.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	Power calculation not reported.	
Overall risk of bias of the RCT	Moderate	Some of the criteria have been fulfilled and where criteria have not been fulfilled it is likely the conclusions of the study may be affected.

Silverman 2019 (RCT)

Study citation	Silverman, W.K., et al., Group- versus parent-involvement CBT for childhood anxiety disorders: Treatment specificity and long-term recovery mediation. Clinical Psychological Science, 2019. 7(4): p. 840-855.	
External validity – selection criteria and characteristics of the RCT		
Population	7-16 years who met DSM-IV for anxiety disorders, diagnosed based on structured clinical interview, using the Anxiety Disorders Interview Schedule for Children (Child and Parent Versions; ADISIV: C/P) n=240 "A small proportion was on a stable dose of serotonin reuptake inhibitors (10% GCBT; 6% PCBT)."	
Setting	Academic clinic, United States	
Intervention	Peer group CBT (GCBT) - 12-14 weekly 60 min sessions using in- and out of-session exposures & CBT strategies n=107	
Comparison	CBT involving parents (PCBT) 12 to 14 weekly sessions of 60 min in duration n=133	
Outcomes	Anxiety symptoms using Revised Children's Manifest Anxiety Scale. The Revised Children's Manifest Anxiety Scale (RCMAS), remission, functional impairment using the Children's Global Assessment Scale (C-GAS)	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation, however allocation not reported. "randomly assigned to either GCBT or PCBT in blocks of seven to avoid delay in the formation of groups."	
Performance bias	Blinding not reported. It is likely that aside from the experimental intervention, the groups were treated the same.	
Detection/outcome bias	Not reported.	
Attrition bias	24/33 participants in intervention and comparison groups, respectively, dropped out. Per protocol.	
Reporting bias	The study reports specified inclusion/exclusion criteria which are appropriate. It is unknown whether the article is free of selective outcome reporting.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	Authors note that this was not an efficacy trial.	
Overall risk of bias of the RCT	Moderate	Some of the criteria have been fulfilled and where criteria have not been fulfilled it is likely the conclusions of the study may be affected.

Stjerneklar 2019 (RCT)

Study citation	Stjerneklar, S., et al., A randomized controlled trial examining the efficacy of an internet-based cognitive behavioral therapy program for adolescents with anxiety disorders. PLoS ONE [Electronic Resource], 2019. 14(9): p. e0222485.	
External validity – selection criteria and characteristics of the RCT		
Population	13-17 years who met DSM-IV for anxiety disorders diagnosed based on structured clinical interview, using the Anxiety Disorders Interview Schedule for Children (Child and Parent Versions; ADISIV: C/P) n=70 "Participants in both conditions were encouraged not to engage in other forms of treatment nor make changes to their use of psychiatric medication during the acute treatment and waitlist period."	
Setting	Centre for Psychological Treatment of Children and Adolescents, Aarhus University, Denmark	
Intervention	8 30min online modules over 14 weeks ChilledOut Online plus weekly 20min phone call. n=35	
Comparison	14 weeks waitlist with no planned contact with the project team n=35	
Outcomes	Anxiety symptoms – clinician rated CSR, adolescent and parent rated using SCAS; anxiety life interference using CALIS; self-efficacy using SEQ-C; mental well-being using WHO-5; and treatment satisfaction was measured using the Experience of Service Questionnaire.	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation, however allocation not described - "The randomization sequence was created with an online computer random number generator using permuted block design with a fixed block size of 10 at a 1:1 allocation ratio… The sequence list was kept concealed from researchers and therapists, stored by an external secretary at the University who administered group assignment to included participants according to the randomization sequence."	
Performance bias	Blinding as above – researcher and therapists (conflicts with above) but not participants – "Adolescents randomized to the ICBT condition were informed of their allocation over the phone by their appointed therapist." It is likely that aside from the experimental intervention, the groups were treated the same.	
Detection/outcome bias	"Assessors were blind to group allocation at pre-assessment and of participants' prior diagnoses at post and follow-up. Assessors were also blind to group allocation at post assessment, although most families did reveal their allocation status during the post interview."	
Attrition bias	2/3 participants in intervention and comparison groups, respectively, dropped out. Additional numbers lost to follow up unclear. ITT.	
Reporting bias	The study reports specified inclusion/exclusion criteria which are appropriate. It is unknown whether the article is free of selective outcome reporting.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	Adequately powered.	
Overall risk of bias of the RCT	Moderate	Many of the criteria have been fulfilled and where criteria have not been fulfilled it is possible the conclusions of the study may be affected.

2.4 APPENDIX I: Map of included systematic reviews and their included studies

Shaded columns reflect systematic reviews superseded by the non-shaded systematic reviews that are included in this evidence report.

RCH GL Search July 2022	Articles in Zhou 2019 NMA Search Nov 2017 101 studies: 30 individual CBT 29 individual CBT with parents 25 group CBT 21 group CBT with parents 11 internet CBT 7 parent-only CBT 6 CBT bibliothrpy 3 individual and group BT 3 individual BT with parents 2 individual and group CBT 2 group BT	James 2020 (Cochrane) Search Oct 2019 87 studies	Sigurvinsdottir 2020 Search date NR 81 studies WL=waitlist TAU=treatment as usual AttCon=attention control I=individual G=group F=family R=remote Plus I v G, I v F, I v R All in zhou except Sportel 2013	Baker 2021 Search Dec 2019 All in zhou except Olivares 2002* Stjerneklar 2019# Swain 2015* Waite 2019# Not in any other srs *Diagnostic criteria not specified in table so may assume not reported in original paper. # Outside of search dates	Guo 2021 Search Oct 2019 Individual v group All in zhou except villabo which is in james	Yin 2021 Search June 2019 All in zhou	Cervin 2022 Search Jan 2020 All in zhou except Waite 2019 Jolstedt 2018 Likely bc outside of search dates Use Cervin ROB for the two extra studies	Yang 2019 Search May 2017 All in zhou except Olivares 2005 which is in james

			Suveg 2017 Gil-Bernal 2009 Supplementary material not available					
				Psychological therapies v control	Individual CBT v group CBT	Parent only group CBT v control Parent only group CBT v child+ parent CBT	tCBT v control	Psych interventions v control
✓	1. Afshari 2014	✓						
✓	2. Arendt 2015	✓	gCBT v WL					
✓	3. Azadeh 2015							
✓	4. Baer 2005	×		✓				✓
✓	5. Barrett 1996	✓	fCBT v WL					
✓	6. Barrett 1998	✓	gCBT v WL					
✓	7. Barrington 2005	✓	iCBT v TAU					
✓	8. Beidel 2000	×						✓
×		Berge 2017 - dental						
×	9. Bergman 2013 - SM	×						
✓	10. Bodden 2008	×						

✓	11. Cartwright-Hatton 2011	✓				✓		
✓	12. Chalfant 2007	✓	iCBT v WL					
✓	13. Chavira 2014							
NR		Cheung 2016 – ABM (thesis)						
✓	14. Chiu 2013	✓						
✓	15. Chu 2016							
✓	16. Cobham 1998							
✓	17. Cobham 2012	×	fCBT v WL rCBT v WL					
✓	18. Cobham 2017	✓				✓		
✓	19. Conaughton 2017		rCBT v WL					
×		Cornacchio 2019 – selective mutism (SM)						
✓	20. Cornwall 1996							
✓	21. Creswell 2015							
✓		Creswell 2017 - CBT						
×		Dadds 1997 - prev						
✓	22. de Groot 2007				✓			
✓	23. Donovan 2014		rCBT v WL					
✓	24. Ebrahiminejad 2016	×		✓				
×	25. Esbjørn 2015 - prepost							
✓	26. Flannery-Schroeder	✓	gCBT v		✓			

	2000		WL					
✓	27. Fujii 2013	✓	iCBT v TAU					
✓		Gallagher 2004 - CBT						
✓	28. Garcia-Lopez 2014							
×?			Gil-Bernal 2009 gCBT v WL					
✓	29. Ginsburg 2002	✓	iCBT v AttCon	✓				
✓	30. Ginsburg 2012	✓	iCBT v TAU					
✓		Ginsburg 2019 - STARS						
×?	31. Hancock 2016							
✓		Hancock 2018 – ACT v CBT						
✓	32. Hayward 2000	×	gCBT v WL	✓				✓
✓	33. Herbert 2009	✓	gCBT v AttCon	✓	✓			✓
✓	34. Hirshfeld-Becker 2010	✓	iCBT v WL					
✓	35. Holmes 2014	✓	gCBT v WL					
✓	36. Hudson 2009	✓	gCBT v AttCon					
✓	37. Ingul 2014	✓	gCBT v AttCon	✓	✓			✓
✓		Ishikawa 2019 - CBT						

✓							Jolstedt 2018	
✓	38. Kendall 1994	✓	iCBT v WL					
✓	39. Kendall 1997	✓	iCBT v WL					
✓	40. Kendall 2008	✓	iCBT v AttCon					
✓		Kennedy 2009 – parents with AD						
✓	41. Khanna 2010	✓	iCBT v AttCon				✓	
× ?		Kidd 2018 - CBT						
✓	42. Last 1998	✓						
✓	43. Lau 2010	✓	iCBT v WL					
×		Lau 2017 - prevention						
✓		Lebowitz 2019 - CBT						
✓	44. Leong 2009							
✓		Leutgeb 2012 - psychotherapy						
✓	45. Liber 2008				✓			
✓	46. Lyneham 2006	×						
✓	47. Manassis 2002				✓			
✓	48. March 2009		rCBT v WL				✓	
✓	49. Masia Warner 2005	✓	gCBT v WL	✓				✓
✓	50. Masia Warner 2007	✓	gCBT v	✓				✓

			AttCon					
×?	51. Masia Warner 2011	✓	iCBT v WL					
✓	52. Masia Warner 2016	✓		✓				✓
✓	53. McConachie 2014	✓						
✓		McNally Keehn 2013 – Coping Cat/ASD	iCBT v WL					
✓	54. Melfsen 2011	✓	iCBT v WL					✓
✓	55. Mendlowitz 1999	×				✓		
✓	56. Monga 2015					✓		
✓	57. Muris 2001				✓			
✓	58. Muris 2002	✓						
✓	59. Muris 2002							
✓		Murphy 2017 – CBT/ ASD						
✓	60. Nauta 2001							
✓	61. Nauta 2003	×	iCBT v WL					
✓		O'Brien 2007 - gCBT						
×	62. Oerbeck 2014 (selective mutism?)	×						
×?		Olivares 2005 - phobia	gCBT v WL					✓
×?				Olivares 02				
×?	63. Olivares 2014	✓						✓
✓		Olivares 2019 – social						

		skills training						
✓		Ollendick 2009 – one session treatment						
× ?	64. Ortbandt 2009							
✓		Ost 2001 – one session treatment						
✓	65. Öst 2015	×						✓
✓	66. Özyurt 2016					✓		
✓		Perrin 2019 - CBT						
× s y m p	67. Pina 2012							
✓	68. Pincus 2010	✓		✓				
×		Rapee 2005 - prevntion						
✓	69. Rapee 2006	✓						
✓		Reaven 2012 – gCBT/ ASD						
✓		Reigada 2015 – CBT/GI						
× ?	70. Rodríguez 2005							
× ?	71. Rosa-Alcázar 2009	✓						✓
✓		Salari 2018 - pCBT						
✓		Salum 2018 – CBT, ABM						
✓	72. Sánchez-García 2009	✓						✓

✓		Santucci 2013 - CAMP						
✓	73. Schneider 2011	✓	iCBT v WL					
✓	74. Schneider 2013							
× ?	75. Sciberras 2015							
✓		Sciberras 2018 – CBT/ ADHD						
×		Shahnavaz 2016 – CBT - dental						
✓		Sharma 2017 – tCBT/ headache						
✓	76. Shortt 2001	✓	fCBT v WL					
✓	77. Silk 2013							
✓		Silk 2018 - iCBT						
✓	78. Silverman 1999	✓	gCBT v WL					
✓	79. Silverman 1999	✓	iCBT v AttCon					
✓	80. Silverman 2009							
×		Simon 2011 - prevntion						
✓	81. Siqueland 2005							
✓	82. Smith 2014	✓						
✓	83. Spence 2000	✓	fCBT v WL					✓
✓	84. Spence 2006	✓	rCBT v WL				✓	

✓	85. Spence 2011	✓	rCBT v WL	✓			✓	
✓	86. Spence 2017		rCBT v WL				✓	✓
✓			Sportel 2013 gCBT v WL					
✓				Stjerneklar 2019				
✓	87. Storch 2013	✓	iCBT v TAU					
✓	88. Storch 2015	✓	gCBT v TAU				✓	
✓	89. Storch 2015		iCBT v TAU					
✓		Southam Gerow 2010 - CBT	gCBT v TAU					
×prepost			Suveg 2017 iCBT v AttCon					
✓				Swain 2015				
✓	90. Thirlwall 2013	✓						
✓	91. Tillfors 2011							✓
×	92. Treadwell 1996							
✓	93. Vigerland 2016		rCBT v WL				✓	
✓		Villabo 2018 - CBT			✓			
✓				Waite 2019			Waite	

							2019	
✓		Walkup 2008 – CAMS/ CBT						
✓	94. Waters 2009	✓				✓		
✓	95. Wergeland 2014	✓	gCBT v WL		✓			
✓	96. White 2013	✓						
✓	97. Whiteside 2015							
✓	98. Wood 2006							
✓	99. Wood 2009	✓	iCBT v WL					
✓	100. Wood 2015	✓	iCBT v WL					
✓	101. Wuthrich 2012		rCBT v WL	✓				

2.5 APPENDIX II: James GRADE summary of findings

SUMMARY OF FINDINGS

Summary of findings 1. CBT compared with waitlist for children and adolescents with anxiety disorders

CBT compared with waitlist for children and adolescents with anxiety disorders

Patient or population: children and adolescents with anxiety disorders

Settings: outpatient clinics/schools

Intervention: CBT

Comparison: waitlist/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Waitlist[1]	CBT				
Remission of primary anxiety diagnosis post-treatment (ITT)	**178 per 1000**	**541 per 1000** (458 to 622)	**OR 5.45** (3.90 to 7.60)	2697 (39 studies)	⊕⊕⊕⊖ **moderate** [2]	Subgroup analyses: • Difference in outcomes for different delivery formats (child-focused, child and parent, parent only) (Chi^2 = 8.57, df = 2, P = 0.01, I^2 = 76.7%) • No difference in outcomes for individual versus group formats (Chi^2 = 0.90, df = 1, P = 0.34; I^2 = 0%) • No difference in outcomes for interventions with different amounts of therapist contact (Chi^2 = 0.52, df = 2, P = 0.77; I^2 = 0%) • No difference in outcomes for participants with and without ASD (Chi^2 = 2.25, df = 1, P = 0.13; I^2 = 55.5%)
Acceptability (number of participants lost to post-treatment assessment)	**104 per 1000**	**112 per 1000** (90 to 141)	**OR 1.09** (0.85 to 1.41)	3158 (45 studies)	⊕⊕⊖⊖ **low** [3]	
Remission of all anxiety diagnoses post-treatment (ITT)	**191 per 1000**	**512 per 1000** (406 to 616)	**OR 4.43** (2.89 to 6.78)	2075 (28 studies)	⊕⊕⊕⊖ **moderate** [2]	Subgroup analyses:

					• Difference in outcomes for different delivery formats (child-focused, child and parent, parent only) (Chi^2 = 8.14, df = 2, P = 0.02, I^2 = 75.4%) • No difference in outcomes for individual versus group formats (Chi^2 = 0.35, df = 1, P = 0.56; I^2 = 0%) • Difference in outcomes for interventions with different amounts of therapist contact (Chi^2 = 10.75, df = 2, P= 0.005; I^2 = 81.4%) • Insufficient studies for subgroup analyses examining outcomes for participants with and without ASD
Reduction in anxiety symptoms (child report) post-treatment	The mean anxiety symptoms (child report) in the CBT groups was **0.67 standard deviations** lower (0.88 to 0.47 lower).	Moderate effect size	2831 (45 studies)	⊕⊕⊖⊖ **low** [4]	Subgroup analyses: • Difference in outcomes for different delivery formats (child-focused, child and parent, parent only) (Chi^2 = 14.67,df = 2, P < 0.001, I^2 = 86.4%) • Difference in outcomes for individual versus group formats (Chi^2 =6.47, df = 1, P = 0.01; I^2 = 84.5%) • No difference in outcomes for interventions with different amounts of therapist contact (Chi^2 = 3.33, df = 2, P = 0.19; I^2 = 39.9%) • No difference in outcomes for participants with and without ASD (Chi^2 = 0.02, df = 1, P = 0.88; I^2 = 0%)
Reduction in anxiety symptoms (parent report) post-treatment	The mean anxiety symptoms (parent report) in the CBT groups was **0.70 standard deviations** lower (0.90 to 0.51 lower).	Moderate effect size	2137 (35 studies)	⊕⊕⊖⊖ **low** [4]	Subgroup analyses: • No difference in outcomes for different delivery formats (child-focused, child and parent, parent only) (Chi^2 = 3.43, df = 2, P = 0.18, I^2 = 41.8%) • Difference in outcomes for individual versus group formats (Chi^2 = 6.79,df = 1, P = 0.009, I^2 = 85.3%) • No difference in outcomes for interventions with different amounts of therapist contact (Chi^2 = 3.77, df = 2, P = 0.15; I^2 = 46.9%) • No difference in outcomes for participants with and without ASD (Chi^2 = 1.42, df = 1, P = 0.23; I^2 = 29.8%)
Reduction in depressive symptoms post-treatment	The mean depressive symptoms in the CBT groups was **0.34 standard deviations** lower (0.51 to 0.17 lower).	Small effect size	1157 (17 studies)	⊕⊕⊕⊖ **moderate** [2]	
Improvement in global function-	The mean global functioning in the CBT groups was **1.03 standard de-**	Large effect size	557 (11 studies)	⊕⊕⊖⊖ **low** [5]	

ing post-treatment	**viations** higher (0.68 to 1.38 higher).					
Adverse events (randomisation to post-treatment)	See comment	See comment	Not estimable	-	See comment	No study reported adverse events in both CBT and waitlist/no treatment groups

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CBT: cognitive behavioural therapy; **CI:** confidence interval; **ITT:** intention-to-treat; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1]Control group risk estimates come from pooled estimates of waitlist groups.
[2]Downgraded one level due to moderate heterogeneity (inconsistency).
[3]Downgraded two levels due large variation in treatment effects across studies (inconsistency) and wide confidence intervals (imprecision).
[4]Downgraded two levels due to substantial heterogeneity (inconsistency).
[5]Downgraded two levels due to substantial heterogeneity (inconsistency) and assessed and reported in small number of eligible studies (study limitations).

Summary of findings 2. CBT compared with treatment as usual for anxiety disorders in children and adolescents

CBT compared with treatment as usual for anxiety disorders in children and adolescents

Patient or population: children and adolescents with anxiety disorders

Settings: outpatient clinics/schools

Intervention: CBT

Comparison: treatment as usual

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk[1]	Corresponding risk				

	Treatment as usual	CBT				
Remission of primary anxiety diagnosis post-treatment (ITT)	**408 per 1000**	**687 per 1000** (383 to 886)	**OR 3.19** (0.90 to 11.29)	487 (8 studies)	⊕⊕⊖⊖ **low** [2]	Subgroup analyses: • Difference in outcomes for different delivery formats (child-focused versus child and parent) ($Chi^2 = 10.90$, df = 1, $P < 0.001$, $I^2 = 90.8\%$) • Insufficient studies for subgroup analyses examining differences in outcomes for individual versus group formats and interventions with varying-amount of therapist contact time • Difference in outcomes for participants with and without ASD ($Chi^2 = 5.71$, df = 1, $P = 0.02$; $I^2 = 82.5\%$)
Acceptability (number of participants lost to post-treatment assessment)	**93 per 1000**	**124 per 1000** (70 to 209)	**OR 1.37** (0.73 to 2.56)	441 (8 studies)	⊕⊕⊖⊖ **low** [3]	
Remission of all anxiety diagnoses post-treatment (ITT)	**414 per 1000**	**660 per 1000** (451 to 820)	**OR 2.74** (1.16 to 6.46)	203 (5 studies)	⊕⊕⊖⊖ **low** [3]	
Reduction in anxiety symptoms (child report) post-treatment	The mean anxiety symptoms (child report) in the CBT groups was **0.15 standard deviations** lower (0.78 lower to 0.48 higher).		Cross 0	214 (6 studies)	⊕⊕⊖⊖ **low** [2]	
Reduction in anxiety symptoms (parent report) post-treatment	The mean anxiety symptoms (parent report) in the CBT groups was **0.32 standard deviations** lower (0.70 lower to 0.06 higher).		Cross 0	228 (7 studies)	⊕⊕⊖⊖ **low** [2]	
Reduction in depressive symptoms post-treatment	See comment		Not estimable	-	See comment	Insufficient evidence to estimate effect
Improvement in global functioning post-treatment	See comment		Not estimable	-	See comment	Insufficient evidence to estimate effect

Adverse events (randomisation to post-treatment)	See comment	See comment	Not estimable	-	See comment	No study reported adverse events in both CBT and Treatment as Usual groups

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CBT: cognitive behavioural therapy; **CI:** confidence interval; **ITT:** intention-to-treat; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1]Control group risk estimates come from pooled estimates of treatment as usual groups.
[2]Downgraded two levels due to at least moderate heterogeneity (inconsistency) and wide confidence intervals and small number of events or participants (imprecision).
[3]Downgraded two levels due to large variation in treatment effects across studies (inconsistency) and wide confidence intervals and small number of events (imprecision).

Summary of findings 3. CBT compared with attention control for anxiety disorders in children and adolescents

CBT compared with attention control for anxiety disorders in children and adolescents

Patient or population: children and adolescents with anxiety disorders

Settings: outpatient clinics/schools

Intervention: CBT

Comparison: attention control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Attention control[1]	Corresponding risk CBT				
Remission of primary anxiety diagnosis post-treatment (ITT)	**293 per 1000**	**486 per 1000** (355 to 617)	**OR 2.28** (1.33 to 3.89)	822 (10 studies)	⊕⊕⊖⊖ **low** [2,]	Subgroup analyses: • Difference in outcomes for different delivery formats (child-focused

						versus child and parent) (Chi^2 = 7.65, df = 1, P = 0.006; I^2 = 86.9%) • No difference in outcomes for individual versus group formats (Chi^2 = 1.22, df = 1, P = 0.27; I^2 = 17.7%) • Insufficient studies for subgroup analyses examining outcomes for interventions with varying amounts of therapist contact, and participants with and without ASD
Acceptability (number of participants lost to post-treatment assessment)	**201 per 1000**	**201 per 1000** (146 to 272)	**OR 1.00** (0.68 to 1.49)	797 (12 studies)	⊕⊕⊖⊖ **low** [3]	
Remission of all anxiety diagnoses post-treatment (ITT)	**185 per 1000**	**385 per 1000** (217 to 584)	**OR 2.75** (1.22 to 6.17)	378 (5 studies)	⊕⊕⊖⊖ **low** [2]	
Reduction in anxiety symptoms (child report) post-treatment	The mean anxiety symptoms (child report) in the CBT groups was **0.31 standard deviations** lower (0.51 to 0.11 lower).		Small effect size	978 (15 studies)	⊕⊕⊕⊖ **moderate** [4]	
Reduction in anxiety symptoms (parent report) post-treatment	The mean anxiety symptoms (parent report) in the CBT groups was **0.25 standard deviations** lower (0.61 lower to 0.11 higher).		Cross 0	638 (8 studies)	⊕⊕⊖⊖ **low** [5]	
Reduction in depressive symptoms post-treatment	The mean depressive symptoms in the CBT groups was **0.18 standard deviations** lower (0.45 lower to 0.09 higher).		Cross 0	613 (10 studies)	⊕⊕⊖⊖ **low** [5]	
Improvement in global functioning post-treatment	See comment		Not estimable	-	See comment	Insufficient evidence to estimate effect
Adverse events (randomisation to post-treatment)	See comment	See comment	Not estimable	-	See comment	No study reported adverse events in both CBT and attention control groups

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CBT: cognitive behavioural therapy; **CI:** confidence interval; **ITT:** intention-to-treat; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1]Control group risk estimates come from pooled estimates of attention control groups.
[2]Downgraded two levels due to at least moderate heterogeneity and large variation in treatment effects (inconsistency) and small number of events (imprecision).
[3]Downgraded two levels due to large variation in treatment effects across studies (inconsistency) and wide confidence intervals and small number of events (imprecision).
[4]Downgraded one level due to moderate heterogeneity (inconsistency).
[5]Downgraded two levels due to at least moderate heterogeneity (inconsistency) and wide confidence intervals (imprecision).

2.6 APPENDIX III: Summary of Zhou 2019 network meta-analysis (NMA) and GRADE

Intervention	Effect estimate vs. placebo (mean overall change in anxiety symptoms)	Confidence in effect estimate vs. placebo (GRADE)	Anxiety symptoms		Acceptability (all cause discontinuation)		QoL & functional improvement	
			No statistically significant difference vs.	Statistically significantly better than	No statistically significant difference vs.	Statistically significantly more acceptable than	No statistically significant difference vs.	Statistically significantly better than
G-CBT	SMD -0.76, 95% CrI -1.16 to -0.36	⊕⊕◯◯ LOW Downgrade by two levels due to study limitations, and heterogeneity	G-BT I/P-BT I/G-BT I/G-CBT	I-CBT G/P-CBT I/P-CBT P-CBT BiB-CBT TAU Int-CBT NT WL PBO	All other interventions	BiB-CBT	All other interventions with data	PBO, WL
G/P-CBT	SMD -0.33, 95% CrI -0.78 to 0.13	⊕◯◯◯ VERY LOW Downgrade by three levels due to study limitations, imprecision, and indirectness	All other interventions	WL	All other interventions	BiB-CBT	All other interventions with data	PBO, WL
I-CBT	SMD -0.32, 95% CrI -0.72 to 0.07	⊕◯◯◯ VERY LOW Downgrade by three levels due to study	All other interventions	WL	All other interventions	BiB-CBT	All other interventions with data	PBO, WL

		limitations, imprecision, and heterogeneity						
I/P-CBT	SMD -0.18, 95% CrI -0.61 to 0.25	⊕⊕◯◯ LOW Downgrade by two levels due to study limitations, and imprecision	All other interventions	WL	All interventions	None	All other interventions with data	PBO, WL
P-CBT	SMD -0.04, 95% CrI -0.67 to 0.60	⊕⊕◯◯ LOW Downgrade by two levels due to study limitations, and imprecision	All other interventions	WL	All interventions	None	All other interventions with data	TAU, PBO, WL
I/G-CBT	SMD 0.03, 95% CrI -1.10 to 1.16	⊕⊕◯◯ LOW Downgrade by two levels due to study limitations, and imprecision	All other interventions, including WL	None	All interventions	None	All interventions with data	None
Int-CBT	SMD 0.06, 95% CrI -0.48 to 0.60	⊕◯◯◯ VERY LOW Downgrade by three levels due to study limitations, imprecision, and indirectness	All other interventions	WL	All interventions	None	All other interventions with data	PBO, WL
BIB-CBT	SMD –0.03, 95% CrI -0.68 to 0.61	⊕⊕◯◯ LOW Downgrade by two levels due to study limitations, and imprecision	All other interventions	WL	All other interventions	None	All interventions with data	None

G-BT	SMD -0.77, 95% CrI -1.76 to 0.22	⊕⊕◯◯ LOW Downgrade by two levels due to study limitations, and imprecision	All other interventions	WL	All interventions	None	No data	No data
I/G-BT	SMD -0.06, 95% CrI -0.94 to 0.82	⊕◯◯◯ VERY LOW Downgrade by three levels due to study limitations, study imprecision, and indirectness	All interventions	None	All interventions	None	All interventions with data	None
I/P-BT	SMD -0.42, 95% CrI -1.29 to 0.44	⊕◯◯◯ VERY LOW Downgrade by three levels due to study limitations, imprecision, and indirectness	All other interventions	WL	All interventions	None	No data	No data
NT	SMD 0.18, 95% CrI -0.66 to 1.03	⊕⊕◯◯ LOW Downgrade by two levels due to study limitations, and imprecision	All other interventions, including WL	None	All other interventions	BiB-CBT	No data	No data
TAU	SMD 0.08, 95% CrI -0.58 to 0.74	⊕⊕◯◯ LOW Downgrade by two levels due to study limitations, and imprecision	All other interventions, including WL	None	All interventions	None	All interventions with data	None
WL	SMD 0.67, 95% CrI 0.27 to 1.07	⊕⊕◯◯ LOW Downgrade by two levels due to	As above	None	All other interventions	BiB-CBT	As above	None

		study limitations, and indirectness						

Figure 3. Network Meta-analysis of Efficacy and Acceptability Posttreatment

Treatment | Efficacy posttreatment | Acceptability

G-CBT	0.21 (0.04 to 3.83)	1.54 (0.34 to 4.56)	0.96 (0.52 to 1.59)	1.00 (0.53 to 1.68)	0.80 (0.42 to 1.38)	1.09 (0.23 to 3.11)	0.57 (0.27 to 1.47)	**0.33 (0.16 to 0.84)**	3.86 (0.16 to 20.36)	0.85 (0.46 to 1.44)	1.38 (0.42 to 3.41)	0.94 (0.40 to 1.90)	3.10 (0.55 to 10.71)	0.93 (0.57 to 1.63)
0.01 (-0.94 to 0.95)	**G-BT**	7.11 (0.24 to 39.16)	4.39 (0.24 to 22.08)	4.55 (0.25 to 23.15)	3.66 (0.20 to 18.34)	5.06 (0.17 to 27.57)	0.75 (0.15 to 16.49)	0.43 (0.09 to 9.48)	19.07 (0.17 to 111.20)	3.99 (0.21 to 20.48)	6.34 (0.26 to 33.66)	4.27 (0.22 to 21.95)	14.77 (0.39 to 87.48)	1.21 (0.27 to 22.51)
-0.34 (-1.21 to 0.54)	-0.35 (-1.59 to 0.90)	**I/P-BT**	0.91 (0.21 to 2.53)	0.62 (0.21 to 2.75)	0.75 (0.18 to 2.07)	0.49 (0.13 to 3.76)	0.39 (0.12 to 2.13)	0.23 (0.07 to 1.20)	0.56 (0.10 to 21.07)	0.81 (0.19 to 2.27)	1.33 (0.20 to 4.62)	0.90 (0.18 to 2.82)	3.13 (0.28 to 13.74)	0.64 (0.22 to 2.72)
-0.44 (-0.82 to -0.06)	-0.46 (-1.41 to 0.52)	-0.10 (-0.94 to 0.74)	**I-CBT**	1.00 (0.60 to 1.80)	0.85 (0.54 to 1.27)	0.78 (0.72 to 3.30)	0.63 (0.30 to 1.58)	**0.37 (0.18 to 0.88)**	0.90 (0.17 to 21.90)	0.92 (0.52 to 1.52)	1.49 (0.47 to 3.70)	1.02 (0.46 to 1.99)	3.51 (0.55 to 12.75)	1.02 (0.67 to 1.67)
-0.43 (-0.82 to -0.04)	-0.44 (-1.41 to 0.53)	-0.09 (-0.97 to 0.78)	0.01 (-0.39 to 0.40)	**G/P-CBT**	0.83 (0.47 to 1.37)	1.14 (0.25 to 3.26)	0.62 (0.32 to 1.39)	**0.35 (0.18 to 0.83)**	4.01 (0.17 to 21.06)	0.90 (0.46 to 1.60)	1.45 (0.44 to 3.69)	0.98 (0.45 to 1.92)	3.40 (0.53 to 12.51)	0.99 (0.67 to 1.55)
-0.58 (-0.99 to -0.18)	-0.59 (-1.56 to 0.38)	-0.24 (-1.08 to 0.60)	-0.14 (-0.45 to 0.16)	-0.15 (-0.53 to 0.23)	**I/P-CBT**	0.93 (0.31 to 3.99)	0.76 (0.36 to 1.91)	0.44 (0.22 to 1.05)	1.08 (0.21 to 26.36)	1.11 (0.60 to 1.90)	1.78 (0.58 to 4.35)	1.22 (0.56 to 2.37)	4.24 (0.65 to 15.51)	1.23 (0.80 to 2.02)
-0.70 (-1.60 to 0.20)	-0.71 (-1.96 to 0.55)	-0.36 (-1.54 to 0.82)	-0.26 (-1.15 to 0.63)	-0.27 (-1.17 to 0.63)	-0.12 (-1.02 to 0.78)	**I/G-BT**	0.56 (0.18 to 3.07)	0.32 (0.10 to 1.77)	5.26 (0.14 to 29.66)	1.13 (0.28 to 3.19)	1.89 (0.29 to 6.70)	1.28 (0.26 to 4.08)	4.43 (0.38 to 19.76)	0.90 (0.32 to 3.95)
-0.73 (-1.31 to -0.14)	-0.73 (-1.79 to 0.33)	-0.38 (-1.36 to 0.59)	-0.29 (-0.87 to 0.29)	-0.29 (-0 .84 to 0.25)	-0.14 (-0.73 to 0.44)	-0.02 (-1.02 to 0.96)	**P-CBT**	0.51 (0.22 to 1.55)	6.31 (0.24 to 34.14)	1.43 (0.53 to 3.14)	2.31 (0.55 to 6.57)	1.55 (0.54 to 3.57)	5.42 (0.70 to 21.27)	1.43 (0.75 to 3.15)
-0.73 (-1.35 to -0.11)	-0.74 (-1.80 to 0.34)	-0.39 (-1.37 to 0.59)	-0.29 (-0.87 to 0.29)	-0.30 (-0.89 to 0.30)	-0.15 (-0.72 to 0.43)	-0.03 (-1.04 to 0.98)	0.00 (-0.74 to 0.74)	**BIB-CBT**	10.83 (0.41 to 58.53)	2.46 (0.93 to 5.31)	3.97 (0.98 to 11.14)	2.67 (0.95 to 6.15)	**9.32 (1.22 to 36.39)**	**2.48 (1.31 to 5.37)**
-0.79 (-1.89 to 0.31)	-0.80 (-2.20 to 0.61)	-0.45 (-1.79 to 0.90)	-0.35 (-1.45 to 0.74)	-0.36 (-1.45 to 0.74)	-0.21 (-1.30 to 0.89)	-0.09 (-1.45 to 1.28)	-0.05 (-1.23 to 1.11)	-0.06 (-1.25 to 1.12)	**I/G-CBT**	1.01 (0.04 to 5.23)	1.62 (0.05 to 8.61)	1.09 (0.04 to 5.67)	3.87 (0.08 to 23.15)	0.26 (0.05 to 5.73)
-0.76 (-1.16 to -0.36)	-0.77 (-1.76 to 0.22)	-0.42 (-1.29 to 0.44)	-0.32 (-0.72 to 0.07)	-0.33 (-0.78 to 0.13)	-0.18 (-0.61 to 0.25)	-0.05 (-0.94 to 0.82)	-0.04 (-0.67 to 0.60)	-0.03 (-0.68 to 0.61)	0.03 (-1.10 to 1.16)	**PBO**	1.71 (0.50 to 4.38)	0.98 (0.48 to 2.40)	2.07 (0.61 to 14.46)	1.13 (0.67 to 2.11)
-0.84 (-1.47 to -0.21)	-0.85 (-1.94 to 0.25)	-0.50 (-1.50 to 0.49)	-0.40 (-1.01 to 0.20)	-0.41 (-1.05 to 0.23)	-0.26 (-0.83 to 0.31)	-0.14 (-1.17 to 0.89)	-0.12 (-0.89 to 0.66)	-0.11 (-0.89 to 0.67)	-0.05 (-1.26 to 1.16)	-0.08 (-0.74 to 0.58)	**TAU**	0.63 (0.25 to 2.13)	1.29 (0.33 to 12.22)	0.70 (0.29 to 2.11)
-0.82 (-1.33 to -0.31)	-0.83 (-1.84 to 0.18)	-0.48 (-1.40 to 0.44)	-0.38 (-0.86 to 0.10)	-0.39 (-0.88 to 0.10)	-0.24 (-0.72 to 0.24)	-0.12 (-1.07 to 0.82)	-0.10 (-0.75 to 0.56)	-0.09 (-0.76 to 0.58)	-0.03 (-1.16 to 1.10)	-0.06 (-0.60 to 0.48)	0.02 (-0.65 to 0.69)	**Int-CBT**	3.85 (0.53 to 14.51)	1.05 (0.59 to 2.05)
-0.94 (-1.69 to -0.20)	-0.95 (-2.16 to 0.26)	-0.60 (-1.75 to 0.54)	-0.50 (-1.34 to 0.33)	-0.51 (-1.35 to 0.33)	-0.36 (-1.21 to 0.49)	-0.24 (-1.41 to 0.93)	-0.22 (-1.16 to 0.73)	-0.21 (-1.18 to 0.76)	-0.15 (-1.49 to 1.18)	-0.18 (-1.03 to 0.66)	-0.10 (-1.07 to 0.87)	-0.12 (-1.08 to 0.78)	**NT**	0.30 (0.08 to 1.89)
-1.43 (-1.76 to -1.09)	**-1.43 (-2.36 to -0.51)**	**-1.09 (-1.93 to -0.25)**	**-0.99 (-1.30 to -0.68)**	**-0.99 (-1.31 to -0.68)**	**-0.84 (-1.16 to -0.53)**	-0.73 (-1.59 to 0.13)	**-0.70 (-1.22 to -0.19)**	**-0.70 (-1.24 to -0.15)**	-0.64 (-1.69 to 0.41)	**-0.67 (-1.07 to -0.27)**	-0.59 (-1.18 to 0.01)	**-0.61 (-1.02 to -0.20)**	-0.49 (-1.31 to 0.33)	**WL**

Treatments are reported in order of efficacy posttreatment with ranking according to surface under the cumulative ranking curves. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Efficacy posttreatment values are given as mean overall change in symptoms (standardized mean differences [SMDs]); SMDs of less than 0 favor the column-defining treatment. Acceptability values are given as all-cause discontinuation (odds ratios [ORs]); an OR of less than 1.00 favors the row-defining treatment. Data in parentheses represent 95% credible intervals. To obtain ORs for comparisons in the opposing direction, reciprocals should be taken. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. Significant results are set in boldface. Bib-CBT indicates bibliotherapy cognitive behavioral therapy; G-BT, group BT without cognitive restructuring; G-CBT, group CBT; G/P-CBT, group CBT with parental involvement; I-CBT, individual CBT; I/G-BT, individual and group BT; I/G-CBT, individual and group CBT; Int-CBT, Internet-assisted CBT; I/P-BT, individual BT with parental involvement; I/P-CBT, individual CBT with parental involvement; NT, no treatment; PBO, psychological placebo; P-CBT, parent-only CBT; TAU, treatment as usual; and WL, wait list.

Figure 4. Network Meta-analysis of Efficacy at End of Follow-Up and Quality of Life and Functional Improvement

Treatment | Efficacy at end of follow-up | Quality of life and functional improvement

P-CBT	...	1.14 (-0.10 to 2.37)	**1.60 (0.20 to 2.98)**	1.15 (-0.18 to 2.47)	1.12 (-0.61 to 2.87)	1.12 (-0.19 to 2.43)	0.86 (-0.42 to 2.14)	1.07 (-0.22 to 2.35)	...	1.20 (-0.27 to 2.67)	1.32 (-0.38 to 3.03)	**1.99 (0.65 to 3.34)**	**1.87 (0.71 to 3.04)**	...
-0.02 (-1.68 to 1.64)	**I/P-BT**	...	...	...	...	...	...	...	...	...	...	...	...	...
0.00 (-1.89 to 1.89)	0.02 (-1.91 to 1.98)	**Int-CBT**	0.46 (-0.28 to 1.19)	0.01 (-0.69 to 0.70)	-0.01 (-1.33 to 1.30)	-0.02 (-0.71 to 0.66)	-0.28 (-0.87 to 0.31)	-0.07 (-0.64 to 0.51)	...	0.06 (-0.89 to 1.00)	0.19 (-1.11 to 1.49)	**0.86 (0.15 to 1.57)**	**0.73 (0.33 to 1.14)**	...
-0.10 (-1.61 to 1.41)	-0.08 (-1.69 to 1.53)	-0.10 (-1.92 to 1.70)	**TAU**	-0.45 (-1.37 to 0.47)	-0.47 (-1.90 to 0.96)	-0.48 (-1.36 to 0.41)	-0.74 (-1.54 to 0.07)	-0.53 (-1.17 to 0.12)	...	-0.40 (-1.52 to 0.73)	-0.27 (-1.71 to 1.18)	0.40 (-0.54 to 1.34)	0.27 (-0.47 to 1.02)	...
-0.15 (-1.28 to 0.99)	-0.13 (-1.46 to 1.21)	-0.15 (-1.75 to 1.45)	-0.04 (-1.10 to 1.00)	**G-CBT**	-0.02 (-1.38 to 1.35)	-0.03 (-0.79 to 0.73)	-0.29 (-0.97 to 0.40)	-0.08 (-0.82 to 0.67)	...	0.05 (-0.90 to 1.02)	0.18 (-1.19 to 1.56)	**0.85 (0.26 to 1.45)**	**0.73 (0.11 to 1.34)**	...
-0.16 (-1.46 to 1.15)	-0.13 (-1.54 to 1.28)	-0.16 (-1.82 to 1.50)	-0.05 (-1.32 to 1.21)	-0.01 (-0.89 to 0.87)	**Bib-CBT**	-0.01 (-1.40 to 1.38)	-0.26 (-1.44 to 0.92)	-0.06 (-1.37 to 1.26)	...	0.08 (-1.45 to 1.60)	0.20 (-1.59 to 1.99)	0.87 (-0.49 to 2.24)	0.75 (-0.54 to 2.04)	...
-0.17 (-1.23 to 0.89)	-0.14 (-1.53 to 1.23)	-0.17 (-1.82 to 1.48)	-0.06 (-1.24 to 1.11)	-0.02 (-0.64 to 0.61)	-0.01 (-0.88 to 0.86)	**G/P-CBT**	-0.26 (-0.99 to 0.48)	-0.05 (-0.73 to 0.64)	...	0.08 (-0.96 to 1.12)	0.21 (-1.16 to 1.58)	**0.88 (0.05 to 1.70)**	**0.75 (0.17 to 1.34)**	...
-0.18 (-1.36 to 1.01)	-0.16 (-1.42 to 1.10)	-0.18 (-1.66 to 1.29)	-0.08 (-1.14 to 0.98)	-0.03 (-0.65 to 0.58)	-0.02 (-0.78 to 0.74)	-0.02 (-0.74 to 0.72)	**I-CBT**	0.21 (-0.37 to 0.79)	...	0.34 (-0.63 to 1.31)	0.46 (-0.88 to 1.82)	**1.13 (0.45 to 0.82)**	**1.01 (0.48 to 1.55)**	...
-0.19 (-1.41 to 1.02)	-0.17 (-1.40 to 1.06)	-0.20 (-1.72 to 1.32)	-0.09 (-1.20 to 1.02)	-0.05 (-0.73 to 0.64)	-0.04 (-0.78 to 0.71)	-0.03 (-0.80 to 0.75)	-0.01 (-0.40 to 0.37)	**I/P-CBT**	...	0.13 (-0.87 to 1.12)	0.26 (-1.09 to 1.61)	**0.93 (0.16 to 1.70)**	**0.80 (0.27 to 1.33)**	...
-0.47 (-2.25 to 1.31)	-0.44 (-2.36 to 1.47)	-0.47 (-2.57 to 1.63)	-0.36 (-2.09 to 1.37)	-0.32 (-1.69 to 1.05)	-0.31 (-1.94 to 1.32)	-0.30 (-1.81 to 1.21)	-0.29 (-1.80 to 1.22)	-0.27 (-1.82 to 1.26)	**G-BT**	...	...	...	...	...
...	...	...	...	...	...	...	...	...	...	**I/G-BT**	0.12 (-1.39 to 1.65)	0.79 (-0.09 to 1.68)	0.67 (-0.21 to 1.96)	...
...	...	...	...	...	...	...	...	...	...	...	**I/G-CBT**	0.67 (-0.73 to 2.07)	0.55 (-0.69 to 1.78)	...
-0.51 (-1.71 to 0.70)	-0.48 (-1.73 to 0.76)	-0.51 (-2.12 to 1.10)	-0.40 (-1.58 to 0.76)	-0.36 (-1.05 to 0.33)	-0.35 (-1.26 to 0.56)	-0.34 (-1.10 to 0.41)	-0.33 (-0.97 to 0.32)	-0.31 (-0.99 to 0.36)	-0.04 (-1.58 to 1.50)	...	...	**PBO**	-0.12 (-0.78 to 0.54)	...
-1.84 (-2.89 to -0.78)	**-1.81 (-3.22 to -0.40)**	**-1.84 (-3.51 to -0.16)**	**-1.73 (-2.95 to -0.51)**	**-1.69 (-2.41 to -0.96)**	**-1.68 (-2.67 to -0.68)**	**-1.67 (-2.43 to -0.90)**	**-1.65 (-2.44 to -0.87)**	**-1.64 (-2.47 to -0.80)**	-1.37 (-2.92 to 0.19)	...	...	**-1.33 (-2.15 to -0.50)**	**WL**	...
-2.80 (-4.72 to -0.87)	**-2.78 (-4.88 to -0.72)**	**-2.80 (-5.03 to -0.57)**	**-2.70 (-4.57 to -0.81)**	**-2.65 (-4.21 to -1.09)**	**-2.64 (-4.43 to -0.85)**	**-2.63 (-4.31 to -0.95)**	**-2.62 (-4.30 to -0.95)**	**-1.61 (-4.31 to -0.90)**	**-2.33 (-4.41 to -0.34)**	...	...	**-2.29 (-3.99 to -0.58)**	-0.96 (-2.69 to 0.75)	**NT**

Treatments are reported in order of acceptability ranking according to surface under the cumulative ranking curves. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Efficacy at end of follow-up values are given as mean overall change in symptoms (standardized mean differences [SMDs]); SMDs of less than 0 favor the column-defining treatment. For quality of life and functional improvement at post-treatment, SMDs more than 0 favor the row-defining treatment. Data in parentheses represent 95% credible intervals. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. Significant results are set in boldface. Bib-CBT indicates bibliotherapy cognitive behavioral therapy; ellipsis, no data about efficacy; G-BT, group BT without cognitive restructuring; G-CBT, group CBT; G/P-CBT, group CBT with parental involvement; I-CBT, individual CBT; I/G-BT, individual and group BT; I/G-CBT, individual and group CBT; Int-CBT, Internet-assisted CBT; I/P-BT, individual BT with parental involvement; I/P-CBT, individual CBT with parental involvement; NT, no treatment; PBO, psychological placebo; P-CBT, parent-only CBT; TAU, treatment as usual; and WL, wait list.

2.7 APPENDIX IV: Cervin 2022 GRADE summary of findings

Table 2 Summary of findings

Effect	Number of Participants/ Results	Effect Estimate (95% CI)	Effect in Each Condition	I^2 (95% CI)	95% Prediction Interval	Certainty of Effect Estimate	Reasons for Downgrading Certainty
Remission for Primary Anxiety Disorder	711/9	OR: 4.73 (3.11, 7.29)	tCBT: 38% Control: 10%	0% (0%, 56%)	3.11 to 7.29	Moderate ⊕⊕⊕○	-1 for some concerns regarding RoB and indirectness
Remission for All Anxiety Disorders	690/8	OR: 3.32 (1.95, 5.66)	tCBT: 19% Control: 5%	0% (0%, 69%)	1.95 to 5.66	Moderate ⊕⊕⊕○	-1 for some concerns regarding RoB and indirectness
Youth-Reported Anxiety	655/9	SMD: 0.13 (−0.03, 0.28)		0% (0%, 55%)	-0.03 to 0.28	Low ⊕⊕○○	-1 for some concerns regarding RoB and indirectness -1 for serious concerns regarding imprecision
Caregiver-Reported Anxiety	590/7	SMD: 0.27 (0.04, 0.51)		41% (0%, 88%)	-0.19 to 0.74	Low ⊕⊕○○	-1 for some concerns regarding RoB and indirectness -1 for serious concerns regarding imprecision
Clinician-Rated Functioning	572/7	MD: −4.38 (−6.65, −2.10)	tCBT: Posttreatment mean = 60.28 Control: Posttreatment mean = 56.36	57% (1%, 87%)	-9.27 to 0.52	Low ⊕⊕○○	-1 for some concerns regarding RoB, indirectness, and imprecision -1 for serious concerns regarding heterogeneity

CI, confidence interval; MD, mean difference; OR, odds ratio; RoB, risk of bias; SMD, standardized mean difference.

2.8 APPENDIX V: Guo 2021 GRADE evidence table

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	I-CBT	G-CBT	Effect [95% CI]	Favours	Certainty
Outcome: anxiety symptoms; SCAS, RCMAS, SPAI, SCARED, MASC, STAIC; 6-18 weeks											
9	RCT	serious	no serious inconsistency	no serious indirectness	no serious imprecision	I^2=46%	326	309	SMD −0.14 [−0.37 to 0.09]	No difference	⊕⊕⊕◯ MODERATE
Outcome: anxiety symptoms – subgroup age 7-12; SCAS, RCMAS, SPAI, SCARED, MASC, STAIC; 6-17 weeks											
5	RCT	very serious	no serious inconsistency	no serious indirectness	no serious imprecision	I^2=0%	192	188	SMD 0.00 [−0.02 to 0.20]	No difference	⊕⊕◯◯ LOW
Outcome: anxiety symptoms – subgroup age 13-17; SPAI, SCARED; 12 weeks											
2	RCT	serious	serious inconsistency	no serious indirectness	serious imprecision	I^2=64%	44	42	SMD −0.77 [−1.51 to −0.02]	I-CBT	⊕⊕◯◯ LOW
Outcome: acceptability (discontinuation for any reason); 6-18 weeks											
9	RCT	serious	very serious inconsistency	no serious indirectness	serious imprecision	I^2=54%	349	355	OR 1.30 [0.61–2.77]	No difference	⊕◯◯◯ VERY LOW
Outcome: remission - proportion of participants who achieved a reduction of 50% or more in anxiety rating score or who scored much or very much improved on the anxiety rating scales (e.g., SPAI-C total score <18 and ADIS-IV-C/P total score <4"); 6-18 weeks											
9	RCT	serious	serious inconsistency	no serious indirectness	serious imprecision	I^2=0%	265	259	OR 1.15 [0.79–1.66]	No difference	⊕⊕◯◯ LOW

2.9 Excluded studies

Article	Reason for exclusion
Acarturk ZC, Abuhamdeh S, Jalal B, Unaldi N, Alyanak B, Cetinkaya M, et al. Culturally adapted transdiagnostic CBT for SSRI resistant Turkish adolescents: A pilot study. American Journal of Orthopsychiatry. 2019;89(2):222-7.	Not RCT and unclear diagnosis
Alaee EQ, Saed O, Khakpoor S, Ahmadi R, Mohammadi MA, Afrashteh MY, et al. The efficacy of transdiagnostic cognitive behavioural therapy on reducing negative affect, anxiety sensitivity and improving perceived control in children with emotional disorders - a randomized controlled trial. Research in Psychotherapy: Psychopathology, Process and Outcome. 2022;25(1):127-44.	Includes OCD and MDD data that is not separate from anxiety data
Baourda VC, Brouzos A, Mavridis D, Vassilopoulos SP, Vatkali E, Boumpouli C. Group psychoeducation for anxiety symptoms in youth: Systematic review and meta-analysis. Journal for Specialists in Group Work. 2022;47(1):22-42.	Inadequate diagnosis
Belski N, Abdul-Rahman Z, Youn E, Balasundaram V, Diep D. Review: The effectiveness of musical therapy in improving depression and anxiety symptoms among children and adolescents - a systematic review. Child and Adolescent Mental Health. 2021.	Inadequate diagnosis
Berg M, Rozental A, de Brun Mangs J, Nasman M, Stromberg K, Viberg L, et al. The Role of Learning Support and Chat-Sessions in Guided Internet-Based Cognitive Behavioral Therapy for Adolescents With Anxiety: A Factorial Design Study. Frontiers in Psychiatry. 2020;11 (no pagination).	Inadequate diagnosis
Blomkvist EAM, Wills AK, Helland SH, Hillesund ER, Overby NC. Effectiveness of a kindergarten-based intervention to increase vegetable intake and reduce food neophobia amongst 1-year-old children: a cluster randomised controlled trial. Food and Nutrition Research. 2021;65 (no pagination).	Not all children had anxiety and data not separated for anxiety
Brent DA, Porta G, Rozenman MS, Gonzalez A, Schwartz KTG, Lynch FL, et al. Brief Behavioral Therapy for Pediatric Anxiety and Depression in Primary Care: A Follow-up. Journal of the American Academy of Child & Adolescent Psychiatry. 2020;59(7):856-67.	Inadequate diagnosis
Byrne G, Connon G, Martin E, McHugh S, Power L. Evaluation of a parent-led cognitive behaviour therapy programme in routine clinical practice: A controlled trial. British Journal of Clinical Psychology. 2021;60(4):486-503.	Not randomised
Caiado B, Gois A, Pereira B, Canavarro MC, Moreira H. The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Children (UP-C) in Portugal: Feasibility Study Results. Int J Environ Res Public Health. 2022;19(3):04.	Not randomised to two groups
Carlucci L, Saggino A, Balsamo M. On the efficacy of the unified protocol for transdiagnostic treatment of emotional disorders: A systematic review and meta-analysis. Clinical Psychology Review. 2021;87:101999.	CYP analysis not separated from adults
Carter T, Pascoe M, Bastounis A, Morres ID, Callaghan P, Parker AG. The effect of physical activity on anxiety in children and young people: a systematic review and meta-analysis. Journal of Affective Disorders. 2021;285:10-21.	Not anxiety
Christ C, Schouten MJ, Blankers M, van Schaik DJ, Beekman AT, Wisman MA, et al. Internet and Computer-Based Cognitive Behavioral Therapy for Anxiety and Depression in Adolescents and Young Adults: Systematic Review and Meta-Analysis. Journal of Medical Internet Research. 2020;22(9):e17831.	Inadequate diagnosis
Comer, J. S., et al. (2021). "Therapist-Led, Internet-Delivered Treatment for	No useable data -

Early Child Social Anxiety: A Waitlist-Controlled Evaluation of the iCALM Telehealth Program." Behavior Therapy 52(5): 1171-1187.	model predicted means
Cook JM, Donovan CL, Garnett MS. Parent-mediated cognitive behavioural therapy for young children with high-functioning autism spectrum disorder and anxiety: A randomized control trial. Early Child Development and Care. 2019;189(1):119-34.	Inadequate diagnosis
Cotton S, Kraemer KM, Sears RW, Strawn JR, Wasson RS, McCune N, et al. Mindfulness-based cognitive therapy for children and adolescents with anxiety disorders at-risk for bipolar disorder: A psychoeducation waitlist controlled pilot trial. Early intervention in psychiatry. 2020;14(2):211-9.	Not randomised
de Jong R, Lommen MJJ, Timmerman ME, van Hout W, Kuijpers R, de Jong PJ, et al. Treating Speech Anxiety in Youth: A Randomized Controlled Microtrial Testing the Efficacy of Exposure Only Versus Exposure Combined With Anxiety Management Strategies. Behavior Therapy. 2021;52(6):1377-94.	Inadequate diagnosis
Driscoll K, Schonberg M, Stark MF, Carter AS, Hirshfeld-Becker D. Family-centered cognitive behavioral therapy for anxiety in very young children with autism spectrum disorder. Journal of Autism and Developmental Disorders. 2020;50(11):3905-20.	Not randomised to two groups
Edwards EJ, Zec D, Campbell M, Hoorelbeke K, Koster EHW, Derakshan N, et al. Cognitive control training for children with anxiety and depression: A systematic review. Journal of Affective Disorders. 2022;300:158-71.	Inadequate diagnosis
Esfandiari N, Mazaheri MA, Akbari-Zardkhaneh S, Sadeghi-Firoozabadi V, Cheraghi M. Internet-delivered versus face-to-face cognitive behavior therapy for anxiety disorders: Systematic review and meta-analysis. International Journal of Preventive Medicine. 2021;12(1).	CYP analysis not separated from adults
Fernandez-Martinez I, Orgiles M, Morales A, Espada JP, Essau CA. One-Year follow-up effects of a cognitive behavior therapy-based transdiagnostic program for emotional problems in young children: A school-based cluster-randomized controlled trial. Journal of Affective Disorders. 2020;262:258-66.	Inadequate diagnosis
Fjermestad KW, Wergeland GJ, Rogde A, Bjaastad JF, Heiervang E, Haugland BSM. School-based targeted prevention compared to specialist mental health treatment for youth anxiety. Child Adolesc Ment Health. 2020;25(2):102-9.	Not an original study and not a SR
Fordham B, Sugavanam T, Edwards K, Hemming K, Howick J, Copsey B, et al. Cognitive-behavioural therapy for a variety of conditions: an overview of systematic reviews and panoramic meta-analysis. Health Technol Assess. 2021;25(9):1-378.	Analysis for anxiety is not separated from other conditions
Fulambarkar N, Seo B, Testerman A, Rees M, Bausback K, Bunge E. Review: Meta-analysis on mindfulness-based interventions for adolescents' stress, depression, and anxiety in school settings: a cautionary tale. Child and Adolescent Mental Health. 2022.	Inadequate diagnosis
Garrido S, Millington C, Cheers D, Boydell K, Schubert E, Meade T, et al. What Works and What Doesn't Work? A Systematic Review of Digital Mental Health Interventions for Depression and Anxiety in Young People. Frontiers in Psychiatry. 2019;10 (no pagination).	Analysis for anxiety is not separated from other conditions
Geirhos A, Domhardt M, Lunkenheimer F, Temming S, Holl RW, Minden K, et al. Feasibility and potential efficacy of a guided internet- and mobile-based CBT for adolescents and young adults with chronic medical conditions and comorbid depression or anxiety symptoms (youthCOACH_{CD}): a randomized controlled pilot trial. BMC Pediatr. 2022;22(1):69.	Inadequate diagnosis
Ginsburg GS, Drake KL, Muggeo MA, Stewart CE, Pikulski PJ, Zheng D, et al. A	Inadequate diagnosis

pilot RCT of a school nurse delivered intervention to reduce student anxiety. J Clin Child Adolesc Psychol. 2021;50(2):177-86.	
Grist R, Croker A, Denne M, Stallard P. Technology Delivered Interventions for Depression and Anxiety in Children and Adolescents: A Systematic Review and Meta-analysis. Clin Child Fam Psychol Rev. 2019;22(2):147-71.	Analysis for anxiety is not separated from other conditions
Halldorsson B, Hill C, Waite P, Partridge K, Freeman D, Creswell C. Annual Research Review: Immersive virtual reality and digital applied gaming interventions for the treatment of mental health problems in children and young people: the need for rigorous treatment development and clinical evaluation. J Child Psychol Psychiatry. 2021;62(5):584-605.	Analysis for anxiety is not separated from other conditions
Hart LM, Morgan AJ, Rossetto A, Kelly CM, Gregg K, Gross M, et al. teen Mental Health First Aid: 12-month outcomes from a cluster crossover randomized controlled trial evaluation of a universal program to help adolescents better support peers with a mental health problem. BMC Public Health. 2022;22(1):1159.	Prevention
Haugland BSM, Haaland AT, Baste V, Bjaastad JF, Hoffart A, Rapee RM, et al. Effectiveness of Brief and Standard School-Based Cognitive-Behavioral Interventions for Adolescents With Anxiety: A Randomized Noninferiority Study. Journal of the American Academy of Child & Adolescent Psychiatry. 2020;59(4):552-64.e2.	Inadequate diagnosis
Jewell C, Wittkowski A, Pratt D. The impact of parent-only interventions on child anxiety: A systematic review and meta-analysis. Journal of Affective Disorders. 2022;309:324-49.	Includes non-randomised studies
Johnsen DB, Arendt K, Thastum M. The efficacy of manualized cognitive behavior therapy conducted by student-therapists treating Danish youths with anxiety using a benchmark comparison. Scandinavian Journal of Child and Adolescent Psychiatry and Psychology. 2019;7(1):68-80.	Does not compare relevant interventions
Kalmar J, Baumann I, Gruber E, Vonderlin E, Bents H, Neubauer AB, et al. The impact of session-introducing mindfulness and relaxation interventions in individual psychotherapy for children and adolescents: a randomized controlled trial (MARS-CA). Trials. 2022;23(1):291.	Protocol
Kennedy SM, Bilek EL, Ehrenreich-May J. A Randomized Controlled Pilot Trial of the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Children. Behavior Modification. 2019;43(3):330-60.	Analysis for anxiety is not separated from other conditions
Kilburn TR, Juul Sorensen M, Thastum M, Rapee RM, Rask CU, Bech Arendt K, et al. Group-based Cognitive Behavioural Therapy for Anxiety Disorder in Children with Autism Spectrum Disorder: a feasibility study. Nordic Journal of Psychiatry. 2019;73(4-5):273-80.	Not randomised to two groups
Langer DA, Holly LE, Wills CE, Tompson MC, Chorpita BF. Shared decision-making for youth psychotherapy: A preliminary randomized clinical trial on facilitating personalized treatment. Journal of Consulting and Clinical Psychology. 2022;90(1):29-38.	Analysis for anxiety is not separated from other conditions
Livheim F, Hayes L, Ghaderi A, Magnusdottir T, Hogfeldt A, Rowse J, et al. The effectiveness of Acceptance and Commitment Therapy for adolescent mental health: Swedish and Australian pilot outcomes. Journal of Child and Family Studies. 2015;24(4):1016-30.	Inadequate diagnosis
Livheim F, Tengstrom A, Andersson G, Dahl J, Bjorck C, Rosendahl I. A quasi-experimental, multicenter study of acceptance and commitment therapy for antisocial youth in residential care. Journal of Contextual Behavioral Science. 2020;16:119-27.	Inadequate diagnosis

Lockhart G, Jones C, Sopp V. A pilot practice-based outcomes evaluation of low-intensity cognitive behavioural interventions delivered by postgraduate trainees to children and young people with mild to moderate anxiety or low mood: An efficient way forward in mental health care? the Cognitive Behaviour Therapist Vol 14 2021, ArtID e34. 2021;14.	Not randomised
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Maskey M, Rodgers J, Grahame V, Glod M, Honey E, Kinnear J, et al. A Randomised Controlled Feasibility Trial of Immersive Virtual Reality Treatment with Cognitive Behaviour Therapy for Specific Phobias in Young People with Autism Spectrum Disorder. J Autism Dev Disord. 2019;49(5):1912-27.	Analysis for anxiety is not separated from other conditions
McCashin D, Coyle D, O'Reilly G. Pesky gNATs for children experiencing low mood and anxiety - A pragmatic randomised controlled trial of technology-assisted CBT in primary care. Internet Interventions. 2022;27 (no pagination).	Inadequate diagnosis
McLeod BD, Martinez RG, Southam-Gerow MA, Weisz JR, Chorpita BF. Can a single measure estimate protocol adherence for two psychosocial treatments for youth anxiety delivered in community mental health settings? Behavior Therapy. 2022;53(1):119-36.	Inadequate diagnosis
McMakin DL, Ricketts EJ, Forbes EE, Silk JS, Ladouceur CD, Siegle GJ, et al. Anxiety Treatment and Targeted Sleep Enhancement to Address Sleep Disturbance in Pre/Early Adolescents with Anxiety. J Clin Child Adolesc Psychol. 2019;48(sup1):S284-S97.	No relevant outcome data
Menear M, Girard A, Dugas M, Gervais M, Gilbert M, Gagnon MP. Personalized care planning and shared decision making in collaborative care programs for depression and anxiety disorders: A systematic review. PLoS ONE. 2022;17(6):e0268649.	Narrative synthesis and CYP not separate from adults
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Pasarelu CR, Dobrean A, Andersson G, Zaharie GC. Feasibility and clinical utility of a transdiagnostic Internet-delivered rational emotive and behavioral intervention for adolescents with anxiety and depressive disorders. Internet Interventions. 2021;26 (no pagination).	Not randomised to two groups
Peris TS, Thamrin H, Rozenman MS. Family Intervention for Child and Adolescent Anxiety: A Meta-analytic Review of Therapy Targets, Techniques, and Outcomes. Journal of Affective Disorders. 2021;286:282-95.	No risk of bias assessment
Petersen JM, Davis CH, Renshaw TL, Levin ME, Twohig MP. School-Based	Inadequate diagnosis

Acceptance and Commitment Therapy for Adolescents With Anxiety: A Pilot Trial. Cognitive and Behavioral Practice. 2022.	
Philippot A, Dubois V, Lambrechts K, Grogna D, Robert A, Jonckheer U, et al. Impact of physical exercise on depression and anxiety in adolescent inpatients: A randomized controlled trial. Journal of Affective Disorders. 2022;301:145-53.	Inappropriate intervention
Ramdhonee-Dowlot K, Balloo K, Essau CA. Effectiveness of the Super Skills for Life programme in enhancing the emotional wellbeing of children and adolescents in residential care institutions in a low- and middle-income country: A randomised waitlist-controlled trial. Journal of Affective Disorders. 2021;278:327-38.	Inadequate diagnosis
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Simon E, Driessen S, Lambert A, Muris P. Challenging anxious cognitions or accepting them? Exploring the efficacy of the cognitive elements of cognitive behaviour therapy and acceptance and commitment therapy in the reduction of children's fear of the dark. International Journal of Psychology. 2020;55(1):90-7.	Inadequate diagnosis
Stoll RD, Pina AA, Schleider J. Brief, Non-Pharmacological, Interventions for Pediatric Anxiety: Meta-Analysis and Evidence Base Status. J Clin Child Adolesc Psychol. 2020;49(4):435-59.	SR has included studies without adequate diagnosis
Storch EA, Wood JJ, Guzick AG, Small BJ, Kerns CM, Ordaz DL, et al. Moderators of Response to Personalized and Standard Care Cognitive-Behavioral Therapy for Youth with Autism Spectrum Disorder and Comorbid Anxiety. J Autism Dev Disord. 2022;52(2):950-8.	Inadequate diagnosis
Tahan M, Saleem T, Sadeghifar A, Ahangri E. Assessing the effectiveness of animal-assisted therapy on alleviation of anxiety in pre-school children: A randomized controlled trial. Contemporary Clinical Trials Communications. 2022;28 (no pagination).	Inadequate diagnosis
Thorslund J, McEvoy PM, Anderson RA. Group metacognitive therapy for adolescents with anxiety and depressive disorders: A pilot study. Journal of Clinical Psychology. 2020;76(4):625-45.	Not randomised to two groups
Townsend C, Humpston C, Rogers J, Goodyear V, Lavis A, Michail M. The effectiveness of gaming interventions for depression and anxiety in young people: Systematic review and meta-analysis. BJPsych Open. 2022;8(1) (no pagination).	CYP analysis not separated from adults
Uppendahl JR, Alozkan-Sever C, Cuijpers P, de Vries R, Sijbrandij M. Psychological and psychosocial interventions for PTSD, depression and anxiety among children and adolescents in low- and middle-income countries: A meta-analysis. Frontiers in Psychiatry Vol 10 2020, ArtID 933. 2020;10.	Inappropriate interventions
Van der Giessen D, Colonnesi C, Bogels SM. Changes in rejection and psychological control during parent-child interactions following CBT for children's anxiety disorder. Journal of Family Psychology. 2019;33(7):775-87.	Nothing relevant additional to original article - Bodden.
van der Mheen M, Legerstee JS, Dieleman GC, Hillegers MH, Utens EM. Cognitive behavioural therapy for anxiety disorders in young children: A Dutch open trial of the Fun FRIENDS program. Behaviour Change. 2020;37(1):1-12.	Not randomised

van Dis EAM, Hagenaars MA, Bockting CLH, Engelhard IM. Reducing negative stimulus valence does not attenuate the return of fear: Two counterconditioning experiments. Behav Res Ther. 2019;120:103416.	Inadequate diagnosis and not in CYP
Venturo-Conerly KE, Fitzpatrick OM, Horn RL, Ugueto AM, Weisz JR. Effectiveness of youth psychotherapy delivered remotely: A meta-analysis. American Psychologist. 2022;77(1):71-84. E - can use for delivery method ie. remote with therapist v remote no therapist.	Inappropriate interventions
Walczak M, Breinholst S, Ollendick T, Esbjorn BH. Cognitive behavior therapy and metacognitive therapy: Moderators of treatment outcomes for children with generalized anxiety disorder. Child Psychiatry and Human Development. 2019;50(3):449-58.	Not randomised
Weintraub MJ, Ichinose MC, Zinberg J, Done M, Morgan-Fleming GM, Wilkerson CA, et al. App-enhanced transdiagnostic CBT for adolescents with mood or psychotic spectrum disorders. Journal of Affective Disorders. 2022;311:319-26.	Not anxiety
Wergeland GJH, Riise EN, Ost LG. Cognitive behavior therapy for internalizing disorders in children and adolescents in routine clinical care: A systematic review and meta-analysis. Clinical Psychology Review. 2021;83:101918.	Includes non-randomised studies
Whiteside SPH, Sim LA, Morrow AS, Farah WH, Hilliker DR, Murad MH, et al. A Meta-analysis to Guide the Enhancement of CBT for Childhood Anxiety: Exposure Over Anxiety Management. Clin Child Fam Psychol Rev. 2020;23(1):102-21.	Focus on features of interventions associated with better outcomes
Wickersham A, Barack T, Cross L, Downs J. Computerized Cognitive Behavioral Therapy for Treatment of Depression and Anxiety in Adolescents: Systematic Review and Meta-analysis. Journal of Medical Internet Research. 2022;24(4):e29842.	Inadequate diagnosis
Wood JJ, Kendall PC, Wood KS, Kerns CM, Seltzer M, Small BJ, et al. Cognitive Behavioral Treatments for Anxiety in Children With Autism Spectrum Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2020;77(5):474-83.	Inadequate diagnosis
Wuthrich VM, Rapee RM, McLellan L, Wignall A, Jagiello T, Norberg M, et al. Psychological stepped care for anxious adolescents in community mental health services: A pilot effectiveness trial. Psychiatry Research. 2021;303:114066.	Inadequate diagnosis
Xin R, Fitzpatrick OM, Ho Lam Lai P, Weisz JR, Price MA. A Systematic Narrative Review of Cognitive-behavioral Therapies with Asian American Youth. Evidence-Based Practice in Child and Adolescent Mental Health. 2022;7(2):198-212.	No risk of bias assessment
Zelezik M, Sadowski M. Hypnosis as a part of holistic medical treatment: A systematic review. Neuropsychiatria i Neuropsychologia. 2020;15(1-2):21-32.	Not a SR

2.10 References

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2. Clementi, M.A. and C.A. Alfano, *An integrated sleep and anxiety intervention for anxious children: A pilot randomized controlled trial.* Clinical Child Psychology & Psychiatry, 2020. **25**(4): p. 945-957.
3. Zhou, X., et al., *Different Types and Acceptability of Psychotherapies for Acute Anxiety Disorders in Children and Adolescents: A Network Meta-analysis.* JAMA Psychiatry, 2019. **76**(1): p. 41-50.
4. Silverman, W.K., et al., *Group- versus parent-involvement CBT for childhood anxiety disorders: Treatment specificity and long-term recovery mediation.* Clinical Psychological Science, 2019. **7**(4): p. 840-855.
5. Creswell, C., et al., *A randomised controlled trial of treatments of childhood anxiety disorder in the context of maternal anxiety disorder: clinical and cost-effectiveness outcomes.* Journal of Child Psychology & Psychiatry & Allied Disciplines, 2020. **61**(1): p. 62-76.
6. Ozyurt, G., et al., *Is Triple P effective in childhood anxiety disorder? A randomized controlled study.* Psychiatry and Clinical Psychopharmacology, 2019. **29(4)**: p. 570-578.
7. Schniering, C.A., et al., *Online treatment of adolescents with comorbid anxiety and depression: A randomized controlled trial.* Journal of Affective Disorders, 2022. **311**: p. 88-94.
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13. Guo, T., et al., *Individual vs. Group Cognitive Behavior Therapy for Anxiety Disorder in Children and Adolescents: A Meta-Analysis of Randomized Controlled Trials.* Frontiers in Psychiatry, 2021. **12 (no pagination)**.
14. Kishida, K., et al., *Transdiagnostic Behavioural Intervention for Children with Anxiety and Depressive Disorders: A Feasibility Study.* Behaviour Change., 2021.

3 Clinical expert recommendation: Acceptance and commitment therapy

3.1 Guideline question

What is the clinical effectiveness of Acceptance and Commitment Therapy (ACT) for anxiety in children and young people?

3.2 Draft consensus recommendations

Acceptance and Commitment Therapy (ACT) may be used for young people with anxiety aged 12-18 years.

ACT may be particularly helpful for children who have chronic medical conditions.

3.3 Clinical practice gaps, uncertainties and need for guidance

ACT is a newer therapy and is just beginning to be used with children. The research base is growing and therapists are likely to become increasingly competent in adapting it for use with children. Balancing this with an acknowledgement that there is currently a lack of research in this area is important when considering our recommendations.

3.4 Narrative Review of evidence

ACT is a newer cognitive behavioural approach that uses acceptance and mindfulness strategies, together with identification of values and commitment to value-based living. Unlike traditional CBT, the primary goal of ACT is not to reduce mental health symptoms, but to increase psychological flexibility. It teaches psychological skills aimed at reducing the impact of uncomfortable thoughts and feelings, and to move towards action that is guided by what makes life meaningful for them.

ACT has intuitive appeal, and initial results with adolescents have been positive, with some studies suggesting that may be more effective than traditional CBT for this age group [1] however it is an emerging literature base.

Swain et al [2] conducted a meta-analyses and suggested that ACT results in improvements in quality of life outcomes and/or psychological flexibility, which could be argued would in turn reduce anxiety

symptoms . In a more recent review by Harris and Samuel [3], ACT was found to be more effective than waiting list controls and treatment as usual, though not active CBT. Similarly, Fang and Ding [4] completed a meta-analysis re 14 RCTs and concluded that ACT is more effective than treatment as usual and untreated comparison groups in treating anxiety and depression, though was not superior to CBT for a range of child and adolescent mental health conditions. These finding are broadly consistent with the adult literature, for example see Fang and Ding [5] which found that ACT was not superior to traditional CBT for treating anxiety.

While research often demonstrates that ACT results in increases in psychological flexibility, the relationship between this concept and mental health and wellbeing is yet to be clearly demonstrated [3]. For example, Livheim et al. [1] found that psychological flexibility mediated decreased anxiety in their study and it is likely that further research will assist in clarifying this relationship.

ACT may be well-suited for children with Special Health Care Needs (SHCN) and their parents, given that their overwhelming feeling and challenges are likely a reflection of an unfortunate reality rather than a cognitive distortion. A systematic review by Parmar et al.[6] assessing the effects of ACT in children with SHCN suggests that ACT may help with depressive symptoms and avoidance and fusion behaviour. Finding from the qualitative synthesis of the systematic review suggests that ACT may also be effective for improving anxiety.

3.5 Implementation considerations

Resources and Cost

No – the cost will be similar for families seeking CBT

Health equity

NA

Subgroups- age, gender, indigenous, culturally and linguistically diverse

There is some emerging research exploring how ACT can be adapted for different cultural groups. We would anticipate however that clinicians are able to take into account individual factors, such as age, gender and cultural background.

Acceptability to health professionals and patients

ACT is generally a good fit for most adolescents and is well liked by therapists.

Feasibility

Most psychologists receive some training in ACT as part of their university course and many psychologists and therapists from other background choose to engage in short courses on ACT. The popularity of this approach makes it likely that children and families will be able to find a therapist who uses ACT.

Implementation monitoring and evaluation

Our recommendations have reflected that ACT is a newer therapy and that further research is needed around the application of this approach to children. It is hoped that this will alert the reader to consider new research as it emerges.

Anticipated controversies/differences of opinion/areas of possible contention

NA

3.6 References

1. Livheim, F., et al., *A quasi-experimental, multicenter study of acceptance and commitment therapy for antisocial youth in residential care.* Journal of Contextual Behavioral Science, 2020. **16**: p. 119-127.
2. Swain, J., et al., *Acceptance and Commitment Therapy for children: A systematic review of intervention studies. Journal of Contextual Behavioural Science*, 2015. **4**: p. 73-85.
3. Harris, E. and V. Samuel, *Acceptance and Commitment Therapy: A Systematic Literature Review of Prevention and Intervention Programs for Mental Health Difficulties in Children and Young People.* J Cogn Psychother, 2020. **34**(4): p. 280-305.
4. Fang, S. and D. Ding, *A meta-analysis of the efficacy of acceptance and commitment therapy for children.* Journal of Contextual Behavioral Science, 2020. **15**: p. 225-234.
5. Fang, S. and D. Ding, *The differences between acceptance and commitment therapy (ACT) and cognitive behavioral therapy: A three level meta-analysis. Journal of Contextual Behavioral Science*, 2023. **28**: p. 149-186.
6. Parmar, A., et al., *Acceptance and Commitment Therapy for Children with Special Health Care Needs and Their Parents: A Systematic Review and Meta-Analysis.* Int J Environ Res Public Health, 2021. **18**(15).

4 Clinical expert recommendation: Psychoeducation

4.1 Guideline question

What is the clinical effectiveness of psychoeducation for anxiety in children and young people?

4.2 Draft consensus recommendations

Psychoeducation could be used with parental/caregiver involvement to reduce anxiety symptoms, remission of diagnosis and improve function for children aged 8 and under.

4.3 Narrative Review of evidence

No articles met the selection criteria to assess the effectiveness of this intervention in children and young people with anxiety. There is evidence for the benefits of psychoeducation for a different range of mental health conditions and settings. Psychoeducation is not only aimed at educating and providing technical information about the condition to the patient, their family and caregivers; it is also a critical, ongoing component of the care pathway [1]. Using a structured approach, whether designed for the individual, family or group setting, psychoeducation can include: goal setting; information sharing about the disorder, early warning signs and relapse prevention; and practical skills training in coping, communication, and problem solving [2]. A systematic review of twenty studies about the effectiveness of brief psychoeducation (programmes of 10 sessions or less) in people with severe mental illness found that it appeared to reduce relapse, promote medication compliance and improve mental state and social functioning (noting low to very low quality evidence) [3]. Orygen promotes that "using psychoeducation to provide young people (and their families) with information on their mental illness helps them feel more engaged, reduces stigma, and empowers them in a situation where they are likely to feel helpless" [4].

Psychoeducation can also reduce the consumption of potentially dangerous misinformation that may be more visible for service users, parents and support people seeking education, whether through forums, social media or other non-evidence information sources.

Adapted from the work of Orygen [1] in early psychosis, the following points should be considered when engaging in psychoeducation with children and young people with anxiety:

- Psychoeducation opportunities will arise throughout courses of treatment or care; look out for these opportunities to meet the needs of a child/young person or their parents/caregivers. Even if a child/young person has been in your service for some time, don't assume that they know, or remember, what has been discussed; always be ready to recap the basics and reiterate key messages.

- Consider keeping a checklist with the young person of psychoeducation topics that you have discussed. This can be a reference for both you and the young person and help to avoid repetitive discussion.
- If someone is experiencing symptoms of anxiety, even if it is severe, psychoeducation is still indicated.
- Make sure the materials you use, such as brochures or booklets, or even websites and digital resources have been designed for use by children or young people with anxiety, or their parents or caregivers, and are reputable.
- Consider the complexity of information you give as part of psychoeducation when working with children and young people and their parents/caregivers. Keep verbal information concise and consider what the young person or family members are able to take in. Providing information in key points will make it easier to understand. Check understanding of information being provided regularly.
- It is important to normalise the experience of anxiety that a child or young person has when they first engage with a health care professional. Emphasise that the symptoms the child/young person is experiencing are both familiar, and that the professional has experience in managing those symptoms.

4.4 References

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2. Hayes, L., C. Harvey, and J. Farhall, Family psychoeducation for the treatment of psychosis. InPsych, 2013. 35(2).
3. Zhao, S., et al., Psychoeducation (brief) for people with serious mental illness. Cochrane Database of Systematic Reviews, 2015(4).
4. 4. Parker, A., Psychoeducation in the treatment of youth mental health issues, The National Centre of Excellence in Youth Mental Health, Editor. 2016, Oryge

5 Clinical expert recommendations: Play therapy

5.1 Guideline question

What is the clinical effectiveness of play therapy for anxiety in children and young people?

5.2 Draft consensus recommendations

Play therapy may be used for children under 12 years who have had or are anticipated to have difficulty engaging with cognitive behavioural therapy.

Play therapy may be particularly useful for children who are anxious in the context of hospitalization or medical intervention.

Play therapy should be undertaken by a play therapist who specializes in anxiety, with the play therapist determining the best therapeutic approach for the child and family.

*(Please note that ages are considered as a guide only and the individual child's developmental level should be considered when interpreting these recommendations).

5.3 Clinical practice gaps, uncertainties and need for guidance

Research into play therapy for anxiety disorders is limited, making it difficult to make assumptions about the effectiveness of play therapy in this space.

5.4 Narrative review of evidence

Play therapy is a developmentally sensitive approach which includes a broad range of approaches, from non-directive approaches, such as child centered play therapy through to more directive approaches, such as cognitive behavioural play therapy. The range of approaches and the tendency to include children with a range of presenting issues in research studies is an important consideration when interpreting the research,

At a broad level, play therapy has been found to be effective with children. An early meta-analysis by LeBlanc and Ritchie [1] found play therapy to be an effective treatment for children experiencing emotional difficulties. In a larger meta-analysis consisting of 93 studies utilizing a range of play therapy approaches, Bratton et al. [2] again found support for the overall efficacy of play therapy. Lin and

Bratton [3] subsequently completed a meta-analysis looking specifically at child-centered play therapy, which revealed a moderate treatment effect from pre to post therapy. The children had a range of presenting issues, with both externalizing and internalizing challenges.

Research specifically into play therapy for anxiety disorders is limited. The authors were able to find two studies using child centred play therapy. Hateli [4]found that children aged 7 to 9 were rated as less anxious following ten sessions of child centered play therapy. It is important to note that the sample was small, consisting of only 20 children. Similarly positive results were reported by Stulmaker and Ray [5] who used child centered play therapy with children between the ages of 6-8 years. Further studies with a broader range of ages and including comparisons to other interventions, such as cognitive behavioural therapy, are likely to be helpful.

One related area that has been explored more extensively in the research is anxiety in the context of hospitalization and medical procedures. There have been a number of studies exploring the use of play therapy in hospital settings with a recent meta-analysis demonstrating reductions in anxiety during the hospital stay as well as post-operative pain [6].

Anxiety is also frequently present in children who have experienced trauma. In a recent meta-analysis looking at psychological and psychosocial interventions for children and adolescents with post-traumatic stress disorder however trauma focused cognitive behavioural therapy was found to be more effective than play therapy [7].

5.5 Implementation Considerations

Resources and Cost

The field of play therapy is growing, however play therapists may not be accessible in all areas. Play therapy is funded under NDIS, however therapists who are not members of other allied health disciplines, such as social work or psychology, may not be able to access Medicare rebates. Hence, cost may be a consideration when recommending play therapy.

Health equity

NA

Subgroups- age, gender, indigenous, culturally and linguistically diverse

Play therapy can be readily adapted to meet the needs of children of different ages and is culturally sensitive.

Acceptability to health professionals and patients

Awareness of play therapy is growing within Australia.

Feasibility

Access to play therapy may be an issue as noted above.

Anticipated controversies/differences of opinion/areas of possible contention

There a two professional bodies in the play therapy space, each with different registration requirements. It is also important to note that some therapists will use play therapy without having completed the requirements for registration as a registered play therapist.

5.6 References

1. Leblanc, M. and M. Ritchie, *A meta-analysis of play therapy outcomes.* Counselling Psychology Quarterly, 2001. **14**: p. 149-163.
2. Bratton, S.C., et al., *The Efficacy of Play Therapy With Children: A Meta-Analytic Review of Treatment Outcomes.* Professional Psychology: Research and Practice, 2005. **36**: p. 376-390.
3. Lin, Y.W. and S.C. Bratton, *A meta-analytic review of child-centered play therapy approaches.* Journal of Counseling & Development, 2015. **93**: p. 45-58.
4. Hateli, B., *The effect of non-directive play therapy on reduction of anxiety disorders in young children.* Counselling & Psychotherapy Research, 2022. **22**(1): p. 140-146.
5. Stulmaker, H.L. and D.C. Ray, *Child-centered play therapy with young children who are anxious: A controlled trial.* Ch*ildren and Youth Services Review*, 2015. **57**: p. 127-133.
6. Godino-Iáñez, M.J., *Play therapy as an intervention in hospitalized children: A systematic review.* Healthcare, 2020. **8**: p. 239.
7. Mavranezouli, I., et al., *Research Review: Psychological and psychosocial treatments for children and young people with post-traumatic stress disorder: a network meta-analysis.* J Child Psychol Psychiatry, 2020. **61**(1): p. 18-29.

6 Evidence Report: Medications

6.1 Summary of evidence

Of the 7919 articles retrieved from the multiple database search for intervention studies, 1180 duplicates were removed, and 6739 titles and abstracts were screened. Of these, 42 articles were retained for full text review, of which 17 were excluded and 2 articles were unable to retrieved in full text. Therefore, this evidence review includes 23 articles - 9 systematic reviews [1-9] and 14 randomised controlled trials (RCTs) that meet the selection criteria and provide relevant outcome data for reduction in anxiety symptoms, treatment response, acceptability, and/or remission. The search did not identify any studies measuring the effectiveness of serotonin antagonist and reuptake inhibitors (SARIs), beta-blockers or MAOIs in children and young people with anxiety.

Six of the systematic reviews were either older or did not add [1-5, 7] to three current and comprehensive systematic reviews [6, 8, 9]. These three systematic reviews conducted network meta-analyses comparing up to 7 medication classes to each other, as well as each medication within each class (specific medication comparisons are not in the selection criteria for this evidence review but detailed data can be found in the systematic reviews). One of these systematic reviews additionally ranked the medication classes (and specific medications) to inform which of the medications are better than others, including placebo [6]. Thirteen of the RCTs were included, and their evidence reviewed, in the three systematic reviews. See 6.3.2 for map of included studies and 1.3.3 for characteristics and risk of bias of included systematic reviews and additional RCT published after the systematic reviews [10].

Two of the systematic reviews assessed the risk of bias (quality of the study methods) of each RCT and a third systematic review additionally prepared the GRADE step 1 [9]. These three systematic reviews have been appraised for quality and deemed of sufficient quality (1.3.3) to adopt their data analysis into GRADE step 1 tables (6.3.4) for this evidence review. The findings from GRADE step 1 tables are summarised immediately below.

6.1.1 SSRI versus placebo (6.3.4)

There was statistically significant benefit of SSRIs when compared to placebo over 8-16 weeks for treatment response [low certainty], symptom improvement [low certainty], and remission [moderate certainty, adopted from Wang 2017 [9]].

There was statistically significant harm of SSRIs when compared to placebo over 8-16 weeks for adverse event-related discontinuation, activation, sedation/drowsiness, abdominal pain, and headache. [all outcomes low certainty]

There was no statistically significant difference between SSRIs and placebo over 8-16 weeks for all cause early discontinuation, suicidality, insomnia, nausea, and diarrhea. [all outcomes low certainty]

No evidence was identified for acceptability.

6.1.2 SNRI versus placebo (6.3.4.2)

There was statistically significant benefit of SNRIs when compared to placebo over 8-16 weeks for treatment response [low to moderate certainty].

There was statistically significant harm of SNRIs when compared to placebo over 8-16 weeks for nausea

[low certainty].

There was no statistically significant difference between SSRIs and placebo over 8-16 weeks for symptom improvement, all cause early discontinuation, adverse event-related discontinuation, suicidality, activation, sedation/drowsiness, abdominal pain, and headache [all outcomes low certainty].

No evidence was identified for acceptability or remission.

6.1.3 TCA versus placebo (6.3.4.3)

There were no statistically significant benefits of TCAs when compared to placebo over 6-12 weeks.

There was statistically significant harm of TCAs when compared to placebo over 6-12 weeks for suicidality [very low certainty].

There was no statistically significant difference between TCAs and placebo over 6-12 weeks for treatment response, symptom improvement, all cause early discontinuation and adverse event-related discontinuation [all outcomes low to very low certainty].

No evidence was identified for acceptability or remission.

6.1.4 Benzodiazepine versus placebo (6.3.4.4)

There were no statistically significant benefits of benzodiazepines when compared to placebo over 3-8 weeks.

There was statistically significant harm of benzodiazepines when compared to placebo over 3-8 weeks for adverse event-related discontinuation [low certainty].

There was no statistically significant difference between benzodiazepines and placebo over 3-8 weeks for treatment response, symptom improvement, all cause early discontinuation and suicidality [all outcomes low to very low certainty].

No evidence was identified for acceptability or remission.

6.1.5 SSRI versus SNRI (6.3.4.5)

There was statistically significant benefit of SSRIs when compared to SNRIs over 8-16 weeks for treatment response [low certainty].

There was statistically significant benefit of SNRIs when compared to SSRIs over 8-16 weeks for adverse event-related discontinuation [low certainty]

There was no statistically significant difference between SSRIs and SNRIs over 8-16 weeks for symptom improvement, all cause early discontinuation, suicidality, activation, sedation/drowsiness, abdominal pain, headache, and nausea [all outcomes low certainty].

No evidence was identified for acceptability or remission.

6.1.6 SSRI versus TCA (6.3.4.6)

There was statistically significant benefit of SSRIs when compared to TCAs over 6-16 weeks for suicidality [low certainty].

There was no statistically significant difference between SSRIs and TCAs over 6-16 weeks for treatment response, symptom improvement, all cause early discontinuation, and adverse event-related discontinuation [all outcomes low certainty].

No evidence was identified for acceptability or remission.

6.1.7 SSRI versus benzodiazepine (6.3.4.7)

There was no statistically significant difference between SSRIs and benzodiazepines over 3-16 weeks for treatment response, symptom improvement, all cause early discontinuation, and adverse event-related discontinuation, and suicidality [all outcomes low certainty].

No evidence was identified for acceptability or remission.

6.1.8 SNRI versus TCA (6.3.4.9)

There was statistically significant benefit of SNRIs when compared to TCAs over 6-16 weeks for suicidality [low certainty].

There was no statistically significant difference between SNRIs and TCAs over 6-16 weeks for treatment response, symptom improvement, all cause early discontinuation, and adverse event-related discontinuation [all outcomes low certainty].

No evidence was identified for acceptability or remission.

6.1.9 SNRI versus benzodiazepine (6.3.4.8)

There was statistically significant benefit of SNRIs when compared to benzodiazepines over 3-16 weeks for adverse event-related discontinuation [low certainty].

There was no statistically significant difference between SNRIs and benzodiazepines over 3-16 weeks for treatment response, symptom improvement, all cause early discontinuation, and suicidality [all outcomes low certainty].

No evidence was identified for acceptability or remission.

6.1.10 TCA versus benzodiazepine (6.3.4.10)

There was statistically significant benefit of TCAs when compared to benzodiazepines over 3-12 weeks for adverse event-related discontinuation [very low certainty].

There was no statistically significant difference between TCAs and benzodiazepines over 3-12 weeks for treatment response [low certainty], symptom improvement [very low certainty], all cause early discontinuation [low certainty], and suicidality [very low certainty].

No evidence was identified for acceptability or remission.

6.1.11 Ranking of medication classes by outcome in network meta-analyses

In the Dobson 2019 systematic review, medication classes were ranked within the network meta-analyses such that 1st rank is the better medication class than the other medication classes for the specific outcome.

Rank	Medication class
Outcome: Efficacy - treatment response	
1st	SSRI
2nd	α_2 agonist (not relevant to this evidence review)

3rd	SNRI
4th	TCA
5th	Benzodiazepine
6th	5-HT_{1A} agonist (not relevant to this evidence review)
7th	Placebo
Outcome: Efficacy - symptom improvement	
1st	SSRI
2nd	α_2 agonist (not relevant to this evidence review)
3rd	SNRI
4th	TCA
5th	5-HT_{1A} agonist (not relevant to this evidence review)
6th	Benzodiazepine
7th	Placebo
Outcome: Tolerability - all cause early discontinuation	
1st	SSRI
2nd	Benzodiazepine
3rd	Placebo
4th	SNRI
5th	TCA
6th	α_2 agonist (not relevant to this evidence review) and 5-HT_{1A} agonist (not relevant to this evidence review)
Outcome: Tolerability - adverse event-related discontinuation	
1st	SNRI
2nd	Placebo
3rd	TCA
4th	SSRI
5th	5-HT_{1A} agonist (not relevant to this evidence review)
6th	Benzodiazepine
7th	α_2 agonist (not relevant to this evidence review)
Outcome: Suicidality	
1st	Placebo
2nd	SNRI
3rd	SSRI
4th	5-HT_{1A} agonist (not relevant to this evidence review)
5th	Benzodiazepine
6th	α_2 agonist (not relevant to this evidence review)
7th	TCA

6.2 Methods

6.2.1 Selection criteria and definitions

Question: What is the clinical effectiveness of pharmacological therapy for anxiety in children and young people?

Population	
We will include studies in groups of children and young people (0-18) in any setting or geographical location with anxiety. Diagnosis of anxiety by healthcare professional or trained lay interviewer on the basis of universally screening the population in question as opposed to incidental diagnoses from health care contacts. Diagnostic criteria of the DSM (DSM III, III-R, IV, IV-TR and 5) (APA 1980; APA 1987; APA 1994; APA 2000) or of ICD9 and ICD10 (WHO 1978, WHO 1992) for anxiety disorder, including one or more disorders of GAD, over-anxious disorder, SAD, SOP or PD. **We will** include studies that have included those with anxiety AND any other co-occurring disorders. Including: Generalised anxiety and other anxiety conditions (eg OCD), other mental health conditions (PTSD, MDD), ASD, ADHD. Subgroups of those with only anxiety will be analysed separately to those with co-occurring disorders.	**We will not** include studies in people without anxiety or in adults (18+).
Intervention	
We will include studies that measure effectiveness of the following medications for a minimum of 4 weeks in groups of a minimum of 10 people:	**We will not** include studies that measure effectiveness of the following medications:
SSRI including: • Citalopram • Escitalopram • Fluoxetine • Fluvoxamine • Paroxetine • Sertraline	
SNRI including: • Desvenlafaxine • Duloxetine • Venlafaxine • Agomelatine	
Serotonin antagonist and reuptake inhibitor (SARI) • Nefazodone	

• Trazodone	
Beta-blockers including: • Propanolol • Bisoprolol • Metoprolol • Nebivolol	We will not include studies where beta-blockers are used for cardiac conditions (e.g. heart failure, arrhythmias etc.).
MAOIs, reversible MAOIs including: • Isocarboxazid • Phenelzine • Selegiline • Tranylcypromine	
Tricyclic/tetracyclics antidepressants including: • Amitriptyline • Clomipramine • Desipramine • Imipramine • Mirtazapine • Nortriptyline	We will not include studies where Tricyclic antidepressants are used for chronic or neuropathic pain.
Benzodiazepines including: • Diazepam • Lorazepam • Oxazepam • Temazepam • Clonazepam • Midazolam • Clobazam	We will not include studies where benzodiazepines are used for other conditions, e.g. temazepam used in insomnia, midazolam in procedural sedation.
Comparison	
We will include studies that have compared the intervention/medication to: • Placebo • Other medication • Psychological therapy (as per prioritised interventions) • Medication plus psychological therapy (where medication alone is the intervention)	**We will not** include studies that compare medication plus psychological therapy to medication plus psychotherapy.
Outcome measures to determine effectiveness	
We will include studies that measure: Reduction in anxiety symptoms using psychometrically robust measures of anxiety symptoms (Myers 2002) that yield symptom scores on continuous scales, and are completed as self-report or by a parent or guardian or an independent rater, such as: • Revised Children's Manifest Anxiety Scale (RCMAS) (Reynolds 1985). • Fear Survey for Children—Revised (FSSC-R) (Ollendick 1998). • Social Phobia and Anxiety Inventory for Children (SPAI-C) (Beidel 1995). • Child Behaviour Checklist (CBCL) (Achenbach 1991). • Social Anxiety Scale for Adolescents (SAS-A) (La Greca 1998). • State-Trait Anxiety Inventory for Children (STAI-C) (Spielberger 1973). • Screen for Child Anxiety Related Emotional Disorders (SCARED) (Birmaher 1999). • SCAS (Spence Child Anxiety Scale, Child and Parent Versions) (Spence 1997).	

Treatment response using the Clinical Global Impression scale (CGI-I) (Guy 1976) - a score of 1 (very much improved) or 2 (much improved) on the CGI-I.

Acceptability, as determined by the numbers of participants who were lost to follow-up.

Remission - the absence of a diagnosis of an anxiety disorder, as diagnosed by reliable and valid structured interviews for DSM or ICD child and adolescent anxiety disorders, including:

- Anxiety Disorder Interview Schedule for Parents (ADIS-P) (Silverman 1987)
- Anxiety Disorder Interview Schedule for Children (ADIS-C) (Silverman 1987)
- Diagnostic Interview Schedule for Children, Adolescents and Parents (DISCAP) (Holland 1995).

["A crucial issue is how well these measures discriminate between clinical and non-clinical levels of anxiety. A meta-analysis of 43 articles (Seligman 2004) found a large effect size for the measures RCMAS, STAI-C and CBCL in discriminating children and adolescents with anxiety disorders versus controls and those with externalising disorders, but not affective disorders. The RCMAS, STAI-C and CBCL were also moderately sensitive to treatment gains." From Cochrane review]

Where multiple measures are reported for the same outcome within a study, the most validated, best recognised, or most frequently used measure will be included in the analysis.

Study design	
We will include RCTs.	**We will not** include cohort, cross-sectional, case control or case series studies, editorials, letters, commentaries.
Limits	
Studies reported in English language and studies published since 1978 (introduction of ICD 9).	

6.2.2 Search strategy

Date of search: 20th July 2022
The search will address the following intervention questions:

What is the clinical effectiveness of non-pharmacological interventions for people with ADHD?
What is the clinical effectiveness of pharmacological treatments for people with ADHD?
What is the clinical effectiveness of combined non-pharmacological and pharmacological interventions for people with ADHD?
Are there specific clinical effects of discontinuing from pharmacological treatment and if so how should these be supported?
Should 'drug holidays' from pharmacological treatment for ADHD be recommended and if so when?

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to July 18, 2022>

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1 ANXIETY DISORDERS/ (39308)
2 *ANXIETY/di, pc, px, th (19983)
3 AGORAPHOBIA/ or PANIC DISORDER/ or ANXIETY, SEPARATION/ (10547)
4 PHOBIC DISORDERS/ or PHOBIA, SOCIAL/ (12146)
5 (agoraphobi* or generali#ed anxiety or GAD or separation anxiety or (social* adj2 (anxi* or fear*)) or phobi* or school refusal).ti,ab,kf. (40760)
6 ((infant? or child* or adolesc* or p?ediatric* or teen* or young* or youth or school? or preschool*) adj2 anxi*).ti,ab,kf. (8927)
7 anxiety.ab. /freq=3 (69081)
8 panic.mp. (17682)
9 (anxiety adj5 (autism or autistic)).ti,ab,kf. (1399)
10 anxiety.mp. and (child development disorders, pervasive/px or autism spectrum disorder/px or autistic disorder/px) (989)
11 or/1-10 (141979)
12 ADOLESCENT/ or CHILD/ or CHILD, PRESCHOOL/ (3285958)
13 (infant? or child* or adolesc* or paediatr* or pediatr*).hw,jn. (3986156)
14 (infant* or child* or boy* or girl* or kids or juvenil* or minors or paediatric* or pediatric* or adolesc* or preadolesc* or pubert* or pubescen* or prepube* or teen* or (young adj (survivor* or offender* or minorit*)) or youth* or school? or preschool* or nurser* or kindergarten).ti,kf. (1674220)
15 (infant? or child* or adolesc* or paediatr* or pediatr*).ab. /freq=3 (842370)
16 or/12-15 (4305961)
17 ((anxi* or phobi* or panic) and (effectiveness or efficacy or evaluat* or intervention or program* or train* or treat* or prevent* or therapy or psychotherapy or trial or study) and (infant? or child* or adolesc* or paediatric* or pediatric* or teen* or young* or youth or school? or preschool*)).ti. (3201)
18 controlled clinical trial.pt. (94966)
19 randomized controlled trial.pt. (573977)
20 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf. (756031)
21 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,kf. (651002)
22 (placebo or ((attention or active) adj control*)).ti,ab,kf. (244844)
23 trial.ab,ti,kf. (718320)
24 ((control* or group* or compar*) adj5 (((care or treatment*) adj2 (usual or standard or routine)) or TAU or CAU)).ab. (36576)
25 ((control* or group* or compar*) adj5 (waitlist* or wait* list* or waiting or WLC)).ab. (9316)

26 or/18-25 (1557956)
27 11 and 16 and 26 (5934)
28 17 and 26 (1186)
29 27 or 28 (5991)
30 ((OCD or obsessive compulsive or PTSD or posttraumatic stress disorder*) not (anxi* or phobi* or agoraphobi* or panic)).ti. (24973)
31 29 not 30 (5939)
32 limit 31 to yr="1978 -Current" (5861)
33 limit 32 to (english language and humans) (5114)

Database: APA PsycInfo <1806 to July Week 2 2022>

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1 anxiety disorders/ or generalized anxiety disorder/ or panic disorder/ or exp phobias/ or separation anxiety disorder/ (40106)
2 *anxiety/ (49787)
3 social anxiety/ (5619)
4 school refusal/ or school phobia/ (788)
5 exp separation anxiety/ (1695)
6 panic/ or panic attack/ or panic disorder/ (10027)
7 (agoraphobi* or generali#ed anxiety or GAD or separation anxiety or (social* adj2 (anxi* or fear*)) or phobi* or school refusal).ti,ab,id. (43217)
8 ((infant? or child* or adolesc* or p?ediatric* or teen* or young* or youth or school? or preschool*) adj2 anxi*).ti,ab,id. (11330)
9 over anxious.ti,ab,id. (32)
10 anxiety.ab. /freq=3 (61996)
11 panic.ti,ab,id,hw. (17529)
12 (anxiety adj5 (autism or autistic)).ti,ab,id. (1206)
13 anxiety.ti,ab,id,tm. and (autism spectrum disorders/ or autistic thinking/ or exp developmental disabilities/) (3356)
14 or/1-13 (134401)
15 pediatrics/ (29128)
16 child psychiatry/ or child psychopathology/ or child psychology/ (14743)
17 adolescent psychiatry/ or adolescent psychopathology/ or adolescent psychology/ (15902)
18 (infant? or child* or adolesc* or paediatr* or pediatr*).hw,jx. (483302)
19 (infant* or child* or boy* or girl* or kids or juvenil* or minors or paediatric* or pediatric* or adolesc* or preadolesc* or pubert* or pubescen* or prepube* or teen* or (young adj (survivor* or offender* or minorit*)) or youth* or school? or preschool* or nurser* or kindergarten).ti,id. (894979)
20 or/15-19 (973363)
21 ((anxi* or phobi* or panic) and (effectiveness or efficacy or evaluat* or intervention or program* or train* or treat* or prevent* or therapy or psychotherapy or trial or study) and (infant? or child* or adolesc* or paediatric* or pediatric* or teen* or young* or youth or school? or preschool*)).ti. (3537)
22 clinical trials.sh. (12078)
23 (randomi#ed or randomi#ation or randomi#ing).ti,ab,id. (101137)
24 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,id. (118490)
25 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id. (28286)
26 (control* and (trial or study or group) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw. (32785)

27 trial.ti. (35485)
28 placebo.ti,ab,id,hw. (42922)
29 treatment outcome.md. (22671)
30 treatment effectiveness evaluation.sh. (26868)
31 mental health program evaluation.sh. (2284)
32 or/22-31 (221078)
33 14 and 20 and 32 (2284)
34 21 and 32 (1026)
35 33 or 34 (2329)
36 ((OCD or obsessive compulsive or PTSD or posttraumatic stress disorder*) not (anxi* or phobi* or agoraphobi* or panic)).ti. (27559)
37 35 not 36 (2302)
38 limit 37 to yr="1978 -Current" (2270)
39 limit 38 to (human and english language) (2021)

Database: Embase Classic+Embase <1947 to 2022 July 18>

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1 anxiety disorder/ or anxiety neurosis/ or generalized anxiety disorder/ or "mixed anxiety and depression"/ or panic/ or exp phobia/ or separation anxiety/ (146125)
2 *anxiety/ (63382)
3 (agoraphobi* or generali#ed anxiety or GAD or separation anxiety or (social* adj2 (anxi* or fear*)) or phobi* or school refusal).ti,ab,kw. (57876)
4 ((infant? or child* or adolesc* or p?ediatric* or teen* or young* or youth or school? or preschool*) adj2 anxi*).ti,ab,kw. (14553)
5 anxiety.ab. /freq=3 (97674)
6 panic.mp. (31009)
7 (anxiety adj5 (autism or autistic)).ti,ab,kw. (1754)
8 anxiety.mp. and (autism/ or asperger syndrome/ or "pervasive developmental disorder not otherwise specified"/) (8706)
9 school refusal/ (136)
10 or/1-9 (268525)
11 juvenile/ or exp adolescent/ or exp child/ (4233526)
12 (infant? or child* or adolesc* or paediatr* or pediatr*).hw,jx. (4385467)
13 (infant* or child* or boy* or girl* or kids or juvenil* or minors or paediatric* or pediatric* or adolesc* or preadolesc* or pubert* or pubescen* or prepube* or teen* or (young adj (survivor* or offender* or minorit*)) or youth* or school? or preschool* or nurser* or kindergarten).ti,kw. (2079235)
14 or/11-13 (4965685)
15 ((anxi* or phobi* or panic) and (effectiveness or efficacy or evaluat* or intervention or program* or train* or treat* or prevent* or therapy or psychotherapy or trial or study) and (infant? or child* or adolesc* or paediatric* or pediatric* or teen* or young* or youth or school? or preschool*)).ti. (3785)
16 randomized controlled trial/ (720770)
17 randomization.de. (94672)
18 controlled clinical trial/ and (Disease Management or Drug Therapy or Prevention or Rehabilitation or Therapy).fs. (255605)
19 *clinical trial/ (19244)
20 placebo.de. (393543)
21 placebo.ti,ab. (348619)
22 trial.ti. (372006)
23 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kw. (1078142)
24 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place*

or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,kw. (887528)
25 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).mp. (350856)
26 (control* and (trial or study or group) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kw,hw. (408650)
27 or/16-26 (2005722)
28 ((animal or nonhuman) not (human and (animal or nonhuman))).de. (6574132)
29 27 not 28 (1826894)
30 10 and 14 and 29 (6279)
31 15 and 29 (1238)
32 30 or 31 (6322)
33 ((OCD or obsessive compulsive or PTSD or posttraumatic stress disorder*) not (anxi* or phobi* or agoraphobi* or panic)).ti. (31657)
34 32 not 33 (6235)
35 limit 34 to yr="1978 -Current" (6104)
36 limit 35 to (human and english language) (5810)
37 limit 36 to exclude medline journals (681)

Database: The Cochrane Library

#1 MeSH descriptor: [Anxiety] this term only 8635
#2 MeSH descriptor: [Anxiety] explode all trees and with qualifier(s): [diagnosis - DI, prevention & control - PC, psychology - PX, therapy - TH] 5829
#3 MeSH descriptor: [Agoraphobia] this term only 449
#4 MeSH descriptor: [Panic Disorder] this term only 983
#5 MeSH descriptor: [Anxiety, Separation] this term only 114
#6 MeSH descriptor: [Phobic Disorders] explode all trees 1466
#7 MeSH descriptor: [Phobia, Social] this term only 278
#8 ((infant or infants or child* or adolesc* or pediatric* or paediatric* or teen* or young* or youth or school* or preschool*) and (anxi* or phobi* or panic)):ti 2508
#9 ((infant or infants or child* or adolesc* or pediatric* or paediatric* or teen* or young* or youth or school* or preschool*) near/2 (anxi* or phobi* or panic)):ab 2181
#10 (agoraphobi* or generalized anxiety or generalised anxiety or GAD or separation anxiety or (social* near/2 (anxi* or fear*)) or phobi* or school refusal):ti,ab,kw 10566
#11 panic:ti,ab,kw 3086
#12 (anxiety near (autism or autistic)):ti,ab,kw 280
#13 MeSH descriptor: [Child Development Disorders, Pervasive] explode all trees 2038
#14 anxiety:ti,ab,kw60614
#15 #13 and #14 198
#16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #10 OR #11 OR #12 OR #15 20518
#17 MeSH descriptor: [Adolescent] this term only 110346
#18 MeSH descriptor: [Child] explode all trees 61542
#19 MeSH descriptor: [Infant] this term only 23634
#20 (infant* or child* or adolesc* or paediatr* or pediatr*):kw,so 234550
#21 (infant* or child* or boy* or girl* or kids or juvenil* or minors or paediatric* or pediatric* or adolesc* or preadolesc* or pre-adolesc* or pubert* or pubescen* or prepube* or pre-pube* or teen* or (young next (survivor* or offender* or minorit*)) or youth* or schoo* or preschool* or nurser* or kindergarten):ti,kw 278537

#22 #17 OR #18 OR #19 OR #20 OR #21 285983
#23 #16 AND #22 5354
#24 #8 OR #9 3520
#25 #23 OR #24 7457
#26 ((OCD or "obsessive compulsive" or PTSD or "posttraumatic stress" or "post-traumatic stress") not (anxi* or phobi* or agoraphobi* or panic)):ti 5759
#27 #25 NOT #26 in Cochrane Reviews, Trials 7372
Notes:

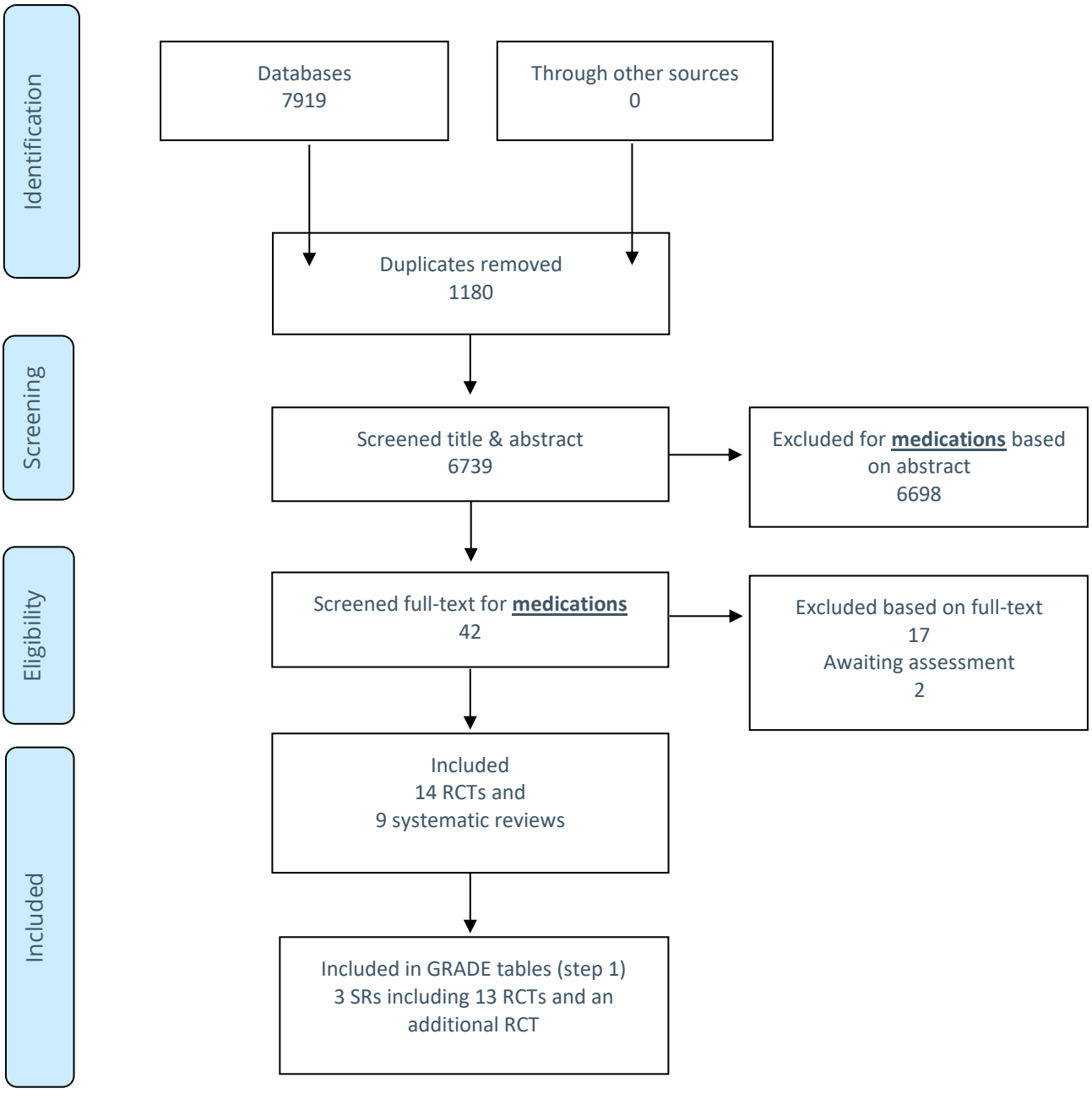
Systematic reviews (39) in the last 5 years (15)

Trials (7333) not already in pubmed (4415) or embase (2551) but that are in CINAHL (88)

Searches were reviewed in October 2023, finding no new evidence to change recommendations.

6.3 Results

6.3.1 Search results - PRISMA flowchart



6.3.2 Map of included studies

Three recent systematic reviews with network meta-analyses were identified by our search and deemed to meet our selection criteria. The randomised controlled trials (RCTs) identified by our search, deemed to meet our selection criteria were included in one or more of the three systematic reviews and sufficiently assessed for risk of bias. One of the systematic reviews, which also addressed combinations of psychological therapy with medication, sufficiently assessed for GRADE certainty [9] and the single comparison and single outcome relevant to this evidence review have been summarised narratively in the evidence summary (6.1.1) and in the evidence review for psychological therapy. There was one additional RCT assessing the SSRI, escitalopram (Strawn 2020 [10]). Thus, the systematic reviews will form the evidence base, supplemented with findings from the recent RCT.

Included systematic reviews identified by our search	**Dobson 2019 [6]** Effect of medication on symptoms and treatment response for children and young people with anxiety disorders. Network meta-analyses.	**Mills 2020 [8]** Effect of medication on adverse events for children and young people with anxiety and those with anxiety and OCD. Network meta-analyses.
Comparisons	SSRIs v placebo √ SNRIs v placebo √ TCA v placebo √ Benzodiazepine v placebo √ SSRI v SNRI √ SSRI v TCA √ SSRI v benzodiazepine √ SNRI v TCA √ SNRI v benzodiazepine √ TCA v benzodiazepine √	SSRIs v placebo √ SNRIs v placebo √ SSRIs v SNRIs √
Risk of bias	Moderate	Moderate
Notes	*Referred to* in Boaden 2020 [7] and Correll 2021 [11] with no additional data. Same included studies as Schwartz 2019 [12] and Wang 2017 (additional studies Pine 2001 and Reinblatt 2009 from RUPP, already included) but can use GRADE narratively for remission [9]. *Replaces* Dobson 2016 [3], Bennett 2016 [13], Ipser 2009 (also OCD but ADs separated) [1], Locher 2017 (also OCD, depressive disorder, PTSD but ADs – but not for SSRI bc one study plus CBT) [4], Strawn 2018 [5], Strawn 2015 [2].	Medications include SSRIs and SNRIs. We can adopt the analyses and risk of bias as determined by Dobson 2019 for the studies relevant to our selection criteria. We can't use the analyses for anxiety+OCD because there is insufficient information about the trials included and their risk of bias.
Randomised controlled trials included in above systematic reviews and identified by our search strategy		
TCA	Gittelman-Klein 1971* Berney 1981 [14] (unclear diagnosis) Klein 1992 [15] Bernstein 1990 [16] Da Costa 2013 [17]	
SSRI	Black 1994* RUPP 2001 [18] (17/14% ADHD) Rynn 2001 [19]	RUPP 2001 [18] Rynn 2001 [19] Birmaher 2003 [20]

	Birmaher 2003 [20] (5/5% ADHD) Wagner 2004 [21] Beidel 2007 [22] (13/12% ADHD) Walkup 2008 [23] (12/12% ADHD) Da Costa 2013 [17]	Wagner 2004 [21] Walkup 2008 [23] Da Costa 2013 [17]
SNRI	Geller 2007(ADHD)* [24] March 2007 [25] Rynn 2007 [26] Strawn 2015 [27]	March 2007 [25] Rynn 2007 [26] Strawn 2015 [27] Geller 2004 (OCD)*
Benzodiazepine	Simeon 1992 [28] Graae 1994 [29] (many ADHD) Bernstein 1990 [16]	

* Gittelman-Klein 1971 was not identified by our search because we searched from 1978 – ok to be included in analysis; Black 1994 was identified by our search but was excluded because the population has elective mutism, ok to include via Dobson because very small numbers and accounted for in GRADE; Geller 2007 was identified by our search and included in anxiety and ADHD – SNRI data from Dobson can't be used because it is combined with anxiety only data; Geller 2004 was not identified by our search, likely because it included children and young people with OCD – ok to include via Dobson because analysis for anxiety only is presented separately.

6.3.3 Characteristics and risk of bias of included articles

Dobson 2019 (Systematic review)

Study citation	Dobson, E. T., et al. (2019). "Efficacy and Tolerability of Pharmacotherapy for Pediatric Anxiety Disorders: A Network Meta-Analysis." Journal of Clinical Psychiatry 80(1): 29.	
External validity – selection criteria and characteristics of the systematic review		
Population, n=	Youth with anxiety disorders 22 RCTs, n=2623	
Selection criteria	"All prospective, randomized, placebo-controlled clinical trials that evaluated a specific pharmacotherapy intervention in the treatment of anxiety disorders in patients < 18 years of age and used a validated rating scale to measure anxiety symptom severity were selected for further analysis. Trials involving concurrent psychotherapy were excluded, as were those that were unavailable in English."	
Intervention	Medication – SSRI, SNRI, TCA, Benzodiazepine (also included but not in our selection criteria – a2 agonist, 5-HT1A Agonist)	
Comparison	Placebo	
Outcome measures	Symptom severity, global improvement, discontinuation, and suicidality data.	
Internal validity – risk of bias in systematic review methods		
Selection bias	It is not reported whether two independent reviewers screened articles or whether reviewers were blind to authors, institutions and affiliations in screening. The review does report specified selection criteria.	
Sampling & publication bias	A comprehensive search strategy is documented. It is not reported whether unpublished studies were searched for.	
Outcome bias	It is not reported whether two independent reviewers extracted data and assessed risk of bias. The Cochrane risk of bias criteria was used.	
Reporting bias	There is a detailed characteristics of included studies table but results of individual studies are not reported or summarised. The strengths and limitations of included studies and potential impact on the results were discussed and appropriate conclusions were made based on appropriately performed meta-analyses.	
Funding bias	Financial disclosures were reported.	
Comments	Data and/or effect sizes for each study are not presented. Funnel plots did not indicate publication bias for treatment response, all-cause discontinuation or discontinuation due to adverse events. Funnel plots indicated possible publication bias for symptom improvement. Have not presented forests plots (OR and CrI) for all-cause discontinuation, discontinuation due to adverse event, and treatment-emergent suicidality despite methods describing their meta-analyses. ***The systematic review is sufficient to adopt the meta-analyses and detailed risk of bias assessments of individual studies into the GRADE (step 1) tables for treatment response and symptom improvement only. Insufficient analysis reported for discontinuation and suicidality.***	
Overall risk of bias of the systematic review	Moderate	Some of the criteria have been fulfilled and where criteria have not been fulfilled it is unlikely the conclusions of the study would be affected.

Mills 2020 (Systematic review)

Study citation	Mills, J. A. and J. R. Strawn (2020). "Antidepressant Tolerability in Pediatric Anxiety and Obsessive-Compulsive Disorders: A Bayesian Hierarchical Modeling Meta-analysis." Journal of the American Academy of Child & Adolescent Psychiatry 59(11): 1240-1251.	
External validity – selection criteria and characteristics of the systematic review		
Population, n=	Children or adolescents with anxiety disorders 10 RCTs in anxiety, n=1826 (8 RCTs in OCD, not relevant here)	
Selection criteria	"Studies were included if they were prospective, randomized, parallel-group, placebo-controlled trials that evaluated SSRIs or SNRIs in the treatment of social, generalized, or separation anxiety disorder or OCD in children or adolescents and systematically captured AEs."	
Intervention	Medication – SSRI, SNRI	
Comparison	Placebo or other intervention	
Outcome measures	Adverse events	
Internal validity – risk of bias in systematic review methods		
Selection bias	It is not reported whether two independent reviewers screened articles or whether reviewers were blind to authors, institutions and affiliations in screening. The review does report specified selection criteria.	
Sampling & publication bias	A comprehensive search strategy is documented. It is not reported whether unpublished studies were searched for.	
Outcome bias	It is not reported whether two independent reviewers extracted data and assessed risk of bias. The Cochrane risk of bias criteria was used.	
Reporting bias	There is a brief characteristics of included studies table but results of individual studies are not reported or summarised. The strengths and limitations of the analysis and potential impact on the results were discussed and appropriate conclusions were made based on appropriately performed meta-analyses.	
Funding bias	Financial disclosures were reported.	
Comments	Data and/or effect sizes for each study are not presented. Funnel plots not reported and publication bias not addressed. Have presented data in three different ways and need to scour the article and supplementary material to figure out which analysis method was used for each. N not reported for any outcome. ***The systematic review is sufficient to adopt the network meta-analyses and detailed risk of bias assessments of individual studies into the GRADE (step 1) tables.***	
Overall risk of bias of the systematic review	Moderate	Some of the criteria have been fulfilled and where criteria have not been fulfilled it is unlikely the conclusions of the study would be affected.

Wang 2017 (Systematic review)

Study citation	Wang, Z., et al. (2017). "Comparative Effectiveness and Safety of Cognitive Behavioral Therapy and Pharmacotherapy for Childhood Anxiety Disorders: A Systematic Review and Meta-analysis." JAMA Pediatrics 171(11): 1049-1056.	
External validity – selection criteria and characteristics of the systematic review		
Population, n=	Children with anxiety disorders Up to 7 RCTs relevant to this evidence review	
Selection criteria	"Eligible studies (1) examined children and adolescents between ages 3 and 18 years with confirmed diagnoses of panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder, or separation anxiety and who received CBT or any medication, alone or in combination; (2) included at least 1 of the controls (CBT, medication, pill placebo, wait-listing/no treatment, or attention control/treatment as usual); and (3) reported outcomes of interest (primary anxiety symptoms, remission, relapse, or any AEs). We included randomized clinical trials (RCTs) and nonrandomized comparative studies."	
Intervention	Medication – SSRI, SNRI, TCA, Benzodiazepine (also included but not in our selection criteria – CBT, CBT+medication)	
Comparison	Placebo (also included but not in our selection criteria – CBT, CBT+medication)	
Outcome measures	Symptom severity, global improvement, discontinuation, and suicidality data.	
Internal validity – risk of bias in systematic review methods		
Selection bias	Independent reviewers screened articles in duplicate but it was not reported whether reviewers were blind to authors, institutions and affiliations in screening. The review does report specified selection criteria.	
Sampling & publication bias	A comprehensive search strategy is documented. It is not reported whether unpublished studies were searched for.	
Outcome bias	Pairs of independent reviewers extracted data and assessed risk of bias. The Cochrane risk of bias criteria and GRADE was used.	
Reporting bias	There is a detailed characteristics of included studies table but results of individual studies are not reported or summarised. The strengths and limitations of included studies and potential impact on the results were discussed and appropriate conclusions were made based on appropriately performed meta-analyses.	
Funding bias	Financial disclosures were reported.	
Comments	Data and/or effect sizes for each study are not presented. Funnel plots to indicate publication bias were not able to performed due to small numbers of included studies. ***The systematic review is sufficiently reported to adopt the meta-analyses, detailed risk of bias assessments of individual studies, and body of evidence GRADE ratings into the summary of evidence.***	
Overall risk of bias of the systematic review	Low	Some of the criteria have been fulfilled and where criteria have not been fulfilled it is unlikely the conclusions of the study would be affected.

Strawn 2020 (RCT)

Study citation	Strawn, J. R., et al. (2020). "Escitalopram in Adolescents With Generalized Anxiety Disorder: A Double-Blind, Randomized, Placebo-Controlled Study." Journal of Clinical Psychiatry 81(5): 25.	
External validity – selection criteria and characteristics of the RCT		
Population	12-17 years who met DSM-IV-TR criteria for generalized anxiety disorder (GAD) using Anxiety Disorders Interview Schedule (ADIS). 19/16% in each group also had ADHD.	
Setting	Outpatients at a single academic site in the United States.	
Intervention	Escitalopram (forced titration to 15 mg/d, then flexible titration to 20 mg/d) (n = 26, mean ± SD age: 14.8 ± 1.7 years) for 8 weeks. Escitalopram was initiated at 5 mg daily for 2 days and titrated to 10 mg daily for 7 days and then 15 mg daily. At the week 4 and 6 visits, escitalopram could be titrated to 20 mg daily. The study incorporated a 1-week screening period and an 8-week double-blind treatment period.	
Comparison	Placebo (n = 25, mean ± SD age: 14.9 ± 1.6 years) for 8 weeks.	
Outcomes	Change in scores on the Pediatric Anxiety Rating Scale (PARS) and Clinical Global Impressions (CGI) scales as well as vital signs and adverse events. Pharmacogenetic testing and plasma measures were reported but not relevant to this evidence review.	
Internal validity – has this study been conducted rigorously in order to reduce bias?		
Selection bias	Adequate method of randomisation and allocation - "Randomization to escitalopram or placebo (1:1) was assigned, in blocks of 4, by investigational pharmacists and was stratified by sex using a random number generator."	
Performance bias	"Patients, caregivers, and investigational staff were blind to treatment assignment"; and it can be assumed that aside from the experimental intervention, the groups were likely to have been treated the same.	
Detection/outcome bias	"Efficacy measures were administered by a blinded study physician who underwent training on the use of the instrument and met predetermined interrater reliability criteria"	
Attrition bias	26/25 participants were allocated to intervention and placebo, respectively, and were analysed, thus assume ITT analysis. 5/6 participants in intervention and placebo groups, respectively, dropped out. 3 in each group due to symptom exacerbation, 1/2 due to lack of efficacy and 1 in each group due to serious adverse event.	
Reporting bias	The study briefly reports specified inclusion/exclusion criteria which are appropriate. It is unknown whether the article is free of selective outcome reporting.	
Funding bias	Conflicts of interest and funding were declared.	
Comments	Under powered - Sample size consisted of 32 patients in the escitalopram group and 32 patients in the placebo group, and 80% power was used to detect group differences of ≥ 0.7 (Cohen d). Imputation occurred via last observation carried forward (LOCF).	
Overall risk of bias of the RCT	Low	Most of the criteria have been fulfilled and where criteria have not been fulfilled it is unlikely the conclusions of the study would be affected.

6.3.4 GRADE tables (GRADE step 1)

6.3.4.1 COMPARISON: Selective serotonin reuptake inhibitor (SSRI) versus placebo in children and young people with anxiety

a. Analysis and risk of bias assessments of individual studies adopted from Dobson 2019 (search 2017). Interventions ranked 1-7 in the network: SSRI, SNRI, TCA, Benzodiazepine, a2 Agonist, 5-HT 1A Agonist, Placebo; with a ranking of 1 indicating most efficacious or most tolerable.
b. Anxiety only analysis and risk of bias assessments of individual studies adopted from Mills 2020 (search 2019). Interventions not ranked. Numbers of participants for each outcome not provided, thus below are maximum sample sizes and studies for each outcome.
c. Recent RCT not included in systematic reviews, Strawn 2020.

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SSRIs	Placebo	Effect [95% credible interval (CrI)]	Favours	Certainty
[c]Outcome: **treatment response – mean improvement**; CGI-S; 8 weeks											
1	RCT	no serious	NA	serious[5]	serious	NA	26	25	Mean change ± SD 2.8 ± 0.3 v 3.6 ± 0.2	SSRIs p=0.032	⊕⊕◯◯ LOW
[c]Outcome: **symptom improvement – mean change from baseline**; PARS; 8 weeks											
1	RCT	no serious	NA	serious[5]	serious	NA	26	25	SSRI: -8.65 ± 1.31 Placebo: -3.52 ± 1.06	SSRIs p= 0.005 [-8.57, -1.70]	⊕⊕◯◯ LOW
[a]Outcome: **treatment response**; CGI; 8-16 weeks; ***meta-analysis***											
8[3]	RCT	serious[4]	no serious	no serious	no serious	I^2=38.6 %	456	397	OR 4.6 [3.1, 7.5]	SSRIs	⊕⊕⊕◯ MODERATE
[a]Outcome: **symptom improvement**; PARS, HARS, LSAS-CA, SPAI-C; 8-16 weeks; ***meta-analysis***											
8[1]	RCT	serious[2]	serious[5]	no serious	no serious	I^2 NR	456	397	OR 5.2 [2.8, 8.8]	SSRIs	⊕⊕◯◯ LOW
[a]Outcome: **treatment response**; CGI; 8-16 weeks; ***network meta-analysis (SSRIs ranked 1st 88%)***											

[3] Black 1994 (fluoxetine, high risk of bias (ROB)), RUPP 2001 (fluvoxamine, high ROB), Rynn 2001 (sertraline, high ROB), Birmaher 2003 (fluoxetine, moderate ROB), Wagner 2004 (paroxetine, moderate ROB), Beidel 2007 (fluoxetine, moderate ROB), Walkup 2008 (sertraline, low ROB), DaCosta 2013 (fluoxetine, high ROB); 1a, all except Black 1994; 1b, all except Rynn 2001; 1c, only Wagner2004 and Walkup 2008

[4] Downgraded once due to the majority of studies being at high or moderate risk of bias and one at low risk of bias

[5] Downgraded once due to statistical heterogeneity not reported in the systematic review for this outcome

8[1]	RCT	serious[2]	serious[6]	serious[7]	no serious	I^2 NR	456	1223	logOR 1.5 [1.1, 2.0]	SSRIs	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; PARS, HARS, LSAS-CA, SPAI-C; 8-16 weeks; ***network meta-analysis (SSRIs ranked 1st 90%)***											
7[1a]	RCT	serious[2]	serious[4]	serious[5]	no serious	I^2 NR	450	1147	MD 5.2 [2.8, 8.8]	SSRIs	⊕⊕◯◯ LOW
[a]Outcome: **all-cause early discontinuation**; 8-16 weeks; ***network meta-analysis (SSRIs ranked 1st 77%)***											
8[1]	RCT	serious[2]	serious[4]	serious[5]	no serious	I^2 NR	456	1230	logOR -0.2 [-0.7, 0.3]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **early discontinuation due to adverse events**; 8-16 weeks; ***network meta-analysis (SSRIs ranked 4th 50%)***											
7[1b]	RCT	serious[2]	serious[4]	serious[5]	no serious	I^2 NR	445	1159	logOR -1.8 [-3.4, 0.4]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **treatment-emergent suicidality**; 8-16 weeks; ***network meta-analysis (SSRIs ranked 3rd 69%)***											
2[1c]	RCT	serious[2]	serious[4]	serious[5]	no serious	I^2 NR	296	452	logOR 1.0 [-2.2, 4.7]	No difference	⊕⊕◯◯ LOW
[b]Outcome: **AE-related discontinuation**; 8-16 weeks											
6[8]	RCT	serious[2]	serious[9]	serious[10]	no serious	I^2=0%	417	893	Mean posterior probability (MPP) ± SD 0.034 ± 0.015	Placebo p = 0.022 [0.005, 0.066]	⊕⊕◯◯ LOW
[b]Outcome: **activation**; 8-16 weeks											
6[6]	RCT	serious[2]	serious[7]	serious[8]	no serious	I^2=0%	417	893	MPP 0.085 ± 0.031 [0.025, 0.146]	Placebo p = 0.0053	⊕⊕◯◯ LOW
[b]Outcome: **sedation/drowsiness**; 8-16 weeks											
6[6]	RCT	serious[2]	serious[7]	serious[8]	no serious	I^2=0%	417	893	MPP 0.077 ± 0.035 [0.011, 0.147]	Placebo p = 0.024	⊕⊕◯◯ LOW
[b]Outcome: **insomnia**; 8-16 weeks											

[6] The authors note the planned node-splitting consistency analysis was restricted. There were 2 closed loops in the star-shaped network.

[7] Primary diagnosis, titration schedule, symptom severity and comorbidity may impact directness. The authors note these respond similarly to antidepressant treatment and share risk factors and neurobiology thus the strong precent for combining. One study (Black 1994) included those with elective mutism which is an exclusion criterion for this guideline.

[8] Rynn 2001 (sertraline, high ROB), Birmaher 2003 (fluoxetine, moderate ROB), RUPP 2001 (fluvoxamine, high ROB), Walkup 2008 (sertraline, low ROB), Wagner 2004 (paroxetine, moderate ROB), DaCosta 2013 (fluoxetine, high ROB)

[9] Downgraded once because while the authors note that the BHM approach assumes trials are not exchangeable and that intertrial differences are incorporated into the model; but that unobserved factors may still affect the likelihood of AEs described in this report. No statistical heterogeneity (all <50%). No further info about consistency/cohesion exploration or results.

[10] Downgraded once because while the authors note that most studies are comparable, studies with high placebo response, studies with high medication response, and different trial durations may impact directness across studies.

6[6]	RCT	serious[2]	serious[7]	serious[8]	no serious	I^2=0%	417	893	MPP 0.042 ± 0.032 [-0.020, 0.104]	No difference p = 0.188	⊕⊕◯◯ LOW
[b]Outcome: **abdominal pain**; 8-16 weeks											
6[6]	RCT	serious[2]	serious[7]	serious[8]	no serious	I^2=0%	417	893	MPP 0.149 ± 0.049 [0.005, 0.248]	Placebo p = 0.026	⊕⊕◯◯ LOW
[b]Outcome: **headache**; 8-16 weeks											
6[6]	RCT	serious[2]	serious[7]	serious[8]	no serious	I^2=0%	417	893	MPP 0.100 ± 0.045 [0.011, 0.188]	Placebo p = 0.027	⊕⊕◯◯ LOW
[b]Outcome: **nausea**; 8-16 weeks											
6[6]	RCT	serious[2]	serious[7]	serious[8]	no serious	I^2=44%	417	893	MPP 0.010 ± 0.033 [-0.055, 0.075]	No difference p = 0.764	⊕⊕◯◯ LOW
[b]Outcome: **diarrhea**; 8-16 weeks											
6[6]	RCT	serious[2]	serious[7]	serious[8]	no serious	I^2=0%	417	893	MPP -0.010 ± 0.026 [-0.062, 0.039]	No difference p = 0.683	⊕⊕◯◯ LOW
[b]Outcome: **suicidality**; 8-16 weeks											
6[6]	RCT	serious[2]	serious[7]	serious[8]	no serious	I^2=0%	417	893	MPP 0.007 ± 0.009 [-0.013, 0.022]	No difference p = 0.669	⊕⊕◯◯ LOW

6.3.4.2 COMPARISON: Serotonin norepinephrine reuptake inhibitor (SNRI) versus placebo in children and young people with anxiety

a. Analysis and risk of bias assessments of individual studies adopted from Dobson 2019 (search 2017). Interventions ranked 1-7 in the network: SSRI, SNRI, TCA, Benzodiazepine, a2 Agonist, 5-HT 1A Agonist, Placebo; with a ranking of 1 indicating most efficacious or most tolerable.
b. Anxiety only analysis and risk of bias assessments of individual studies adopted from Mills 2020 (search 2019). Interventions not ranked.

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SNRIs	Placebo	Effect [95% credible interval (CrI)]	Favours	Certainty
[a]Outcome: **treatment response**; CGI, 50% improvement on PARS; 8-16 weeks; ***meta-analysis***											
5[11]	RCT	serious[12]	no serious	no serious	no serious	I^2=0%	484	506	OR 2.4 [1.7, 3.6]	SNRIs	⊕⊕⊕◯ MODERATE
[a]Outcome: **symptom improvement**; PARS, SAS-CA; 8-16 weeks; ***meta-analysis***											

[11] Geller 2007 (+ADHD, atomoxetine, high ROB), March 2007 (venlafaxine, low ROB), Rynn 2007 A and B (venlafaxine, both high ROB), Strawn 2015 (duloxetine, low ROB)
[12] Downgraded once due to the majority of studies being at high risk of bias and two at low risk of bias

5[9]	RCT	serious[10]	serious[13]	no serious	no serious	I^2 NR	484	506	OR 2.5 [-0.1, 5.1]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **treatment response**; CGI, 50% improvement on PARS; 8-16 weeks; ***network meta-analysis (SNRIs ranked 3rd 59%)***											
5[9]	RCT	serious[10]	serious[14]	serious[15]	no serious	I^2 NR	484	1223	logOR 0.9 [0.5, 1.3]	SNRIs	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; PARS, SAS-CA; 8-16 weeks; ***network meta-analysis (SNRIs ranked 3rd 60%)***											
5[9]	RCT	serious[10]	serious[12]	serious[13]	no serious	I^2 NR	484	1147	MD 2.5 [-0.1, 5.1]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **all-cause early discontinuation**; 8-16 weeks; ***network meta-analysis (SNRIs ranked 4th 50%)***											
5[9]	RCT	serious[10]	serious[12]	serious[13]	no serious	I^2 NR	484	1230	logOR 0.1 [-0.4, 0.5]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **early discontinuation due to adverse events**; 8-16 weeks; ***network meta-analysis (SNRIs ranked 1st 91%)***											
5[9]	RCT	serious[10]	serious[12]	serious[13]	no serious	I^2 NR	484	1159	logOR 0.4 [-0.9, 1.7]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **treatment-emergent suicidality**; 8-16 weeks; ***network meta-analysis (SNRIs ranked 2nd 73%)***											
5[9]	RCT	serious[10]	serious[12]	serious[13]	no serious	I^2 NR	484	452	logOR 0.6 [-1.2, 2.8]	No difference	⊕⊕◯◯ LOW
[b]Outcome: **AE-related discontinuation**; 8-16 weeks											
4[16]	RCT	serious[17]	serious[18]	serious[19]	no serious	I^2=0%	417	893	Mean posterior probability (MPP) ± SD 0.005 ± 0.016	No difference p = 0.753 [-0.027, 0.037]	⊕⊕◯◯ LOW

[13] Downgraded once due to statistical heterogeneity not reported in the systematic review for this outcome

[14] The authors note the planned node-splitting consistency analysis was restricted. There were 2 closed loops in the star-shaped network.

[15] Primary diagnosis, titration schedule, symptom severity and comorbidity may impact directness across studies. The authors note these are commonly studied together and respond similarly to antidepressant treatment and share risk factors and neurobiology thus the strong precent for combining. One study included those with co-occurring ADHD which was planned as a separate analysis for this guideline, thus the study is included again in the NMA from Villas-Boas 2019.

[16] March 2007 (venlafaxine, low ROB), Rynn 2007 A and B (venlafaxine, both high ROB), Strawn 2015 (duloxetine, low ROB)

[17] Downgraded once due to two studies at high risk of bias and two at low risk of bias

[18] Downgraded once because while the authors note that the BHM approach assumes trials are not exchangeable and that intertrial differences are incorporated into the model; but that unobserved factors may still affect the likelihood of AEs described in this report. No statistical heterogeneity (all <50%). No further info about consistency/cohesion exploration or results.

[19] Downgraded once because while the authors note that most studies are comparable, studies with high placebo response, studies with high medication response, and different trial durations may impact directness across studies.

[b]Outcome: **activation**; 8-16 weeks										
4[14]	RCT	serious[15]	serious[16]	serious[17]	no serious	I^2=0%	417	893	MPP 0.020 ± 0.014 [-0.007, 0.048]	No difference p = 0.152	⊕⊕◯◯ LOW
[b]Outcome: **sedation/drowsiness**; 8-16 weeks										
4[14]	RCT	serious[15]	serious[16]	serious[17]	no serious	I^2=0%	417	893	MPP 0.050 ± 0.029 [-0.006, 0.107]	No difference p = 0.080	⊕⊕◯◯ LOW
[b]Outcome: **abdominal pain**; 8-16 weeks										
4[14]	RCT	serious[15]	serious[16]	serious[17]	no serious	I^2=0%	417	893	MPP 0.031 ± 0.032 [-0.031, 0.094]	No difference p = 0.326	⊕⊕◯◯ LOW
[b]Outcome: **headache**; 8-16 weeks										
4[14]	RCT	serious[15]	serious[16]	serious[17]	no serious	I^2=0%	417	893	MPP -0.003 ± 0.041 [-0.083, 0.077]	No difference p = 0.937	⊕⊕◯◯ LOW
[b]Outcome: **nausea**; 8-16 weeks										
4[14]	RCT	serious[15]	serious[16]	serious[17]	no serious	I^2=0%	417	893	MPP 0.081 ± 0.026 [0.029, 0.133]	Placebo p = 0.002	⊕⊕◯◯ LOW
[b]Outcome: **suicidality**; 8-16 weeks										
4[14]	RCT	serious[15]	serious[16]	serious[17]	no serious	I^2=0%	417	893	MPP 0.010 ± 0.012 [-0.014, 0.036]	No difference p = 0.394	⊕⊕◯◯ LOW

6.3.4.3 COMPARISON: Tricyclic antidepressant (TCA) versus placebo in children and young people with anxiety

a. Analysis and risk of bias assessments of individual studies adopted from Dobson 2019 (search 2017). Interventions ranked 1-7 in the network: SSRI, SNRI, TCA, Benzodiazepine, a2 Agonist, 5-HT 1A Agonist, Placebo; with a ranking of 1 indicating most efficacious or most tolerable.

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	TCAs	Placebo	Effect [95% credible interval (CrI)]	Favours	Certainty
[a]Outcome: **treatment response**; CGI, global improvement; 6-12 weeks; ***meta-analysis***											
4[20]	RCT	very serious[21]	no serious	no serious	serious[22]	I^2=24.6%	68	60	OR 2 .0 [0.8, 4.9]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; RXMAS, MASC; 8-12 weeks; ***meta-analysis***											
2[23]	RCT	very serious[19]	serious[24]	no serious	very serious[25]	I^2 NR	18		OR 1.4 [-0.1, 5.1]	No difference	⊕◯◯◯ VERY LOW
[a]Outcome: **treatment response**; CGI, global improvement; 6-12 weeks; ***network meta-analysis (TCAs ranked 4th 48%)***											
4[18]	RCT	very serious[19]	serious[26]	serious[27]	no serious	I^2 NR	68	1223	logOR 0.7 [-0.2, 1.6]	difference	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; RXMAS, MASC; 8-12 weeks; ***network meta-analysis (TCAs ranked 4th 45%)***											
2[21]	RCT	very serious[19]	serious[24]	serious[25]	serious[28]	I^2 NR	18	1147	MD 1.4 [-5.2, 7.9]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **all-cause early discontinuation**; 6-12 weeks; ***network meta-analysis (TCAs ranked 5th 38%)***											
5[29]	RCT	very serious[19]	serious[24]	serious[25]	no serious	I^2 NR	77	1230	logOR 0.6[-0.6, 1.7]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **early discontinuation due to adverse events**; 6-12 weeks; ***network meta-analysis (TCAs ranked 3rd 68%)***											

[20] Gittelman-Klein 1971 (imipramine, high ROB), Berney 1981 (clomipramine, high ROB), Klein 1992 (imipramine, high ROB), da Costa 2013 (clomipramine, high ROB)
[21] Downgraded twice because all the studies are at high risk of bias
[22] Downgraded once due to wide confidence intervals
[23] Bernstein 1990 (imipramine, high ROB), da Costa 2013 (clomipramine, high ROB)
[24] Downgraded once due to statistical heterogeneity not reported in the systematic review for this outcome
[25] Downgraded twice due to wide confidence intervals and few participants
[26] The authors note the planned node-splitting consistency analysis was restricted. There were 2 closed loops in the star-shaped network.
[27] Primary diagnosis, titration schedule, symptom severity and comorbidity may impact directness across studies. The authors note these are commonly studied together and respond similarly to antidepressant treatment and share risk factors and neurobiology thus the strong precent for combining.
[28] Downgraded once due to small sample size of intervention arm
[29] Gittelman-Klein 1971, Berney 1981, Klein 1992, da Costa 2013, Bernstein 1990

2[30]	RCT	very serious[19]	serious[24]	serious[25]	serious[26]	I^2 NR	20	1159	logOR -0.8 [-5.0, 3.3]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **treatment-emergent suicidality**; 8 weeks; ***network meta-analysis (TCAs ranked 7th 12%)***											
1[31]	RCT	very serious[19]	serious[24]	serious[25]	serious[26]	I^2 NR	9	452	logOR 25.1 [4.5, 57.4]	Placebo	⊕◯◯◯ VERY LOW

6.3.4.4 COMPARISON: Benzodiazepine versus placebo in children and young people with anxiety

a. Analysis and risk of bias assessments of individual studies adopted from Dobson 2019 (search 2017). Interventions ranked 1-7 in the network: SSRI, SNRI, TCA, Benzodiazepine, a2 Agonist, 5-HT 1A Agonist, Placebo; with a ranking of 1 indicating most efficacious or most tolerable.

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	BNZs	Placebo	Effect [95% credible interval (CrI)]	Favours	Certainty
[a]Outcome: **treatment response**; CGI; 3-4 weeks; ***meta-analysis***											
2[32]	RCT	very serious[33]	no serious	no serious	very serious[34]	I^2=0%	29	25	OR 1.4 [0.3, 6.1]	No difference	⊕◯◯◯ VERY LOW
[a]Outcome: **symptom improvement**; RCMAS; 8 weeks; ***meta-analysis***											
1[35]	RCT	very serious[31]	serious[36]	no serious	very serious[31]	I^2 NR	7		OR -0.4 [-9.7, 9.1]	No difference	⊕◯◯◯ VERY LOW
[a]Outcome: **treatment response**; CGI; 3-4 weeks; ***network meta-analysis (BNZs ranked 5th 32%)***											

[30] Klein 1992 (imipramine, high ROB), da Costa 2013 (clomipramine, high ROB)
[31] Bernstein 1990 (imipramine, high ROB)
[32] Simeon 1992 (alprazolam, high ROB), Graae 1994 (clonidine, high ROB)
[33] Downgraded twice because all the studies are at high risk of bias
[34] Downgraded twice due to wide confidence intervals and few participants
[35] Bernstein 1990 (imipramine, high ROB)
[36] Downgraded once due to statistical heterogeneity not reported in the systematic review for this outcome

2[29]	RCT	very serious[31]	serious[37]	serious[38]	no serious[39]	I^2 NR	29	1223	logOR 0.33 [-1.2, 1.8]	difference	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; RCMAS; 8 weeks; ***network meta-analysis (BNZs ranked 6th 31%)***											
1[31]	RCT	very serious[31]	serious[35]	serious[36]	serious[37]	I^2 NR	7	1147	MD -0.4 [-9.7, 9.1]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **all-cause early discontinuation**; 3-8 weeks; ***network meta-analysis (BNZs ranked 2nd 74%)***											
3[40]	RCT	very serious[31]	serious[35]	serious[36]	serious[37]	I^2 NR	36	1230	logOR 0.3 [-1.3, 2.1]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **early discontinuation due to adverse events**; 3 weeks; ***network meta-analysis (BNZs ranked 6th 12%)***											
1[41]	RCT	very serious[31]	serious[35]	serious[36]	serious[37]	I^2 NR	12	1159	logOR -21.6[-76.8,-1.3]	Placebo	⊕⊕◯◯ LOW
[a]Outcome: **treatment-emergent suicidality**; 3-8 weeks; ***network meta-analysis (BNZs ranked 5th 36%)***											
2[42]	RCT	very serious[31]	serious[35]	serious[36]	serious[37]	I^2 NR	24	452	logOR 11.9 [-0.7, 39.3]	No difference	⊕⊕◯◯ LOW

OR, odds ratio; MD, mean difference; PARS, Pediatric Anxiety Rating Scale; HARS, Hamilton Anxiety Rating Scale; LSAS-CA, Liebowitz Social Anxiety Scale for Children and Adolescents; SPAI-C, Social Phobia and Anxiety Inventory for Children; RCMAS, Revised Children's Manifest Anxiety Scale; MASC, Multidimensional Anxiety Rating Scale for Children

[37] The authors note the planned node-splitting consistency analysis was restricted. There were 2 closed loops in the star-shaped network.

[38] Primary diagnosis, titration schedule, symptom severity and comorbidity may impact directness across studies. The authors note these are commonly studied together and respond similarly to antidepressant treatment and share risk factors and neurobiology thus the strong precent for combining.

[39] Downgraded once due to small sample size of intervention arm

[40] Simeon 1992 (alprazolam, high ROB), Graae 1994 (clonidine, high ROB), Bernstein 1990 (imipramine, high ROB)

[41] Graae 1994 (clonidine, high ROB)

[42] Graae 1994 (clonidine, high ROB), Bernstein 1990 (imipramine, high ROB)

6.3.4.5 COMPARISON: SSRIs versus SNRIs in children and young people with anxiety

a. Analysis and risk of bias assessments of individual studies adopted from Dobson 2019 (search 2017). Interventions ranked 1-7 in the network: SSRI, SNRI, TCA, Benzodiazepine, a2 Agonist, 5-HT 1A Agonist, Placebo; with a ranking of 1 indicating most efficacious or most tolerable.

b. Anxiety only analysis and risk of bias assessments of individual studies adopted from Mills 2020 (search 2019). Interventions not ranked. Numbers of participants for each outcome not provided, thus below are maximum sample sizes and studies for each outcome.

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SSRIs	SNRIs	Effect [95% credible interval (CrI)]	Favours	Certainty
[a]Outcome: **treatment response**; CGI, 50% improvement on PARS; 8-16 weeks; ***network meta-analysis (SSRIs ranked 1st 88%, SNRIs ranked 3rd 59%)***											
8/5[43]	RCT	serious[44]	serious[45]	serious[46]	no serious	I^2 NR	456	484	logOR 0.6 [0.1, 1.3]	SSRIs	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; PARS, HARS, LSAS-CA, SPAI-C, SAS-CA; 8-16 weeks; ***network meta-analysis (SSRIs ranked 1st 90%, SNRIs ranked 3rd 60%)***											
7/5[41a]	RCT	serious[42]	serious[43]	serious[44]	no serious	I^2 NR	450	484	MD 2.7 [-0.7, 7.3]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **all-cause early discontinuation**; 8-16 weeks; ***network meta-analysis (SSRIs ranked 1st 77%, SNRIs ranked 4th 50%)***											
8/5[41]	RCT	serious[42]	serious[43]	serious[44]	no serious	I^2 NR	456	484	logOR -0.3 [-0.9, 0.4]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **early discontinuation due to adverse events**; 8-16 weeks; ***network meta-analysis (SSRIs ranked 4th 50%, SNRIs ranked 1st 91%)***											
7/5[41b]	RCT	serious[42]	serious[43]	serious[44]	no serious	I^2 NR	445	484	logOR -2.2 [-4.3, -0.3]	SNRIs	⊕⊕◯◯ LOW
[a]Outcome: **treatment-emergent suicidality**; 8-16 weeks; ***network meta-analysis (SSRIs ranked 3rd 69%, SNRIs ranked 2nd 73%)***											
2/5[41c]	RCT	serious[42]	serious[43]	serious[44]	no serious	I^2 NR	296	484	logOR 0.4 [-3.6, 4.4]	No difference	⊕⊕◯◯ LOW
[b]Outcome: **AE-related discontinuation**; 8-16 weeks											

[43] SSRIs: Black 1994 (fluoxetine, high ROB), RUPP 2001 (fluvoxamine, high ROB), Rynn 2001 (sertraline, high ROB), Birmaher 2003 (fluoxetine, moderate ROB), Wagner 2004 (paroxetine, moderate ROB), Beidel 2007 (fluoxetine, moderate ROB), Walkup 2008 (sertraline, low ROB), DaCosta 2013 (fluoxetine, high ROB); SNRIs: Geller 2007 (+ADHD, atomoxetine, high ROB), March 2007 (venlafaxine, low ROB), Rynn 2007 A and B (venlafaxine, both high ROB), Strawn 2015 (duloxetine, low ROB). 41a, all except Black 1994. 41b, all except Rynn 2001. 41c, only Wagner2004 and Walkup 2008 for SSRIs.

[44] Downgraded once due to the majority of studies being at high or moderate risk of bias and few at low risk of bias.

[45] The authors note the planned node-splitting consistency analysis was restricted. There were 2 closed loops in the star-shaped network.

[46] Primary diagnosis, titration schedule, symptom severity and comorbidity may impact directness. The authors note these respond similarly to antidepressant treatment and share risk factors and neurobiology thus the strong precent for combining. One study (Black 1994) included those with elective mutism which is an exclusion criterion for this guideline.

6[47]	RCT	serious[48]	serious[49]	serious[50]	no serious	I^2=0%	417	893	MPP ± SD 0.029 ± 0.022 [-0.014, 0.072]	No difference p = 0.191	⊕⊕◯◯ LOW
[b]Outcome: **activation**; 8-16 weeks											
6[6]	RCT	serious[46]	serious[47]	serious[48]	no serious	I^2=0%	417	893	MPP 0.065 ± 0.034 [-0.001, 0.133]	No difference p = 0.054	⊕⊕◯◯ LOW
[b]Outcome: **sedation/drowsiness**; 8-16 weeks											
6[6]	RCT	serious[46]	serious[47]	serious[48]	no serious	I^2=0%	417	893	MPP 0.028 ± 0.045 [-0.061, 0.117]	No difference p = 0.539	⊕⊕◯◯ LOW
[b]Outcome: **abdominal pain**; 8-16 weeks											
6[6]	RCT	serious[46]	serious[47]	serious[48]	no serious	I^2=0%	417	893	MPP 0.119 ± 0.059 [0.004, 0.235]	SNRIs p = 0.043	⊕⊕◯◯ LOW
[b]Outcome: **headache**; 8-16 weeks											
6[6]	RCT	serious[46]	serious[47]	serious[48]	no serious	I^2=0%	417	893	MPP 0.102 ± 0.061 [-0.018, 0.221]	No difference p = 0.093	⊕⊕◯◯ LOW
[b]Outcome: **nausea**; 8-16 weeks											
6[6]	RCT	serious[46]	serious[47]	serious[48]	no serious	I^2=44%	417	893	MPP -0.072 ± 0.043 [-0.155, -0.014]	No difference p = 0.099	⊕⊕◯◯ LOW
[b]Outcome: **suicidality**; 8-16 weeks											
6[6]	RCT	serious[46]	serious[47]	serious[48]	no serious	I^2=0%	417	893	MPP -0.007 ± 0.015 [-0.037, 0.023]	No difference p = 0.655	⊕⊕◯◯ LOW

[47] SSRIs: Rynn 2001 (sertraline, high ROB), Birmaher 2003 (fluoxetine, moderate ROB), RUPP 2001 (fluvoxamine, high ROB), Walkup 2008 (sertraline, low ROB), Wagner 2004 (paroxetine, moderate ROB), DaCosta 2013 (fluoxetine, high ROB); SNRIs: March 2007 (venlafaxine, low ROB), Rynn 2007 A and B (venlafaxine, both high ROB), Strawn 2015 (duloxetine, low ROB)
[48] Downgraded once due to the majority of studies being at high or moderate risk of bias and few at low risk of bias.
[49] Downgraded once because while the authors note that the BHM approach assumes trials are not exchangeable and that intertrial differences are incorporated into the model; but that unobserved factors may still affect the likelihood of AEs described in this report. No statistical heterogeneity (all <50%). No further info about consistency/cohesion exploration or results.
[50] Downgraded once because while the authors note that most studies are comparable, studies with high placebo response, studies with high medication response, and different trial durations may impact directness across studies.

6.3.4.6 COMPARISON: SSRI versus TCA in children and young people with anxiety

a. Analysis and risk of bias assessments of individual studies adopted from Dobson 2019 (search 2017). Interventions ranked 1-7 in the network: SSRI, SNRI, TCA, Benzodiazepine, a2 Agonist, 5-HT 1A Agonist, Placebo; with a ranking of 1 indicating most efficacious or most tolerable.

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SSRIs	TCAs	Effect [95% credible interval (CrI)]	Favours	Certainty
[a]Outcome: **treatment response**; CGI, global improvement; 6-16 weeks; ***network meta-analysis (SSRIs ranked 1st 88%, TCAs ranked 4th 48%)***											
8/4[51]	RCT	serious[52]	serious[53]	serious[54]	no serious	I^2 NR	456	68	logOR 0.8 [-0.1, 1.9]	difference	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; PARS, HARS, LSAS-CA, SPAI-C, RCMAS, MASC; 8-16 weeks; ***network meta-analysis (SSRIs ranked 1st 90%, TCAs ranked 4th 45%)***											
7/2[55]	RCT	serious[50]	serious[51]	serious[52]	serious[56]	I^2 NR	450	18	MD 3.9 [-2.7, 11.3]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **all-cause early discontinuation**; 6-16 weeks; ***network meta-analysis (SSRIs ranked 1st 77%, TCAs ranked 5th 38%)***											
8/5[49a]	RCT	serious[50]	serious[51]	serious[52]	no serious	I^2 NR	456	77	logOR -0.8[-2.0, 0.5]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **early discontinuation due to adverse events**; 6-16 weeks; ***network meta-analysis (SSRIs ranked 4th 50%, TCAs ranked 3rd 68%)***											
7/2[49b]	RCT	serious[50]	serious[51]	serious[52]	serious[54]	I^2 NR	445	20	logOR -1.0 [-5.1, 3.2]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **treatment-emergent suicidality**; 8-16 weeks; ***network meta-analysis (SSRIs ranked 3rd 69%, TCAs ranked 7th 12%)***											

[51] SSRIs: Black 1994 (fluoxetine, high ROB), RUPP 2001 (fluvoxamine, high ROB), Rynn 2001 (sertraline, high ROB), Birmaher 2003 (fluoxetine, moderate ROB), Wagner 2004 (paroxetine, moderate ROB), Beidel 2007 (fluoxetine, moderate ROB), Walkup 2008 (sertraline, low ROB), DaCosta 2013 (fluoxetine, high ROB); TCAs: Gittelman-Klein 1971 (imipramine, high ROB), Berney 1981 (clomipramine, high ROB), Klein 1992 (imipramine, high ROB), da Costa 2013 (clomipramine, high ROB). 49a, plus Bernstein 1990 (TCA). 49b, all except Rynn 2001 (SSRI), Gittelman-Klein 1971 (TCA) and Berney 1981 (TCA). 49c, only Wagner2004 and Walkup 2008 (SSRI) and Bernstein 1990 (TCA).

[52] Downgraded once due to the majority of studies being at high or moderate risk of bias and few at low risk of bias.

[53] The authors note the planned node-splitting consistency analysis was restricted. There were 2 closed loops in the star-shaped network.

[54] Primary diagnosis, titration schedule, symptom severity and comorbidity may impact directness across studies. The authors note these are commonly studied together and respond similarly to antidepressant treatment and share risk factors and neurobiology thus the strong precent for combining.

[55] RUPP 2001 (fluvoxamine, high ROB), Rynn 2001 (sertraline, high ROB), Birmaher 2003 (fluoxetine, moderate ROB), Wagner 2004 (paroxetine, moderate ROB), Beidel 2007 (fluoxetine, moderate ROB), Walkup 2008 (sertraline, low ROB), DaCosta 2013 (fluoxetine, high ROB); TCAs: Bernstein 1990 (imipramine, high ROB), da Costa 2013 (clomipramine, high ROB).

[56] Downgraded once due to small sample size of intervention arm

2/1[49c]	RCT	serious[50]	serious[51]	serious[52]	serious[54]	I^2 NR	296	9	logOR -24.1[-56.5,-3.1]	SSRIs	⊕⊕◯◯ LOW

6.3.4.7 COMPARISON: SSRI versus benzodiazepine in children and young people with anxiety

a. Analysis and risk of bias assessments of individual studies adopted from Dobson 2019 (search 2017). Interventions ranked 1-7 in the network: SSRI, SNRI, TCA, Benzodiazepine, a2 Agonist, 5-HT 1A Agonist, Placebo; with a ranking of 1 indicating most efficacious or most tolerable.

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SSRIs	BNZs	Effect [95% credible interval (CrI)]	Favours	Certainty
[a]Outcome: **treatment response**; CGI; 3-16 weeks; ***network meta-analysis (SSRIs ranked 1st 88%, BNZs ranked 5th 32%)***											
8/2[57]	RCT	serious[58]	serious[59]	serious[60]	serious[61]	I^2 NR	456	29	logOR 1.2 [-0.3, 2.8]	difference	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; PARS, HARS, LSAS-CA, SPAI-C, RCMAS; 8-16 weeks; ***network meta-analysis (SSRIs ranked 1st 90%, BNZs ranked 6th 31%)***											
7/1[62]	RCT	serious[56]	serious[57]	serious[58]	serious[59]	I^2 NR	450	7	MD 5.7 [-3.9, 15.6]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **all-cause early discontinuation**; 3-16 weeks; ***network meta-analysis (SSRIs ranked 1st 77%, BNZs ranked 2nd 74%)***											
8/3[55a]	RCT	serious[56]	serious[57]	serious[58]	serious[59]	I^2 NR	456	36	logOR -0.6 [-2.4, 1.2]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **early discontinuation due to adverse events**; 3-16 weeks; ***network meta-analysis (SSRIs ranked 4th 50%, BNZs ranked 6th 12%)***											
7/1[55b]	RCT	serious[56]	serious[57]	serious[58]	serious[59]	I^2 NR	445	12	logOR 19.8 [-0.5,75.1]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **treatment-emergent suicidality**; 3-16 weeks; ***network meta-analysis (SSRIs ranked 3rd 69%, BNZs ranked 5th 36%)***											

[57] SSRIs: Black 1994 (fluoxetine, high ROB), RUPP 2001 (fluvoxamine, high ROB), Rynn 2001 (sertraline, high ROB), Birmaher 2003 (fluoxetine, moderate ROB), Wagner 2004 (paroxetine, moderate ROB), Beidel 2007 (fluoxetine, moderate ROB), Walkup 2008 (sertraline, low ROB), DaCosta 2013 (fluoxetine, high ROB); BNZs: Simeon 1992 (alprazolam, high ROB), Graae 1994 clonidine, high ROB). 55a, plus BNZs: (clonidine, high ROB). 55b, all except Rynn 2001 (SSRI), plus Graae 1994 (BNZ).

[58] Downgraded once due to the majority of studies being at high or moderate risk of bias and one at low risk of bias.

[59] The authors note the planned node-splitting consistency analysis was restricted. There were 2 closed loops in the star-shaped network.

[60] Primary diagnosis, titration schedule, symptom severity and comorbidity may impact directness across studies. The authors note these are commonly studied together and respond similarly to antidepressant treatment and share risk factors and neurobiology thus the strong precent for combining.

[61] Downgraded once due to small sample size of one intervention arm.

[62] RUPP 2001 (fluvoxamine, high ROB), Rynn 2001 (sertraline, high ROB), Birmaher 2003 (fluoxetine, moderate ROB), Wagner 2004 (paroxetine, moderate ROB), Beidel 2007 (fluoxetine, moderate ROB), Walkup 2008 (sertraline, low ROB), DaCosta 2013 (fluoxetine, high ROB); BNZs: Bernstein 1990 (imipramine, high ROB)

2/2[63]	RCT	serious[56]	serious[57]	serious[58]	serious[59]	I^2 NR	296	24	logOR 11.0 [-38.4, 2.4]	No difference	⊕⊕◯◯ LOW

6.3.4.8 COMPARISON: SNRI versus benzodiazepine in children and young people with anxiety

a. Analysis and risk of bias assessments of individual studies adopted from Dobson 2019 (search 2017). Interventions ranked 1-7 in the network: SSRI, SNRI, TCA, Benzodiazepine, a2 Agonist, 5-HT 1A Agonist, Placebo; with a ranking of 1 indicating most efficacious or most tolerable.

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SNRIs	BNZs	Effect [95% credible interval (CrI)]	Favours	Certainty
[a]Outcome: **treatment response**; CGI, 50% improvement on PARS; 3-16 weeks; ***network meta-analysis (SNRIs ranked 3rd 59%, BNZs ranked 5th 32%)***											
5/2[64]	RCT	serious[65]	serious[66]	serious[67]	serious[68]	I^2 NR	484	29	logOR 0.6 [-1.0, 2.1]	difference	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; PARS, HARS, LSAS-CA, SPAI-C, RCMAS, SAS-CA; 3-16 weeks; ***network meta-analysis (SNRIs ranked 3rd 60%, BNZs ranked 6th 31%)***											
5/1[62a]	RCT	serious[63]	serious[64]	serious[65]	serious[66]	I^2 NR	484	7	MD 2.9 [-6.9, 12.5]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **all-cause early discontinuation**; 3-16 weeks; ***network meta-analysis (SNRIs ranked 4th 50%, BNZs ranked 2nd 74%)***											
5/3[62b]	RCT	serious[63]	serious[64]	serious[65]	serious[66]	I^2 NR	484	36	logOR -0.3 [-2.1, 1.4]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **early discontinuation due to adverse events**; 3-16 weeks; ***network meta-analysis (SNRIs ranked 1st 91%, BNZs ranked 6th 12%)***											
5/1[62c]	RCT	serious[63]	serious[64]	serious[65]	serious[66]	I^2 NR	484	12	logOR 22.0 [1.7,77.2]	SNRIs	⊕⊕◯◯ LOW
[a]Outcome: **treatment-emergent suicidality**; 3-16 weeks; ***network meta-analysis (SNRIs ranked 2nd 73%, BNZs ranked 5th 36%)***											

[63] SSRIs: Wagner 2004 and Walkup 2008 (SSRI); BNZs: Graae 1994 (clonidine, high ROB), Bernstein 1990 (imipramine, high ROB)

[64] SNRIs: Geller 2007 (+ADHD, atomoxetine, high ROB), March 2007 (venlafaxine, low ROB), Rynn 2007 A and B (venlafaxine, both high ROB), Strawn 2015 (duloxetine, low ROB). BNZs: Simeon 1992 (alprazolam, high ROB), Graae 1994 (clonidine, high ROB). 62a, all SNRIs plus one BNZ: Bernstein 1990 (imipramine, high ROB). 62b, all SNRIs and BNZs. 62c, all SNRIs plus one BNZ: Graae 1994.

[65] Downgraded once due to the majority of studies being at high or moderate risk of bias and two at low risk of bias.

[66] The authors note the planned node-splitting consistency analysis was restricted. There were 2 closed loops in the star-shaped network.

[67] Primary diagnosis, titration schedule, symptom severity and comorbidity may impact directness across studies. The authors note these are commonly studied together and respond similarly to antidepressant treatment and share risk factors and neurobiology thus the strong precent for combining.

[68] Downgraded once due to small sample size of one intervention arm.

5/2[69]	RCT	serious[63]	serious[64]	serious[65]	serious[66]	I^2 NR	484	24	logOR -11.3[-38.8, 1.6]	No difference	⊕⊕◯◯ LOW

[69] All SNRIs and BNZs: Graae 1994 (clonidine, high ROB), Bernstein 1990 (imipramine, high ROB).

6.3.4.9 COMPARISON: SNRI versus TCA in children and young people with anxiety

a. Analysis and risk of bias assessments of individual studies adopted from Dobson 2019 (search 2017). Interventions ranked 1-7 in the network: SSRI, SNRI, TCA, Benzodiazepine, a2 Agonist, 5-HT 1A Agonist, Placebo; with a ranking of 1 indicating most efficacious or most tolerable.

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SNRIs	TCAs	Effect [95% credible interval (CrI)]	Favours	Certainty
[a]Outcome: **treatment response**; CGI, 50% improvement on PARS, global improvement; 6-16 weeks; ***network meta-analysis (SNRIs ranked 3rd 59%, TCAs ranked 4th 48%)***											
5/4[70]	RCT	serious[71]	serious[72]	serious[73]	no serious	I^2 NR	484	68	logOR 0.2 [-0.8, 1.2]	difference	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; PARS, HARS, LSAS-CA, SPAI-C, RCMAS, MASC; 8-16 weeks; ***network meta-analysis (SNRIs ranked 3rd 60%, TCAs ranked 4th 45%)***											
5/2[68a]	RCT	serious[69]	serious[70]	serious[71]	serious[74]	I^2 NR	484	18	MD 1.1 [-5.9, 8.2]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **all-cause early discontinuation**; 6-16 weeks; ***network meta-analysis (SNRIs ranked 4th 50%, TCAs ranked 5th 38%)***											
5/5[68b]	RCT	serious[69]	serious[70]	serious[71]	no serious	I^2 NR	484	77	logOR -0.5 [-1.8, 0.7]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **early discontinuation due to adverse events**; 6-16 weeks; ***network meta-analysis (SNRIs ranked 1st 91%, TCAs ranked 3rd 68%)***											
5/2[68c]	RCT	serious[69]	serious[70]	serious[71]	serious[72]	I^2 NR	484	20	logOR 1.2 [-3.0, 5.6]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **treatment-emergent suicidality**; 8-16 weeks; ***network meta-analysis (SNRIs ranked 2nd 73%, TCAs ranked 7th 12%)***											
5/1[68d]	RCT	serious[69]	serious[70]	serious[71]	serious[72]	I^2 NR	484	9	logOR -24.5[-56.7,-3.8]	SNRIs	⊕⊕◯◯ LOW

[70] SNRIs: Geller 2007 (+ADHD, atomoxetine, high ROB), March 2007 (venlafaxine, low ROB), Rynn 2007 A and B (venlafaxine, both high ROB), Strawn 2015 (duloxetine, low ROB). TCAs: Gittelman-Klein 1971 (imipramine, high ROB), Berney 1981 (clomipramine, high ROB), Klein 1992 (imipramine, high ROB), da Costa 2013 (clomipramine, high ROB). 68a, all SNRIs plus TCAs: Bernstein 1990 (imipramine, high ROB), da Costa 2013 (clomipramine, high ROB). 68b, all SNRIs and TCAs. 68c, all SNRIs plus TCAs: Klein 1992 and da Costa 2013. 68d, all SNRIs plus one TCA: Bernstein 1990.

[71] Downgraded once due to the majority of studies being at high or moderate risk of bias and two at low risk of bias.

[72] The authors note the planned node-splitting consistency analysis was restricted. There were 2 closed loops in the star-shaped network.

[73] Primary diagnosis, titration schedule, symptom severity and comorbidity may impact directness across studies. The authors note these are commonly studied together and respond similarly to antidepressant treatment and share risk factors and neurobiology thus the strong precent for combining.

[74] Downgraded once due to small sample size of one intervention arm.

6.3.4.10 COMPARISON: Benzodiazepine versus TCA in children and young people with anxiety

a. Analysis and risk of bias assessments of individual studies adopted from Dobson 2019 (search 2017). Interventions ranked 1-7 in the network: SSRI, SNRI, TCA, Benzodiazepine, a2 Agonist, 5-HT 1A Agonist, Placebo; with a ranking of 1 indicating most efficacious or most tolerable.

	Quality assessment						No. participants				
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	BNZs	TCAs	Effect [95% credible interval (CrI)]	Favours	Certainty
[a]Outcome: **treatment response**; CGI, global improvement; 3-12 weeks; ***network meta-analysis (BNZs ranked 5th 32%, TCAs ranked 4th 48%)***											
2/4[75]	RCT	very serious[76]	serious[77]	serious[78]	serious[79]	I^2 NR	29	68	logOR 0.4 [-1.4, 2.1]	difference	⊕⊕◯◯ LOW
[a]Outcome: **symptom improvement**; RCMAS, MASC; 8-12 weeks; ***network meta-analysis (BNZs ranked 6th 31%, TCAs ranked 4th 45%)***											
1/2[68a]	RCT	very serious[74]	serious[75]	serious[76]	very serious[80]	I^2 NR	7	18	MD 1.8 [-7.1, 10.4]	No difference	⊕◯◯◯ VERY LOW
[a]Outcome: **all-cause early discontinuation**; 3-12 weeks; ***network meta-analysis (BNZs ranked 2nd 74%, TCAs ranked 5th 38%)***											
3/5[68b]	RCT	very serious[74]	serious[75]	serious[76]	serious[77]	I^2 NR	36	77	logOR 0.2 [-1.7, 2.0]	No difference	⊕⊕◯◯ LOW
[a]Outcome: **early discontinuation due to adverse events**; 3-12 weeks; ***network meta-analysis (BNZs ranked 6th 12%, TCAs ranked 3rd 68%)***											
1/2[68c]	RCT	very serious[74]	serious[75]	serious[76]	very serious[78]	I^2 NR	12	20	logOR 20.6 [0.0, 76.1]	TCAs	⊕◯◯◯ VERY LOW
[a]Outcome: **treatment-emergent suicidality**; 3-8 weeks; ***network meta-analysis (BNZs ranked 5th 36%, TCAs ranked 7th 12%))***											
2/1[68d]	RCT	very serious[74]	serious[75]	serious[76]	very serious[78]	I^2 NR	24	9	logOR 10.4 [-1.1,38.0]	No difference	⊕◯◯◯ VERY LOW

[75] BNZs: Simeon 1992 (alprazolam, high ROB), Graae 1994 (clonidine, high ROB); TCAs: Gittelman-Klein 1971 (imipramine, high ROB), Berney 1981 (clomipramine, high ROB), Klein 1992 (imipramine, high ROB), da Costa 2013 (clomipramine, high ROB). 62a, BNZ: Bernstein 1990 (imipramine, high ROB) plus TCAs: Bernstein 1990 (imipramine, high ROB), da Costa 2013 (clomipramine, high ROB). 62b, all TCAs and BNZs. 62c, BNZ: Graae 1994 plus TCAs: Klein 1992 and da Costa 2013. 62d, BNZs: Graae 1994 (clonidine, high ROB), Bernstein 1990 (imipramine, high ROB) plus TCA: Bernstein 1990.

[76] Downgraded twice because all of the studies are at high risk of bias.

[77] The authors note the planned node-splitting consistency analysis was restricted. There were 2 closed loops in the star-shaped network.

[78] Primary diagnosis, titration schedule, symptom severity and comorbidity may impact directness across studies. The authors note these are commonly studied together and respond similarly to antidepressant treatment and share risk factors and neurobiology thus the strong precent for combining.

[79] Downgraded once due to small sample size of one intervention arm.

[80] Downgraded twice due to small sample size of both intervention arms.

6.3.5 Excluded studies

Article	Reason for exclusion
Abikoff, H., et al. (2005). "Sequential pharmacotherapy for children with comorbid attention-deficit/hyperactivity and anxiety disorders." Journal of the American Academy of Child & Adolescent Psychiatry **44**(5): 418-427.	Anxiety is OCD
Bedard, A. C. and R. Tannock (2008). "Anxiety, methylphenidate response, and working memory in children with ADHD." Journal of Attention Disorders **11**(5): 546-557.	Medication period was 4 days
Biederman, J., et al. (1993). "A double-blind placebo controlled study of desipramine in the treatment of ADD: III. Lack of impact of comorbidity and family history factors on clinical response." Journal of the American Academy of Child & Adolescent Psychiatry 32(1): 199-204.	Unclear diagnostic criteria
Diamond, I. R., et al. (1999). "Response to methylphenidate in children with ADHD and comorbid anxiety." Journal of the American Academy of Child & Adolescent Psychiatry 38(4): 402-409.	Non-primary diagnosis of anxiety
Emslie, G. J., et al. (1998). "Treatment of children with antidepressants: focus on selective serotonin reuptake inhibitors." Depression & Anxiety 8 Suppl 1: 13-17.	Narrative review
Geller, D., et al. (2007). "Atomoxetine treatment for pediatric patients with attention-deficit/hyperactivity disorder with comorbid anxiety disorder." Journal of the American Academy of Child & Adolescent Psychiatry 46(9): 1119-1127.	Unclear diagnostic criteria
Ginsburg, G. S., et al. (2006). "Somatic symptoms in children and adolescents with anxiety disorders." Journal of the American Academy of Child & Adolescent Psychiatry 45(10): 1179-1187.	Not randomised
Hidalgo, R. B., et al. (2007). "An effect-size analysis of pharmacologic treatments for generalized anxiety disorder." Journal of Psychopharmacology 21(8): 864-872.	Combines adults with CYP
Kreiter, D., et al. (2021). "Symptom-network dynamics in irritable bowel syndrome with comorbid panic disorder using electronic momentary assessment: A randomized controlled trial of escitalopram vs. placebo." Journal of Psychosomatic Research 141: 110351.	Combines adults with CYP
Londono Tobon, A., et al. (2018). "A Systematic Review of Pharmacologic Treatments for School Refusal Behavior." Journal of Child & Adolescent Psychopharmacology 28(6): 368-378.	Inappropriate diagnostic criteria and outcome data
Lu, L., et al. (2022). "Acute neurofunctional effects of escitalopram during emotional processing in pediatric anxiety: a double-blind, placebo-controlled trial." Neuropsychopharmacology 47(5): 1081-1087.	No relevant outcome data
McDougle, C. J., et al. (2022). "A randomized double-blind, placebo-controlled pilot trial of mirtazapine for anxiety in children and adolescents with autism spectrum disorder." Neuropsychopharmacology 47(6): 1263-1270.	Symptoms not diagnosis
Offidani, E., et al. (2013). "Excessive mood elevation and behavioral activation with antidepressant treatment of juvenile depressive and anxiety disorders: a systematic review." Psychotherapy & Psychosomatics 82(3): 132-141.	No relevant outcome data
Tannock, R., et al. (1995). "Differential effects of methylphenidate on working memory in ADHD children with and without comorbid anxiety." Journal of the American Academy of Child & Adolescent Psychiatry 34(7): 886-896.	No relevant outcome data
Uthman, O. A. and J. Abdulmalik (2010). "Comparative efficacy and acceptability of pharmacotherapeutic agents for anxiety disorders in children and adolescents: a mixed treatment comparison meta-analysis."	OCD data combined with anxiety disorders

Current Medical Research & Opinion 26(1): 53-59.	
Villas-Boas, C. B., et al. (2019). "Pharmacological treatment of attention-deficit hyperactivity disorder comorbid with an anxiety disorder: a systematic review." International Clinical Psychopharmacology 34(2): 57-64.	Inappropriate diagnostic criteria
Wincor, M. Z., et al. (1991). "Alprazolam levels and response in panic disorder: preliminary results." Journal of Clinical Psychopharmacology 11(1): 48-51.	Combines adults with CYP

6.5 References

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