Child and adolescent mental disorders module - evidence profile CAMH4: Pharmacological interventions for children and adolescents with emotional disorders

WHO mhGAP guideline update: Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders

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Contents

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders, available at: https://www.who.int/publications/i/item/9789240084278

1. Background

Common mental disorders, such as depression and anxiety, have reached alarming prevalence rates during the COVID-19 pandemic, doubling the pre-pandemic estimates. In 2020, it was estimated that 1 in 4 children and adolescents experienced clinically elevated symptoms of depression, and 1 in 5 experienced clinical symptoms of anxiety (Racine et al., 2021). Notably, an earlier age of depression or anxiety's onset was related to increased chronicity, comorbidities, and disease burden in adulthood (Zisook et al., 2007; Essau et al., 2014). The current context manifests the urgent need to address mental health problems in the youth population.

Psychological treatment is widely recommended as a first-line treatment approach for mild depression and anxiety in youth. However, more severe manifestations of these disorders might require a prescription of psychiatric medications (National Collaborating Centre for Mental Health, 2013; National Institute for Health and Care Excellence, 2019). Previous meta-analyses examining the effects of antidepressants in youth with depression and anxiety have found inconclusive results, with some studies suggesting an increased risk of suicidality after the start of antidepressants (Cipriani et al., 2016; Vitiello & Davico, 2018; Locher et al., 2018; Zhou et al., 2020).

In recent years, new and high-quality trials assessing the effectiveness and safety of psychiatric medication in children might have been published., Thus, recent meta-analyses could provide evidence that should be considered in clinical guidelines. In the current report, we aimed to present the results of a systematic review of meta-analyses covering the efficacy and safety of pharmacotherapy for youth emotional disorders. Focus on Tricyclic Antidepressants (TCA), Selective Serotonin Reuptake Inhibitors (SSRI), and Benzodiazepines, we evaluated whether these pharmacotherapies are more effective and as safe as treatment as usual or placebo in children and adolescents with depression and anxiety. We reviewed the effects in a wide range of outcomes, including symptom reduction, adverse effects, improvements in functioning, remission, and user and family satisfaction.

2. Methodology

Evidence from recent meta-analyses covering the effectiveness and safety of pharmacotherapy for children and adolescents with emotional disorders were summarized.

2.1. PICO question

CAMH: In children and adolescents with emotional disorders, what is the effectiveness and safety, of using pharmacological interventions?

Population (P): Children and adolescents with emotional disorders, anxiety and/or depression
Intervention (I): Pharmacological interventions, antidepressants (SSRIs, TCAs), benzodiazepines
Comparator (C): Placebo, treatment as usual
Outcomes (O):

List of critical outcomes:

- **Critical outcome 1:** Reduction of symptoms
- **Critical outcome 2:** Adverse effects

List of important outcomes:

- **Important outcome 1:** Improved functioning/quality of life
- **Important outcome 2:** Reduction in risk behaviours
- **Important outcome 3:** Remission
- **Important outcome 4:** User and family satisfaction

2.2. Search strategy

Existing systematic reviews were identified by conducting searches in the following bibliographic databases:

- PubMed
- PsycInfo
- Embase
- Cochrane reviews
- Global Index Medicus

The search strings were designed in collaboration with a Medical Information Specialist at the VU (C.H.M Planting c.h.m.planting@vu.nl). We designed the search strings by combining blocks with free and index terms indicative for 1) Depression (Type of Participants), or 2) Anxiety (Type of Participants), 3) Children or adolescents (Type of Participants), 4) Antidepressants (TCA and SSRIs) or Benzodiazepines (Types of interventions), and 5) terms related to systematic reviews and meta-analyses (Type of studies). The search strings for PubMed can be accessed in the Appendix. In line with the WHO guideline methodology, indicating that evidence obtained for the development of guidelines should be as recent as possible (World Health Organization, 2014), the period of the searches was from 1 January 2019 until 31 January 2022. No restrictions were applied for language.

2.3. Data collection and analysis

As the first stage in selecting relevant studies, records retrieved from the bibliographic databases were assessed for eligibility by examining their titles and abstracts based on the inclusion and exclusion criteria developed a priori. Studies were included if they were (i) Systematic reviews of randomized controlled trials (RCTs). (ii) Had child or adolescent participants (< 18 years) with a primary diagnosis of depression or anxiety as established by a diagnostic interview or elevated symptoms of depression according to cut off scores on self-report scales. (iii) Evaluated the effectiveness or safety of SSRIs, TCAs or benzodiazepines compared to pill placebo/ treatment as usual (iv) Reported outcomes regarding mental health symptoms, adverse effects, quality of life and functioning, reduction in risky behaviours and user and family satisfaction. We excluded studies that

had participants with secondary depression (due to medical conditions/illness, trauma, etc), bipolar disorder, autism spectrum disorder, attention deficit hyperactivity disorder and obsessive-compulsive disorder. The full text of articles found to be potentially relevant based on their titles and abstracts were retrieved and examined, considering the same inclusion criteria in the second stage of study selection. Data from eligible studies were extracted into pre-defined templates that include the general characteristics of the study, population, intervention, comparator and outcomes. When there was an overlap between studies (i.e. they evaluated the same antidepressant medications, in similar target populations, and reported the same outcomes), we selected the meta-analysis based on the following criteria and in the following order: (i) Recency (more recent publication covering a more recent search period) (ii) number of included RCTs, (iii) broadness of the review (covering multiple antidepressants and groups of antidepressants compared to pill placebo and/or treatment as usual, with a wide range of outcomes) (iv) AMSTAR ratings.

Two reviewers (AA and MC/CM) independently assessed the eligibility of the studies identified and extracted data from study reports. Discrepancies between the reviewers were resolved through discussions. The search strategy and results reporting the databases searched, the strategy used to search each database, the total number of citations retrieved from each database, and the reasons for excluding some publications after reviewing the full text have been documented. The flow of articles throughout the search and up to the final cohort of included studies is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, which includes the number of excluded articles and the reasons for any exclusions at the full-text screening stage.

2.4. Selection and coding of identified records

Rayyan and Endnote were used for the management of references. Rayyan was used during the first two stages of the project, involving the selection of studies based on titles, abstracts, and full texts. Endnote was used to store the references and pdfs of the included studies for the remaining stages of the project. Data extraction was conducted in excel files with a predefined format which was designed by the involved reviewers. A wide range of study level data regarding date of searches, target population characteristics, type of intervention and control, average length of interventions, total number of participants, mean age and risk of bias were extracted. All data was collected by two independent reviewers and discrepancies were resolved through discussions.

2.5. Quality assessment

The quality of the included systematic reviewers was assessed with the **AMSTAR quality appraisal tool 2**. Two independent researchers (AA and MC/CM) applied the AMSTAR-2 checklist to the included studies, and any disagreements were discussed with a third researcher.

The certainty of the evidence was assessed using **GRADE** (Grading of Recommendations, Assessment, Development and Evaluations). When available, we extracted the GRADE assessments from the meta-analysis. When the GRADE assessment was not available, we assessed it ourselves examining the following criteria:

- **Risk of bias (RoB):** We extracted the RoB ratings from the individual studies included in the meta-analyses (when available). We calculated the percentage of trials rated at low, high, and unclear risk of bias. Based on this information, and in order to take consistent decisions across the available evidence, we rated the RoB GRADE item using a decision tree. The decision tree can be accessed in the appendix.
- **Inconsistency:** We judged inconsistency by examining heterogeneity statistics: I^2, which indicates the percentage of heterogeneity between effect sizes, and its 95% confidence interval (95% CI). When the 95% CI of the I^2 is not reported, we computed it and used it in our judgements. We judged inconsistency as serious when I^2 was over 75% and its 95% CI substantially overlaps with the category of considerable heterogeneity (above 75%). Substantial overlap was estimated with the median of the 95% CI. If the 95% CI was not available or could not be calculated, we rated it as serious if heterogeneity was larger than

50% (category of substantial heterogeneity). If I^2 was not reported and could not be calculated, we rated it as serious.

- **Indirectness**: Direct evidence was derived from research that directly compares the interventions which we are interested in, delivered to the participants in which we are interested, and that measures the outcomes important to patients. We rated for each particular comparison how indirect the reviewed evidence was in terms of population, intervention, and outcomes.
- **Imprecision**: We rated this item based on a standard power calculation ($\alpha = 0.05$ and $\beta = 0.20$) for detecting an effect size of 0.2, which requires a sample size of 400 participants in total. We judged as serious for all analyses that included less than 400 participants. Analyses including less than 100 participants was rated as very serious. A rating of serious was given when the number of participants included in the analyses was not available.
- **Other considerations**: For this item we explored publication bias. We rated it as serious if there was evidence for publication bias in the meta-analyses, based on statistical tests. However, we did not downgrade the evidence if a meta-analysis did not investigate it.

2.6. Analysis of subgroups or subsets

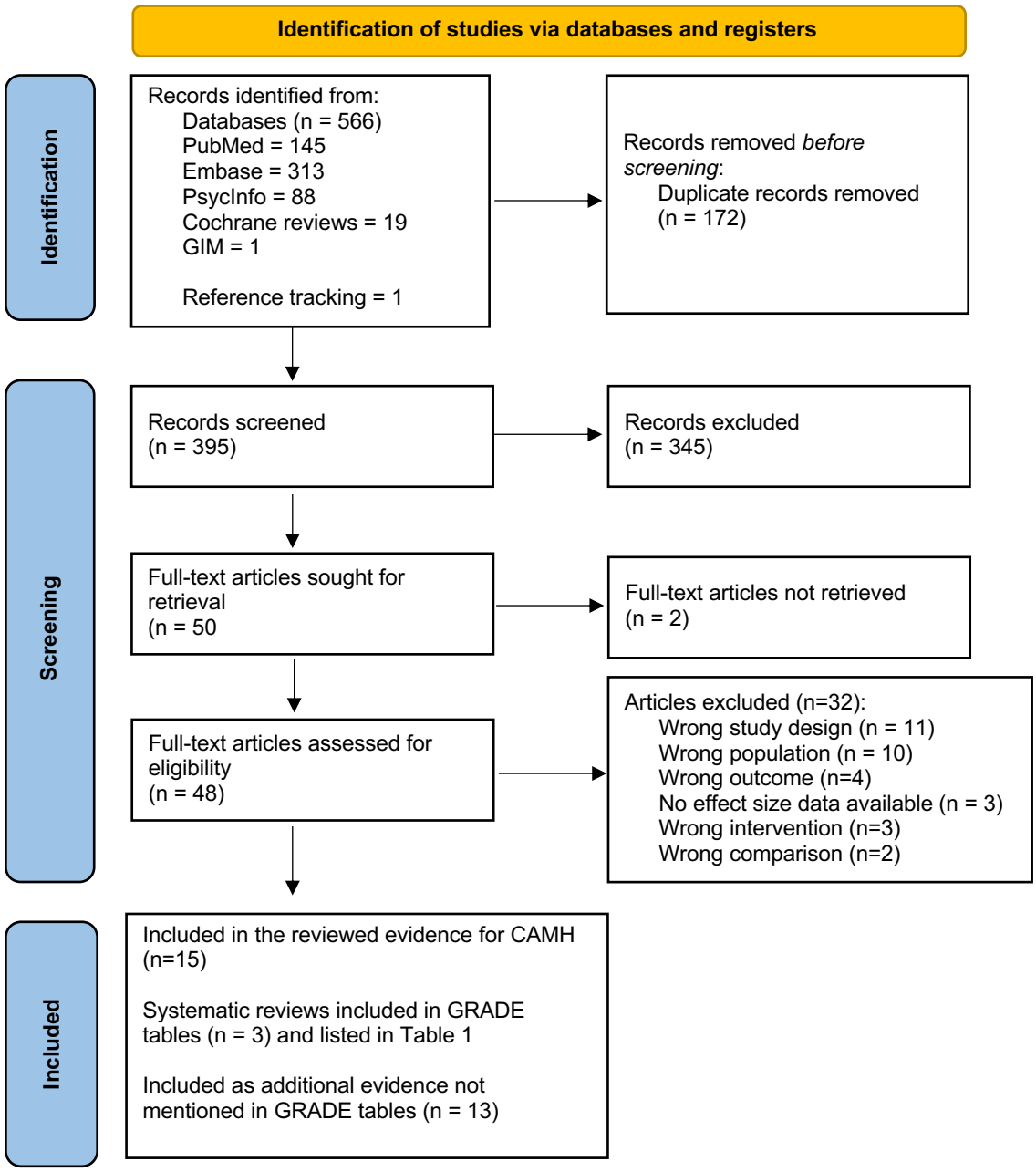
The subgroups or subsets that are available in the included meta-analyses were:

- Specific target groups of population: e.g. type of emotional disorder (anxiety, depression),
- Types of pharmacological interventions: SSRIs, TCAs, benzodiazepines

3. Results

3.1. Systematic reviews and/or studies identified by the search process

Fig. 1. PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only



3.2. List of studies included and excluded

3.2.1. Included in GRADE tables/footnotes

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3.2.2. Included in GRADE tables/footnotes

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Table 1. PICO Table

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE (Name, Year)	Justification/Explanation for systematic review used
1A	Pharmacotherapy (Selective Serotonin Reuptake Inhibitors) compared to pill placebo in children and adolescents with emotional disorders	Mental health symptoms (Anxiety)	Dobson, 2019	Most recent high-quality meta-analysis available on the effects of SSRI vs pill placebo on anxiety symptoms in children and adolescents
		Mental health symptoms (Depression)	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of SSRI vs pill placebo on depressive symptoms in children and adolescents
		Adverse effects	Dobson, 2019	Most recent high-quality meta-analysis available on the adverse effects of SSRI vs pill placebo children and adolescents with pediatric anxiety
		Improved Quality of life and Functioning	-	No available recent meta-analytic evidence on this outcome (N/A)
		Reduction in Risky behaviours	-	N/A
		Remission	-	N/A
		User and family satisfaction	-	N/A
1B/C	Pharmacotherapy (Fluoxetine) compared to pill placebo and treatment as usual in children and adolescents with emotional disorders	Mental health symptoms	Zhou, 2020	Most recent high-quality meta-analysis available on the effects of Fluoxetine (SSRI) vs pill placebo and treatment as usual on depressive symptoms in children and adolescents
		Adverse effects	Zhou, 2020	Most recent high-quality meta-analysis available on the adverse effects of Fluoxetine (SSRI) vs pill placebo and treatment as usual in children and adolescents with depressive disorders
		Improved Quality of life and Functioning	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of Fluoxetine (SSRI) vs pill placebo on improved functioning in children and adolescents

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE (Name, Year)	Justification/Explanation for systematic review used
		Reduction in Risky behaviours	-	N/A
		Remission	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of Fluoxetine (SSRI) vs pill placebo on remission/relapse in children and adolescents
		User and family satisfaction	-	N/A
1D/E	Pharmacotherapy (Citalopram) compared to pill placebo in children and adolescents with emotional disorders	Mental health symptoms	Zhou, 2020	Most recent high-quality meta-analysis available on the effects of Citalopram (SSRI) vs pill placebo and treatment as usual on depressive symptoms in children and adolescents
		Adverse effects	Zhou, 2020	Most recent high-quality meta-analysis available on the adverse effects of Citalopram (SSRI) vs pill placebo and treatment as usual in children and adolescents with depressive disorders
		Improved Quality of life and Functioning	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of Citalopram (SSRI) vs pill placebo on improved functioning in children and adolescents
		Reduction in Risky behaviours	-	N/A
		Remission	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of Citalopram (SSRI) vs pill placebo on remission/relapse in children and adolescents
		User and family satisfaction	-	N/A
1F/G	Pharmacotherapy (Escitalopram) compared to pill placebo and treatment as usual in children and adolescents with emotional disorders	Mental health symptoms	Zhou, 2020	Most recent high-quality meta-analysis available on the effects of Escitalopram (SSRI) vs pill placebo and treatment as usual on depressive symptoms in children and adolescents

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE (Name, Year)	Justification/Explanation for systematic review used
		Adverse effects	Zhou, 2020	Most recent high-quality meta-analysis available on the adverse effects of Escitalopram (SSRI) vs pill placebo and treatment as usual in children and adolescents with depressive disorders
		Improved Quality of life and Functioning	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of Escitalopram (SSRI) vs pill placebo on improved functioning in children and adolescents
		Reduction in Risky behaviours	-	N/A
		Remission	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of Escitalopram (SSRI) vs pill placebo on remission/relapse in children and adolescents
		User and family satisfaction	-	N/A -
1H/I	Pharmacotherapy (Paroxetine) compared to pill placebo and treatment as usual in children and adolescents with emotional disorders	Mental health symptoms	Zhou, 2020	Most recent high-quality meta-analysis available on the effects of Paroxetine (SSRI) vs pill placebo and treatment as usual on depressive symptoms in children and adolescents
		Adverse effects	Zhou, 2020	Most recent high-quality meta-analysis available on the adverse effects of Paroxetine (SSRI) vs pill placebo and treatment as usual in children and adolescents with depressive disorders
		Improved Quality of life and Functioning	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of Paroxetine (SSRI) vs pill placebo on improved functioning in children and adolescents
		Reduction in Risky behaviours	-	N/A
		Remission	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of Paroxetine (SSRI) vs pill placebo on remission/relapse in children and adolescents

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE (Name, Year)	Justification/Explanation for systematic review used
		User and family satisfaction	-	N/A
1J/K	Pharmacotherapy (Sertraline) compared to pill placebo and treatment as usual in children and adolescents with emotional disorders	Mental health symptoms	Zhou, 2020	Most recent high-quality meta-analysis available on the effects of Sertraline (SSRI) vs pill placebo and treatment as usual on depressive symptoms in children and adolescents
		Adverse effects	Zhou, 2020	Most recent high-quality meta-analysis available on the adverse effects of Sertraline (SSRI) vs pill placebo and treatment as usual in children and adolescents with depressive disorders
		Improved Quality of life and Functioning	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of Sertraline (SSRI) vs pill placebo on improved functioning in children and adolescents
		Reduction in Risky behaviours	-	N/A
		Remission	Hetrick, 2021	Most recent high-quality meta-analysis available on the effects of Sertraline (SSRI) vs pill placebo on remission/relapse in children and adolescents
		User and family satisfaction	-	N/A
2A	Pharmacotherapy (Tricyclic Antidepressants) compared to pill placebo in children and adolescents with emotional disorders	Mental health symptoms	Dobson, 2019	Most recent high-quality meta-analysis available on the effects of TCA vs pill placebo on anxiety symptoms in children and adolescents
		Adverse effects	Dobson, 2019	Most recent high-quality meta-analysis available on the adverse effects of TCA vs pill placebo children and adolescents with pediatric anxiety
		Improved Quality of life and Functioning	-	N/A
		Reduction in Risky behaviours	-	N/A

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE (Name, Year)	Justification/Explanation for systematic review used
		Remission	-	N/A
		User and family satisfaction	-	N/A
2B/C	Pharmacotherapy (Imipramine) compared to pill placebo and treatment as usual in children and adolescents with emotional disorders	Mental health symptoms	Zhou, 2020	Most recent high-quality meta-analysis available on the effects of Imipramine (TCA) vs pill placebo and treatment as usual on depressive symptoms in children and adolescents
		Adverse effects	Zhou, 2020	Most recent high-quality meta-analysis available on the adverse effects of Imipramine (TCA) vs pill placebo and treatment as usual in children and adolescents with depressive disorders
		Improved Quality of life and Functioning	-	N/A
		Reduction in Risky behaviours	-	N/A
		Remission	-	N/A
		User and family satisfaction	-	N/A
2D/E	Pharmacotherapy (Desipramine) compared to pill placebo and treatment as usual in children and adolescents with emotional disorders	Mental health symptoms	Zhou, 2020	Most recent high-quality meta-analysis available on the effects of Desipramine (TCA) vs pill placebo and treatment as usual on depressive symptoms in children and adolescents
		Adverse effects	Zhou, 2020	Most recent high-quality meta-analysis available on the adverse effects of Desipramine (TCA) vs pill placebo and treatment as usual in children and adolescents with depressive disorders
		Improved Quality of life and Functioning	-	N/A
		Reduction in Risky behaviours	-	N/A
		Remission	-	N/A

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE (Name, Year)	Justification/Explanation for systematic review used
		User and family satisfaction	-	N/A
2F/G	Pharmacotherapy (Amitriptyline) compared to pill placebo and treatment as usual in children and adolescents with emotional disorders	Mental health symptoms	Zhou, 2020	Most recent high-quality meta-analysis available on the effects of Amitriptyline (TCA) vs pill placebo and treatment as usual on depressive symptoms in children and adolescents
		Adverse effects	Zhou, 2020	Most recent high-quality meta-analysis available on the adverse effects of Amitriptyline (TCA) vs pill placebo and treatment as usual in children and adolescents with depressive disorders
		Improved Quality of life and Functioning	-	N/A
		Reduction in Risky behaviours	-	N/A
		Remission	-	N/A
		User and family satisfaction	-	N/A
2H/I	Pharmacotherapy (Clomipramine) compared to pill placebo and treatment as usual in children and adolescents with emotional disorders	Mental health symptoms	Zhou, 2020	Most recent high-quality meta-analysis available on the effects of Clomipramine ((TCA) vs pill placebo and treatment as usual on depressive symptoms in children and adolescents
		Adverse effects	Zhou, 2020	Most recent high-quality meta-analysis available on the adverse effects of Clomipramine (TCA) vs pill placebo and treatment as usual in children and adolescents with depressive disorders
		Improved Quality of life and Functioning	-	N/A
		Reduction in Risky behaviours	-	N/A
		Remission	-	N/A
		User and family satisfaction	-	N/A

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE (Name, Year)	Justification/Explanation for systematic review used
2J/K	Pharmacotherapy (Nortriptyline) compared to pill placebo and treatment as usual in children and adolescents with emotional disorders	Mental health symptoms	Zhou, 2020	Most recent high-quality meta-analysis available on the effects of Nortriptyline (TCA) vs pill placebo and treatment as usual on depressive symptoms in children and adolescents
		Adverse effects	Zhou, 2020	Most recent high-quality meta-analysis available on the adverse effects of Nortriptyline (TCA) vs pill placebo and treatment as usual in children and adolescents with depressive disorders
		Improved Quality of life and Functioning	-	N/A
		Reduction in Risky behaviours	-	N/A
		Remission	-	N/A
		User and family satisfaction	-	N/A
3	Pharmacotherapy (Benzodiazepines) compared to pill placebo in children and adolescents with emotional disorders	Mental health symptoms	Dobson, 2019	Most recent high-quality meta-analysis available on the effects of benzodiazepine vs pill placebo on anxiety symptoms in children and adolescents
		Adverse effects	Dobson, 2019	Most recent high-quality meta-analysis available on the adverse effects of benzodiazepine vs pill placebo children and adolescents with pediatric anxiety
		Improved Quality of life and Functioning	-	N/A
		Reduction in Risky behaviours	-	N/A
		Remission	-	N/A
		User and family satisfaction	-	N/A

SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic Antidepressants

3.3. Narrative description of studies that contributed to GRADE analysis[1]

Dobson et al. (2019) OBJECTIVE: To evaluate the efficacy and tolerability of pharmacotherapy in pediatric anxiety disorders using network meta-analysis. DATA SOURCES: PubMed, Cochrane Database, Web of Science, PsycNET, and ClinicalTrials.gov were searched for double-blind, controlled pharmacotherapy trials in youth with anxiety disorders from 1966 to September 2017. DATA SELECTION: All double-blind, placebo-controlled trials of pharmacotherapy in the treatment of pediatric patients with generalized, social, and/or separation anxiety disorders were included. DATA EXTRACTION: We extracted demographic, symptom severity, global improvement, discontinuation, and suicidality data. Risk of bias was assessed with the Cochrane risk-of-bias tool, and a network meta-analysis comparing the efficacy and tolerability of medications and medication classes was performed using the gemtc package (R). RESULTS: We identified 20 citations (22 RCTs, 24 treatment arms) with 2 623 patients. Selective serotonin reuptake inhibitors (SSRIs) were the only class that was superior in reducing anxiety (standardized mean difference: 5.2; credible interval [CrI:2.8 - 8.8]) and in likelihood of treatment response compared to placebo (odds ratio [OR]: 4.6; CrI: 3.1 - 7.5). Serotonin-norepinephrine reuptake inhibitor (SNRI) and α_2 agonist treatment were associated with more frequent treatment response compared to placebo. The likelihood of treatment response was greater for SSRIs compared to SNRIs (OR: 1.9; CrI: 1.1 - 3.5). All-cause discontinuation and treatment-emergent suicidality significantly differed among medications but not medication class. CONCLUSIONS: Although multiple medications reduce anxiety in children and adolescents, treatment response, tolerability, and treatment-emergent suicidality differ among these medications and medication classes. Determining whether efficacy and tolerability differences represent true differences (or reflect differences in trial design) requires additional head-to-head medication trials and-to exclude the impact of missing treatment interventions-requires trials of medications that successfully treat anxiety in adults but that have not been evaluated in youth.

Hetrick et al. (2021) BACKGROUND: Major depressive disorders have a significant impact on children and adolescents, including on educational and vocational outcomes, interpersonal relationships, and physical and mental health and well-being. There is an association between major depressive disorder and suicidal ideation, suicide attempts, and suicide. Antidepressant medication is used in moderate to severe depression; there is now a range of newer generations of these medications. OBJECTIVES: To investigate, via network meta-analysis (NMA), the comparative effectiveness and safety of different newer generation antidepressants in children and adolescents with a diagnosed major depressive disorder (MDD) in terms of depression, functioning, suicide-related outcomes and other adverse outcomes. The impact of age, treatment duration, baseline severity, and pharmaceutical industry funding was investigated on clinician-rated depression (CDRS-R) and suicide-related outcomes. SEARCH METHODS: We searched the Cochrane Common Mental Disorders Specialized Register, the Cochrane Library (Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR)), together with Ovid Embase, MEDLINE and PsycInfo till March 2020. SELECTION CRITERIA: Randomized trials of six- to 18-year-olds of either sex or any ethnicity with clinically diagnosed major depressive disorder were included. Trials that compared the effectiveness of newer generation antidepressants with each other or with a placebo were included. Newer generation antidepressants included: selective serotonin reuptake inhibitors; selective norepinephrine reuptake inhibitors (SNRIs); norepinephrine reuptake inhibitors; norepinephrine dopamine reuptake inhibitors; norepinephrine dopamine disinhibitors (NDDIs); and tetracyclic antidepressants (TeCAs). DATA COLLECTION AND ANALYSIS: Two reviewers independently screened titles/abstracts and full texts, extracted data, and assessed risk of bias. We analysed dichotomous data as Odds Ratios (ORs), and continuous data as Mean Difference (MD) for the following outcomes: depression symptom severity (clinician rated), response or remission of depression symptoms, depression symptom severity (self-rated), functioning, suicide-related outcomes and overall adverse outcomes. Random-effects network meta-analyses were conducted in a frequentist framework using multivariate meta-analysis. Certainty of

[1]Please note that this section includes the abstracts as taken directly from the publications.

evidence was assessed using Confidence in Network Meta-analysis (CINeMA). We used "informative statements" to standardize the interpretation and description of the results. MAIN RESULTS: Twenty-six studies were included. There were no data for the two primary outcomes (depressive disorder established via clinical diagnostic interview and suicide), therefore, the results comprise only secondary outcomes. Most antidepressants may be associated with a "small and unimportant" reduction in depression symptoms on the CDRS-R scale (range 17 to 113) compared with placebo (high certainty evidence: paroxetine: MD -1.43, 95% CI: -3.90 to 1.04; vilazodone: MD -0.84, 95% CI: -3.03 to 1.35; desvenlafaxine MD -0.07, 95% CI: -3.51 to 3.36; moderate certainty evidence: sertraline: MD -3.51, 95% CI: -6.99 to -0.04; fluoxetine: MD -2.84, 95% CI: -4.12 to -1.56; escitalopram: MD -2.62, 95% CI: -5.29 to 0.04; low certainty evidence: duloxetine: MD -2.70, 95% CI: -5.03 to -0.37; vortioxetine: MD 0.60, 95% CI: -2.52 to 3.72; very low certainty evidence for comparisons between other antidepressants and placebo). There were "small and unimportant" differences between most antidepressants in reduction of depression symptoms (high- or moderate-certainty evidence). Results were similar across other outcomes of benefit. In most studies risk of self-harm or suicide was an exclusion criterion for the study. Proportions of suicide-related outcomes were low for most included studies and 95% confidence intervals were wide for all comparisons. The evidence is very uncertain about the effects of mirtazapine (OR 0.50, 95% CI: 0.03 - 8.04), duloxetine (OR 1.15, 95% CI: 0.72 - 1.82), vilazodone (OR 1.01, 95% CI: 0.68 - 1.48), desvenlafaxine (OR 0.94, 95% CI: 0.59 - 1.52), citalopram (OR 1.72, 95% CI: 0.76 - 3.87) or vortioxetine (OR 1.58, 95% CI: 0.29 - 8.60) on suicide-related outcomes compared with placebo. There is low certainty evidence that escitalopram may "at least slightly" reduce odds of suicide-related outcomes compared with placebo (OR 0.89, 95% CI: 0.43 - 1.84). There is low certainty evidence that fluoxetine (OR 1.27, 95% CI: 0.87 - 1.86), paroxetine (OR 1.81, 95% CI: 0.85 - 3.86), sertraline (OR 3.03, 95% CI: 0.60 - 15.22), and venlafaxine (OR 13.84, 95% CI: 1.79 - 106.90) may "at least slightly" increase odds of suicide-related outcomes compared with placebo. There is moderate certainty evidence that venlafaxine probably results in an "at least slightly" increased odds of suicide-related outcomes compared with desvenlafaxine (OR 0.07, 95% CI: 0.01 - 0.56) and escitalopram (OR 0.06, 95% CI: 0.01 - 0.56). There was very low certainty evidence regarding other comparisons between antidepressants. AUTHORS' CONCLUSIONS: Overall, methodological shortcomings of the randomized trials make it difficult to interpret the findings with regard to the efficacy and safety of newer antidepressant medications. Findings suggest that most newer antidepressants may reduce depression symptoms in a small and unimportant way compared with placebo. Furthermore, there are likely to be small and unimportant differences in the reduction of depression symptoms between the majority of antidepressants. However, our findings reflect the average effects of the antidepressants, and given depression is a heterogeneous condition, some individuals may experience a greater response. Guideline developers and others making recommendations might therefore consider whether a recommendation for the use of newer generation antidepressants is warranted for some individuals in some circumstances. Our findings suggest sertraline, escitalopram, duloxetine, as well as fluoxetine (which is currently the only treatment recommended for first-line prescribing) could be considered as a first option. Children and adolescents considered at risk of suicide were frequently excluded from trials, so that we cannot be confident about the effects of these medications for these individuals. If an antidepressant is being considered for an individual, this should be done in consultation with the child/adolescent and their family/caregivers and it remains critical to ensure close monitoring of treatment effects and suicide-related outcomes (combined suicidal ideation and suicide attempt) in those treated with newer generation antidepressants, given findings that some of these medications may be associated with greater odds of these events. Consideration of psychotherapy, particularly cognitive behavioural therapy, as per guideline recommendations, remains important.

Zhou et al. (2020) BACKGROUND: Depressive disorders are common in children and adolescents. Antidepressants, psychotherapies, and their combination are often used in routine clinical practice; however, available evidence on the comparative efficacy and safety of these interventions is inconclusive. Therefore, we sought to compare and rank all available treatment interventions for the acute treatment of depressive disorders in children and adolescents. METHODS: We did a systematic review and network meta-analysis. We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of

Science, PsycInfo, ProQuest, CINAHL, LiLACS, international trial registries, and the websites of regulatory agencies for published and unpublished randomized controlled trials from database inception until 1 January 2019. We included placebo-controlled and head-to-head trials of 16 antidepressants, seven psychotherapies, and five combinations of antidepressant and psychotherapy that are used for the acute treatment of children and adolescents (≤ 18 years old and of both sexes) with depressive disorder diagnosed according to standard operationalized criteria. Trials recruiting participants with treatment-resistant depression, bipolar disorder, psychotic depression, treatment duration of less than 4 weeks, or an overall sample size of fewer than ten patients were excluded. We extracted data following a predefined hierarchy of outcome measures, and assessed risk of bias and certainty of evidence using validated methods. Primary outcomes were efficacy (change in depressive symptoms) and acceptability (treatment discontinuation due to any cause). We estimated summary standardized mean differences (SMDs) or odds ratios (ORs) with credible intervals (CrIs) using network meta-analysis with random effects. This study was registered with PROSPERO, number CRD42015020841. FINDINGS: From 20 366 publications, we included 71 trials (9 510 participants). Depressive disorders in most studies were moderate to severe. In terms of efficacy, fluoxetine plus cognitive behavioural therapy (CBT) was more effective than CBT alone (-0.78, 95% CrI: -1.55 to -0.01) and psychodynamic therapy (-1.14, -2.20 to -0.08), but not more effective than fluoxetine alone (-0.22, -0.86 to 0.42). No pharmacotherapy alone was more effective than psychotherapy alone. Only fluoxetine plus CBT and fluoxetine were significantly more effective than pill placebo or psychological controls (SMDs ranged from -1.73 to -0.51); and only interpersonal therapy was more effective than all psychological controls (-1.37 to -0.66). Nortriptyline (SMDs ranged from 1.04 to 2.22) and waiting list (SMDs ranged from 0.67 to 2.08) were less effective than most active interventions. In terms of acceptability, nefazodone and fluoxetine were associated with fewer drop-outs than sertraline, imipramine, and desipramine (ORs ranged from 0.17 to 0.50); imipramine was associated with more drop-outs than pill placebo, desvenlafaxine, fluoxetine plus CBT, and vilazodone (2.51 to 5.06). Most of the results were rated as "low" to "very low" in terms of confidence of evidence according to Confidence In Network Meta-Analysis. INTERPRETATION: Despite the scarcity of high-quality evidence, fluoxetine (alone or in combination with CBT) seems to be the best choice for the acute treatment of moderate-to-severe depressive disorder in children and adolescents. However, the effects of these interventions might vary between individuals, so patients, carers, and clinicians should carefully balance the risk-benefit profile of efficacy, acceptability, and suicide risk of all active interventions in young patients with depression on a case-by-case basis. FUNDING: National Key Research and Development Program of China.

3.4. Grading the Evidence

Table 2. Grade Table 1A: Pharmacotherapy (Select Serotonin Reuptake Inhibitors) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in children and adolescents with depression and anxiety
Population Children and adolescents with pediatric depression [a] or anxiety [b]
Bibliography: Dobson, 2019; Hetrick, 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Anxiety symptom improvement - Dobson, 2019										
7	RCTs	serious [c]	serious [d]	not serious	not serious	publication bias strongly suspected [e]	832	OR **5.2** [CrI: 2.2 - 8.8]	⨁◯◯◯ VERY LOW	CRITICAL
Mental health symptoms – Depressive symptom improvement Hetrick, 2021										
21	RCTs	very serious [h]	not serious	not serious	serious [I]	none	Not reported [J]	MD **-2.30** (CDRS-R scale)[CI : -3.20 to -1.39]	⨁◯◯◯ VERY LOW	CRITICAL
Mental health symptoms – Treatment response (anxiety) - Dobson, 2019										
7	RCTs	serious [c]	not serious	not serious	not serious	none	832	OR **4.6** [3.1 to 7.5] Log OR **1.5** [CrI: 1.1 - 2.0]	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse effects – All cause discontinuation – Dobson, 2019										
7	RCTs	serious [c]	not serious	not serious	not serious	none	832	Log OR **-0.2** [CrI: -0.7 - 0.3]	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse effects – Discontinuation due to adverse effects – Dobson, 2019										

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
7	RCTs	serious [c]	not serious	not serious	not serious	none	832	Log OR **-1.8** [CrI: -3.4 to -0.4]	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse effects – Suicidality – Dobson, 2019										
7	RCTs	serious [c]	serious [f]	not serious	not serious	none	832	Log OR **1.0** [CrI: -2.2 to 4.7]	⨁⨁◯◯ LOW	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **CrI:** Credible interval; **Log OR**: Log of Odds Ratio; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Anxiety symptom improvement - Above 0 favours treatment; below 0 favours control

Depressive symptom improvement – Below 0 favours treatment; above 0 favours control

Treatment response – OR – Above 1 favours treatment; below 1 favours control; Log OR - Above 0 favours treatment; below 0 favours control

All cause discontinuation - Below 0 Favours treatment; above 0 Favours control

Discontinuation due to adverse effects - Above 0 favours treatment; below 0 favours control

Suicidality - Below 0 Favours treatment; above 0 Favours control

a. Dobson, 2019: Pharmacotherapies include Fluoxetine, Citalopram, Escitalopram, Paroxetine, Sertraline. The average age was 11.6 years (range 5-17). Most of the trials required at least moderate anxiety symptom severity as an inclusion criterion.
b. Hetrick, 2021: Pharmacotherapies include Fluoxetine, Fluvoxamine, Sertraline, Paroxetine. The average age ranged from 14.4 to 16.0 years in the adolescent trials and 11.5 to 13.3 years in the trials of children and adolescents. The mean symptom severity scores across all the trials indicated moderate to severe depression.
c. Vast majority of the included studies (> 60%) have an unclear risk of bias and this seriously affects the certainty of evidence
d. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
e. Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias
f. This has been rated as serious, as the 95% CI could not be calculated, and heterogeneity was larger than 50% (i^2 = 61.3%)
g. Certainty assessment is based on the CINeMA approach conducted by the study
h. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as very serious because a vast majority of the studies (> 60%) have a high risk of bias.
i. This has been rated serious because the number of participants included in the analyses is not available
j. The total number of participants is only available for all pharmacotherapy vs placebo comparisons together

Table 3. Grade Table 1B: Pharmacotherapy (Fluoxetine) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020; Hetrick, 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020 [b]										
NR	RCTs	serious	very serious	not serious	not serious	none	Not reported	SMD **-0.51** [CrI: -0.84 to -0.18]	⨁◯◯◯ [b] VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020 [b]										
NR	RCTs	serious	serious	not serious	serious	none	Not reported	OR **0.78** [CrI: 0.56 - 1.15]	⨁◯◯◯ [b] VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020 [b]										
NR	RCTs	serious	not serious	not serious	very serious	none	Not reported	OR **1.11** [CrI: 0.74 - 1.75]	⨁◯◯◯ [b] VERY LOW	CRITICAL
Improved quality of life and functioning – Improvement in functioning – Hetrick, 2021										
NR	RCTs	very serious [c]	not serious	not serious	serious [d]	none	Not reported	MD **1.92** (CGAS scale) [CI : 1.64 - 2.20]	⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – Remission/response – Hetrick, 2021										

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
NR	RCTs	very serious [c]	not serious	not serious	serious [d]	none	Not reported	OR **1.33** [CI: 0.85 - 2.07]	⨁◯◯◯ VERY LOW	IMPORTANT
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence Interval; **CrI:** Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

Improvement in functioning – above 0 Favours treatment; below 0 Favours control

Remission – above 1 Favours treatment; below 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder. Hetrick, 2021: The average age ranged from 14.4 to 16.0 years in the adolescent trials and 11.5 to 13.3 years in the trials of children and adolescents. The mean symptom severity scores across all the trials indicated moderate to severe depression.
b. Certainty assessment is based on the CINeMA approach conducted by the study
c. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as very serious because a vast majority of the studies (> 60%) have a high risk of bias.
d. This has been rated serious because the number of participants included in the analyses is not available

Table 4. Grade Table 1C: Pharmacotherapy (Fluoxetine) compared to treatment as usual in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	**SMD -0.79** [CrI: -1.59 to 0.02]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **0.53** [CrI: 0.15 - 1.33]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **616.7** [CrI: 0.03 - 2314]	⊕◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder
b. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported

Table 5. Grade Table 1D: Pharmacotherapy (Citalopram) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020; Hetrick, 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020 [b]										
NR	RCTs	very serious	not serious	not serious	very serious	none	Not reported	SMD **0.33** [CrI: -0.83 to 1.48]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020 [b]										
NR	RCTs	very serious	not serious	not serious	very serious	none	Not reported	OR **1.75** [CrI: 0.66 - 6.57]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020 [b]										
NR	RCTs	very serious	not serious	not serious	very serious	none	Not reported	OR **1.18** [CrI: 0.35 - 6.85]	⊕◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – Improvement in functioning – Hetrick, 2021										
NR	RCTs	very serious [c]	not serious	not serious	serious [d]	none	Not reported	MD **2.50** (CGAS scale) [CI : -1.52 to 6.52]	⊕◯◯◯ VERY LOW	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – Remission/response – Hetrick, 2021										

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
NR	RCTs	very serious [c]	not serious	not serious	serious [d]	none	Not reported	OR **1.21** [CI: 0.73 - 2.02]	⨁◯◯◯ VERY LOW	IMPORTANT
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **CrI:** Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control
All cause discontinuation - Below 1 Favours treatment; above 1 Favours control
Suicidality - Below 1 Favours treatment; above 1 Favours control
Improvement in functioning – above 0 Favours treatment; below 0 Favours control
Remission – above 1 Favours treatment; below 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder. Hetrick, 2021: The average age ranged from 14.4 to 16.0 years in the adolescent trials and 11.5 to 13.3 years in the trials of children and adolescents. The mean symptom severity scores across all the trials indicated moderate to severe depression.

b. Certainty assessment is based on the CINeMA approach conducted by the study

c. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as very serious because a vast majority of the studies (>60%) have a high risk of bias.

d. This has been rated serious because the number of participants included in the analyses was not available

Table 6. Grade Table 1E: Pharmacotherapy (Citalopram) compared to treatment as usual in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	**SMD 0.05** [CrI: -1.35 to 1.45]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1.63** [CrI: 0.23 lower - 5.53 higher]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1154** [CrI: 0.04 lower - 3572 higher]	⨁◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
-	-	-	-	-	-	-	-	-	-	IMPORTANT
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder
b. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported

Table 7. Grade Table 1F: Pharmacotherapy (Escitalopram) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020; Hetrick, 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020 [b]										
NR	RCTs	serious	not serious	not serious	very serious	none	Not reported	SMD **-0.17** [CrI: -0.88 to 0.54]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020 [b]										
NR	RCTs	serious	not serious	not serious	very serious	none	Not reported	OR **1.40** [CrI: 0.77 - 2.86]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020 [b]										
NR	RCTs	serious	not serious	not serious	very serious	none	Not reported	OR **0.94** [CrI: 0.44 - 2.55]	⨁◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – Improvement in functioning – Hetrick, 2021										
NR	RCTs	very serious [c]	not serious	not serious	serious [d]	none	Not reported	MD **2.28** (CGAS scale) [CI : 0.23 - 4.32]	⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – Remission/response – Hetrick, 2021										

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
NR	RCTs	very serious [c]	not serious	not serious	serious [d]	none	Not reported	OR **1.33** [CI: 0.85 - 2.07]	⨁◯◯◯ VERY LOW	IMPORTANT
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **CrI:** Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

Improvement in functioning – above 0 Favours treatment; below 0 Favours control

Remission – above 1 Favours treatment; below 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder. Hetrick, 2021: The average age ranged from 14.4 to 16.0 years in the adolescent trials and 11.5 to 13.3 years in the trials of children and adolescents. The mean symptom severity scores across all the trials indicated moderate to severe depression.

b. Certainty assessment is based on the CINeMA approach conducted by the study

c. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as very serious because a vast majority of the studies (> 60%) have a high risk of bias.

d. This has been rated serious because the number of participants included in the analyses was not available

Table 8. Grade Table 1G: Pharmacotherapy (Escitalopram) compared to treatment as usual in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	**SMD -0.45** [CrI: -1.50 to 0.62]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1.04** [CrI: 0.23 - 2.96]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **680.9** [CrI: 0.03 - 2227]	⊕◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported

Table 9. Grade Table 1H: Pharmacotherapy (Paroxetine) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020; Hetrick, 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020 [b]										
NR	RCTs	serious	not serious	not serious	very serious	none	Not reported	SMD **-0.16** [CrI: -0.67 to 0.35]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020 [b]										
NR	RCTs	serious	not serious	not serious	serious	none	Not reported	OR **1.3** [CrI: 0.81 - 2.27]	⨁⨁◯◯ LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020 [b]										
NR	RCTs	serious	not serious	not serious	serious	none	Not reported	OR **1.71** [CrI: 0.81 - 5.05]	⨁⨁◯◯ LOW	CRITICAL
Improved quality of life and functioning – Improvement in functioning – Hetrick, 2021										
NR	RCTs	very serious [c]	not serious	not serious	serious [d]	none	Not reported	MD **1.60** (CGAS scale) [CI : -2.48 to 5.68]	⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – Remission/response – Hetrick, 2021										

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
NR	RCTs	very serious [c]	not serious	not serious	serious [d]	none	Not reported	OR **1.05** [CI: 0.1 - 1.55]	⨁◯◯◯ VERY LOW	IMPORTANT
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **CrI:** Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

Improvement in functioning – above 0 Favours treatment; below 0 Favours control

Remission – above 1 Favours treatment; below 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder. Hetrick, 2021: The average age ranged from 14.4 to 16.0 years in the adolescent trials and 11.5 to 13.3 years in the trials of children and adolescents. The mean symptom severity scores across all the trials indicated moderate to severe depression.

b. Certainty assessment is based on the CINeMA approach conducted by the study

c. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as very serious because a vast majority of the studies (> 60%) have a high risk of bias.

d. This has been rated serious because the number of participants included in the analyses was not available

Table 10. Grade Table 1I: Pharmacotherapy (Paroxetine) compared to treatment as usual in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	**SMD -0.44** [CrI: -1.36 to 0.51]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **0.93** [CrI: 0.22 - 2.49]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1430** [CrI: 0.06 - 3919]	⨁◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported

Table 11. Grade Table 1J: Pharmacotherapy (Sertraline) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020; Hetrick, 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020 [b]										
NR	RCTs	very serious	not serious	not serious	very serious	none	Not reported	SMD **0.11** [CrI: -0.49 to 0.71]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020 [b]										
NR	RCTs	very serious	not serious	not serious	serious	none	Not reported	OR **0.62** [CrI: 0.31 - 1.12]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020 [b]										
NR	RCTs	very serious	not serious	not serious	very serious	none	Not reported	OR **0.45** [CrI: 0.08 - 1.33]	⊕◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – Improvement in functioning – Hetrick, 2021										
NR	RCTs	very serious [c]	not serious	not serious	serious [d]	none	Not reported	MD **1.31** (CGAS scale) [CI : -1.61 to 4.23]	⊕◯◯◯ VERY LOW	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – Remission/response – Hetrick, 2021										

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
NR	RCTs	very serious [c]	not serious	not serious	serious [d]	none	Not reported	OR **1.55** [CI: 0.86 - 2.80]	⨁◯◯◯ VERY LOW	IMPORTANT
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **CrI:** Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

Improvement in functioning – above 0 Favours treatment; below 0 Favours control

Remission – above 1 Favours treatment; below 1 Favours control

a. **Zhou, 2020:** The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder. **Hetrick, 2021:** The average age ranged from 14.4 to 16.0 years in the adolescent trials and 11.5 to 13.3 years in the trials of children and adolescents. The mean symptom severity scores across all the trials indicated moderate to severe depression.

b. Certainty assessment is based on the CINeMA approach conducted by the study

c. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as very serious because a vast majority of the studies (> 60%) have a high risk of bias.

d. This has been rated serious because the number of participants included in the analyses was not available

Table 12. Grade Table 1K: Pharmacotherapy (Sertraline) compared to treatment as usual in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	**SMD -0.39** [CrI: -1.17 to 0.39]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1.16** [CrI: 0.30 - 3.03]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1650** [CrI: 0.10 - 6481]	⊕◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment								Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]	Certainty	Importance
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. **Zhou, 2020:** The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported

Table 13. Grade Table 2A: Pharmacotherapy (Tricyclic Antidepressants) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in children and adolescents with anxiety
Population: Children and adolescents with pediatric anxiety [a]
Bibliography: Dobson, 2019

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Anxiety symptom improvement - Dobson, 2019										
2	RCTs	serious [b]	serious [c]	not serious	serious [d]	publication bias strongly suspected [e]	Not reported	OR **1.4** [Crl: -5.2 to 7.9]	⨁◯◯◯ VERY LOW	CRITICAL
Mental health symptoms – Treatment response (anxiety) - Dobson, 2019										
4	RCTs	serious [b]	not serious	not serious	serious [d]	none	Not reported	OR **2.0** [0.8 to 4.9] Log OR **0.7** [Crl: -0.2 to 1.6]	⨁⨁◯◯ LOW	CRITICAL
Adverse effects – All cause discontinuation – Dobson, 2019										
NR	RCTs	serious [b]	not serious	not serious	serious [d]	none	Not reported	Log OR **0.6** [Crl: -0.6 to 1.7]	⨁⨁◯◯ LOW	CRITICAL
Adverse effects – Discontinuation due to adverse effects – Dobson, 2019										
NR	RCTs	serious [b]	not serious	not serious	serious [d]	none	Not reported	Log OR **-0.8** [Crl: :-5.0 to 3.3]	⨁⨁◯◯ LOW	CRITICAL
Adverse effects – Suicidality – Dobson, 2019										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	Log OR **25.1** [Crl: 4.5 - 57.4]	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment								Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]	Certainty	Importance
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **Log OR**: Log of Odds Ratio; **OR:** Odds Ratio; **RCTs**: randomized controlled trials

Interpretation of outcomes:

Anxiety symptom improvement - Above 0 favours treatment; below 0 favours control

Treatment response - OR – Above 1 Favours treatment; below 1 Favours control; Log OR - Above 0 Favours treatment; below 0 Favours control

All cause discontinuation - Below 0 Favours treatment; above 0 Favours control

Discontinuation due to adverse effects - Above 0 favours treatment; below 0 favours control

Suicidality - Below 0 Favours treatment; above 0 Favours control

a. **Dobson, 2019:** Pharmacotherapies include: Imipramine, clomipramine. The average age was 11.6 years (range 5-17). Most of the trials required at least moderate anxiety symptom severity as an inclusion criterion.

b. Vast majority of the included studies (> 60%) have an unclear risk of bias and this seriously affects the certainty of evidence

c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence

d. Number of participants included in the analysis is not reported

e. Statistical tests (Egger's test) suggest the presence of publication bias

Table 14. Grade Table 2B: Pharmacotherapy (Imipramine) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment [b]								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	not serious	not serious	not serious	very serious	none	Not reported	SMD **-0.03** [CrI: -0.75 to 0.68]	⨁⨁◯◯ LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	not serious	not serious	not serious	not serious	none	Not reported	OR **2.51** [CrI: 1.26 - 6.24]	⨁⨁⨁⨁ HIGH	CRITICAL
Adverse effects – Suicidality - Zhou, 2020										
NR	RCTs	not serious	not serious	not serious	very serious	none	Not reported	OR **0.59** [CrI: 0.19 - 3.07]	⨁⨁◯◯ LOW	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment [b]								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. Certainty assessment is based on the CINeMA approach conducted by the study.

Table 15. Grade Table 2C: Pharmacotherapy (Imipramine) compared to treatment as usual in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	**SMD -0.31** [CrI: -1.38 to 0.76]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1.97** [CrI: 0.40 - 5.95]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **490.8** [CrI: 0.02 - 1979]	⊕◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment								Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**	**Certainty**	**Importance**
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported

Table 16. Grade Table 2D: Pharmacotherapy (Desipramine) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment [b]								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious	not serious	not serious	very serious	none	Not reported	SMD **-0.43** [CrI: -1.26 to 0.39]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious	serious	not serious	serious	none	Not reported	OR **2.21** [CrI: 0.88 - 7.67]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - not reported										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
User and family satisfaction – not reported										

Certainty assessment [b]								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. Certainty assessment is based on the CINeMA approach conducted by the study.

Table 17. Grade Table 2E: Pharmacotherapy (Desipramine) compared to treatment as usual in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	**SMD -0.71** [CrI: -1.85 to 0.43]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1.99** [CrI: 0.31 - 6.84]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - not reported										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
User and family satisfaction – not reported										

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported

Table 18. Grade Table 2F: Pharmacotherapy (Amitriptyline) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment [b]								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious	not serious	not serious	very serious	none	Not reported	SMD **0.08** [CrI: -1.11 to 1.27]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious	not serious	not serious	very serious	none	Not reported	OR **1.16** [CrI: 0.29 - 12.13]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - not reported										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
User and family satisfaction – not reported										

Certainty assessment [b]								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. Certainty assessment is based on the CINeMA approach conducted by the study

Table 19. Grade Table 2G: Pharmacotherapy (Amitriptyline) compared to treatment as usual in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	**SMD -0.20** [CrI: -1.63 to 1.24]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1.93** [CrI: 0.12 - 9.39]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - not reported										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
User and family satisfaction – not reported										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported

Table 20. Grade Table 2H: Pharmacotherapy (Clomipramine) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
Mental health symptoms – Change in depressive symptoms – Zhou, 2020 [b]										
NR	RCTs	not serious	not serious	not serious	very serious	none	Not reported	SMD **0.33** [CrI: -0.83 to 1.48]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – All cause discontinuation – Zhou, 2020 [b]										
NR	RCTs	not serious	not serious	not serious	very serious	none	Not reported	OR **1.75** [CrI: 0.66 - 6.57]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – Suicidality – Zhou, 2020										
NR	RCTs	serious [c]	serious [d]	not serious	serious [e]	none	Not reported	OR **1.18** [CrI: 0.35 - 6.85]	⊕◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms – Below 0 Favours treatment; above 0 Favours control

All cause discontinuation – Below 1 Favours treatment; above 1 Favours control

Suicidality – Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. Certainty assessment is based on the CINeMA approach conducted by the study
c. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
d. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
e. Number of participants included in the analysis is not reported

Table 21. Grade Table 2I: Pharmacotherapy (Clomipramine) compared to treatment as usual in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	**SMD 0.05** [CrI: -1.35 to 1.45]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1.63** [CrI: 0.23 - 5.53]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **1154** [CrI: 0.04 - 3572]	⨁◯◯◯ VERY LOW	CRITICAL
Improved quality of life and functioning – Zhou, 2020										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported

Table 22. Grade Table 2J: Pharmacotherapy (Nortriptyline) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment [b]								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious	not serious	not serious	very serious	none	Not reported	SMD **1.14** [CrI: 0.46 - 1.81]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious	not serious	not serious	very serious	none	Not reported	OR **0.76** [CrI: 0.28 - 3.41]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - not reported										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
User and family satisfaction – not reported										

Certainty assessment [b]								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. Certainty assessment is based on the CINeMA approach conducted by the study

Table 23. Grade Table 2K: Pharmacotherapy (Nortriptyline) compared to treatment as usual in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to treatment as usual in children and adolescents with depressive disorders
Population: Children and adolescents with depressive disorders [a]
Bibliography: Zhou, 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Change in depressive symptoms - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	**SMD 0.86** [CrI: -0.15 to 1.89]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation - Zhou, 2020										
NR	RCTs	serious [b]	serious [c]	not serious	serious [d]	none	Not reported	OR **0.75** [CrI: 0.10 - 2.64]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality - not reported										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
User and family satisfaction – not reported										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference

Interpretation of outcomes:

Depressive symptoms - Below 0 Favours treatment; above 0 Favours control

All cause discontinuation - Below 1 Favours treatment; above 1 Favours control

Suicidality - Below 1 Favours treatment; above 1 Favours control

a. Zhou, 2020: The mean age of the participants was 14 years (Range 3-20). A majority of the participants (75.5%) had moderate to severe major depressive disorder.
b. The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious because the proportion of studies with a high risk of bias is above 25%.
c. Estimates of heterogeneity are not available in the meta-analysis, and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported

Table 25. Grade Table 3: Pharmacotherapy (Benzodiazepines) compared to pill placebo in children and adolescents with emotional disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in children and adolescents with anxiety
Population: Children and adolescents with pediatric anxiety [a]
Bibliography: Dobson, 2019

Certainty assessment								Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of patients**	**Absolute [95% CrI]**		
Mental health symptoms – Anxiety symptom improvement - Dobson, 2019										
1	RCTs	very serious[b]	serious [c]	not serious	serious [d]	publication bias strongly suspected [e]	Not reported	OR **-0.4** [CrI: -9.7 to 9.1]	⨁◯◯◯ VERY LOW	CRITICAL
Mental health symptoms – Treatment response (anxiety) - Dobson, 2019										
2	RCTs	very serious[b]	not serious	not serious	serious [d]	none	Not reported	OR **1.4** [CrI: 0.36 - 6.1] Log OR **0.33** [CrI: -1.2 to 1.8]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – All cause discontinuation – Dobson, 2019										
NR	RCTs	very serious[b]	serious [c]	not serious	serious [d]	none	Not reported	Log OR **0.3** [CrI: -1.3 to 2.1]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Discontinuation due to adverse effects – Dobson, 2019										
NR	RCTs	very serious[b]	serious [c]	not serious	serious [d]	none	Not reported	Log OR **-21.6** [CrI: -76.8 to -1.3]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse effects – Suicidality – Dobson, 2019										
NR	RCTs	very serious[b]	not serious	not serious	serious [d]	none	Not reported	Log OR **11.9** [CrI: -0.7 to 39.3]	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [95% CrI]		
Improved quality of life and functioning – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Reduction in risky behaviour – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Remission – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
User and family satisfaction – not reported										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CrI: Credible interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials

Interpretation of outcomes:

Anxiety symptom improvement - Above 0 favours treatment; below 0 favours control

Treatment response - OR – Above 1 Favours treatment; below 1 Favours control; Log OR - Above 0 Favours treatment; below 0 Favours control

All cause discontinuation - Below 0 Favours treatment; above 0 Favours control

Discontinuation due to adverse effects - Above 0 favours treatment; below 0 favours control

Suicidality - Below 0 Favours treatment; above 0 Favours control

a. Dobson, 2019: Pharmacotherapies include Alprazolam and Clonidine. The average age was 11.6 years (range 5-17). Most of the trials required at least moderate anxiety symptom severity as an inclusion criterion.
b. 50 % of the studies have a high risk of bias and 50% have an unclear risk of bias. This seriously affects the certainty of evidence
c. Estimates of heterogeneity are not available in the meta-analysis and this seriously affects the certainty of the evidence
d. Number of participants included in the analysis is not reported
e. Statistical tests (Egger's test) suggest the presence of publication bias

3.5. Additional evidence not mentioned in GRADE tables

Baker 2021: Prescription of multiple medications concurrently for children and adolescents has increased in recent years. Examination of this practice has been undervalued relative to its incidence. This article reviews studies investigating effectiveness of medication combinations for youth with attention-deficit/hyperactivity disorder (ADHD). A literature search identified studies that combined two or more prescribed medications for the treatment of ADHD. Included studies focused on youth; had study design of randomized controlled trial (RCT), nonrandomized trial, or case review (n > 10); and included an outcome measure of treatment effectiveness. Thirty-nine pertinent studies were identified. All studies combined two medications, with the vast majority including a stimulant (n = 37). The largest group (n = 16) combined stimulant and alpha-agonist, finding greater efficacy than alpha- agonist alone but not stimulant alone in all cases. A few RCTs found benefit from the addition of risperidone or divalproex to stimulant for comorbid aggression. Four studies adding atomoxetine found mixed reports of benefit, including the only small RCT showing no benefit. RCTs with selective serotonin reuptake inhibitors found minimal evidence of benefit for mood or anxiety comorbidities. The best studied combination is stimulant and alpha-agonist; addition of alpha-agonist to stimulant seems effective for residual symptoms of ADHD. Stimulant plus risperidone has the most evidence of efficacy for comorbid aggression or disruptive behaviour. Limited support exists for the effectiveness of other medication combinations, including no trials studying three or more medications concurrently. Combinations frequently yielded more side-effects, leaving monotherapy preferable if a sufficient treatment response can be achieved.

Correll 2021: Top-tier evidence on the safety/tolerability of 80 medications in children/adolescents with mental disorders has recently been reviewed in this journal. To guide clinical practice, such data must be combined with evidence on efficacy and acceptability. Besides medications, psychosocial interventions and brain stimulation techniques are treatment options for children/adolescents with mental disorders. For this umbrella review, we systematically searched network meta-analyses (NMAs) and meta-analyses (MAs) of randomized controlled trials (RCTs) evaluating 48 medications, 20 psychosocial interventions, and four brain stimulation techniques in children/adolescents with 52 different mental disorders or groups of mental disorders, reporting on 20 different efficacy/acceptability outcomes. Co-primary outcomes were disease-specific symptom reduction and all-cause discontinuation (“acceptability”). We included 14 NMAs and 90 MAs, reporting on 15 mental disorders or groups of mental disorders. Overall, 21 medications outperformed placebo regarding the co-primary outcomes, and three psychosocial interventions did so (while seven outperformed waiting list/no treatment). Based on the meta-analytic evidence, the most convincing efficacy profile emerged for amphetamines, methylphenidate and, to a smaller extent, behavioural therapy in attention-deficit/hyperactivity disorder; aripiprazole, risperidone and several psychosocial interventions in autism; risperidone and behavioural interventions in disruptive behaviour disorders; several antipsychotics in schizophrenia spectrum disorders; fluoxetine, the combination of fluoxetine and cognitive behavioural therapy (CBT), and interpersonal therapy in depression; aripiprazole in mania; fluoxetine and group CBT in anxiety disorders; fluoxetine/selective serotonin reuptake inhibitors, CBT, and behavioural therapy with exposure and response prevention in obsessive-compulsive disorder; CBT in post-traumatic stress disorder; imipramine and alarm behavioural intervention in enuresis; behavioural therapy in encopresis; and family therapy in anorexia nervosa. Results from this umbrella review of interventions for mental disorders in children/adolescents provide evidence-based information for clinical decision making.

De Bruijn 2021: Functional Abdominal Pain Disorders (FAPDs) present a considerable burden to paediatric patients, impacting quality of life, school attendance and causing higher rates of anxiety and depression disorders. There are no international guidelines for the management of this condition. A previous Cochrane Review in 2011 found no evidence to support the use of antidepressants in this context. Objective: To evaluate the current evidence for the efficacy and safety of antidepressants for FAPDs in children and adolescents. Search methods: In this updated

review, we searched The Cochrane Library, PubMed, MEDLINE, Embase, PsycInfo and two clinical trial registers from inception until February 3th, 2020. We also updated our search of databases of ongoing research, reference lists and 'grey literature' from inception to February 3th, 2020. Selection criteria: We included randomized controlled trials (RCTs) comparing antidepressants to placebo, to no treatment or to any other intervention, in children aged 4 to 18 years with a FAPD diagnosis as per the Rome or any other defined criteria (as defined by the authors). The primary outcomes of interest included treatment success (as defined by the authors), pain severity, pain frequency and withdrawal due to adverse events. Data collection and analysis: All citations were reviewed independently by two authors, with disagreement solved with a third-party arbiter. All potential studies had full texts reviewed, and once again, independent decisions made, with disagreement solved by consensus. Data extraction and risk of bias assessment was completed independently following Cochrane standards. Where homogenous data was available, meta-analysis was performed using a random effects model. GRADE assessement of the certainty of the evidence was performed. Main results: Three studies were eligible for inclusion: two using amitriptyline (AMI) and one using citalopram. The studies recruited 223 children diagnosed with either Rome II or Rome III criteria. For the primary outcome of treatment success, two studies used report of success on a symptom-based Likert scale, with either a two- point reduction or the two lowest levels defined as success. The other study defined success as a 15% improvement in Quality of life (QOL) rating scales, which could not be included in the meta-analysis due to the heterogeneity of the outcome measure. There is insufficient evidence to determine the effects of antidepressants compared with placebo on treatment success (risk ratio (RR) 1.17, 95% confidence interval (CI) [0.87 - 1.56]; 2 studies, 205 participants; low certainty evidence). We downgraded the evidence due to significant imprecision due to extremely sparse data. We are uncertain whether children were more likely to withdraw due to adverse events with antidepressants or placebo, RR 3.80 (95% CI: 0.61 - 23.57, very serious imprecision due to low events and number of participants. Sensitivity analysis using a fixed effect model and analysing just for AMI found no change in this result. Due to heterogeneous and limited reporting, no further meta-analysis was possible for other outcomes of pain severity or frequency.

Driot, 2019: Objective. – To develop a practical guide for the management of child and adolescent depression for general practitioners (GPs), suited to their practice frame, that can be implemented on a website aimed to help GPs to manage the main mental disorders encountered in primary care. Method. – A systematic meta-review was performed as recommended by the PRISMA statement. Each step, articles' selection, inclusion, methodological assessment and data extraction for the narrative synthesis was independently performed by two researchers. A study protocol was registered on PROSPERO (number CRD42016042710). The databases PubMed, Cochrane and Web of Science were explored. Each step was performed independently by two researchers following PRISMA. Meta-analyses and systema tic reviews (including guidelines based on a systematic review), published between 2002 and 2015, in English or French, dealing with the therapeutic management, in primary care, of patients aged 6 to 18 years old with a major depressive disorder (MDD) were included. Grey literature was explored searching methodological and report qualities were assessed using the AGREE II, PRISMA checklist and R-AMSTAR grid. A narrative synthesis was performed to produce the practical guide, prioritizing data from the best evaluated articles. An expert group of GPs' and one child psychiatrist validated the guide in its final form. Results. – Thirty-eight studies were included: 12 recommendations, 5 systematic reviews and 21 meta- analyses. The best evaluated guideline had an AGREE-II assessment of 81%, and the best evaluated meta- analysis had an assessment of 86% for R-AMSTAR and 96% for PRISMA. The average scores of the R-AMSTAR and PRISMA assessments were 65% and 72% respectively. The average score of the AGREE II grid assessment was 57%. The data were synthesized into a practical guide for the GPs' practice, corresponding to the different consultation times. MDD diagnosis should be done on the DSM or ICD basis. The Childrens' Depression Rating Scale-revised or the Revised Beck Depression Inventory are useful in primary care for MDD appraisal in children and adolescents. For mild MDD a supportive psychotherapy and surveillance for 4 to 6 weeks is preconized in primary care. In the absence of improvement, a specific and structured psychotherapy is recommended, and the patient should be

addressed to a child psychiatrist. For moderate to severe MDD, the young patient should be addressed to a specialist in child psychiatry. A psychotherapy, which can be associated with fluoxetine, especially in adolescents, is indicated with a revaluation of the pharmacological treatment between 4 to 8 weeks. A weekly follow-up by the GP is recommended during the first month, especially after the initiation of an antidepressant to assess the suicidal risk. Beyond the first month, a consultation should be scheduled every two weeks. Conclusion. – A clinical guide was created from the best evidence-based data to help GPs in the management of child and adolescent MDD. A French-language website, aimed to assist GPs in mental disease management and available during their consultation, will be created based on the compilation of this meta-review with other similar meta-reviews.

Hamil, 2021: More than half of youth with anxiety and obsessive-compulsive disorders report sleep disturbances. Furthermore, the most effective psychopharmacologic interventions for these disorders—selective serotonin reuptake inhibitors (SSRIs)—may themselves increase insomnia as well as tiredness/sedation. However, the risk of sleep-related problems for specific SSRIs has not been examined meta-analytically. We sought to examine sleep-related adverse events (AEs) across specific SSRIs in clinical trials of youth with anxiety disorders as well as obsessive compulsive disorder (OCD) using Bayesian hierarchical modeling (BHM). Data were included from studies involving five SSRIs: fluoxetine, fluvoxamine, paroxetine, sertraline, and escitalopram. Compared with placebo, sertraline was associated with a greater likelihood of insomnia. Fluoxetine was associated with more treatment-emergent sedation. No significant sedation differences were observed between placebo and fluvoxamine, escitalopram, paroxetine, or sertraline. Also, no significant insomnia differences were observed between placebo and fluoxetine, paroxetine, fluvoxamine, or escitalopram. These findings suggest that sleep-related side-effects are associated with specific SSRIs and have important clinical implications.

Li 2019: Objective: The high placebo response rate may hamper the discovery of antidepressants in children and adolescents with major depressive disorder (MDD). The aim of the study was to clarify the relationship between the placebo response rate and clinical trial outcomes of the use of antidepressants in children and adolescents, and distinguish main factors responsible to placebo response rate. Methods: The PubMed and Cochrane Library databases were searched for double-blind randomized placebo-controlled trials of the new-generation antidepressants for the acute treatment of MDD in children and adolescents. The response rate differences (RDs) between placebo group and treatment group under different level of placebo response rate were pooled by random-effects meta-analysis. The classification thresholds for low, medium, and high placebo response rate were set at < 40%, 40%–50%, and ‡ 50%, respectively. Predictors of placebo response rate were explored using meta-regression. Results: The analysis included 18 trials with 4365 participants. This study found that the lower the placebo response rate, the greater the efficacy differences between antidepressants and placebo. In the high, moderate, and low placebo response rate subgroups, the response RDs (95% CI) between antidepressants and placebo were 8 (1–14)%, 10 (2–17)%, and 21 (9–32)%, respectively. The meta-regression showed that the number of study sites was the factor most associated with placebo response rate, and that response rate increased 3% with every additional 10 study sites. Conclusions: The clinical outcome was related to the placebo response rates in the clinical trials of antidepressants in children and adolescents with MDD. The efficacy differences between antidepressants and placebo will be maximized when placebo response rates are reduced. The number of study sites was the factor most associated with the placebo response rates.

Mills 2020: Objective: To compare adverse events (AEs), suicidality, and AE-related discontinuation in double-blind, placebo-controlled trials of pediatric patients with obsessive-compulsive disorder (OCD) and anxiety disorders treated with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Method: MEDLINE, PubMed, Web of Science, PsycInfo, and Embase were searched for peer-reviewed, English-language articles from inception through 1 March 2019. We identified prospective, randomized SSRI and SNRI studies in patients < 18 years of

age with OCD or generalized, separation, or social anxiety disorders. AE rates were extracted and medication-placebo differences were examined using Bayesian hierarchical models, then posterior estimates of relative risk (RR) were determined for each AE by medication class and disorder. Results: Data were included from 18 trials (2 631 patients) and 7 medications (16 SSRI and 4 SNRI trials). Compared with placebo, SSRIs were associated with a greater likelihood of AE-related discontinuation (RR 3.59, credible interval [CrI] 0.019 – 0.067, P 1⁄4 = 0.0003), activation (RR 2.39, CrI: 0.048 – 0.125, P 1⁄4 - 0.003), sedation (RR 1.94, CrI: 0.035 – 0.157, P 1⁄4 = 0.002), insomnia (RR 1.93, CrI: 0.040 – 0.149, P 1⁄4 = 0.001), abdominal pain (RR 1.53, CrI: 0.032 – 0.164, P 1⁄4 = 0.005), and headache (RR 1.24, CrI: 0.003 – 0.139, P 1⁄4 = 0.04). Activation was more common with SSRIs (versus SNRIs, RR 1.32, CrI: 0.018 – 0.114, P 1⁄4 = 0.007). Neither SSRIs nor SNRIs were associated with treatment-emergent suicidality.
Conclusion: In pediatric OCD and anxiety disorders, SSRIs (compared with placebo) are associated with distinct AEs and greater AE-related discontinuation, although their tolerability does not differ between anxiety disorders and OCD. Compared with SNRIs, SSRIs are more likely to produce activation. Class-related AEs are important for clinicians to consider, particularly in light of data suggesting differences in class-related efficacy. Whereas SSRIs are superior to SNRIs and the treatment of choice for anxiety, for youths who become activated on SSRIs, SNRIs might represent a good second choice given their reported efficacy and lower risk of activation.

Mossman 2021: Objective: To identify predictors of medication-placebo differences in double-blind placebo-controlled antidepressant trials in children and adolescents with anxiety and depression. Methods: Clinical trials in patients < 18 years of age with major depressive disorder or generalized, separation or social anxiety disorders were obtained from PubMed, the Cochrane Database and clinicaltrials.gov searches from inception through 2019. Forty-nine trials (43 published and 6 unpublished) of anxiety (κ = 13) and depression (κ = 36) evaluated 19 antidepressants in 8642 child and adolescent patients; placebo and medication response rates, trial characteristics, disorder, medication class, and funding source were extracted. Antidepressant-placebo differences were examined using Bayesian hierarchical models and estimates of response were determined for trial design, disorder, and medication class variables. Using meta-regression, correlates of antidepressant-placebo difference and placebo response were examined. Results: Funding source differentiated medication-placebo differences regardless of disorder. Industry trials had larger placebo response rates (mean difference: 0.189 ± 0.066, credible interval [CrI]: 0.067 to 0.33, P = 0.0008) and smaller medication-placebo differences (-0.235 ± 0.078, CrI: -0.397 to -0.086, P = 0.005) compared with federally funded trials. However, medication response was similar for industry- and federally-funded studies (-0.046 ± 0.042, CrI: -0.130 to 0.038, P = 0.252). Conclusions: The impact of study sponsorship on trial outcome supports the assertion that industry-funded trials with high placebo response rates and small drug-placebo differences are "failed trials" and should not be described as "negative trials" or used to determine public health estimates of antidepressant efficacy in children and adolescents with anxiety and depression. Identifying the proper role and value of industry-funded trials is critical to establishing the evidence base for antidepressants in youth.

Reyad 2020: BACKGROUND: Fluoxetine is a serotonin-specific reuptake inhibitor antidepressant and is the only approved pharmacological treatment for major depressive disorder (MDD) in children and adolescent. METHODS: We searched the published randomized controlled-trials to review fluoxetine efficacy and tolerability using the databases PubMed, EudraCT, ClinicalTrials.gov, and Cochrane Central Register of Controlled Trials for fluoxetine role in managing MDD in children and adolescents. A meta-analysis was conducted using the identified 7 clinical trials to assess efficacy using the outcomes: Children's Depression Rating Scale-Revised (CDRS-R), Clinical Global Impressions-Severity of Illness (CGI-S) and Clinical Global Impressions-Improvement (CGI-I) response rate. The risk of discontinuation due to adverse effects and common side-effects were examined. RESULTS: The mean difference in change from baseline for CDRS-R was -2.72 (95% confidence interval [CI], -3.96, -1.48) favoring fluoxetine treatment (P < 0.001). Similarly, mean difference for CGI-S was -0.21 (95% CI: -0.36 to -0.06). The risk ratio (RR) of discontinuing due to adverse events was 0.98 (95% CI: 0.54 -

1.83), with RR for headache side-effects 1.34 (95% CI: 1.03 - 1.74) and rash 2.6 (95% CI: 1.32 - 5.14). CONCLUSION: Fluoxetine demonstrates significant improvements in symptom intensity control in young patients suffering from MDD and is considered well tolerated with similar rates of trials discontinuation; however, fluoxetine was associated with a higher risk of headache and rash side-effects. These findings will guide psychiatrists and pharmacists in their clinical role for supporting the care of young mental health patients.

Schwartz 2019: QUESTION: Anxiety disorders are the most prevalent childhood mental disorders. They also start early and persist, causing high individual and collective costs. To inform policy and practice, we therefore asked: What is the best available research evidence on preventing and treating these disorders? METHODS: We sought randomized controlled trials (RCTs) evaluating interventions addressing anxiety problems in young people. We identified RCTs by searching CINAHL, ERIC, MEDLINE, PsycInfo and Web of Science. Thirty-three RCTs met inclusion criteria-evaluating 8 prevention programmes, 12 psychosocial treatments and 7 pharmacological treatments. We then conducted meta-analyses by intervention type. FINDINGS: For prevention, the cognitive-behavioural therapy (CBT) programme Coping and Promoting Strength stood out for reducing anxiety diagnoses. For psychosocial treatment, 9 CBT interventions also reduced diagnoses: Cool Kids; Cool Little Kids Plus Social Skills; Coping Cat; Coping Koala; One-Session Treatment; Parent Education Program; Skills for Academic and Social Success; Strongest Families and Timid to Tiger. Successful CBT interventions were used with children ranging from pre-schoolers to teens in homes, communities/schools and clinics. For pharmacological treatment, selective-serotonergic-reuptake-inhibitors (SSRIs) significantly improved symptoms. Fluoxetine stood out for also reducing post-test diagnoses, but caused adverse events. Meta-analyses indicated strongest effects for CBT (Log OR = 0.95; 95% CI: 0.69 - 1.21) and SSRI treatments (1.57; 1.09 - 2.06). CONCLUSIONS: CBT is effective for preventing and treating childhood anxiety-across a range of ages and formats. Fluoxetine is also an effective treatment but side-effects must be managed. CBT prevention and treatment interventions should be made widely available, adding fluoxetine in severe cases.

Sharma 2019: OBJECTIVE: To study the drop-out rates in trials of selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs). METHODS: This study is a systematic review and meta-analysis of trials. The main outcome measure: Overall drop-out rate. Secondary outcomes were drop-outs due to adverse events and lack of effect. We obtained clinical study reports (CSRs) of five antidepressant drugs from the European Medicines Agency and the UK's Medicines and Healthcare products Regulatory Agency. The eligibility criteria for selecting studies: double-blind randomized, placebo-controlled trials for any indication. DATA EXTRACTION AND ANALYSIS: The primary outcome was extracted by two researchers independently and meta-analysed using the Mantel-Haenszel method (fixed effect model). The secondary outcomes were extracted by one researcher and checked by another. Sensitivity analyses were performed using Peto's odds ratio and beta binomial methods, due to presence of null events, and by excluding unreliable trials. RESULTS: We included 71 CSRs (67 319 pages) with information on 73 trials (11 057 patients on SSRI or SNRI drugs, and 7 369 on placebo). There were minor discrepancies within the CSRs when a modified intention to treat principle was used and patients lost to follow up early in the trial were not accounted for. Significantly more patients dropped out on active drug than on placebo, risk ratio 1.08 (95% CI: 1.03 - 1.13), with no difference between adults and children/ adolescents, RR=1.08 (1.03 - 1.13) and 1.07 (0.95 - 1.21), respectively. When three trials with a prior single-blind phase on active drug were removed, the difference was a risk ratio of 1.12 (1.07 - 1.18), whereas the result was the same after removal of three trials with fraudulent data or other issues with data validity, risk ratio 1.08 (1.03 - 1.13). There were more drop-outs due to adverse events on active drug than on placebo, risk ratio 2.63 (2.33 - 2.96). There were fewer drop-outs due to lack of effect, risk ratio 0.47 (0.43 - 0.53). However, this result is biased; when more people drop-out due to adverse effects, fewer can drop-out because of lack of effect. CONCLUSIONS: By using CSRs, we were able to demonstrate for the first time that more patients dropped out on active drug than on placebo. As it can be argued that the drop-out rate reflects the patients' overall assessment of the balance between benefits and

harms, our review adds to the growing concern that SSRIs and SNRIs might not have the desired effect. Our review also highlights the importance of using CSRs for undertaking reviews of drugs.

Villas Boas 2019: The purpose of this study was to conduct a systematic review of the pharmacological options available to treat patients diagnosed with attention-deficit hyperactivity disorder and anxiety disorder, for generating evidence on the safest, most-effective and tolerable pharmacotherapy. To this end, a systematic search was performed in three electronic databases (MEDLINE, Scopus and Directory of Open Access Journals; December 2017). Randomized, double-blind, parallel-design clinical trials evaluating the efficacy, safety or tolerability of therapies for attention-deficit hyperactivity disorder and anxiety disorder in children and adolescents or adults were considered. A total of 1960 articles were retrieved from the databases, of which five studies were included in the qualitative synthesis. Two of these studies evaluated the drug atomoxetine, another study evaluated desipramine, and the remaining two studies evaluated methylphenidate, with fluvoxamine being associated with methylphenidate in one of the trials. Owing to the high heterogeneity among studies, it was not possible to combine data for meta-analyses. Although only few studies have been evaluated in this systematic review, the results point to a more significant benefit of atomoxetine. This is probably because this drug was studied in a wider age range and evaluated by more specific scales for both disorders. To further strengthen this evidence, randomized, controlled and multicentre clinical trials with larger sample sizes should be conducted.

Kato 2020: A significant clinical issue encountered after a successful acute major depressive disorder (MDD) treatment is the relapse of depressive symptoms. Although continuing maintenance therapy with antidepressants is generally recommended, there is no established protocol on whether or not it is necessary to prescribe the antidepressant used to achieve remission. In this meta- analysis, the risk of relapse and treatment failure when either continuing with the same drug used to achieved remission or switching to a placebo was assessed in several clinically significant subgroups. The pooled odds ratio (OR) (±95% confidence intervals (CI)) was calculated using a random effects model. Across 40 studies (n = 8 890), the relapse rate was significantly lower in the antidepressant group than the placebo group by about 20% (OR = 0.38, CI: 0.33 – 0.43, P < 0.00001; 20.9% vs 39.7%). The difference in the relapse rate between the antidepressant and placebo groups was greater for tricyclics (25.3%; OR = 0.30, CI: 0.17 – 0.50, P < 0.00001), SSRIs (21.8%; OR = 0.33, CI: 0.28 – 0.38, P < 0.00001), and other newer agents (16.0%; OR = 0.44, CI: 0.36 – 0.54, P < 0.00001) in that order, while the effect size of acceptability was greater for SSRIs than for other antidepressants. A flexible dose schedule (OR = 0.30, CI: 0.23 – 0.48, P < 0.00001) had a greater effect size than a fixed dose (OR = 0.41, CI: 0.36 – 0.48, P < 0.00001) in comparison to placebo. Even in studies assigned after continuous treatment for more than 6 months after remission, the continued use of antidepressants had a lower relapse rate than the use of a placebo (OR = 0.40, CI: 0.29 – 0.55, P < 0.00001; 20.2% vs 37.2%). The difference in relapse rate was similar from a maintenance period of 6 months (OR = 0.41, CI: 0.35 – 0.48, P < 0.00001; 19.6% vs 37.6%) to over 1 year (OR = 0.35, CI: 0.29 – 0.41, P < 0.00001; 19.9% vs 39.8%). The all-cause drop-out of antidepressant and placebo groups was 43% and 58%, respectively, (OR = 0.47, CI: 0.40 – 0.55, P < 0.00001). The tolerability rate was ~4% for both groups. The rate of relapse (OR = 0.32, CI: 0.18 – 0.64, P = 0.0010, 41.0% vs 66.7%) and all-cause drop-out among adolescents was higher than in adults. To prevent relapse and treatment failure, maintenance therapy, and careful attention for at least 6 months after remission is recommended. SSRIs are well-balanced agents, and flexible dose adjustments are more effective for relapse prevention.

4. From Evidence to Recommendations

4.1. Summary of findings

Table 26. Summary of findings table

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
GRADE Table 1A Pharmacotherapy (**Selective Serotonin Reuptake Inhibitors)** compared to pill placebo in children and adolescents with emotional disorders	Dobson, 2019; Hetrick, 2021	Mental health symptoms	Anxiety symptom improvement	7	OR **5.2** [Crl: 2.2 - 8.8]	⊕◯◯◯ VERY LOW
			Depressive symptom improvement	21	MD **-2.30** (CDRS-R) [CI : -3.20 to -1.39]	⊕◯◯◯ VERY LOW
			Treatment response (anxiety)	7	OR **4.6** [3.1 to 7.5] Log OR **1.5** [Crl: 1.1 - 2.0]	⊕⊕⊕◯ MODERATE
		Adverse effects	All cause discontinuation	7	Log OR **-0.2** [Crl:-0.7 to 0.3]	⊕⊕⊕◯ MODERATE
			Discontinuation due to adverse effects	7	Log OR **-1.8** [Crl: -3.4 to -0.4]	⊕⊕⊕◯ MODERATE
			Suicidality	7	Log OR **1.0** [Crl: -2.2 to 4.7]	⊕⊕◯◯ LOW
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
GRADE Table 1B Pharmacotherapy (**Fluoxetine)** compared to pill placebo in children and adolescents with emotional disorders	Zhou, 2020; Hetrick, 2021	Mental health symptoms	Depressive symptoms	NR	SMD **-0.51** [CrI: -0.84 to -0.18]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **0.78** [CrI: 0.56 - 1.15]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **1.11** [CrI: 0.74 - 1.75]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	Improvement in functioning	NR	MD **1.92** (CGAS) [CI: 1.64 - 2.20]	⊕◯◯◯ VERY LOW
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	Remission/response	NR	OR **1.33** [CI: 0.85 - 2.07]	⊕◯◯◯ VERY LOW
		User and family satisfaction	-	-	-	N/A
GRADE Table 1C Pharmacotherapy (**Fluoxetine)** compared to treatment as usual in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	**SMD -0.79** [CrI: -1.59 to 0.02]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **0.53** [CrI: 0.15 - 1.33]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **616.7** [CrI: 0.03 - 2314]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A
GRADE Table 1D Pharmacotherapy **(Citalopram)** compared to pill placebo in children and adolescents with emotional disorders	Zhou, 2020; Hetrick, 2021	Mental health symptoms	Depressive symptoms	NR	SMD **0.33** [CrI: -0.83 to 1.48]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.75** [CrI: 0.66 - 6.57]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **1.18** [CrI: 0.35 - 6.85]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	Improvement in functioning	NR	MD **2.50** (CGAS scale) [CI : -1.52 to 6.52]	⊕◯◯◯ VERY LOW
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	Remission/response	NR	OR **1.21** [CI: 0.73 - 2.02]	⊕◯◯◯ VERY LOW
		User and family satisfaction	-	-	-	N/A
GRADE Table 1E Pharmacotherapy **(Citalopram)** compared to treatment as usual in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	**SMD 0.05** [CrI: -1.35 to 1.45]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.63** [CrI: 0.23 - 5.53]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **1154** [CrI: 0.04 - 3572]	⊕◯◯◯ VERY LOW

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A
GRADE Table 1F Pharmacotherapy **(Escitalopram)** compared to pill placebo in children and adolescents with emotional disorders	Zhou, 2020; Hetrick, 2021	Mental health symptoms	Depressive symptoms	NR	SMD **-0.17** [CrI: -0.88 to 0.54]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.40** [CrI: 0.77 - 2.86]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **0.94** [CrI: 0.44 - 2.55]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	Improvement in functioning	NR	MD **2.28** (CGAS scale) [CI : 0.23 - 4.32]	⊕◯◯◯ VERY LOW
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	Remission/response	NR	OR **1.33** [CI: 0.85 - 2.07]	⊕◯◯◯ VERY LOW
		User and family satisfaction	-	-	-	N/A
GRADE Table 1G Pharmacotherapy **(Escitalopram)** compared to treatment as usual in children and adolescents	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	**SMD -0.45** [CrI: -1.50 to 0.62]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.04** [CrI: 0.23 - 2.96]	⊕◯◯◯ VERY LOW

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
with emotional disorders			Suicidality	NR	OR **680.9** [CrI: 0.03 - 2227]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A
GRADE Table 1H Pharmacotherapy **(Paroxetine)** compared to pill placebo in children and adolescents with emotional disorders	Zhou, 2020; Hetrick, 2021	Mental health symptoms	Depressive symptoms	NR	SMD **-0.16** [CrI: -0.67 to 0.35]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.3** [CrI: 0.81 - 2.27]	⊕⊕◯◯ LOW
			Suicidality	NR	OR **1.71** [CrI: 0.81 - 5.05]	⊕⊕◯◯ LOW
		Improved Quality of life and Functioning	Improvement in functioning	NR	MD **1.60** (CGAS scale) [CI : -2.48 to 5.68]	⊕◯◯◯ VERY LOW
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	Remission/response	NR	OR **1.05** [CI: 0.1 - 1.55]	⊕◯◯◯ VERY LOW
		User and family satisfaction	-	-	-	N/A

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
GRADE Table 1I Pharmacotherapy **(Paroxetine)** compared to treatment as usual in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	**SMD -0.44** [CrI: -1.36 to 0.51	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **0.93** [CrI: 0.22 - 2.49]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **1430** [CrI: 0.06 - 3919]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A
GRADE Table 1J Pharmacotherapy **(Sertraline)** compared to pill placebo in children and adolescents with emotional disorders	Zhou, 2020; Hetrick, 2021	Mental health symptoms	Depressive symptoms	NR	SMD **0.11** [CrI: -0.49 to 0.71]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **0.62** [CrI: 0.31 - 1.12]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **0.45** [CrI: 0.08 - 1.33]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	Improvement in functioning	NR	MD **1.31** (CGAS scale) [CI : -1.61 to 4.23]	⊕◯◯◯ VERY LOW
		Reduction in Risky behaviours	-	-	-	N/A

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
		Remission	Remission/response	NR	OR **1.55** [CI: 0.86 - 2.80]	⊕◯◯◯ VERY LOW
		User and family satisfaction	-	-	-	N/A
GRADE Table 1K Pharmacotherapy **(Sertraline)** compared to treatment as usual in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	SMD **-0.39** [Crl: -1.17 to 0.39]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.16** [Crl: 0.30 - 3.03]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **1650** [Crl: 0.10 - 6481]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A
GRADE Table 2A Pharmacotherapy (**Tricyclic Antidepressants)** compared to pill placebo in children and adolescents with emotional disorders	Dobson, 2019	Mental health symptoms	Anxiety symptom improvement	2	OR **1.4** [Crl :-5.2 to 7.9]	⊕◯◯◯ VERY LOW
			Treatment response (anxiety)	4	OR **2.0** [0.8 to 4.9] Log OR **0.7** [Crl: -0.2 to 1.6]	⊕⊕◯◯ LOW
		Adverse effects	All cause discontinuation	NR	Log OR **0.6** [Crl: -0.6 to 1.7]	⊕⊕◯◯ LOW
			Discontinuation due to adverse effects	NR	Log OR **-0.8** [Crl: -5.0 to 3.3]	⊕⊕◯◯ LOW

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
			Suicidality	NR	Log OR **25.1** [Crl: 4.5 - 57.4]	⊕◯◯◯ VERY LOW
		Improved quality of life and functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A
GRADE Table 2B Pharmacotherapy **(Imipramine)** compared to pill placebo in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	SMD **-0.03** [Crl :-0.75 to 0.68]	⊕⊕◯◯ LOW
		Adverse effects	All cause discontinuation	NR	OR **2.51** [Crl: 1.26 - 6.24]	⊕⊕⊕⊕ HIGH
			Suicidality	NR	OR **0.59** [Crl: 0.19 - 3.07]	⊕⊕◯◯ LOW
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
GRADE Table 2C Pharmacotherapy **(Imipramine)** compared to treatment as usual in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	**SMD -0.31** [CrI: -1.38 to 0.76]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.97** [CrI: 0.40 - 5.95]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **490.8** [CrI: 0.02 - 1979]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
GRADE Table 2D Pharmacotherapy **(Desipramine)** compared to pill placebo in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	SMD **-0.43** [CrI: -1.26 to 0.39]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **2.21** [CrI: 0.88 - 7.67]	⊕◯◯◯ VERY LOW
			Suicidality	-	-	N/A
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
GRADE Table 2E Pharmacotherapy **(Desipramine)** compared to treatment as usual in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	**SMD -0.71** [CrI: -1.85 to 0.43]	⨁◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.99** [CrI: 0.31 - 6.84]	⨁◯◯◯ VERY LOW
			Suicidality	-	-	N/A
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
GRADE Table 2F Pharmacotherapy **(Amitriptyline)** compared to pill placebo in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	SMD **0.08** [CrI: -1.11 to 1.27]	⨁◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.16** [CrI: 0.29 - 12.13]	⨁◯◯◯ VERY LOW
			Suicidality	-	-	N/A
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
GRADE Table 2G Pharmacotherapy **(Amitriptyline)** compared to treatment as usual in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	**SMD -0.20** [CrI: -1.63 to 1.24]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.93** [CrI: 0.12 - 9.39]	⊕◯◯◯ VERY LOW
			Suicidality	-	-	N/A
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
GRADE Table 2H Pharmacotherapy **(Clomipramine)** compared to pill placebo in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	SMD **0.33** [CrI: -0.83 to 1.48]	⊕⊕◯◯ LOW
		Adverse effects	All cause discontinuation	NR	OR **1.75** [CrI: 0.66 - 6.57]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **1.18** [CrI: 0.35 - 6.85]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
GRADE Table 2I Pharmacotherapy **(Clomipramine)** compared to treatment as usual in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	**SMD 0.05** [CrI: -1.35 to 1.45]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **1.63** [CrI: 0.23 - 5.53]	⊕◯◯◯ VERY LOW
			Suicidality	NR	OR **1154** [CrI: 0.04 - 3572]	⊕◯◯◯ VERY LOW
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
GRADE Table 2J Pharmacotherapy **(Nortriptyline)** compared to pill placebo in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	SMD **1.14** [CrI: 0.46 - 1.81]	⊕⊕◯◯ LOW
		Adverse effects	All cause discontinuation	NR	OR **0.76** [CrI: 0.28 -3.41]	⊕◯◯◯ VERY LOW
			Suicidality	-	-	N/A
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
		User and family satisfaction	-	-	-	N/A

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
GRADE Table 2K Pharmacotherapy **(Nortriptyline)** compared to treatment as usual in children and adolescents with emotional disorders	Zhou, 2020	Mental health symptoms	Depressive symptoms	NR	**SMD 0.86** [Crl: -0.15 to 1.89]	⨁◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	OR **0.75** [Crl: 0.10 - 2.64]	⨁◯◯◯ VERY LOW
			Suicidality	-	-	N/A
		Improved Quality of life and Functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A
GRADE Table 3 Pharmacotherapy **(Benzodiazepines)** compared to pill placebo in children and adolescents with emotional disorders	Dobson, 2019	Mental health symptoms and disorders	Anxiety symptom improvement	1	OR **-0.4** [Crl: -9.7 to 9.1]	⨁◯◯◯ VERY LOW
			Treatment response (anxiety)	2	OR **1.4** [Crl: 0.36 - 6.1] Log OR **0.33** [Crl: -1.2 to 1.8]	⨁◯◯◯ VERY LOW
		Adverse effects	All cause discontinuation	NR	Log OR **0.3** [Crl: -1.3 to 2.1]	⨁◯◯◯ VERY LOW
			Discontinuation due to adverse effects	NR	Log OR **-21.6** [Crl: -76.8 to -1.3]	⨁◯◯◯ VERY LOW
			Suicidality	NR	Log OR **11.9** [Crl: -0.7 to 39.3]	⨁◯◯◯ VERY LOW
		Improved quality of life and functioning	-	-	-	N/A
		Reduction in Risky behaviours	-	-	-	N/A
		Remission	-	-	-	N/A

GRADE table	Source	Outcome	Specific outcome	RCTs	Effects	Certainty of the evidence
		User and family satisfaction	-	-	-	N/A

4.2. Evidence to decision

Table 27. Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a recognized priority (such as based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]	☐ No ☐ Probably no ☐ Probably yes ☒ **Yes** ☐ Varies ☐ Don't know	• During 2020, it was estimated that 1 in 4 youth experienced clinically elevated symptoms of depression, and 1 in 5 youth experienced clinical symptoms of anxiety (Racine et al., 2021). Severe manifestations of these disorders might require the prescription of psychiatric medications (National Collaborating Centre for Mental Health, 2013; National Institute for Health and Care Excellence, 2019). • Previous meta-analyses examining the effects of antidepressants in youth with depression and anxiety have found inconclusive results, with some studies suggesting an increased risk of suicidality after the start of some antidepressant clusters such as SSRI's (Cipriani et al., 2016; Vitiello & Davico, 2018; Locher et al., 2018; Zhou et al., 2020).	
Desirable Effects	How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.			
	• Judgements for each outcome for which there is a desirable effect • How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ **Varies** ☐ Don't know	**<u>Anxiety symptoms (patients with pediatric anxiety)</u>** • As a group, **SSRIs** were significantly more effective than pill placebo in improving anxiety symptoms • There was no significant difference between both all **TCAs** pooled and **Benzodiazepines** compared to pill placebo in improving anxiety symptoms • While there was a significantly higher treatment response for the pooled **SSRIs** compared to pill placebo,	Additional considerations from Zhou et al. 2020: "Nortriptyline was worse than most active interventions; however, the interpretation of this result was limited by the inconsistent loop of nortriptyline versus

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			there were no significant differences between pooled **TCAs** and **benzodiazepines** compared to pill placebo **<u>Depression symptoms (patients with pediatric depression)</u>** • All **SSRIs** pooled together showed a significant improvement in depressive symptomatology, compared to pill placebo • Fluoxetine (SSRI) was significantly better than pill placebo in improving depressive symptoms. There was no evidence for significant superiority of any of the other antidepressants compared to pill placebo. • Pill placebo was significantly better than Nortriptyline (TCA) in improving depressive symptoms. • None of the antidepressants were significantly better than TAU in improving depressive symptoms.	fluoxetine versus pill placebo."
Undesirable Effects	How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.			
	• Judgements for each outcome for which there is an undesirable effect • How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☐ Trivial ☒ **Varies** ☐ Don't know	**<u>Adverse effects</u>** • There were significantly more all-cause discontinuations in Imipramine (TCA) compared to pill placebo • Group SSRIs and Benzodiazepines had significantly more discontinuations due to adverse effects than pill placebo. There was no significant difference between group TCAs and pill placebo in discontinuations due to adverse effects. • In patients with pediatric anxiety (Dobson et al., 2019), group TCAs were significantly associated with more suicidal behaviours and ideation compared to pill placebo. There was no evidence for a significant difference in suicidality between benzodiazepines and pill placebo. • In patients with pediatric depression (Zhou et al., 2020), there was no evidence of a difference between other antidepressants and control conditions (i.e. TAU and pill placebo) in suicidal behaviours and thoughts.	Additional evidence from Dobson et al. 2019 – pediatric anxiety: **Paroxetine** (SSRI): Treatment-emergent suicidality was significantly **<u>greater</u>** in paroxetine-treated patients compared to those receiving placebo. **Sertraline** (SSRI): Treatment-emergent suicidality was significantly **<u>lower</u>** in paroxetine-treated patients compared to those receiving placebo. **Venlafaxine** (SNRI): not examined in this clinical guideline, but was linked with an **increased** risk of

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				suicide behaviour (Zhou et al., 2020): "Our evidence linked venlafaxine alone to an increased effect on suicidal behaviour or ideation, which might be due to better reporting of venlafaxine data. Owing to the absence of reliable data on suicidality for many antidepressants, comprehensive assessment of the risk of suicidality for all interventions was not possible. Prescribers should closely monitor suicide risk when children and adolescents take any antidepressant drugs, particularly at the beginning of treatment"
Certainty of evidence	What is the overall certainty of the evidence of effects? The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).			
	• What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision? • See GRADE guidance regarding detailed judgements about the quality of evidence or certainty in estimates of effects	☐ Very low ☒ **Low** ☐ Moderate ☐ High ☐ No included studies	• Most of the outcomes were rated as very low and low certainty across all GRADE tables. • The certainty of the evidence is moderate for the effects of SSRI on treatment response (anxiety), all cause discontinuation, and discontinuation due to adverse effects. • The certainty of the evidence was rated as high for the outcome involving an increased rate of all-cause discontinuations for Imipramine (compared to pill placebo).	

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Values	Is there important uncertainty about or variability in how much people value the main outcomes? The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called "utility values".			
	• Is there important uncertainty about how much people value each of the main outcomes? • Is there important variability in how much people value each of the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ **Probably no important uncertainty or variability** ☐ No important uncertainty or variability	• There was no direct evidence to evaluate values and preferences of people. • A qualitative systematic review (Gronholm et al., 2023) was conducted to assess values, resources, cost effectiveness, health equity quality and non-discrimination, feasibility and human rights related factors in mental health care and mental health services. • Overall, the studies reviewed highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and well-being. The utility value could be limited by certain factors and barriers present in the health systems. For instance, low awareness, poor funding and poor political buy-in, or other social barriers. Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e. the relative value they attach to the desirable and undesirable outcomes) the more likely it is that an option should be recommended.			
	• Judgements regarding each of the four preceding criteria • To what extent do the following considerations influence the balance between the desirable and undesirable effects: - How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates)?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☐ Probably favours the intervention	• Overall, SSRIs pooled together were more effective in reducing anxiety and depressive symptoms than pill placebo. Fluoxetine was the only individual antidepressant that proved superiority over placebo. There is no evidence indicating that any SSRI is superior to treatment as usual, and there is evidence indicating that SSRIs show significantly higher adverse effects than pill placebo (discontinuation due to adverse effects). There is evidence indicating that paroxetine could be	Additional evidence from Dobson et al. 2019 – pediatric anxiety: **Paroxetine** (SSRI): Treatment-emergent suicidality was significantly **greater** in paroxetine-treated patients compared to those receiving placebo.

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	- People's attitudes towards undesirable effects (how risk averse they are)? - People's attitudes towards desirable effects (how risk seeking they are)?	☐ Favours the intervention ☒ **Varies** ☐ Don't know	associated with a significantly higher suicidality than placebo in patients with pediatric anxiety, while sertraline is associated with a reduction of suicidality in these patients. • There is no evidence indicating that **TCAs** are superior to pill placebo. Administering Nortriptyline (TCA) could be worse than administering pill placebo. Evidence indicates that TCAs could be potentially harmful, since these antidepressants were significantly associated with more suicidal behaviours and ideation compared to pill placebo • There is no evidence indicating that **Benzodiazepines** are superior to pill placebo, while benzodiazepines show significantly higher adverse effects than pill placebo (discontinuation due to adverse effects). There was no evidence for a significant difference in suicidality between benzodiazepines and pill placebo.	**Sertraline** (SSRI): Treatment-emergent suicidality was significantly **lower** in paroxetine-treated patients compared to those receiving placebo.
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which fewer resources are required? • How large is the difference in each item of resource use for which more resources are required? • How large an investment of resources would the option require or save?	☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Don't know**	There was no direct evidence to evaluate resource requirements.	

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?			
	• Have all-important items of resource use that may differ between the options being considered been identified? • How certain is the evidence of differences in resource use between the options being considered (see GRADE guidance regarding detailed judgements about the quality of evidence or certainty in estimates)? • How certain is the cost of the items of resource use that differ between the options being considered? • Is there important variability in the cost of the items of resource use that differ between the options being considered?	☐ Very low ☐ Low ☐ Moderate ☐ High ☒ **No included studies**	There was no direct evidence to evaluate resource requirements.	
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? The greater the cost per unit of benefit, the less likely it is that an option should be a priority.			
	• Judgements regarding each of the six preceding criteria • Is the cost effectiveness ratio sensitive to one-way sensitivity analyses? • Is the cost effectiveness ratio sensitive to multivariable sensitivity analysis? • Is the economic evaluation on which the cost effectiveness estimate is based reliable? • Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☐ Probably favours the intervention ☐ Favours the intervention ☐ Varies ☒ **No included studies**	No reviews examining cost effectiveness identified	

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? (WHO INTEGRATE) Health equity and equality reflect a concerted and sustained effort to improve health for individuals across all populations, and to reduce avoidable systematic differences in how health and its determinants are distributed. Equality is linked to the legal principle of non-discrimination, which is designed to ensure that individuals or population groups do not experience discrimination on the basis of their sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other characteristics. All recommendations should be in accordance with universal human rights standards and principles. The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favour of this intervention.			
	• How are the condition and its determinants distributed across different population groups? Is the intervention likely to reduce or increase existing health inequalities and/or health inequities? Does the intervention prioritize and/or aid those furthest behind? • How are the benefits and harms of the intervention distributed across the population? Who carries the burden (e.g. all), who benefits (e.g. a very small sub-group)? • How affordable is the intervention for individuals, workplaces or communities? • How accessible - in terms of physical as well as informational access - is the intervention across different population groups? • Is there any suitable alternative to addressing the condition, does the intervention represent the only available option? Is this option proportionate to the need, and will it be subject to periodic review?	☐ Reduced ☐ Probably reduced ☐ Probably no impact ☒ **Probably increased** ☐ Increased ☐ Varies ☐ Don't know	There was no direct evidence to evaluate health equity, equality and non-discrimination. The qualitative review (Gronholm et al., 2023) noted considerations for ensuring MNS interventions are equitable, equally available and non-discriminatory: • Accessibility, physical/practical considerations • time & travel constraints. • Accessibility, informational barriers • Affordability - medication and treatment costs These factors may be exacerbated for: • People with low education/literacy (e.g. written instructions, psychoeducation materials) • Low resource settings - affordability/cost considerations exacerbated.	

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e. the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies** ☐ Don't know	There was no direct evidence to evaluate feasibility. The qualitative review (Gronholm et al., 2023) also considered feasibility, and how this can be enhanced in the following areas: • Acceptability of interventions for stakeholders - requires increased engagement with specialist staff, increased visibility of the task-sharing workforce within health facilities, perception of usefulness by providers and service users (e.g. via positive feedback), context-specific interventions, standardized implementation steps for simpler decision-making and delivery • Health worker workload, competency - requires training, refreshers, supervision; networking with others in same role. • Availability of a task-sharing workforce; • Availability of caregivers; • Participant education and literacy requires verbal explanations/tasks; • Logistical issues - such as e.g. mobile populations, affordability of travel to receive care, lack of private space; • Limited resources/mental health budget. Sustainability considerations identified were: • Training and supervision; • Integrating into routine clinical practice.	

CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? (WHO INTEGRATE) This criterion encompasses two distinct constructs: The first refers to an intervention's compliance with universal human rights standards and other considerations laid out in international human rights law beyond the right to health (as the right to health provides the basis of other criteria and sub-criteria in this framework). The second, sociocultural acceptability, is highly time-specific and context-specific and reflects the extent to which those implementing or benefiting from an intervention as well as other relevant stakeholder groups consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favour of this intervention.			
• Is the intervention in accordance with universal human rights standards and principles? • Is the intervention socioculturally acceptable to patients/beneficiaries as well as to those implementing it? To which extent do patients/beneficiaries value different non-health outcomes? • Is the intervention socioculturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other relevant characteristics? • How does the intervention affect an individual's, population group's or organization's autonomy, i.e. their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies** ☐ Don't know	There was no direct evidence to evaluate alignment with human rights principle and sociocultural acceptability. Treatment discontinuation (due to all causes) has been used as proxy for feasibility of antidepressants in children (Zhou et al. 2020). Nefazodone and fluoxetine were associated with fewer drop-outs than sertraline, imipramine, and desipramine (ORs ranged from 0·17 to 0·50); imipramine was associated with more drop-outs than pill placebo, desvenlafaxine, fluoxetine plus CBT, and vilazodone (2·51 to 5·06). Most of the results were rated as "low" to "very low" in terms of confidence of evidence according to Confidence In Network Meta-Analysis. The qualitative review (Gronholm et al., 2023) noted several considerations which would impact the right to health and access to health care. (e.g. stigma and discrimination and lack of confidentiality could affect the help-seeking among service users). • The importance of sociocultural acceptability of MNS interventions was clearly expressed. Pre-intervention considerations that consider cultural and social aspects improve the acceptability of implemented interventions. • When interventions were perceived as appropriate for the culture and target group, the content and medium of the intervention received more positive feedback from service users and caregivers Also, considerations of age, sex and language have been highlighted as important to acceptability and accessibility.	

CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
the privacy and dignity of concerned stakeholders justified?			

4.3. Summary of judgements

Table 28. Summary of judgements

Priority of the problem	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ **Yes**
Desirable effects*	- Don't know	✓ **Varies**		- Trivial	- Small	- Moderate	- Large
Undesirable effects*	- Don't know	✓ **Varies**		- Large	- Moderate	- Small	- Trivial
Certainty of the evidence*	- No included studies			- Very low	✓ **Low**	- Moderate	- High
Values				- Important uncertainty or variability	- Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	- No important uncertainty or variability
Balance of effects*	- Don't know	✓ **Varies**	- Favours no comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours intervention
Resources required	✓ **Don't know**	- Varies	- Large costs	- Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of the evidence on required resources	✓ **No included studies**			- Very low	- Low	- Moderate	- High
Cost–effectiveness	✓ **No included studies**	- Varies	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours intervention
Equity, equality and non-discrimination	- Don't know	- Varies	- Reduced	Probably reduced	- Probably no impact	✓ **Probably increased**	- Increased
Feasibility	- Don't know	✓ **Varies**		- No	- Probably No	- Probably Yes	- Yes
Human rights and sociocultural acceptability	- Don't know	✓ **Varies**		- No	- Probably No	- Probably Yes	- Yes

✓Indicates category selected, -Indicates category not selected
*Note: Separate ratings provided for pediatric anxiety and pediatric depression for these aspects.

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Appendix I: Search terms used to identify systematic reviews

PubMed

1# Depression
"Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR “depress*”[tiab] OR “dysthymi*”[tiab] OR “mood disorder*”[tiab] OR “affective disorder*”[tiab] OR “dysphoric disorder*”[tiab]

2#Anxiety
“Anxiety disorders” [Mesh] OR "Anxiety"[Mesh] OR "Fear"[Mesh] OR "shyness"[MeSH Terms] OR shyness[tiab] OR shy[tiab] OR “anxiet*”[tiab] OR “agoraphobi*”[tiab] OR “panic”[tiab] OR “social phobi*”[tiab] OR “phobi*”[tiab] OR “obsessive-compulsive”[tiab] OR “neurotic disorder*”[tiab] OR “hoarding*”[tiab] OR “OCD”[tiab] OR “neurotic anxiet*”[tiab] OR “anxious*”[tiab] OR “emotional disorder*”[tiab] OR fear[tiab] OR worry[tiab] OR worrying[tiab] OR worries[tiab] OR GAD[tiab] OR Arachnophobia[tiab] OR Ophidiophobia[tiab] OR Acrophobia[tiab] OR Cynophobia[tiab] OR Claustrophobia[tiab] OR Mysophobia[tiab] OR Aerophobia[tiab] OR Trypophobia[tiab] OR Carcinophobia[tiab] OR Thanatophobia[tiab] OR Glossophobia[tiab] OR Monophobia[tiab] OR Ornithophobia[tiab] OR Alektorophobia[tiab] OR Trypanophobia[tiab] OR Anthropophobia[tiab] OR Aquaphobia[tiab] OR Autophobia[tiab] OR Hemophobia[tiab] OR Xenophobia[tiab] OR Ailurophobia[tiab] OR Nyctophobia[tiab] OR Phobophobia[tiab] OR Philophobia[tiab] OR Triskaidekaphobia[tiab] OR Emetophobia[tiab] OR Entomophobia[tiab] OR Zoophobia[tiab] OR Scelerophobia[tiab] OR Cibophobia[tiab] OR Tokophobia[tiab] OR Pseudodysphagia[tiab] OR Gerascophobia[tiab] OR Technophobia[tiab] OR Ergophobia[tiab] OR Coulrophobia [tiab] OR Photophobia[tiab] OR Numerophobia[tiab] OR Taphophobia [tiab]

3# Children + Adolescents
“Child”[Mesh] OR “Adolescent” [Mesh] OR “Young Adult”[Mesh] OR child[tiab] OR children [tiab] OR childhood [tiab] OR teen [tiab] OR teens [tiab] OR teenager* [tiab] OR adolescen*[tiab] OR “young person*”[tiab] OR youth*[tiab] OR boy[tiab] OR boys[tiab] OR girl[tiab] OR girls[tiab] OR “young adult*”[tiab] OR juvenile*[tiab] OR “young people*”[tiab] OR youngsters [tiab] OR student*[tiab] OR college[tiab] OR schoolchild*[tiab] OR preadolescen*[tiab] OR “junior high*”[tiab] OR highschool*[tiab] OR “senior high”[tiab] OR minors[tiab] OR boyhood[tiab] OR girlhood[tiab] OR prepubert*[tiab] OR minors[tiab] OR pediatric[tiab] OR paediatric[tiab] OR puberty[tiab] OR preschool*[tiab] OR kid[tiab] OR kids[tiab]

4# Antidepressants + benzodiazepines
"Antidepressive Agents"[Mesh:NoExp] OR "Serotonin Uptake Inhibitors"[Mesh] OR "Antidepressive Agents, Tricyclic" [Mesh] OR "Fluoxetine"[Mesh] OR "Citalopram"[Mesh] OR "Sertraline"[Mesh] OR "Nortriptyline"[Mesh] OR "Antidepressive Agents" [Pharmacological Action] OR "Serotonin Uptake Inhibitors" [Pharmacological Action] OR "Antidepressive Agents, Tricyclic" [Pharmacological Action] OR "antidepressiv*"[tiab] OR "anti-depressiv*"[tiab] OR antidepressant*[tiab] OR "anti-depressant*"[tiab] OR thymoleptic*[tiab] OR thymoanaleptic*[tiab] OR "Serotonin Reuptake Inhibitor*"[tiab] OR "Serotonin Re-uptake Inhibitor*"[tiab] OR "Serotonin uptake Inhibitor*"[tiab] OR “serotonin specific reuptake inhibitor*”[tiab] OR “serotonin specific re-uptake inhibitor*”[tiab] OR SSRI*[tiab] OR TCA[tiab] OR TCAs[tiab] OR alaproclate [tiab] OR Citalopram [tiab] OR Celexa [tiab] OR Cipramil [tiab] OR Escitalopram [tiab] OR Lexapro [tiab] OR Cipralex [tiab] OR Fluoxetine [tiab] OR Prozac [tiab] OR Sarafem [tiab] OR Fluvoxamine [tiab] OR Luvox [tiab] OR Faverin [tiab] OR Paroxetine [tiab] OR Paxil [tiab] OR Seroxat [tiab] OR Sertraline [tiab] OR Zoloft [tiab] OR Lustral [tiab] OR Vilazodone [tiab] OR Viibryd [tiab] OR femoxetine [tiab] OR indalpine [tiab] OR Zimeldine [tiab] OR Amitriptyline [tiab] OR Elavil [tiab] OR Endep [tiab] OR Amitriptylinoxide [tiab] OR Amioxid [tiab] OR Ambivalon [tiab] OR Equilibrin [tiab] OR Clomipramine [tiab] OR Anafranil [tiab] OR Desipramine [tiab] OR Norpramin [tiab] OR Pertofrane [tiab] OR Dibenzepin [tiab] OR Noveril [tiab] OR Victoril [tiab] OR Dimetacrine [tiab] OR Istonil [tiab] OR Dosulepin [tiab] OR Prothiaden [tiab] OR Doxepin [tiab] OR Adapin [tiab] OR Sinequan [tiab] OR Imipramine [tiab] OR Tofranil [tiab] OR Lofepramine

[tiab] OR Lomont [tiab] OR Gamanil [tiab] OR Melitracen [tiab] OR Dixeran [tiab] OR Melixeran [tiab] OR Trausabun [tiab] OR Nitroxazepine [tiab] OR Sintamil [tiab] OR Nortriptyline [tiab] OR Pamelor [tiab] OR Aventyl [tiab] OR Noxiptiline [tiab] OR Agedal [tiab] OR Elronon [tiab] OR Nogedal [tiab] OR Opipramol [tiab] OR Insidon [tiab] OR Pipofezine [tiab] OR Azafen [tiab] OR Azaphen [tiab] OR Protriptyline [tiab] OR Vivactil [tiab] OR Trimipramine [tiab] OR Surmontil [tiab] OR Amoxapine [tiab] OR Asendin [tiab] OR cericlamine [tiab] OR dapoxetine [tiab] OR ifoxetine [tiab] OR litoxetine [tiab] OR lubazodone [tiab] OR moxifetin [tiab] OR nomelidine [tiab] OR norcitalopram [tiab] OR norfluoxetine [tiab] OR seproxetine [tiab] OR norsertraline [tiab] OR omiloxetine [tiab]

5# SR + MA filter

("Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR metaanaly*[tiab] OR meta-analy*[tiab] or metanaly*[tiab] OR "Systematic Review" [Publication Type] OR systematic[sb] OR meta-analysis[Filter] OR systematicreview[Filter] OR "Cochrane Database Syst Rev"[Journal] or prisma[tiab] OR “preferred reporting items”[tiab] OR prospero[tiab] OR ((systemati*[ti] OR umbrella[ti] OR “structured literature”[ti]) AND (review[ti] OR overview[ti])) OR “systematic review”[tiab] OR “umbrella review”[tiab] OR “structured literature review”[tiab] OR “systematic qualitative review”[tiab] OR “systematic quantitative review”[tiab] OR “systematic search and review”[tiab] OR “systematized review”[tiab] OR “systematised review”[tiab] OR “systemic review”[tiab] OR “systematic literature review”[tiab] OR “systematic integrative literature review”[tiab] OR “systematically review”[tiab] OR “scoping literature review”[tiab] OR “scoping review”[tiab] OR “systematic critical review”[tiab] OR “systematic integrative review”[tiab] OR “systematic evidence review”[tiab] OR “systematic integrative literature review”[tiab] OR “systematic mixed studies review”[tiab] OR “systematized literature review”[tiab] OR “systematic overview”[tiab] OR “Systematic narrative review”[tiab] OR “narrative review”[tiab] OR metasynthes*[tiab] OR meta-synthes*[tiab]) NOT ("Comment" [Publication Type] OR "Letter" [Publication Type] OR "Editorial" [Publication Type] OR (("Animals"[Mesh] OR "Models, Animal"[Mesh]) NOT "Humans"[Mesh]))

 # Timeframe

2019-2022

Appendix II: Decision Tree used to evaluate ROB GRADE item

Fig. 2. Developed tree for the assessment of the risk of bias item in GRADE

- No data available for risk of bias → serious

- When vast majority (> 60%) of trials are low risk → not serious
- When low risk is between 50-60%:
  - High risk < 25% → not serious
  - High risk > 25% → serious

- When vast majority (> 60%) is high risk → very serious
- When high risk is between 50-60%:
  - Low risk < 25% → very serious
  - Low risk > 25% → serious

- When vast majority is unclear risk (> 60%) → serious
- When unclear risk is between 50-60%:
  - High risk < 25% → not serious
  - High risk > 25% → serious

- If unclear/high/low risk are all < 50%:
  - High risk < 25% → not serious
  - High risk > 25% → serious