Effectiveness of interventions for anxiety and depression in children: an umbrella review of meta-analyses

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Summary

Background
Anxiety and depression are the most common mental health conditions for children and young people (CYP). However, recommendations for treatment approaches vary. We aimed to identify the most effective interventions for treating CYP with anxiety and depression through an umbrella synthesis of recent literature.

Methods
For this umbrella review (meta-analysis of meta-analyses) we conducted a search of five electronic databases (PubMed, Medline, PsycInfo, Web of Science, ASSIA) from 1 October 2017 to 1 October 2022. Eligible meta-analyses reported on interventions for CYP (≤18 years) with anxiety or depression and/or associated symptoms; prevention or risk studies were excluded. Summary data were manually extracted, and standardized effect sizes (Cohen's d) were compared across interventions at different levels of specificity.

Findings
We identified 42 meta-analyses (520 effect sizes); of these, 37 meta-analyses (378 effects) were included in statistical analyses. For anxiety, psychosocial ($d = -0.52$, 95% confidence interval (CI) [-0.57, -0.47], $p < 0.001$) and pharmacological interventions ($d = -0.60$, 95% CI [-0.75, -0.45], $p < 0.001$) were equally effective ($t(17.00) = -1.58$, $p = 0.133$). For depression, physical ($d = -0.50$, CI [-0.61, -0.39], $p < 0.001$) and psychosocial ($d = -0.35$, CI [-0.39, -0.32], $p < 0.001$) interventions were most effective, followed by pharmacological ($d = -0.17$, CI [-0.20, -0.15], $p < 0.001$), ($F(2, 32.3) = 41.0$, $p < 0.001$). Most interventions were more effective at treating CYP with anxiety than depression, including psychosocial (MD = -0.17, CI [-0.24, -0.09], $t(295.29) = -4.29$, $p < 0.001$) and pharmacological interventions (MD = -0.66, CI [-1.04, -0.28], $t(16.23) = -3.65$, $p = 0.002$).

Interpretation
In addition to psychosocial therapies, pharmacological interventions could be a first-line treatment for CYP with anxiety. The effectiveness of physical interventions for depression is a significant emerging finding, as is the comparatively limited effectiveness of pharmacological treatments; both should be reflected in practice guidelines. Future research should focus on understanding, developing, and providing more effective interventions for CYP with depression.

Introduction

Anxiety and depression are the most common mental health conditions among children and young people (CYP).[1] A recent meta-analysis of over 80,000 CYP found clinically-significant anxiety in one in five and depression in one in four,[2] with similar rates reported elsewhere.[3–5]

Untreated anxiety and depression in CYP are associated with negative long-term outcomes.[6–8] Cognitive behavioral therapy (CBT) and second-generation antidepressants (including selective serotonin reuptake inhibitors (SSRIs)) are among the most common interventions for both.[4,9–12] Treatments can be broadly categorized as psychosocial or pharmacological. Additionally, in the last two decades physical interventions (e.g., exercise therapies) have been increasingly explored for depression.[13–16]

There is discussion among policymakers, practitioners, and researchers surrounding the relative effectiveness of treatments.[17] Meta-analyses are common, but usually focus on specific treatments and can present competing findings, sustaining debate.

For CYP with anxiety disorders, one meta-analysis found CBT more effective than SSRIs,[18] while an alternative network meta-analysis found only pharmacological interventions, not CBT, were more effective than placebo.[19] Meanwhile, governments and nonprofits promote CBT as a first-line treatment for anxious CYP, but maintain ambiguity about pharmacological interventions, particularly in "severe" cases.[20,21]

Similarly for CYP with depression, several studies and meta-analyses present contradictory findings, suggesting that either CBT[22,23] or SSRIs[24–26] are the more effective long-term treatment. Public health guidance is also mixed: most British bodies suggest that SSRIs should never be a standalone first-line treatment for CYP with depression,[12,27] while some American ones endorse it as a viable first-line option.[28] Physical interventions have been increasingly studied for CYP with depression primarily at the mild to moderate level and appear effective,[29] but are rarely a recommended treatment option.

Still other meta-analyses have found no significant difference in the efficacy of psychosocial versus pharmacological interventions for anxiety or depression.[30,31]

Despite the debates surrounding treatment of youth anxiety and depression, researchers, practitioners, and policymakers agree on the importance of evidence-based interventions.[11,12,32,33] This umbrella review aims to provide a comprehensive synthesis of research on interventions for CYP with anxiety and depression to help inform policy and practice, by answering the following questions:

1. What interventions are provided for CYP with anxiety and/or depression?
2. How effective are these interventions in treating CYP's symptoms of anxiety and depression and improving remission rates?

Methods

Search strategy and selection criteria

This umbrella review (meta-analysis of meta-analyses) followed best practice guidance.[34] A search of five electronic databases (PubMed, Medline, PsycInfo, Web of Science, ASSIA), including grey literature, was conducted on 1 October 2022. The search was limited to five years (1 October 2017 to 1 October 2022) after a preliminary ten-year search indicated potential for significant overlap in studies between older and newer meta-analyses (appendix pp 2-5). The final search produced 8703 results; after manual removal of duplicates, 6255 records remained (figure 1).[35]

Meta-analytic and systematic reviews from any country were accepted provided they focused on CYP aged 18 and younger with anxiety or depression symptoms/diagnoses. Eligible mental health interventions were pharmacological, psychosocial (including family and group therapies), and physical. Only English-language publications were included due to lack of translation resources and to ensure accessibility for all screeners (appendix p 6).

Titles and abstracts were screened by the first author; 46% of publications were double-screened by additional reviewers. The prevalence-adjusted and bias-adjusted kappa (PABAK) was calculated, finding excellent agreement of 0.98.[36] 106 publications were identified at this stage and brought to full text review (figure 1).

Publications were screened by at least two researchers at full text review. When two reviewers disagreed on an inclusion decision, a third researcher reviewed the article and their decision resolved the disagreement. Forty-two articles met inclusion criteria for the umbrella review and 64 failed to meet these criteria (figure 1).

Data analysis

Characteristics and outcomes from included articles were extracted during this review stage, with all data double-coded and collated, and/or checked by the first author against the original text. Disagreements were resolved by discussion and reference to text. Data extraction of the final 42 articles resulted in 520 effect sizes (appendix p 7).

As most studies reported outcomes in Cohen's *d*, all other effect sizes were transformed to Cohen's *d* to facilitate comparison. Transformation was done on Psychometrica.[37] For effect sizes that were transformed (OR, RR) or calculated (MD), standard error was calculated manually from provided confidence intervals. For results originally reported in SMD, Cohen's *d*, or Hedge's *g*, standard error was calculated using R. All subsequent analyses were conducted using R (appendix pp 8-9).

Two reviewers independently assessed the quality of each included publication using AMSTAR 2 (appendix pp 10-12).[38] Results of homogeneity tests (I^2 or Q) for primary outcomes were also extracted and coded on a binary scale (0–large heterogeneity/sign Q or I > 50%; 1–

homogeneity/non-sign Q or I < 50%). Ratings were compared and collated by the first author, and disagreements were resolved by review of the publications.

Role of the funding source

Results

Forty-two meta-analyses with 520 effect sizes were identified (figure 1). Studies were of relatively high quality but generally did not report reasons for study design or funding sources of included studies (appendix pp 10-12). Effect sizes (ES) were based on four[14,39–43] to 188 primary studies[44] with between 127[14] and 5901 participants.[43] There were 386 effects for anxiety, 131 for depression, and three for combined outcomes. There was not enough data on pre- versus post-intervention effects to report in this review.[13,43,45] Additionally, four meta-analyses only reported effects from active treatment comparisons (e.g., individual versus group CBT),[46–49] and seven meta-analyses included some comparative effects.[19,50–55] These effects could not be combined with the majority; final outcomes are from treatment versus control conditions. Another 22 effects from four meta-analyses[30,52,56,57] could not be transformed due to lack of information and were excluded. Therefore, final results of the umbrella review were based on 37 meta-analyses and 378 effect sizes (table 1; appendix p 13).

For anxiety there were 272 effects, with ds ranging from -2.68 to 0.63 for psychosocial interventions (255 ES) and from -2.38 to -0.01 for pharmacological interventions (17 ES) (figure 2). Negative effect sizes indicate symptom reduction and/or increased remission rates compared to controls. There were no effects for physical interventions for anxiety. Conditions included unspecified anxiety disorders (208), unspecified anxious symptoms (39), social anxiety (16), unspecified depressive symptoms associated with anxiety disorders (7), and selective mutism (2).

Interventions for anxiety were categorized at three levels, by psychosocial versus pharmacological at the least granular (Level 1) and by specific intervention at the most (Level 3). Mid-level categorization (Level 2) separated CBT-based (CBT, mixed psychotherapy with CBT sessions, and family interventions, which were CBT-based) from non-CBT-based interventions (table 2).

For CYP with elevated levels of anxiety, both psychosocial (d= -0.52, 95% CI [-0.57, -0.47], p<0.001) and pharmacological (d= -0.60, 95% CI [-0.75, -0.45], p<0.001) interventions significantly improved outcomes compared to controls (Level 1). Effects of the intervention types were not significantly different (t(17.00)= -1.58, p= 0.133) (figure 3).

The following interventions (with >3 ES) showed significant improvement in anxiety outcomes compared to controls (Level 3): behavioral therapy (BT) (d= -0.83, 95% CI [-1.04, -0.62], p<0.001); bias modification (d= -0.21, 95% CI [-0.28, -0.14], p<0.001); CBT (d= -0.54, 95% CI [-0.60, -0.48], p<0.001); family interventions (d= -0.47, 95% CI [-0.66, -0.27], p<0.001); mindfulness-based interventions (MBIs) (d= -0.21, 95% CI [-0.29, -0.13], p<0.001); mixed psychotherapies including CBT (d= -0.64, 95% CI [-0.79, -0.50], p<0.001); and second-generation antidepressants (d= -0.61, 95% CI [-0.77, -0.46], p<0.001).

Levene's test indicated unequal variances (F(2,269)= 7.41, p<0.001), so a Welch's ANOVA was conducted. There was significant variation in the effects of the intervention types (F(2,33.6)= 7.45, p= 0.002), (figure 4). See Table 3 for full results.

For grouped interventions (Level 2), Levene's test again indicated unequal variances (F(2,269)= 7.41, p<0.001). A Welch's ANOVA revealed significant variation in the effects of the intervention types (F(2,33.6)= 7.45, p =0.002). Games-Howell post-hoc tests showed that CBT-based psychotherapies were significantly more effective than non-CBT-based psychotherapies (MD= -0.22, 95% CI [-0.37, -0.07], p= 0.003). Antidepressants were also significantly more effective than non-CBT-based interventions (MD= -0.48, 95% CI [-0.96, -0.01], p= 0.047). However, two effect sizes were identified as outliers (±3 standard deviations from the mean), and when removed this difference was no longer significant. No other anxiety results were substantially changed by their inclusion (table 4, figure 5).

For depression there were 106 effects, with *d*s ranging from -0.92 to 0.06 for psychosocial interventions (70 ES), -0.33 to -0.03 for pharmacological interventions (22 ES), and -0.82 to 0.05 for physical interventions (14 ES) (figure 6). Conditions included unspecified depressive symptoms (57), unspecified depressive disorders (26), major depressive disorder (22), and unspecified anxious symptoms associated with depressive disorders (1).

Interventions for depression were also categorized at three levels, with the addition of physical interventions in Level 1, the separation of second-generation from mixed antidepressants at Level 2, and various specific interventions at Level 3 (table 5).

For CYP with elevated levels of depression, psychosocial (d= -0.35, CI [-0.39, -0.32], p<0.001), pharmacological (d= -0.17, CI [-0.20, -0.15], p<0.001), and physical (d= -0.50, CI [-0.61, -0.39], p<0.001) interventions all significantly improved outcomes compared to controls (Level 1). Levene's test indicated heterogeneity of variances (F(2,103)= 4.23, p= 0.017). A Welch's ANOVA revealed a significant effect of intervention type on depression outcomes (F(2,32.3)= 41.0, p<0.001). Games-Howell post-hoc tests indicated that physical (MD= -0.35, CI [-0.50, -0.20], p<0.001) and psychosocial (MD= -0.20, CI [-0.27, -0.14], p<0.001) interventions were both associated with more symptom improvement and higher remission rates than pharmacological interventions (figure 7).

The following interventions (with >3 ES) showed significant improvement in depression outcomes compared to controls (Level 3): CBT (d= -0.28, CI [-0.33, -0.22], p<0.001); family interventions (d= -0.33, CI [-0.46, -0.20], p<0.001); interpersonal therapy (IPT) (d= -0.71, CI [-0.88, -0.54], p<0.001); mixed antidepressants (d= -0.17, CI [-0.21, -0.14], p<0.001); mixed psychotherapies including CBT (d = -0.34, CI [-0.37, -0.30], p<0.001); physical exercise (d = -0.50, CI [-0.61, -0.39], p < 0.001); and second-generation antidepressants (d = -0.18, CI [-0.22, -0.14], p<0.001). Mixed psychotherapies including CBT was the only depression outcome where a statistical outlier (±3 standard deviations from the mean) was identified, but its inclusion did not substantially change results.

At Level 3, Levene's test indicated homogeneity of variance, (F(6,95)= 1.75, p= 0.118). A one-way ANOVA revealed significant variation in the effects of the intervention types (F(6,95) = 16.24, p<0.001), (figure 8). Notably, IPT was significantly more effective than all other interventions, including physical exercise (MD= -0.21, CI [-0.41, -0.01], p= 0.037). No significant differences emerged within comparisons of other psychosocial interventions. See Table 6 for full results.

When grouped (Level 2), Levene's test indicated unequal variance $F_{(4,101)}= 3.81$, $p= .006$. A Welch's ANOVA revealed significant variation in the effects of the intervention types $(F_{(4,28.7)}= 28.4$, $p<0.001)$, (figure 9). Physical exercise interventions and non-CBT based psychotherapies did not significantly differ (MD= -0.10, CI [-0.40, 0.20], p= 0.848) but were significantly more effective than other interventions. CBT-based psychotherapies were also significantly more effective than second-generation antidepressants (MD= 0.15, CI [0.06, 0.24], p<0.001) and mixed antidepressants (MD= 0.18, CI [0.11, 0.24], p<0.001). See Table 7 for full results.

There were also significant differences in the effectiveness of the same interventions for anxiety versus depression.

Across categorization levels, most interventions with data for both depression and anxiety were associated with significantly higher levels of improvement for anxiety than depression. At Level 1, this included psychosocial interventions (MD= -0.17, CI [-0.24, -0.09], t(295.29)= -4.29, p<0.001) and pharmacological interventions (MD= -0.66, CI [-1.04, -0.28], t(16.23)= -3.65, p= 0.002). At Level 2, this included CBT-based psychotherapies (MD= -0.23, CI [-0.31, -0.15], t(285.67)= -5.91, p<0.001). At Level 3, this included CBT (MD= -0.23, CI [-0.33, -0.13], t(81.93)= -4.44, p<0.001), mixed psychotherapies including CBT (MD= -0.40, CI [-0.60, -0.21], t(24.63)= -4.24, p<0.001), and second-generation antidepressants (MD= -0.67, CI [-1.08, -0.27], t(15.53)= -3.55, p= 0.003).

Only non-CBT based psychotherapies (Level 2) were associated with significantly more improvement for depression than for anxiety (MD= 0.27, CI [0.07, 0.47], t(17.36)= 2.83, p= 0.011). There was no significant difference for family interventions (MD= 0.08, t(29.16)= -0.58, p= 0.568).

Five outliers (±3 standard deviations from the mean) were identified between anxiety and depression outcomes, but their inclusion did not substantially impact results.

Moderation analyses were also conducted where possible.

For transformed effect sizes (to Cohen's *d*), psychosocial interventions were significantly more effective in the overall treatment of CYP's anxiety and depression than pharmacological interventions (F(1,79)= 21.27, p<0.001); however, for untransformed effect sizes, there was no significant difference (F(1,292)= 0.44, p= 0.507) (figure 10).

Additionally, psychosocial interventions were significantly more effective than pharmacological interventions in targeting remission for CYP with depression and anxiety (F(1,64)= 9.48, p= 0.003), but there was no significant difference in the effectiveness of the two intervention types for reducing symptom severity (F(1,286) = 0.51, p= 0.477) (figure 11).

There was not enough data to calculate an interaction effect for physical interventions, or to check for moderation of anxiety and depression outcomes separately. Sample context (clinical,

community), outcome reporter (parent, clinician, child, other), and specific diagnosis (only calculable for anxiety) did not significantly moderate outcomes.

Discussion

This umbrella review details evidence from 37 meta-analyses and 378 effect sizes exploring the effectiveness of psychological, pharmacological, and physical interventions for CYP with depression and anxiety. Analyses revealed significant differences in the effectiveness of treatments, particularly for depression, and a significant discrepancy in the effectiveness of the same interventions when treating anxiety versus depression.

For CYP with anxiety, psychosocial and pharmacological interventions were equally effective. CBT, family interventions, BT, MBIs, second-generation antidepressants, and mixed psychotherapies including CBT all reduced symptoms and increased rates of remission.

Differences emerged when psychosocial treatments were separated into CBT-based and non-CBT-based psychotherapies. CBT-based psychotherapies led to more improvement than non-CBT-based psychotherapies, and were similarly effective to antidepressants. Current public health recommendations for CYP with anxiety highlight CBT-based psychotherapies as an effective first-line treatment.[20,21] However, clearer guidance is needed on pharmacological treatments, particularly antidepressants, as our review demonstrates that they are equally as effective a standalone treatment.

Additionally, psychotherapies such as CBT and BT were associated with significantly better outcomes than MBIs. While this aligns with the literature,[39,43,58] policy recommendations for treating anxiety in CYP still support use of MBIs, particularly in schools.[59,60] MBIs may be less effective than other interventions because they provide less proactive mechanisms for addressing symptoms in the long-term,[39,58] or because they are often facilitated by non-mental health professionals, such as school or charity staff.[43]

For CYP with depression, psychosocial, pharmacological, and physical interventions were all effective. Physical and psychosocial interventions were associated with greater reduction in symptoms and higher likelihood of remission than pharmacological interventions. IPT, a non-CBT-based psychotherapy, was the most effective intervention, followed by physical exercise interventions. However, physical interventions are most commonly used to treat subthreshold depressive symptoms, which are generally more responsive to treatment than moderate and severe depression.[29] For psychosocial interventions, both CBT-based psychotherapies and non-CBT-based psychotherapies were more effective in the treatment of depression than second-generation or mixed antidepressants. Other than IPT, there was no significant variation between specific psychotherapies, nor between antidepressant categories.

There has been considerable debate in the literature regarding the comparative effectiveness of psychotherapy and pharmacology for treating depression.[61,62] This debate is compounded by inconsistent policy recommendations for CYP.[12,27,28] The distinctions evidenced by this review are significant emerging findings, suggesting that antidepressants, despite being developed to treat depression,[63] are the least effective standalone treatment for CYP. Physical interventions are typically not highlighted as a first-line treatment in practice recommendations[12,28] or in the intervention debate.[61,62] This may be an oversight, particularly for CYP with mild depression, given the high association with symptom improvement and increased likelihood of remission.

Contrastingly, IPT is often included in policy and practice as an alternative psychosocial treatment to CBT, a recommendation supported by these findings.[12,28] Despite appearing more effective, however, IPT is considerably under-researched compared to CBT (with seven IPT effect sizes in this depression review, and 21 CBT). This review adds to mounting calls for additional evidence on IPT,[12] and further considerations into which mechanisms make it more effective for depression compared to other treatments.

Generally, interventions with results for anxiety and depression were more effective for treating anxiety. This included CBT and second-generation antidepressants. It is possible that interventions focus more specifically on the mechanisms of anxiety, and improvements found in depressed CYP function through a reduction of comorbid anxiety symptoms, rather than through a reduction of depressive symptoms themselves.[64] This could also explain why even treatments originally used to treat depression, such as antidepressants, appear significantly more effective for treating anxiety. The evidence aligns with psychiatric initiatives that encourage adopting neuroscience-based nomenclature for psychotropics, rather than naming them according to the diagnoses they may or may not best treat.[65]

Our findings for CYP expand on a somewhat controversial perspective that has been emerging in adult depression literature, calling into question the effectiveness of existing interventions for depression generally.[66,67] Considering the potential long-term effects of untreated or undertreated depression in CYP,[7] there is a clear need for further research into the development of new or modified effective interventions.

One exception to this finding were non-CBT based psychotherapies, which were associated with higher levels of improvement in depression than anxiety. This category included psychosocial interventions such as BT, positive psychology, IPT, and MBIs. As noted above, IPT was the most effective psychotherapy for depression; no reviews explored IPT for anxiety. This, alongside the lack of research on physical interventions for youth anxiety, highlights a dearth in the meta-analytic evidence-base of anxiety interventions that has only started to be addressed in the last two years.[68,69] Given the effectiveness of other overlapping interventions for anxiety, and emerging evidence on IPT[70,71] and exercise,[68,69] policymakers and practitioners should monitor developments and consider expanding recommendations for anxiety treatments accordingly.

Our review provides a comprehensive update of recent literature through October 2022, including meta-analyses from four continents. However, it has limitations which should be acknowledged. First, although demographic data including gender and race ratios were extracted, this information was unavailable for 60-100% of effects (appendix p 14). Therefore, moderation analyses with this data were not feasible. Missing data also prevented analysis on treatment frequency, duration, and follow-up. Second, effect sizes were standardized to Cohen's d to enable utilization of higher-level statistical tests. Transformation assumes equal groups. While we attempted to extract intervention and control group sizes, for over half of included effects this data was unavailable, and most meta-analyses did not control for variation in group size across individual studies. Analysis indicated that transformation of effect sizes significantly moderated the relationship between intervention type (psychosocial versus pharmacological) and outcome. There was not enough power to assess moderation for anxiety and depression outcomes separately. While this aligns with statistical methods in previous umbrella reviews,[72-74] it

provides important context for interpretation of results. Third, of the original 520 effect sizes, only 3 reported results exclusively for CYP with co-morbid depression and anxiety, meaning there was not enough data to explore treatments for co-occurring diagnoses. This may limit practice implications, as rates of comorbidity are high – generally estimated at over 50% in the general population,[75] and potentially higher in symptom overlap.[76] Relatedly, no included effects reported combined psychosocial and pharmacological interventions. This may also limit practical application, as combination treatment is often recommended with pharmacology,[12,20,27] and has generally been found to be more effective than either approach individually.[77,78]

This review found that for CYP with anxiety, antidepressants and CBT-based psychotherapies were equally effective at improving symptoms and increasing remission rates; contrastingly, for depression in CYP, physical exercise interventions and IPT were most effective, followed by other psychotherapies, then antidepressants. Overall, CBT-based psychotherapies and pharmacological interventions were both found to be more effective for treating anxiety than depression. Given these findings, this review suggests updates are needed to treatment recommendations for CYP with anxiety and depression. Future research should consider the mechanisms through which depression affects specific psychological and physiological systems in CYP, and which elements are under-addressed by current therapeutic practices.

Acknowledgements

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