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Screening for Depression, Anxiety, and Suicide Risk in Children and Adolescents: An Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To review the evidence on screening (benefits and harms of screening, accuracy of screening, benefits and harms of treatment) for suicide risk, anxiety, and depression in children and adolescents in settings relevant to primary care in the United States for the U.S. Preventive Services Task Force.

Data Sources: PubMed, the Cochrane Library, PsycINFO, CINAHL and trial registries through July 19, 2021; bibliographies from retrieved articles, outside experts, and surveillance of the literature through June 1, 2022.

Study Selection: Two investigators independently selected English-language studies using a priori defined criteria. We included trials that evaluated the benefits or harms of screening for suicide risk, anxiety, or depression compared with no screening or usual care. We included studies of screening with instruments feasible in primary care settings. For treatment benefits and harms, we included drugs approved for pediatric use by the Food and Drug Administration. For suicide and depression treatment studies, we included any eligible psychotherapy or collaborative care interventions. For anxiety, we restricted nonpharmacological interventions to cognitive behavioral therapy (CBT). Eligible outcomes included test accuracy, symptoms, response, remission, loss of diagnosis, all-cause mortality, functioning, suicide-related symptoms or events, withdrawal due to adverse events, serious adverse events, and harms from screening. We also included systematic reviews reporting on harms of treatment. We excluded studies with poor methodological quality.

Data Extraction and Analysis: One investigator extracted data and a second checked accuracy. Two reviewers independently rated methodological quality for all included studies. When at least three similar studies were available, we conducted meta-analyses.

Data Synthesis: We included 80 studies (in 106 publications). No studies evaluated the direct benefits of screening compared with no screening or usual care. Seventeen studies reported on accuracy of screening instruments for one or more conditions; of these, one reported on suicide (N=580), 10 on anxiety (N=3,260), seven on depression (N=3,316), and two on anxiety or depression (N=695). Studies reported a wide range for sensitivity and specificity across a variety of instruments, with no more than one or two studies on each instrument. For suicide, sensitivity ranged from 0.87 to 0.91, and specificity was 0.60. For anxiety, sensitivity generally ranged from 0.34 to 1.00, and specificity from 0.47 to 0.98. For depression, sensitivity ranged from 0.59 to 0.94, and specificity from 0.38 to 0.96. Two RCTs (N=2,675) compared short-term distress from screening for suicide risk and reported no significant differences between those screened and those who were not screened.

Sixty randomized, controlled trials (RCTs) addressed benefits of treatment; of these, 16 reported on suicide risk interventions (N=3,034), 29 on anxiety treatment (N=2,970), 13 on depression treatment (N=2,156), and two on depression or anxiety treatment (N=236). Interventions addressing suicide risk or self-harm reported lower scores for the Beck Hopelessness Scale (pooled mean difference: -2.35 [95% confidence interval [CI], -4.06 to -0.65]; N=644; k=4) for

intervention arms when compared with control arms. Findings for other measures were mixed or not statistically significantly different.

Of the 29 RCTs on anxiety treatment, 22 were on CBT; six were on pharmacotherapy; and one had multiple arms evaluating CBT, sertraline, and CBT plus sertraline. The evidence suggests CBT was associated with gains on several pooled measures of symptom improvement (magnitude of change varies by outcome measure), response (pooled relative risk [RR]: 1.89 [95% CI, 1.17 to 3.05]; N=606; k=6; I2=64%), remission (RR: 2.68 [95% CI, 1.48 to 4.88]; N=321; k=4), and loss of diagnosis (RRs range from 3.02 to 3.09), when compared with usual care or wait-list. The evidence on functioning for CBT was mixed. The evidence suggests pharmacotherapy, when compared with placebo, was associated with gains on two pooled measures of symptom improvement (mean difference Pediatric Anxiety Rating Scale: -4.0 [95% CI, -5.5 to -2.5], N=726, k=5 and mean difference Clinical Global Impressions-Severity: -0.84 [95% CI, -1.13 to -0.55]; N=550, k=4) and response (RR: 2.11 [95% CI, 1.58 to 2.98]; N=370; k=5) but was mixed on measures of functioning.

Of the 13 RCTs on depression treatment, eight were on psychotherapy; two on pharmacotherapy; one on CBT, fluoxetine, and their combination; and one on collaborative care. Results for psychotherapy varied by measure. Two pooled estimates suggested that psychotherapy is associated with improved symptoms (Beck Depression Inventory [BDI] or BDI-II standardized mean difference: -0.58 [95% CI, -0.83 to -0.34]; N=471; k=4 and Hamilton Depression Scale mean difference: -2.25 [95% CI,-4.09 to -0.41]; N=262; k=3), clinical response (3 studies with statistically significant results using varying thresholds), and loss of diagnosis (RR: 1.73 [95% CI, 1.00 to 3.00; N=395; k=4) but no statistically significant differences for other measures. The evidence suggested statistically pharmacotherapy was associated with improvement for one measure of symptoms (Children's Depression Rating Scale-Revised [CDRS-R] mean difference -3.76 [95% CI, -5.95 to -1.57, N=793; k=3), and pharmacotherapy was associated with improvement for remission, but the pooled differences were not statistically significant. The single collaborative care trial (N=101) found that collaborative care was associated with improved symptoms at 6 months (CDRS-R change: 8.5 [95% CI, 13.4 to -3.6]), response by 12 months (odds ratio [OR] for ≥50% reduction in CDRS-R score: 3.3 [95% CI, 1.4 to 8.2], and remission (OR for Patient Health Questionnaire-9 <5 at 6 months: 5.2 [95% CI, 1.6 to 17.3]). The study reported no statistically significant benefits on measures of functioning.

Twenty studies (19 randomized controlled trials and 1 meta-analysis) addressed harms. Of these, two reported on suicide risk interventions (N=885), 11 on anxiety treatment (N=1,293), and seven on depression treatment (N=1,352).

Two RCTs of interventions to reduce suicide risk or self-harm reported no statistically significant differences in adverse events.

Of the 11 RCTs reporting harms of anxiety treatments, four evaluated CBT; six evaluated pharmacotherapy; and one evaluated CBT, sertraline, and their combination. The evidence from CBT studies yielded inconsistent results on suicide-related events; these studies also suggested lower rates of withdrawal due to adverse events and serious adverse events in the CBT arms. Suicide-related events and withdrawals due to adverse events in pharmacotherapy studies were

rare and not statistically significant; however, they were more commonly reported in pharmacotherapy arms when compared with placebo arms.

Of the seven studies reporting harms of depression treatment, three evaluated pharmacotherapy; two evaluated psychotherapy; one evaluated CBT, fluoxetine, and their combination; and one evaluated collaborative care (1,276 from trials). Suicide-related outcomes, withdrawal as a result of adverse events, and serious adverse events were not statistically significant between study arms but were more frequent for pharmacotherapy when compared with placebo; inconsistencies in the evidence further reduced certainty. The evidence from the collaborative care study was inconsistent.

Limitations: No studies were available that reported benefits of screening compared with no screening. Limited evidence was available on harms of screening, long-term outcomes, test accuracy, and suicide risk and depression treatment in children. Treatment-as-usual comparators for suicide risk interventions included active treatments. The review was limited to drugs approved for pediatric use by the Food and Drug Administration (FDA). For anxiety, psychotherapy was limited to CBT.

Conclusions: We found no eligible studies that reported on benefits directly arising from screening when compared with usual care or no screening. Limited direct evidence suggests no short-term harms from screening for suicide risk. The evidence for screening for suicide risk, anxiety, and depression in children and adolescents relied on indirect evidence on the accuracy of screening and the benefits and harms of treatment. The evidence suggests that some screening instruments are reasonably accurate for anxiety and depression, but the evidence is limited for suicide risk screening instruments. Both pharmacotherapy and psychotherapy treatments have some benefit for some depression and anxiety outcomes (specifically, CBT for anxiety alone was reviewed); the evidence is limited for suicide risk interventions. Harms are rare in treatment studies but more frequent in pharmacotherapy arms when compared with placebo. Evidence gaps persist in children younger than age 11 years for test accuracy; depression and suicide risk interventions; and screening and treatment differences by sex, race/ethnicity, sexual orientation, and gender identity.

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Chapter 1. Introduction

Scope and Purpose

The United States Preventive Services Task Force (USPSTF) will use this report to issue updated recommendations for screening for suicide risk and depression in children and adolescents and to consider a new recommendation for screening for anxiety in this population. In 2014, the USPSTF concluded there was insufficient evidence to assess the balance of benefits and harms of *screening for suicide risk* in adolescents, adults, and older adults in primary care (I statement). In 2016, the USPSTF issued a recommendation for *screening for major depressive disorder* (MDD) in adolescents ages 12 to 18 years, noting that screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate followup (B recommendation).[1] The USPSTF also concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for MDD in children ages 11 years or younger (I statement). The current review focuses on evidence for screening for suicide risk, anxiety, and depression in children and adolescents because screening instruments, implementation of screening, and outcomes for these conditions have overlap. Mental health conditions in children and adolescents may present as physical symptoms and may occur concurrently, presenting primary care physicians with opportunities to screen for one or more conditions. The review includes studies of benefits and harms of screening, accuracy of screening, and benefits and harms of treatment.

Condition Definition

Suicide

Suicide is defined as a death caused by self-inflicted injurious behavior with the intent to result in death because of the behavior.[2, 3] Suicidal attempts and ideation occur more frequently than deaths from suicide. Suicide attempts refer to nonfatal, self-directed, and potentially injurious behavior that is intended to result in death. Suicidal ideation refers to thinking about, considering, or planning suicide.[4] Self harm may occur with or without suicidal intent. Nonsuicidal self-injury (self-harm without the intent to cause one's own death) may predict[5, 6] or co-occur[7-10] with suicidal ideation and behavior. Definitions of self-harm or self-directed violence can vary widely,[2] and nonsuicidal self-injury may not always be distinguished from self-harm with suicidal intent. A common measure, deliberate self-harm, does not always specify intent[11] and can also predict suicide attempts.[12] The scope of this review includes suicide, suicide attempts, suicidal ideation, and deliberate self-harm.

Anxiety

Although anxiety as a response to stress is normal, anxiety disorders are characterized by greater duration or intensity of impairment. The *Diagnostic and Statistical Manual-5* (DSM-5)[13] recognizes seven different types of anxiety disorders in children and adolescents: generalized

anxiety disorder (GAD), social anxiety disorder, panic disorder, agoraphobia, specific phobias, separation anxiety disorder, and selective mutism. Categories that were included under anxiety disorders in previous editions of the DSM but are no longer included as part of DSM-5 anxiety disorders are obsessive-compulsive disorder (OCD), acute stress disorder, and posttraumatic stress disorder. The scope of this review includes studies focusing on one or more anxiety disorders, defined by the DSM criteria at the time of the study, as long as the study did not focus on OCD, acute stress disorder, or posttraumatic stress disorder.

Depression

Depression is a mood disorder marked by symptoms related to how a person feels, thinks, and goes about their daily activities. According to DSM-5, MDD in children and adolescents is characterized by mild to severe persistent feelings (at least 2 weeks) of sadness or a lack of interest or pleasure in everyday pursuits, irritability, poor concentration, and somatic complaints such as difficulty sleeping, decreased energy, and changes in appetite. The scope of this review includes studies in which the majority of participants had MDD.

Etiology, Natural History, and Risk Factors

Substantial comorbidity exists between anxiety, depression, and suicide. However, differences in the pattern of overlap indicate that adolescents with depression are more likely to exhibit comorbid anxiety than the converse.[14] Moreover, evidence (from the Great Smokey Mountains Study) indicated that children who were depressed with comorbid anxiety, specifically GAD, had a higher risk of suicide than children with pure anxiety disorders.[15] Yet, across all three conditions, adverse childhood experiences influenced the likelihood of suicide, anxiety, or depression. These experiences may arise from a complex and interacting set of familial, peer, or societal factors and may vary by race and ethnicity. Additionally, individual factors, including age, sex, gender identity and sexual orientation, and genetic predisposition, also may serve as risk factors across all the conditions. These mental health conditions have long-term effects that may include chronic mental and physical health conditions, functional impairment, increased risk for substance abuse, and premature mortality.[16-19]

Suicide

Although young children rarely attempt or die by suicide, they do reveal some preoccupation with death or suicide, either in talk or in play, and these themes are considered to signal major depression in preschool children[20, 21] and are a significant predictor of future suicidal ideation and other psychiatric disorders.[22] More commonly, suicidal behaviors first emerge during later childhood and adolescence.[22, 23] Studies of Canadian[24] and U.S. adolescents[23] showed that the prevalence of attempts among ideators was 25.5 percent in the Canadian cohort and 33.9 percent in the U.S. cohort; the gender difference in prevalence was only significant in the U.S. sample. Notably the prevalence of attempts was 3 times as great in those with a plan (60.8%) as in those without a plan (20.4%). A third cohort study found that 20.6 percent of youth who both reported

suicidal ideation and reported nonsuicidal self-harm went on to attempt suicide compared with 1.4 percent of youth who did not report either ideation or nonsuicidal self-harm.[25]

The most substantial risk factors for youth suicide are adverse childhood experiences and mental health disorders, including family history of suicide or mental health disorders, previous suicide attempts, life stressors such as interpersonal losses, legal or disciplinary problems, history of trauma, and parent-child conflict.[26-29] Suicide risk varies by gender or sex and type of behavior (note that some studies may use sex and gender terms interchangeably; the following discussion uses the language in the original publications). Males had a higher rate of suicide (17.9 per 100,000) than females (5.4 per 100,000) in 2017.[30] However, the risk of suicide attempts was greater in females than males.[31] Lesbian, gay, bisexual, transgender, and queer (LGBTQ) adolescents exhibit elevated rates of suicide ideation and attempts compared with heterosexual adolescents.[11, 32, 33] One study of adolescents who identified as LGBTQ found that they were victimized more often by other youth, and peer victimization was associated with suicidal ideation and attempts, suggesting one reason for the higher suicidality rate in this population.[34]

Major depression as a risk for suicide may have a different role in childhood versus adolescence. In one large epidemiologic sample,[35] suicide attempts in children younger than age 13 years were more strongly related to child maltreatment compared with adolescents for whom suicide attempts were more strongly related to depression. In adolescents, continuity of depression has been found to place youth at greater risk for suicidal ideation, nonsuicidal self-harm, and suicide attempts.[36] Other factors associated with suicidal ideation and attempts include physical and sexual abuse; bullying; social isolation and loneliness; impulsivity; very high or very low engagement in health behaviors, low concentrations of serotonin metabolism; and variations in genes related to serotonin synthesis, transport, signaling, and catabolism.[11, 24, 37-44]

Anxiety

Data from the Oregon Adolescent Depression Project reported that the incidence of the first episode of anxiety was higher in childhood (ages 5 to 12.9 years) than in adolescence (ages 13 to 17.9 years), and an anxiety disorder emerging in childhood or adolescence increased the likelihood of future anxiety disorder.[45] Several reviews of anxiety disorders in children and adolescents reported longitudinal associations of anxiety disorders over time both with the same disorder and other anxiety or depressive disorders, suggesting the heightened risk for secondary depression.[46-48] The earliest emerging anxiety disorder in childhood is separation anxiety disorder.[49] Other anxiety disorders with emergence in preschool and early school years include selective mutism and GAD, whereas social anxiety and specific phobias generally develop during the later school years.[50]

Important risks and correlates of anxiety disorders include genetic, personality, and environmental factors. Studies have reported genetic contributions to the development of anxiety.[51-53] Behavioral inhibition is a risk factor for developing anxiety disorders, particularly social anxiety,[47, 51, 54, 55] as is harm avoidance.[51, 56] Attachment difficulties are also associated with social anxiety.[56-58]

Although many factors can contribute to the development of anxiety disorders in children, some studies and reviews have reported links between the development of anxiety disorders and parenting characteristics such as overprotection[49, 51, 52, 59, 60] and interparental conflict.[52, 60] As with other psychopathological disorders, adverse environmental conditions such as early parental separation, child maltreatment, and traumatic parental death, as well as poverty and low socioeconomic status (SES), were cited as contributing to the development of anxiety disorders.[46, 53, 59] Lastly, a higher prevalence of anxiety has been found in youth with low SES compared with youth with higher SES.[53]

Depression

Although there is evidence that depression can emerge as early as 3 years of age,[61-63] the first diagnosis of depression is more common in adolescence or adulthood than childhood.[64-66] However, studies also showed substantial continuity of depression from preschool to school age, with the likelihood of school-age depression almost 3 times as great in children with preschool-onset depression. Studies have also found that adolescents with a diagnosis of depression are more likely to have depression at a later time,[67, 68] up to 4 times as likely in one study as those with no psychiatric disorder.[67]

Several studies have found substantial comorbidity between depression and other psychiatric disorders. Preschool-age children with depression were also 3.5 times as likely to develop school-age anxiety disorder and 3.7 times as likely to develop school-age attention-deficit/hyperactivity disorder than children without preschool depression.[63] Children and adolescents with depression had a greater likelihood of having a concurrent anxiety disorder,[65, 69] about 4 times greater in one cohort.[65] Other concurrent psychiatric disorders found in children and adolescents with depression include oppositional defiant disorder[67] and substance use disorder.[65] Gender-specific comorbidities found in one study[67] included substance use disorder (males) and conduct disorder (females). Adolescents with past depression were more than twice as likely to have anxiety at a later time point.[67]

Risk factors for depression include individual factors (genetics, biology, affect, cognition, behavior) that interact with social contextual factors at the proximal level (peers, family, school) and distal level (neighborhood, culture, government).[70, 71] Individual risk factors for depression in youth include genetic predisposition, female gender, and increasing age.[57, 72] Other risk factors include bullying, either as perpetrators or as victims, adverse life events, early exposure to stress, maltreatment, and an insecure parental relationship.[73-75] Risk factors are also believed to interact to increase the odds of depression;[66, 74, 76-78] additionally, maltreatment can reduce the effectiveness of evidence-based interventions.[75]

Prevalence and Burden

Suicide

Suicide Deaths

Suicide is the second leading cause of death among youth ages 10 to 19 years.[79] Using the Centers for Disease Control and Prevention's (CDC's) Web-based Injury Statistics Query and Reporting System (WISQARS) data from 2019,[80] a total of 2,744 youth ages 10 to 19 years died by suicide, of which 534 were younger youth (ages 10 to 14 years of age) and 2,2210 were older adolescents (ages 15 to 19 years). This translates to a suicide rate for children and younger adolescents, ages 10 to 14 years, of 2.6 per 100,000. The comparable rate for males and females ages 10 to 14 years was 3.1 per 100,000 and 2.0 per 100,000, respectively. Older adolescents, ages 15 to 19 years, died by suicide at a rate of 10.5 per 100,000, and the rate for males was more than 3 times that of females: 15.8 per 100,000 for males and 5.0 per 100,000 for females. In youths ages 10 to 14 years, White children and younger adolescents have a similar rate of dying by suicide compared with Black children and adolescents of the same age: 1.3 versus 1.4 per 100,000 for White and Black children, respectively; however, the suicide rate among White adolescents is nearly double the rate for Black adolescents: 8.4 per 100,000 and 4.2 per 100.000, respectively. More concerning is the upward trend in suicide rates for Black youth; from 2003 to 2017, the data show that the largest change was in the 15- to 17-year-old group (4.9%) and among females (6.6%).[81] Overall, American Indian children and adolescents die by suicide at the highest rates: 2.5 per 100,000 and 16.1 per 100,000, in the younger and older age groups, respectively[80] In 2015, 16 percent of the suicides in youth ages 15 to 17 years were lesbian, gay, bisexual, transgender, and queer or questioning (LGBTQ), and 24 percent of the suicides in children ages 12 through 14 years were LGBTQ children.[82]

Suicide Attempts

In 2019, results from the Youth Risk Behaviors Surveillance (YRBS) survey[3] indicated that 8.9 percent of students (grades 9 to 12) had attempted suicide in the prior 12 months. Prevalence of suicide attempts was highest among female (11.0%), Black (11.8%), and LGBTQ students (23.4%).[83] The most recent data on suicide behavior in LGBTQ youth is from the 2020 National Survey on LGBTQ Youth Mental Health conducted by the Trevor Project.[84] This survey found that 20 percent of transgender and binary youth ages 13 to 24 years reported suicide attempts in 2020, and 21 percent of Black LGBTQ youth attempted suicide. In the Profiles of Study Life: Attitudes and Behaviors Survey of Adolescents 11 to 19 years conducted between 2012 and 2015, male transgender adolescents experienced the highest rate of attempted suicide of 50.8 percent, whereas male adolescents irrespective of sexual identity had the lowest prevalence rate, 9.8 percent.[85]

Suicidal Ideation

Data from the 2019 YRBS[3, 86] indicate that 18.8 percent of youth in 9th through 12th grade seriously contemplated attempting suicide, and 15.7 percent made a suicide plan. Students attempting suicide or making plans were more likely to be female, White, or LGBTQ. Data from

the 2020 National Survey on LGBTQ Youth Mental Health indicate that 42 percent of LGBTQ youth ages 13 to 24 years seriously contemplated suicide.[84] In addition, 52 percent of transgender and binary youth seriously considered suicide, whereas the percentage of cisgendered LGBTQ youth who considered suicide is 32 percent. Forty-seven percent of Black LGBTQ youth seriously considered suicide as compared with 39 percent of White LGBTQ youth.

Importantly, two recent studies[87, 88] found discordant reports of parent and youth reporting of suicidality. Specifically, both studies found that parents were often unaware of their child's suicidal ideation and/or attempts, and the Jones study[88] found that youth often denied having suicidal thoughts even though their parents reported suicidality. This discordance in reports between parents and children suggests that children at risk for suicide may go undetected.

Anxiety

Estimates from the 2020 National Survey of Children's Health (NSCH) were that 7.8 percent of children ages 3 to 17 years had a current anxiety disorder; 0.7 percent reported severe anxiety.[89] Reports using the older 2016 NSCH provided comparisons by demographic factors, indicating no statistically significant differences in prevalence rates between males and females.[90] Anxiety problems were most common among non-Hispanic White children compared with children of other racial/ethnic backgrounds and in older (ages 12 to 17 years) as compared with younger children (ages 3 to 5 years and ages 6 to 11 years). Data from the National Survey on LGBTQ Youth Mental Health indicated that 72 percent of LGBTQ youth reported symptoms of GAD, and 77 percent of transgender and nonbinary youth reported GAD symptoms.[84]

Depression

The NSCH provides parent-reported diagnosed depression for children ages 3 through 17 years.[89] In 2020, 3.4 percent of U.S, children were estimated to currently have depression, and 0.3 percent were considered to be severe. Comparisons between groups based on demographic categories that are available from the 2016 NSCH indicated that depression was significantly more common among adolescents ages 13 to 17 years as compared with younger groups and in non-Hispanic Whites as compared with Hispanic and non-Hispanic Black youth.[90] Other U.S. depression estimates relying on adolescent self-report come from the National Survey on Drug Use and Health (NSDUH).[91] The NSDUH, an annual survey of children ages 12 to 17 years, reported the prevalence of a major depressive episode (MDE) in the past year and MDE with major impairment. An MDE is defined as follows: in the past 12 months as one or more periods of at least 2 weeks when the youth felt depressed or lost interest or pleasure in daily activities for most of the day, nearly every day as well as problems with sleeping, eating, energy, concentration, self-worth, or having recurrent thoughts of death or recurrent suicidal ideation. An MDE with severe impairment is defined a depression caused severe problems with the youth's ability to do chores at home, do well at work or school, get along with their family, or have a social life. In the 2019 NSDUH, past-year prevalence of an MDE was estimated as 15.7 percent (or 3.8 million adolescents) and MDE with severe impairment was 11.1 percent (or 2.2 million adolescents). The prevalence of depression in primary care settings may be up to twice as high as in community samples of children and adolescents.[61, 63-65]

Mental Health Disorders and Racial Disparities

As noted previously, the rate of suicide deaths is highest among American Indian youth[80] (but may vary by tribe and geographic setting)[92] and lowest among Black youth when compared with White youth. Previous studies suggested Black youth may have had lower rates of mental health disorders when compared with White youth, but more recent cohorts of Black adolescents or children have reported having a higher prevalence of suicide rates,[80, 93] increase in suicide attempts[58, 94, 95] and anxiety disorders[90, 96] and greater increases in the prevalence of depression than in the past.[96] Multiple factors, including socioeconomic status, childhood adversity, family structure, and neighborhood effects, may influence patterns of prevalence by race or ethnicity. The effects of racial disparities and structural racism intersect with these factors.[97] Researchers noted the familial and societal impact of mass incarceration among Black males (rates of imprisonment among Black males increased by 3 times between 1969 and 1999), higher rates of increase in child poverty for Black children, higher rates of unemployment for Black adults, and a decline in the percentage of Black parents with college degrees.[96] An increase in nonmarital births resulting in increasing prevalence of single-parent households may also play a role in the increase in the prevalence of depression.[96] For U.S. adults, access to financial (income), physical (home ownership), and social assets (marital status and education) may explain part of the differences in prevalence between non-Hispanic Black and Hispanic persons when compared with White persons.[98] Whether the relationship for family income holds for children and adolescents requires further research: one study suggested that higher household income may be associated with a higher risk of MDD among African American males, possibly because of the more frequent exposure to racial discrimination and reduced availability of social support from the African American community.[99, 100] In addition to these larger societal risk factors, other risk factors may include lack of access to health insurance, providers, medication (resulting in lower rates of treatment for non-White populations);[101] underdiagnosis (e.g., because of implicit clinician bias);[102] overdiagnosis (e.g., of conduct disorders instead of mood disorders);[103] and misdiagnosis (because of lack of equivalence in assessment measures).[101, 104]

A culturally informed Adverse Childhood Experiences (ACEs) model posits that racial discrimination is an adverse childhood experience that influences mental and behavioral health in youth. These experiences may be blatant or subtle (e.g., microaggressions), repeated or distinct, time limited or prolonged, but they are all potentially traumatic events that, in the context of historic trauma, structural racism, and biopsychological vulnerability, can worsen mental health outcomes.[105] When coupled with well-documented lower engagement with mental health services,[106-109] these higher rates point to a high level of unmet need in Black youth.[110]

Similar patterns of historic trauma, ACEs, and substance abuse may explain higher rates of mental health disorders in American Indian/Alaska Native youth;[92, 111, 112] specific risk factors and their variation by tribe or geography are less well studied.

Rationale for Screening and Screening Strategies

Screening for suicide risk, anxiety, and depression is intended to identify these conditions in children and adolescents not already identified as having the condition and then engage them

effectively in confirmatory diagnostic evaluations, referrals, followup, or treatments as needed. Research has suggested that about half of adolescents with depression are not diagnosed until adulthood.[113] Screening may be particularly effective for these mental health conditions given the stigma associated with seeking care for such conditions. Although depression is common, only 2 to 3 percent of adolescents present with a primary psychiatric complaint; many present as physical problems.[114-116] A longitudinal study of deaths by suicide between 2000 and 2010 across health maintenance organizations in 11 States found that although only 16.3 percent of persons younger than age 20 years who died by suicide had a mental health visit in the 4 weeks before death, 37.9 percent used any healthcare services. In the 52 weeks before death, these rates were even higher for any use of healthcare services at 77.4 percent; 31.8 percent had a mental health visit.[117] These patterns suggest a role for screening in primary care. However, to realize the benefits of screening, effective treatment must be available that the family and child or adolescent are willing to engage in. Evidence suggests that mental health specialty care completion rates are low for youth referred from general medical settings.[118] This loss to followup between identification and treatment completion may pose a particular challenge for persons who are screen detected, where the net benefit of treatment may be lower than in persons who present with clinically overt symptoms.

Screening Strategies

The nature of the target conditions (suicide risk, anxiety, depression) requires patient- or caregiver-reported screening instruments. Although many instruments have been developed to assist with diagnostic evaluation for mental health conditions or broad-based socioemotional behavior and function, not all are feasible for screening in primary care settings because of length. Many instruments that are used for screening for depression and anxiety were initially developed for epidemiologic studies for surveillance or to evaluate response to treatment. Most depression instruments evaluate for common symptoms related to depression and also include one or more items related to suicidal ideation. Anxiety instruments are more heterogenous, some are designed to evaluate for a specific anxiety disorder (e.g., social anxiety disorder), while others are designed to evaluate across the breadth of existing anxiety disorders. Assessments designed to evaluate youth suicide risk typically involve one component related to evaluating current ideation and self-harm behaviors, but also involve an assessment for past attempts and behaviors given the strong correlation between past behaviors and future risk. Instruments designed to screen across conditions may be more efficient than instruments targeting single conditions; however, trans-condition instruments are longer and require more time to administer, reducing feasibility in primary care settings and may be less accurate for any specific condition.

Treatment Approaches

Suicide

Therapeutic interventions targeting at-risk youth include psychotherapy and pharmacotherapy.[119, 120] These therapies seek to reduce suicidal ideation, behaviors, and attempts. Psychotherapeutic approaches may include short-term psychoeducation or longer-term interpersonal psychotherapy, cognitive behavioral therapy (CBT), dialectical behavioral therapy (DBT), mentalization therapy,

and trauma-informed therapy. Pharmacotherapy may include antidepressants, antipsychotics, and mood stabilizers. In addition to these treatments, safety planning interventions, which generally include caregivers, may also be designed to reduce the access to or lethality of means of suicide. These therapies may be combined with interventions to address social determinants of health. For example, individually focused interventions that primary care providers can participate in or provide referrals to may seek to educate families of those in crisis about safely storing medications and firearms, distributing gun safety locks, and removing other items that could be used for an attempt.[121, 122]

Anxiety

Treatments for anxiety disorders includes psychotherapy, pharmacotherapy, and combinations.[123] CBT is among the most commonly used approach, but other approaches include parent-child interaction therapy, problem-solving therapy, DBT, exposure therapies, hypnosis, social skills training, mindfulness therapy, psychodynamic psychotherapy, family therapy, attention modification program, motivational interviewing, trauma-informed therapy, and eye movement desensitization reprocessing therapy.[124-127] Duloxetine, a serotonin–norepinephrine reuptake inhibitor (SNRI), is the only Food and Drug Administration (FDA)-approved medication for GAD in children age 7 or older. Pharmacological interventions prescribed on an off-label basis include selective serotonin reuptake inhibitors (SSRIs); other SNRIs; benzodiazepines; tricyclic antidepressants; and other drugs such as mebicarum, buspirone, mirtazapine, and nefazodone.

Depression

Treatments for MDD includes psychotherapy, pharmacotherapy, and combinations.[128-130] Different types of psychotherapy are used in treating children and adolescents with depression, but CBT and interpersonal therapy (IPT) have the most evidence supporting their effectiveness.[131-133] Other types of therapy used clinically for treating depression include supportive psychotherapy, family therapy, psychodynamic therapy, behavioral therapy, DBT, and trauma-informed therapy.[134] Although several antidepressants are approved for treating MDD in adult populations, fluoxetine is the only medication that the FDA has approved for use in treating MDD in children age 8 years or older. In addition, the FDA has approved escitalopram to treat MDD in adolescents ages 12 to 17 years. Other medications may sometimes be prescribed to children on an off-label basis including sertraline (approved in persons 6 years or older for obsessive-compulsive disorder [OCD]), fluvoxamine (approved in persons 8 years or older for OCD), and clomipramine (approved in persons 10 years or older for OCD).[135] In 2003, the FDA recommended that paroxetine not be used for treating MDD in children and adolescents because of reports of possible suicidal ideation and suicide attempts in children and adolescents taking paroxetine for depression. In 2004, the FDA issued a public warning about an increased risk of suicidality in children and adolescents treated with all antidepressants. The FDA currently requires these medications to carry a boxed warning about the potential danger of suicidality.

Clinical Practice in the United States

Evidence is limited on the implementation of routine screening in the United States. One survey of 727 primary care physicians in the United States in 2003 and 2004 found that 76 percent believe in the importance of talking to adolescent patients about their mental health, but only 46 percent said that they always asked their patients about their mental health.[136] Analysis of data from the 2005 to 2010 National Ambulatory Medical Care and National Hospital Ambulatory Medical Care Survey found that depression screening occurred in as few as 0.2 percent of visits, with variations by race/ethnicity and region. The study reported lower odds of screening among Hispanic patients than White non-Hispanic patients and lower odds in the West compared with the Northeast.[137] More recent insurance claims data (2010 to 2014) for 12- to 14-year-old adolescents with private insurance also indicated low rates of coding for depression screening at 1.8 percent.[138] Evidence on the rates of screening for other disorders were also limited and, when available, indicated low rates of screening ranging from 10 percent or less among pediatric emergency medicine physicians[139] to 23 percent in the primary care setting.[140]

Recommendations of Other Organizations

Suicide

Guidelines for screening for suicide are described in **Table 1**. The American Academy of Family Physicians follows the USPSTF recommendation.[141] The American Academy of Pediatrics (AAP) recommends universal screening for suicide youth 12 years of age and older and screening when clinically indicated for youth 8 to 12 years of age.[142] For younger children (younger than age 8), the guidelines recommend assessing for suicidal thought and behaviors if warning signs exist. The American Academy of Child and Adolescent Psychiatry (AACAP) policy statement supports screening for suicide risk across physical and mental health settings.[143] The Joint Commission recommends that organizations screen all individuals for suicidal ideation using a validated screening tool.[144]

Anxiety

AACAP notes the lack of empirically based guidelines on screening but offers resources for screening.[145] The National Institute for Health and Clinical Excellence (NICE) recommends screening.[146]

Depression

U.S.-based guideline groups (Guidelines for Adolescent Depression in Primary Care [GLAD-PC, supported by AAP, AACAP, and the American Psychiatric Association][147]) recommend routine screening for depression. The Canadian Task Force is updating its guidelines,[148] which earlier rated the evidence as insufficient.[149]

Multiple Psychiatric Conditions

AAP-Bright Futures[150] and the American College of Obstetricians and Gynecologists[151] are consistent in recommending screening for emotional and behavioral issues, with followup diagnostic and treatment services (**Table 1**).

Chapter 2. Methods

Key Questions and Analytic Framework

The scope and key questions (KQs) were developed by the Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers. **Figure 1** depicts the analytic framework and KQs that guided the review.

Five KQs were developed for this review:

1. Do depression, anxiety, or suicide risk screening programs in primary care or comparable settings result in improved health outcomes in children and adolescents?
2. Do instruments to screen for depression, anxiety, or suicide risk accurately identify children and adolescents with depression, anxiety, and increased risk of suicide in primary care or comparable settings?
3. What are the harms associated with screening for depression, anxiety, or suicide risk in primary care or comparable settings in children and adolescents?
4. Does treatment (psychotherapy, pharmacotherapy, or collaborative care) of depression, anxiety, or suicide risk result in improved health outcomes in children and adolescents?
5. What are the harms of treatment (psychotherapy, pharmacotherapy, or collaborative care) in children and adolescents who are treated for depression, anxiety, or suicide risk?

In addition to addressing the KQs, this review also looked for evidence related to six contextual questions (CQs):

1. What is the diagnostic yield from screening for depression, anxiety, or suicide risk in typical primary care practice settings?
2. What are the minimal clinically important differences (the smallest value of benefit to patients) for symptoms and functioning on the most common instruments used to measure response to treatment of depression, anxiety, or suicide risk?
3. What are the U.S. FDA boxed warnings for pharmacotherapy for the treatment of depression, anxiety, or suicide risk in children and adolescents?
4. What psychotherapies other than CBT are used to treat anxiety in children and adolescents?
5. What is the effectiveness of evidence-based treatment in children and adolescents with persistent depressive disorder (PDD) and depressive disorders not otherwise specified (DDNOS)?
6. What proportion of children and adolescents who screen positive for depression, anxiety, or increased suicide risk engage with care (i.e., return for clinical evaluation and treatment)?

These CQs were not a part of this systematic review. They are intended to provide additional background information. **Appendix A** presents a summary of the literature addressing these questions.

Data Sources and Searches

This review includes three conditions and builds on prior reviews for the USPSTF for suicide risk[119] and depression,[152] and AHRQ Effective Healthcare Program (EHC) reviews on anxiety[123] and depression.[153] As a result date limits vary by topic and database. PubMed and the Cochrane Library were searched on April 28, 2020. PsycINFO and CINAHL were searched on April 30, 2020. Depression searches were limited to articles published from January 1, 2015 to April 28, 2020; anxiety searches were limited to articles published from January 1, 2017 to April 28, 2020; and suicide risk searches were limited to articles published between June 1, 2012 to April 28, 2020. We conducted a bridge search on July 19, 2021, and surveillance through June 1, 2022. Search terms and Medical Subject Headings (MeSH) focused on terms that describe relevant populations, tests, interventions, outcomes, and study designs was used when applicable. The search relied primarily on the previous systematic reviews for the USPSTF (depression,[152] suicide[119]) and the AHRQ EHC (anxiety[123]) to identify potentially relevant studies published before the last search data in each of the three reviews. Complete search terms and limits are listed in **Appendix B**. ClinicalTrials.gov was searched for unpublished literature. To supplement electronic searches, reference lists of relevant articles, systematic reviews, and studies meeting the inclusion criteria were reviewed.

Study Selection

We developed inclusion and exclusion criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs with input from the USPSTF (**Appendix C**). We included English-language studies of children and adolescents age 18 years or younger on average conducted in countries categorized as "very high" on the 2019 Human Development Index.[154]

When possible, we aligned inclusion and exclusion criteria across the three conditions (suicide risk, anxiety, depression), with the exception of three criteria. First, population inclusion criteria were broader for depression treatment studies (KQs 4 and 5) than for anxiety or suicide risk. For depression, although the population criterion focuses on MDD (as defined by the DSM), we included treatment studies that had as few as 51 percent of participants with MDD to include studies with participants with PDD or DDNOS. This approach ensures consistency with the prior USPSTF review on screening for depression in children.[152] Furthermore, we addressed the effectiveness of treatment for PDD and DDNOS in a CQ. For other conditions, we required that treatment studies limit participants to those with anxiety disorder or with increased suicide risk. As noted earlier, anxiety disorders can vary widely, and their onset may vary by age. Given this heterogeneity, eligible anxiety disorders included GAD, social anxiety disorder, panic disorder, agoraphobia, separation anxiety disorder, and selective mutism. Definitions for increased risk of suicide varied by study but could include suicidal ideation (suicidal thoughts or plan for suicide), history of suicide attempts (nonfatal, self-directed, and potentially injurious behavior that is intended to result in death), and deliberate self-harm.

Second, for depression and suicide risk interventions, we were more inclusive of a wide range of psychotherapy, counseling, and care delivery models (such as collaborative care and care

management) than for anxiety. For anxiety, we limited nonpharmacological interventions to CBT in the interest of efficiency.

Third, we were more inclusive of a wide range of comparators for suicide risk interventions. We included treatment-as-usual comparators because ethical concerns limit the ability to conduct comparative studies using placebo or wait-list controls. For depression and anxiety interventions, we restricted comparators to placebo, wait-list, no intervention, attention control, and usual care. We did not include treatment-as-usual studies in specialist settings for these conditions because the comparison may understate the benefits of screening in primary care where the comparison is likely to be usual care in primary care settings.

Fourth, we accounted for the condition in assessing the accuracy of screening. For anxiety and depression, we required eligible studies to compare the accuracy of screeners with structured clinical interviews using standard diagnostic criteria. For suicide risk, however, we required the screener to be compared with an assessment of increased suicide risk based on an interview by a qualified professional.

For all conditions, a priori priority subpopulations of interest included younger age (children vs. adolescents), race/ethnicity, sex, gender identity, and sexuality. We limited pharmacotherapy to pharmacotherapy agents approved for pediatric use (e.g., clonidine, duloxetine, fluoxetine, escitalopram, sertraline, fluvoxamine). Interventions were required to be relevant to or referable from primary care; school-wide and community screening and interventions were excluded as a result. Eligible health outcomes across all conditions for KQ 1 and KQ 4 (screening and treatment benefits) included depression or anxiety symptoms as measured through validated instruments, clinical response, or remission; suicide deaths, suicide attempts and deliberate self-harm or suicidal ideation; all-cause mortality; quality of life measured using validated scales or instruments; and functioning (using validated scales or instruments, days of missed school, sleep-related outcomes). Eligible harms included treatment avoidance, deterioration in patient-provider relationship, labeling or stigma, inappropriate/unnecessary treatment, serious adverse effects, withdrawals due to adverse effects, and suicidality. Eligible settings across all KQs included primary care clinics, including school-based health clinics, and virtual or community-based settings. For screening questions (KQs 1 through 3), we also included studies recruiting from general emergency departments and schools. For treatment questions (KQs 4 and 5), we also included specialty clinics. We excluded studies of school-wide screening for KQ 1. We included RCTs for KQs 1, 3, 4, and 5 and diagnostic accuracy studies for KQ 2. Additionally, we included nonrandomized, controlled trials for KQ 1 and KQ 3. We included observational studies for the harms questions (KQ 3 and KQ 5). For KQ 5, we included systematic reviews of comparative cohort and case-control observational studies to capture rare harms but restricted pharmacotherapy harms studies to large (>1,000 participants) comparative cohort and case-control observational studies published after eligible systematic reviews.

Titles and abstracts were independently reviewed by two investigators; those marked for potential inclusion by either reviewer were retrieved for evaluation of the full text. The full texts were then independently reviewed by two investigators to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

Quality Assessment and Data Abstraction

For newly identified studies, two senior reviewers independently assessed each study's methodological quality using predefined criteria developed by the USPSTF (**Appendix D**) conducted using instruments devised for each of the included study designs, specifically Cochrane ROB 2.0 for randomized studies of interventions[155] (KQs 1, 3, 4, and 5), the ROBINS-I tool[156] for nonrandomized studies of interventions[123] (KQ 5), ROBIS for systematic reviews (KQ 5),[157] and the QUADAS-2 instrument[158] for diagnostic accuracy (KQ 2)**.** We re-rated all previously included accuracy studies (KQ 2). We spot-checked and carried forward quality ratings of studies included in two recent AHRQ EHC reports on depression[153] and anxiety[123] in children and adolescents.[153] Studies reporting benefits and harms may have been assigned different quality ratings for benefits and harms. Disagreements were resolved by discussion. Only studies rated as having good or fair quality were included in the synthesis.
For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. All data extractions were checked by a second investigator for completeness and accuracy.

Data Synthesis and Analysis

Findings for each KQ were summarized qualitatively and in tabular format. The overall strength of the evidence for each KQ was assessed as high, moderate, low, or insufficient based on the overall quality of the studies, consistency of results between studies, precision of findings, risk of reporting bias, and limitations of the body of evidence, using methods developed for the USPSTF and the EPC program.[159] Additionally, the applicability of the findings to U.S. primary care populations and settings was assessed. Discrepancies were resolved through consensus discussion.

Additionally, when at least three independent and similar studies were available, pooled effects for relative risks for categorical outcomes and standardized and weighted mean differences for continuous outcomes random-effects models were generated using the inverse-variance weighted method of DerSimonian and Laird. Absolute risk differences were presented for outcomes with signals of benefit or harm. The clinical and methodological heterogeneity of the studies was assessed according to established guidance,[160] and similarities and differences in populations, tests, treatments, comparators, outcomes, and study designs were assessed qualitatively. Statistical heterogeneity of findings was assessed with the I^2 statistic; 0 percent to 40 percent might not be important; 30 percent to 60 percent may represent moderate heterogeneity; 50 percent to 90 percent may represent substantial heterogeneity; and 75 percent to 100 percent represents considerable heterogeneity.[161] All quantitative analyses were conducted using Comprehensive Meta-Analysis (Version 3.3) software.[162] We considered pooled findings statistically significant when the 95% confidence intervals (CIs) excluded the null value. We assessed the potential for publication bias through visual inspection of a funnel plot when at least 10 studies were included in an analysis.

U.S. Preventive Services Task Force Involvement

The authors worked with USPSTF liaisons throughout the review process to develop and refine the analytic framework, key questions, and scope of the work. AHRQ staff provided project oversight, reviewed the report, and assisted in conducting an external review of the draft evidence synthesis.

Expert Review and Public Comment

The draft Research Plan was posted on the USPSTF website for public comment from April 30, 2020, to May 27, 2020. Regarding suggested edits to the KQs, one commenter noted that screening is intended to identify those at increased risk for any of the eligible conditions (anxiety, depression, suicide risk, or a combination), not just those at increased risk of suicide. In response, the USPSTF edited the key questions to remove the qualifier "increased risk of suicide" and instead refers to "suicide risk." One comment suggested a focus on implementation barriers rather than the effectiveness of screening. Although we agree that these factors are important, the review is intended to support a screening recommendation. Commenters suggested edits to the CQs to improve clarity. In response, we revised CQ 2 to clarify that the term "minimal clinically important differences" refers to the smallest value of benefit to patients. We revised CQ 3 and CQ 4 to specify that the population of interest is children and adolescents. We qualified CQ 5 as being limited to evidence-based treatments and clarified that engagement with care in CQ 6 refers to returning for clinical evaluation and treatment.

Regarding suggested edits to the inclusion and exclusion criteria, one commenter suggested focusing on screen-detected populations in reviewing the treatment literature. Although we agree that for treatment questions, screen-detected populations are ideal, the evidence is likely to be extremely sparse. As a result, we are not restricting treatment studies to screen-detected populations alone. One commenter suggested excluding clomipramine because it is not a first-line therapy; in response, we excluded clomipramine. Some reviewers asked about the exclusion of active comparators for treatment questions. The USPSTF considers comparative effectiveness to be outside of its scope. Commenters suggested several outcomes; in response, we have clarified that we will include validated outcomes for prespecified outcomes for KQ 1 and KQ 4 and have added false alarm and false reassurance to outcomes for KQ 3. Some comments focused on priority populations; the review will report on priority populations defined by age, sex, race/ethnicity, gender identity, and sexuality. Some comments highlighted the importance of context, applicability, type of intervention, and type of disorder. We considered these factors in the analysis, when data were available. A final research plan was posted on the USPSTF's website on August 13, 2020.

The draft evidence review was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers and was revised based on comments received. Specifically, we added followup data from an included study and revised the abstraction of an existing study. We also revised data on prevalence and burden in the introduction section. The draft evidence review will also be posted for public comment. Revisions will be made based on

comments received, and any references suggested by expert or public reviewers will be evaluated for inclusion/exclusion.

Chapter 3. Results

We screened 37,706 titles and abstracts and 798 full-text articles to identify 80 unique studies from 106 publications for inclusion (**Figure 2**).[163-268] Nine of these studies were new to the update of suicide[164, 179-181, 192, 194, 202, 212-215, 221, 222, 229, 236] and 8 primary studies and one meta-analysis were new to the update of depression.[172, 173, 176, 187, 204, 205, 216, 217, 248, 249, 266] We identified no studies reporting on the benefits (KQ 1) of screening.

We identified 17 studies on accuracy of screening (KQ 2).[166, 170-172, 188, 189, 199, 218, 219, 223, 230-232, 234, 235, 247, 250] Of these, one reported on suicide,[247] 10 on anxiety,[166, 171, 188, 199, 218, 219, 230-232, 250] seven on depression,[170, 172, 189, 199, 219, 223, 235] and two on combined screeners for anxiety or depression.[219, 234] Three of these studies reported on more than one condition.[199, 219, 234] We included two studies, both on harms of screening for suicide risk (KQ 3).[267, 268] Sixty studies were included for benefits (KQ 4); of these, 16 reported on suicide,[164, 179-182, 191-194, 197, 200-202, 212-215, 221, 222, 229, 236, 245, 265] 29 on anxiety,[163, 165, 167-169, 177, 178, 183, 190, 195, 196, 198, 203, 206, 220, 224-228, 237-244, 246, 251, 253-262] 13 on depression,[174-176, 185-187, 204, 205, 207-211, 216, 217, 233, 248, 249, 252, 266] and two on depression or anxiety.[184, 263, 264] Twenty studies were included on harms (KQ 5), including two on suicide,[179-181, 192] 11 on anxiety,[168, 169, 224-228, 238, 239, 242-244, 253-262] and seven on depression.[173, 176, 185, 186, 207-211, 233, 252, 266] Details of quality assessments of included studies and studies excluded based on poor quality are provided in **Appendix D**. **Appendix E** presents details of screeners, reference standards, and outcome measures. **Appendix F** presents detailed results organized by outcome and **Appendix G** presents forest plots for meta-analyses described in Chapter 3. **Appendix H** presents results for off-target symptoms (e.g., improvement in anxiety for interventions designed to address depression). **Appendix I** presents complete evidence tables for all studies. **Appendix J** lists studies excluded at full-text screening.

The results below present findings by KQ first, then by condition for suicide risk, anxiety, depression, and finally studies requiring dual diagnoses or including more than one diagnosis. Within each section, we describe study characteristics and results for each outcome for the overall population and for specific populations (for priority populations defined by age, sex, race/ethnicity, gender identity, and sexuality and within age groups).

KQ 1. Do Depression, Anxiety, or Suicide Risk Screening Programs in Primary Care or Comparable Settings Result in Improved Health Outcomes in Children and Adolescents?

We found no eligible studies addressing KQ 1 on direct evidence for health outcomes of screening for depression, anxiety, or suicide risk on health outcomes in primary care or primary care–relevant settings. KQs 2 and 4 provide indirect evidence by summarizing the accuracy of screening and benefits of treatment, respectively.

KQ 2. Do Instruments to Screen for Depression, Anxiety, or Suicide Risk Accurately Identify Children and Adolescents With Depression, Anxiety, and Increased Risk of Suicide in Primary Care or Comparable Settings?

Suicide Risk

We included one fair-quality study, which was included in the previous review.[247]

Study Characteristics

The one identified study recruited participants (N=580) from seven high schools in the Pacific Northwest region of the United States.[247] Eligible participants were potential high school dropouts ages 14 to 20 years. Forty-two percent were female; 57 percent were White, 20 percent were African American, 14 percent were Asian American, 8 percent were Latino, and 2 percent were American Indian. Authors used the Suicide Risk Screen (SRS), a 20-item screener, that was embedded into a longer questionnaire. The screen is considered positive if the youth scores in any one of three categories designating increased risk. This study evaluated the SRS against two reference standards both of which were completed within 7 to 10 days of screening. The first reference standard was a direct suicide risk as determined during the Measure of Adolescent Potential for Suicide (MAPS) clinical interview, and the second reference standard was a clinical risk assessment (CRA) global rating made after completing the MAPS.

Results of Included Studies

The prevalence of increased suicide risk was 19 percent based on the Direct Suicide Risk reference standard and 22 percent based on the Clinical Risk Assessment reference standard.[247] The sensitivity and specificity of the SRS against the DSR reference standard was 0.91 and 0.60, respectively.[247] Against the CRA reference standard, the sensitivity and specificity were 0.87 and 0.60, respectively.[247]

Results: Findings for Specific Populations

Subgroup Analyses

Authors reported no results by populations of interest prespecified for this update.

Findings Within Age Groups

All studies reported results for adolescent participants.

Anxiety

Study Characteristics

We included 10 studies that assessed accuracy of screeners for detecting anxiety,[166, 171, 188, 199, 218, 219, 230-232, 250] all of which were of fair quality. Detailed study characteristics are provided in **Appendix I Table 1**. All 10 studies were new in this update. Three studies[166, 199, 230] were located in the United States; two[171, 188] in Spain; two[231, 232] in Finland; and one each in the Netherlands,[218] United Kingdom,[219] and Taiwan.[250] Six studies recruited their samples from schools;[171, 188, 218, 231, 232, 250] three recruited from primary care,[166, 199, 230] and one from hospital outpatient departments and pediatric mental health clinics.[219]

Studies examining accuracy of anxiety screeners included adolescents only[188, 199, 230-232, 250] and both children and adolescents.[166, 171, 218, 219] In studies where sex was reported,[166, 171, 188, 199, 218, 219, 230] the percentage of females ranged from 43 to 63 percent. In the four studies that reported race/ethnicity,[166, 199, 219, 230] the percentage of non-White youth ranged from 1 to 58 percent.

Index Screeners

Overall, the studies assessed 12 different screeners for detecting anxiety in youth, some of which were examined in multiple studies. **Appendix E Table 1** provides a brief description of each. Three studies evaluated the Screen for Child Anxiety Related Disorders (SCARED),[166, 171, 218] administering both the parent and child versions. Canals et al[171] also assessed the SCARED short version with both parents and children respondents. Two studies evaluated the Social Anxiety Scale (SAS), one of which[166] assessed the use for children (SAS-C) and both of which assessed the version for adolescents (SAS-A).[166, 188] Whereas Bailey et al[166] administered the SAS-C and the SAS-A with both parents and children/adolescents as informants, Garcia-Lopez et al[188] administered the SAS-A to adolescents only. Two studies[188, 250] evaluated the Social Phobia Inventory (SPIN), and two studies[188, 232] evaluated the related Mini-SPIN, all with adolescents; however, Garcia-Lopez et al[188] did not report sensitivity or specificity and thus is not discussed further. One study assessed the Social Worries Questionnaire (SWQ-P),[166] administering it to parents of both children and adolescents. One study each evaluated the Paediatric Index of Emotional Distress (PI-ED),[219] the Autonomic Nervous System Questionnaire (ANS),[230] and the Patient Health Questionnaire—Adolescents (PHQ-A),[199] for detecting panic disorder and GAD. One study[188] assessed the Social Phobia and Anxiety Inventory-Brief (SPAI-B), the Social Phobia Inventory (SoPhI), the Escala para la Deteccion de Ansiedad Social (EDAS), and the Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA) with adolescents. The Garcia-Lopez study[188] only reported area under the curve (AUC) rather than sensitivity or specificity data for the SPIN, Mini-SPIN, EDAS, LSAS-CA, or SoPhI; these data appear in the evidence tables in **Appendix I Table 1** but are not discussed hereafter. The results focus on the nine instruments (comprising 15 variations) with results on sensitivity and specificity.

Reference Standards

In all cases, the diagnostic assessment used as the reference standard was a clinical interview. **Appendix E Table 2** provides a description of each interview. Three studies[166, 188, 230] used the

Anxiety Disorders Interview Schedule for DSM-IV-for Children (ADIS). One study[166] interviewed parents, one study[230] interviewed adolescents, and one study[188] interviewed both parents and adolescents. Two studies[171, 250] interviewed the children and adolescents using the MINI International Neuropsychiatric Interview for Kids (MINI-Kid). Two studies[231, 232] used the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL). One study each interviewed the youth with the Child edition of the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* Version IV (DSM-IV) (child edition of the structured clinical interview for DSM-IV [KSCID]),[269] the Computerized Diagnostic Schedule for Children (C-DISC),[219] and a diagnostic interview using items from several different interview schedules.[199] Five of the eight studies[171, 219, 230, 250] provided information on the timing of the diagnostic assessment in relation to the screening. One study[219] clinically interviewed participants at the same time as the screener was administered, one study[171] interviewed participants within a week of the screener administration, and four studies[230-232, 250] administered the diagnostic assessment within a month of the screener.

Results of Included Studies

Results pertaining to accuracy are found in **Table 2** and are organized by condition. All but one study[230] reported prevalence. The prevalence of anxiety disorders based on the clinical interviews ranged from 2.5 percent to 41 percent. The three studies with the highest prevalence (i.e., 20%, 24%, and 41%)[171, 188, 218] oversampled youth with scores on the screener that were in the at-risk range; thus, we did not use these values when calculating the percentage of false-positives and false-negatives per 1,000 screens. The estimates of prevalence varied by condition. The lowest prevalence of 2.5 percent was for a study detecting GAD,[199] and two studies with unselected samples each had a prevalence of 13 percent, one to detect GAD[218, 219] and one to detect social anxiety disorder.[166]

Global Anxiety

One study evaluated the SCARED[171] to detect global anxiety. In the study of the SCARED, the authors administered the full version of 41 items and a short 10-item version to both children and their parents. Cutoff scores to determine a positive screener varied by screener and respondent. Using the reported index test thresholds,[171] sensitivity ranged between 0.34 and 0.76, and specificity ranged between 0.68 and 0.87 for varying cutoffs on the screeners. With the exception of the full screener administered to children, all sensitivity values were lower than specificity values.

GAD

Three studies assessed screeners to detect GAD. One study[199] assessed the PHQ-A. The sensitivity was 0.5 and the specificity was 0.98. The second study[218] examined the SCARED-GAD scale, finding a somewhat higher sensitivity (0.64) but lower specificity (0.63) than the PHQ-A. The third study assessed the PI-ED (Anxiety Scale)[171] and had a higher sensitivity (0.88) with a comparable specificity (0.85).

Panic Disorder

Two studies assessed screeners for detecting panic disorder—the ANS[230] and the PHQ-A.[199] The study of the ANS assessed accuracy for three versions, with two, three, and four questions. The sensitivity was 1.0 for all versions, whereas the specificity ranged between 0.47 and 0.66. The PHQ-A reported a sensitivity of 0.42 and a specificity of 0.99.

Separation Anxiety Disorder

Only one study[218] examined a screener to detect separation anxiety disorder in adolescents. Using the SCARED—Separation Anxiety Scale, the study found sensitivity to be 0.88 and specificity 0.73.

Social Anxiety Disorder

Several studies reported on screeners to detect social anxiety disorder. Two studies assessed the SAS,[166, 188] one of which administered both the child and adolescent versions.[166] The sensitivity of the SAS varied as a function of the respondent. In one study[188] in which adolescents were the respondents, sensitivity was 0.93 but was 0.75 in another study[166] when parents were responding about their adolescents' symptoms. Specificity in the two studies was comparable—0.80[166] and 0.78.[188] Sensitivity and specificity for parent-reported social anxiety disorder in children[166] was 0.78 and 0.74, respectively.

Three studies assessed the SPIN[231, 250] or the Mini-SPIN.[232] Sensitivity was similar in the two SPIN studies: 0.82[231] and 0.80,[250] as was specificity: 0.85[231] and 0.77,[250] with similar thresholds for a positive screening: 24[231] and 25.[250] The study examining the Mini-SPIN[232] found equally high sensitivity and specificity despite significantly fewer items (3 as opposed to 17 in the SPIN).

Reports on three other screeners to detect social anxiety disorder were in two studies. One study[188] found that the Social Anxiety Scale for Adolescents (SASA) had sensitivity of 0.93 and specificity of 0.79 and that the SPAI-B had sensitivity and specificity of 0.86 and 0.88, respectively. The second study[166] reported that the SWQ had sensitivity of 0.67 for detecting social anxiety disorder in children and 0.83 for detecting social anxiety disorder in adolescents; specificity was 0.94 in children and 0.84 in adolescents.

Any Anxiety Disorder

Two studies[199, 218] examined the utility of screeners to detect any anxiety disorder. One assessed the PHQ-A[199] for detecting either panic disorder or GAD, finding a prevalence of 5 percent, sensitivity of 50 percent, and a specificity of 98 percent. The second study[218] used the SCARED, combining the adolescents who screened positive for GAD, separation anxiety disorder, and/or social anxiety disorder. In this study, the prevalence was 20 percent, with a sensitivity of 0.88 and a specificity of 0.56.

Based on the reported sensitivity and specificity data, the number of false-negatives and false-positives per 1,000 screening tests at the lowest (2.5%)[199] and highest (13)[166, 219, 230] prevalence in an unselected population reported in the included studies is presented in **Table 2**. Three studies reported a higher prevalence for anxiety, but we did not use these values because they sampled all the screen-positive cases, resulting in an artificially high prevalence value. With the exception of the scales from the PHQ-A,[199] the number of false-negatives is lower than the number of false-positives.

Results: Findings for Specific Populations

Subgroup Analyses

No subgroup analyses for specific populations were reported.

Findings Within Age Groups

Seven studies reported on adolescents , and reported on eight instruments (PHQ-A, ANS, SAS, SASA, SPAI-B, SCARED-SP, SPIN, Mini SPIN) for GAD, global anxiety, panic disorder, and social anxiety disorder.[166, 188, 199, 230-232, 250] Inclusion criteria ranged from 12 to 18, with a mean age of 14.8.

Four studies reported on older children and adolescents on seven instruments (full scale, subscale, or short versions of SCARED, PI-ED, and SAS) for GAD, SAD, separation anxiety, and global anxiety.[166, 171, 270, 271] Inclusion criteria for these studies ranged 7 to 17 years, with a mean of 11.0 years.

No studies reported on younger children.

Only one study (Bailey et al. 2006[166]) reported results separately for adolescents and children for the same instruments (SCARED-SP, SAS-A, SAS-C, and SWQ); these results did not suggest consistent differences in sensitivity and specificity by age of the children, and variations in instruments and thresholds may explain differences in results. No other studies reported on both children and adolescents for a single instrument and condition.

Across instruments and conditions, differences between studies reporting on adolescents versus adolescents and children also did not suggest age-related patterns; the wide range of instruments, thresholds, and conditions preclude making conclusions about accuracy for children versus adolescents.

Depression

We included seven fair-quality studies of diagnostic test accuracy.[170, 172, 189, 199, 219, 223, 235] Two studies were new to this update.[172, 219] Brief study characteristics are provided in **Table 3**.

Study Characteristics

Three studies were conducted in the United States,[189, 199, 235] and the rest were conducted in various countries in Europe[170, 172, 219] and Australia.[223] One study[219] enrolled both children and adolescents, while the rest enrolled only adolescents. Studies enrolled boys and girls in relatively equal proportions. In the studies conducted in the United States, the proportion of participants who were Black was between 1 percent and 25 percent; in the rest of the studies, participants were nearly entirely White or race and ethnicity was not reported. Two studies recruited participants from clinical settings (primary care,[172] mix of primary care and outpatient mental health service[219]), one study recruited participants from primary care and school nurse offices,[199] and the rest of the studies recruited from either school-based samples[189, 223, 235] or the community.[170]

Index Screeners

Authors of the included studies assessed seven different screening instruments (Beck Depression Inventory [BDI],[170, 235] Center for Epidemiologic Studies-Depression [CES-D],[189, 235] Clinical Interview Schedule—Revised [CIS-R],[223] Hopkins Symptom Checklist [HSCL],[172] PHQ-A,[199] PI-ED Depression Subscale,[219] and the World Health Organization Five Item Well-Being Index [WHO-5][172]). Some authors assessed more than one instrument or more than one threshold for a positive screen for the same instrument. Few studies prespecified thresholds for a positive screen. **Appendix E Table 1** includes detailed screening test characteristics.

Reference Standards

Authors used clinical diagnostic interviews administered either concurrently or within 4 weeks of screening as a reference standard; most (but not all) reference standards were structured diagnostic clinical interviews tied to existing diagnostic criteria such as the DSM. Detailed reference standard information is included in **Appendix E Table 2**. All studies reported sensitivity and specificity for current MDD; many also reported positive and negative predictive value. Only one study reported results separately for boys and girls.[189] No other data for specific populations were reported.

Results of Included Studies

The prevalence of major depression based on reference standard diagnostic clinical interviews ranged from 3 percent to 9 percent across studies enrolling persons recruited from school or community-based settings[170, 189, 223, 235] and was 11 percent in all three of the studies enrolling persons from nonpsychiatric clinical settings.[172, 199, 219]

Two studies evaluated the original BDI;[170, 235] the BDI-II published in 1996 was a substantial revision to the original BDI. Both studies reported sensitivity and specificity at a score threshold of 11 or higher (scores less than 9 are considered no or minimal depression, scores between 10 and 18 are considered "mild to moderate" depression[272] in adults). At a score threshold of 11, the sensitivity and specificity were 0.84 and 0.81, respectively, in one study[219, 235] and 0.90 and 0.86,

respectively, in the other study.[170] One of these studies also provided estimates of sensitivity and specificity at lower and higher thresholds (**Table 3**).[170]

Two studies evaluated the CES-D but did not evaluate the same thresholds.[189, 235] On this instrument, a score of 16 or more is considered positive for subthreshold depression in adults.[273] In one study, the sensitivity and specificity of a threshold score of 24 or more were 0.84 and 0.75, respectively.[235] The other study reported sensitivity and specificity separately for boys and girls at four different scoring thresholds (12, 16, 20, and 22). At the threshold of 16, the sensitivity in boys was 0.59 and in girls was 0.83, and the specificity in boys was 0.66 and in girls was 0.53.[189]

The CIS-R,[223] HSCL,[172] PHQ-A,[199] PI-ED,[219] and WHO-5[172] were each only evaluated in one study. Across these instruments, the reported sensitivity ranged from 0.18 to 0.94, and the specificity ranged from 0.80 to 0.97. The outlier values were for CIS-R (reported sensitivity of 0.18 and specificity of 0.97, from analysis weighting for selection into the second phase of the study).[223] Calculated sensitivity without weighting resulted in a sensitivity of 0.74 and specificity of 0.78.[223]

Based on the reported sensitivity and specificity data, the number of false-negatives and false-positives per 1,000 screening tests at the lowest (3%)[235] and highest (11%)[172, 219] prevalences reported in the included studies are reported in **Table 3**. For nearly all studies, the number of false-negatives is lower than the number of false-positives.

Results: Findings for Specific Populations

Subgroup Analyses

One study reported accuracy results separately for boys and girls for the CES-D instrument.[189] The area AUC in boys was 0.61 and in girls was 0.77. Except for the lowest score threshold evaluated (greater than or equal to 12), the sensitivity in boys was markedly lower than in girls. The specificity at all four thresholds evaluated was higher in boys than in girls. Authors did not conduct formal statistical significance testing of these differences by sex.

The only study enrolling both children and adolescents did not report results separately by age.[219] No studies reported results by any other specific populations prespecified in our research plan.

Findings Within Age Groups

Only one study, as noted above, enrolled children along with adolescents and did not report the results by age.[189] All other studies were restricted to adolescents.

Anxiety or Depression

Two fair-quality studies reported the accuracy of a positive screening test for either or both anxiety or depression diagnoses.[219, 234] One study reported on the sensitivity and specificity of the

PI-ED for either GAD or MDD,[219] and the other study reported on the accuracy of the 5-item Mental Health Index (MHI-5) for anxiety or depression.[234]

Study Characteristics

Authors conducted the study evaluating the PI-ED among youth ages 8 to 17 years (mean age 12 years) recruited from eight hospital outpatient pediatric departments in Scotland and from child and adolescent mental health clinics or psychology services.[219] Nearly half (48%) were female, and nearly all were White. The-PI-ED test (score threshold of 20 or higher) was compared with the Computerized Diagnostic Schedule for Children, a type of structured clinical interview. Authors conducted the study evaluating the MHI-5 among youth ages 10 to 15 years (mean age 12 years) recruited from schools in Spain, and nearly half were female (49%). Authors evaluated both the full 5-item MHI-5 instrument and also the 3-item "distress" factor; the 2-item well-being factor was not evaluated. The MHI-5 screener was also compared with a structured clinical interview (Anxiety Disorders Interview Schedule for DSM-IV: Child and Parent Version).

Results of Included Studies

The sensitivity and specificity of the PI-ED for either a diagnosis of GAD, MDD, or both at a score threshold of 20 was 0.83 and 0.93, respectively.[219] The AUC for the full MHI-5 instrument for anxiety or depression was 0.78 (95% CI, 0.64 to 0.93). The authors reported that the optimal threshold was a score of 3 or higher on the 3-item distress factor of the full MHI-5, which yielded a sensitivity of 0.69 and a specificity of 0.72 (AUC 0.80; 95% CI, 0.68 to 0.92 for the 3-item distress factor).[234]

Results: Findings for Specific Populations

Subgroup Analyses

Authors reported no results by specific populations of interest prespecified for this update.

Findings Within Age Groups

Both studies included children and adolescents; neither reported on children and adolescents separately.

KQ 3. What Are the Harms Associated With Screening for Depression, Anxiety, or Suicide Risk in Primary Care or Comparable Settings in Children and Adolescents?

Suicide Risk

Summary

We included two RCTs of fair quality (described in 2 articles).[267, 268] Neither study is new to this update. Detailed study, population, intervention characteristics, and results are provided in **Appendix I Table 2 through Table 4**.

Study Characteristics

We identified two fair-quality trials (total randomized N=2,675) conducted in high school settings relevant to this KQ.[267, 268] Both studies randomly assigned students to complete items relating to suicidal ideation and behaviors as part of an assessment of universal mental health screening[267] or as part of larger questionnaires concerning the evaluation of a workshop.[268] In the universal screening study (N=2,342), half of the classrooms in six high schools located in Nassau, Suffolk, and Westchester counties (New York State) were randomized to receive the suicide questions on the first day (intervention group), and the other half received them on the second day (control group).[267] In the workshop evaluation study (N=333), half of the students in Year 10 at a single all-boys school in Melbourne, Australia, were randomized to receive the suicide items on the first day (intervention group), while the others received them on the second day (control group).[268] Both studies compared measures of distress between Day 1 screened and Day 2 students to assess the impact of screening for suicidal risk.

Results

The universal screening study reported no differences in distress immediately after the screening questionnaire or in persistent distress (measured 2 days later) between the intervention and control groups as measured by the adolescent version of the Profile of Mood States (POMS-A).[267] POMS-A is designed to capture transient mood states and is sensitive to change over short periods of time; detailed POMS-A results are reported in Appendix I Table 4.[267] Similarly, a workshop evaluation study reported no significant difference in five of the six POMS-A subscales.[268] One subscale (vigor) was significantly different between groups, but this may be due to chance.[268]

The universal screening measured suicidal ideation in both groups on the Day 2 survey and found no significant differences between groups (mean score 6.5 [standard deviation (SD): 11.5] vs. 6.2 [10.5], p=0.86) as measured by the Suicidal Ideation Questionnaire-Junior (SIQ-JR) instrument on the rates of participants with suicidal ideation between the first and second surveys (4.7% vs. 3.9%, p=0.49).[267] These results suggest that exposure to the suicide screening items on Day 1 in the intervention group did not result in any increases in suicidal ideation.[267]

In the workshop evaluation study, authors asked students about their level of distress in answering questions about self-harm and suicide after both groups had answered the suicide screening items: 5.2 percent reported that it was "moderately distressing" and 3.7 percent reported that it was "very distressing."[268] Fifty percent reported that it was "not at all distressing."[268]

Neither study examined screening-related harms by sex, race, or ethnicity.

Depression

We did not identify any studies reporting on harms of screening for depression.

Anxiety

We did not identify any studies reporting on harms of screening for anxiety.

Anxiety or Depression

We did not identify any studies reporting on harms of screening in populations with anxiety or depression.

KQ 4. Does Treatment (Psychotherapy, Pharmacotherapy, or Collaborative Care) of Depression, Anxiety, or Suicide Risk Result in Improved Health Outcomes in Children and Adolescents?

Suicide Risk

Summary

We included 16 RCTs of good or fair quality (described in 23 articles).[164, 179-182, 191-194, 197, 200-202, 212-215, 221, 222, 229, 236, 245, 265] Nine of these studies are new to this update.[164, 179-181, 192, 194, 202, 212-215, 221, 222, 229, 236] Detailed study, population, intervention characteristics, and results are provided in **Appendix I Table 5 through Table 16**. Detailed outcomes included in meta-analyses are provided in **Appendix F Table 1 and Table 2**. Meta-analysis forest plots are provided in **Appendix G Figure 1 through Figure 7**.

Study Characteristics

The characteristics of the included studies are summarized in **Table 4**. Fourteen studies admitted children based on elevated suicide risk,[164, 179-181, 191-194, 197, 200-202, 212-215, 221, 222, 229, 236, 265] and two studies admitted children with suicide risk and self-reported depressive symptoms (BDI>19[245] or BDI>20[182]).

Mean ages ranged from 14 to 18 years. All 16 included studies focused on adolescents (ages 11 to 19 years)[164, 179-182, 191-194, 197, 200-202, 212-215, 221, 222, 229, 236, 245, 265] and included a majority of female participants. Ten studies reported a majority of White participants,[164, 191, 192, 194, 197, 200-202, 221, 222, 229, 236] one study included a majority of African American participants,[182] and five studies did not report race or ethnicity.[179-181, 193, 212, 245, 265]

All included studies examined psychotherapy, counseling, support, or a combination with variable intensity and duration. Fifteen studies compared these interventions with treatment as usual (TAU),[164, 179-182, 191-193, 197, 200-202, 212-215, 221, 222, 229, 236, 245, 265] and one study compared intervention to attention control.[194] Fifteen of the included trials[164, 179-182, 191-194, 200-202, 212-215, 221, 222, 229, 236, 245, 265] examined one active arm, and one trial[194] examined three active treatment arms. Five trials included individual child-/adolescent-only interventions,[194, 197, 202, 221, 222, 245] three included child-/adolescent-only group-based interventions,[191-193] one included family-based intervention,[179-181] three included caregiver-/supporting adult–only interventions,[197, 200, 201, 229] and six included a combination of individual child-/adolescent-, caregiver-/supporting adult-, group-, or family-based interventions.[164, 182, 197, 212-215, 236, 265] Duration of treatment ranged between one single session to weekly sessions over 12 months. Overall, 11 trials[164, 179-182, 191-193, 212-215, 229, 236, 245, 265] examined interventions that required 3 or more sessions), and five trials[194, 197, 200-202, 221, 222] examined interventions requiring fewer than 3 sessions). No evidence was captured that examined pharmacotherapies.

All 16 studies reported on suicide or self-harm–related outcomes, 13 studies reported on depression,[179-182, 191-194, 197, 200, 202, 212-215, 236, 245, 265] three studies reported on anxiety,[192, 197, 245] one trial reported on burdensomeness,[194] eight studies reported on functioning,[179-181, 191, 193, 200, 212-215, 221, 222, 229, 265] two studies reported on response,[182, 194] and one study reported on all-cause mortality.[201] Time of measurement across all outcomes ranged from 2 weeks to 14 years.

Two studies recruited participants from schools;[197, 245] five recruited from child and adolescent mental health services; one recruited from emergency departments and community mental health services;[229] two recruited from emergency departments and child and adolescent mental health services;[221, 222, 236] one recruited from emergency departments and primary care offices;[182] one recruited from emergency departments, inpatient/patient hospitalization, and outpatient services;[164] one recruited solely from a hospital emergency department;[202] one recruited from psychiatric outpatient clinics;[181, 212-215] one recruited participants from schools and public gathering places frequented by adolescents;[194] and one study recruited participants from inpatient settings following psychiatric hospitalization.[200, 201]

Included studies were conducted in the United States,[164, 182, 194, 197, 200-202] United Kingdom,[179-181, 191, 192, 221, 222, 236, 265] Australia,[193, 229] Norway,[181, 212-215] and Taiwan.[245] Six of the included studies[179-181, 191, 193, 194, 212-215, 265] were rated as good quality, and 10 studies[164, 182, 192, 197, 200-202, 221, 222, 229, 236, 245] were rated fair quality. Two of the included studies reported on specific populations of interest.[179-182]

Results: Suicide Deaths

Psychotherapy, Counseling, Support, or Combined Interventions vs. Treatment as Usual or Attention Control

Three studies reported on the effects of suicide or self-harm interventions with variable intensity and duration on suicide deaths at the end of treatment (19 weeks to 12 months).[191, 200, 212-215] Studies compared dialectical behavior therapy (DBT),[212-215] youth-nominated support team,[200] or group therapy[191] with TAU. Two of the interventions[191, 212-215] were high contact (>3 sessions), and one intervention[200] was low contact (<3 sessions). Two studies[191, 212-215] reported no suicide deaths at the end of treatment in either arm. One study, using a youth-nominated support team approach (n=346) reported no statistically significant differences between intervention and control at the end of treatment (0 vs. 1, p=NR).[200] A longer term followup of that study, 11 to 14 years after psychiatric hospitalization for suicide risk (baseline for the study), found no statistically significant differences in suicide-related deaths.[201] One study of DBT continued to record no deaths in either arm at the 3-year followup.[212-215]

Results: Suicide-Related Hospitalization or Emergency Department Use

Psychotherapy, Counseling, Support, or Combined Interventions vs. Treatment as Usual or Attention Control

Five studies reported on the effects of suicide or self-harm interventions with variable intensity and duration on suicide-related hospitalization or emergency department use at the end of treatment (12 weeks to 2 years) (**Appendix F Table 1**).[164, 179-181, 192, 212-215, 221, 222] Four studies reported nonsignificant differences between intervention and TAU, and one study[164] reported significant differences. Included studies examined family therapy,[179-181] DBT,[212-215] therapeutic assessment,[221, 222] mentalization-based therapy (MBT)[192], and CBT.[164] Four of the interventions[164, 192, 212-215] were high contact (≥3 sessions), and one intervention[221, 222] was low contact (<3 sessions).

Results were pooled for the three studies reporting on use of hospitals or emergency departments: hospital attendance for self-harm,[179-181] self-harm presentation to accident and emergency department,[221, 222] or self-harm presentation to emergency department.[212-215] These studies resulted in a pooled RR of 0.998 (**Appendix G Figure 1**, 95% CI, 0.67 to 1.50; N=978; k=3; I^2=21%; p=0.28). One study did not report sufficient data to permit pooling and reported no statistically significant differences in the mean number of self-harm emergency department presentations between MBT and TAU (0.36 vs. 0.23, p=NR).[192] A fifth study[164] reported significant differences between intervention and TAU; the study reported that the probability of survival at 3-month post-treatment without an emergency department visit for suicidality was lower for the TAU group (0.71, SE 0.11) compared with CBT (0.90, SE 0.07, Z=2.00, p=0.045, number needed to treat=5.26); in sensitivity analyses, these differences were no longer statistically significant. The differences for hospitalization were not statistically significantly different.

The study reporting on self-harm presentation to emergency departments also reported on hospital admissions due to self-harm and found no statistically significant differences between DBT and TAU (2% vs. 5%, p=NS).[212-215]

One study reported on hospital attendance for self-harm event at 12 months, 18 months, and 36 months and continued to find no statistically significant differences between family therapy and TAU.[179-181] One study of MBT continued to report no statistically significant differences between arms in mean number of self-harm emergency department presentations at 24 weeks.[192]

Results: Suicide Attempts or Episode of Deliberate Self-Harm

Psychotherapy, Counseling, Support, or Combined Interventions vs. Treatment as Usual or Attention Control

Nine studies reported on the effects of suicide or self-harm interventions with variable intensity and duration on suicide attempts or episodes of deliberate self-harm at the end of treatment (0 to 36 months).[164, 179-181, 191-193, 200, 212-215, 236, 265] Included studies compared DBT-informed CBT,[164] family therapy,[179-181] group psychotherapy,[191, 193] MBT,[192] youth-nominated support team,[200] DBT,[212-215] mentalization-based treatment,[236] or developmental group therapy[265] with TAU. Eight of the interventions[164, 179-181, 191-193, 212-215, 236, 265] were high contact (>3 sessions), and one intervention[200] was low contact (<3 sessions). Studies reported on a variety of outcomes including mean number of self-harm events,[179-181, 212-215, 265] number of self-harm events,[179-181, 191, 193, 236, 265] number of suicide attempts,[200] frequency of self-harm,[191] severity of self-harm,[191] Risk-Taking and Self-Harm Inventory for Adolescents (RTSHI),[192, 236] nonsuicidal self-injury,[164] and percentage with suicide ideation.[164] Study sample sizes ranged from 42 to 832. The most commonly reported measures were mean number of self-harm events and number of self-harm events. The detailed results of the included studies are summarized in **Appendix F Table 1**.

Table 5 presents pooled estimates of effect for end-of-treatment measures, specifically mean number of self-harm events (3 studies)[179-181, 212-215, 265] and proportion of self-harm events (5 studies).[179-181, 191, 193, 236, 265] Both estimates of effect were not statistically significant and had wide confidence intervals. One study, included in the meta-analysis of posttreatment results, continued to report statistically nonsignificant differences in number of self-harm events between arms at the 1-year. At the 3-year followup, unadjusted analyses favored the intervention. After adjustment for variables used in stratification at randomization (gender, presence of depressive disorder at the time of randomization, and having had at least one suicide attempt within the last 4 months), the differences were no longer statistically significant.[212-215]

Five studies[164, 191, 192, 200, 265] reported on other suicide attempt or deliberate self-harm outcomes (number of suicide attempts, frequency of self-harm, severity of self-harm, number of persons repeating self-harm, nonsuicidal self-injury, percentage with suicide ideation, and RTSHI) posttreatment (0 to 12 months). Included studies compared DBT-informed CBT,[164] group psychotherapy,[191] MBT,[192] youth-nominated support team,[200] or developmental group therapy[265] with TAU. Four of the interventions[164, 191, 192, 265] were high contact (>3 sessions), and one intervention[200] was low contact (<3 sessions). These results did not consistently demonstrate statistically significant differences favoring the intervention arm. Studies reported significant

differences between intervention and TAU on the outcomes of number of persons repeating self-harm (6% vs. 32%; OR, 6.3 [95% CI, 1.4 to 28.7]),[265] percentage with suicide ideation (0% vs. 18.2%; p=0.01),[164] and nonsuicidal self-injury (estimated probabilities of survival without: 0.55 vs. 0.43; p=0.05).[164] No statistically significant differences were reported when the intervention was compared with TAU on the number of suicide attempts,[200] frequency of self-harm,[191] severity of self-harm,[191] and RTSHI scores.[192] A study of group psychotherapy continued to report no statistically significant differences in frequency and severity of self-harm between arms at 6 to 12 months.[191] A study of MBT continued to report no statistically significant differences in RTSHI total score and RTSHI self-harm subscales between arms at 24 and 36 weeks.[192]

Results: Suicidal Ideation

Psychotherapy, Counseling, Support, or Combined Interventions vs. Treatment as Usual or Attention Control

Twelve studies reported on the effects of suicide or self-harm interventions with variable intensity and duration on measures of suicide risk.[179-182, 191, 193, 194, 197, 200, 202, 212-215, 236, 245, 265] Included studies compared family therapy,[179-181] attachment-based therapy,[182] group psychotherapy,[191, 193] youth-nominated support team,[200] motivational interviewing,[202] DBT,[212-215] MBT,[236] intensive interpersonal psychotherapy for depressed adolescents with suicidal risk (IPT-A-IN),[245] internet-based CBT,[194] child interview with counseling,[197] parent sessions,[197] child interview with counseling plus parent sessions,[197] or developmental group therapy.[265] Eight of the interventions[179-182, 191, 193, 212-215, 236, 245, 265] were high contact (>3 sessions), and four interventions[194, 197, 200, 202] were low contact (<3 sessions). Eleven studies compared intervention with TAU,[179-182, 191, 193, 197, 200, 202, 212-215, 236, 245, 265] and one study compared intervention with attention control.[194] Studies reported on a variety of measures including the Beck Scale for Suicide Ideation (BSS), Beck Hopelessness Scale (BHS), Suicidal Ideation Questionnaire (SIQ), SIQ-JR, Hopelessness Scale for Children (HSFC), Scale for Suicidal Ideation (SSI), Adolescent Suicide Questionnaire–Revised (ASQ-R), burdensomeness, and individual suicide risk indicators. Study sample sizes ranged from 48 to 832. The detailed results of the included studies are summarized in **Appendix F Table 2**.

The most commonly reported measures were the BHS, SIQ-JR, and SIQ. **Table 6** presents pooled estimates for these measures. Our studies[200, 202, 212-215, 245] reported on the BHS at the end of treatment (2 months to 19 weeks).

Seven studies[182, 191, 193, 200, 202, 212-215, 265] reported on the SIQ or SIQ-JR at the end of treatment (2 months to 7 months). The pooled estimate for the BHS was statistically significant and favored treatment arms when compared with controls. The pooled estimate and results from individual studies for the SIQ/SIQ-J, however, favored treatment arms, but the confidence intervals spanned the null.

Regarding longer term outcomes, findings were mixed. Two studies reporting nonsignificant differences on the BHS at 6 weeks and 19 weeks posttreatment continued to report nonsignificant differences on the BHS at additional follow-ups ranging between 3 months and 3.1 years.[200, 212-215] One study of attachment-based family therapy continued to find statistically

significant differences favoring the intervention arm on the SIQ-JR between arms at 24 weeks.[182] One study of youth-nominated support team continued not to find statistically significant differences on the SIQ-JR between study arms at 3 months or 12 month.[200] One study of DBT continued not to find any significant difference between study arms on the SIQ-JR at 3.1 years.[212-215] A study of group psychotherapy[191] and a study of group therapy[193] both continued not to find statistically significant differences on the SIQ at 12 months.

Six studies[179-182, 194, 197, 229, 245] reported on other suicide risk measures (ASQ-R, BSS, HSFC, SSI, individual suicide risk indicators) at the end of treatment (2 weeks to 12 months) that we could not pool because studies used heterogeneous measures or were not sufficient to pool.

Three studies reported on the BSS at the end of treatment, but the specific measures could not be pooled.[179-181, 194, 245] Specifically, one study reported that a smaller proportion of participants in family therapy reported suicide ideation based on the BSS compared with TAU at the end of treatment (OR, 0.64 [95% CI, 0.44 to 0.94]; p=0.024), but no statistically significant differences were reported at the 18-month followup (OR, 0.76 [95% CI, 0.49 to 1.16]; p=0.20).[179-181] Two additional studies reported continuous measures of the BSS and found inconsistent results. One reported a statistically significant difference between the IPT-A-IN and TAU at the end of treatment (6 weeks, 8.73 vs. 11.89; p=0.05),[245] and one reported no statistically significant differences between internet CBT and information-only control at the end of treatment (2.05 vs. 4.49, p=0.12) and at the 8-week followup (1.69 vs. 2.57; p=0.92).[194]

Results from other single studies on the ASQ-Jr, HSFC, SSI, and individual suicide risk indicators generally demonstrated at least some statistically significant benefit for suicide risk intervention.[182, 197, 229] The only exception was one study that found no differences on the HSFC, but the same study found significantly lower odds of suicidal ideation using the BSS, as noted above.[179-181]

One study[194] reported on the effects of suicide or self-harm intervention on perceived burdensomeness at the end of treatment (2 weeks) and 8 weeks posttreatment. The study compared internet CBT with information-only control. The study reported no statistically significant differences in mean perceived burdensomeness scores between internet CBT and information control at posttreatment (17.76 vs. 18.81, p=0.26) or at 8 weeks posttreatment (13.90 vs. 15.8; p=0.10).

Results: Response, Remission, and Loss of Diagnosis

Psychotherapy, Counseling, Support, or Combined Interventions vs. Treatment as Usual or Attention Control

Two studies reported on the effects of suicide or self-harm intervention on clinical response at the end of treatment (8 to 12 weeks).[182, 194] One study compared attachment-based therapy to enhanced usual care and reported statistically significant differences between groups, favoring intervention.[182] The study reported greater clinical response in the intervention group compared with TAU based on SIQ-JR scores (defined as $\leq$13) at the end of treatment and 24 weeks posttreatment (12 weeks: 87% vs. 52%, OR, 6.30 [95% CI, 1.76 to 22.61]; 24 weeks: OR, 4.41;

p=0.008). The study also reported that intervention was associated with greater clinical response based on SSI scores (defined as 0 vs. 1 suicide attempt) at the end of treatment and at the 24-week followup (12 weeks: 69% vs. 35%, OR, 4.45 [95% CI, 1.33 to 13.56]; 24 weeks: OR, 5.37 [95% CI, 1.56 to 18.48], p=0.006). A second study comparing internet CBT to information-only control reported no statistically significant differences in response (defined as perceived burdensomeness <14.61) between groups (24% vs. 10%, calculated OR, 2.82 [95% CI, 0.80 to 9.91]) at the end of treatment (8 weeks).[194]

Results: All-Cause Mortality

Psychotherapy, Counseling, Support, or Combined Interventions vs. Treatment as Usual or Attention Control

A long-term followup of a study on a youth-nominated support team approach,[200] 11 to 14 years after psychiatric hospitalization for suicide risk (baseline for the study), found a higher number of deaths in the National Death Index in the treatment as usual group when compared with the active treatment group (13/225 vs. 2/223; hazard ratio: 6.62 [95% CI, 1.49 to 29.35]).[201] The National Death Index can under-ascertain deaths.[274] The same study did not demonstrate an effect on the primary outcome of suicidal ideation; as a result, findings by chance or through other mechanisms of action (such as improved problem solving) cannot be ruled out.

Results: Functioning

Psychotherapy, Counseling, Support, or Combined Interventions vs. Treatment as Usual or Attention Control

Eight studies reported on the effects of suicide or self-harm interventions compared with TAU on functioning outcomes in adolescents.[179-181, 191, 193, 200, 212-215, 221, 222, 229, 265] **Table 7** presents pooled estimates of effect for end-of-treatment outcomes on the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA)[191, 193, 229, 265] and Children's Global Assessment Scale (CGAS).[193, 213, 222] Both estimates of effect found no statistically significant differences in functioning and had wide confidence intervals spanning the null.

Regarding longer term outcomes, one study[229] included the meta-analysis for HoNOSCA and demonstrated a statistically significant improvement in functioning favoring at the intervention group posttreatment also found statistically significant differences favoring the intervention group at the 6-month followup (M [SD]=4.77 [4.45] vs. 12.72 [5.29], p<.01).

Three studies reporting on other measures of functioning including the Child and Adolescent Functional Assessment Scale (CAFAS),[200] General Health Questionnaire (GHQ),[180] Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES),[180] and Strengths and Difficulties Questionnaire (SDQ),[193] reported nonsignificant differences in functioning outcomes at posttreatment and followup.

Results: Findings for Specific Populations

Subgroup Analyses

Findings for specific populations are reported in **Appendix I Table 15**. No studies reported results by race/ethnicity, sexual identity, or gender orientation. One study[179] comparing family therapy (N=415) with TAU (N=417) reported nonsignificant differences in hospital attendances for self-harm events as a function of age (chi-square: 0.4730, p=0.49) or sex (chi-square: 1.5219, p=0.2173).

Findings Within Age Groups

All studies reported results for adolescent participants.

Anxiety

Summary

As noted previously, we limited the synthesis to CBT for psychotherapy; we included pharmacotherapies approved by the FDA for children and adolescents. We included 29 RCTs (described in 40 articles) of good or fair quality.[163, 165, 167-169, 177, 178, 183, 190, 195, 196, 198, 203, 206, 220, 224-228, 237-244, 246, 251, 253-262] All studies are new to this report because this topic has not been addressed previously by the Task Force. Detailed study, population, intervention characteristics, and results are provided in **Appendix I Tables 17 through 22**. Detailed outcomes are provided in **Appendix F Table 3 through Table 11**. Meta-analysis forest plots are provided in **Appendix G Figure 8 through Figure 24**.

Study Characteristics

The characteristics of the included trials are summarized in **Table 8**. Sixteen studies enrolled children with any anxiety disorder to the trial.[163, 167, 168, 177, 183, 190, 195, 198, 203, 206, 237, 241, 242, 246, 251, 253] The most common primary diagnoses in these studies were social anxiety disorder and GAD. Of the studies requiring specific anxiety disorders for trial eligibility, five required GAD,[196, 224, 238, 243, 244] four required social anxiety disorder,[165, 220, 239, 240] two required selective mutism,[169, 178] and two required either GAD, social anxiety disorder, or separation anxiety.[225-228, 254-262] Nine studies set a threshold for severity, ranging from requiring clinically important symptoms or functional impairment to specific minimum thresholds on the Clinical Global Impressions-Severity (CGI-S), Pediatric Anxiety Rating Scale (PARS), or anxiety disorders interview schedule for DSM-IV for Children-Children/Parents (ADIS-C/P) clinician severity ratings (CSR).[168, 196, 220, 225-227, 237, 238, 243, 251]

The mean age of enrolled populations ranged from 4.1 to 17.4 years. Three studies focused on early childhood (ages 3 to 7 years),[183, 195, 237] 11 focused on later childhood (ages 6 to 14 years),[165, 167, 178, 196, 203, 206, 220, 240, 241, 246, 251] 11 spanned childhood and adolescence,[163, 168, 169, 177, 190, 198, 224-228, 238, 243, 254-262] and four focused solely on adolescence.[239, 242, 244, 253] Nine of 29 studies had a majority of male participants.[167, 203, 206, 225-228, 237, 238, 246, 251]

Nineteen of 29 studies provided information about the race or ethnicity of enrolled populations. With the exception of one study with all Japanese participants (set in Japan).[198] White participants were a majority in all studies.[168, 177, 178, 190, 195, 206, 224-228, 237, 238, 241, 243, 244, 246, 251, 253-262]

Pharmacotherapy trials, with one exception,[169] used narrow inclusion criteria and excluded persons with other psychiatric conditions. In contrast, psychotherapy trials did not routinely exclude participants with other psychiatric conditions.

Half the studies advertised widely for recruitment.[165, 167, 168, 177, 178, 183, 190, 195, 196, 198, 203, 206, 239, 241, 242] A minority of studies relied solely on referrals from mental health professionals,[163, 220, 224-228, 237, 238, 244, 246, 251, 253] two were recruited entirely through schools,[169, 240] and two did not specify the clinical setting for recruitment.[243, 254-262] Ten studies recruited participants from the United States,[168, 169, 178, 190, 195, 225-228, 237, 238, 244, 254-262] and one drew from multiple countries, including the United States, Mexico, and South Africa, but had a majority of participants from the United States.[243] The other 19 studies recruited participants from other countries with a very high human development index, namely Australia, the United Kingdom, Denmark, Germany, Norway, Hong Kong, Japan, Spain, and Sweden.

With respect to interventions evaluated, 22 RCTs evaluated CBT,[163, 165, 167, 177, 178, 190, 195, 196, 198, 203, 206, 220, 224, 237, 239, 241, 242, 246, 251, 253] six evaluated pharmacotherapy,[168, 169, 225-228, 238, 243, 244] and one evaluated both CBT and pharmacotherapy and combinations of CBT and sertraline.[254-262] As a reminder, psychological interventions in this review for the USPSTF were limited to CBT because it is the most commonly used intervention for anxiety disorders. Our search identified other types of psychological interventions used to treat anxiety disorders, and these are cataloged in **Appendix A**.

The most commonly studied CBT intervention was individually directed CBT, and the most commonly studied pharmacotherapies were sertraline and fluoxetine. Typically, these interventions were compared with wait-list for CBT and placebo for pharmacotherapy.

For CBT, the duration of therapy ranged from 5 days for group CBT to 31 weeks for individual CBT. The modal duration was 12 weeks. Although trials commonly reported weekly therapy lasting for 30 to 90 minutes, the intensity of treatment could be as high as 5 consecutive days of six to eight hour-long sessions for a 5-day group CBT trial[178] or 25 individual 50-minute sessions for the 31-week therapy.[239]

Studies relied largely on in-person delivery of interventions; two studies reported on internet CBT.[242, 253]

Fourteen CBT studies reported results comparing a single treatment arm with wait-list control.[163, 165, 177, 178, 183, 195, 196, 198, 203, 224, 239, 241, 242, 253] Two CBT studies reported results comparing a single treatment arm with TAU in primary care settings.[190, 237]

For pharmacotherapy, the duration of treatment ranged from 8 to 12 weeks, with doses being adjusted either flexibly or in a preplanned manner during therapy. Two studies reported

concurrent psychoeducational therapy,[178, 225-228] and one reported medication therapy management visits.[238]

Six pharmacotherapy studies compared fluoxetine,[168, 169] fluvoxamine,[225-228] sertraline,[238] escitalopram,[244] or duloxetine[243] with placebo.

Six studies had more than one active arm compared with wait-list control.[167, 206, 220, 240, 246, 251] Five had two arms comparing individual CBT versus group CBT,[251] group CBT with and without cognitive restructuring,[240] brief CBT versus full CBT,[246] and child-focused CBT versus parent- or family-inclusive CBT.[167, 220] A sixth compared three variants of parent-guided CBT, supported by telephone, email, or as needed, against a wait-list control.[206]

One had three active arms compared with placebo or wait-list control. This study (Child/Adolescent Anxiety Multimodal Study, or CAMS) evaluated CBT, sertraline, and CBT plus sertraline versus placebo.[254-262]

All studies reported on continuous or categorical outcome measures for anxiety symptoms, and nearly all studies (except three) reported on response, remission, or loss of diagnosis. Nine studies reported on depression outcomes, and fourteen on functioning. Studies generally reported results at the end of treatment, with the timing ranging from 4 weeks to 6 months; a minority reported results at 12 months.[190, 220]

Six studies reported on analyses of specific populations.[167, 190, 241]

Results: Anxiety Symptoms

Psychotherapy vs. Wait-List Controls, Treatment as Usual, or Placebo

All 24 CBT studies reported on anxiety symptoms. Studies did not report minimal clinically important differences, but scores above established thresholds indicated clinical benefit and are presented in **Table 9** for pooled estimates. All outcomes for each study are reported in **Appendix F Table 3** and these were used to generate meta-analyses (**Appendix G Figure 8 through Figure 14**). **Table 9** presents pooled estimates of effect for end-of-treatment measures, specifically ADIS CSR (12 studies[163, 177, 178, 183, 196, 198, 206, 224, 237, 242, 253, 275]); child-rated Spence Children's Anxiety Scale (SCAS) (9 studies[163, 177, 196, 198, 203, 206, 242, 246, 253]); parent-rated SCAS (9 studies[163, 177, 196, 198, 203, 206, 242, 246, 253]); child-rated SPAI (4 studies[165, 220, 239, 240, 275]); CGI-S (3 studies[190, 237, 254-262]); Multidimensional Anxiety Scale for Children (MASC) (3 studies[220, 251, 254-262, 275]); and Revised Children's Manifest Anxiety Scale (RCMAS) (3 studies[167, 206, 241]). Results for nearly all measures suggested clinically and statistically significant differences favoring CBT over wait-list control, TAU in primary care, or placebo. The only exceptions was for MASC (3 studies[220, 251, 254-262, 275]). Studies reporting parent- and child-rated MASC outcomes did not consistently show statistically significant differences favoring CBT over wait-list control or placebo. Studies reporting on MASC did not offer a threshold for clinically meaningful effect, and an evaluation of MASC suggests that it may not be possible to identify cutoff scores.[276]

In addition, we found results for several posttreatment measures that we could not pool, either because of heterogeneity in measures or because we found only one or two studies. Heterogenous measures included child-reported SCARED outcomes. measured at 10 to 12 weeks from baseline.[190, 224, 254-262] One study reported on subscales for SCARED for GAD and anxiety[224] rather than total scores, and the details regarding the scale and scoring were unclear. Studies reporting parent- and child-rated SCARED outcomes did not consistently show statistically significant differences favoring CBT over wait-list control.

We found one or two studies on several other symptom measures, specifically two studies each on the Fear Survey Schedule for Children-Revised (FSCC-R),[167, 220] Social Anxiety Scale Children (SASC),[165, 240] and PARS[237, 254] and one study each on parent-reported Social Phobia and Anxiety Inventory (SPAI),[220, 275] Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA),[239] Preschool Anxiety Scale (PAS),[183] Penn State Worry Questionnaire for Children (PSWQ-C),[224] Selective Mutism Questionnaire (SMQ),[178] CGI-I,[195] and Diagnostic Interview Schedule for Children, Adolescents, and Parents (DISCAP).[241] With the exception of one study,[167] all reported at least one measure favoring CBT compared with wait-list control or placebo for anxiety symptoms.

Three studies reported on outcomes after the initial posttreatment assessment, at 6 and 12 months, using three different instruments. The results were mixed. One study reported on child-rated SPAI outcomes at 6 months and found statistically significant differences favoring CBT.[240] Two studies reported no statistically significant differences at 12 months using CGI-S outcomes[190] and SCARED.[190]

Pharmacotherapy vs. Placebo

Six studies reported on the effects of pharmacotherapy on anxiety symptoms when compared with placebo (one each on duloxetine,[243] escitalopram,[244] fluoxetine,[168] and fluvoxamine[225-228] and two on sertraline[238, 254-262]) (**Appendix F Table 4**). The studies enrolled persons with any anxiety disorder[168, 225-228] or specifically persons with GAD.[238, 243, 244] These studies reported on outcomes at the end of treatment using a variety of instruments, including the PARS, CGI-S, ADIS, RCMAS, SCARED, and MASC. Pooled estimates of effect for the PARS[168, 225-228, 243, 244, 254-262] and CGI-S (4 studies[238, 243, 244, 254-262]) suggested clinically and statistically significant improvement for both measures (**Table 9**). One or two studies reported findings for other measures (proportion with CGI-S less than 4; continuous measures of the CGI-I, SCARED-C, SCARED-P, child-rated MASC, parent-rated MASC, RCMAS, Hamilton Anxiety Rating Scale [HAM-A], and ADIS-CSR),[168, 238, 254-262] precluding pooling the results. In all but one instance,[255] studies reported statistically significant differences favoring pharmacotherapy.

Combination Therapy (Sertraline Plus CBT) vs. Placebo

One study reported on outcomes comparing sertraline plus CBT with placebo.[254-262] The study reported on multiple measures of symptoms including the PARS,[254] CGI-S,[254] child-rated MASC,[255] parent-rated MASC,[255] SCARED-C,[255] and SCARED-P.[255] Results varied by instrument and respondent. PARS scores were significantly different favoring combination treatment at 12 weeks (calculated mean difference: -5.20 [95% CI, -6.91 to -3.50][254]), but not

when evaluating changes from baseline to 12 weeks. Scores for the CGI-S (calculated mean difference: -1.4 [95% CI, -1.77 to -1.03][254]) and parent-reported MASC (33.4 vs. 49.1, adjusted p<0.001) suggested benefit for the combined therapy arm when compared with placebo.[255] Results for SCARED (9.6 vs. 19.5, adjusted p<0.001)[255] were statistically significant and favored combination therapy, but child-reported measures of the MASC and SCARED did not yield statistically significant differences between treatment and control groups.

Results: Response, Remission, or Loss of Anxiety Diagnosis

Psychotherapy vs. Wait-List Controls, Treatment as Usual, or Placebo

Eight studies reported on clinical response,[178, 190, 195, 237-239, 242, 244, 253-262] seven on remission of anxiety symptoms,[163, 198, 206, 237, 239, 242, 254-262] and 19 on loss of diagnosis. **Table 10** presents pooled results for these outcomes; detailed outcomes are in **Appendix F Table 5 through Table 7**.

Of the eight studies reporting measures of clinical response,[178, 190, 195, 237-239, 242, 244, 253-262] six reported CGI-I response defined as moderately or markedly improved symptoms at the end of treatment, with outcomes measured at 4 weeks to 6 months from baseline (CGI-I score of 1 or 2);[178, 190, 195, 237, 254] the pooled RR was 1.89 (**Appendix G Figure 17,** 95% CI, 1.17 to 3.05; N=606; k=6; I^2=64%). A seventh study defined response as reduction in the LSAS-CA total score of 31 percent or more.[239] The study reported statistically significant differences favoring CBT (66% vs. 20%, p=0.006). The eighth study defined response as a clinically reliable change in SCAS scores.[242] The study reported statistically significant differences favoring CBT on the child-reported SCAS (69% vs. 26%, p=0.001) and mother-reported SCAS (69% vs. 22%, p<0.001) but not for the father-reported SCAS (35% vs. 19%, p=0.156).

Of the seven studies reported on anxiety remission,[163, 198, 206, 237, 239, 242, 254-262] four defined remission as clinically significant change on the child-reported SCAS at the end of treatment, varying from 8 to 16 weeks from baseline.[163, 198, 206, 242] One study reported outcomes for three separate arms compared with wait-list: telephone, email, and client-initiated CBT.[206] The pooled estimate of effect (averaging across multiple study arms in the study with more than 1 active arm) yielded an RR of 2.68 (**Appendix G Figure 18,** 95% CI, 1.48 to 4.88; N=321; k=4; I^2=48%). Of these four studies, one also reported clinically significant change favoring CBT on the mother-reported SCAS (51.8% vs. 11.3%, p≤0.001) and father-reported SCAS (41.8 vs. 9.8, p≤0.001).[163] Another reported clinically significant change favoring CBT on the mother-reported SCAS (26% vs. 6%, p=0.032) but not for the father-reported SCAS (4% vs. 7%, p=1.00).[242] One of these four studies also reported no clinically significant change on a parent-reported SCAS (32.0% vs. 20.83%, p=0.38.[198] The fifth study defined remission as a LSAS-CA score of 30 or less and reported statistically significant differences favoring CBT (47% vs. 6%, p=0.0009).[239] The sixth study defined remission as a ADIS-CSR score less than 4 and reported statistically significant differences favoring CBT (66.7% vs. 10.0%, p=0.011).[237] The seventh study defined remission as a CGI-S score of 2 or less and a CGI-I score of 1.[262] The study reported no statistically significant differences on the CGI-S (35.9% vs. 27.1%, p=0.49) or the CGI-I (20.4% vs. 15.0%, p=0.61).

Nineteen studies reported on loss of anxiety diagnosis using a variety of measures (presence or absence of primary anxiety diagnosis or any anxiety diagnosis) using clinical interviews (ADIS, K-SADS, DISCAP, and Structured Clinical Interview for DSM-IV [SCID]).[163, 167, 177, 178, 183, 190, 195, 196, 198, 203, 206, 220, 224, 238, 241, 242, 244, 246, 251, 253-262, 275]

Of the 19 studies, 17 reported on loss of any diagnosis, measured primarily using the ADIS structured clinical interview at the end of treatment (6 weeks to 6 months from baseline).[163, 167, 177, 183, 190, 195, 196, 198, 203, 206, 224, 238, 241, 242, 244, 246, 251, 253-262] Fifteen could be pooled.[163, 167, 177, 183, 190, 195, 196, 198, 224, 241, 242, 246, 251, 253] The pooled estimate of effect (averaging across multiple study arms in studies with more than one active arm[246, 251]) yielded an RR of 3.09 (**Appendix G Figure 19**, 95% CI, 1.98 to 4.80; N=1,414; k=15; I^2=65%). Of the remaining two studies, one study did not report sufficient data to permit pooling but reported statistically significant differences when comparing each of three CBT arms (telephone, email, or client initiated) with a wait-list control.[206] A second study also could not be pooled because the authors reported on a more expansive definition of loss of diagnosis (presence or absence of anxiety diagnosis or symptoms);[203] this study also reported statistically significant differences favoring the CBT arm.

Fourteen studies reported on loss of the primary anxiety diagnosis, measured primarily using the ADIS structured clinical interview, at the end of treatment with outcomes measured ranging from 6 weeks to 12 months from baseline.[163, 177, 178, 183, 190, 196, 198, 206, 220, 224, 242, 246, 251, 253, 275] Of these, 13 could be pooled.[163, 177, 178, 183, 190, 196, 198, 220, 224, 242, 246, 251, 253, 275] The pooled estimate of effect (averaging across multiple study arms in studies with more than one active arm[220, 246, 251, 275]) yielded an RR of 3.02 (**Appendix G Figure 20**, 95% CI, 1.84 to 4.95; N=1,079; k=13; I^2=75%). One study did not report sufficient data to permit pooling but reported statistically significant differences across three CBT arms (telephone, email, or client initiated) when compared with a wait-list control.[206]

Pharmacotherapy vs. Placebo

All pharmacotherapy studies reported on clinical response; all reported statistically significant improvement favoring pharmacotherapy; detailed outcomes are in **Appendix F Table 8**. Five (2 on fluoxetine, 2 on sertraline, and 1 on escitalopram) reported on clinician-rated response defined as moderately or markedly improved symptoms at the end of treatment, varying from 8 to 12 weeks from baseline (CGI-I scores of 1 or 2);[168, 169, 238, 244, 254-262] the pooled RR was 2.11 (95% CI, 1.58 to 2.98; N=370; k=5; I^2=18%). Four of the five studies reported statistically significant differences favoring the intervention arms; the fifth study, focusing on selective mutism, did not report statistically significant differences in clinician- or teacher-rated CGI-I scores but did report statistically significant results for parent ratings on the CGI-I scale.[169]

A sixth study, on fluvoxamine, defined response as CGI-I less than 3; that is, the authors included minimal improvement (CGI-I=3) at 8 weeks as response.[225-228] The study reported statistically significant differences favoring fluvoxamine (76% vs. 29%, p<0.001) but did not report statistically significant differences with the more traditional definition of response (CGI-I <3). The seventh study, on duloxetine, defined response as 50 percent improvement on PARS severity for GAD.[243] The study reported statistically differences favoring duloxetine (59% vs. 42%, p≤0.05).

Three studies reported on remission at the end of treatment (9 to 12 weeks from baseline, **Table 10**); detailed outcomes are in **Appendix F Table 9**. These included two sertraline studies[238, 254-262] and one duloxetine study.[243] These results could not be pooled because the measurement of the outcome varied. The results were not consistent across the varied measures. One study limited the definition of remission to CGI-I=1, that is, marked improvement in symptoms, and reported no statistically significant differences at 9 weeks (18% vs. 0%, calculated p=0.28).[238] A second study included CGI-I=1 as a definition of remission but also looked at CGI-S less than or equal to 2 and loss of diagnosis as additional measures of remission at 12 weeks and found that the only measure yielding statistically significant differences favoring the intervention arm was loss of diagnosis. The results favored the sertraline arm when compared with the placebo arm (45.9% vs. 23.7%; OR, 2.84 [95% CI, 1.01 to 4.67]; p=0.05).[262] A third study defined remission as CGI-S less than or equal to 2 or as PARS severity for GAD less than or equal to 8 at 10 weeks and reported results favoring duloxetine for both measures.

Combination Therapy (Sertraline Plus CBT) vs. Placebo

One study reported on outcomes comparing sertraline plus CBT with placebo.[254-262] The study reported statistically significantly higher odds (OR, 13.6 [95% CI, 6.9 to 26.8]; p<0.001) of response (CGI-I of 1 or 2)[254] and loss of diagnosis based on structured clinical interview (OR, 7.47 [95% CI, 2.63 to 12.64]; p=0.01)[262] at 12 weeks but not remission, defined as CGI-S score of 2 or less and CGI-I score of 1. For remission, the confidence intervals were very wide and spanned the null.[262]

Results: All-Cause Mortality

Psychotherapy vs. Wait-List Controls, Treatment as Usual, or Placebo

No CBT studies reported on all-cause mortality.

Pharmacotherapy vs. Placebo

One study of duloxetine reported no deaths during the 10-week treatment in either arm.[243] No other pharmacotherapy studies reported on all-cause mortality.

Combination Therapy (Sertraline Plus CBT) vs. Placebo

No studies of combination therapy reported on all-cause mortality.

Results: Quality of Life and Functioning

Psychotherapy vs. Wait-List Controls, Treatment as Usual, or Placebo

Twelve studies reported on functioning and quality-of-life outcomes after CBT treatment, when compared with wait-list, TAU, or placebo controls; detailed outcomes are in **Appendix F Table 10**.[163, 178, 183, 190, 196, 224, 242, 246, 251, 253-262, 275] Of these, eight studies, offering individual or group CBT to parents, children, or both, reported on CGAS scores at the end of treatment (with

outcomes measured ranging from 4 to 14 weeks).[178, 183, 190, 196, 224, 251, 253-262] With the exception of one study focusing on selective mutism,[178] studies enrolled youth with GAD or any anxiety disorder. Three studies reported parent-reported CAIS scores.[246, 253, 255] The pooled estimate of effect for CGAS (**Table 11**) indicated statistically significant improvement for participants in the CBT arm when compared with participants in the control arm. For CAIS, however, inconsistencies in direction of effect across the studies resulted in differences between the arms that spanned the null.

Other measures of functioning such as the Child Anxiety Life Interference Scale (CALIS), Child Anxiety Life Interference Scale-Child (CALIS-C), Pediatric QOL Inventory-P, Quality of Life Inventory for Children [QOLI], PQ-LES-Q, and sleep-related problems were reported in one or two studies.[163, 242] Results were mixed or did not demonstrate statistically significant differences.

Pharmacotherapy vs. Placebo

Three studies (duloxetine,[243] fluoxetine,[168] and sertraline[254-262]) reported on CGAS scores (a measure of functioning) at the end of treatment (10 to 12 weeks). **Table 11** presents pooled estimates of effect for CGAS showing statistically significant differences favoring the pharmacotherapy when compared with placebo. Two studies reported on functional remission (CGAS scores≥70).[168] One, on duloxetine, reported a statistically significant difference between arms favoring duloxetine (59% vs, 42%, p≤0.05),[243] and the other, on fluoxetine, reported no statistically significant difference.[168]

The sertraline study also reported parent- and child-reported school functioning (CAIS)[259] and sleep-related problems.[258] Child-reported outcomes were not statistically significant. Some parent-reported outcomes (Child Anxiety Impact Scale-Parent) and sleep-related problems associated with separation (but not dysregulated sleep overall) were statistically significantly improved in the treatment arm when compared with placebo.

Combination Therapy (Sertraline Plus CBT) vs. Placebo

One study reported on outcomes comparing sertraline plus CBT with placebo.[254-262] The study reported on multiple measures of symptoms including CGAS,[254] CAIS,[255] and sleep-related problems.[255] CGAS scores were significantly different at 12 weeks favoring combination therapy (calculated mean difference: 8.50 [95% CI, 5.55 to 11.45][254]) as were parent-reported measures of CAIS at followup (7.4 vs. 15.2, adjusted p<0.001[255]) and sleep problems related to separation (p=.01), but not for child-reported measures of functioning (CAIS)[259] or other sleep problems.[258]

Results: Findings for Specific Populations

Appendix F Table 11 presents qualitative results for specific populations. No studies reported on results by gender identity or sexual orientation.

Subgroup Analyses

Four CBT studies reported analyses of specific populations.[167, 190, 241, 254-262] All four studies reported analyses by age.[167, 190, 241, 255, 260] Two studies[241, 255] reported no statistically significant differences in self-,[241, 255] parent-,[255] or clinician-reported[241] measures of symptomatology or severity by age. A third study reported significantly higher response rates at post-treatment, but not at 1-year follow-up, for older participants who received CBT when compared with TAU.[190] A fourth study reported significantly higher rates of loss of diagnosis at post-treatment and 1-year follow-up for younger participants (7 to 10 years) receiving child and parent-focused CBT in comparison with those receiving child-focused CBT.[167] Two studies reported analyses by sex.[167, 241] One[241] reported no statistically significant differences for clinician-rated severity or self-reported measures of anxiety by sex and the second[167] reported significantly higher rates of loss of diagnosis at post-treatment and 1-year follow-up for female participants receiving child and parent-focused CBT. One study reported analyses by race and ethnicity.[256, 261] No statistically significant differences in response, remission, or relapse were reported by race.[261] Clinicians reported significantly more severe anxiety symptoms for participants of Hispanic ethnicity who received CBT.[256]

Three pharmacotherapy (duloxetine,[243] fluvoxamine,[225-228] and sertraline[254-262]) studies reported analyses for populations of interest. All three studies reported analyses by age.[226, 243, 255, 260] Three studies reported no statistically significant differences in symptoms,[255] symptom severity,[243] and all evaluated outcomes[226]) by age. All three studies reported analyses by sex.[226, 243, 259] Two studies[226, 243] reported no statisically significant sifferences in for evaluated outcomes (GAD severity in one study[243] and all outcomes in the other study[226]) by sex. One study[259] reported significantly less parent-reported, but not youth-reported, anxiety-related school impairments among males who received Sertraline compared to pill placebo. Two studies[226 , 261] reported analyses by race. Both reported no statistically significant differences in anxiety symptomalogy or severity,[226] response[226, 261] or remission or loss of diagnosis[261] by race. One study reported analyses by ethnicity.[256] Parents reported significantly more severe anxiety symptoms for participants of Hispanic ethnicity who received Sertraline.

One study[254-262] of combined pharmacotherapy and CBT reported analyses for symptoms,[255, 256, 259] response and remission,[261] by age,[255, 260] sex,[259] ethnicity,[256] or race.[261] No statistically significant differences in symptoms were reported by age.[255] Statistically significant differences favored combined treatment in parent-reported psychosocial functioning were reported by sex.[259] Parents, but not youth, reported a greater benefit in anxiety-related school impairments among males who received sertraline in combination with CBT than among females when compared with placebo recipients.[259] No statistically significant differences in response, remission, or relapse were reported by race[261] or ethnicity.[256]

Findings Within Age Groups

Categorization of studies into groups mapping to children or adolescents is challenging. Three studies limited their inclusion to young children, with ages ranging from 3 to 7 years.[183, 195, 237] Four studies limited inclusion to adolescents only, with ages ranging from 13 to 20 years.[239, 242, 244, 253] The remaining 22 studies were focused on older children (5 to 14 years; 12 studies)[165, 167,

[177, 178, 196, 203, 206, 220, 240, 241, 251] or children and adolescents (7 to 18; 10 studies).[163, 168, 169, 190, 198, 224, 225, 238, 243, 254] Although studies varied in their specific inclusion criteria and whether they included adolescents, the majority of studies had a mean age between 10 and 14 years.

The results for young children only and adolescents only are largely consistent with the results for the entire evidence base in demonstrating benefit for symptom improvement.

For younger children, all three studies focused on CBT and reported consistent statistically signficant benefits for anxiety symptoms in two[183, 237] of three studies.[183, 195, 237] Two studies reported on response and both reported statistically significant differences favoring CBT.[195, 237] The single studies reporting on remission[237] and functioning,[183] respectively, suggested statistically signficant differences favoring CBT. The results for loss of diagnosis were not consistently statistically significant in favoring CBT in the two studies reporting on this outcome.[183, 195]

For adolescents, three studies[239, 242, 253] reported on CBT and one reported on pharmacotherapy, specifically escitalopram.[244] Two[239, 242] of the three[239, 242, 253] CBT studies reported consistent statistically significant improvement in anxiety symptoms, response, and remission; one reported no statistically significant differences.[253] Only one CBT study reported on loss of diagnosis and found no statistically signficant differences.[253] Two studies reported on functioning, and neither consistently found statistically significant differences.[242, 253] The escitalopram study reported improvement in symptoms and response.[244]

Depression

Summary

We included 13 fair-quality RCTs for KQ 4[174-176, 185, 187, 204, 207, 216, 233, 248, 249, 252, 266] (described in 20 publications[186, 205, 208-211, 217]). Seven RCTs[176, 187, 204, 205, 216, 217, 248, 249, 266] were new in this update for KQ 4. One study that was included in the previous USPSTF report on depression treatment and screening for KQ 4 was excluded from this report for ineligible intervention. This study tested citalopram, which was not included in the current review.[277] Detailed study, population, intervention characteristics, and results are provided in **Appendix I Tables 25 through Table 30**. Detailed outcomes are provided in **Appendix F Table 14 through Table 28**. Meta-analysis forest plots are provided in **Appendix G Figure 25 through Figure 32**.

Study Characteristics

The characteristics of the included studies are summarized in **Table 12**. Six RCTs admitted children or adolescents meeting DSM criteria for MDD,[175, 176, 185, 207, 216, 252] and five RCTs admitted those with MDD based on a clinical interview (K-SADS, K-SADS-EC, MINI).[204, 233, 248, 249, 266] Two RCTs admitted children with MDD, dysthymia, or depressive disorder not otherwise specified and enrolled a sample in which more than 50 percent of participants met DSM criteria for MDD.[174, 187] Eight RCTs set a threshold for severity, ranging from requiring clinical important symptoms to specific minimum thresholds on BDI-II, CDRS-R, Hamilton Depression Rating Scale (HAM-D), and PHQ-9.[185, 187, 207, 216, 233, 248, 249, 252]

Mean ages ranged from 5 to 17.5 years.[204, 205, 249] One RCT focused on early childhood (ages 3 to 6 years);[204, 205] two focused on older children and adolescents (age ranges from 7 to 14 years and 6 to 17 years);[187, 252] and 10 focused on adolescents (age ranges from 12 to 17 years to 15 to 19 years).[174-176, 185, 207, 216, 233, 248, 249, 266] Two had a majority male participants.[187, 204, 205] Eight RCTs provided statistics on race, with the exception of one study with 71 percent Hispanic participants.[216] White participants were a majority in all RCTs that reported race.[176, 185, 187, 204, 205, 207, 233, 252]

Common exclusion criteria were substance misuse or substance use disorder; bipolar disorder, schizophrenia, or other serious mental health disorders; intellectual disability; autism spectrum disorders; and suicide-related concerns.

Two pharmacotherapy RCTs investigated escitalopram.[185, 252] One three-arm trial compared included a group that received fluoxetine.[207] The most commonly assessed psychotherapy was CBT. Six RCTs focused on CBT.[174-176, 187, 248, 249] Among these, two included individual CBT,[175, 176] one family CBT,[187] one group CBT,[174] and two internet-delivered CBT.[248, 249] Three RCTs studied psychotherapies other than CBT. One focused on interpersonal psychotherapy[216] and the other on Parent Child Interaction Therapy-Emotion Development.[204, 205] One RCT studied collaborative care.[233] One focused on internet-based psychodynamic therapy.[266]

Eleven RCTs (2 on pharmacotherapy, 8 on psychotherapy, 1 on collaborative care) had a single active treatment compared with attention control or supportive contact, wait-list control, TAU, or placebo. Both pharmacotherapy RCTs compared escitalopram with placebo.[185, 252] Psychotherapy studies compared treatment with attention control,[248, 249] supportive contact, [266] wait-list control,[204, 205] TAU,[175, 176, 216] or placebo.[187] The collaborative care study compared the intervention with enhanced usual care; treatments included a choice of antidepressants, brief CBT, or both.[233] Another trial, using a collaborative care approach, is discussed under psychotherapy because all participants in the active arm received CBT.[175] One RCT had two active arms, group CBT with and without parent session, compared with wait-list control.[174] One RCT had three active arms (fluoxetine, CBT, and fluoxetine plus CBT) compared with placebo.[207]

Two pharmacotherapy trials compared escitalopram with placebo.[185, 252] One three-arm trial compared fluoxetine, CBT, and placebo.[207] One study compared collaborative care with enhanced usual care.[233] Six studies focused on CBT.[174-176, 187, 248, 249] Among these, two compared individual CBT with TAU,[175, 176] one compared family CBT with placebo,[187] one compared group CBT with and without additional parent sessions with wait-list,[174] and two compared internet-delivered CBT with an attention control group.[248, 249] Three studies focused on counseling other than CBT.[204, 216, 266] One compared interpersonal psychotherapy and TAU,[216] the second compared Parent Child Interaction Therapy-Emotion Development with a wait-list control,[204, 205] and the third compared internet-based psychodynamic therapy with supportive contact.[266]

Intervention durations ranged from 8 weeks to 12 months. Most studies reported results at the end of treatment. All 13 RCTs reported on continuous outcomes for depression symptoms. The most commonly reported measures were the CDRS-R[176, 185, 187, 207, 233, 252] and BDI.[174, 216, 248, 249]

Nine RCTs reported response,[175, 176, 185, 207, 233, 248, 249, 252, 266] ten RCTs reported remission,[175, 176, 185, 187, 207, 216, 233, 248, 249, 266] and five RCTs reported loss of depression diagnosis.[174, 204, 205, 207, 248, 249] Three RCTs reported anxiety outcomes,[248, 249, 266] three studies reported suicide-related outcomes,[176, 185, 207, 252] and nine studies reported functioning outcomes.[174, 176, 185, 187, 204, 205, 207, 216, 233, 252] Five studies reported harms.[185, 207, 233, 252, 266] No psychotherapy studies reported harms.

RCTs relied on in-person delivery of interventions, except for two that reported on internet-delivered CBT[248, 249] and one that reported on internet-based psychodynamic therapy.[266]

Half the RCTs advertised widely for recruitment;[174, 187, 207, 248, 249, 252, 266] three recruited from health systems and pediatric clinics;[175, 176, 233] one RCT recruited from preschools, daycares, primary care, and mental health facilities;[204, 205] one RCT recruited from mental health clinics;[216] and one RCT did not specify the recruitment setting.[185] Ten studies were conducted in the United States,[174-176, 185, 187, 204, 205, 207, 216, 233, 252] and three studies were conducted in Sweden.[248, 249, 266]

Results: Depression Symptoms

Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo

Ten studies reported outcomes related to changes in depression symptoms.[174-176, 187, 204, 207, 216, 248, 249, 266] All outcomes for each study are reported in **Appendix I**, and for outcomes reported by at least three studies, we conducted meta-analyses (**Appendix G**). **Table 13** presents pooled estimates of the effect for end-of-treatment measures, specifically the BDI/BDI-II,[174, 216, 248, 249] CDRS-R,[176, 187, 207] and HAM-D[174, 175, 216] scales. Two of the pooled effects (BDI/BDI-II and HAM-D) suggested a statistically significant benefit of treatment compared with controls, while the third pooled estimate (CDRS-R) demonstrated no significant effect.

Several studies also reported other measures of depression symptoms in addition to measures that we pooled (**Appendix F Table 14**). For some studies, findings from these additional measures (Mood and Feelings Questionnaire,[249] mean CGI-I and CGI-S,[216] and Revised Children's Anxiety and Depression Scale [RADS][207]) were consistent with what has already been reported by those studies using BDI, BDI-II, CDRS-R, or HAM-D measures. In other cases, findings were not consistent. Two studies by the same author of the same intervention (individual, in-person CBT) compared with TAU, which included any health services, including psychopharmacotherapy, provided by their usual care provider, reported using the CES-D and found mixed results.[175, 176] One of these studies, published in 2005, reported larger, but nonstatistically significant different improvements in CES-D scores at 52 weeks, consistent with findings from the HAM-D outcomes also reported in that study.[175] The later of the two studies, published in 2016, larger, statistically significant improvements in CES-D scores at 52 weeks, consistent with reported benefits for the CDRS measure at 52 weeks.[176] These larger improvements in the treatment group persisted at 104 weeks but were no longer statistically significant, also consistent with CDRS findings at 104 weeks.[176] A third study reported a larger improvement in PHQ-9 score for the treatment group, but this difference was not statistically significant.[248] A fourth study evaluated parent-child interaction therapy focused on emotion development compared with wait-list controls and reported outcomes at 18 weeks using the K-SADS-CD MDD core score and the Preschool Feelings Checklist scale.[204] Participants allocated

to the treatment had statistically significant larger improvements on both outcomes (p<0.000).[204] Lastly, a study comparing internet-based psychodynamic therapy with supportive contact found no statistically significant difference in the primary outcome measured by the Quick Inventory of Depressive Symptomatology for Adolescents (QIDS-A17-SR); a secondary outcome of Montgomery Åsberg Depression Rating Scale–self-rated (MADRS-S) demonstrated a difference favoring the active treatment.[266]

Pharmacotherapy vs. Placebo

Three studies reported on the effects of pharmacotherapy on depression symptoms when compared with placebo (2 on escitalopram[185, 252] and 1 on fluoxetine[207]) (**Appendix F Table 15**). Three studies reported on outcomes at the end of treatment using CDRS-R,[185, 207, 252] two reported the CGI-I and CGI-S,[185, 252] and one reported RADS.[207] Study sample sizes ranged from 109[207] to 158.[185]

Table 13 reports pooled differences on the CDRS-R indicating statistically significant benefit favoring pharmacotherapy. Results on other measures did not always yield statistically significant differences favoring pharmacotherapy. On the CGI-S, Emslie et al[185] reported a significant difference favoring escitalopram when compared with placebo at 8 weeks, whereas Wagner et al[252] did not report a statistically significant difference. March et al[207] did not find a statistically significant difference between fluoxetine and placebo on the RADS at 12 weeks.

Combination Therapy (Fluoxetine Plus CBT) vs. Placebo

One study comparing fluoxetine plus CBT to placebo reported on depression symptoms measured by the CDSR-R and RADS-2 (**Appendix F Table 16**).[207] The results were consistent for CDSR-R and RADS-2 in reporting statistically significant benefits for fluoxetine plus CBT. There was a statistically significant difference in the change in CDSR-R from baseline to 12 weeks when compared with placebo (33.79 vs. 41.8, p=0.001). There was also a statistically significant difference in the change in RADS-2 from baseline to 12 weeks when compared with placebo (56.95 vs. 66.7, p=0.001).

Collaborative Care vs. Treatment as Usual

One study comparing a collaborative care intervention with TAU reported on depression symptoms measured by the CDSR-R (**Appendix F Table 17**). Intervention patients had an 8.5-point greater decrease in mean CDRS-R score from baseline than treatment-as-usual participants (95% CI, -13.4 to -3.6; p=0.001) at 6 months and a 9.4-point greater decrease from baseline at 12 months (95% CI, -15.0 to -3.8; p=0.001). A test of the interaction between group effects and time was statistically significant at p<0.001.[233]

Results: Response, Remission, or Loss of Diagnosis

Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo

Regarding response, three studies reported responses on the BDI and BDI-II scale (**Appendix F Table 18**).[216, 248, 249] These studies could not be pooled because of the varied thresholds used; however, all reported statistically significant differences favoring psychotherapy.

Other measures of response included CGI ≥ 2[207, 210] and <5[176] depression symptoms for 8 weeks and fulfilling the Reliable Change Index [266, 278]The results were not consistent. One study defined response as CGI greater than or equal to 2 and did not report statistically significant differences.[207, 210] Another study defined response defined as 8 or more weeks below with the threshold of five or more depression symptoms necessary for full diagnosis but where full recovery has not yet occurred; the results were statistically significantly different favoring CBT at 52 and 104 weeks from baseline.[176] A third study used the Reliable Change Index, that is, a way to ensure that the magnitude of change for individuals is statistically reliable, while scoring 2 standard deviations below the pretreatment mean and found a statistically significant difference favoring the active treatment.[266]

Two studies defined remission as a CDRS-R score ≤ 28; neither reported statistically significant differences.[187, 207, 210] A third study defined remission as a QIDS-A17-SR score of 6 or lower and found a statistically significant difference favoring the active treatment.[266]

One study reported on recovery, defined as longer than or equal to 8 weeks of no or minimal symptoms on weekly Diagnostic Status Ratings (≤1–2) and little or no impairment. The results were statistically significantly different favoring CBT at 52 and 104 weeks from baseline.[176]

Five studies reported on loss of diagnosis.[174, 204, 207, 210, 248, 249] Of these, four (all in adolescents) reported sufficient data to be pooled.[174, 207, 248, 249] The pooled estimate and results from individual studies favored the treatment arms, but the confidence intervals spanned the null. A fifth study,[204] of parent-child interaction therapy in young children (mean age: 5 years), could not pooled with the other studies but also reported results favoring the psychotherapy arm. Specifically, the study reported adjusted odds ratios when comparing the control arm with the intervention of 9.52 (95% CI, 8.44 to 10.74).[204]

Pharmacotherapy vs. Placebo

One study on escitalopram and one on fluoxetine reported response defined as the proportion of participants with CGI-I ≤ 2. Neither study found statistically significant differences between pharmacotherapy and placebo (**Appendix F Table 19**).[207, 252]

All three pharmacotherapy studies (2 on escitalopram and 1 on fluoxetine) reported on the proportion of participants with CDRS-R score less than or equal to 28 at the end of treatment (8 or 12 weeks). This measure was termed as remission in two studies[185, 207, 210] and response in one.[252] **Table 14** presents pooled results. The pooled estimate and results from individual studies favored treatment arms, but the confidence intervals spanned the null.[185, 207, 210, 252]

One study on fluoxetine reported loss of MDD diagnosis based on K-SADS-P/L interview and found that a significantly greater proportion of those receiving fluoxetine no longer met MDD criteria at 12 weeks compared with placebo (78.6% vs. 60.4%, p=0.007).[207, 210]

Combination Therapy (Fluoxetine Plus CBT) vs. Placebo

One study[207, 210] found that the combination therapy arm had a higher and statistically significant rate of response (CGI-I≤2: 71.0% vs. 34.8%; p=0.0001[207]), remission (CDRS-R≤28: 37% vs. 17%; OR: 3.0 [95% CI, 1.58 to 5.79][210]), and loss of diagnosis (no longer meeting DSM-IV criteria for MDD using the K-SADS-P/L: 85.3% vs. 60.4%; OR: 4.1 [95% CI, 2.00 to 8.44][210]) when compared with placebo (**Appendix F Table 20**).

Collaborative Care vs. Treatment as Usual

The collaborative care study found intervention participants were more likely than treatment-as-usual patients to achieve depression response (≥50% reduction in CDRS-R score from baseline) by 12 months (OR, 3.3 [95% CI, 1.4 to 8.2]; p=0.009) but not by 6 months (OR, 3.1 [95% CI, 1.2 to 7.9]; p=0.02). Intervention participants were significantly more likely to achieve depression remission (PHQ-9 < 5) at both 6 months (OR, 5.2 [95% CI, 1.6 to 17.3]; p=0.007) and 12 months (OR, 3.9 [95% CI, 1.5 to 10.6]; p=0.007) (**Appendix F Table 21 and Table 22**).[233]

Results: All-Cause Mortality

Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo

No studies reported on all-cause mortality.

Pharmacotherapy vs. Placebo

No studies reported on all-cause mortality.

Combination Therapy (Fluoxetine Plus CBT) vs. Placebo

No studies reported on all-cause mortality.

Collaborative Care vs. Treatment as Usual

No studies reported on all-cause mortality.

Results: Functioning

Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo

Six studies reported functioning outcomes, including quality-of-life outcomes.[174-176, 204, 205, 207, 211, 216] Four[175, 176, 207, 211, 216] of five studies reporting on CGAS could be pooled; the results

suggested no statistically significant differences (**Table 15**). A fifth study,[204] of parent-child interaction therapy in young children, did not report exact p-values and could not pooled with the other studies, but the results favor psychotherapy with a Cohen's d of 1.16, p<0.0001.

In addition to CGAS, studies also reported functioning with other measures (**Appendix F Table 23**). Nearly all studies reported larger improvements in functioning or quality of life with treatment; however, most studies were not powered on these outcomes; thus, estimates may have been imprecise and may not have reached statistical significance. One study reported functioning using the SAS-SR and reported statistically significant larger improvements with interpersonal psychotherapy compared with TAU (school-based clinic care),[216] and a second reported significantly larger improvements in functioning as measured by the PECFAS[204] and total sleep problems as measured by CBCL;[205] these findings were consistent with CGAS outcomes also reported by these studies. A third study reported no statistically significant differences in functioning at 12 weeks between participants allocated to individual, in-person CBT compared with no CBT with a placebo pill as measured with the HoNOSCA and PQ-LES-Q measures, also consistent with CGAS findings of no effect for this study.[207, 211] In a fourth study, despite finding a statistically significant favorable effect of individual, in-person CBT compared with TAU at 52 weeks as measured by CGAS, the authors observed differences in quality of life as measured by the PEDS-QL measure that were not statistically significant.[176] A fifth study reported statistically significant improvements in the mental health component score of the Short-Form 12 (SF-12) for an individual, in-person CBT compared with TAU; SF-12 physical component scores and the CGAS scores were also improved more with treatment, but these results were not statistically significant.[175] Finally, a sixth study reported statistically significant larger improvements in functioning as measured by the Global Assessment of Functioning for the two variations of group CBT intervention compared with placebo.[174]

Pharmacotherapy vs. Placebo

Three studies reported functioning outcomes, including quality of life (**Appendix F Table 25**).[185, 207, 252] Pooled results for CGAS indicated statistically significant differences favoring pharmacotherapy (**Table 15**).

In addition to change in CGAS scores, one study reported outcomes using the HoNOSCA and PQ-LES-Q measures.[207, 211] Although participants allocated to treatment showed larger improvements on these measures consistent with CGAS outcomes, findings were not statistically significant.[207, 211] In addition, the proportion of participants achieving a CGAS score of less than 70 (the threshold associated with no impairment) was 20 percent in the treatment group compared with 19 percent in the placebo group (p=NS).

Combination Therapy (Fluoxetine Plus CBT) vs. Placebo

The Treatment for Adolescents with Depression Study (TADS) study reported functioning outcomes.[207, 211] In this study, combination therapy was associated with larger improvement in functioning as measured by the CGAS, HoNOSCA, and PQ-LES-Q at 12 weeks compared with no CBT/placebo control (**Appendix F Table 27**).

Collaborative Care vs. Treatment as Usual

The collaborative care study measured functional status on the Columbia Impairment Scale. Differences between the intervention and control arms were not significant at an a priori p-value threshold of less than or equal to 0.01 at 6 months (mean difference, -4.4 [95% CI, -8.4 to -0.5]; p=0.03) or 12 months (mean difference, -4.3 [95% CI, -8.3 to -0.3]; p=0.04).[233]

Results: Findings for Specific Populations

Subgroup Analyses

Appendix F Table 29 presents qualitative results for specific populations. Two CBT studies reported analyses for specific populations.[174, 207-211] One study reported analyses by age.[208] Adolescents who were younger than 16-years-old at baseline had significantly greater improvement in clinician-rated symptom severity than adolescents who were 16 or older across all treatment conditions.[208] No statistically significant differences in functioning were reported by age.[211] Two studies reported no statistically significant differences in functioning[211] or recovery rates[174] by sex. One study reported no statistically significant differences in functioning by race or ethnicity.[211]

Two pharmacotherapy studies (escitalopram[252] and fluoxetine[207-211]) reported analyses for specific populations. Both studies reported on functioning outcomes by age.[211, 252] One study reported that 12- to 17-year-old adolescents, but not 6- to 11-year-old children, in the treatment group had significantly better improvements on a clinician-rated measure of functioning than their counterparts in the pill placebo group.[252] One study reported no statistically significant differences in clinician- or self-reported functioing by age.[211] Both studies reported on symptom severity by age.[208, 252] One study reported that 12- to 17-year-old adolescents, but not 6- to 11-year-old children, in the treatment group had significantly better improvements on measures of symptom severity than their counterparts in the pill placebo group.[252] One study reported that adolescents who were younger than 16-years-old at baseline had significantly greater improvement in clinician-rated symptom severity than adolescents who were 16 or older across all treatment conditions.[208] One study reported on symptom improvement by age.[252] The study found that 12- to 17-year-old adolescents, but not 6- to 11-year-old children, in the treatment group had significantly better clinician-rated improvement in symptoms than their counterparts in the pill placebo group. One study reported no statistically significant differences in functioning by sex, race, or ethnicity.[211]

One study[207-211] of combined pharmacotherapy (fluoxetine) and CBT reported analyses on symptom severity[208] and overall functioning[211] by age,[208] sex,[211] or race/ethnicity.[211] Adolescents who were younger than 16-years-old at baseline had significantly greater improvement in clinician-rated symptom severity than adolescents who were 16 or older across all treatment conditions.[208] No statistically significant differences in functioning were reported by age, sex, or race/ethnicity.[211]

Findings Within Age Groups

One study of psychotherapy (parent-child interaction therapy) restricted inclusion to young children, ages 3 to 6 years, with a mean age of 5 years.[204] The study reported statistically significant benefit for symptoms, loss of diagnosis, and functioning for psychotherapy. We found no studies of pharmacotherapy in children.

Two studies recruited both children and adolescents. One study on omega-3, individual-family psychoeducational psychotherapy, and their combination recruited children from ages 7 to 14 years, with a mean age of 11.6 years.[187] The study found that individual-family psychoeducational psychotherapy when compared with placebo did not produce statistically significant differences for symptoms or remission. A second study, on escitalopram, recruited children from 6 to 17 years, with a mean age of 12.3 years. The study found no statistically significant differences for symptoms, response, or functioning.[252]

All other studies were restricted to adolescents only, with ages for inclusion ranging from 12 to 19 years and mean age ranging from 14.6 to 17.5 years. One study had three arms contributing to evidence on psychotherapy, pharmacotherapy, and their combination. In all, the evidence on adolescents included seven studies on psychotherapy,[174-176, 207, 216, 248, 249] two on pharmacotherapy,[185, 207] one on combination therapy,[207] and one on collaborative care,[233] and their results are described in the main results above.

Anxiety or Depression

We included two studies of fair quality (described in 3 articles) that studied children with anxiety or depression.[184, 263, 264] Detailed study, population, intervention characteristics, and results are provided in **Appendix I Tables 35 through Table 40**.

Study Characteristics

One study (N=51) included participants ages 12 to 17 years (mean age: 15.8) with a primary diagnosis of any DSM-IV anxiety disorder (including obsessive compulsive disorder) or depression.[184] The second study (N=185) included children and adolescents ages 8 to 16 years (mean age: 11.3) meeting DSM-IV criteria for full or probable diagnoses of separation anxiety, GAD, social anxiety disorder, MDD, dysthymic disorder, or minor depression.[263, 264] In both studies, anxiety disorders were more common than depressive disorders. Female participants constituted 57 percent[184] to 58 percent[263, 264] of the samples. The majority of participants were Hispanic (59%, excluding non-Hispanic White participants) in one study[184] and White in the other (excluding Hispanic participants).[263, 264]

Both studies offered a transdiagnostic approach drawing on cognitive science, with a minimum of eight weekly sessions. One study offered up to maximum of 12 sessions[184] and the other up to 21 sessions.[263, 264] The comparison group was put on a wait-list in one study[184] or offered an assisted referral in the other.[263, 264]

The studies reported on anxiety and depression symptoms and functioning. Additionally, one study reported on response at 16 weeks (end of treatment)[263] and response and remission at 32 weeks.[264]

Both studies were conducted in the United States and included clinical referrals and self-referrals. The results below describe outcomes for the overall sample in each study.

Results: Anxiety Symptoms

Psychotherapy Interventions vs. Wait-List or Assisted Referral Controls

One study (mean age: 15.8 years) reported ADIS clinician severity rating scale and reported statistically significant differences favoring treatment at followup (4.1 vs. 5.4 at 8 weeks, $p<0.006$) and change from baseline to followup.[184] The threshold for meeting the criteria for diagnosis is 4. The second study (mean age: 11.3 years) reported on PARS and similarly found statistically significant improvements at followup (16 weeks) and change from baseline to followup; the study reported followup values of PARS below 12 (the threshold for clinical response[279]) in both arms (8.6 vs. 11.4).[263, 264] The benefits continued to be statistically significantly different at 32 weeks ($p=0.003$, details not reported).[264]

Both studies reported on CGI-S and CGI-I scores. Both reported statistically significant differences for CGI-S favoring treatment (2.6 vs. 3.4, calculated mean difference -0.80 [95% CI, -1.19 to -0.41];[184] 4.1 vs. 5.1, mean difference: -1.00, $p<0.006$[263]) and CGI-I (2.3 vs. 3.1, calculated mean difference -0.80 [95% CI, -1.23 to -0.37];[184] 3.04 vs. 4.00, mean difference: -0.96, $p=0.016$[263]) favoring transdiagnostic treatment over wait-list or assisted referral.

Results: Depression Symptoms

Psychotherapy Interventions vs. Wait-List or Assisted Referral Controls

One study reported results for RCADS scores at the end of treatment and the second on CDRS-R scores at the end of treatment at 16 weeks and at 32 weeks. Neither study reported statistically significant differences for measures of depression.[184, 263] However, as noted above, both studies reported significantly different CGI-S and CGI-S scores at followup, favoring transdiagnostic treatment over wait-list or assisted referral.

Results: Response, Remission, and Loss of Diagnosis

Psychotherapy Interventions vs. Wait-List or Assisted Referral Controls

One study reported statistically significant results favoring treatment for response, defined as CGI-I≤2, posttreatment at 16 weeks (56.8% vs. 28.2%, $p<0.001$)[263] and at 32 weeks (67.5% vs 4.31%[264]). The differences for remission (36.3% vs. 22.2%) at 32 weeks, defined as CGI-I=1, favored transdiagnostic treatment over assisted referral but were not statistically significant ($p=0.06$).[264]

Results: All-Cause Mortality

No studies reported on all-cause mortality.

Results: Quality of Life and Functioning

One study reported no statistically significant differences in the Adolescent Life Interference Scale (ALIS) at 8 weeks.[184] The second study reported statistically significant differences favoring treatment in CGAS at 16 (68.5 vs. 61.9, p=0.001[263]) and 32 weeks (70.9 vs. 65.0, p=0.004[264]); CGAS scores greater than or equal to 70 represent functional remission.

Results: Findings for Specific Populations

Subgroup Analyses

One study reported that ethnicity moderated response to transdiagnostic treatment, with Hispanic youths having a heightened response and greater improvements in functioning than other participants when compared with Hispanic youths in the assisted referral arm.[263]

Findings Within Age Groups

One study[184] included adolescents only with recruitment restricted to ages 12 to 17 years and a mean age of 15.8 years, and a second study[263, 264] included both children and adolescents with inclusion ranging from 8 to 16 years and a mean age of 11.3 years. Neither reported results for children versus adolescents.

KQ 5. What Are the Harms of Treatment (Psychotherapy, Pharmacotherapy, or Collaborative Care) in Children and Adolescents Who Are Treated for Depression, Anxiety, or Suicide Risk?

Suicide Risk

Summary

We included two RCTs of good or fair quality (described in 4 articles).[179-181, 192] Detailed study, population, and intervention characteristics are provided in **Appendix I Table 16**.

Study Characteristics

The characteristics of the included studies are summarized in **Table 4**. Two studies admitted children based on elevated suicide risk.[179-181, 192]

Mean ages ranged from 14 to 16 years. Included studies focused on adolescence: one study included adolescents 11 to 17 years[179-181] and one study included adolescents 12 to 18 years.[192] The majority of both samples were female.[179-181, 192] One study included mostly White Scottish adolescents,[192] and one study did not report race or ethnicity.[179-181]

Included studies examined family therapy[179-181] and MBT.[192] Both studies compared intervention with TAU. Duration of treatment ranged between six and 12 sessions over 12 months. No evidence was captured that examined pharmacotherapies.

The two included studies[179-181, 192] reported on any adverse events, and one study[179-181] reported on incidence of serious adverse events and other harms. Time of measurement across outcomes ranged from 12 weeks to 4 years.

The two included studies recruited participants from child and adolescent mental health services in the United Kingdom.[179-181, 192] One study[179-181] was rated good quality, and one study[192] was rated fair quality.

Results: Other Adverse Events

One study[179-181] reported on adverse events, serious adverse events, and other harms during the 12- to 18-month followup period. Similar numbers of adverse events, including attendance at minor injury units, walk-in centers, accident and emergency centers, and re-referral to mental health services, occurred in the family therapy group (54%) and treatment-as-usual group (52%). Serious adverse events, defined as hospital attendance, also occurred at similar rates across the intervention (38%) and control (34%) arms. Two participants assigned to the family therapy group died between 3 and 4 years post-randomization. Neither death was related to self-harm. One additional study[192] reported five adverse events among four participants, but the occurrences were not considered to be trial related and not reported by group.

Results: Findings for Specific Populations

Subgroup Analyses

No study reported on harms for specific populations.

Findings Within Age Groups

Both studies were in adolescents only.

Anxiety

Summary

As noted previously, we limited the synthesis to CBT for psychotherapy; we included pharmacotherapies approved by the FDA for children and adolescents. Eleven studies of good or

fair quality addressed harms (described in 22 articles).[168, 169, 224-228, 238, 239, 242-244, 253-262] Detailed study, population, intervention characteristics, and results are provided in **Appendix I Table 24**.

Study Characteristics

Four studies evaluating CBT,[224, 239, 242, 253] six evaluating pharmacotherapy,[168, 169, 238, 243, 244] and one study with three arms evaluating CBT, sertraline, and combination therapy[254-262] addressed harms. **Table 16** describes these studies in detail.

Results: Suicide Deaths, Suicide Attempts and Deliberate Self-Harm, or Suicidal Ideation

Psychotherapy vs. Wait-List Controls, Treatment as Usual, or Placebo

Two studies of individual CBT reported on suicidal ideation, attempts, or self-harm behavior.[253-262] One study (internet, child plus parent) of 60 participants[253] reported that two participants in the wait-list control group withdrew from the study because of risk of suicide by 17 weeks; the study did not note similar withdrawals in the CBT arm. A second child-focused in-person study reported on self-harm behavior without suicidal attempt (1/139 [0.7%] vs. 0/76 [0%]), suicidal ideation (5/139 [3.6%] vs. 1/76 [1.3%]), and suicidal attempts (no events in either arm) by 12 weeks.[254-262]

Pharmacotherapy vs. Placebo

Three studies reported on suicide-related harms at the end of treatment at 8 to 12 weeks (duloxetine,[243] escitalopram,[244] and sertraline[254-262]). No studies reported suicide deaths, two studies reported on suicide attempts (1/26 for escitalopram vs. 0/25 events for placeb;[244] no events in 1 study for either sertraline or placebo[254-262]); three reported on suicidal ideation or worsening of suicidality (1/135 vs. 0/137 for duloxetine vs. placebo;[243] 6/26 for escitalopram vs. 2/25 for placebo;[244] 0/133 for sertraline vs. 1/76 for placebo[254-262]), and two studies reported on self-injurious behavior (2/26 for escitalopram vs. 1/25 for placebo;[244] 1/133 for sertraline vs. 0/76 for placebo[254-262]) (**Appendix F Table 12**). Suicide-related harms were rare, and the differences were not statistically significantly different.

Combination Therapy (Pharmacotherapy and Psychotherapy) vs. Placebo

One study reported on outcomes comparing sertraline plus CBT with placebo.[254-262] The study reported more self-harm behaviors without suicide attempts (1.4% [2/140] vs. 0) and suicidal ideation (3.6% [5/140] vs. 1.3% [1/76]) in the combination arm at 12 weeks, but no suicide attempts in either arm.[254]

Results: Other Adverse Events

Psychotherapy vs. Wait-List Controls, Treatment as Usual, or Placebo

Two child-focused studies of individual CBT reported on serious adverse events.[254-262] One study of 73 participants[239,] reported a single adverse event in the wait-list control group of

hospitalization due to the need to remove a dental brace by 31 weeks. No serious adverse events were reported in either arm in the other study by 12 weeks.[254-262]

Four studies reported on withdrawal due to side effects for treatments ranging from 10 to 14 weeks.[224, 242, 253-262] The studies varied in type of CBT: they included individual and group therapy, delivered in person and on the internet, and child-focused and child and parent therapy. The RR of withdrawal due to side effects was 0.39 (95% CI, 0.08 to 1.87; N=372; k=5; I^2=0%, **Appendix G Figure 33**).

One study reported no homicidal ideation or events in either arm of an individual in-person child-focused CBT when compared with placebo by 12 weeks.[254-262]

Pharmacotherapy vs. Placebo

Three studies reported on serious adverse events (duloxetine,[243] escitalopram,[244] and sertraline[254-262]). The escitalopram study reported one individual experiencing serious adverse events in both arms.[244] The other two studies reported one individual experiencing serious adverse events in the treatment arm and none in the placebo arm.[243, 254]

Five studies (1 each on duloxetine,[243] escitalopram,[244] fluvoxamine,[225-228] and sertraline,[254-262] and fluoxetine[168]) reported on withdrawal due to adverse events. Together, the RR of withdrawal across all drugs was 1.72 (95% CI, 0.57 to 5.18; N=734; k=5; I^2: 26%; **Appendix G Figure 34**). The risk of withdrawal due to adverse events appeared to be elevated for fluvoxamine and fluoxetine.

One study reported that two participants (1.5%) experienced homicidal ideation (but no homicidal attempts in the intervention and none in placebo arm).[254]

Fluoxetine studies reported greater frequency[168] or severity[169] of some adverse events. adverse events reported at statistically higher frequency in the pharmacotherapy arm included gastrointestinal events[168, 225] and neurological complaints.[168] Although other pharmacotherapy studies reported higher frequency of some other harms in the treatment arm when compared with placebo, the differences did not reach statistical significance at p=0.05 (**Appendix F Table 13**).

Combination Therapy (Pharmacotherapy and Psychotherapy) vs. Placebo

One study reported on outcomes comparing sertraline plus CBT with placebo.[254-262] The study reported few or no occurrences of serious adverse events (1 event in the combined therapy arm and no events in the placebo arm), withdrawal due to adverse events (1 event in each arm), homicidal ideation (no events in either arm), and homicidal attempts (no events in either arm). The study did, however, report a higher frequency pf psychiatric adverse events (29.3% vs. 13.2%, calculated absolute risk difference: 16/100 [95% CI, 5 to 27]) and all harms-related adverse events, that is, self-injurious behavior and homicidal ideation (10.0% vs. 1.3%, calculated absolute risk difference: 9/100 [95% CI, 3 to 14]) in the combined therapy arm when compared with placebo.

Results: Findings for Specific Populations

Subgroup Analyses

One study with three arms (CBT, sertraline, and CBT plus sertraline)[167, 190, 241, 254-262] reported on harms for specific populations. The authors reported that the rate of psychiatric adverse events, but not physical adverse events, was significantly higher in children compared to adolescents across all treatment arms.[260] The rate of overall adverse events was significantly higher in children than adolescents who received sertraline.[260]

Findings Within Age Groups

No studies reported on harms in young children.

Results for older children or children and adolescents are described above.

Results for studies of adolescents only suggested lower rates of harms for CBT[239, 242, 253] and higher rates of harms for escitalopram,[244] but results were not statistically significant.

Depression

Summary

We included seven studies for KQ 5 (described in 12 articles).[173, 176, 185, 186, 207-211, 233, 252, 266] All KQ 5 studies are also included in KQ 4 except for one meta-analysis, which was new to this review update.[173] One study that was included in the previous USPSTF report on depression was excluded from this report for ineligible intervention. This study tested citalopram, which was not included in this current update.[277]

Study Characteristics

The characteristics of the included studies are summarized in **Table 17**. Detailed study, population, intervention characteristics, and results are provided in **Appendix I Table 32 through Table 34**. Detailed outcomes are provided in **Appendix F Table 30 through Table 38**.

Results: Suicide Deaths, Suicide Attempts and Deliberate Self-Harm, or Suicidal Ideation

Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo

Two studies of CBT interventions reported on suicide-related events (**Appendix F Table 30 and Table 31**).[176, 207, 209] Suicide-related events included suicide attempts and new or worsened ideation. Both reported higher but not statistically significantly different rates in the treatment arm. One study, comparing CBT plus TAU with TAU, reported five events among 106 participants (4.7%) in the CBT with TAU arm compared with two events among 106 participants (1.9%) in the TAU arm (RR, 2.50 [95% CI, 0.50 to 12.60]).[176] At study entry, all had recently declined or discontinued antidepressants prematurely. During a year-long followup, a minority of

participants received antidepressants in each arm (9.4% in the CBT plus TAU arm and 7.6% in the TAU arm). The second study, TADS,[207, 209] reported inconsistent results across various TADS publications. TADS included four study arms: CBT, fluoxetine, combined CBT and fluoxetine, and a placebo comparator. The events reported by parents and patients were reviewed and subsequently recoded using the Columbia-Classification Algorithm for Suicidal Assessment in a reanalysis. The first analysis published by study authors in 2004 reported five events among 109 participants (4.6%) in the CBT arm compared with four events among 112 participants (3.6%) in the placebo arm (RR, 1.26 [95% CI, 0.35 to 4.57]).[207] Safety results of reanalyzed data published in 2006 reported three (2.7%) events in the placebo arm, resulting in a higher RR of 1.68 (95% CI, 0.41 to 6.87).[209] An extended analysis of TADS was published in 2009 that included suicide-related events through blinded (baseline to week 12) and unblinded phases (week 12 to week 36) of the trial.[280] These analyses are not eligible for the current systematic review because they include events that occurred after unblinding and clinical management of nonresponders. However, the publication included a graphic indicating that five suicide-related events occurred in the placebo arm by week 12, of which two occurred in participants on SSRIs at the time of the event. The placebo arm did not appear to include TAU: the authors reported that they discarded a community-based TAU group because of concerns about variability and access to care.[207] No further details or per-protocol analyses are available from the authors. A per-protocol analysis that reassigns placebo participants receiving SSRIs to the pharmacotherapy arm would change the denominators and, therefore, relative risks for all comparisons in the study.

The TADS study reported no statistically significant differences on suicidal ideation measured by the SIQ-Jr scale.[207]

Pharmacotherapy vs. Placebo

Three studies reported on suicide-related outcomes using a variety of measures (**Appendix F Table 32 and Table 33**). One study explicitly reported that no completed suicides occurred;[252] the others did not report data on deaths.[207, 209, 252] The two escitalopram studies reported similar rates of events potentially related to suicide or self-harm when compared with placebo (1 event among 129 participants [0.8%] vs. 2 events among 132 participants [1.5%];[252] 6 events among 157 participants [3.8%] vs. 6 events among 155 participants [3.9%][185]). The fluoxetine study (TADS)[207, 209] reported inconsistent results across various publications on suicide-related events. The first analysis published by study authors in 2004 suggested a higher but nonstatistically significant rate of suicide-related events in the fluoxetine arm when compared with placebo (9 events among 109 participants [8.3%] vs. 4 events among 112 participants [3.4%]; RR, 2.31 [95% CI, 0.73 to 7.29]).[207] Safety results published in 2006 reported 10 (9.2%) events in the intervention and three (2.7%) in the placebo arm resulting in a higher RR, 3.43 (95% CI, 0.97 to 12.11).[209]

Two studies reported no statistically significant differences on suicidal ideation measured by the SIQ-Jr scale.[185, 207]

One network meta-analysis examined harms across a range of drugs and populations, including those ineligible for the current review (**Appendix I Table 34**). The rate of suicide-related

behaviors or ideation events appeared similar for escitalopram versus placebo (15/290 [5%] vs. 15/294 [5%], 2 studies) and for fluoxetine versus placebo (51/521 [10%] vs. 44/514 [9%], 7 studies).[173]

Pharmacotherapy Plus CBT vs. Placebo

A single study on combination therapy, the TADS trial, reported on suicide-related events, with results varying by publication source (**Appendix F Table 34 and Table 35**).[207, 209] The first analysis published by study authors in 2004 reported six suicide-related events among 107 participants (5.6%) in the combined arm compared with four events among 112 participants (3.4%) in the placebo arm (RR, 1.57 [95% CI, 0.46 to 5.41]).[207] Safety results published in 2006 reported five (4.7%) events in the intervention and three (2.7%) in the placebo arm, resulting in a higher RR, 1.75 (95% CI, 0.43 to 7.12).[209]

One study reported a statistically significant difference on suicidal ideation measured by the SIQ-Jr scale, favoring combination therapy (mean score at followup: 11.79 vs. 15.01, p=0.02) in adjusted analyses but not in comparisons of mean differences.[207]

Collaborative Care vs. Treatment as Usual

The study did not report suicide-related outcomes.

Results: Other Adverse Events

Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo

No study reported on withdrawal due to adverse events. The TADS study reported no differences in rate of harm-related adverse events (which included self-harm without suicidal intent, suicide attempt, and harm to others) in the CBT arm when compared with placebo (5 events among 111 participants [4.5%] vs. 6 events among 112 participants [5.4%, OR: 0.8 [95% CI, 0.25 to 2.81]) (**Appendix F Table 36**).[207] One study used an open-ended question on the QIDS-A17-SR to assess potential negative effects and found that no participant in the treatment arm deteriorated reliably on the QIDS-A17-SR when compared with three participants in the control arm.[266]

Pharmacotherapy vs. Placebo

Two escitalopram trials reported on withdrawal due to adverse events and serious adverse events (**Appendix F Table 37**). One trial reported higher rates in the treatment arm for both outcomes (4 (2.6%) withdrawals in the treatment arm and 1 (0.6%) in the placebo arm; 4 (2.6%) serious adverse events in the treatment arm and 2 (1.3%) in the placebo arm[185]). The second reported similar rates in both arms for both outcomes (2 [1.5%] withdrawals due to adverse events vs. 2 [1.5%]; 2/131 [1.5%] serious adverse events vs. 3/133 [2.3%]).[252] These differences were not statistically significantly different in either study.

The fluoxetine study (TADS) study reported a higher but not statistically significantly different rate of harm-related adverse events in the combined therapy arm when compared with placebo

(13 events among 109 participants [11.9%] vs. 6 events among 112 participants [5.4%, OR: 2.4, [95% CI, 0.87 to 6.54]).[207]

Pharmacotherapy + CBT vs. Placebo

No study reported on withdrawal due to adverse events. The TADS study reported a higher but not statistically significantly different rate of harm-related adverse events in the combined therapy arm when compared with placebo (9 events among 107 participants [8.4%] vs. 6 events among 112 participants [5.4%, OR: 1.6 [95% CI, 0.56 to 4.72]) (**Appendix F Table 38**).[207]

Collaborative Care vs. Treatment as Usual

A single trial of collaborative care found no differences in psychiatric hospitalizations among intervention patients compared with control patients (6% vs. 4%, respectively). More control patients experienced an ED visit with a primary psychiatric diagnosis than intervention patients (1 [2%] vs. 5 [10%] patients, respectively); however, this study was not powered to detect differences.[233]

Results: Findings for Specific Populations

Subgroup Analyses

No study reported on harms for specific populations.

Findings Within Age Groups

The only study in children did not report on harms.[204]

One of the two studies in children and adolescents, specifically on omega-3, individual-family psychoeducational psychotherapy, and their combination, did not report on the harms of individual-family psychoeducational psychotherapy when compared with placebo.[187] One study on escitalopram reported similar or lower rates of harms in the treatment arm.[252]

The remainder of the studies reported on adolescents only; the results are summarized above.

Anxiety or Depression

Results: Suicide Deaths, Suicide Attempts and Deliberate Self-Harm, or Suicidal Ideation

No studies reported on suicide outcomes.

Results: Other Adverse Events

No studies reported on other adverse events.

Results: Findings for Specific Populations

No study reported on harms for specific populations.

Chapter 4. Discussion

Summary of Evidence

We summarize the evidence, including strength of evidence ratings, by KQ in **Table 18**.

Benefits of Screening (Key Question 1)

We did not identify any studies reporting on the direct benefits of screening.

Screening Test Accuracy (Key Question 2)

We only identified one study assessing the accuracy of screening for suicide risk in adolescents evaluated against a clinical diagnostic interview reference standard; the instrument used was the SRS, a 20-item instrument that was embedded in a longer questionnaire, and the study population was recruited from youth identified as potential high school dropouts.[247] We rated the strength of evidence for screening as insufficient because of inconsistency in estimates based on the reference standard used, imprecision, and study limitations. Given that most depression screening instruments include an assessment of suicidal ideation, it is unclear whether a separate, stand-alone instrument to screen for increased suicide risk has value for universal screening in primary care practice. The Ask Suicide Screening Questions (ASQ) is a brief 4-item instrument that was initially developed for youth age 8 years or older in emergency department settings but has since been evaluated in other medical settings including outpatient specialty and primary care.[281, 282] The Joint Commission recommends suicide risk screening for all medical patients in all medical settings, including outpatient practices.[283] The National Institute for Mental Health developed an ASQ toolkit to support implementation of suicide risk screening in medical settings, including for youth in primary care.[284] We identified one study evaluating the ASQ in outpatient settings, including primary care, but we excluded it because its accuracy was compared against another suicide risk screening instrument and not against a diagnostic clinical interview by a qualified professional.[282]

We identified evidence for test accuracy related to seven different instruments for screening for MDD, but five of those instruments were limited to single-study bodies of evidence.[172, 199, 219, 223] Across this body of evidence, the sensitivity of screening tests compared with clinical diagnostic interview ranged from 0.59 to 0.94, and we rated most comparisons as low strength of evidence. Specificity ranged from 0.53 to 0.97, and we rated this body of evidence as moderate strength of evidence. All but one study were focused exclusively on adolescents.

The depression module (PHQ-9) of the full PHQ is the instrument highlighted for use in screening for depression by the AAP in a quality improvement collaborative designed to improve diagnostic performance for depression.[285] The Centers for Medicare & Medicaid Services Merit-based Incentive Payment System and the National Committee on Quality Assurance HEDIS measure set include a depression screening quality measure that is applicable to persons age 12

and older.[286-288] These measures require that standardized screening tools normalized and validated based on age for which they are being used should be used for screening, but they do not specify a specific tool. Similarly, the AAP Guidelines for Adolescent Depression in Primary Care recommended screening using a formal self-report tool.[147] For these measures and guidelines, multiple tools are listed, but the CES-D is the only instrument included in this review update that are among the listed examples. We identified one study of the accuracy of the full PHQ modified for adolescents, and we identified no studies evaluating the PHQ-9, which is the depression module of the full PHQ. The PHQ-9 may offer advantages over the CES-D with respect to feasibility of implementation because it is already the basis for quality measures related to monitoring depression remission and response to treatment and includes an item specific to suicidal ideation (unlike the CES-D). However, the full PHQ, which also includes modules for anxiety, somatoform disorders, eating disorders, and substance abuse, may be more feasible for use as a transdiagnostic screener compared to the use of separate screeners for different conditions.[289]

Based on the accuracy characteristics for the one included study of PHQ-A in this update review,[199] per 1,000 screening tests conducted, 58 false-positives and eight false-negatives would be generated at the low end of MDD prevalence (3%), and 53 false-positives and 30 false-negatives would be generated at the high end of prevalence (11%). As noted above, we did not identify any evidence related to the harms of screening. The relative frequency of false-negatives is smaller than the number of false-positives, and most of the other instruments included in this update follow a similar pattern. Positive results would require additional diagnostic evaluation to sort out true-positives from false-positives, but it is likely that some youth screening positive but not meeting diagnostic criteria for MDD may have PDD (formerly known as dysthymia) or other behavioral health conditions with symptoms similar to depression. The consequences of a false-negative would largely depend on the severity of the missed diagnosis; the likelihood of missing a severely depressed youth is small because most screen-detected depression is likely to be mild to moderate. However, even mildly to moderately depressed youth may have suicidal ideation, and the consequences of missing such symptoms could be serious.

We examined nine different instruments (i.e., ANS, PHQ-A, PI-ED, SAS, SASA, SCARED, SPAI, SPIN, and SWQ) to screen for anxiety, most of which screened for specific anxiety disorders such as GAD, social anxiety disorder, separation anxiety disorder, and panic disorder. Some screening instruments with subscales screened for more than one anxiety disorder. Thus, we evaluated 15 different approaches (e.g., full scale, subscales) for detecting anxiety disorders, and we had only a single study body of evidence for nine of the approaches (from four studies).[188, 199, 218, 219] Across all of the screeners and subscales and thresholds for a positive test evaluated, sensitivity ranged between 0.34 and 1.00; we rated most comparisons low strength of evidence. Specificity for this body of evidence ranged between 0.47 and 0.98, and we rated about half of the comparisons as moderate strength of evidence and the other half as low strength of evidence. The confidence intervals around the estimates of sensitivity and specificity were often wide, indicating a lack of precision for most screeners. Of the 10 studies that assessed screeners to detect anxiety, four included both children and adolescents, and the remainder included adolescents only.

In all but two studies, youth were the respondents, and in one of the two both youth and parents completed the same screeners.[171] This study administered both the full and the short versions of the SCARED to parents and youth ages 9 to 13 years. Sensitivity was greater for the screeners in which youth were the respondents, suggesting that youth are better reporters of their own distress. However, there were more false-positives per 1,000 screens for the youth-administered screeners. Specificity was only minimally worse when youth were the respondents.

One screener designed to detect panic disorder, the ANS, is notable for the perfect sensitivity in all three versions—two items, three items, and five items. The perfect sensitivity of the ANS does not appear to be related to the fact that adolescents were respondents because most of the other screeners were given to youth, and the ANS is the only one with such high sensitivity. In fact, the PHQ-A, which also included adolescents as respondents, had a much lower sensitivity when compared with a clinical diagnosis of panic disorder. Rather, it is more likely that the targeted nature of the ANS's content contributed to its ability to perfectly detect adolescents with panic disorder. The two gateway items concerned sudden physical and mental feelings of fright or anxiety. In contrast, the PHQ-A is a broader tool used more often to detect depression as well as other mental health disorders.

The difference in accuracy between a broad screening tool and one that is more targeted is seen when comparing the SCARED full scale and some of the SCARED subscales. Sensitivity of the full-scale SCARED with youth as respondents was 0.76,[171] whereas sensitivity on the SCARED separation anxiety scale was 0.88.[218] In contrast, the sensitivity of the more global SCARED GAD scale was 0.64.[171]

To facilitate adoption of screening in primary care, screeners should not only be accurate but be short. Both the SCARED and the SPIN have shorter versions that were administered in some of the included studies. The 10-item SCARED short version for youth was somewhat lower (0.67) than the full 41-item version (0.76) with respect to global anxiety symptoms.[171] With a sensitivity of 0.86, the 3-item Mini-SPIN[232] was equivalent to that of the 17-item SPIN (0.82)[231] Thus, accuracy was not compromised for the Mini-SPIN with respect to identifying social anxiety disorder.

Across all screeners and subscales, the rate of false-positives was as high as 500 per 1,000 screens for a range of prevalence values from 2.5 percent to 13 percent. In contrast, the rate of false-negatives for the same range of prevalence values did not exceed 100 per 1,000 screens. The consequences of a high rate of false-positives indicate that many families may needlessly be concerned about their children's mental health. However, good practice dictates that those who are screened positive should receive a clinical evaluation that can rule out an anxiety disorder. The consequences of the lower rate of false-negatives indicate that fewer truly anxious youth will be missed by a screening program. Yet, astute parents and primary care providers may recognize that even in the absence of screen-detected anxiety youth whose physical complaints include stomachaches, headaches, fatigue, or muscle tension without an organic cause may be manifesting anxiety. Good practice indicates that these youth may also benefit from a clinical evaluation for anxiety disorders.

Harms of Screening (Key Question 3)

We did not identify any studies reporting on the direct harms of screening for anxiety or depression. Two RCTs reported no increased distress or suicidal ideation following screening for suicide risk.[267, 268]

Benefits and Harms of Treatment (Key Questions 4 and 5)

Suicide

Sixteen RCTs of interventions to reduce suicide risk or self-harm addressed the benefits of treatment,[164, 179-182, 191-194, 197, 200-202, 212-215, 221, 222, 229, 236, 245, 265] and two reported on harms of treatment.[179, 192] Nine of 16 RCTs were new to this update.[164, 179-181, 192, 194, 202, 212-215, 221, 222, 229, 236] The previous review found statistically nonsignificant increases in suicide attempts for psychotherapy interventions and no benefits for suicidal ideation, raising the possibility of harm.[179, 192] One newly identified update to a previously included study found no statistically significant differences in suicide deaths but found benefits in all-cause mortality over the long term.[201] Newly identified studies do not report on suicide attempts, and the evidence base on self-harm events is inconsistent. The updated evidence base (including prior and new studies) suggests improvements in suicidal ideation resulting from treatment, but this finding was only statistically significant for one measure. The evidence suggested no statistically significant differences on all other outcomes. Notably, all studies included TAU comparators, which for ethical reasons must be active comparators, such as standard psychotherapy, individual counseling, family sessions, medication assessment and review, medication, and other care coordination activities. Comparable intensity of therapy in study arms, coupled with low event rates for some outcomes (such as suicide deaths, hospitalizations, and suicide attempts), is likely to make differences between study arms difficult to detect. We rated the evidence as low for benefit on suicidal ideation but insufficient for evaluating outcomes such as suicide attempts, hospitalizations, and deaths. Only two studies reported on various harms outcomes (such as attendance at minor injury units, walk-in centers, and accident and emergency centers; re-referral to mental health service; and hospital attendance). The available evidence did not indicate a higher frequency of events in the treatment arm. We rated the strength of evidence as low for no harm. Only one study reported analyses of specific populations. The evidence suggested that hospital attendance for self-harm events did not vary by age across adolescents.

Anxiety

Twenty-nine RCTs on treatment of anxiety in children and adolescents addressed benefits,[163, 165, 167-169, 177, 178, 183, 190, 195, 196, 198, 203, 206, 220, 224-228, 237-244, 246, 251, 253-262] and 11 addressed harms.[168, 169, 224, 238, 239, 242-244, 253-262] All are new in this update. These studies provided evidence on CBT, pharmacotherapy, and a combination of CBT and sertraline. Consistent, precise, statistically significant differences existed for most anxiety outcomes for CBT and pharmacotherapy, and we rated the strength as evidence as moderate for benefit for nearly all outcomes. For response, remission, loss of diagnosis, and functioning, the evidence suggests statistically significant

differences favoring CBT; there is less evidence for pharmacotherapy on these outcomes, but the available evidence indicates benefits for clinical response. Results were less consistent for other outcomes. The evidence on CBT is more voluminous (23 RCTs) compared with pharmacotherapy (7 RCTs). Most pharmacotherapy studies (6 of 7) required specific anxiety diagnoses, that is, GAD, separation anxiety, or social anxiety disorders, whereas a minority of CBT studies specified diagnosis (10 of 24). The remainder targeted any anxiety diagnosis. Anxiety studies covered a wide range of ages, from preschool (ages 3 to 7 years)[183, 195, 237] through adolescence, though 11 studies were focused exclusively on adolescents. Studies focusing on younger children (ages 3 to 7 years[183, 195, 237]) were consistent with the overall findings in demonstrating benefits for symptoms and clinical response.

Few CBT trials reported on harm outcomes, and we rated the strength of this evidence as insufficient. The evidence suggests that suicide-related harms, serious adverse events, and withdrawal due to adverse events are rare in pharmacotherapy studies but more frequent in the treatment arm; thus, we rated this evidence as low for harms.

Few studies reported analyses by age, sex, race, or ethnicity. Studies reporting on analyses of anxiety symptoms consistently reported no effect of age or sex, but there is insufficient evidence available on anxiety symptoms by race or ethnicity. There is insufficient evidence available on specific populations for other outcomes.

Depression

Thirteen RCTs on treatment of depression in children and adolescents addressed benefits,[174-176, 185, 187, 204, 205, 207, 216, 233, 248, 249, 252] and five addressed harms.[176, 185, 207, 233, 252, 266] Eight RCTs were new in this update for KQ 4, all focusing on psychotherapy.[175, 176, 187, 204, 205, 216, 248, 249, 266] Additionally, one meta-analysis of pharmacotherapy is new to the update on harms.[173] The prior report on depression in children and adolescents included two trials on psychotherapy; neither[174, 207] showed improvement on remission or recovery. These two trials were inconsistent on symptoms, response, and functioning. The updated evidence on psychotherapy suggests some benefits for symptom improvement, clinical response, and loss of diagnosis, but the results are not consistent across all measures for other outcomes. The evidence for pharmacotherapy suggests benefit for symptom improvement, but the results are not consistent across all measures for other outcomes. Thus, we rated the strength of evidence for psychotherapy and pharmacotherapy as low for benefit.

The evidence on harms is limited but suggests a higher frequency of suicide-related outcomes for psychotherapy and pharmacotherapy. Notably, one multi-arm trial (Treatment for Adolescent Depression Study, or TADS) with inconsistent reporting on suicide-related events across its various publications contributed to the evidence on psychotherapy, pharmacotherapy, and their combination. These discrepancies increase the uncertainty regarding harms of treatment and have led to a call for independent reanalysis of the TADS results.[290, 291] The FDA notes a higher frequency of suicide-related events in boxed warnings for antidepressants.[292] The underlying FDA review for this warning relied on drug trials in populations ineligible for this review.[293]

The prior report found very limited evidence on treatments in children: no psychotherapy trials and just one pharmacotherapy trial[252] recruited children younger than age 12 years. This updated review included two new studies in children. Of these, one recruited children ages 7 to 14 years, with an average age of 11.6.[187] This trial is a comparison of psychoeducation psychotherapy plus placebo vs. placebo, where the primary purpose was to examine the effectiveness of omega-3 fatty acids. The sample size for therapy and placebo arms together was 37 participants. The second study of children was a larger trial (N=229)[204, 205]of parent-child interaction therapy (PCIT). The results were not consistent across the two studies: the PCIT trial suggested improved symptoms, loss of diagnosis, and improved functioning, whereas the psychoeducation psychotherapy did not find benefits for treatment for symptoms or remission.

Few studies reported analyses by age, sex, race, or ethnicity. The available evidence on functioning outcomes by age is inconsistent, and there is insufficient evidence available on functioning outcomes by sex, race, or ethnicity. There is insufficient evidence available for specific populations on other outcomes.

Limitations of the Evidence

We did not identify any direct evidence for the benefits of screening for suicide risk, anxiety, and depression and very limited evidence on harms for suicide risk alone, among children or adolescents in primary care or primary care–relevant settings. Despite the large number of potential instruments that could be used for screening, we identified only one to two studies for any given instrument for the KQ on test accuracy (KQ 2). Further, these studies often evaluated multiple thresholds for determining a positive test, but it is not clear whether the optimal thresholds reported by such studies would remain optimal when used across different age groups or populations. Existing quality measures related to depression screening list examples of several instruments that can be used, but we identified surprisingly little research for those tools. Although studies reporting psychometric characteristics of these tools exists, few have studies evaluating them against a reference standard that includes a clinical diagnostic interview. The PHQ-A is capable of screening across conditions (suicide risk, anxiety, depression), but it is only applicable to adolescents. Although other instruments are available that assess a broad range of mental, behavioral, and emotional health areas, such instruments are typically designed for epidemiologic studies or to augment clinical history-taking and diagnosis and are too long to be considered feasible for use as brief screening instruments in primary care settings. We identified no studies reporting on the harms of screening.

Related to the benefits and harms of treatment, fewer studies were conducted in children compared with adolescents. Although studies generally reported outcomes using validated measures of symptoms, minimally important differences in children and adolescents for these measures are lacking and whether statistically significant differences in mean symptoms scores are clinically meaningful is uncertain. Despite this limitation in such measures, response, remission, and loss of diagnosis outcomes generally mirrored changes in symptom scores, suggesting that the differences observed are likely clinically meaningful. For all conditions, heterogeneity in type and duration of psychotherapy interventions, underlying anxiety and

depression subtypes, risk factors, and comorbidities somewhat limited our certainty about the magnitude of benefit for such interventions.

For suicide studies, more than half the studies included participants with comorbid conditions but did not always report how these conditions were treated. Ongoing therapy for these comorbid conditions may have attenuated the effect of the interventions.

Trauma and maltreatment are risk factors for suicide, anxiety, and depression in children,[294, 295] but no trauma-focused interventions were found to be eligible for this review. Another constraint in interpreting the evidence for psychotherapy relates to the comparators. For suicide, the comparator arms generally included active comparators that may result in understated benefits for the intervention arm. For depression and anxiety, multi-arm studies of drugs, psychotherapy, and their combination,(TADS[207-211] Child/Adolescent Anxiety Multimodal Study, or CAMS[254-262]) compared these active treatments with placebo. In these cases, the lack of blinding for the psychotherapy and combination therapy arms may also bias outcome reporting.

For pharmacotherapy interventions, the evidence is largely limited to short-term benefits (typically up to 12 weeks). The evidence for increased suicidal events across all three topics is hampered by imprecision because of rare events, conflicting reporting in the published studies for depression in particular, and varying definitions for this type of harm. The ethical considerations and logistical challenges of conducting studies in children often limit the size of trials; future research studies that employ the same type of study designs are likely to encounter similar difficulties with adequately powering trials for rare outcomes.

Treatment studies necessarily exclude low-risk participants from trials to maximize the potential for finding an effect. Screen-detected populations may include low-risk individuals; as a result, whether the benefit observed in treatment studies applies to screen-detected populations is unclear. Further, rates of treatment enrollment and retention in research studies are likely different than what can be expected in routine clinical practice.

Future Research Needs

More RCTs are needed on the benefits and harms directly arising from screening for suicide risk, anxiety, and depression among children and adolescents in primary care settings (or similar settings), when compared with no screening or usual care. Future research could also elucidate the advantages and disadvantages of combined screening for depression and suicide risk, as currently happens with some instruments (e.g., PHQ-9). Although some studies have demonstrated that screening for depression alone may not be adequate to identify those at high risk for suicide, such studies were conducted among hospitalized medically ill youth and may not be applicable to youth seen in primary care practice.[296, 297] Because multiple types of anxiety disorders exist, future research could elucidate trade-offs between screening instruments designed to identify any anxiety disorder versus instruments designed for specific anxiety disorders. Lastly, the use of computerized adaptive screening could be explored to allow for the use of broader screening instruments to screen across condition but yet limit respondent burden.

The existing evidence focuses on adolescents, reflecting the higher prevalence of mental health disorders among them. More research on treatment in children is also warranted, across all types of therapies. However, traditional RCTs randomizing individual treatments will necessarily be constrained in size (because of the challenges of recruitment in younger children and because of lower rates of depression and suicide risk) and, therefore, statistical power by ethical and logistical considerations. Cluster-randomized trials and pragmatic trials[298] may help address size considerations for trials of children or adolescents but may also continue to carry risks of bias in outcome measurement because blinding is not likely to be feasible. Publication of hitherto unreported data on rare or no suicide events from ongoing and completed trials will help supplement the relatively sparse evidence on this outcome.

Studies infrequently measure long-term outcomes or conduct analyses of populations of interest. No studies reported on sexual orientation or gender identity in subgroup analyses; given that these are known risk factors for suicide in particular, further research is needed. In light of rising suicide rates among Black children, more work needs to be done on accurate identification and effective prevention of suicide risk among them.[110] No studies focused on American Indian youth, who have the highest rates of suicide deaths in the United States.

Little is known about minimal clinically important differences for the multitude of outcome measures evaluated in this report. Studies establishing these thresholds will help stakeholders interpret the existing evidence.

Limitations of the Review

We limited this review to studies published in English that were conducted in very highly developed countries to maximize applicability of findings to primary care settings in the United States. As a result of the restriction of the screening benefits (KQ 1) and accuracy (KQ 2) questions to primary care and primary care–relevant settings, this review does not address the outcomes from schoolwide or communitywide screening that may result in increased referrals to primary care.

Similarly, we limited the scope of the KQ on test accuracy (KQ 2) to screening instruments feasible for use in primary care settings. For suicide risk, this review was limited to evaluating the diagnostic accuracy of instruments to identify youth at high risk for suicide as compared with a diagnostic clinical interview and did not include predictive accuracy studies. Future reviews on this topic might consider including studies that evaluate the accuracy of screening instruments to predict future suicidal behavior (e.g., suicide attempts, nonfatal self-injury).

For our review, for suicide risk intervention and anxiety treatment questions, all participants in eligible trials needed to have an anxiety diagnosis or recognized suicide risk. As a result, we may have excluded studies with participants with subsyndromal anxiety or studies that included a spectrum of recognized suicide risk. We expanded the inclusion criteria for treatment studies of depression to those where 50 percent or more of participants had MDD in an attempt to identify studies that included other relevant depression diagnoses. Nonetheless, this criterion resulted in

the review excluding studies that may have otherwise been eligible and demonstrated benefit.[299, 300]

Because questions on the treatment of these conditions are framed relatively narrowly to support a screening recommendation, eligible studies compared treatment with no treatment, usual care, or placebo. As a result, the review cannot speak to the suggested sequence of treatments (e.g., psychotherapy vs. pharmacotherapy for depression). Because ethical concerns limit the ability to conduct comparative studies for suicide prevention using placebo or wait-list controls, we included treatment-as-usual comparators with durations and intensity comparable to active arms. Nonetheless, this review does not summarize the state of evidence for studies comparing two active interventions simultaneously[301] or comparing usual care and active treatments sequentially,[302] as may be the case in some suicide prevention studies.

We limited the scope of pharmacotherapy agents to drugs approved by the FDA for pediatric use and often likely to be first-line therapy for treatment for screen-detected conditions because of their relevance to primary care. We also limited the scope of psychotherapy for anxiety to CBT; Appendix A summarizes the evidence for other available therapies. We refer readers to recent AHRQ Effective Health Care Program reviews for more comprehensive information about additional medications that may not be used as first-line treatment and comparative effectiveness of various psychotherapy and pharmacotherapy treatments for depression[153] and anxiety[123] in children and adolescents.

We also focused on health outcomes as benefits. Studies that focus on healthcare utilization (e.g., demonstrating an increase in referral or uptake of services) or intermediate outcomes would have been excluded from the review if they did not also report on health outcomes. In practice, achieving positive results following the implementation of an intervention requires adequate diagnostic followup (Appendix A, CQ 1) and engagement with care (Appendix 1 CQ 6).

Conclusions

We found no eligible studies that reported on benefits directly arising from screening when compared with usual care or no screening. Limited direct evidence suggests no short-term harms from screening for suicide risk. The evidence for screening for suicide risk, anxiety, and depression in children and adolescents relies on indirect evidence on the accuracy of screening and the benefits and harms of treatment. Both pharmacotherapy and psychotherapy treatments have some benefit for some depression and anxiety outcomes (specifically, CBT for anxiety alone was reviewed); the evidence is limited for suicide risk interventions. Harms are rare in treatment studies but more frequent in pharmacotherapy arms when compared with placebo. Evidence gaps persist in children younger than age 11 years for test accuracy, depression and suicide risk interventions, and for screening and treatment differences by sex, race/ethnicity, sexual orientation, and gender identity.

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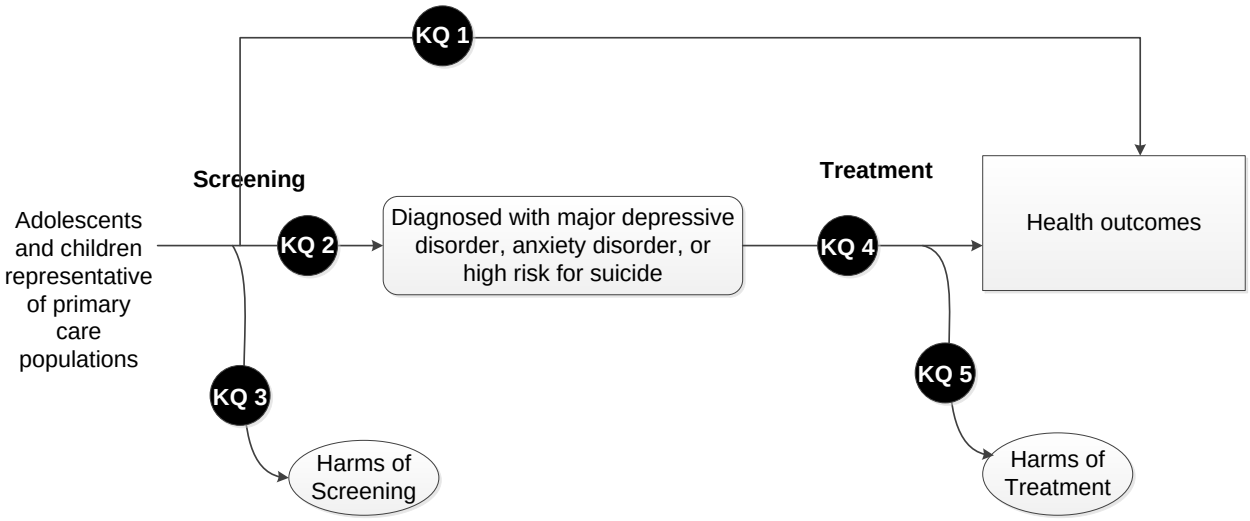
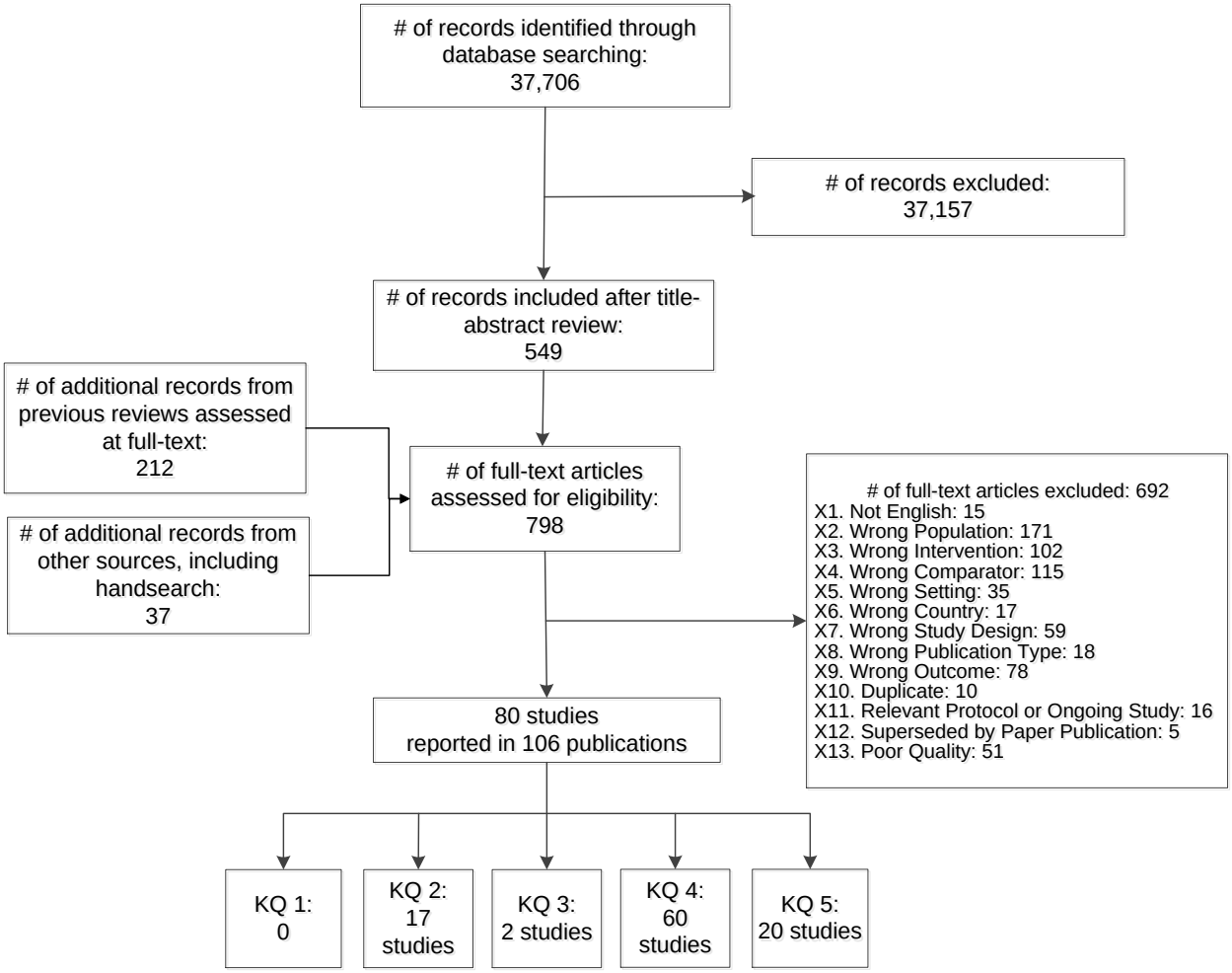
Figure 1. Analytic Framework



Abbreviation: KQ=key question.

Figure 2. Flow Diagram of Studies



Abbreviations: KQ=key question; X=exclusion number.

Table 1. Non-USPSTF Guidelines and Recommendations on Screening for Anxiety, Depression, and Suicide Risk for Children and Adolescents

Organization	Recommendation
	Suicide Risk
The American Academy of Child and Adolescent Psychiatry, 2019[143]	Recommends screening for suicide risk across physical and mental healthcare settings and the urgent identification of and clinical intervention for children and youth at risk for suicide.
American Academy of Pediatrics, Bright Futures, 2022[142]	Recommends universal screening for youth 12 years or older and screening when clinically indicated for youth 8 to 11 years. For youth under age 8, screening is not indicated but pediatricians should assess for suicidal thought and behaviors if warning signs of suicide risk or parent report of suicidal behaviors are present.
American Academy of Family Physicians, 2017[141]	Supports the USPSTF recommendation.
The Joint Commission National Patient Safety Goal for Suicide Prevention, 2019[144]	Organizations should screen all individuals served for suicidal ideation using a validated screening tool and monitor implementation and effectiveness of policies and procedures for screening individuals at risk for suicide and take actions to improve compliance as needed.
	Anxiety
American Academy of Child and Adolescent Psychiatry (AACAP), 2020[145]	Notes the lack of empirical recommendations on screening for anxiety disorders in children or adolescents and points to freely available screening instruments.
National Institute for Health and Clinical Excellence (NICE), 2017[146]	Recommends asking children or young people about their feelings of anxiety, fear, avoidance, or distress and conducting comprehensive assessments of those reporting those feelings.
	Depression
Guidelines for Adolescent Depression in Primary Care (GLAD-PC), 2018[147]	Recommends annual universal depression screening of youth 12 years or older with a formal screening tool, identification of patients at high risk for depression, coordination of depression care, and establishment of a safety plan.
National Institute for Health and Clinical Excellence (NICE), 2019[303]	Notes that healthcare professionals in primary care settings should be familiar with screening for mood disorders. Healthcare professionals in primary care, schools, and other relevant community settings should be trained to detect symptoms of depression and assess children and young people who may be at risk of depression. Training should include the evaluation of recent and past psychosocial risk factors.
American Academy of Family Physicians, 2017[141]	Supports the USPSTF recommendation.
	Multicondition
American Academy of Pediatrics (AAP), Bright Futures, 2015[150]	Recommends screening annually for emotional and behavioral problems for adolescent patients ages 12 years or older.
American College of Obstetricians and Gynecologists, 2017 (reaffirmed in 2020)[151]	During preventive care visits, all adolescents should be screened for any mental health disorder in a confidential setting (if allowed by the laws of that locality).

Abbreviations: AACAP=American Academy of Child and Adolescent Psychiatry; AAP=American Academy of Pediatrics; AMA=American Medical Association; GLAD-PC=Guidelines for Adolescent Depression in Primary Care; NICE=National Institute for Health and Clinical Excellence; USPSTF=U.S. Preventive Services Task Force.

Table 2. Results of Diagnostic Test Accuracy Studies on Screening for Anxiety Compared With Structured Clinical Interview (KQ 2)

Author, Year Quality	Age Range; Mean Age (SD), Years	Total N (% Female)	Index Test Cutoff	Respondent	Prevalence %	Sensitivity (95% CI)	Specificity (95% CI)	Per 1,000 Screens Across a Prevalence From 3% to 13% No. False-Negatives	Per 1,000 Screens Across a Prevalence From 3% to 13% No. False-Positives
Anxiety (Global, that is positive on total anxiety score)									
Screen for Anxiety Related Emotional Disorders (SCARED)									
Canals et al, 2012[171] Fair	11 (1.0) 9 to 13	562 (55)	SCARED-C Cutoff ≥ 25	Youth	24	0.76 (0.68 to 0.92)	0.68 (0.63 to 0.72)	6 to 31	278 to 312
			SCARED-P Cutoff ≥ 17	Parents	24	0.63 (0.54 to 0.74)	0.70 (0.65 to 0.74)	9 to 48	261 to 293
			SCARED-C Short Cutoff ≥ 3	Youth	24	0.67 (0.59 to 0.74)	0.74 (0.70 to 0.78)	8 to 43	226 to 254
			SCARED-P Short Cutoff ≥ 3	Parents	24	0.34 (0.26 to 0.42)	0.86 (0.82 to 0.89)	17 to 86	122 to 137
GAD									
Patient Health Questionnaire—Adolescent (PHQ-A)									
Johnson et al, 2002[199] Fair	16 (1.2) 13 to 18	403 (63)	PHQ-A Cutoff NR	Youth	2.5	0.50 (0.24 to 0.76)	0.98 (0.86 to 0.99)	13 to 65	17 to 20
SCARED—GAD Scale									
Muris et al, 2001[218] Fair	10 (1.4) 7 to 14	82 (61)	SCARED-C Male cutoff ≥ 10 Female cutoff ≥ 13	Youth	13	0.64 (0.35 to 0.85)	0.63 (0.52 to 0.74)	9 to 47	322 to 361
Paediatric Index of Emotional Distress (PI-ED)—Anxiety Scale									
O'Connor et al, 2016[219] Fair	12 (2.5) 8 to 17	100 (48)	PI-ED Cutoff ≥ 9	Youth	6	0.88[b] (0.53 to 98)	0.85 (0.78 to 0.90)	3 to 16	130 to 146
Panic Disorder									
Autonomic Nervous System Questionnaire (ANS)									
Queen et al, 2012[230] Fair	14 (1.8) 12 to 17	45 (43)	ANS 2 questions (cutoff ≥ 1)	Youth	NR	1.00 (NR)	0.47 (NR)	0 to 0	461 to 517
			ANS 3 questions (cutoff ≥ 2)	Youth	NR	1.00 (NR)	0.57 (NR)	0 to 0	374 to 419
			ANS 5 questions (cutoff ≥ 3)	Youth	NR	1.00 (NR)	0.65 (NR)	0 to 0	304 to 341
Patient Health Questionnaire—Adolescent (PHQ-A)									
Johnson et al, 2002[199] Fair	16 (1.2) 13 to 18	403 (63)	PHQ – A Cutoff NR	Youth	3	0.42 (0.19 to 0.68)	0.99 (0.97 to 1.0)	15 to 75	9 to 10

Table 2. Results of Diagnostic Test Accuracy Studies on Screening for Anxiety Compared With Structured Clinical Interview (KQ 2)

Author, Year Quality	Age Range; Mean Age (SD), Years	Total N (% Female)	Index Test Cutoff	Respondent	Prevalence %	Sensitivity (95% CI)	Specificity (95% CI)	Per 1,000 Screens Across a Prevalence From 3% to 13% No. False-Negatives	Per 1,000 Screens Across a Prevalence From 3% to 13% No. False-Positives
Separation Anxiety Disorder									
Screen for Anxiety Related Emotional Disorders (SCARED)-Separation Anxiety Scale									
Muris et al, 2001[218] Fair	10 (1.4) 7 to 14	82 (61)	SCARED-C Male cutoff ≥ 10 Female cutoff ≥ 12	Youth	10	0.88 (0.52 to 0.98)	0.73 (0.62 to 0.82)	3 to 16	235 to 263
Social Anxiety Disorder									
Screen for Anxiety Related Emotional Disorders (SCARED)—Social Phobia Scale									
Bailey et al, 2006[166] Fair	Children Mean: NR 8 to 12	101	SCARED-SP cutoff ≥5	Parents	9	0.78 (0.45 to 0.94)	0.69 (0.59 to 0.78)	6 to 29	226 to 254
	Adolescents 14 (1.3) 13 to 16	89 (49)*	SCARED-SP Cutoff ≥ 6	Parents	13	0.83 (0.55 to 0.95)	0.81 (0. 71 to 0.88)	4 to 22	165 to 185
Social Anxiety Scale (SAS) Children/Adolescents									
Bailey et al, 2006[166] Fair	Children Mean: NR 8 to 12	101	SAS-C Cutoff ≥ 45	Parents	9	0.78 (0.45 to 0.94)	0.74 (0.65 to 0.82)	6 to 29	148 to 166
	Adolescents 14 (1.3 13 to 17	89 (49)*	SAS-A Cutoff ≥ 47	Parents	13	0.75 (0.47 to 0.91)	0.80 (0.69 to 0.87)	6 to 32	174 to 195
Garcia-Lopez et al, 2015[188] Fair	15 (1.3) 12 to 18	1,034 (54)	SAS-A Cutoff ≥ 48	Youth	41	0.93 (0.91 to 0.96)	0.78 (0.74 to 81)	2 to 9	189 to 215
Social Anxiety Scale for Adolescents (SASA)									
Garcia-Lopez et al, 2015[188] Fair	15 (1.3) 12 to 18	1,034 54	SASA Cutoff ≥ 73	Youth	41	0.93 (0.85 to 0.98)	0.79 (0.70 to 87)	2 to 9	183 to 205
Social Phobia and Anxiety Inventory-Brief (SPAI-B)									
Garcia-Lopez et al, 2015[188] Fair	15 (1.3) 12 to 18	1034 (54)	SPAI-B Cutoff ≥26.4	Youth	41	0.86 (0.83 to 0.89)	0.88 (0.85 to 0.91)	4 to 18	104 to 117
Social Phobia Inventory (SPIN)/Mini Social Phobia Inventory (Mini-SPIN)									
Ranta et al, 2007[231] Fair	14.7 (1.1) 12 to 17	350 (49)	SPIN Cutoff ≥ 24	Youth	6	0.82 (0.61 to 0.93)	0.85 (0.81 to 0.89)	5 to 23	130 to 146

Table 2. Results of Diagnostic Test Accuracy Studies on Screening for Anxiety Compared With Structured Clinical Interview (KQ 2)

Author, Year Quality	Age Range; Mean Age (SD), Years	Total N (% Female)	Index Test Cutoff	Respondent	Prevalence %	Sensitivity (95% CI)	Specificity (95% CI)	Per 1,000 Screens Across a Prevalence From 3% to 13% No. False-Negatives	Per 1,000 Screens Across a Prevalence From 3% to 13% No. False-Positives
Tsai et al, 2009[250] Fair	Mean NR 13 to 15	144 (50)	SPIN Cutoff ≥25	Yourh	10	0.80 (0.55 to 0.93)	0.77 (0.69 to 0.83)	5 to 26	200 to 224
Ranta et al, 2012[232] Fair	14.7 (1.1) 12 to 17	350 (49)	Mini-SPIN Cutoff ≥ 6	Youth	6	0.86 (0.67 to 0.92)	0.84 (0.79 to 0.87)	4 to 18	139 to 156
Social Worries Questionnaire (SWQ)									
Bailey et al, 2006[166]	Children Mean NR 8 to 12	101	SWQ Cutoff ≥ 10	Parents	9	0.67 (0.35 to 0.88)	0.94 (0.88 to 0.98)	8 to 43 4 to 22	52 to 58 139 to 156
	Adolescents 14 (1.3) 13 to 17	89 (49)*	SWQ Cutoff ≥ 5.3	Parents	13	0.83 (0.55 to 0.95)	0.84 (0.74 to 0.90)		
Any Anxiety Disorder (at least one specific anxiety disorder)									
Screen for Anxiety Related Emotional Disorders (SCARED)									
Johnson et al, 2002[199] Fair	16 (1.2) 13 to 18	403 (63)	PHQ-A Cutoff NR	Youth	5	0.50 (0.30 to 0.70)	0.98 (0.96 to 0.99)	12 to 65	17 to 20
Screen for Anxiety Related Emotional Disorders (SCARED)									
Muris et al, 2001[218] Fair	10 (1.4) 7 to 14	82 (61)	SCARED-C NA	Youth	20	0.88 (0.63 to 0.96)	0.56 (0.44 to 0.67)	3 to 16	383 to 429

* Percentage of females in Bailey is for entire sample.

Abbreviations: ANS=Autonomic Nervous System Questionnaire; CI=confidence interval; GAD=general anxiety disorder; KQ=key question; NA=not applicable; NR=not reported; PHQ-A=Patient Health Questionnaire—Adolescent; PI-ED=pediatric index of emotional distress; SAS=social anxiety scale; SAS-A (SASA)=social anxiety scale-adolescents; SASC=social anxiety scale for children; SCARED=Screen for Anxiety Related Emotional Disorders; SCARED-C=Screen for Anxiety Related Emotional Disorders Child version; SCARED-P=Screen for Anxiety Related Emotional Disorders – Parent version; SCARED-SP=Screen for Anxiety Related Emotional Disorders-Social Phobia Scale; SD=standard deviation; SPAI-B=social phobia and anxiety inventory-brief; SPIN=Social Phobia Inventory; SWQ=social worries questionnaire.

Table 3. Characteristics and Results of Test Accuracy Studies for Screening for Major Depressive Disorder Compared With Structured Clinical Interview (KQ 2)

Author, Year Quality	Age Range; Mean Age (SD), Years	Total N (% Female)	Index Test Cutoff	Prevalence (%)	Sensitivity	Specificity	Per 1,000 Screens Across a Prevalence From 3% to 11% No. False-Negatives	Per 1,000 Screens Across a Prevalence From 3% to 11% No. False-Positives
Beck Depression Inventory (BDI)								
Canals et al, 2001[170] Fair	17.5 to 18.5 18 (NR)	290 (50)	≥10 ≥11 ≥14 ≥16	Unclear	1.0 0.90 0.90 0.90	0.82 0.86 0.92 0.96	0 to 0 3 to 11 3 to 11 3 to 11	175 to 160 136 to 125 78 to 71 39 to 36
Roberts et al, 1991[235] Fair	15 to 18* 16.6 (1.2)	1,704 (53)	≥11	3	0.84	0.81	5 to 18	184 to 169
Center for Epidemiologic Studies—Depression (CES-D)								
Roberts et al, 1991[235] Fair	15 to 18* 16.6 (1.2)	1,704 (53)	≥24		0.84	0.75	5 to 18	243 to 223
Garrison et al, 1991[189] Fair	12 to 15 NR	143 boys	≥12 ≥16 ≥20 ≥22	8.2	0.85 0.59 0.19 0.18	0.49 0.66 0.78 0.83	5 to 17 12 to 45 24 to 89 25 to 90	495 to 454 330 to 303 213 to 196 165 to 151
		189 girls	≥12 ≥16 ≥20 ≥22	8.7	0.84 0.83 0.84 0.83	0.38 0.53 0.70 0.77	5 to 18 5 to 19 5 to 18 5 to 19	601 to 552 456 to 418 291 to 267 223 to 205
Clinical Interview Schedule—Revised (CIS-R)								
Patton et al, 1999[223] Fair	NR† 15.7 (0.5)	158 (53‡)	NA§	6	0.18 (95% CI, 0.05 to 0.32)‖	0.97 (95% CI, 0.96 to 0.99)¶	25 to 90	29 to 27
Hopkins Symptom Checklist (HSCL)								
Christensen et al, 2015[172] Fair	14 to 16 NR	294 (NR)	≥9	11	0.85 (95% CI, 0.70 to 0.94)	0.78 (95% CI, 0.72 to 0.83)	5 to 17	213 to 196
Patient-Health Questionnaire—Adolescent (PHQ-A)								
Johnson et al, 2002[199] Fair	13 to 18 16 (1.2)	403 (63)	NA§	9	0.73 (calculated 95% CI, 0.58 to 0.85)	0.94 (calculated 95% CI, 0.91 to 0.96)	8 to 30	58 to 53

Table 3. Characteristics and Results of Test Accuracy Studies for Screening for Major Depressive Disorder Compared With Structured Clinical Interview (KQ 2)

Author, Year Quality	Age Range; Mean Age (SD), Years	Total N (% Female)	Index Test Cutoff	Prevalence (%)	Sensitivity	Specificity	Per 1,000 Screens Across a Prevalence From 3% to 11% No. False-Negatives	Per 1,000 Screens Across a Prevalence From 3% to 11% No. False-Positives
Pediatric Index of Emotional Distress (PI-ED) Depression Subscale								
O'Connor et al, 2016[219] Fair	8 to 17 12 (2.5)	135 (48)	≥8	11	0.94 (calculated 95% CI, 0.71 to 0.99)	0.81 (calculated 95% CI, 0.73 to 0.87)	2 to 7	184 to 169
World Health Organization Five Item Well-being Index (WHO-5)								
Christensen et al, 2015[172] Fair	14 to 16 NR	294 (NR)	≥11	11	0.88 (95% CI, 0.74 to 0.96)	0.80 (95% CI, 0.74 to 0.84)	4 to 13	194 to 178

* This study enrolled persons in high school; 11% were younger than 15 and 13% were age 18 or older.

† The study targeted students in Year 9 of school.

ǂ Proportion in the full study sample; not all were included in the diagnostic test accuracy analysis.

§ Not applicable as test is scored according to an algorithm as either positive or negative.

‖ Based on weighted adjustment; the unweighted sensitivity was 0.74.

¶ Based on weighted adjustment; the unweighted specificity was 0.78.

Abbreviations: BDI=Beck Depression Inventory; CES-D=Center for Epidemiological Studies-Depression; CI=confidence interval; CIS-R=Clinical Interview Schedule-Revised; KQ=key question; NA=not applicable; NR=not reported; PI-ED=Pediatric Index of Emotional Distress; SD=standard deviation; WHO-5=World Health Organization Five Item Well-being Index.

Table 4. Key Characteristics of Included Suicide Risk Studies

Study Characteristics	Subcharacteristics	Number of Studies	Percent
Population characteristics:	Child (mean age <13, ages range from 5 to 12 years)	0	0
Child or adolescent	Adolescent (mean age ≥13, ages range from 11 to 19 years)	16[164, 179-182, 191-194, 197, 200, 202, 212-215, 221, 222, 229, 236, 245, 265]	100
	Both (mean age varies, ages range from 5 to 19 years)	0	0
Population characteristics:	Mostly female	16[164, 179-182, 191-194, 197, 200, 202, 212-215, 221, 222, 229, 236, 245, 265]	100
Gender	Mostly male	0	0
Population characteristics:	Mostly White	11[164, 191, 192, 194, 197, 200, 202, 212-215, 221, 222, 229, 236]	69
Race	Mostly non-White	1[182]	6
	Not reported	4[179-181, 193, 245, 265]	25
Population characteristics:	Suicide only	15[164, 179-182, 191-194, 197, 200, 202, 212-215, 221, 222, 229, 236, 245, 265]	94
Diagnosis	Suicide and depression	1[245]	6
Intervention characteristics:	Nonpharmacological	16[164, 179-182, 191-194, 197, 200, 202, 212-215, 221, 222, 229, 236, 245, 265]	100
Types of interventions	Pharmacological	0	0
	Both	0	0
Comparator	Treatment as usual	15[164, 179-182, 191-193, 197, 200, 202, 212-215, 221, 222, 229, 236, 245, 265]	94
	Attention control	1[194]	6
Outcomes	Reporting benefits	16[164, 179-182, 191-194, 197, 200, 202, 212-215, 221, 222, 229, 236, 245, 265]	100
	Reporting harms	2[179-181, 192]	13
Geographic setting	United States of America	6[164, 182, 194, 197, 200, 202]	38
	United Kingdom	6[179-181, 191, 192, 221, 222, 236, 265]	38
	Australia	2[193, 229]	13
	Norway	1[212-215]	6
	Taiwan	1[245]	6
Recruitment setting	Child and adolescent mental health services	5[179-181, 191-193, 265]	31
	Emergency department	1,[202]	6
	Psychiatic outpatient	1[181, 212-215]	6
	Schools	2[197, 245]	13
	Combination	6[164, 182, 194, 221, 222, 229, 236]	38
	Not specified	1[200]	6
Treatment setting	In person	11[164, 179-182, 191-193, 212-215, 221, 222, 229, 236, 265]	69
	Web/computer	1[194]	6
	Combination (computer, in person, phone)	4[197, 200, 202, 245]	25

Table 5. Suicide Attempts or Episode of Deliberate Self-Harm for Suicide or Self-Harm Interventions: Pooled Estimates

Intervention	Time of Outcome Measurement	Outcome Measure, Range, Threshold	Treatment Range at Followup	Comparator Range at Following	Pooled Results
Family therapy, DBT, developmental group therapy	19 weeks to 18 months	Mean number of self-harm events	0.6 to 9.0	1.2 to 22.50	Mean difference: -0.76 (95% CI, -2.15 to 0.63); N=972; k=3;[179-181, 212-215, 265] I^2=68 **Appendix G Figure 2**
Group psychotherapy, family therapy, mentalization-based treatment, developmental group therapy	6 to 18 months	Proportion with self-harm events	0.55 to 88	1.1 to 83	RR: 0.88 (95% CI, 0.63 to 1.24); N=1,040; k=5;[179-181, 191, 193, 236, 265] I^2=80 **Appendix G Figure 3**

Abbreviations: CI=confidence interval; DBT=dialectical behavior therapy; k=number of studies; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; N=number; OR=odds ratio.

Table 6. Suicidal Ideation for Suicide or Self-Harm Interventions: Pooled Estimates

Intervention	Time of Outcome Measurement	Outcome Measure, Range, Threshold	Outcome Range	Outcome Threshold Indicating Clinically Meaningful Effect	Treatment Range at Followup	Comparator Range at Following	Pooled Results
Youth-nominated support team, motivational interviewing, DBT, IPT-A-IN	2 months to 19 weeks	BHS	0 to 20[304]	≥9 indicative of suicide intentions[304]	5.66 to 7.74	7.80 to 12.42	Mean difference: -2.35 (95% CI, -4.06 to -0.65); N=644; k=4;[200, 202, 212-215, 245] I^2=46% **Appendix G Figure 4**
Attachment-based family therapy, group psychotherapy, group therapy, youth-nominated support team, motivational interviewing, DBT, developmental group therapy	2 months to 71 weeks	SIQ or SIQ-Jr	SIQ: 0 to 180 SIQ-JR: 0 to 90[305]	SIQ ≥:41[306] indicative of suicidal ideation SIQ-JR[307] ≥ 31 indicative of suicidal ideation	SIQ: 41.3 to 74.11 SIQ-JR: 5.2 to 25.55	SIQ: 39.7 to 76.40 SIQ-JR: 16.2 to 29.71	Standardized mean difference*: -0.18 (95% CI, -0.36 to 0.01); N=1,111; k=7;[182, 191, 193, 200, 202, 212-215, 265] I^2=45%; p=0.09 **Appendix G Figure 5**

* Results standardized to pool across two different instruments.

Abbreviations: BHS=Beck Hopelessness Scale; CI=confidence interval; DBT=dialectical behavior therapy; IPT-A-IN=intensive interpersonal psychotherapy for depressed adolescents with suicidal risk; k=number of studies; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; N=number; SIQ=Suicidal Ideation Questionnaire ; SIQ-Jr=Suicidal Ideation Questionnaire-Junior.

Table 7. Functioning for Suicide or Self-Harm Interventions: Pooled Estimates

Intervention	Time of Outcome Measurement	Outcome Measure, Range, Threshold	Outcome Range	Outcome Threshold Indicating Clinically Meaningful Effect	Treatment Range at Followup	Comparator Range at Followup	Pooled Results
Group psychotherapy; group therapy; developmental group therapy; psychoeducation for parents	8 weeks to 7 months	HoNOSCA	0 to 52[308]	Scores greater than 13 indicate impairment of clinical significance	8.4 to 16.8	6.9 to 17.6	Mean difference: -0.40 (95% CI, -2.55 to 1.78); N=509; k=4;[191, 193, 229, 265] I^2=56% **Appendix G Figure 6**
Therapeutic assessment; individual and family DBT; group therapy	8 to 71 weeks	CGAS	1 to 100[309]	>70: no clinically significant functional impairment <41: major impairment to functioning in several areas[309]	58.5 to 65.7	60.1 to 64.22	Mean difference: 1.30 (95% CI, -2.52 to 5.12); N=195; k=3;[193, 213, 222] I^2=30% **Appendix G Figure 7**

Abbreviations: CGAS=Children's Global Assessment Scale; CI=confidence interval; DBT=dialectical behavior therapy; HoNOSCA=Health of the Nation Outcome Scales for Children and Adolescents; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; k=number of studies; N=number; RR=relative risk.

Table 8. Key Characteristics of Included Anxiety Studies for Benefits

Study Characteristics	Subcharacteristics	Number of Studies	Percent
Population characteristics: Child or adolescent	Child (mean age <13)	24	82.7
	Adolescent (mean age ≥13)	5	17.39
Population characteristics: Gender	Mostly female	19	65.5
	Mostly male	9	31.0
	Equal distribution	1	3.4
Population characteristics: Race	Mostly White	17	58.6
	Mostly non-White	1	3.4
	Not reported	11	37.9
Population characteristics: Diagnosis	Any anxiety disorder	17	58.6
	GAD	5	17.2
	Social anxiety disorder	4	13.8
	Selective mutism	2	6.9
	GAD, social anxiety disorder, or separation anxiety	1	3.4
Intervention characteristics: Types of interventions	Nonpharmacological	22	75.9
	Pharmacological	6	20.7
	Multiple arms of CBT, pharmacotherapy, and combination	1	3.4
Comparator	Treatment as usual	2	6.9
	Placebo comparator	7	24.1
	Wait-list comparator	20	69.0
Geographic setting	United States	10	34.5
	Australia	6	20.7
	United Kingdom	3	10.3
	Denmark	2	6.9
	Germany	2	6.9
	Norway	1	3.4
	Hong Kong	1	3.4
	Japan	1	3.4
	Spain	1	3.4
	Sweden	1	3.4
	Multiple countries	1	3.4
Recruitment setting*	Community recruitment	15	NA
	Referrals from mental health professionals	10	NA
	Schools	13	NA
	Not specified	2	NA

* Studies may recruit from multiple settings.

Abbreviations: CBT=cognitive behavioral therapy; GAD=generalized anxiety disorder.

Table 9. Anxiety Interventions and Change in Anxiety Symptoms: Pooled Estimates of Effect

Intervention	Time of Outcome Measurement	Outcome Measure	Outcome Range	Outcome Threshold Indicating Clinically Meaningful Effect	Treatment Range at Followup	Comparator Range at Following	Pooled Results
Psychotherapy							
Individual or group Child-focused, child+parent focused, parent focused In person, email, telephone, or internet*	4 to 17 weeks from baseline	ADIS-CSR for the primary diagnosis or all diagnoses†	0 to 8[310]	4 (moderate degree of impairment) or greater indicates a clinical diagnosis[310]	1.9 to 4.2	3.6 to 6.2	Mean difference: -2.01 (95% CI, -2.74 to -1.29); N=579; k=11;[163, 177, 178, 183, 196, 198, 224, 237, 242, 253, 275] I^2=83%‡ **Appendix G Figure 8**
Individual or group Child-focused, child+parent focused, parent focused In person, email, telephone, or internet§	6 to 17 weeks from baseline	SCAS-C	38 items rated on a 0 to 3 scale, maximum of 114	Cutoffs vary by age and gender from 33 to 50[311] (higher scores represent worse outcomes)	21.6 to 34.9	29.4 to 42.1	Mean difference: -7.81 (95% CI, -10.99 to -4.63; N=668; k=9;[163, 177, 196, 198, 203, 206, 242, 246, 253] I^2=29% **Appendix G Figure 13**
Individual or group Child-focused, child+parent focused, parent focused In person, email, telephone, or internet§	6 to 17 weeks from baseline	SCAS-P	38 items rated on a 0 to 3 scale, maximum of 114	Cutoffs vary by age and gender from 33 to 50[311] (higher scores represent worse outcomes)	18.8 to 33.1	24.2 to 41.3	Mean difference: -6.06 (95% CI, -9.58 to -2.56); N=652; k=9;[163, 177, 196, 198, 203, 206, 242, 246, 253] I^2=58% **Appendix G Figure 14**
Individual or group Child-focused, child+parent focused In person‖	6 to 17 weeks from baseline	SPAI-C	0 to 52[312]	≥18 indicates social anxiety disorder[312]	12.5 to 15.5	22.8 to 30.8	Standardized mean difference¶: -1.17 (95% CI, -1.99 to -0.35); N=277; k=4;[165, 220, 239, 240, 275] I^2=87% **Appendix G Figure 12**
Individual Child-focused or parent-led In person	5 to 12 weeks from baseline	CGI-S	1 to 7[313]	2: borderline ill 3: mildly ill 4: moderate illness[313]	2.0 to 4.0	3.3 to 4.2	Mean difference: -0.60 (95% CI, -1.14 to -0.06); N=453; k=3;[190, 237, 254-262] I^2=75% **Appendix G Figure 9**
Individual or group Child-focused, child+parent focused In person#	12 weeks from baseline	MASC	0 to 117	Unclear,[276] cutoff scores may not be possible to establish	40.9 to 48.8	42.9 to 54.7	Mean difference: -4.66 (95% CI, -9.66 to 0.34); N=435; k=3;[220, 251, 254-262, 275] I^2=66% **Appendix G Figure 10**
Individual or group Child-focused, child+parent focused In person, email, telephone, or internet**	10 to 12 weeks from baseline	RCMAS		≥19[314] indicates clinically significant levels of anxiety	6.6 to 10.9	9.8 to 15.7	Mean difference: -3.08 (95% CI, -5.91 to -0.24); N=241; k=3;[167, 206, 241] I^2=71% **Appendix G Figure 11**

Table 9. Anxiety Interventions and Change in Anxiety Symptoms: Pooled Estimates of Effect

Intervention	Time of Outcome Measurement	Outcome Measure	Outcome Range	Outcome Threshold Indicating Clinically Meaningful Effect	Treatment Range at Followup	Comparator Range at Following	Pooled Results
Pharmacotherapy							
Fluoxetine, fluvoxamine, duloxetine, escitalopram, sertraline	8 to 12 weeks from baseline	PARS	0 to 25[315]	>11.5[316] discriminates youth without anxiety disorders from those with anxiety disorders	8.1 to 9.8	9.3 to 15.9	Mean difference: -4.0 (95% CI, -5.5 to -2.5); N=726; k=5;[168, 225-228, 243, 244, 254-262] I^2=81% **Appendix G Figure 16**
Duloxetine, escitalopram, sertraline	8 to 12 weeks from baseline	CGI-S	1 to 7[313]	2: borderline ill 3: mildly ill 4: moderate illness[313]	2.4 to 3.0	3.1 to 3.9	Mean difference: -0.84 (95% CI, -1.13 to -0.55); N=550; k=4;[238, 243, 244, 254-262] I^2=75% **Appendix G Figure 15**

* We averaged the results across arms for the two studies with multiple treatment arms (child directed or child and parent directed[220] telephone vs. email vs. client initiated "on their own"[206] compared with wait-list).

† We selected or combined CSR ratings for primary diagnoses when available.

ǂ Pooled standardized mean differences that included all studies (including one reporting only Cohen's d estimates of effect[206]) also suggested a statistically significant difference (-1.17 [95% CI, -1.56 to -0.78]; N=676; k=12; I^2=79%).

§ We averaged the results across arms for the two studies with multiple treatment arms (brief vs. full CBT,[246] telephone vs. email vs. client initiated "on their own"[206] compared with wait-list).

ǁ We averaged the results across arms for the two studies with multiple treatment arms (with or without cognitive restructuring,[240] child or child+parent[220, 275]).

¶ Reported as standardized mean difference because two of the did not present sufficient information to calculate mean differences.

We averaged the results across arms for the two studies with multiple treatment arms (child or child+parent,[220, 275] individual or group[251]).

** We averaged the results across arms for the two studies with multiple treatment arms (child directed or child and parent directed[317]).

Abbreviations: ADIS-CSR=Anxiety Disorders Interview Schedule clinician severity ratings; CBT=cognitive behavioral therapy; CGI-S=Clinical Global Impressions-Severity; CI=confidence interval; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; k=number of studies; MASC=Multidimensional Anxiety Scale for Children; N=number; PARS=Pediatric Anxiety Rating Scale; RCMAS=Revised Children's Manifest Anxiety Scale; SCAS-C=Spence Children's Anxiety Scale-Child-rated; SCAS-P=Spence Children's Anxiety Scale-Parent-rated; SPAI-C=Social Phobia and Anxiety Inventory for Children.

Table 10. Anxiety Interventions and Clinical Response, Remission From Anxiety, and Loss of Diagnosis: Pooled Estimates of Effect

Intervention	Time of Outcome Measurement	Outcome Measure	Outcome Range	Outcome Threshold Indicating Clinically Meaningful Effect	Treatment Range at Followup	Comparator Range at Followup	Pooled Results
Psychotherapy							
Individual or group therapy Child-, parent-, or child+parent-focused therapy In-person therapy	4 weeks to 6 months from baseline	Proportion with a clinical response (CG1=1 or 2)	0 to 100	CGI-I scores of 1 or 2 indicate moderate marked improvement, proportion threshold unclear	40% to 83%	0 to 37%	RR: 1.89 (95% CI, 1.17 to 3.05); N=606; k=6;[178, 190, 195, 237, 253, 254] I^2=64% **Appendix G Figure 17**
Individual or group therapy Child-, parent-, or child+parent-focused therapy In person, email, telephone, internet therapy	8 to 16 weeks from baseline	Remission from anxiety symptoms on child-rated SCAS	0 to 100	Unclear "clinically significant change"	43% to 62%	6% to 38%	RR: 2.68 (95% CI, 1.48 to 4.88); N=321; k=4;[163, 198, 206, 242] I^2=48%* **Appendix G Figure 18**
Individual, group, or individual+group therapy Child-, parent-, or child+parent-focused therapy In person, telephone, internet therapy	8 to 16 weeks from baseline	Loss of all anxiety diagnoses	0 to 100	No diagnosis following a structured clinical interview	15% to 80%	0 to 35%	RR: 3.09 (95% CI, 1.98 to 4.80); N=1,414; k=15;[163, 167, 177, 183, 190, 195, 196, 198, 224, 241, 242, 246, 251, 253] I^2=65%† **Appendix G Figure 19**
Individual, group, or individual+group therapy Child-, parent-, or child+parent-focused therapy In person, telephone, internet therapy	6 weeks to 12 months from baseline	Loss of primary anxiety diagnosis	0 to 100	No diagnosis following a structured clinical interview	7% to 80%	0 to 43%	RR: 3.02 (95% CI, 1.84 to 4.95); N=1,079; k=13;[163, 177, 178, 183, 190, 196, 198, 220, 224, 242, 246, 251, 253, 275] I^2=75%‡ **Appendix G Figure 20**
Pharmacotherapy							
Escitalopram, fluoxetine, sertraline	8 to 12 weeks from baseline	Proportion with a clinical response (CGI=1 or 2)	0 to 100 for proportion	CGI-I scores of 1 or 2 indicate moderate marked improvement, proportion threshold unclear	50% to 91%	9% to 44%	RR: 2.11 (95% CI, 1.58 to 2.98); N=370; k=5;[168, 169, 238, 244, 254-262] I^2=18% **Appendix G Figure 21**

* We averaged the results across arms for one study with three intervention arms: telephone, email, and client-initiated CBT.[206]

† We averaged the results across arms for three studies with two intervention arms: individual and group CBT,[251] brief and full CBT,[246] and child directed and child and family directed therapy.[167]

‡ We averaged the results across arms for three studies with two intervention arms: individual and group CBT,[251] brief and full CBT,[246] and child and child+parent CBT.[220, 275]

Abbreviations: CBT=cognitive behavioral therapy; CG=control group; CGI-I=Clinical Global Impressions-Improvement; CI=confidence interval; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; k=number of studies; N=number; RR=relative risk; SCAS=Spence Children's Anxiety Scale.

Table 11. Anxiety Interventions and Functional Status: Pooled Estimates of Effect

Intervention	Time of Outcome Measurement	Outcome Measure	Outcome Range	Outcome Threshold Indicating Clinically Meaningful Effect	Treatment Range at Followup	Comparator Range at Following	Pooled Results
Psychotherapy							
Individual or group therapy In person, internet or combined Child-, parent-, or child+parent-focused therapy	4 to 12 weeks from baseline	CGAS	1 to 100[309]	>70: no clinically significant functional impairment <41: major impairment to functioning in several areas[309]	53.6 to 82.1	52.5 to 61.9	Mean difference: 7.54 (95% CI, 2.84 to 12.23); N=811; k=8;[178, 183, 190, 196, 224, 251, 253-262] I^2=90% **Appendix G Figure 23**
Individual or group therapy In person, telephone, internet or combined Child-, parent-, or child+parent-focused therapy	8 to 12 weeks from baseline	CAIS	0 to 81[318]	<7: no anxiety diagnoses[319]	6.4 to 21.8	15.2 to 19.6	Mean difference: -2.23 (95% CI, -5.88 to 1.43); N=403; k=3;[246, 253, 255] I^2=38% **Appendix G Figure 22**
Pharmacotherapy							
Duloxetine, fluoxetine, sertraline	10 to 12 weeks from baseline	CGAS	1 to 100[309]	>70: no clinically significant functional impairment <41: major impairment to functioning in several areas[309]	62.1 to 68.5	59.3 to 64.6	Mean difference: 5.14 (95% CI, 3.21 to 7.08); N=551; k=3;[168, 243, 254-262] I^2=0% **Appendix G Figure 24**

Abbreviations: CAIS=Children's Anxiety Impact Scale; CGAS=Children's Global Assessment Scale; CI=confidence interval; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; k=number of studies; N=number.

Table 12. Key Characteristics of Included Depression Studies for Benefits

Study Characteristics	Subcharacteristics	Number of Studies	Percent
Population characteristics: Child or adolescent	Child (mean age <13)	3	23.1
	Adolescent (mean age ≥13)	10	76.9
Population characteristics: Gender	Mostly female	11	84.6
	Mostly male	2	15.4
Population characteristics: Race	Mostly White	7	53.8
	Mostly non-White	1	7.7
	Not reported	5	38.5
Population characteristics: Diagnosis*	MDD	13	100.0
	PDD/DD/DNOS	4	30.1
Intervention characteristics: Types of interventions	Nonpharmacological	8	61.5
	Pharmacological	2	15.4
	Multiple arms of CBT, pharmacotherapy, and combination	2	15.4
	Collaborative care	1	7.7
Comparator	Attention control	3	23.1
	Placebo comparator	4	30.8
	Treatment as usual	4	30.8
	Wait-list comparator	2	15.4
Geographic setting	United States	10	76.9
	Sweden	3	23.1
Recruitment setting	Advertised widely	7	53.8
	Health systems and clinics	3	23.1
	Schools and mental health clinics	1	7.7
	Mental health clinics	1	7.7
	Not specified	1	7.7

*Not mutually exclusive.

Abbreviations: CBT=cognitive behavior therapy; MDD=major depressive disorder; PDD/DD/DNOS=persistent depressive disorder/dysthymia disorder/depression not otherwise specified.

Table 13. Depression Interventions and Depression Symptoms: Pooled Estimates of Effect

Intervention	Time of Outcome Measurement	Outcome Measure	Outcome Range	Outcome Threshold Indicating Clinically Meaningful Effect	Treatment Range at Followup	Comparator Range at Following	Pooled Results
Psychotherapy[310]							
Internet-based individual CBT group in-person CBT with and without parents, interpersonal psychotherapy*	8 to 12 weeks	BDI or BDI-II	BDI: 0 to 39[216] BDI-II: 0 to 63[320]	BDI: <10: minimal depression 10 to 18: mild to moderate depression 19 to 29: moderate to severe depression ≥30: severe depression[170, 235] BDI-II: 0–13: minimal depression 14–19: mild depression 20–28: moderate depression 29–63: severe depression[320]	BDI: 8.4 to 13.3 BDI-II: 16 to 19.9	BDI: 12.3 to 16 BDI-II: 24.8 to 25.2	Standardized mean difference: -0.58 (95% CI,-0.83 to -0.34); N=471; k=4;[174, 216, 248, 249] I^2=0%† **Appendix G Figure 25**
Individual in-person youth CBT, group in-person CBT with and without parents, interpersonal psychotherapy*	8 to 52 weeks from baseline	HAM-D	Unclear (2 studies[174, 175] used a 14-item version of HAM-D)	Unclear	4.9 to 8.7	6.5 to 12.8	Mean difference: -2.25 (95% CI,-4.09 to -0.41); N=262; k=3;[174, 175, 216] I^2=0% **Appendix G Figure 26**
Individual in-person CBT, family CBT	12 to 52 weeks from baseline	CDRS-R	17 to 113[321]	≥40 indicates depression ≤28 indicates remission (minimal or no symptoms[321])	30.0 to 42.1	28.2 to 41.8	Mean difference: 0.77 (95% CI,-0.97 to 2.48); N=471; k=3;[176, 187, 207] I^2=0% **Appendix G Figure 27**
Pharmacotherapy							
Escitalopram, fluoxetine	8 to 12 weeks from baseline	CDRS-R	17 to 113[321]	≥40 indicates depression ≤28 indicates remission (minimal or no symptoms[321])	32.6 to 36.3	36.4 to 41.8	Mean difference: -3.76 (95% CI,-5.95 to -1.57); N=793; k=3;[185, 207, 252] I^2=49% **Appendix G Figure 28**

* We averaged the results across arms for the study with multiple treatment arms (group in-person CBT with or without parents[174]) compared with wait-list.
† Mean differences standardized to pool BDI and BDI-II measures.
‡ Mean differences for BDI ranged from -4.3 to -3.9, favoring psychotherapy. Mean differences for BDI-II ranged from -8.8 to -5.3, favoring psychotherapy.

Abbreviations: BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory, version 2; CBT=cognitive behavioral therapy; CI=confidence interval; CDRS-R=Children's Depression Rating Scale-Revised; CI=confidence interval; HAM-D=Hamilton Depression Rating Scale; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; k=number of studies: N=number.

Table 14. Depression Interventions and Remission From Depression, and Loss of Diagnosis: Pooled Estimates of Effect

Intervention	Time of Outcome Measurement	Outcome Measure	Outcome Range	Outcome Threshold Indicating Clinically Meaningful Effect	Treatment Range at Followup	Comparator Range at Following	Pooled Results
Psychotherapy							
CBT	8 to 12 weeks from baseline	Loss of diagnosis measured by clinical interviews	0 to 100 for proportion	NA	56% to 71%	16% to 60%	RR: 1.73 (95% CI, 1.00 to 3.00); N=395; k=4;[174, 207, 248, 249] I^2=81%* **Appendix G Figure 29**
Pharmacotherapy							
Escitalopram, fluoxetine	8 to 12 weeks from baseline	Remission from depression symptoms (CDRS-R≤28)	0 to 100 for proportion	CDRS-R≤28 indicates moderate marked improvement, proportion threshold unclear	23% to 46%	17% to 38%	RR: 1.20 (95% CI, 1.00 to 1.45), N=793; k=3;[185, 207, 210, 252] I^2=0% **Appendix G Figure 30**

* We averaged the results across arms for one study with two intervention arms: with and without parent sessions.[174]

Abbreviations: CBT=cognitive behavioral therapy; CDRS-R=Children's Depression Rating Scale-Revised; CI=confidence interval; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; k=number of studies; NA=not applicable; RR=relative risk.

Table 15. Depression Interventions and Functional Status: Pooled Estimates of Effect

Intervention	Time of Outcome Measurement	Outcome Measure	Outcome Range	Outcome Threshold Indicating Clinically Meaningful Effect	Treatment Range at Followup	Comparator Range at Following	Pooled Results
Psychotherapy							
Individual in-person CBT, interpersonal psychotherapy	12 to 52 weeks from baseline	CGAS	1 to 100[309]	>70: no clinically significant functional impairment <41: major impairment to functioning in several areas[309]	60.0 to 72.3	59.3 to 74.1	Mean difference: 1.52 (95% CI, -1.54 to 4.58); N=601; k=4;[176, 207, 216] I^2=66% **Appendix G Figure 31**
Pharmacotherapy							
Escitalopram, fluoxetine	8 to 12 weeks from baseline	CGAS	1 to 100[309]	>70: no clinically significant functional impairment <41: major impairment to functioning in several areas[309]	62.1 to 68.5	59.3 to 64.6	Mean difference: 2.60 (95% CI, 0.78 to 4.42); N=793; k=3;[185, 207, 252] I^2=0% **Appendix G Figure 32**

Abbreviations: CBT=cognitive behavioral therapy; CGAS=Children's Global Assessment Scale; CI=confidence interval; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; k=number of studies; N=number.

Table 16. Key Characteristics of Included Anxiety Studies for Harms

Study Characteristics	Subcharacteristics	Number of Studies	Percent
Population characteristics: Child or adolescent	Child (mean age <13)	6	54.5
	Adolescent (mean age ≥13)	5	45.5
Population characteristics: Gender	Mostly female	8	72.7
	Mostly male	2	18.2
	Equal distribution	1	9.1
Population characteristics: Race	Mostly White	8	72.7
	Not reported	3	27.3
Population characteristics: Diagnosis	Any anxiety disorder	3	27.3
	GAD	4	36.4
	Social anxiety disorder	1	9.1
	Selective mutism	1	9.1
	GAD, social anxiety disorder, or separation anxiety	2	18.2
Intervention characteristics: Types of interventions	Nonpharmacological	4	36.4
	Pharmacological	6	54.5
	Multiple arms of CBT, pharmacotherapy, and combination	1	9.1
Comparator	Placebo comparator	7	63.6
	Wait-list comparator	4	36.4
Geographic setting	United States	6	54.5
	United Kingdom	2	18.2
	Denmark	1	9.1
	Germany	1	9.1
	Multiple countries	1	9.1
Recruitment setting	Community recruitment	3	27.3
	Referrals from mental health professionals	5	45.5
	Schools	1	9.1
	Not specified	2	18.2

Abbreviations: CBT=cognitive behavioral therapy; GAD=generalized anxiety disorder.

Table 17. Key Characteristics of Included Depression Studies for Harms

Study Characteristics	Subcharacteristics	Number of Studies	Percent
Population characteristics: Child or adolescent	Child (mean age <13)	1	14.3
	Adolescent (mean age ≥13)	6	85.7
Population characteristics: Gender	Mostly female	7	100.0
	Mostly male	0	0.0
Population characteristics: Race	Mostly White	4	57.1
	Mostly non-White	0	0.0
	Not reported	3	42.9
Population characteristics: Diagnosis	MDD	7	100.0
	PDD/DD/DNOS	1	14.3
Intervention characteristics: Types of interventions	Nonpharmacological	2	28.6
	Pharmacological	3	42.9
	Multiple arms of CBT, pharmacotherapy, and combination	1	14.3
	Collaborative care	1	14.3
Comparator	Placebo comparator	3	42.9
	Treatment as usual	2	28.6
	Placebo or another antidepressant	1	14.3
	Attention control	1	14.3
Geographic setting	United States	5	71.4
	Multiple countries	1	14.3
	Sweden	1	14.3
Recruitment setting	Advertised widely	3	42.9
	Health systems and clinics	2	28.6
	Not specified	2	28.6

Abbreviations: CBT=cognitive behavioral therapy; GAD=generalized anxiety disorder; MDD=major depressive disorder; PDD/DD/DNOS=persistent depressive disorder/dysthymia disorder/depression not otherwise specified.

Table 18. Summary of Outcomes

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
KQ 1 Benefits of screening	None	Not applicable	Not applicable	Not applicable	Insufficient	NA
KQ 2 Accuracy of screening	Suicide: 1 study (580)	Varies by reference standard Sensitivity range: 0.87 to 0.91 Specificity: 0.60	Consistency unknown, imprecise	Unclear whether thresholds were established a priori or whether interviewers were blinded; single study	Insufficient	Participants were potential high school dropouts; instrument was a 20-item screener embedded into a longer questionnaire so unclear whether feasible in primary care
	Anxiety: 10 studies[166, 171, 188, 199, 218, 219, 230-232, 250] (3,260)	Varies by screener, threshold, and condition Sensitivity range: 0.34 to 1.00 Specificity range: 0.47 to 0.99	Consistency unknown, imprecise	No replication of results for specific thresholds and screeners, unclear whether thresholds were established a priori or whether index and reference standard results were blinded	Low to moderate (varies by instrument)	Participants were primarily adolescents, but children were included in 4 studies. Applicable to both primary care and school-based settings. A variety of different screeners, only two are widely used in practice for detecting anxiety (i.e., SCARED and SPIN)
	Depression: 7 studies[170, 172, 189, 199, 219, 223, 235] (3,316)	Varies by screener and threshold Sensitivity (excluding outliers) range: 0.59 to 0.94 Specificity range (excluding outliers): 0.38 to 0.96 PHQ-A: sensitivity, 0.73 (95% CI, 0.58 to 0.85); specificity, 0.94 (95% CI, 0.91 to 0.96)	Consistent when multiple studies are available, precise for specificity, precision varies for sensitivity	Unclear whether thresholds were established a priori or whether index and reference standard results were blinded; no replication of approaches for most screeners	Low to moderate for sensitivity (varies by instrument) Moderate for specificity	Primarily adolescents as only one study included children younger than age 12 years; seven different screeners evaluated but most not being used in practice; the most commonly cited instrument for use in current practice is PHQ-9

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
KQ 3 Harms of screening tests	Suicide: 2 RCTs[267, 268] (2,675) Depression: 0 studies Anxiety: 0 studies	No significant differences in measures of short-term distress/emotions for students exposed to suicide screening items compared with those not exposed (2 RCTs) No significant differences in suicidal ideation between students exposed to screening items and those not exposed (1 RCT)	Consistent, precise	Fair-quality trials with some attrition; only evaluated measures of immediate and short-term emotions (over 1 to 2 days)	Low for no short-term harms from screening for suicide risk; insufficient for screening for depression and anxiety	High school students; one study entirely comprised males
KQ 4: Benefits of treatment	Suicide: 16 RCTs[164, 179-182, 191-194, 197, 200, 202, 212-215, 221, 222, 229, 236, 245, 265] (3,034)	Statistically significant difference favoring interventions on all deaths in the National Death Index (hazard ratio for treatment as usual: 6.62 [95% CI, 1.49 to 29.35]; N=448; k=1); Beck Hopelessness Scale (pooled mean difference: -2.35 (95% CI, -4.06 to -0.65); N=644; k=4; I^2=46%); nonstatistically differences favoring suicide risk interventions on the SIQ and SIQ-Junior, mixed on other measures No statistically significant differences on suicide deaths, hospitalization or ED visits, number of self-harm events, proportion with self-harm events, or functioning	Consistent, imprecise	All interventions cannot mask treatment, leading to the potential for bias in outcome reporting; all comparison groups are TAU comparisons, which in many cases were quite active treatments and could bias results toward null effects	*Psychotherapy* Low for benefit for suicidal ideation and clinical response; insufficient for all other outcomes	Applicable to adolescents (predominantly females); no studies recruited children younger than age 11 years; most recruited from mental health or specialist settings

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
KQ 4: Benefits of treatment (continued)	Anxiety: 29 RCTs (22 on CBT, 6 on pharmaco-therapy, 1 on CBT, sertraline, and combination)[163, 165, 167-169, 177, 178, 183, 190, 195, 196, 198, 203, 206, 220, 224-228, 237-244, 246, 251, 253-262] (2,970)	*CBT*: Statistically significant differences favoring CBT on several pooled measures of symptom improvement, response (pooled RR: 1.89 [95% CI, 1.17 to 3.05]; N=606; k=5; I^2=64%), remission (RR: 2.68 [95% CI, 1.48 to 4.88]; N=321; k=4; I^2=48%), and loss of diagnosis (RRs range from 3.02 to 3.09) Statistically significant improvement on Children's Global Assessment Scale (pooled mean difference: 7.54 [95% CI, 2.84 to 12.23]; N=811; k=8; I^2=90%) but not Children's Anxiety Impact Scale *Pharmacotherapy:* Statistically significant differences favoring pharmacotherapy on pooled measures of symptom improvement and response (RR: 2.11 [95% CI, 1.58 to 2.98]; N=370; k=5; I^2=18%). Statistically significant differences favoring pharmacotherapy on pooled functional measure (Children's Global Assessment Scale): mean difference: 5.14 [95% CI, 3.21 to 7.08]; N=551; k=3; I^2=0%, but not other measures of functioning	*CBT* Mostly consistent, mostly precise Pharmaco-therapy Mostly consistent, mostly precise	Potential for bias from attrition, additionally CBT studies cannot mask treatments, leading to the potential for bias in outcome reporting	*CBT:* Moderate for anxiety symptoms, response, remission, and loss of diagnosis; low for functioning depending on the measure used *Pharmaco-therapy:* Moderate for anxiety symptoms, response, remission, and loss of diagnosis; low for functioning depending on the measure used	15 CBT studies targeted any anxiety disorders; only 1 pharmacotherapy study targeted any anxiety disorders Studies addressed youth from ages 3 to 20 years, but 11 were conducted exclusively in adolescents Psychotherapy studies were limited to CBT; pharmacotherapy studies were limited to drugs with FDA approval for pediatric use

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
KQ 4: Benefits of treatment (continued)	Depression: 13 RCTs[174-176, 185, 187, 204, 205, 207, 216, 233, 248, 249, 252, 266] (2 on pharmaco-therapy; 9 on psychotherapy; 1 on CBT, fluoxetine, and combination; 1 on collaborative care) (2,156)	*Psychotherapy:* Varied by measure with some pooled estimates of effect favoring psychotherapy for symptoms (BDI or BDI-II standardized mean difference: -0.58 [95% CI,-0.83 to -0.34]; N=471; k=4; I^2=0%; Hamilton Depression mean difference: -2.25 [95% CI,-4.09 to -0.41]; N=262; k=3; I^2=0%), clinical response (3 studies with statistically significant results using varying thresholds), and loss of diagnosis (RR: 1.73 [95% CI, 1.00 to 3.00]; N=395; k=4; I^2=81%), but other outcome measures do not consistently demonstrate a statistically significant difference *Pharmacotherapy:* Statistically significant differences favoring pharmacotherapy for one measure of symptoms (Children's Depression Rating Scale-Revised mean difference: -3.76 [95% CI, -5.95 to -1.57]; N=793; k=3; I^2=49%) Pooled differences favor pharmacotherapy but are not statistically significant for remission Other outcome measures do not demonstrate a statistically significant difference *Collaborative care:* Statistically significant differences favoring collaborative care for symptoms at 6 months (CDRS-R change: 8.5 [95% CI, 13.4 to -3.6]; p=0.001), response by 12 months (OR for ≥50% reduction in CDRS-R score from baseline: 3.3 [95% CI, 1.4 to 8.2]); remission (OR for PHQ-9 <5 at 6 months: 5.2 [95% CI, 1.6 to 17.3]; no benefits for functioning)	Mostly consistent, Mostly imprecise	Psychotherapy cannot mask treatment, leading to the potential for bias in outcome reporting	*Psychotherapy:* Low for benefit for all outcomes other than remission *Pharmaco-therapy*: Low for benefit for all outcomes other than response *Collaborative care:* Low for benefit for symptoms, response, and remission Insufficient for functioning	Studies addressed youth from ages 3 to 19 years, but 9 were conducted exclusively in adolescents Pharmacotherapy studies were limited to drugs with FDA approval for pediatric use

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
KQ 5: Harms of treatment	Suicide: 2 RCTs[179, 192] (885)	No statistically significant differences on adverse events (such as attendance at minor injury units, walk-in centers, accident and emergency centers; re-referral to mental health service; and hospital attendance)	Consistent, imprecise	All interventions cannot mask treatment, leading to the potential for bias in outcome reporting; all comparison groups are TAU comparisons, which in many cases were quite active treatments and could lead to bias toward null effects	Insufficient	Applicable to adolescents, primarily females in these trials, both recruited from mental health or specialist settings
	Anxiety: 11 RCTs[168, 169, 224-228, 238, 239, 242-244, 253-262] (4 on CBT; 6 on pharmaco-therapy; 1 on CBT, sertraline, and combination) (1,293)	*Psychotherapy:* Inconsistent results on suicide-related events; harms were events and not statistically significant *Pharmacotherapy:* More suicide-related events and withdrawals due to adverse events in the pharmacotherapy arm but harms were rare and not statistically significant	Consistent to mostly consistent, imprecise	All CBT interventions cannot mask treatment, leading to the potential for bias in outcome reporting	*Psychotherapy:* Insufficient evidence *Pharmaco-therapy:* Low for harms	2 of 4 CBT studies included any anxiety disorders; 1 of 7 pharmacotherapy studies included any anxiety disorders Studies addressed children from age 5 to 20 years, but 4 were conducted exclusively in adolescents Psychotherapy studies are limited to CBT, and pharmacotherapy studies are limited to drugs with FDA approval for pediatric use

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
KQ 5: Harms of treatment (continued)	Depression: 6 RCTs[176, 185, 186, 207-211, 233, 252, 266] and 1 meta-analysis[173] (3 on pharmaco-therapy; 2 on psychotherapy; 1 on CBT, fluoxetine, and combination; 1 on collaborative care) (1,352 from trials)	*Psychotherapy:* Increased risk for suicide-related outcomes in one study, magnitude unclear due to inconsistent study reporting; no differences in negative effects in one trial *Pharmacotherapy:* Increased risk of suicide-related outcomes, withdrawal due to adverse events and serious adverse events, magnitude unclear due to inconsistent study reporting *Collaborative care:* Inconsistent results for psychiatric hospitalizations and emergency department visits	Consistent to inconsistent, imprecise	Psychotherapy trials cannot mask treatment, leading to the potential for bias in outcome reporting, inconsistent results across publications from one trial	*Psychotherapy:* Insufficient *Pharmaco-therapy:* Low for harms *Collaborative care:* Insufficient	Studies addressed youth from ages 6 to 18 years, but 5 were conducted exclusively in adolescents Pharmacotherapy studies were limited to drugs with FDA approval for pediatric use.

Abbreviations: BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory, version 2; CBT=cognitive behavioral therapy; CDRS-R=Children's Depression Rating Scale-Revised; CI=confidence interval; ED=emergency department; FDA=Food and Drug Administration; I^2=percentage of variation across studies that is due to heterogeneity rather than chance; k=number of studies; KQ=key question; MDD=major depressive disorder; N=number of participants; NA=not applicable; OR=odds ratio; PHQ-9=Patient Health Questionnaire-9; PHQ-A=Patient Health Questionnaire—Adolescent; RCT=randomized, controlled trial; RR=relative risk; SIQ=Suicidal Ideation Questionnaire; TAU=treatment as usual.

CQ 1: What is the diagnostic yield from screening for anxiety, depression, or increased suicide risk in typical primary care settings?

Given the seriousness of unmet mental health needs in youth, identification of depression, anxiety, and risk for suicide is critical. With nearly half of all youth birth to 17 years having access to healthcare in a medical home,[1] primary care is a logical place for detecting these conditions in youth. Recent research has begun to examine the extent of screening for mental health disorders in pediatric primary care as well as the outcomes of screening, including diagnosis and referral. In addition to studies included for the key question on screening test accuracy (KQ 2), we examined recent literature on screening in primary care for depression (n=11),[2-10] anxiety (n=1),[11] or suicide (n=2)[4, 12] to describe the outcomes following a positive screening. Some of these studies reported on more than the focal mental health condition.

Screening for depression. The studies included for KQ 2 (screening test accuracy)[13-19] each examined the prevalence of depression. However, only three of the seven studies recruited youth from primary care;[13] in these three studies the prevalence of depression across varied populations ranged from 8.2 percent to 11 percent. We included seven additional studies that did not meet criteria for KQ 2 studies of accuracy but that had relevant information for examining the outcome of depression screening in primary care settings.[2-4, 6, 9, 10, 20] Only one of these studies[10] provided data that permitted us to calculate the prevalence of depression. Thus, we report the positive predictive value (PPV) to describe the yield of diagnosing depression following a positive screen.

Appendix A Table 1 details the outcome of a positive screen reported in these studies, all of which included one of the PHQ versions (i.e., PHQ-A, PHQ-9, PHQ-9M). Three studies[6, 10, 20] reported the diagnosis of depression following a positive screen, and two of these studies[6, 10] found that depression diagnoses increased after implementing an intervention designed to improve the rate of depression screening. The Bose study[10] found that the rate of depression diagnoses went from 1 percent before their intervention to 13 percent afterward and to 39 percent of those with a positive screen.[10] Although the rate of diagnosed depression did not increase in the Lewandowski study, the number of adolescents (134) diagnosed with depression tripled over the three waves of the study; in the last year of their study, the rate of depression diagnosis following a positive screen was 36 percent.[6] Importantly, neither the Bose nor Lewandowski studies had control groups. The Stafford study reported that of the adolescents who had a positive screen, 71 percent received a diagnosis of depression.[20] One additional study,[2] reported that 20% of the youth who screened positive on the PHQ-9 were not depressed as indicated on medical chart abstraction, but it is not clear whether they or the remaining 80% underwent a formal depression diagnosis. Although the remainder of the studies[2-4, 9, 10, 20] did not diagnose depression directly, they made referrals to mental health providers, which may have included diagnosis along with service provision. However, this is unknown.

Screening for anxiety. Among the 10 studies included for KQ 2 (screening test accuracy), only four recruited youth in primary care settings.[13, 21-23] The prevalence of anxiety disorders across varied populations in these four studies ranged from 2.5 percent to 13 percent. Only one additional study reported on implementation of a screening program in primary care that was designed to detect anxiety disorders and mental health utilization.[11] Although the study administered the SCARED and SAS screeners as well as clinical interviews via telephone, the

investigators did not report any data that examined the rate of anxiety disorders in relation to screening data. Prevalence rates determined from the interviews with 190 parents using the ADIS were 3.2 percent for GAD, 6.8 percent for a social anxiety disorder, and 16.8 percent for any anxiety disorder. The detection rates from screening and rates of anxiety disorder from a clinical interview were similar, but the positive predictive value of the two screening measures is unknow, because, as noted above, the investigators did not report any data that examined the rate of anxiety disorders in relation to screening.

Screening for suicide. In the single study included for KQ 2 (screening test accuracy), the prevalence of high suicide risk among a population of potential high school dropouts recruited from seven high schools in the Pacific Northwest region of the United States was between 19 and 22 percent depending on the reference standard used.[24] Two studies that were not eligible for inclusion in KQ 2, because they did not have an eligible comparator, provided additional information about detection of persons at high risk for suicide in primary care[4, 12] The Etter study screened for suicidality with a single question as well as for depression using the PHQ-9.[12] In the sample of over 2,134 youth, 131 (6%) endorsed suicidality. Providers documented followup actions for all but 20 of the youth. Of the remaining 109 youth, providers indicated that 93 were not suicidal after provider assessment, suggesting that of those who endorsed the suicidality question, 15 percent were at high risk for suicide. The Farley study,[4] which was primarily a study to assess identification and management of adolescent depression in a large pediatric care network, administered the PHQ-9 along with two optional suicide risk questions. They found that 597 (8.6%) of the 6,923 adolescents completing the screener were flagged for suicide risk, but they did not examine followup for this group, other than to report that all but 230 (17%) had elevated depression scores on the PHQ. They did report that 15 of the 1,797 youth with elevated PHQ depression scores were deemed to be at high risk of suicide, and they followed emergency procedures for these youth. If these youth were part of the 498 with elevated scores who were also flagged for suicide risk, then the rate of high suicide risk in those who endorsed suicide questions is 3 percent; however, there is no information about the 99 adolescents flagged for suicide risk who had PHQ scores in the normal range.

The takeaway from this group of studies is that few studies conducted in primary care address the prevalence of anxiety, depression, or elevated risk of suicide or the rates of diagnosing these disorders after a positive screen.

CQ 2: What are the minimal clinically important differences (the smallest value of benefit to patients) for symptoms and functioning on the most common instruments used to measure response to treatment of depression, anxiety, or suicide risk?

Recent systematic reviews on anxiety[25] and depression[26] have noted the lack of research in minimal clinically important differences. A supplemental search of PubMed for this systematic review yielded no relevant citations for children with depression, anxiety, or suicide risk; systematic reviews on the topic also confirmed the lack of evidence.[27] The depression review relied on distribution-based methods (that is, methods based on statistical properties of the distribution of outcome measures[28]) for judging minimal clinically important differences, due to the lack of anchor-based methods (that is, methods based on direct questioning of patients,

providers, or caregivers). Distribution-based methods do not account for patient preferences[28] or identify any particular values for minimal clinically important differences (MCID); rather, they indicate that values above and below prespecified units of standard deviations are likely not important or not minimal.[29] In the absence of these MCID values, information about the established thresholds for the outcome measures offers some basis for judging whether the results are clinically meaningful. Tables 5, 6, 7, 9, 11, 13, and 15 in the main report lists these thresholds for pooled analyses along with a range of values for the treatment and comparison arms.

CQ 3: What are the U.S. Food and Drug Administration boxed warnings for pharmacotherapy for the treatment of depression, anxiety, or suicide risk in children and adolescents?

The current Food and Drug Administration (FDA) boxed warning, contraindications, pediatric warnings, and pediatric use statements for all drugs included in this review are shown below in Appendix A Table 2. The FDA issued a boxed warning for children and adolescents for all antidepressants in 2004 based on an FDA-conducted pooled analysis that found increased risk of suicidality when pooling across all antidepressants and all indications.[30] All drugs used in studies included in this review were selective serotonin reuptake inhibitors (SSRIs) and carry a boxed warning stating that there is "[i]ncreased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders." Some warnings contain extra guidance stating that prescribers should "monitor for worsening and emergence of suicidal thoughts and behaviors."

SSRIs as a class may be associated with a higher risk of serious adverse events among adolescents and children with MDD and with a higher risk of withdrawal due to adverse events among adolescents with MDD. A 2020 comparative effectiveness review found paroxetine, which was excluded from this current USPSTF review update because it is not FDA approved for children or adolescents, may be associated with a higher risk of suicidal ideation or behaviors in adolescents with MDD. The evidence from the comparative effectiveness review was insufficient for other SSRIs as a drug class across populations and depressive disorders for outcomes related to suicide.[26]

The FDA has approved two SSRIs to treat MDD in children or adolescents (fluoxetine for children age 8 years or older and escitalopram for adolescents ages 12 to 17 years).

CQ 4: What psychotherapies other than cognitive behavioral therapy are used to treat anxiety in children?

CBT has the largest evidence base for treatment of anxiety disorders in children. Several other less well-studied interventions have been evaluated for treating anxiety in children and adolescents.

Nine RCTs reported on attention bias modification treatment (ABMT) as a psychotherapy to treat anxiety disorders in children and adolescents.[31-39] ABMT is based on the theory that attention training toward positive stimuli can reduce anxiety. The protocol uses a computerized dot-probe task to assess the individual's threat bias and then to treat the bias by systematically

redirecting attention away from the threat stimuli.[40] Across this body of evidence, two RCTs[32, 39] found some benefit for treatment of anxiety disorders with ABMT,[32, 39] while six RCTs[31, 33-38] found no significant benefit of the intervention in decreasing anxiety.

Other interventions to treat anxiety in children have a smaller evidence base. One RCT[41] compared 10 weeks of acceptance and commitment therapy (ACT) to CBT to wait-list control in 193 children with anxiety disorder diagnoses and found that ACT and CBT were both superior to wait-list control and gains were maintained at 3 months post treatment. ACT and CBT produced similar outcomes. Psychodynamic psychotherapy is another intervention that has been less well studied, but one RCT[42] was found comparing psychodynamic psychotherapy treatment (PDT) to CBT and wait-list control in 107 adolescents with social anxiety disorder ages 14 through 20 years. Both PDT and CBT were superior to wait-list control.

CQ 5: What is the effectiveness of evidence-based treatment in children and adolescents with persistent depressive disorder and depressive disorders not otherwise specified?

The recent AHRQ Effective Health Care systematic review on the effectiveness of treatment for depression in children and adolescents noted that the evidence base is sparse for persons with persistent depressive disorder (PDD) and depressive disorders not otherwise specified (DDNOS) and varies by age and disorder.[26] This review found insufficient evidence to evaluate the effectiveness of pharmacological treatments for PDD or DDNOS among children and adolescents. Regarding nonpharmacological approaches, family therapy and CBT compared with wait-list or active control may improve symptoms, response, and functional status among children or adolescents with PDD or DDNOS. The strength of evidence for all outcomes is low. The rest of this section describes studies that were included for this evidence based on the AHRQ EHC review.[26]

One RCT[43] with medium risk of bias compared family-based interpersonal therapy (IPT) with active control in children (ages 7 to 12 years) with a range of depressive disorders including PDD and DDNOS in a 14-week intervention. Family-based IPT improved clinician-, self-, and parent-reported depressive symptoms. The mean difference on the clinician-reported scale (CDRS-R) was -0.50 (95% CI, -2.48 to 0.10). The mean difference on the self-reported Mood and Feelings Questionnaire for Children (MFQ-C) was -6.50 (95% CI, -7.85 to 5.15). The mean difference on the parent-reported Mood and Feelings Questionnaire (MFQ-P) was -5.60 (95% CI, -6.49 to 4.71). The authors of the AHRQ EHC review concluded that the evidence was insufficient to judge the effectiveness of family-based IPT when compared with active control for remission.[26]

Two RCTs, one with high risk of bias[44] and one with some[45] risk-of-bias concerns, compared CBT with wait-list control among adolescents with a range of depressive disorders including PDD. The duration of the intervention spanned 8[45] to 12[44] weeks. Compared with wait-list control, CBT improved self-reported depressive symptoms (mean difference [Beck Depression Inventory (BDI)], -5.90 [95% CI, -10.89 to -0.92]) and improved clinician-reported functional impairment (mean difference [Global Assessment of Functioning (GAF)], 6.5 [95% CI, 0.68 to 12.32]). The authors of the AHRQ EHC review concluded that the evidence was insufficient to

judge whether there were improvements noted in clinician- or parent-reported depressive symptoms, recovery, or response.[26]

Three RCTs, two with some risk-of-bias concerns[46-48] and a third with high risk of bias,[49] that included children and adolescents (ages 7 to 18 years) compared family therapy with active control in studies that were 8 to 16 weeks long. Compared with active control, one study[46] found that family therapy showed higher rates of adequate clinical depression response with a 50 percent reduction in CDRS-R scores from baseline to posttreatment (risk difference, 179/1,000 [95% CI, 25 more cases to 333 more cases]). The authors of the AHRQ EHC review concluded that the evidence was insufficient to evaluate the effectiveness of family therapy and active control for clinician- or self-reported depressive symptoms, depression response, remission, recurrence, and clinician- or self-reported functional impairment.[26]

The existing evidence base offers limited indication of benefit for children and adolescents with PDD or DDNOS. The lack of evidence on pharmacological treatments and on the effects of interventions in children stand out as gaps and may serve as areas for future research. In addition, new research should establish minimally important differences to help understand the trade-offs between benefits and harms. Well-designed trials will contribute to a stronger body of evidence and greater certainty in the estimate of effectiveness.

Our update search for the USPSTF review update yielded no additional relevant citations to this contextual question.

CQ 6: What proportion of children and adolescents who screen positive for depression, anxiety, or increased suicide risk engage with care (i.e., return for clinical evaluation and treatment)?

We identified five studies that addressed followup for those screening positive for depression.[4, 50-52] One retrospective chart review of three large healthcare systems (two health maintenance organization and one network of community health centers) found that of 4,612 adolescents newly screened positive for depression in primary care, 854 (19%) received no followup visit of any type within the following 3 months. Of those who did have at least one visit, 824 (22%) did not have depression symptoms addressed. The remaining 2,934 (78%) were started on therapy (n=1,315), antidepressant medication (n=891), or combined therapy (n=728). Of those started on antidepressants, 356 (40%) did not have a followup within 3 months.[50]

Another study of 16-year-old patients screened for depression with the PHQ-9M at one of 31 sites of a large pediatric primary care practice found an association between more severe depression and increased likelihood to followup.[4] Of 466 patients with a PHQ-9M score of 11 to 27, 349 (75.4%) had followup of some type (depression diagnosis, behavioral health referral, medication, or repeated PHQ-9) within the following year.[4] Of the 1,331 patients screening positive for more mild depression (PHQ-9M score of 5 to 10), only 530 (39.9%) had followup of some sort.[4]

One study of 10 primary care clinics screening for depression using PHQ-2/PHQ-9 found that of the 796 patients with a PHQ-9 score of 10 or more, 638 were referred to behavioral health treatment and only 370 (58%) engaged in such treatment.[51]

One study of adolescents screening for psychiatric illness (oppositional defiant disorder, attention deficit hyperactivity disorder, depression, suicide, anxiety, separation, and others) using the Mini International Neuropsychiatric Interview (MINI) screener in an emergency room found that 200 screened positive.[53] All who screened positive were given a referral to a mental health provider, and less than 2 percent of those patients had followed up with a mental health provider when asked during telephone followup after 6 weeks.[53]

Only one identified study looked at followup rates of those screening positive for suicide, in this case from an urgent care clinic setting. Patients 12 years or older were routinely screened by nursing using a two-question screener. If positive, a social worker administered the Columbia Suicide Severity Rating Scale (C-SSRS). Of 75 adolescents screening positive on the C-SSRS, 10 were admitted into psychiatric inpatient care, four were admitted to medical inpatient units, one left against medical advice, one was transferred to the emergency department, and 59 were referred to mental health professionals. Of those 59 referred to mental health professionals, it is not documented how many actually accessed care.[54]

No identified studies examined followup after screening positive for anxiety.

Taken together, these studies suggest that many adolescents who screen positive for depression in primary care will engage in treatment of some type and will be more likely to followup if screening positive for more severe depression. While not definitive, these studies suggest that likelihood of following up may be higher if screened in primary care rather than emergency department settings. This may be a factor of continuity, of primary care or mental health access and availability, or of other unseen factors.

Appendix A Table 1. Outcomes of Depression Screening

Study	N	Screener	Positive Screen	Depression Diagnoses	Referral
Aalsma et al, 2018[2]	2,038	PHQ-2 then PHQ-9	303 (15%)	NA	128 (42%)
Bose et al, 2021[10]	73	PHQ-A (cutoff ≥5)	29 (40%)	12 (45%)*	9.2%†
Chowdhury et al, 2020[3]	1,213	PHQ-9 (cutoff ≥5)	96 (8%)	NA	42 (44%)
Farley et al, 2020[4]	10,713	PHQ-9M (cutoff ≥5)	1,797 (17%)	NA	449 (25%)
Lewandowski et al, 2016[6]	2,283	PHQ-9	435 (19%)	134 (36%)‡	NA
Stafford et al, 2020[20]	80§	PHQ-2 then PHQ-9 (cutoff ≥9)	80§	57 (74%)‖	10 (12%)
Sudhanthar et al, 2015[9]	NA	PHQ-2 then PHQ-9	NA	NA	38% increase¶

*No information provided regarding diagnostic procedure for depression.
†The number of individuals who were referred and what the 9.2% represents were unclear.
‡Of those with incident-positive PHQ-9.
§Study only included adolescents who screened positive for depression.
‖Of those who were managed in primary care.
¶No n's were reported.

Abbreviations: NA=not available; PHQ=Patient Health Questionnaire.

Appendix A Table 2. FDA Boxed Warnings for Medication Included in Updated Review of Screening for Anxiety, Depression, and Suicide Risk in Children and Adolescents

Name of Drug	Date Searched	Date on FDA Label	Boxed Warning	Contraindications	Pediatric Warnings	Pediatric Use Statements
Clomipramine[55]	April 27, 2021	March 2019	Yes	History of hypersensitivity to clomipramine or other tricyclic antidepressants, use of MAOIs, use of linezolid or intravenous methylene blue, and those in acute recovery period from myocardial infarction.	None	Clomipramine hydrochloride is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD).
Duloxetine[56]	February 9, 2021	December 2008	Yes	It should not be used concomitantly or in close temporal proximity with a MAOI or in patients with uncontrolled narrow-angle glaucoma.	Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders.	Not approved for use in pediatric patients.
Escitalopram[57]	February 11, 2021	January 2017	Yes	It should not be used concomitantly or within 14 days of an MAOI. It should not be used concomitantly with linezolid, intravenous methylene blue, or pimozide, or in patients with known hypersensitivity to escitalopram or citalopram or any of the inactive ingredients.	Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders.	Approved for acute and maintenance treatment of MDD in adolescents ages 12 to 17 years Not approved for use in patients younger than 12 years. Safety and effectiveness have not been established in pediatric patients younger than 18 years with generalized anxiety disorder.
Fluoxetine[58]	February 11, 2021	January 2017	Yes	It should not be used concomitantly or within 5 weeks of an MAOI or thioridazine. It should not be used concomitantly with linezolid, intravenous methylene blue, or pimozide. If used in combination with olanzapine, the contraindications for Symbyax should also be observed.	Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders. Monitor for worsening and emergence of suicidal thoughts and behaviors.	Approved for use in pediatric patients with MDD and OCD. Safety and effectiveness in patients younger than 8 years with MDD and younger than 7 years with OCD have not been established. Safety and effectiveness in combination with olanzapine in patients younger than 10 years for depressive episodes associated with bipolar I disorder have not been established.

Appendix A Table 2. FDA Boxed Warnings for Medication Included in Updated Review of Screening for Anxiety, Depression, and Suicide Risk in Children and Adolescents

Name of Drug	Date Searched	Date on FDA Label	Boxed Warning	Contraindications	Pediatric Warnings	Pediatric Use Statements
Fluvoxamine[59]	February 11, 2021	April 2008	Yes	It should not be used concomitantly or within 14 days of an MAOI. It should not be used concomitantly with tizanidine, thioridazine, alosetron, or pimozide.	Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders.	Not approved for use in pediatric patients except those with OCD.
Sertraline[60]	February 11, 2021	December 2016	Yes	It should not be used concomitantly or within 14 days of an MAOI. It should not be used concomitantly with pimozide or disulfiram (oral solution only) or in patients with known hypersensitivity to sertraline or excipients.	Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors.	Safety and effectiveness in pediatric patients other than those with OCD have not been established.

Abbreviations: FDA=Food and Drug Administration; MAOI=monoamine oxidase inhibitor; MDD=major depressive disorder; OCD=obsessive compulsive disorder.

Appendix A Table 3. Screening and Engagement With Care

Study #	Screening Tool	Setting	Diagnosis(es) Addressed in Followup Statistics	Followup Rates
O'Connor et al, 2016[50]	PHQ-9	3 healthcare centers	Depression	Of 4,612 screened positive or newly diagnosed with depression, 854 (19%) did not engage in followup of any kind. Of the 891 started on antidepressants at followup, 356 (40%) had no subsequent followup within 3 months.
Farley et al, 2020[4]	PHQ-9M	31 sites of pediatric primary care practice in U.S. mid-Atlantic region	Depression	466 had PHQ-9M score 11–27 349 (75.4%) had followup of some type in the following year 1,331 had score of 5–10 530 (39.9%) had mental health followup of some type
Thompson et al, 2018[51]	PHQ-2/PHQ-9	10 primary care clinics	Depression	Of 796 that had a PHQ-9 of 10 or above, 638 were referred to additional services, of which 370 (58%) were engaged in treatment
Downey et al, 2018[53]	MINI	Emergency department	Suicide, depression, ODD, ADHD, anxiety, separation	41% of 200 children screened positive for some sort of psychiatric illness. All were referred to mental health provider and <2% of patients had followed up when asked via telephone followup in 6 weeks
Patel et al, 2018[54]	2-question screener, followed by C-SSRS by social worker	Urgent care	Suicide	Of 75 positive C-SSRS screens, 10 psychiatric admissions, 4 medical admissions, 1 left against medical advice, 1 transfer to emergency department, and 59 were referred to mental health (with no indication from this study of followup from there)

Abbreviations: ADHD=attention-deficit/hyperactivity disorder; C-SSRS=Columbia Suicide Severity Rating Scale; MINI= Mini International Neuropsychiatric Interview; ODD=oppositional defiant disorder; PHQ=Patient Health Questionnaire; PHQ-2=Patient Health Questionnaire-2 questions; PHQ-9=Patient Health Questionnaire-9 questions; PHQ-9M= Patient Health Questionnaire-9 questions Modified; U.S.=United States.

MEDLINE® via PubMed

Suicide Risk: January 1, 2012, through April 28, 2020
Anxiety: January 1, 2017 to April 28, 2020
Depression: June 1, 2012 to April 28, 2020

Search	Query	Results
1	"Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR Depression[MeSH] OR depress*[Title/Abstract] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed[Title/Abstract] OR "Dysthymic Disorder"[Mesh] OR dysthymia OR dysthymic OR "Persistent Depressive Disorder"[ALL FIELDS]	496,379
2	Mass Screening[MeSH] OR screen[tiab] OR screening[tiab] OR screened[tiab] OR screens[tiab] OR "case finding"[tiab] OR casefinding[tiab] OR "beck depression inventory" OR "beck depression inventories" OR "Center for Epidemiologic Studies Depression Scale"[All Fields] OR "Center for Epidemiologic Studies Depression Scales"[All Fields] OR "depression inventory"[tiab] OR "depression inventories"[tiab] OR "depression scale"[tiab] OR "depression scales"[tiab] OR "depression rating scale"[tiab] OR "depression rating scales"[tiab] OR Kutcher*[tiab] OR "mood and feelings questionnaire"[All Fields] OR "mood and feelings questionnaires"[All Fields] OR "Patient Health Questionnaire-Adolescent Version"[All Fields] OR Reynold*[tiab] OR "self report rating scale"[All Fields] OR "self report rating scales"[All Fields] OR BDI[tiab] OR CES-D[tiab] OR ChilD-S[tiab] OR DesTeen[tiab] OR MFQ-SF[tiab] OR PHQ-2[tiab] OR PHQ-A[tiab] OR RCDS[tiab]	862,015
3	#1 AND #2	69,492
4	#1 AND #2 Filter: from 2015 - 2020	26,844
5	#1 AND #2 Filter: English, from 2015 - 2020	26,092
6	#1 AND #2 Filter: English, Child: birth-18 years, from 2015 - 2020	4,688
7	adolescen*[tiab] OR boys[tiab] OR child*[tiab] OR children[tiab] OR girls[tiab] OR pediatric[tiab] OR paediatric*[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR teenaged[tiab] OR teenager*[tiab] OR toddler*[tiab]	1,737,521
8	#5 AND #7	4,576
9	#6 OR #8	6,839
10	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case reports"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] or horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae	10,206,468
11	#9 NOT #10	6,741

Appendix B. Search Strategies

Search	Query	Results
12	"Anti-Anxiety Agents"[Mesh] OR "Antidepressive Agents"[MeSH] OR "Serotonin Uptake Inhibitors"[MeSH] OR "Tranquilizing Agents"[Mesh] OR antidepressant*[tiab] OR "antidepressives"[tiab] OR "antidepressive agents"[tiab] OR "antidepressive drug"[tiab] OR "antidepressive drugs"[tiab] OR "norepinephrine reuptake inhibitor"[all fields] OR "norepinephrine reuptake inhibitors"[all fields] OR "selective serotonin reuptake inhibitor"[tiab] OR "selective serotonin reuptake inhibitors"[tiab] OR ssri[tiab] OR ssris[tiab] OR "serotonin norepinephrine reuptake inhibitor"[All Fields] OR "serotonin norepinephrine reuptake inhibitors"[All Fields] OR snri*[All Fields] OR "TCA antidepressants"[All Fields] OR "tricyclic antidepressant"[All Fields] OR "tricyclic antidepressants"[All Fields] OR anafranil[All Fields] OR celexa[tiab] OR Citalopram[MeSH] OR citalopram[tiab] OR clomipramine[MeSH] OR clomipramine[tiab] OR "duloxetine"[Mesh] OR duloxetine[tiab] OR escitalopram[tiab] OR Fluoxetine[MeSH] OR fluoxetine[tiab] OR Fluvoxamine[MeSH] OR fluvoxamine[tiab] OR ketamine[MeSH] OR ketamine[tiab] OR Lexapro[tiab] OR "Lithium Compounds/therapeutic use"[Mesh] OR lithium[tiab] OR luvox[tiab] OR Sertraline[MeSH] OR sertraline[tiab] OR Zoloft[tiab]	246,639
13	#1 AND #12	68,565
16	"Behavior Therapy"[MeSH] OR "Cognitive Behavioral Therapy"[Mesh] OR "Combined Modality Therapy"[Mesh] OR Counseling[MeSH] OR "Delivery of Health Care, Integrated"[Mesh] OR "Directive Counseling"[MeSH] OR "Family Therapy"[MeSH] OR "Parents/education"[MeSH] OR "Patient Care Management"[Mesh] OR "Problem Solving"[MeSH] OR Psychotherapy[MeSH] OR "Psychotherapy, Group"[MeSH] OR "Risk Reduction Behavior"[Mesh] OR "Self-Help Groups"[MeSH] OR (behavior*[tiab] AND (therap*[tiab] or treatment*[tiab] OR intervention*[tiab])) OR CBT[tiab] OR (cognitive[tiab] AND (therap*[tiab] OR treatment*[tiab] OR intervention*[tiab])) OR "care delivery"[tiab] OR "care management"[tiab] OR "collaborative care"[tiab] OR "combination therapy"[tiab] OR "combined modality"[tiab] OR counsel*[tiab] OR "delivery of care"[tiab] OR "dialectical behavior therapy"[All fields] OR "family therapy"[tiab] OR "family support"[tiab] OR interpersonal therap*[tiab] OR interpersonal intervention*[tiab] OR "means restriction"[tiab] OR "means restrictions"[All Fields] OR "mentalization therapy"[All fields] OR (parent*[tiab] AND education[tiab]) OR "problem solving"[tiab] OR "psychoeducation"[tiab] OR psychotherap*[tiab] OR (risk*[tiab] AND reduc*[tiab]) OR "self help"[tiab]	2,120,901
17	#1 AND #16	99,177
18	#13 OR #17	148,472
19	#13 OR #17 Filter: from 2015 - 2020	44,779
20	#13 OR #17 Filter: English, from 2015 - 2020	43,229
21	#13 OR #17 Filter: English, Child: birth-18 years, from 2015 - 2020	6,611
22	#20 AND #7	6,389
23	#21 OR #22	9,511
24	#23 NOT #10	8,910
25	"cochrane database syst rev"[ta] OR "systematic review"[ti] OR "meta-analysis"[pt] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab] OR "systematic literature review"[ti] OR ("systematic review"[tiab] AND review[pt]) OR "this systematic review"[tw] OR "umbrella review"[tiab]	270,232
26	#24 AND #25	543
27	#24 NOT #26	8,367
29	"Anxiety Disorders"[Mesh] OR "Anxiety"[Mesh] OR agoraphobia OR anxiety[ti] OR "generalized anxiety disorder" OR mutism OR "panic disorder" OR phobia* OR "separation anxiety disorder" OR "social anxiety disorder"	169,198

Appendix B. Search Strategies

Search	Query	Results
30	"Mass Screening"[MeSH] OR screen[tiab] OR screening[tiab] OR screened[tiab] OR screens[tiab] OR "case finding"[tiab] OR casefinding[tiab] OR "Children's Manifest Anxiety Scale"[All Fields] OR "Multidimensional Anxiety Scale for Children"[All Fields] OR "Pediatric Anxiety Rating Scale"[All Fields] OR "Revised Children's Manifest Anxiety Scale"[All Fields] OR "Screen for Child Anxiety Related Disorders"[All Fields] OR "Spence's Children's Anxiety Scale"[All Fields] OR "State-Trait Anxiety Inventory for Children"[All Fields] OR "Youth Anxiety Measure for DSM-5"[All Fields] OR MASC[tiab] OR "MASC-2 SR"[All Fields] OR MASC-10[tiab] OR PARS[tiab] OR RCMAS[tiab] OR SCARED[tiab] OR SCAS[tiab] OR SCAS-8[tiab] OR STAIC[tiab] OR STAIC-S[tiab] OR YAM-5[tiab]	802,488
31	#29 AND #30	8,121
32	#29 AND #30 Filter: English	7,694
33	#29 AND #30 Filter: English, Child: birth-18 years	2,684
34	#32 AND #7	1,992
35	#33 OR #34	3,092
36	#35 NOT #10	3,010
37	#29 AND #12	16,939
39	#29 AND #16	45,405
40	#37 OR #39	56,846
41	#37 OR #39 Filter: English	50,283
42	#37 OR #39 Filter: English, from 2017 - 2020	8,320
43	#37 OR #39 Filter: English, Child: birth-18 years, from 2017 - 2020	1,986
44	#42 AND #7	1,818
45	#43 OR #44	2,619
46	#45 NOT #10	2,389
47	#46 AND #25	147
48	#46 NOT #47	2,242
49	"Suicide"[Mesh] OR "Suicide, Attempted"[Mesh] OR "Suicide, Completed"[Mesh] OR "Suicidal Ideation"[Mesh] OR parasuicid*[ti] OR "self harm"[ti] OR "Self-Injurious Behavior"[Mesh] OR suicid*[ti]	77,404
50	"Mass Screening"[MeSH] OR screen[tiab] OR screening[tiab] OR screened[tiab] OR screens[tiab] OR "case finding"[tiab] OR casefinding[tiab] OR "Adapted-SAD PERSONS"[All Fields] OR "Beck Hopelessness Scale"[All Fields] OR "Beck Scale for Suicide Ideation"[All Fields] OR "Center for Epidemiologic Studies-Depression Scale"[All Fields] OR "Child Suicide Assessment"[All Fields] OR "Columbia Suicide Severity Rating Scale"[All Fields] OR "Columbia Teen Screen"[All Fields] OR "Firestone Assessment of Self-Destructive Thoughts"[All Fields] OR "Harkavy Asnis Suicide Survey"[All Fields] OR "Inventory for Suicidal Ideation"[All Fields] OR "Multi-attitude Suicide Tendency Scale for Adolescents"[All Fields] OR "Paykel Suicide Items"[All Fields] OR "Positive and Negative Suicide Ideation Inventory"[All Fields] OR "Scale for Suicide Ideation"[All Fields] OR "Self-harm behavior questionnaire"[All Fields] OR "Suicide Behaviors Questionnaire"[All Fields] OR "Suicidal Ideation Questionnaire"[All Fields] OR "Suicidality Occurring in Paediatrics-Suicidality Assessment Scale"[All Fields] OR "Suicide Assessment Five-Step Evaluation and Triage"[All Fields] OR "Suicide Probability Scale"[All Fields] OR BSI[tiab] OR CES-D[tiab] OR CSA[tiab] OR C-SSSR[tiab] OR CTS[tiab] OR HASS-II[tiab] OR ISO-30[tiab] OR PANSI[tiab] OR SSI[tiab] OR SHBQ[tiab] OR SBQ-14[tiab] OR SBQ-C[tiab] OR SIQ[tiab] OR SIQ-Junior[tiab] OR STOP-SAS[tiab] OR SAFE-T[tiab] OR SPS[tiab] OR SRS[tiab]	837,759
51	#49 AND #50	3,485

Appendix B. Search Strategies

Search	Query	Results
52	#49 AND #50 Filter: English	3,320
53	("2012/06/01"[Date - Publication] : "2020/12/31"[Date - Publication]) Filter: English	8,460,381
54	#52 AND #53	1,951
55	#52 AND #53 Filter: Child: birth-18 years	681
56	#54 AND#7	235
57	#55 OR #56	810
58	#57 NOT #10	786
59	#49 AND #12	4,971
60	#49 AND #16	15,458
61	#59 OR #60	18,818
62	#59 OR #60 Filter: English	16,713
63	#62 AND #53 Filter: English	6,314
64	#62 AND #53 Filter: English, Child: birth-18 years	2,143
65	#63 AND #7	1,511
66	#64 OR #65	2,569
67	#66 NOT #10	2,403
68	#67 AND #25	102
69	#67 NOT #68	2,301
70	"Pediatric Symptom Checklist-17" OR PSC[tiab] OR "Revised Children's Anxiety and Depression Scale"[All Fields] OR RCADS[tiab] OR RCADS-25[tiab] OR "Strength and Difficulties Questionnaires"[All Fields] OR SDQ[tiab]	8,116
71	(#1 OR #29 OR #49) AND #70	432
72	(#1 OR #29 OR #49) AND #70 Filter: English	421
73	(#1 OR #29 OR #49) AND #70 Filter: English, Child: birth-18 years	231
74	#72 AND #7	284
75	#73 OR #74	306
76	#75 NOT #10	300

Cochrane Library

Suicide Risk: January 1, 2012, through April 28, 2020
Anxiety: January 1, 2017 to April 28, 2020
Depression: June 1, 2012 to April 28, 2020

Search	Query	Results
1	[mh "Depressive Disorder"] or [mh "Depressive Disorder, Major"] or [mh Depression] or depress*:ti,ab or depression:ti,ab or depressive:ti,ab or depressed:ti,ab or [mh "Dysthymic Disorder"] or dysthymia:ti,ab,kw or dysthymic:ti,ab,kw or "Persistent Depressive Disorder":ti,ab,kw	75575
2	[mh “Mass Screening”] OR screen:ti,ab OR screening:ti,ab OR screened:ti,ab OR screens:ti,ab OR "case finding":ti,ab OR casefinding:ti,ab OR "beck depression inventory" OR "beck depression inventories" OR "Center for Epidemiologic Studies Depression Scale":ti,ab,kw OR "Center for Epidemiologic Studies Depression Scales":ti,ab,kw OR "depression inventory":ti,ab OR "depression inventories":ti,ab OR "depression scale":ti,ab OR "depression scales":ti,ab OR "depression rating scale":ti,ab OR "depression rating scales":ti,ab OR Kutcher*:ti,ab OR "mood and feelings questionnaire":ti,ab,kw OR "mood and feelings questionnaires":ti,ab,kw OR "Patient Health Questionnaire-Adolescent Version":ti,ab,kw OR Reynold*:ti,ab OR "self report rating scale":ti,ab,kw OR "self report rating scales":ti,ab,kw OR BDI:ti,ab OR CES-D:ti,ab OR ChilD-S:ti,ab OR DesTeen:ti,ab OR MFQ-SF:ti,ab OR PHQ-2:ti,ab OR PHQ-A:ti,ab OR RCDS:ti,ab	82010
3	#1 AND #2	20931
4	Address:pt OR “autobiography”:pt OR “bibliography”:pt OR “biography”:pt OR “case control” OR "case report" OR “case reports” OR “case series” OR “comment”:pt OR "comment on" OR congress:pt OR “cross-sectional” OR “dictionary”:pt OR “directory”:pt OR “editorial”:pt OR “festschrift”:pt OR “historical article”:pt OR “interview”:pt OR lecture:pt OR "legal case":pt OR “legislation”:pt OR letter:pt OR “news”:pt OR “newspaper article”:pt OR “patient education handout”:pt OR “periodical index”:pt OR “retrospective cohort” OR ([mh "Animals"] NOT [mh "Humans"]) OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae	64667
5	#3 NOT #4	20194
6	MeSH descriptor: [Child] explode all trees	2623
7	MeSH descriptor: [Infant] explode all trees	16136
8	MeSH descriptor: [Adolescent] explode all trees	101062
9	adolescen*:ti,ab OR boys:ti,ab OR child*:ti,ab OR children:ti,ab OR girls:ti,ab OR pediatric:ti,ab OR paediatric*:ti,ab OR teen:ti,ab OR teens:ti,ab OR teenage:ti,ab OR teenaged:ti,ab OR teenager*:ti,ab OR toddler*:ti,ab	146691
10	#6 OR #7 OR #8 OR #9	235130
11	#5 AND #10	3330

Appendix B. Search Strategies

Search	Query	Results
12	[mh "Anti-Anxiety Agents"] OR [mh "Antidepressive Agents"] OR [mh "Serotonin Uptake Inhibitors"] OR [mh "Tranquilizing Agents"] OR antidepressant*:ti,ab OR "antidepressives":ti,ab OR "antidepressive agents":ti,ab OR "antidepressive drug":ti,ab OR "antidepressive drugs":ti,ab OR "norepinephrine reuptake inhibitor":ti,ab,kw OR "norepinephrine reuptake inhibitors":ti,ab,kw OR "selective serotonin reuptake inhibitor":ti,ab OR "selective serotonin reuptake inhibitors":ti,ab OR ssri:ti,ab OR ssris:ti,ab OR "serotonin norepinephrine reuptake inhibitor":ti,ab,kw OR "serotonin norepinephrine reuptake inhibitors":ti,ab,kw OR snri*:ti,ab,kw OR "TCA antidepressants":ti,ab,kw OR "tricyclic antidepressant":ti,ab,kw OR "tricyclic antidepressants":ti,ab,kw OR anafranil:ti,ab,kw OR celexa:ti,ab OR [mh Citalopram] OR citalopram:ti,ab OR [mh clomipramine] OR clomipramine:ti,ab OR [mh duloxetine] OR duloxetine:ti,ab OR escitalopram:ti,ab OR [mh Fluoxetine] OR fluoxetine:ti,ab OR [mh Fluvoxamine] OR fluvoxamine:ti,ab OR [mh ketamine] OR ketamine:ti,ab OR Lexapro:ti,ab OR [mh "Lithium Compounds"/TU] OR lithium:ti,ab OR luvox:ti,ab OR [mh Sertraline] OR sertraline:ti,ab OR Zoloft:ti,ab	35486
13	#1 AND #12	16373
14	[mh "Behavior Therapy"] OR [mh "Cognitive Behavioral Therapy"] OR [mh "Combined Modality Therapy"] OR [mh Counseling] OR [mh "Delivery of Health Care, Integrated"] OR [mh "Directive Counseling"] OR [mh "Family Therapy"] OR [mh "Parents"/ED] OR [mh "Patient Care Management"] OR [mh "Problem Solving"] OR [mh Psychotherapy] OR [mh "Psychotherapy, Group"] OR [mh "Risk Reduction Behavior"] OR [mh "Self-Help Groups"] OR (behavior*:ti,ab AND (therap*:ti,ab or treatment*:ti,ab OR intervention*:ti,ab)) OR CBT:ti,ab OR (cognitive:ti,ab AND (therap*:ti,ab OR treatment*:ti,ab OR intervention*:ti,ab)) OR "care delivery":ti,ab OR "care management":ti,ab OR "collaborative care":ti,ab OR "combination therapy":ti,ab OR "combined modality":ti,ab OR counsel*:ti,ab OR "delivery of care":ti,ab OR "dialectical behavior therapy":ti,ab,kw OR "family therapy":ti,ab OR "family support":ti,ab OR interpersonal therap*:ti,ab OR interpersonal intervention*:ti,ab OR "means restriction":ti,ab OR "means restrictions":ti,ab,kw OR "mentalization therapy":ti,ab,kw OR (parent*:ti,ab AND education:ti,ab) OR "problem solving":ti,ab OR "psychoeducation":ti,ab OR psychotherap*:ti,ab OR (risk*:ti,ab AND reduc*:ti,ab) OR "self help":ti,ab	242343
15	#1 AND #14	29310
16	#13 OR #15	4188
17	#16 AND #10	7668
18	#17 NOT (clinicaltrials or trialsearch):so	5975
19	#11 NOT (clinicaltrials or trialsearch):so	2345
20	[mh "Anxiety Disorders"] OR [mh "Anxiety"] OR agoraphobia OR anxiety:ti OR "generalized anxiety disorder" OR mutism OR "panic disorder" OR phobia* OR "separation anxiety disorder" OR "social anxiety disorder"	23453
21	[mh "Mass Screening"] OR screen:ti,ab OR screening:ti,ab OR screened:ti,ab OR screens:ti,ab OR "case finding":ti,ab OR casefinding:ti,ab OR "Children's Manifest Anxiety Scale":ti,ab,kw OR "Multidimensional Anxiety Scale for Children":ti,ab,kw OR "Pediatric Anxiety Rating Scale":ti,ab,kw OR "Revised Children's Manifest Anxiety Scale":ti,ab,kw OR "Screen for Child Anxiety Related Disorders":ti,ab,kw OR "Spence's Children's Anxiety Scale":ti,ab,kw OR "State-Trait Anxiety Inventory for Children":ti,ab,kw OR "Youth Anxiety Measure for DSM-5":ti,ab,kw OR MASC:ti,ab OR "MASC-2 SR":ti,ab,kw OR MASC-10:ti,ab OR PARS:ti,ab OR RCMAS:ti,ab OR SCARED:ti,ab OR SCAS:ti,ab OR SCAS-8:ti,ab OR STAIC:ti,ab OR STAIC-S:ti,ab OR YAM-5:ti,ab	66544
22	#20 AND #21	1372
23	#22 AND #10	503
24	#23 NOT (clinicaltrials or trialsearch):so	345

Appendix B. Search Strategies

Search	Query	Results
25	#20 AND (#12 OR #14)	12437
26	#25 AND #10	3535
27	#26 NOT (clinicaltrials or trialsearch):so	3022
28	[mh "Suicide"] OR [mh "Suicide, Attempted"] OR [mh "Suicide, Completed"] OR [mh "Suicidal Ideation"] OR parasuicid*:ti OR "self harm":ti OR [mh "Self-Injurious Behavior"] OR suicid*:ti	2323
29	[mh "Mass Screening"] OR screen:ti,ab OR screening:ti,ab OR screened:ti,ab OR screens:ti,ab OR "case finding":ti,ab OR casefinding:ti,ab OR "Adapted-SAD PERSONS":ti,ab,kw OR "Beck Hopelessness Scale":ti,ab,kw OR "Beck Scale for Suicide Ideation":ti,ab,kw OR "Center for Epidemiologic Studies-Depression Scale":ti,ab,kw OR "Child Suicide Assessment":ti,ab,kw OR "Columbia Suicide Severity Rating Scale":ti,ab,kw OR "Columbia Teen Screen":ti,ab,kw OR "Firestone Assessment of Self-Destructive Thoughts":ti,ab,kw OR "Harkavy Asnis Suicide Survey":ti,ab,kw OR "Inventory for Suicidal Ideation":ti,ab,kw OR "Multi-attitude Suicide Tendency Scale for Adolescents":ti,ab,kw OR "Paykel Suicide Items":ti,ab,kw OR "Positive and Negative Suicide Ideation Inventory":ti,ab,kw OR "Scale for Suicide Ideation":ti,ab,kw OR "Self-harm behavior questionnaire":ti,ab,kw OR "Suicide Behaviors Questionnaire":ti,ab,kw OR "Suicidal Ideation Questionnaire":ti,ab,kw OR "Suicidality Occurring in Paediatrics-Suicidality Assessment Scale":ti,ab,kw OR "Suicide Assessment Five-Step Evaluation and Triage":ti,ab,kw OR "Suicide Probability Scale":ti,ab,kw OR BSI:ti,ab OR CES-D:ti,ab OR CSA:ti,ab OR C-SSSR:ti,ab OR CTS:ti,ab OR HASS-II:ti,ab OR ISO-30:ti,ab OR PANSI:ti,ab OR SSI:ti,ab OR SHBQ:ti,ab OR SBQ-14:ti,ab OR SBQ-C:ti,ab OR SIQ:ti,ab OR SIQ-Junior:ti,ab OR STOP-SAS:ti,ab OR SAFE-T:ti,ab OR SPS:ti,ab OR SRS:ti,ab	72731
30	#28 AND #29	336
31	#30 AND #10	118
32	#31 NOT (clinicaltrials or trialsearch):so	85
33	#28 AND (#12 OR #14)	1577
34	#33 AND #10	527
35	#34 NOT (clinicaltrials or trialsearch):so	427

Psychinfo

Suicide Risk: January 1, 2012, through April 30, 2020
Anxiety: January 1, 2017 to April 30, 2020
Depression: June 1, 2012 to April 30, 2020

#	Query	Limiters/Expanders	Results
S1	DE "Depression (Emotion)" OR DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR depressive OR depression OR depressed OR dysthymic OR dysthymia	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	360,288
S2	DE "Health Screening" OR DE "Screening Tests" OR screen OR screening OR screened OR screens OR "case finding" OR casefinding OR "beck depression inventory" OR "beck depression inventories" OR "Center for Epidemiologic Studies Depression Scale" OR "Center for Epidemiologic Studies Depression Scales" OR "depression inventory" OR "depression inventories" OR "depression scale" OR "depression scales" OR "depression rating scale" OR "depression rating scales" OR Kutcher* OR "mood and feelings questionnaire" OR "mood and feelings questionnaires" OR "Patient Health Questionnaire-Adolescent Version" OR Reynold* OR "self report rating scale" OR "self report rating scales" OR BDI OR CES-D OR ChilD-S OR DesTeen OR MFQ-SF OR PHQ-2 OR PHQ-A OR RCDS	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	230,416
S3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	128,078
S4	S3	Limiters - Publication Year: 2015-2020; English; Language: English; Population Group: Human Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	38,863
S5	S4	Limiters - Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs) Search modes - Boolean/Phrase	7,802
S6	PZ Abstract Collection OR PZ Bibliography OR PZ Clarification OR PZ Column/Opinion OR BK Conference Proceedings OR PZ Comment/Reply OR PZ Dissertation OR PT Dissertation Abstract OR PZ Editorial OR PT Enclyclopedia OR PZ Encyclopedia Entry OR PZ Interview OR PZ Letter OR PZ Obituary OR PZ Poetry OR “case control” OR "case report" OR “case reports” OR “case series” OR "comment on" OR “cross-sectional” OR “retrospective cohort” OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,120,371
S7	S5 NOT S6	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	6,788

Appendix B. Search Strategies

#	Query	Limiters/Expanders	Results
S8	DE "Tranquilizing Drugs" OR DE "Antidepressant Drugs" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Serotonin Reuptake Inhibitors" OR antidepressant* OR "antidepressives" OR "antidepressive agents" OR "antidepressive drug" OR "antidepressive drugs" OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR ssri OR ssris OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR snri* OR "TCA antidepressants" OR "tricyclic antidepressant" OR "tricyclic antidepressants" OR anafranil OR celexa OR DE "Citalopram" OR citalopram OR DE "Chlorimipramine" OR clomipramine OR duloxetine OR escitalopram OR DE "Fluoxetine" OR fluoxetine OR DE "Fluvoxamine" OR fluvoxamine OR DE "Ketamine" OR ketamine OR Lexapro OR lithium OR luvox OR DE "Sertraline" OR sertraline OR Zoloft	Search modes - Boolean/Phrase	71,843
S9	S1 AND S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	42,787
S10	DE "Behavior Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Counseling" OR DE "Community Counseling" OR DE "Cross Cultural Counseling" OR DE "Educational Counseling" OR DE "Group Counseling" OR DE "Microcounseling" OR DE "Psychotherapeutic Counseling" OR (TX integrated AND DE "Health Care Delivery") OR DE "Family Therapy" OR DE "Strategic Family Therapy" OR DE "Interpersonal Psychotherapy" OR DE "Mentalization" OR DE "Psychoeducation" OR DE "Structural Family Therapy" OR (DE "Parents" AND TX education) OR DE "Treatment Planning" OR DE "Caring Behaviors" OR DE "Problem Solving" OR DE "Psychotherapy" OR DE "Group Psychotherapy" OR DE "Self-Help Techniques" OR (behavior* AND (therap* or treatment* OR intervention*)) OR CBT OR (cognitive AND (therap* OR treatment* OR intervention*)) OR "care delivery" OR "care management" OR "collaborative care" OR "combination therapy" OR "combined modality" OR counsel* OR "delivery of care" OR "dialectical behavior therapy" OR "family therapy" OR "family support" OR interpersonal therap* OR interpersonal intervention* OR "means restriction" OR "means restrictions" OR "mentalization therapy" OR (parent* AND education) OR "problem solving" OR "psychoeducation" OR psychotherap* OR (risk* AND reduc*) OR "self help"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,084,659
S11	S1 AND S10	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	131,338
S12	S9 OR S11	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	157,878
S13	S12	Limiters - Publication Year: 2015-2020; English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	6,570

Appendix B. Search Strategies

#	Query	Limiters/Expanders	Results
S14	S13 NOT S6	Search modes - Boolean/Phrase	5,405
S15		Limiters - Methodology: - Systematic Review, META ANALYSIS, METASYNTHESIS Search modes - Boolean/Phrase	43,300
S16	S14 AND S15	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	165
S17	S14 NOT S16	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,240
S18	DE "Agoraphobia" OR DE "Anxiety" OR DE "Anxiety Disorders" OR DE "Generalized Anxiety Disorder" OR DE "Mutism" OR DE "Elective Mutism" OR DE "Obsessive Compulsive Disorder" OR DE "Panic Attack" OR DE "Panic Disorder" OR DE "Phobias" OR DE "Separation Anxiety" OR DE "Separation Anxiety Disorder" OR DE "Social Anxiety" OR DE "Social Phobia" OR DE "Trichotillomania" OR agoraphobia OR TI anxiety OR "generalized anxiety disorder" OR mutism OR "panic disorder" OR phobia* OR "separation anxiety disorder" OR "social anxiety disorder"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	147,222
S19	DE "Health Screening" OR DE "Screening Tests" OR screen OR screening OR screened OR screens OR "case finding" OR casefinding OR "Children's Manifest Anxiety Scale" OR "Multidimensional Anxiety Scale for Children" OR "Pediatric Anxiety Rating Scale" OR "Revised Children's Manifest Anxiety Scale" OR "Screen for Child Anxiety Related Disorders" OR "Spence's Children's Anxiety Scale" OR "State-Trait Anxiety Inventory for Children" OR "Youth Anxiety Measure for DSM-5" OR MASC OR "MASC-2 SR" OR MASC-10 OR PARS OR RCMAS OR SCARED OR SCAS OR SCAS-8 OR STAIC OR STAIC-S OR YAM-5	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	135,018
S20	S18 AND S19	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	9,564
S21	S20	Limiters - English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	3,977
S22	S21 NOT S6	Limiters - English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	3,377

Appendix B. Search Strategies

#	Query	Limiters/Expanders	Results
S23	S18 AND (S8 OR S10)	Search modes - Boolean/Phrase	62,758
S24	S23	Limiters - Publication Year: 2017-2020; English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	1,687
S25	S24 NOT S6	Search modes - Boolean/Phrase	1,434
S26	S25	Limiters - Methodology: - Systematic Review, META ANALYSIS, METASYNTHESIS Search modes - Boolean/Phrase	55
S27	S25 NOT S26	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,379
S28	DE "Attempted Suicide" OR DE "Head Banging" OR DE "Self-Inflicted Wounds" OR DE "Self-Injurious Behavior" OR DE "Self-Mutilation" OR DE "Self-Poisoning" OR DE "Suicidal Ideation" OR DE "Suicidality" OR DE "Suicide" OR parasuicid*:ti OR "self harm":ti OR suicid*:ti	Search modes - Boolean/Phrase	47,432
S29	DE "Health Screening" OR DE "Screening Tests" OR screen OR screening OR screened OR screens OR "case finding" OR casefinding OR "Adapted-SAD PERSONS" OR "Beck Hopelessness Scale" OR "Beck Scale for Suicide Ideation" OR "Center for Epidemiologic Studies-Depression Scale" OR "Child Suicide Assessment" OR "Columbia Suicide Severity Rating Scale" OR "Columbia Teen Screen" OR "Firestone Assessment of Self-Destructive Thoughts" OR "Harkavy Asnis Suicide Survey" OR "Inventory for Suicidal Ideation" OR "Multi-attitude Suicide Tendency Scale for Adolescents" OR "Paykel Suicide Items" OR "Positive and Negative Suicide Ideation Inventory" OR "Scale for Suicide Ideation" OR "Self-harm behavior questionnaire" OR "Suicide Behaviors Questionnaire" OR "Suicidal Ideation Questionnaire" OR "Suicidality Occurring in Paediatrics-Suicidality Assessment Scale" OR "Suicide Assessment Five-Step Evaluation and Triage" OR "Suicide Probability Scale" OR BSI OR CES-D OR CSA OR C-SSSR OR CTS OR HASS-II OR ISO-30 OR PANSI OR SSI OR SHBQ OR SBQ-14 OR SBQ-C OR SIQ OR SIQ-Junior OR STOP-SAS OR SAFE-T OR SPS OR SRS	Search modes - Boolean/Phrase	145,902
S30	S28 AND S29	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,110

Appendix B. Search Strategies

#	Query	Limiters/Expanders	Results
S31	S30	Limiters - Published Date: 20120601-20201231; English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	784
S32	S31 NOT S6	Limiters - Published Date: 20120601-20201231; English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	639
S33	S28 AND (S8 OR S10)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	21,608
S34	S33	Limiters - Published Date: 20120601-20201231; English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	2,063
S35	S34 NOT S6	Search modes - Boolean/Phrase	1,632
S36	S35	Limiters - Methodology: - Systematic Review, META ANALYSIS, METASYNTHESIS Search modes - Boolean/Phrase	39
S37	S35 NOT S36	Search modes - Boolean/Phrase	1,593
S38	"Pediatric Symptom Checklist-17" OR PSC OR "Revised Children's Anxiety and Depression Scale" OR RCADS OR RCADS-25 OR "Strength and Difficulties Questionnaires" OR SDQ	Search modes - Boolean/Phrase	2,378
S39	(S1 OR S18 OR S28) AND S38	Search modes - Boolean/Phrase	523

#	Query	Limiters/Expanders	Results
S40	S39	Limiters - English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	345
S41	S40 NOT S6	Search modes - Boolean/Phrase	281

Psychinfo

Suicide Risk: January 1, 2012, through April 30, 2020
Anxiety: NA
Depression: NA

#	Query	Limiters/Expanders	Results
S1	(MH "Suicide+") OR TI parasuicid*OR TI "self harm" OR (MH "Self-Injurious Behavior") OR TI suicid*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	38,801
S2		Limiters - Published Date: 20120601-20201231; English Language; Exclude MEDLINE records; Human; Age Groups: Infant, Newborn: birth-1 month, Infant: 1-23 months, Child, Preschool: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years; Language: English Search modes - Boolean/Phrase	150,128
S3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,855
S4	PT Biography OR PT Cartoon OR PT Commentary OR PT Directories OR PT Editorial OR PT Games OR PT Glossary OR PT Interview OR PT Legal Case OR PT Letter OR PT Obituary OR PT Poetry OR “comment on” OR “cross-sectional” OR “retrospective cohort” OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae	Search modes - Boolean/Phrase	1,348,371
S5	S3 NOT S4	Search modes - Boolean/Phrase	1,507

Appendix B. Search Strategies

#	Query	Limiters/Expanders	Results
S6	(MH "Health Screening") OR TI screen OR AB screen OR TI screening OR AB screening OR TI screened OR AB screened OR TI screens OR AB screens OR TI "case finding" OR AB "case finding" OR TI casefinding OR AB casefinding OR "Adapted-SAD PERSONS" OR "Beck Hopelessness Scale" OR "Beck Scale for Suicide Ideation" OR "Center for Epidemiologic Studies-Depression Scale" OR "Child Suicide Assessment" OR "Columbia Suicide Severity Rating Scale" OR "Columbia Teen Screen" OR "Firestone Assessment of Self-Destructive Thoughts" OR "Harkavy Asnis Suicide Survey" OR "Inventory for Suicidal Ideation" OR "Multi-attitude Suicide Tendency Scale for Adolescents" OR "Paykel Suicide Items" OR "Positive and Negative Suicide Ideation Inventory" OR "Scale for Suicide Ideation" OR "Self-harm behavior questionnaire" OR "Suicide Behaviors Questionnaire" OR "Suicidal Ideation Questionnaire" OR "Suicidality Occurring in Paediatrics-Suicidality Assessment Scale" OR "Suicide Assessment Five-Step Evaluation and Triage" OR "Suicide Probability Scale" OR TI BSI OR AB BSI OR TI CES-D OR AB CES-D OR TI CSA OR AB CSA OR TI C-SSSR OR AB C-SSSR OR TI CTS OR AB CTS OR TI HASS-II OR AB HASS-II OR TI ISO-30 OR AB ISO-30 OR TI PANSI OR AB PANSI OR TI SSI OR AB SSI OR TI SHBQ OR AB SHBQ OR TI SBQ-14 OR AB SBQ-14 OR TI SBQ-C OR AB SBQ-C OR TI SIQ OR AB SIQ OR TI SIQ-Junior OR AB SIQ-Junior OR TI STOP-SAS OR AB STOP-SAS OR TI SAFE-T OR AB SAFE-T OR TI SPS OR AB SPS OR TI SRS OR AB SRS	Search modes - Boolean/Phrase	212,836
S7	S5 AND S6	Search modes - Boolean/Phrase	163
S8	(MH "Antianxiety Agents+") OR (MH "Antidepressive Agents+") OR (MH "Serotonin Uptake Inhibitors+") OR (MH "Tranquilizing Agents+") OR TI antidepressant* OR AB antidepressant* OR TI antidepressives OR AB antidepressives OR TI "antidepressive agents" OR AB “antidepressive agents” OR TI "antidepressive drug" OR AB "antidepressive drug" OR "antidepressive drugs" OR "antidepressive drugs" OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR TI ssri OR AB ssri OR TI ssris OR AB ssris OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR snri* OR "TCA antidepressants" OR "tricyclic antidepressant" OR "tricyclic antidepressants" OR anafranil OR celexa OR citalopram OR clomipramine OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR ketamine OR Lexapro OR lithium OR luvox OR sertraline OR Zoloft	Search modes - Boolean/Phrase	71,793
S9	S5 AND S8	Search modes - Boolean/Phrase	44

Appendix B. Search Strategies

#	Query	Limiters/Expanders	Results
S10	(MH "Behavior Therapy+") OR (MH "Cognitive Therapy+") OR (MH "Combined Modality Therapy+") OR (MH "Counseling+") OR (MH "Health Care Delivery, Integrated") OR (MH "Family Therapy") OR (MH "Patient Care/AM/MT/NU/OG/ST") OR (MH "Problem Solving+") OR (MH "Psychotherapy+") OR (MH "Psychotherapy, Group+") OR (MH "Support Groups+") OR (behavior* AND (therap* or treatment* OR intervention*)) OR CBT OR (cognitive AND (therap* OR treatment* OR intervention*)) OR "care delivery" OR "care management" OR "collaborative care" OR "combination therapy" OR "combined modality" OR counsel* OR "delivery of care" OR "dialectical behavior therapy" OR "family therapy" OR "family support" OR interpersonal therap* OR interpersonal intervention* OR "means restriction" OR "means restrictions" OR "mentalization therapy" OR (parent* AND education) OR "problem solving" OR "psychoeducation" OR psychotherap* OR (risk* AND reduc*) OR "self help"	Search modes - Boolean/Phrase	777,586
S11	S5 AND S10	Search modes - Boolean/Phrase	590
S12	S9 OR S11	Search modes - Boolean/Phrase	616
S13	S12	Limiters - Publication Type: Meta Analysis, Meta Synthesis, Systematic Review Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	49
S14	S12 NOT S13	Search modes - Boolean/Phrase	567

Appendix C Table 1. Inclusion and Exclusion Criteria

Criteria	Include	Exclude
Condition definition	Major depressive disorder, as defined by DSM criteria (present in at least 50% of the enrolled study population) Anxiety disorders include generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, separation anxiety disorder, and selective mutism Definitions for increased risk of suicide may vary by study but may include suicidal ideation (suicidal thoughts or plan for suicide), history of suicide attempts (nonfatal, self-directed, and potentially injurious behavior that is intended to result in death), and deliberate self-harm Included studies may address these conditions individually or in combination	Other mental health disorders (e.g., obsessive compulsive disorder, posttraumatic stress disorder, psychotic disorders, bipolar disorder, cyclothymia, adjustment disorder with depressed mood), persistent depressive disorder/dysthymia, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, and depression not otherwise specified; substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition, and anxiety not otherwise specified
Population	**KQs 1–3:** Children and adolescents (mean age ≤18 years). Studies may include: • Unselected primary care population • Primary care patients without known depression, anxiety disorders, or increased risk of suicide (including deliberate self-harm) • Comparable community-based population **KQs 4, 5:** Children and adolescents (age ≤18 years) with major depressive disorder, anxiety disorders, or increased risk of suicide A priori priority populations of interest include by age (children vs. adolescents), race/ethnicity, sex, gender identity, and sexuality	• Adults (age ≥19 years) • Studies in which more than 50% of the population are age 19 years or older • Studies limited to populations that are not broadly generalizable to primary care populations (e.g., populations with mental health conditions other than anxiety, depression, and increased suicide risk); persons with treatment-resistant depression or anxiety; persons in residential, institutional, or inpatient settings; persons with developmental disorders (e.g., autism spectrum disorder, ADHD); persons in the midst of a suicidal crisis that are identified through their use of healthcare services related to a suicide attempt (e.g., in the emergency department); studies that require patients to have a specific clinical condition for enrollment (e.g., cancer, chronic illness, epilepsy)

Appendix C Table 1. Inclusion and Exclusion Criteria

Criteria	Include	Exclude
Interventions	**KQs 1–3:** Screening interventions with or without additional provider or patient-facing elements such as referral support, treatment guidelines, symptoms monitoring, and standardized treatment. Screening tools must be brief standardized instruments designed to identify persons with major depressive disorder, anxiety disorders, or an increased risk of suicide; self-report with or without parental report, clinician administered, or electronically delivered (<5 minutes if clinician administered, <15 minutes if self-administered) instruments are eligible **KQs 4, 5 (depression and suicide):** • Counseling (e.g., psychotherapy, psychoeducation, suicide means restriction) • Care delivery models targeting improved mental health outcomes (e.g., collaborative care, care management) • Pharmacotherapy agents approved for pediatric use (e.g., duloxetine, fluoxetine, escitalopram, sertraline, fluvoxamine), generally first-line • Include combination therapies **KQs 4, 5 (anxiety):** • Cognitive behavioral therapy (including exposure therapy)* • Include eligible psychotherapy studies regardless of mode of intervention • Pharmacotherapy agents approved for pediatric use (e.g., clonidine, duloxetine, fluoxetine, escitalopram, sertraline, fluvoxamine), generally first-line • Include combination therapies	**KQs 1–3:** Studies reporting on a screening instrument that does not have established validity and scoring mechanism or thresholds for use within clinical practice **KQs 4, 5 (all disorders):** Other treatment modalities (e.g., exercise, light therapy, transcranial magnetic nerve stimulation, electroshock treatment, diet and herbal supplements such as St. John's wort and other complementary and alternative medicine, social marketing, policy, system-level interventions, or adjunctive agents to enhance the effects of antidepressants) Interventions involving components that could not be replicated in most healthcare settings, including environmental components (media messages, public signage), interventions on groups in closed (preexisting) social networks (e.g., in daycares, schools), or those requiring the parent to have the target condition Pharmacotherapeutic agents that are not FDA approved for pediatric use (e.g., paroxetine, vortioxetine) **KQs 4, 5 (anxiety):** Psychotherapy other than cognitive behavioral therapy
Comparators	**KQs 1, 3 (screening):** Usual care/no screening **KQ 2 (depression and anxiety):** Clinical diagnosis based on structured clinical interview by qualified professional using standard diagnostic criteria in place at the time of the study (e.g., *DSM-IV* or *DSM-5*) **KQ 2 (suicide):** Assessment of increased suicide risk based on clinical interview by qualified professional **KQs 4, 5 (psychotherapy and care delivery):** • No intervention • Wait-list control (i.e., delayed treatment) • Attention control (i.e., receives interpersonal interaction but no other elements of the active intervention) • Usual care (e.g., referral to treatment, non-standardized treatment, or unclear treatment services) **KQs 4, 5 (suicide risk only):** Treatment as usual (the provision of standard treatment services not governed by a study protocol, but at a duration and level of intensity consistent with active treatment interventions) are also eligible **KQs 4, 5 (pharmacotherapy):** Placebo (including placebo along with psychotherapy, when compared with the active agent plus the same psychotherapy intervention (e.g., CBT plus placebo vs. CBT plus medication would be eligible)	**KQs 1, 3:** No comparator **KQ 2:** Another screening instrument, non-standardized clinical diagnosis (i.e., diagnosis not made based on existing *DSM* criteria at the time of the study) **KQs 4, 5:** No comparator, active intervention (i.e., comparative effectiveness) (e.g., medication X vs. medication Y would not be eligible. CBT plus medication X vs. CBT plus medication Y would not be eligible) **KQ 4, 5 (anxiety and depression):** Treatment as usual comparator groups where the comparator group receives standard treatment services that involve a reasonably standardized active intervention provided outside of a study protocol are not eligible

Appendix C Table 1. Inclusion and Exclusion Criteria

Criteria	Include	Exclude
Outcomes	**KQs 1, 4:** • Depression or anxiety symptoms, remission or diagnosis, or response • Suicide deaths, suicide attempts and deliberate self-harm, or suicidal ideation • All-cause mortality • Quality of life measured using validated scales or instruments • Functioning (using validated scales or instruments, days of missed school) **KQ 2:** • Sensitivity, specificity, or data to calculate one or both • Negative predictive value, positive predictive value, area under the curve/ area under the receiver operating characteristic/receiver operating characteristic, diagnostic odds/likelihood ratios, Youden's index **KQ 3:** • False alarm • False reassurance **KQs 3, 5:** • Treatment avoidance • Deterioration in patient-provider relationship • Labeling or stigma • Inappropriate/unnecessary treatment **KQ 5 (pharmacotherapy only):** • Serious adverse effects • Withdrawals due to adverse effects • Suicidality	**All KQs:** All other outcomes
Outcome assessment timing	No minimum followup	Not applicable
Setting	**KQs 1–3:** Recruitment of participants from: • Primary care settings (e.g., pediatrics, family medicine, or school-based health clinics) • Virtual or community settings such as schools, if population comparable to general primary care (i.e., focus on "healthy" children or adolescents, or broad spectrum of medical and mental health conditions in rates comparable to primary care setting)† • General emergency departments **KQs 4, 5:** Treatment in: • Primary care or specialty clinics, including school-based health clinics • Virtual or community-based settings • General EDs are eligible for recruitment of patients to an intervention; however, interventions delivered solely/entirely within an ED setting are not eligible	**KQ 1:** Studies conducting school-wide or community-wide screening are not eligible. **KQs 1–3:** • Referred or established patients at mental health clinics • Inpatient/residential facilities • Correctional facilities • Psychiatric emergency departments **KQs 4, 5:** Treatment in: • Correctional facilities • Schools involving school-wide interventions • Inpatient/residential facilities • Psychiatric emergency departments

Appendix C Table 1. Inclusion and Exclusion Criteria

Criteria	Include	Exclude
Study design	**KQs 1, 3:** RCTs, CCTs **KQ 2:** Studies of diagnostic test accuracy‡ **KQ 3:** RCTs, CCTs, observational studies **KQ 4:** RCTs **KQ 5:** • RCTs • Systematic reviews of comparative cohort and case-control observational studies • Harms of pharmacotherapy only: large (>1,000 participants) comparative cohort and case-control observational studies published after identified systematic reviews that include observational studies	All other study designs **KQ 2:** Psychometric development and internal (e.g., split sample) validation studies of new instruments; case-control studies (i.e., designs that limit the study sample to only those with and without known mental health symptoms) **KQs 1–4:** Systematic reviews of RCTs *(reviews will only be used to identify relevant studies)*
Study geography	Primary studies that primarily take place in countries categorized as "Very High" on the 2019 Human Development Index (as defined by the United Nations Development Programme)	Reviews in which >50% of included studies take place in countries not categorized as "Very High" on the Human Development Index
Publication language	English	Any language other than English
Quality rating	Fair- or good-quality studies	Poor-quality studies

* We summarized the effect of other non-CBT interventions for anxiety as a contextual question, using a best-evidence approach.
† We intended to restrict inclusion of school-based recruitment to studies conducting the screening in other settings (e.g., mental health clinics) but on review of studies, elected to include all studies using a school-based recruitment because of the difficulty of ascertaining the location of screening in some studies.
‡ We cataloged all studies reporting on instruments that otherwise meet all eligibility criteria, but our synthesis will focus on the instruments that are reported in more than one study.

Abbreviations: ADHD=attention deficit hyperactivity disorder; AUC=area under the curve; AUROC=area under the receiver operating characteristic; CBT=cognitive behavioral therapy; CCT=controlled, clinical trial; DSM=Diagnostic and Statistical Manual of Mental Disorders; ED=emergency department; FDA=U.S. Food and Drug Administration; KQ=key question; NPV=negative predictive value; PPV=positive predictive value; RCT=randomized, controlled trial; ROC=receiver operating characteristic.

Randomized, Controlled Trials and Cohort Studies

Criteria

- Initial assembly of comparable groups
- Randomized, controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements that are equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is lacking for RCTs.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Sources: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force, 2015;[61] Harris et al, 2001.[62]

Systematic Reviews

Criteria

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of Ratings Based on Above Criteria

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

Sources: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force, 2015;[61] Harris et al, 2001.[62]

Appendix D Table 1. Individual Study Quality Assessment of Harms of Screening Studies Based on Cochrane RoB 2.0 (KQ 3)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Harms	Harms Comments
Gould et al, 2005[63]	Some concerns	Low	Low	Low	Some concerns	Some concerns	Method of randomization not reported, minimal baseline characteristics reported to assess adequacy of randomization; no trial registration or study protocol cited to determine whether analysis conducted was prespecified.
Robinson et al, 2011[64]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns	No baseline characteristics provided to assess adequacy of randomization; between 20% and 40% of students had missing data and unclear how missing data are related to outcome of distress; no trial registration or evidence of a prespecified analysis plan.

Appendix D Table 2. Individual Study Quality Assessment of Treatment Studies Based on Cochrane RoB 2.0 (KQ 4 & KQ 5)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Efficacy	Efficacy Comments	Harms RoB	Harms Comments
Arendt et al, 2016[65]	Low	Some concerns	Low	Low	Low	Some concerns	No blinding possible.	Not Applicable	
Asarnow et al, 2017[66]	Low	Low	Some concerns	Low	Some concerns	Some concerns	Some differential attrition but reasonable sensitivity analyses conducted to demonstrate likely not a major concern; pilot study without clearly specified primary outcome or timepoint with multiple analyses conducted.	Not Applicable	
Asbrand et al, 2020[67]	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns	Wait-list control so participants and interventionists were not masked and PROs were used.	Not Applicable	
Atkinson et al, 2014[68]	Low	Low	High	Low	Low	High	High and differential attrition.	High	High and differential attrition
Baer et al, 2005[69]	High	High	Low	High	Low	High		Not Applicable	
Barrett et al, 1996[70]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	Potential for bias from attrition.	Not Applicable	
Barrett et al, 1998[71]	Some concerns	High	Low	Low	Low	High		Not Applicable	
Beidel et al, 2007[72]	Some concerns	High	High	High	Low	High		Not Applicable	
Birmaher et al, 2003[73]	Some concerns	Some concerns	Some concerns	Some concerns	Low	Some concerns	Differential attrition for side effects (disinhibition), potentially risking effective unmasking during outcome assessment, but the study notes that participants and staff had the same rate of accurate guesses of treatment across all arms.	Some concerns	
Black et al, 1994[74]	Some concerns	Low	Low	Some concerns	Low	Some concerns		Not Applicable	
Brent et al, 1997[49]	Some concerns	High	High	High	Low	High	No patient or provider blinding, unknown outcome assessor blinding, high attrition, several in the study should have been ineligible.	High	High and possibly differential attrition, unblinded outcome assessors, participants and clinicians not blinded

Appendix D Table 2. Individual Study Quality Assessment of Treatment Studies Based on Cochrane RoB 2.0 (KQ 4 & KQ 5)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Efficacy	Efficacy Comments	Harms RoB	Harms Comments
Clarke et al, 2016[75]	Some concerns	Some concerns	Low	Low	Low	Some concerns	Patient and provider not blinded; patients, parents, and clinical personnel awareness of treatment could influence outcomes.	Some concerns	
Clarke et al, 2005[76]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	No allocation concealment and patients and providers not blinded.	Not Applicable	
Clarke et al, 1999[45]	Some concerns	Some concerns	High	Some concerns	Low	Some concerns	Randomization and allocation concealment not reported; patients not blinded, awareness of intervention could influence outcomes; high attrition and unknown differential attrition.	Not Applicable	Moderate attrition, no details on randomization or allocation concealment or blinding, awareness of intervention could influence outcomes
Cobham et al, 2017[77]	Some concerns	Low	Low	Low	Low	Some concerns		Not Applicable	
Cobham et al, 2012[78]	High	Some concerns	Low	Low	Some concerns	High	No allocation concealment.	Not Applicable	
Cornacchio et al, 2019[79]	Low	Some concerns	Low	Low	Low	Some concerns	Participants and therapists aware of treatment status.	Not Applicable	
Cottrell et al, 2018[80]	Low	Low	Low	Low	Low	Low		Not Applicable	
Diamond et al, 2002[81]	Some concerns	Some concerns	Low	Some concerns	High	High	Awareness of intervention could influence outcomes.	High	
Diamond et al, 2010[82]	Low	Low	Low	Some concerns	Low	Some concerns	Outcome assessors not masked but administered PROs, not clinical interviews. Masking of intervention to patients and caregivers not feasible.	Not Applicable	
Donovan et al, 2014[83]	Low	Some concerns	High	Low	Low	Some concerns	Some concerns for all outcomes other than PAS, high ROB for PAS.	Not Applicable	
Ehrenreich-May et al, 2017[84]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns	No information about randomization or allocation concealment; masking of participants and outcome assessment of PROs not feasible and wait-list control	Not Applicable	

Appendix D Table 2. Individual Study Quality Assessment of Treatment Studies Based on Cochrane RoB 2.0 (KQ 4 & KQ 5)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Efficacy	Efficacy Comments	Harms RoB	Harms Comments
							group, no prespecified analysis plan.		
Emslie et al, 2014[85]	Low	Low	Some concerns	Low	Low	High	High and differential attrition.	High	High and differential attrition
Emslie et al, 2009[86]	Some concerns	Low	Low	Low	Low	Some concerns	Awareness of the intervention could influence outcomes. No allocation concealment and patients and providers not blinded.	Not Applicable	
Emslie et al, 2002[87]	Some concerns	Low	High	Low	Low	High	High and differential attrition with LOCF for ITT without further investigation, no sensitivity analysis. Possible imbalance at baseline.	Not Applicable	
Emslie et al, 1997[88]	Some concerns	Low	High	Some concerns	Low	High	High and differential attrition.	High	High and differential attrition
Flannery-Schroeder et al, 2000[89]	Some concerns	High	Low	High	Low	High		Not Applicable	
Fristad et al, 2019[90]	Low	Some concerns	Low	Low	Low	Some concerns	Therapy not masked.	Low	
Gallagher et al, 2004[91]	Some concerns	High	Some concerns	High	Low	High		Not Applicable	
Ginsburg et al, 2020[92]	Low	Low	Some concerns	Low	Some concerns	Some concerns	Nearly a quarter of data was missing at post treatment for some measures, imputed; no prespecified analysis plan.	Not Applicable	
Green et al, 2011[93]	Low	Low	Low	Low	Low	Low	Masking of intervention to participants and caregivers not feasible.	Not Applicable	
Griffiths et al, 2019[94]	Low	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns for ED presentation for self-harm outcome; high concerns for all other outcomes because of >50% missing data at post treatment and beyond.	High	5 AEs reported but no description of the events, only that they weren't related to the study. Also not reported by group.
Hancock et al, 2018[41]	Low	Some concerns	High	Low	Low	High	Differential attrition that likely influenced the results.	Not Applicable	
Hazell et al, 2009[95]	Low	Low	Low	Low	Low	Low	Masking of intervention to patients and caregivers not feasible.	Not Applicable	

Appendix D Table 2. Individual Study Quality Assessment of Treatment Studies Based on Cochrane RoB 2.0 (KQ 4 & KQ 5)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Efficacy	Efficacy Comments	Harms RoB	Harms Comments
Hetrick et al, 2017[96]	Low	Low	High	Low	Low	High	High concerns from differential and high attrition with no analysis of impact of missing data.	Not Applicable	
Hill et al, 2019[97]	Low	Low	Low	Low	Some concerns	Low		Not Applicable	
Hirshfeld-Becker et al, 2010[98]	Low	Some concerns	Some concerns	Low	Low	Some concerns		Not Applicable	
Holmes et al, 2014[99]	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns		Not Applicable	
Hooven et al, 2012[100]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	No information about randomization, allocation concealment and minimal information about baseline characteristics; masking of caregivers not feasible and mostly PROs used, unclear whether some measures used are valid and reliable; attrition not reported by group; no prespecified analysis plan.	High	
Infantino et al, 2016[101]	Some concerns	High	Low	High	Low	High		Not Applicable	
Ingul et al, 2014[102]	Low	Low	High	Low	Low	High	High attrition.	Not Applicable	
Ishikawa et al, 2019[103]	Low	Some concerns	Low	Low	Low	Some concerns	Some concerns due to fact that assignment to treatment is not masked.	Not Applicable	
Kendall et al, 1997[104]	Some concerns	High	High	High	Low	High		Not Applicable	
Kendall et al, 1994[105]	Some concerns	High	Some concerns	High	Low	High		Not Applicable	
Khanna et al, 2010[106]	High	High	Low	High	Low	High		Not Applicable	
King et al, 2015[107]	Some concerns	Low	Low	Low	Some concerns	Some concerns	Some concerns because method of randomization not reported, unclear whether allocation concealment was adequate, minimal baseline characteristics presented to judge adequacy of	Not Applicable	

Appendix D Table 2. Individual Study Quality Assessment of Treatment Studies Based on Cochrane RoB 2.0 (KQ 4 & KQ 5)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Efficacy	Efficacy Comments	Harms RoB	Harms Comments
							randomization, no prespecified analysis plan.		
King et al, 2009[108]	Low	Low	Some concerns	Low	Low	Some concerns	Modest attrition, unclear masking of participants and interventionists.	Not Applicable	
Last et al, 1998[109]	Some concerns	High	High	High	Low	High		Not Applicable	
Lau et al, 2010[110]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns		Not Applicable	
Luby et al, 2018[111]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns	Wait-list control prevented masking of participants and interventionists and PROs used; no prespecified analysis plan.	Not Applicable	
Lyneham et al, 2006[112]	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns		Not Applicable	
March et al, 2004[113]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	High attrition, unclear allocation status, no patient blinding in some groups.	Some concerns	High attrition but no differential attrition, no specified outcome blinding or patient/intervention provider blinding reported.
March et al, 2009[114]	Some concerns	High	Low	High	Low	High		Not Applicable	
Mehlum et al, 2014[115]	Low	Low	Low	Low	Low	Low		Not Applicable	
Melfsen et al, 2011[116]	Some concerns	High	High	High	Low	High		Not Applicable	
Mufson et al, 1999[117]	Some concerns	Some concerns	High	Low	Low	High	Not blinded, high attrition, very large differential attrition.	High	High and differential attrition, awareness of intervention could influence outcomes
Mufson et al, 2004[118]	Low	Low	Low	Low	Some concerns	Some concerns	No prespecified analysis plan.	Not Applicable	
Nauta et al, 2003[119]	High	Some concerns	Low	Some concerns	Some concerns	High	Did not follow an accepted strategy for randomization and allocation concealment, excluded some participants from being assigned to wait-list condition and baseline imbalances between the two	Not Applicable	

Appendix D Table 2. Individual Study Quality Assessment of Treatment Studies Based on Cochrane RoB 2.0 (KQ 4 & KQ 5)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Efficacy	Efficacy Comments	Harms RoB	Harms Comments
							active treatment groups, masking not feasible and use of PROs, no information about whether clinical outcome assessors were masked, no prespecified analysis plan.		
Öst et al, 2015[120]	Low	Low	Some concerns	Some concerns	Low	Some concerns		Not Applicable	
Ougrin et al, 2013[121]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Masking of clinicians not feasible, allocation concealment not possible and unclear whether clinicians were involved in recruitment; long term outcomes not part of original trial analysis plan.	Not Applicable	
Perrin et al, 2019[122]	Low	Low	Low	Some concerns	Low	Some concerns		Not Applicable	
Pincus et al, 2010[123]	High	Some concerns	Low	Some concerns	Some concerns	High	Potential for randomization issues.	Not Applicable	
Pine et al, 2001[124]	Some concerns	Low	Some concerns	Low	Low	Some concerns	Potential for attrition bias.	Some concerns	
Pineda et al, 2013[125]	Low	Some concerns	Low	Low	Low	Some concerns	Masking not feasible.	Not Applicable	
Rapee et al, 2006[126]	Some concerns	High	High	High	Low	High		Not Applicable	
Richardson et al, 2014[127]	Low	Low	Low	Low	Low	Low		Low	
Rossello et al, 1999[44]	Some concerns	Some concerns	High	High	Some concerns	High	No ITT analyses conducted; randomization method not reported; blinding of assessors not reported; no group differences reported at baseline other than for outcomes so do not know how groups may have differed on sociodemographic characteristics, etc., and analyses were not adjusted. High and differential attrition.	Not Applicable	
Rossouw et al, 2012[128]	Low	Some concerns	Low	Low	Low	Some concerns	Treatment not masked (not feasible).	Some concerns	Treatment not masked (not feasible).

Appendix D Table 2. Individual Study Quality Assessment of Treatment Studies Based on Cochrane RoB 2.0 (KQ 4 & KQ 5)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Efficacy	Efficacy Comments	Harms RoB	Harms Comments
Rudy et al, 2017[129]	Some concerns	Low	Low	Low	Some concerns	Some concerns	No information about method of randomization and allocation concealment and some imbalances at baseline that may be due to small sample size; no prespecified analysis plan.	Not Applicable	
Rynn et al, 2001[130]	Some concerns	Low	Low	Low	Low	Some concerns		Not Applicable	
Salzer et al, 2018[42]	Low	Some concerns	Some concerns	Low	Low	Some concerns	High attrition and inability to blind participants or therapists.	Low	
Sánchez-García et al, 2009[131]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns	Insufficient information to rate most domains.	Not Applicable	
Santucci et al, 2013[132]	Low	High	Low	High	Some concerns	High		Not Applicable	
Schneider et al, 2011[133]	Some concerns	High	Low	High	Low	High		Not Applicable	
Pineda et al, 2013[125]	Low	Some concerns	Low	Low	Low	Some concerns	Masking not feasible.	Not Applicable	
Rapee et al, 2006[126]	Some concerns	High	High	High	Low	High		Not Applicable	
Richardson et al, 2014[127]	Low	Low	Low	Low	Low	Low		Low	
Rossello et al, 1999[44]	Some concerns	Some concerns	High	High	Some concerns	High	No ITT analyses conducted; randomization method not reported; blinding of assessors not reported; no group differences reported at baseline other than for outcomes so do not know how groups may have differed on sociodemographic characteristics, etc., and analyses were not adjusted. High and differential attrition.	Not Applicable	
Rossouw et al, 2012[128]	Low	Some concerns	Low	Low	Low	Some concerns	Treatment not masked (not feasible).	Some concerns	Treatment not masked (not feasible).
Rudy et al, 2017[129]	Some concerns	Low	Low	Low	Some concerns	Some concerns	No information about method of randomization and allocation concealment and	Not Applicable	

Appendix D Table 2. Individual Study Quality Assessment of Treatment Studies Based on Cochrane RoB 2.0 (KQ 4 & KQ 5)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Efficacy	Efficacy Comments	Harms RoB	Harms Comments
							some imbalances at baseline that may be due to small sample size; no prespecified analysis plan.		
Rynn et al, 2001[130]	Some concerns	Low	Low	Low	Low	Some concerns		Not Applicable	
Salzer et al, 2018[42]	Low	Some concerns	Some concerns	Low	Low	Some concerns	High attrition and inability to blind participants or therapists.	Low	
Sánchez-García et al, 2009[131]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns	Insufficient information to rate most domains.	Not Applicable	
Santucci et al, 2013[132]	Low	High	Low	High	Some concerns	High		Not Applicable	
Schneider et al, 2011[133]	Some concerns	High	Low	High	Low	High		Not Applicable	
Rynn et al, 2001[130]	Some concerns	Low	Low	Low	Low	Some concerns		Not Applicable	
Salzer et al, 2018[42]	Low	Some concerns	Some concerns	Low	Low	Some concerns	High attrition and inability to blind participants or therapists.	Low	
Sánchez-García et al, 2009[131]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns	Insufficient information to rate most domains.	Not Applicable	
Santucci et al, 2013[132]	Low	High	Low	High	Some concerns	High		Not Applicable	
Schneider et al, 2011[133]	Some concerns	High	Low	High	Low	High		Not Applicable	
Shortt et al, 2001[134]	Some concerns	Low	Low	Some concerns	Low	Some concerns	No information on randomization and blinding of outcome assessors.	Some concerns	
Silverman et al, 1999[135]	Some concerns	Some concerns	High	Low	Low	High	Potential for attrition bias.	Not Applicable	
Smith et al, 2014[136]	Some concerns	Some concerns	High	Low	Low	High	Potential for attrition bias.	Not Applicable	
Spence et al, 2017[137]	Some concerns	High	Some concerns	High	Some concerns	High		Not Applicable	
Spence et al, 2006[138]	Some concerns	High	Low	High	Low	High		Not Applicable	
Spence et al, 2000[139]	Low	High	Low	High	Low	High		Not Applicable	
Spence et al, 2011[140]	Some concerns	High	High	High	Low	High		Not Applicable	

Appendix D Table 2. Individual Study Quality Assessment of Treatment Studies Based on Cochrane RoB 2.0 (KQ 4 & KQ 5)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Efficacy	Efficacy Comments	Harms RoB	Harms Comments
Stjerneklar et al, 2019[141]	Low	Some concerns	Low	Low	Low	Some concerns	Wait list control and no masking. Nothing reported on masking of assessors. However, in the discussion it does say that the masking of assessors was broken.	Not Applicable	
Strawn et al, 2015[142]	Low	Low	Some concerns	Low	Low	Some concerns	77% attrition, ITT analyses performed.	Some concerns	
Strawn et al, 2020[143]	Low	Low	Some concerns	Low	Low	Some concerns		Low	
Tang et al, 2009[144]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns	Methods of randomization and allocation concealment not reported, no information about how many participants were analyzed or missing data; no prespecified analysis plan.	Not Applicable	
Thirlwall et al, 2013[145]	Low	Some concerns	Some concerns	Low	Low	Some concerns	Differential attrition, but sensitivity analyses suggest no difference.	Not Applicable	
Tillfors et al, 2011[146]	Some concerns	Some concerns	High	Some concerns	Low	High	Potential for differential attrition, lack of information on randomization, allocation concealment, and blinding.	Not Applicable	
Topooco et al, 2018[147]	Some concerns	Low	Low	Some concerns	Low	Some concerns	Risk of bias of outcome measurements showed some concern.	Low	
Topooco et al, 2019[148]	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns for assignment to intervention and some concerns for measurement of outcome.	Low	
Vigerland et al, 2016[149]	Some concerns	High	Low	High	Low	High		Not Applicable	
Villabø et al, 2018[150]	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns	Youth and therapists aware of assignment; no information regarding whether trial analyzed in accordance with prespecified plan; no information about trial registry.	Not Applicable	
Wagner et al, 2006[151]	Some concerns	Some concerns	High	Some concerns	Low	Some concerns	High attrition but no differential attrition, no specified outcome blinding or patient/intervention provider blinding reported.	Some concerns	High overall attrition.

Appendix D Table 2. Individual Study Quality Assessment of Treatment Studies Based on Cochrane RoB 2.0 (KQ 4 & KQ 5)

Author, Year	Domain 1 RoB	Domain 2 RoB	Domain 3 RoB	Domain 4 RoB	Domain 5 RoB	Overall RoB Efficacy	Efficacy Comments	Harms RoB	Harms Comments
Waite et al, 2019[152]	Some concerns	Some concerns	Some concerns	Some concerns	Low	Some concerns	Wait-list and no masking and missing data.	Low	
Walkup et al, 2008[153]	Low	Some concerns	Low	Low	Low	Some concerns	Participants assigned to combined sertraline and CBT were aware of their sertraline assignment.	Some Concerns	Participants assigned to combined sertraline and CBT were aware of their sertraline assignment
Warner et al, 2011[154]	Some concerns	High	Low	High	Low	High		Not Applicable	
Waters et al, 2009[155]	Some concerns	Some concerns	High	Low	Low	High		Not Applicable	
Weersing et al, 2017[156]	Some concerns	Some concerns	Some concerns	Some concerns	Low	Some concerns	Masking of intervention not feasible. Potential for bias from differential attrition and issues with blinding in outcome assessment.	Not Applicable	
Weihs et al, 2018[157]	Some concerns	Low	Some concerns	Some concerns	Low	High	Unclear methods of randomization and allocation concealment, how ITT was done, whether outcome assessors were blinded.	Some concerns	Unclear methods of randomization and allocation concealment, how ITT was done, whether outcome assessors were blinded.
Wergeland et al, 2014[158]	Some concerns	High	Low	High	Low	High	Potential for bias in randomization and outcome assessment.	Not Applicable	
Wood et al, 2001[159]	Low	Low	Low	Low	Low	Low	No information on missing data or how it was handled.	Not Applicable	
Wuthrich et al, 2012[160]	Some concerns	High	Low	High	Low	High		Not Applicable	

Abbreviations: AE=adverse event; CBT=cognitive behavioral therapy; ED=emergency department; ITT=intent to treat; LOCF=last observation carried forward; PAS=Preschool Anxiety Scale; PRO=patient-reported outcome; ROB\RoB=risk of bias.

Appendix D Table 3. Individual Study Quality Assessment of Meta-Analysis on the Risk of Bias Assessment Tool for Systematic Reviews (ROBIS)

Author Year	Study Eligibility Concern	Identification and Selection of Studies Concern	Data Collection and Study Appraisal Concern	Synthesis and Findings Concern	Risk of Bias
Cipriani et al, 2016[161]	Low	Low	Low	Low	Low

Abbreviations: ROBIS=Risk of Bias Assessment Tool for Systematic Reviews.

Appendix D Table 4. Individual Study Quality Assessment of Diagnostic Accuracy Studies Based on the QUADAS-2 Tool Part 1

Author Year	Did the study adequately describe methods of patient selection?	Did the study describe the index test and describe how it was conducted and interpreted?	Did the study describe the reference standard and how it was conducted and interpreted?	Did the study describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table?	Did the study describe included patients (prior testing, presentation, use of index test and setting)?	Did the study describe the time interval and any interventions between index test(s) and reference standard?
Bailey et al, 2006[21]	Yes	Yes	Yes	Yes	Yes	No
Canals et al, 2001[17]	Yes	Yes	Yes	No	Yes	Yes
Canals et al, 2012[162]	Yes	Yes	Yes	Yes	Yes	Yes
Christensen et al, 2015[15]	Yes	Yes	Yes	Yes	Yes	Yes
Cunha et al, 2008[163]	Yes	Yes	Yes	Yes	Yes	Unclear
Garcia-Lopez et al, 2015[164]	Yes	Yes	Yes	Yes	Yes	No
Gardner et al, 2007[165]	Yes	Yes	Yes	Unclear	Yes	Yes
Hopper et al, 2012[166]	Yes	Yes	Yes	Yes	Yes	No
Johnson et al, 2002[13]	Yes	Yes	Yes	Yes	Yes	Yes
Johnson et al, 2006[167]	Yes	Yes	Yes	No	Yes	Yes
Katon et al, 2008[168]	Yes	Yes	Yes	Yes	Yes	Yes
Muris et al, 2001[169]	Yes	Yes	Yes	No	Yes	Yes
O'Connor et al, 2016[14]	Yes	Yes	Yes	No	Yes	Yes
Patton et al, 1999[19]	Yes	Yes	Yes	No	Yes	No
Queen et al, 2012[23]	Yes	Yes	Yes	Yes	Yes	Yes
Ranta et al, 2007[170]	Yes	Yes	Yes	Unclear	Yes	Yes
Ranta et al, 2012[171]	Yes	Yes	Yes	Yes	Yes	Yes
Rivera-Riquelme et al, 2019[172]	Yes	Yes	Unclear	Unclear	Yes	Yes
Roberts et al, 1991[16]	Yes	Yes	Yes	Yes	Yes	Yes
Thompson et al, 1999[24]	Yes	Yes	Yes	No	Yes	No
Tsai et al, 2009[173]	Yes	Yes	Yes	Yes	Yes	Yes
Patton et al, 1999[19]	Yes	Yes	Yes	No	Yes	Yes

Abbreviations: QUADAS-2=Quality Assessment of Diagnostic Accuracy Studies.

Appendix D Table 5. Individual Study Quality Assessment of Diagnostic Accuracy Studies Based on the QUADAS-2 Tool Part 2

Author Year	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?	Was a case-control design avoided?	If a threshold was used, was it prespecified?
Bailey et al, 2006[21]	Yes	Unclear	Yes	Unclear	Yes	No
Canals et al, 2001[17]	Yes	Yes	Yes	Yes	Yes	No
Canals et al, 2012[162]	No	Yes	Yes	Yes	Unclear	Yes
Christensen et al, 2015[15]	Yes	Yes	Yes	Yes	Yes	No
Cunha et al, 2008[163]	Unclear	Yes	Yes	Unclear	Yes	No
Garcia-Lopez et al, 2015[164]	No	Unclear	Yes	Unclear	Yes	No
Gardner et al, 2007[165]	No	Yes	Yes	Yes	Yes	Yes
Hopper et al, 2012[166]	Yes	Yes	Yes	Unclear	Yes	No
Johnson et al, 2002[13]	Yes	No	Yes	Yes	Yes	No
Johnson et al, 2006[167]	Yes	Unclear	Unclear	Yes	Yes	Yes
Katon et al, 2008[168]	Yes	Yes	Yes	Yes	Yes	Yes
Muris et al, 2001[169]	No	Unclear	Yes	Yes	Yes	Yes
O'Connor et al, 2016[14]	Yes	No	Unclear	Yes	Yes	No
Patton et al, 1999[19]	Yes	Yes	Yes	Unclear	Yes	Unclear
Queen et al, 2012[23]	Yes	Unclear	Yes	Yes	Yes	No
Ranta et al, 2007[170]	Yes	Yes	Yes	Yes	Yes	Yes
Ranta et al, 2012[171]	Yes	Unclear	Yes	Yes	Yes	Yes
Rivera-Riquelme et al, 2019[172]	Yes	Yes	Yes	Yes	Yes	Yes
Roberts et al, 1991[16]	Unclear	Yes	Yes	Unclear	Yes	No
Thompson et al, 1999[24]	Yes	Yes	Yes	Unclear	Yes	Unclear
Tsai et al, 2009[173]	Yes	Unclear	Yes	Yes	Yes	Unclear
Patton et al, 1999[19]	Yes	Yes	Unclear	Yes	Yes	Unclear

Abbreviations: QUADAS-2=Quality Assessment of Diagnostic Accuracy Studies.

Appendix D Table 6. Individual Study Quality Assessment of Diagnostic Accuracy Studies Based on the QUADAS-2 Tool Part 3

Author Year	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?	Did the study avoid inappropriate exclusions?	Did all patients receive the same reference standard?	Were all patients included in the analysis?
Bailey et al, 2006[21]	Unclear	Yes	Yes	Yes	Yes
Canals et al, 2001[17]	Yes	No	Yes	Yes	No
Canals et al, 2012[162]	Yes	Yes	Unclear	Yes	Yes
Christensen et al, 2015[15]	Yes	Yes	Yes	Yes	Unclear
Cunha et al, 2008[163]	Yes	Yes	No	Yes	Yes
Garcia-Lopez et al, 2015[164]	Unclear	Yes	Yes	Yes	Yes
Gardner et al, 2007[165]	Yes	No	No	Yes	No
Hopper et al, 2012[166]	Yes	No	Yes	Yes	No
Johnson et al, 2002[13]	No	Yes	Yes	Yes	No
Johnson et al, 2006[167]	No	No	Yes	No	No
Katon et al, 2008[168]	Yes	Yes	Yes	Yes	No
Muris et al, 2001[169]	Unclear	Yes	No	Yes	Yes
O'Connor et al, 2016[14]	No	Yes	Yes	Yes	Yes
Patton et al, 1999[19]	Unclear	No	Yes	Yes	No
Queen et al, 2012[23]	Unclear	Yes	Yes	Yes	Yes
Ranta et al, 2007[170]	Yes	No	Yes	Yes	No
Ranta et al, 2012[171]	Unclear	Yes	Yes	Yes	Yes
Rivera-Riquelme et al, 2019[172]	Yes	No	Yes	Yes	No
Roberts et al, 1991[16]	Yes	Yes	Yes	Yes	Yes
Thompson et al, 1999[24]	Unclear	No	Yes	Yes	No
Tsai et al, 2009[173]	Unclear	Yes	Yes	Yes	Yes
Patton et al, 1999[19]	Unclear	Yes	Yes	Yes	No

Abbreviations: QUADAS-2=Quality Assessment of Diagnostic Accuracy Studies.

Appendix D Table 7. Individual Study Quality Assessment of Diagnostic Accuracy Studies Based on the QUADAS-2 Tool, Part 4

Author Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or interpretation have introduced bias?	Could the patient flow have introduced bias?	Are there concerns that the included patients do not match the review question?
Bailey et al, 2006[21]	Unclear	Unclear	Unclear	Unclear	Unclear
Canals et al, 2001[17]	No	Unclear	No	No	No
Canals et al, 2012[162]	Yes	No	No	No	Yes
Christensen et al, 2015[15]	No	Unclear	No	No	No
Cunha et al, 2008[163]	Yes	Unclear	No	Unclear	Unclear
Garcia-Lopez et al, 2015[164]	Unclear	Unclear	Unclear	Unclear	No
Gardner et al, 2007[165]	Yes	No	No	Yes	Yes
Hopper et al, 2012[166]	No	Unclear	No	Unclear	No
Johnson et al, 2002[13]	Unclear	Yes	Yes	Yes	No
Johnson et al, 2006[167]	No	Unclear	Yes	Yes	No
Katon et al, 2008[168]	No	No	No	Unclear	No
Muris et al, 2001[169]	Yes	Unclear	Unclear	No	No
O'Connor et al, 2016[14]	No	Yes	Yes	No	Unclear
Patton et al, 1999[19]	No	Unclear	Unclear	Unclear	No
Queen et al, 2012[23]	Unclear	Yes	Unclear	No	No
Ranta et al, 2007[170]	No	No	No	Unclear	No
Ranta et al, 2012[171]	No	Unclear	Unclear	No	No
Rivera-Riquelme et al, 2019[172]	No	No	No	Unclear	No
Roberts et al, 1991[16]	Unclear	Unclear	No	Unclear	No
Thompson et al, 1999[24]	No	Unclear	Unclear	Unclear	No
Tsai et al, 2009[173]	No	Unclear	Unclear	Unclear	Yes
Patton et al, 1999[19]	No	Unclear	Unclear	No	No

Abbreviations: QUADAS-2=Quality Assessment of Diagnostic Accuracy Studies.

Appendix D Table 8. Individual Study Quality Assessment of Diagnostic Accuracy Studies Based on the QUADAS-2 Tool Part 5

Author Year	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	Overall Study Quality	Rationale for Overall Rating
Bailey et al, 2006[21]	No	No	Fair	Only 99 participants (from the 1,470 that were randomly selected to participate) completed the full study so applicability uncertain. Blinding of index test and reference test results not reported, interval between testing NR, index test thresholds not prespecified.
Canals et al, 2001[17]	No	No	Fair	Thresholds for index test were not prespecified.
Canals et al, 2012[162]	No	No	Fair	Spectrum bias possible given the way the sample was selected (high and low scorers on the SCARED instrument administered the prior year).
Christensen et al, 2015[15]	No	No	Fair	Index test thresholds not prespecified.
Cunha et al, 2008[163]	No	No	Poor	Selection into this analysis based on results of prior tests/evaluations as part of a larger study, participants with and without diagnoses were selected, this analysis excluded all participants with a diagnosis of ADHD or other mood disorder, index test thresholds not prespecified, interval between index and reference test not specified.
Garcia-Lopez et al, 2015[164]	No	No	Fair	Sample assembled based on scoring above a threshold on index test and then a random sample of those who scored below threshold; blinding of index test and referent tests not reported, interval of administration between index and reference test not reported, thresholds not prespecified.
Gardner et al, 2007[165]	No	No	Poor	Sample was derived from a separate study that screened persons for entry into a study of anxiety and abdominal pain and mood disorders and mental health service use; thus, only children who screened positive on the SMFQ or SCARED were included thus high likelihood of spectrum bias. Children who did not screen positive did not receive a reference test, so sensitivity and specificity in an unselected primary care population cannot be determined.
Hopper et al, 2012[166]	No	No	Fair	Index threshold not specified; interval between index and reference test NR; only a sample of the entire screened population received a reference test, but the sample selected appears to represent the spectrum of scores.

Appendix D Table 8. Individual Study Quality Assessment of Diagnostic Accuracy Studies Based on the QUADAS-2 Tool Part 5

Author Year	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	Overall Study Quality	Rationale for Overall Rating
Johnson et al, 2002[13]	No	No	Poor	Only a small proportion of those eligible actually participated in the study so although recruitment was consecutive, potential for selection bias. Several thresholds evaluated for index text, unclear timing between index screening test and clinical interview. Interviewers not masked to results of index text. Of 373 who agreed to participate, only 294 were included (78.9%), and no information is provided on those who were missing from the sample. The information on the index and reference standard were collected by the same interviewer during the telephone call, so the interviewer had knowledge of the index test and reference standard results.
Johnson et al, 2006[167]	No	No	Poor	Only patients who had a positive screen received a clinical interview to confirm risk for suicide.
Katon et al, 2008[168]	No	No	Fair	Participants with an interval between index and reference test of more than 18 days were excluded from the analysis.
Muris et al, 2001[169]	No	No	Fair	Inappropriate exclusions of patients for the analysis; recruitment methods NR; whether results of index and reference tests were masked was NR.
O'Connor et al, 2016[14]	No	No	Poor	Same interviewer administered the index test and reference standard so results not masked, thresholds for index test not prespecified, unclear that lay administers of reference standard with high school degree and 12 hours of training is equivalent to a clinician interview and diagnosis. Study specifically recruited children with asthma in addition to healthy children, so applicability to general population is uncertain.
Patton et al, 1999[19]	No	No	Fair	Index test threshold seems to have been based on normative data; unclear whether reference test interviewers were blinded to the index test results; unclear interval between index and reference test; only a sample of participants from the full sample were selected to receive the reference test and unclear how that sample was selected; however, it appears the sample did include participants from the low and high spectrum of scores.
Queen et al, 2012[23]	No	No	Fair	Thresholds for index test were not prespecified, unclear whether results of index and referent test were blinded, sample was enriched with some persons from specialty mental health settings.

Appendix D Table 8. Individual Study Quality Assessment of Diagnostic Accuracy Studies Based on the QUADAS-2 Tool Part 5

Author Year	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	Overall Study Quality	Rationale for Overall Rating
Ranta et al, 2007[170]	No	No	Fair	Not all screened persons received the reference test; all those who screened positive received reference test plus 2 participants who screened negative were selected randomly for the reference test for each person that screened positive.
Ranta et al, 2012[171]	No	No	Fair	Blinding of index and reference test not reported, index test thresholds not prespecified.
Rivera-Riquelme et al, 2019[172]	No	No	Fair	Only a sample of participants matched on sex scoring in the low and medium score ranges received the reference standard and were included in the analysis.
Roberts et al, 1991[16]	No	No	Fair	Selection based on initial screening test scores, included all subjects above a prespecified threshold, and a random selection of participants from below the threshold; index test thresholds not prespecified, interval between index and reference test up to a month.
Thompson et al, 1999[24]	Unclear	Unclear	Fair	Unclear threshold for MHI index test; interval between index and reference standard not specified; only a random sample of all persons screened received diagnostic reference standard.
Tsai et al, 2009[173]	No	No	Fair	Index test did not have prespecified thresholds used, unclear whether index test was blinded to results of reference test.
Patton et al, 1999[19]	Unclear	No	Fair	Unclear whether SRS thresholds for the risk group was established a priori, unclear whether interviewers were blinded to results of the SRS; two possible reference standards used (direct suicide risk, clinical risk assessment); SRS was embedded in larger survey so unclear how its validity may be different if used as a stand-alone instrument.

Abbreviations: ADHD=attention deficit hyperactivity disorder; MHI=Mental Health Index; NR=not reported; QUADAS-2=Quality Assessment of Diagnostic Accuracy Studies; SCARED=Screen for Anxiety Related Emotional Disorders; SMFQ=Short Mood and Feelings Questionnaire; SRS=Suicide Risk Screen.

Appendix E Table 1. Screening Instruments for Anxiety and Depression Used in Test Accuracy Studies (KQ 2)

Instrument	Full Name	Description	Scoring, Range	Studies Using Instrument
ANS[174]	Autonomic Nervous System Questionnaire	5-item self-report measuring panic symptoms in the past 6 months. The first two items directly ask whether in the past 6 months the respondent has ever had a sudden spell or an attack of feeling frightened, anxious, or very uneasy and/or a spell or an attack with the heart racing, feeling faint, or an inability to catch one's breath. A "no" response to both questions is considered a negative screen. Items 3–5 for those who answered yes to one or two of the first questions ask about spontaneity, frequency, and anticipatory worry about panic attacks.	Each item on a 3-point scale (not at all worried, somewhat worried, or very worried). The total score range is 0 to 5.	Queen et al, 2012[23]
BDI[175]	Beck Depression Inventory	A 21-item scale that measures cognitive, behavioral, affective, and somatic components of depression symptoms. Items comprise four statements rated from 0 to 3 in terms of intensity. Respondents are asked to report the one that most accurately describes their own feelings. This original version of the inventory has largely been replaced by the BDI-II.	Score <10 minimal depression, 10 to 18 mild to moderate depression, 19 to 29 moderate to severe depression, and 30 to 36 severe depression.	Canals et al, 2001;[17] Roberts et al, 1991[16]
CES-D[18, 176-178]	Center for Epidemiologic Studies-Depression	A 20-item self- or interviewer-administered scale that assess past-week symptoms. Respondents asked to indicate frequency of past-week symptoms as "rarely or none of the time" (scored as 0), "some or a little of the time" (scored as 1), "occasionally or a moderate amount of time" (scored as 2), and "most or all of the time" (scored as 3). A version modified for children is referred to as the CES-DC.	Scores range from 0 to 60. Higher scores indicate worse symptoms; a score of 16 or higher is considered positive for depression.	Garrison et al, 1991[18] Roberts et al, 1991[16]
CIS-R[179]	Clinical Interview Schedule Revised	A computerized branched questionnaire to assess symptoms of depression and anxiety in nonclinical populations. It includes 14 subscales specific to the frequency, severity, persistence, and intrusiveness of common symptoms.	A screen is positive if it fulfills the algorithm for ICD-10 depressive disorder.	Patton et al, 1999[#58903}
EDAS[180]	Escala para la Deteccion de Ansiedad Socia	A 26-item youth report that measures social anxiety. Items assess fear of speaking or acting in ways that would be embarrassing, youths' social avoidance, distress, and interference. Administration time is 16 minutes.	Two items are dichotomous, and the remaining items are on a 5-point scale (0 to 4). The nondichotomous items are summed for the total score ranging from 24 to 120.	Garcia-Lopez et al, 2015[164]

Appendix E Table 1. Screening Instruments for Anxiety and Depression Used in Test Accuracy Studies (KQ 2)

Instrument	Full Name	Description	Scoring, Range	Studies Using Instrument
HSCL[181, 182]	Hopkins Symptom Checklist	A 10- or 6-item depression subscale derived from the Symptom Checklist-90. Items asking about troublesome feelings with responses scored as no (1), slightly (2), much (3), and very much (4).	Score ranges from 10 to 40 for the 10-item version. A score of 16 was considered the optimal threshold for screening in the initial validation study.	Christensen et al, 2015[15]
LSAS-CA[183]	The Liebowitz Social Anxiety Scale for Children and Adolescents	A youth-reported 24-item scale to measure social anxiety appropriate for children and adolescents. The screener assesses total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and performance avoidance. Administration time is 12 minutes.	The screener uses a 4-point Likert scale (0 to 3). Total scores range from 0 to 72.	Garcia-Lopez et al, 2015[164]
MHI-5	Mental Health Index	The MHI-5 is a 5-item version of the 38-item MHI. The 5 items pertain to mood in the past month.	Originally designed as a 6-point Likert scale, modified to 4-point Likert scale. Total scores range from 0 to 15. Higher scores indicate better mental health.	Rivera-Riquera et al, 2018[172]
PHQ-A[184]	Patient Health Questionnaire-Adolescents	Derived from the original PRIME-MD screening questionnaire and clinical interview; PHQ-A is a 67-item self-administered questionnaire that can be administered in 5 minutes or less to assess anxiety and depressive disorders. Clinicians quickly review completed questionnaires and apply diagnostic algorithms, which appear at the bottom of the printed page. The instrument is used to screen for panic disorder and GAD among other psychiatric disorders including depression and substance use.	NR	Johnson et al, 2002[13]
PI-ED	Paediatric Index of Emotional Distress – Total Scale; Anxiety Subscale; Depression Subscale	A brief, self-report screening tool based on HADS to measure 16 anxiety and depression symptoms that is suitable for children and adolescents ages 8 to 16 years. Items are scored on a 4-point scale from 3 to 0 (always, a lot of the time, sometimes, not at all). Includes a total score, an anxiety subscale, and a depression subscale.	Items are scored on a 4-point scale, 0 to 3 from “always” to “not at all.” Total score ranges from 0 to 21.	O’Connor et al, 2016[14]

Appendix E Table 1. Screening Instruments for Anxiety and Depression Used in Test Accuracy Studies (KQ 2)

Instrument	Full Name	Description	Scoring, Range	Studies Using Instrument
SCARED[185-187]	Screen for Anxiety Related Emotional Disorders	41-Item parent and child self-report measure used to screen for anxiety disorders in children ages 8 to 18 years. A total score is available as well as for the following scales: GAD, separation anxiety disorder, panic disorder, and social anxiety disorder. Administration time is 10 minutes. A 10-item short form is also available.	Each item is rated on a 3-point scale ranging from 0 to 2 ("almost never," "sometimes," "often"). Score ranges from 0 to 82. Total score >25 may indicate anxiety disorder; subscale scores also available (panic: score of 7 or more; GAD: score of 9 or more; social anxiety: score of 8 or more; separation anxiety: score of 5 or more).	Bailey et al, 2006[21] Canals et al, 2012[162] Muris et al, 2001[169]
SAS[188, 189]	Social Anxiety Scale	An 18-item screener plus four filler items used to assess social anxiety in children in relation to peers. It includes three scales: Fear of Negative Evaluation, Social Avoidance and Distress-Specific to New Peers and New Situations, and General Social Avoidance and Distress. Includes both a child and adult report version. The SAS for Adolescents (SAS-A) is a revision of the SAS to make it developmentally appropriate for adolescents. SAS-A includes 18 items and same three scales with both an adolescent and parent version.	Each item on a 5-point scale ("not at all" to "all the time"). Total score ranges from 18 to 90.	Bailey et al, 2006[21] Garcia-Lopez et al, 2015[164]
SASA[190]	Social Anxiety Scale for Adolescents (Slovenian measure)	28-item instrument measuring social anxiety with two scales: one measuring fears, worries, and anticipation of a negative peer evaluation and the second assessing social tension/relaxation, speech or behavior inhibition, and readiness to exposure in social situations. Administration time is 12 minutes.	All items are on a 5-point scale. The total score ranges from 28 to 140.	Garcia-Lopez et al, 2015[164]
SoPhI[191]	Social Phobia Inventory	A 21-item scale to assess social anxiety using DSM-IV criteria, including an item assessing duration of symptoms (social anxiety must be present for at least 6 months). Administration time is 10 minutes.	All items are rated on a 5-point scale, with the total score ranging from 21 to 105.	Garcia-Lopez et al, 2015[164]
SPAI-B[192]	Social Phobia and Anxiety Inventory - Brief	16-item scale measuring social anxiety in adolescents. The screener assesses cognitive, somatic, and behavioral symptoms. Administration time is 9 minutes.	Each item is rated on a 5-point Likert scale. The total ranges from 0 to 64.	Garcia-Lopez et al, 2015[164]

Appendix E Table 1. Screening Instruments for Anxiety and Depression Used in Test Accuracy Studies (KQ 2)

Instrument	Full Name	Description	Scoring, Range	Studies Using Instrument
SPIN[193] Mini-SPIN[194, 195]	Social Phobia Inventory/Mini Social Phobia Inventory	17 items measuring behavioral, physiological, and cognitive symptomatology associated with social anxiety; fear in social situations; avoidance of performing in social situations; and physiological discomfort in social situations. Time to administer is 8 minutes. The MiniSPIN is a 3-item version of the scale measuring avoidance and fear of embarrassment.	Each item is rated on a 5-point 0 to 4 scale ("not at all" to "extremely"), with a total score ranging from 0 to 68 for the full instrument and from 0 to 12 for the Mini SPIN.	Garcia-Lopez et al, 2015[164] Ranta et al, 2007[170] Ranta et al, 2012[171] Tsai et al, 2009[173]
SWQ[196]	Social Worries Questionnaire	10-Item parent-report screener to assess social anxiety symptomatology in youth ages 8 to 17 years. It measures the degree to which the youth avoids or worries about particular social situations.	Each item on a 3-point scale (not true to mostly true). Total scores range from 0 to 20.	Bailey et al, 2006[21]
WHO-5[197, 198]	World Health Organization Five Item Well-Being Index	A 5-item scale asking about feelings in the past 2 weeks derived from a subscale developed from the Short-Form 36 (SF-36). Response categories are all of the time (5), most of the time (4), more than half of the time (3), less than half of the time (2), some of the time (1), and at no time (0).	This scale is generally converted to a scale of 0 to 100 by multiplying the sum score by 4. Higher scores represent more well-being.	Christensen et al, 2015[15]

Abbreviations: ANS=Autonomic Nervous System Questionnaire; BDI=Beck Depression Inventory; CES=Center for Epidemiological Studies; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; EDAS=escala para la deteccion de ansiedad socia; GAD=generalized anxiety disorder; HADS=Hospital Anxiety and Depression Scale; HSCL13=Hopkins Symptom Checklist-13; ICD-10=International Classification of Diseases, Tenth Revision; KQ=key question; LSAS-CA=Liebowitz Social Anxiety Scale for Children and Adolescents; MHI=Mental Health Index; MiniSPIN=Mini-Social Phobia Inventory; NR=not reported; PHQ-A=Patient Health Questionnaire-Adolescent; PI-ED=Pediatric Index of Emotional Distress; PRIME-MD=Primary Care Evaluation of Mental Disorders; SAS=Social Anxiety Scale; SAS-A=Social Anxiety Scale for Adolescents; SCARED=Screen for Anxiety Related Emotional Disorders; SF-36=Short Form (36) Health Survey; WHO-5=World Health Organization Five Item Well-being Index.

Appendix E Table 2. Reference Standard Instruments for Anxiety Test Accuracy Studies (KQ 2)

Reference Measure	Description	Studies Using Reference Measure
Anxiety Disorders Interview Schedule for DSM: Child and Parent Version (ADIS C/P)	A semi-structured interview designed to diagnosis anxiety disorders as well as depression and behavioral disorders based on DSM criteria for children and adolescents.	Bailey et al, 2006;[21] Garcia-Lopez et al, 2015;[164] Queen et al, 2012;[23] Rivera-Riquelme et al, 2019[172]
Composite International Diagnostic Interview (CIDI)	A comprehensive, structured interview designed to be used by trained lay interviewers for the assessment of mental disorders according to the definitions and criteria of ICD-10 and DSM.	Christensen et al, 2015;[15] Patton et al, 1999[19]
Computerized Diagnostic Schedule for Children (C-DISC)	A structured diagnostic instrument that can be self-completed. It covers diagnoses for anxiety disorders, mood disorders, disruptive disorders, and miscellaneous disorders.	O'Connor et al, 2016[14]
Diagnostic clinical interview	Diagnostic clinical interview with mental health professional that includes items from the Structured Clinical Interview for DSM-III-R, PRIME-MD Clinical Evaluation Guide, and DSM-IV Global Assessment of Functioning.	Johnson et al, 2002[13]
Measure of Adolescent Potential for Suicide (MAPS) Clinical Interview	Includes direct suicide ratings (DSR) recorded during the interview, which are determined by the frequency and intrusiveness of suicidal thoughts, levels of suicide plans/preparation/intent, lethality of prior attempts, and present vs. past suicide threat. Ratings on each domain range from 0 (not at all or low lethality) to 6 (very serious or high lethality) with overall score the average of 4 ratings. High suicide risk defined as the upper 20th percentile cut-point of the DSR.	Thompson et al, 1999[24]
Mini-Neuropsychiatric Interview for Kids (MINI-Kid)	A structured diagnostic interview for children and adolescents based on DSM and ICD-10 criteria that is used to diagnose 23 Axis 1 disorders.	Canals et al, 2012;[162] Tsai et al, 2009[173]
Schedule for affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (K-SADs-PL)	A semi-structured clinical interview that covers 32 DSM child and adolescent diagnoses including both MDD and anxiety disorders such as panic disorder, SepAD, SocAD, and GAD.	Ranta et al, 2007;[170] Ranta et al, 2012;[171] Roberts et al, 1991;[16] Garrison et al, 1991[18]
Schedules for Clinical Assessment in Neuropsychiatry (SCAN)	A semi-structured diagnostic interview aligned to ICD-10 and DSM criteria.	Canals et al, 2001;[17]
Structured Clinical Interview for DSM-IV for Children (K-SCID)	K-SCID for DSM-IV generates DSM-IV diagnoses on children, with probe questions to facilitate assessing whether diagnostic criteria are met.	Muris et al, 2001[169]

Abbreviations: ADIS=Anxiety Disorders Interview Schedule; C-DISC=Computerized Diagnostic Schedule for Children; CIDI=Composite International Diagnostic Interview; DSM=Diagnostic and Statistical Manual of Mental Disorders; DSR=direct suicide ratings; GAD=generalized anxiety disorder; ICD-10=International Classification of Diseases, Tenth Revision; KQ=key question; K-SAD=Schedule for Affective Disorders and Schizophrenia for School-Age Children; MAPS=Measure of Adolescent Potential for Suicide; MDD=major depressive disorder; MINI-Kid=MINI international neuropsychiatric interview for kids; PRIME-MD=Primary Care Evaluation of Mental Disorders; SepAD=separation anxiety disorder; SocAD=social anxiety disorder.

Appendix F Table 1. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide-Related Hospitalizations or Emergency Department Use, Suicide Attempts, and Episodes of Deliberate Self-Harm

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Number of Events (%)	Placebo N	Number of Events (%)	Between-Group P Value
Family CBT	Asarnow et al, 2017[66]	15	12 weeks	Percentage with SA	3 months	20	0 (0)	22	4 (18)	0.01
	Asarnow et al, 2017[66]	15	12 weeks	NSSI	3 months	20	Probabilities of survival without (SE) 0.55 (0.11)	22	Probabilities of survival without (SE) 0.43 (0.14)	0.054
Family Therapy	Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200]	14	6-7 sessions over 6 months	Self-harm events per participant	36 months	415	Mean (SD) 1.0 (2.19)	417	Mean (SD) 1.2 (3.22)	NR
	Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200]	14	6-7 sessions over 6 months	SASII self-harm event	12 to 18 months	415	202 (75)	417	147 (70)	NR
	Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200]	14	6-7 sessions over 6 months	Hospital attendance for self-harm event	12 months	415	NR	417	NR	0.56
Group psycho-therapy	Green et al, 2011[93]	12 to 14 years, N (%) IG1: 69 (38) CG: 70 (38) 15 to 17 years, N (%) IG1: 114 (62) CG: 113 (62)	6 weeks followed by boosters until participants felt better	Frequency of self-harm	0-6 months	181	Frequency 4.6	181	Frequency 4.4	0.91
	Green et al, 2011[93]	12 to 14 years, N (%) IG1: 69 (38) CG: 70 (38) 15 to 17 years, N (%) IG1: 114 (62) CG: 113 (62)	6 weeks followed by boosters until participants felt better	Mild severity of self-harm	6-12 months	178	68 (38)	180	76 (42)	NS
	Green et al, 2011[93]	12 to 14 years, N (%) IG1: 69 (38) CG: 70 (38) 15 to 17 years, N (%) IG1: 114 (62) CG: 113 (62)	6 weeks followed by boosters until participants felt better	Marked Problem of self-harm	6-12 months	178	24 (13)	180	21 (12)	NS

Appendix F Table 1. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide-Related Hospitalizations or Emergency Department Use, Suicide Attempts, and Episodes of Deliberate Self-Harm

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Number of Events (%)	Placebo N	Number of Events (%)	Between-Group P Value
	Green et al, 2011[93]	12 to 14 years, N (%) IG1: 69 (38) CG: 70 (38) 15 to 17 years, N (%) IG1: 114 (62) CG: 113 (62)	6 weeks followed by boosters until participants felt better	Severe Severity of self-harm	6-12 months	178	11(6)	180	13 (7)	NS
	Green et al, 2011[93]	12 to 14 years, N (%) IG1: 69 (38) CG: 70 (38) 15 to 17 years, N (%) IG1: 114 (62) CG: 113 (62)	6 weeks followed by boosters until participants felt better	Self-harm resulting in injury	6-12 months	180	1 (0.05)	180	2 (1.1)	NR
Group MBT	Griffiths et al, 2019[94]	16	12 sessions over 12 weeks	Self-Harm subscale (RTSHI)	12 weeks	22	Mean (SD) 26.00 (12.57)	26	Mean (SD) 12 (12.28)	NS
	Griffiths et al, 2019[94]	16	12 sessions over 12 weeks	RTSHI Total	12 weeks	22	Mean (SD) 38.78 (19.65)	26	Mean (SD) 36.00 (18.80)	NS
	Griffiths et al, 2019[94]	16	12 sessions over 12 weeks	Self-harm ED presentation	12 weeks	22	Mean (range) 0.36 (0 to 2)	26	Mean (range) 0.23 (0 to 2)	NS
Group therapy	Hazell et al, 2009[95]	14	6+ sessions over 12 months	Engaged in repetition of self-harm	8 weeks	34	30 (88)	34	24 (71)	0.07
Develop-mental Group Therapy	Wood et al, 2001[159]	14	Median of 8 group sessions and 2.5 indiviual sessions over 6 months	Number of episodes of deliberate self-harm	7 months	32	Mean (95% CI) 0.6 (0.3 to 0.9)	31	Mean (95% CI) 1.8 (0.6 to 3.0)	NR
	Wood et al, 2001[159]	14	Median of 8 group sessions and 2.5 indiviual sessions over 6 months	Number of persons repeating self-harm	7 months	32	2 (6)	31	10 (32)	OR, 6.3 (1.4 to 28.7)

Appendix F Table 1. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide-Related Hospitalizations or Emergency Department Use, Suicide Attempts, and Episodes of Deliberate Self-Harm

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Number of Events (%)	Placebo N	Number of Events (%)	Between-Group P Value
Individual and Family DBT	Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203]	16	1 weekly individual session, 1 weekly multifamily skills training, and family sessions and telephone coaching outside of sessions as needed, over 19 weeks	Self-harm episode	19 weeks	39	Mean (95% CI) 9.0 (4.8 to 13.2)	38	Mean (95% CI) 22.5 (11.4 to 33.5)	0.05
	Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203]	16	1 weekly individual session, 1 weekly multifamily skills training, and family sessions and telephone coaching outside of sessions as needed, over 19 weeks	Admitted to hospital due to self-harm	19 weeks	39	1 (2)	38	2 (5)	NS
	Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203]	16	1 weekly individual session, 1 weekly multifamily skills training, and family sessions and telephone coaching outside of sessions as needed, over 19 weeks	ER visit due to self-harm	19 weeks	39	2 (5)	38	5 (13)	NS
Therapeutic assessment	Ougrin et al, 2013[121] Ougrin, 2011[204]	16	1 session	One or more presentation to A&E with self-harm	2 years	35	7 (20)	34	9 (26)	0.53

Appendix F Table 1. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide-Related Hospitalizations or Emergency Department Use, Suicide Attempts, and Episodes of Deliberate Self-Harm

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Number of Events (%)	Placebo N	Number of Events (%)	Between-Group P Value
Individual and family MBT	Rossouw et al, 2012[128]	15	Weekly sessions over 12 months	Self-harm (RTSHI)	12 months	40	Log mean (SE) 1.33 (0.22)	40	Log mean (SE) 2.01 (0.21)	<0.01
	Rossouw et al, 2012[128]	15	Weekly sessions over 12 months	At least one incident of self-harm	12 months	40	22 (56)	40	33 (83)	0.01
Youth-nominated support team	King et al, 2009[108]	16	1 session and phone contact over flexible time period	Suicide attempt	12 months	175	29 (17)	171	35 (20)	0.51

Abbreviations: A&E=accident and emergency; CBT=cognitive behavioral therapy; CG=control group; CI=confidence interval; DBT=dialectical behavioral therapy; ED=emergency department; ER=emergency room; IG=intervention group; MBT=mentalization-based therapy; N=number; NR=not reported; NS=not significant; NSSI=non-suicidal self-injury; OR=odds ratio; RTSHI=Risk-Taking and Self-Harm Inventory for Adolescents; SA=suicide attempt; SASII=Suicide Attempt Self-Injury Interview; SD=standard deviation; SE=standard error.

Appendix F Table 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Family CBT	Asarnow et al, 2017[66]	15	12 weeks	Percent with suicide attempts		20	NR	22	NR	NA	NA
Family Therapy	Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200]	14	6-7 sessions over 6 months	BSS	12 months	415	0.26 (0.05)	417	0.36 (0.05)	OR (95% CI): 0.64 (0.44 to 0.94)	0.024
	Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200]	14	6-7 sessions over 6 months	HSFC	12 months	415	4.8 (0.40)	417	5.1 (0.43)	Mean difference: -0.3 (-1.1 to 0.4)	0.38
	Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200]	14	6-7 sessions over 6 months	CDRS-R	12 months	248	33.2(1.46)	189	33.9(1.57)	Mean difference: -0.6 (-3.1 to 1.9)	0.62
	Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200]	14	6-7 sessions over 6 months	PQ-LES	12 months	415	49.9 (1.12)	417	48.8 (1.13)	Mean difference: 1.1 (-0.5 to 2.7)	0.18
	Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200]	14	6-7 sessions over 6 months	GHQ	12 months	415	12.8 (0.61)	417	13.5 (0.65)	Mean difference: -0.7 (-1.8 to 0.3)	0.19
Attachment-Based Family Therapy	Diamond et al, 2010[82]	15	5 to 8 sessions over 12 weeks	SIQ-Jr	12 weeks	35	5.2 (1.6-8.8)	31	16.2 (10.1-22.2)	NR	NR
	Diamond et al, 2010[82]	15	5 to 8 sessions over 12 weeks	SSI	12 weeks	35	69.2 (50.2-88.2)	31	34.6 (15.0-54.2)	NR	NR
	Diamond et al, 2010[82]	15	5 to 8 sessions over 12 weeks	BDI-II	12 weeks	35	12.6 (8.0-17.2)	31	18.5 (12.9-24.0)	NR	NR
Group psychotherapy	Green et al, 2011[93]	12 to 14 years, N (%) IG1: 69 (38) CG: 70 (38) 15 to 17 years, N (%) IG1: 114 (62) CG: 113 (62)	6 weeks followed by boosters until participants felt better	SIQ	6 months	171	61.5 (45.5)	9	59.9 (48.4)	0.07 (-8.60 to 8.75)	0.99

Appendix F Table 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Group psychotherapy (continued)	Green et al, 2011[93]	12 to 14 years, N (%) IG1: 69 (38) CG: 70 (38) 15 to 17 years, N (%) IG1: 114 (62) CG: 113 (62)	6 weeks followed by boosters until participants felt better	MFQ	6 months	171	28.5 (16.1)	178	27.6 (16.5)	-0.44 (-3.49 to 2.61)	0.78
	Green et al, 2011[93]	12 to 14 years, N (%) IG1: 69 (38) CG: 70 (38) 15 to 17 years, N (%) IG1: 114 (62) CG: 113 (62)	6 weeks followed by boosters until participants felt better	HoNOSCA	6 months	172	12.2 (6.3)	180	12.6(6.1)	-0.55 (-1.64 to 0.54)	0.32
Group MBT	Griffiths et al, 2019[94]	16	12 sessions over 12 weeks	RCADS MD	12 weeks	22	20.39 (4.74)	26	18.15 (6.57)		NS
Group therapy	Hazell et al, 2009[95]	14	6+ sessions over 12 months	SIQ	8 weeks	34	74.11 (41.75)	37	76.40 (54.28)		p=0.80
	Hazell et al, 2009[95]	14	6+ sessions over 12 months	MFQ	8 weeks	34	30.91 (17.25)	37	32.38 (19.94)		p=0.60
	Hazell et al, 2009[95]	14	6+ sessions over 12 months	CGAS	8 weeks	25	58.54 (8.70)	25	60.59 (10.69)		
	Hazell et al, 2009[95]	14	6+ sessions over 12 months	HoNOSCA	8 weeks	26	16.77 (7.12)	29	15.00 (9.28)		
	Hazell et al, 2009[95]	14	6+ sessions over 12 months	SDQ	8 weeks	33	17.66 (6.58)	37	18.89 (7.16)		
Developmental Group Therapy	Wood et al, 2001[159]	14	Median of 8 group sessions and 2.5 indiviual sessions over 6 months	SIQ	7 months	28	47.3 (50.5)	27	39.7 (46.7)	7.5 (-18.8 to 33.9)	

Appendix F Table 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Developmental Group Therapy (continued)	Wood et al, 2001[159]	14	Median of 8 group sessions and 2.5 indiviual sessions over 6 months	MFQ	7 months	29	18.8 (16.0)	27	15.3 (13.0)	3.5 (-4.4 to 11.3)	
	Wood et al, 2001[159]	14	Median of 8 group sessions and 2.5 indiviual sessions over 6 months	HoNOSCA	7 months	31	8.4 (6.4)	31	6.9 (6.1)	1.5 (-1.7 to 4.7)	NR
Individual internet CBT	Hill et al, 2019[97]	17	2 sessions 1 week apart	BSS	2 weeks	41	2.05 (3.27)	39	4.49 (6.01)		0.12
	Hill et al, 2019[97]	17	2 sessions 1 week apart	RADS-2	2 weeks	41	23.12 (4.50)	39	24.64 (5.90)		0.45
Interpersonal psychotherapy	Tang et al, 2009[144]	15	2 weekly sessions and weekly phone call, over 6 weeks	BHS	6 weeks	35	7.74 (5.29)	38	12.42 (4.08)		P<0.01
	Tang et al, 2009[144]	15	2 weekly sessions and weekly phone call, over 6 weeks	BSS	6 weeks	35	8.97 (10.77)	38	16.29 (7.99)		P<0.01
	Tang et al, 2009[144]	15	2 weekly sessions and weekly phone call, over 6 weeks	BDI-II	6 weeks	35	19.97 (14.68)	38	31.58 (12.01)		P<0.001

Appendix F Table 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual and Family DBT	Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203]	16	1 weekly individual session, 1 weekly multifamily skills training, and family sessions and telephone coaching outside of sessions as needed, over 19 weeks	SIQ-Jr	71 weeks	38	20.45 (19.15)	37	22.05 (21.86)	Between-group difference in slope: 0.15	0.110
	Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203]	16	1 weekly individual session, 1 weekly multifamily skills training, and family sessions and telephone coaching outside of sessions as needed, over 19 weeks	BHS	19 weeks	39	6.23 (5.30)	38	9.06 (6.53)	Between-group difference in slope: -0.13	0.071

Appendix F Table 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual and Family DBT (continued)	Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203]	16	1 weekly individual session, 1 weekly multifamily skills training, and family sessions and telephone coaching outside of sessions as needed, over 19 weeks	SMFQ	19 weeks	39	10.19 (5.04)	38	12.58 (6.62)	-0.10	0.179
	Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203]	16	1 weekly individual session, 1 weekly multifamily skills training, and family sessions and telephone coaching outside of sessions as needed, over 19 weeks	MADRS	19 weeks	39	12.29 (7.52)	38	15.76 (8.14)	-0.22	P=0.019

Appendix F Table 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual and Family DBT (continued)	Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203]	16	1 weekly individual session, 1 weekly multifamily skills training, and family sessions and telephone coaching outside of sessions as needed, over 19 weeks	CGAS	71 weeks	38	65.68 (11.81)	37	64.22 (14.13)	Between-group difference in slope: 0.03	0.067
Individual and family MBT	Rossouw et al, 2012[128]	15	Weekly sessions over 12 months	MFQ	12 months	40	9.26 (1.27)	40	11.54 (1.14)		P<0.05
Motivational interviewing	King et al, 2015[107]	18	1 session	SIQ-Jr	2 months	24	21.46 (17.4)	22	24.28 (17.3)		NS
	King et al, 2015[107]	18	1 session	BHS	2 months	24	5.66 (5.2)	22	8.64 (5.7)		NS
	King et al, 2015[107]	18	1 session	RADS-2-SF	2 months	24	25.38 (4.7)	22	30.87 (4.0)		P<0.01
Therapeutic assessment	Ougrin et al, 2013[121] Ougrin, 2011[204]	16	1 session			35		35			
	Ougrin et al, 2013[121] Ougrin, 2011[204]	16	1 session	CGAS	3 months	35	64.6 (12.9)	35	60.1 (9.9)	4.49 (-0.98 to 9.96)	NR
Youth-Nominated Support Team	King et al, 2009[108]	16	1 session and weeky telephone contact, 1 session and phone contact over flexible time period	BHS	6 weeks	NR	6.82 (NR)	NR	7.80 (NR)		0.09

Appendix F Table 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Youth-Nominated Support Team (continued)	King et al, 2009[108]	16	1 session and weeky telephone contact, 1 session and phone contact over flexible time period	SIQ-Jr	6 weeks	NR	25.55 (NR)	NR	29.71 (NR)		0.04
	King et al, 2009[108]	16	1 session and weeky telephone contact, 1 session and phone contact over flexible time period	CDRS-R	6 weeks	NR	39.6 (NR)	NR	40.80 (NR)		0.40
	King et al, 2009[108]	16	1 session and weeky telephone contact, 1 session and phone contact over flexible time period	CAFAS	3 months	168	15.20 (NR)	174	15.77 (NR)		0.58
RAP-P	Pineda et al, 2013[125]	15	4 sessions over 4 to 8 weeks	ASQ-R,	Post-treatment	22	8.73 (4.88)	18	11.89 (5.47)		p=0.05
	Pineda et al, 2013[125]	15	4 sessions over 4 to 8 weeks	HoNOSCA	Post-treatment	22	13.45 (5.89)	18	17.61 (5.20)		p<0.01

Appendix F Table 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Promoting Care, Assess, Respond, Empower	Hooven et al, 2012[100]	16	C-Care, 1 session, 2 hours total P-CARE, 2 sessions, 2 hours total C-Care plus P-CARE, 1 child session, 2 hours total; 2 parent sessions, 2 hours total	Suicide Ideation	1 month	153 155 164	IG1 Rate of change: -1.131 IG2 Rate of change: -1.033 IG2 Rate of change: -1.451	143	-0.917	NA	G1 and G2 vs. CG: NS G3 vs. CG: P<0.001
	Hooven et al, 2012[100]	16	C-Care, 1 session, 2 hours total P-CARE, 2 sessions, 2 hours total C-Care plus P-CARE, 1 child session, 2 hours total; 2 parent sessions, 2 hours total	Direct Suicide Threat	1 month	153 155 164	IG1 Rate of change: -0.443 IG2 Rate of change: -0.294 IG2 Rate of change: -0.556	143	-0.318	NA	G1 and G2 vs. CG: NS G3 vs. CG: P<0.05

Appendix F Table 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Promoting Care, Assess, Respond, Empower (continued)	Hooven et al, 2012[100]	16	C-Care, 1 session, 2 hours total P-CARE, 2 sessions, 2 hours total C-Care plus P-CARE, 1 child session, 2 hours total; 2 parent sessions, 2 hours total	CES-D	1 month	153	-0.951	143	-0.685	NA	P<0.01
	Hooven et al, 2012[100]	16	C-Care, 1 session, 2 hours total P-CARE, 2 sessions, 2 hours total C-Care plus P-CARE, 1 child session, 2 hours total; 2 parent sessions, 2 hours total	CES-D	1 month	155	-0.815	143	-0.685	NA	NS

Appendix F Table 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Promoting Care, Assess, Respond, Empower (continued)	Hooven et al, 2012[100]	16	C-Care, 1 session, 2 hours total P-CARE, 2 sessions, 2 hours total C-Care plus P-CARE, 1 child session, 2 hours total; 2 parent sessions, 2 hours total	CES-D	1 month	164	-1.021	143	-0.685	NA	P<0.01

Abbreviations: ASQ-R=Adolescent Suicide Questionnaire–Revised; BDI-II=Beck Depression Inventory, version 2; BHS=Beck Hopelessness Scale; BSS=Beck Scale for Suicide Ideation; C-Care=Counselors Care, Assess, Respond, Empower; CAFAS=Child and Adolescent Functional Assessment Scale; CBT=cognitive behavioral therapy; CDRS-R=Children's Depression Rating Scale-Revised; CES-D=Center for Epidemiological Studies-Depression; CG=control group; CGAS=Children's Global Assessment Scale; CI=confidence interval; DBT=dialectical behavioral therapy; G=group; GHQ=General Health Questionnaire, 12 questions; HSFC=Hopelessness Scale for Children; HoNOSCA=Health of the Nation Outcome Scales for Children and Adolescents; HSFC=Hopelessness Scale for Children; IG=intervention group; IG=intervention group; MADRS=Montgomery–Åsberg Depression Rating Scale; MBT=mentalization-based therapy; MFQ=mood & feelings questionnaire; N=number; NA=not applicable; NR=not reported; NS=not significant; OR=odds ratio; P-Care=Parents-Counselors Care, Assess, Respond, Empower; PQ-LES=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; RADS-2=Reynolds Adolescent Depression Scale, 2nd Edition; RADS-2-SF=Reynolds Adolescent Depression Scale, 2nd Edition: Short Form; RAP-P=Resourceful Adolescent Parent Program; RCADS MD=Revised Children's Anxiety and Depression Scale-Depression; SD=standard deviation; SDQ=Strengths and Difficulties Questionnaire; SE=standard error; SIQ=Suicidal Ideation Questionnaire; SIQ-Jr=Suicidal Ideation Questionnaire-Junior; SMFQ=Short Mood and Feelings Questionnaire; SSI=Scale for Suicidal Ideation; vs.=versus.

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Group CBT	Arendt et al, 2016[65]	11.8	Manualized group CBT program (Cool Kids), 10 weeks	ADIS CSR primary diagnosis	10	56	2.16 (SD: 2.59)	53	5.45 (SD: 1.90)	Partial eta squared=0.35	<0.001
	Arendt et al, 2016[65]	11.8	Manualized group CBT program (Cool Kids), 10 weeks	ADIS CSR all diagnosis	10	56	5.21 (SD: 5.19)	53	10.75 (SD: 5.63)	Partial eta squared=0.22	<0.001
	Arendt et al, 2016[65]	11.8	Manualized group CBT program (Cool Kids), 10 weeks	SCAS-youth	10	56	21.57 (SD: 14.42)	53	32.55 (SD: 15.64)	Partial eta squared=0.18	<0.001
	Arendt et al, 2016[65]	11.8	Manualized group CBT program (Cool Kids), 10 weeks	SCAS-P mother	10	56	22.25 (SD: 12.59)	53	37.04 (SD: 16.95)	Partial eta squared=0.24	<0.001
	Arendt et al, 2016[65]	11.8	Manualized group CBT program (Cool Kids), 10 weeks	SCAS-P father	10	56	23.56 (SD: 13.87)	53	32.63 (SD: 16.17)	Partial eta squared=0.19	<0.001
	Asbrand et al, 2020[67]	11.3	Exposure-based group CBT, 12 weeks	SPAI-C	12	31	NR	36	NR	F(2,116.6)=5.87	0.004
	Asbrand et al, 2020[67]	11.3	Exposure-based group CBT, 12 weeks	SASC-R child	12	31	NR	36	NR	F(2,115.6)=1.16	0.316
	Asbrand et al, 2020[67]	11.3	Exposure-based group CBT, 12 weeks	SASC-R parent	12	31	NR	36	NR	F(2,114.4)=1.01	0.366

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Group CBT (continued)	Cornacchio et al, 2019[79]	6.6	Group CBT program that relies on the early child format of Parent Child Interaction Therapy, 5 days	ADIS CSR selective mutism	4	14	4.2 (SD: 0.9)	15	4.6 (SD: 0.7)	Effect size Cohen's d=-0.50	>0.05
	Cornacchio et al, 2019[79]	6.6	Group CBT program that relies on the early child format of Parent Child Interaction Therapy, 5 days	ADIS CSR social anxiety	4	14	4.0 (SD: 0.8)	15	4.0 (SD: 0.8)	Effect size Cohen's d=-0.50	>0.05
	Cornacchio et al, 2019[79]	6.6	Group CBT program that relies on the early child format of Parent Child Interaction Therapy, 5 days	SMQ-P home subscale	4	14	2.2 (SD: 0.4)	15	1.7 (SD: 0.7)	Cohen's d=0.36	>0.05
	Cornacchio et al, 2019[79]	6.6	Group CBT program that relies on the early child format of Parent Child Interaction Therapy, 5 days	SMQ-P social subscale	4	14	1.2 (SD: 0.6)	15	0.7 (SD: 0.7)	Cohen's d=0.58	<0.05

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Group CBT (continued)	Holmes et al, 2014[99]	9.6	Group CBT program termed "No Worries!" that utilizes the A-B-C model, 10 weeks	ADIS-C/P CSR	10	17	3.59 (SD: 1.3)	19	6.21 (SD: 0.79)	Partial-eta squared=0.43	<0.001
	Holmes et al, 2014[99]	9.6	Group CBT program termed "No Worries!" that utilizes the A-B-C model, 10 weeks	SCAS-P GAD symptoms	10	20	NR	22	NR	Partial eta squared=0.09	0.048
	Holmes et al, 2014[99]	9.6	Group CBT program termed "No Worries!" that utilizes the A-B-C model, 10 weeks	SCAS-P GAD symptoms	10	17	6.17 (SD: 2.71)	19	6.84 (2.29)	NR	0.053
	Holmes et al, 2014[99]	9.6	Group CBT program termed "No Worries!" that utilizes the A-B-C model, 10 weeks	SCAS-P total symptoms	10	17	29.94 (SD: 12.70)	19	31.47 (SD: 8.79)	NR	P=NS
	Holmes et al, 2014[99]	9.6	Group CBT program termed "No Worries!" that utilizes the A-B-C model, 10 weeks	SCAS-C GAD symptoms	10	17	7.41 (SD: 4.65)	19	8.42 (SD: 4.56)	NR	P=NS

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Group CBT (continued)	Holmes et al, 2014[99]	9.6	Group CBT program termed "No Worries!" that utilizes the A-B-C model, 10 weeks	SCAS-C total symptoms	10	17	34.88 (SD: 20.25)	19	40.84 (SD: 19.93)	NR	P=NS
	Lau et al, 2010[110]	8 years 7 months	Coping Cat CBT group-treatment program, 11 weeks	SCAS-C	13	24	24.6 (SD: 10.5) (9.7 decrease from baseline)	21	38.8 (SD: 13.7) (1.8 increase from baseline)	Effect size partial eta squared=0.27	<0.001
	Lau et al, 2010[110]	8 years 7 months	Coping Cat CBT group-treatment program, 11 weeks	SCAS-P	13	24	28.8 (SD: 10.3) (decrease 4.2 from baseline);	21	36.5 (SD: 11.0) (increase 1.3 from baseline)	Effect size partial eta squared=0.11	<0.05
	Sanchez-Garcia et al, 2009[131]	11.91	Group CBT referred to as Intervencion en Adolescentes con Fobia Social, 12 weeks	SPAI-C	12	IG1: 28 IG2: 29	IG1: 15.45 (SD: 7.77); IG2: 12.75 (SD: 8.03);	25	30.80 (SD: 5.75)	IG1 vs. CG: effect size=2.23 IG2 vs. CG: effect size=2.51	IG1 vs. CG <0.001 IG2 vs. CG <0.001
	Sanchez-Garcia et al, 2009[131]	11.91	Group CBT referred to as Intervencion en Adolescentes con Fobia Social, 12 weeks	SPAI-C	24	IG1: 28 IG2: 29	IG1:11.91 (SD: 6.03) IG2: 13.21 (SD: 8.55)	25	27.64 (SD: 4.01)	IG1 vs. CG: effect size=3.04 IG2 vs. CG effect size=2.08	IG1 vs. CG <0.001 IG2 vs. CG <0.001
	Sanchez-Garcia et al, 2009[131]	11.91	Group CBT referred to as Intervencion en Adolescentes con Fobia Social, 12 weeks	SASC-R	12	IG1: 28 IG2: 29	IG1: 15.89 (SD: 6.81) IG2: 11.45 (SD: 6.48)	25	35.36 (SD: 5.33)	IG1 vs. CG: effect size=3.16 IG2 vs. CG effect size=3.94	IG1 vs. CG <0.001 IG2 vs. CG <0.001

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Group CBT (continued)	Sanchez-Garcia et al, 2009[131]	11.91	Group CBT referred to as Intervencion en Adolescentes con Fobia Social, 12 weeks	SASC-R	24	IG1: 28 IG2: 29	IG1:12.14 (SD: 6.86) IG2: 12.24 (SD: 7.34)	25	38.80 (SD: 6.71)	IG1 vs. CG: effect size=2.44 IG2 vs. CG effect size=2.90	<0.001 IG2 vs. CG <0.001
Individual CBT	Barrett et al, 1996[70]	9.3	Individual CBT using using Coping Koala Workbook, 12 weeks	RCMAS	12	28	IG1: 9.0 (6.8) IG2: 6.6 (4.6)	23	11.6 (SD: 6.0)	NR	IG1 vs. CG: P=NS IG2 vs. CG: P=NS
	Barrett et al, 1996[70]	9.3	Individual CBT using using Coping Koala Workbook, 12 weeks	FSSCR	12	28	IG1: 119.9 (26.0) IG2: 114.2 (20.2)	23	134.3 (SD: 32.6)	NR	IG1 vs. CG: P=NS IG2 vs. CG: P=NS
	Ginsburg et al, 2020[92]	10.9	Individual CBT consisting of 7 core modules, 12 weeks	CGI-S	12	148	3.97	68	4.15	NR	0.38
	Ginsburg et al, 2020[92]	10.9	Individual CBT consisting of 7 core modules, 12 weeks	CGI-S	52	148	3.61	68	3.41	NR	0.34
	Ginsburg et al, 2020[92]	10.9	Individual CBT consisting of 7 core modules, 12 weeks		12	148	20.25	68	21.72	Cohen's d=0.29	0.05
	Ginsburg et al, 2020[92]	10.9	Individual CBT consisting of 7 core modules, 12 weeks	SCARED-P	52	148	17.74	68	15.12	NR	0.44
	Ginsburg et al, 2020[92]	10.9	Individual CBT consisting of 7 core modules, 12 weeks	SCARED-C	12	148	22.82	68	23.65	NR	0.87
	Ginsburg et al, 2020[92]	10.9	Individual CBT consisting of 7 core modules, 12 weeks	SCARED-C	52	148	19.63	68	20.54	NR	0.65

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual CBT (continued)	Perrin et al, 2019[122]	13.4;	Individual, GAD-specific CBT, 10 weeks	ADIS GAD severity	10	20	1.9 (SD: 2.3)	20	5.7 (SD: 1.1)	Effect size partial eta squared=0.54	<0.001
	Perrin et al, 2019[122]	13.4;	Individual, GAD-specific CBT, 10 weeks	SCARED-R-C (anxiety)	10	20	15.2 (SD: 12.5)	20	46.3 (SD: 15.9)	Effect size partial eta squared=0.53	<0.001
	Perrin et al, 2019[122]	13.4;	Individual, GAD-specific CBT, 10 weeks	SCARED-R-P (anxiety)	10	20	18.9 (SD: 12.4)	20	38.2 (SD: 14.9)	Effect size partial eta squared=0.37	<0.001
	Perrin et al, 2019[122]	13.4;	Individual, GAD-specific CBT, 10 weeks	SCARED-R-C (GAD)	10	20	4.6 (SD: 5.2)	20	12.9 (SD: 4.2)	Effect size partial eta squared=0.47	<0.001
	Perrin et al, 2019[122]	13.4;	Individual, GAD-specific CBT, 10 weeks	SCARED-R-P (GAD)	10	20	6.5 (SD: 4.3)	20	11.2 (SD: 4.7)	Effect size partial eta squared=0.24	<0.001
	Perrin et al, 2019[122]	13.4;	Individual, GAD-specific CBT, 10 weeks	PSWQ-C	10	20	10.6 (SD: 12.2)	20	31.1 (SD: 7.2)	Effect size partial eta squared=0.4	<0.001
	Salzer et al, 2018[42]	17.4	Individual CBT focused on reducing self-focused attentional and safety behaviors, 31 weeks	LSAS-CA change from baseline	Post-treatment	34	NR	39	NR	Effect size Cohen's d (95% CI); 0.61 (0.14 to 1.08)	0.0112
	Salzer et al, 2018[42]	17.4	Individual CBT focused on reducing self-focused attentional and safety behaviors, 31 weeks	SPAI change from baseline	Post-treatment	34	NR	39	NR	Effect size Cohen's d (95% CI); 0.75 (0.27 to 1.22)	0.0021
	Villabo et al, 2018[150]	10.5	Individual CBT using the Coping Cat manual, 12 weeks	MASC-child	12	IG1: 55; IG2: 55	IG1:48.61 (SE 1.48) IG2: 48.8 (SE: 1.65)	55	51.95 (SE: 1.60)	Effect size Hedges g (95% CI); IG1 vs CG: 0.28 (0.10 to 0.65); IG2 vs CG: 0.26 (0.12 to 0.64)	IG1 vs CG: P=NS; IG2 vs. CG: P=NS

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual CBT (continued)	Villabo et al, 2018[150]	10.5	Individual CBT using the Coping Cat manual, 12 weeks	MASC-parent	12	IG1: 55 IG2: 55	IG1: 47.25 (SE: 2.58) IG2: 49.72 (SE: 2.46)	55	50.86 (SE: 2.45)	Effect size Hedges g (95% CI); IG1 vs. CG: 0.20 (0.18 to 0.61); IG2 vs. CG: 0.06 (-0.34 to 0.48)	IG1 vs CG: P=NS; IG2 vs. CG: P=NS
Individual CBT, Sertraline, Individual CBT+Sertraline	Walkup et al, 2008[153]; Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	Individual CBT using Coping Cat program adapted for child's age and length of the study, 12 weeks	PARS change from baseline	12	IG1: 139 IG2: 133 IG3: 140	IG1: 10.8 (SD: 5.9) IG2: 9.8 (SD: 6.2) IG3: 7.4 (SD: 6.0)	76	12.6 (SD: 6.3)	IG1 vs. CG: Effect size Hedge's g (95% CI): 0.31 (0.02 to 0.59); IG2 vs. CG: Effect size Hedges g (95% CI): 0.45 (0.17 to 0.74); IG3 vs. CG: Effect size Hedge's g (95% CI): 0.86 (0.56 to 1.15)	IG1 vs. CG: P=0.01; IG2 vs. CG: P=NS; IG3 vs. CG: P=NS
	Walkup et al, 2008[153]; Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	Individual CBT using Coping Cat program adapted for child's age and length of the study, 12 weeks	CGI-S change from baseline	12	IG1: 139 IG2: 133 IG3: 140	IG1: 3.3 (SD: 1.3) IG2: 3.0 (SD: 1.3) IG3: 2.4 (SD: 1.3)	76	3.8 (SD: 1.4)	NR	NR

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual CBT, Sertraline, Individual CBT+Sertraline (continued)	Walkup et al, 2008[153]; Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	Individual CBT using Coping Cat program adapted for child's age and length of the study, 12 weeks	MASC-C	12	IG1: 139 IG2: 133 IG3: 140	IG1: 40.9 (SD: 10.4) IG2: 38.2 (SD: 10.7) IG3: 39.5 (10.8)	76	42.9 (SD: 11.8)	IG2 vs. CG: b=−4.68, t=−2.80	IG2 vs. CG: adjusted P=0.03; All other comparisons not statistically significant, P NR
	Walkup et al, 2008[153]; Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	Individual CBT using Coping Cat program adapted for child's age and length of the study, 12 weeks	MASC-P	12	IG1: 139 IG2: 133 IG3: 140	IG1: 42.1 (SD: 16.1) IG2: 37.9 (SD: 17.3) IG3: 33.4 (SD: 16.9)	76	49.1 (SD: 16.9)	IG1 vs. CG: b=−7.0, t=−2.9 IG2 vs. CG: b=−11.1, t=−4.4 IG3 vs. CG: b=−15.7, t=−6.4	IG1 vs. CG; adjusted P<0.001; IG2 vs. CG; adjusted P<0.001; IG3 vs. CG: adjusted P<0.001

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual CBT, Sertraline, Individual CBT+Sertraline (continued)	Walkup et al, 2008[153]; Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	Individual CBT using Coping Cat program adapted for child's age and length of the study, 12 weeks	SCARED-C	12	IG1: 139 IG2: 133 IG3: 140	IG1: 12.4 (SD: 11.4) IG2: 9.3 (SD: 11.9) IG3: 9.4 (SD: 11.6)	76	13.8 (SD: 12.1)	NR	No statistically significant differences between arms, P NR;
	Walkup et al, 2008[153]; Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	Individual CBT using Coping Cat program adapted for child's age and length of the study, 12 weeks	SCARED-P	12	IG1: 139 IG2: 133 IG3: 140	IG1: 16.9 (SD: 11.2) IG2: 11.0 (SD: 11.7) IG3: 9.6 (SD: 11.4)	76	19.5 (SD: 11.8)	IG1 vs. CG: NR IG2 vs. CG: b=−7.9, t=−4.7 IG3 vs. CG: b=−9.8, t=−5.9	IG1 vs. CG: adjusted P=0.26; IG2 vs. CG: adjusted P<0.001; IG3 vs. CG: adjusted P<0.001
	Ost et al, 2015[212]	11.6	Individual weekly sessions and social skills group weekly sessions for the child and parent training about SocAD, 12 weeks	CSR change from baseline	12	IG1: 16 IG2: 16	IG1: 3.25 (SD: 0.39) IG2: 3.69 (SD: 1.66)	23	5.95 (SD: 1.15)	F=26.6	<0.001; IG1 vs. CG: P=sig, NR, favoring IG1; IG2 vs. CG: P=sig, NR, favoring IG2

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual CBT, Sertraline, Individual CBT+Sertraline (continued)	Ost et al, 2015[212]	11.6	Individual weekly sessions and social skills group weekly sessions for the child and parent training about SocAD, 12 weeks	SPAI-C change from baseline	12	IG1: 16 IG2: 16	IG1: 12.5 (SD: 8.9) IG2: 19.1 (SD: 12.0)	23	22.8 (SD: 9.4)	F=5.0	<0.05; IG1 vs. CG: P=sig, NR, favoring IG1; IG2 vs. CG: P=sig, NR, favoring IG2
	Ost et al, 2015[212]	11.6	Individual weekly sessions and social skills group weekly sessions for the child and parent training about SocAD, 12 weeks	MASC change from baseline	12	IG1: 16 IG2: 16	IG1: 35.8 (SD: 16.0) IG2: 43.2 (SD: 18.1)	23	54.7 (SD: 15.3)	F=4.6	<0.05; IG1 vs. CG: P=sig, NR, favoring IG1; IG2 vs. CG: P=NS
	Ost et al, 2015[212]	11.6	Individual weekly sessions and social skills group weekly sessions for the child and parent training about SocAD, 12 weeks	CDI change from baseline	12	IG1: 16 IG2: 16	IG1: 6.4 (SD: 6.1) IG2: 9.3 (SD: 9.7)	23	11.0 (SD: 7.7)	F=1.2	P=NS
	Ost et al, 2015[212]	11.6	Individual weekly sessions and social skills group weekly sessions for the child and parent training about SocAD, 12 weeks	SPAI-P change from baseline	12	IG1: 16 IG2: 16	IG1: 19.8 (SD: 10.7) IG2: 24.6 (SD: 12.5)	23	29.8 (SD: 8.7)	F=4.2;	<0.05; IG1 vs. CG: P=sig, NR, favoring IG1; IG2 vs. CG: P=NS

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual CBT, Sertraline, Individual CBT+Sertraline (continued)	Ost et al, 2015[212]	11.6	Individual weekly sessions and social skills group weekly sessions for the child and parent training about SocAD, 12 weeks	FSSCR change from baseline	12	IG1: 16 IG2: 16	IG1: 109.1 (SD: 23.7) IG2: 117.3 (SD: 30.2)	23	119.3 (SD: 32.6)	F=0.8	>0.05; IG1 vs. CG: P=NS; IG2 vs. CG: P=NS
Internet CBT	Donovan et al, 2014[83]	4.1	Online individual parent-focused CBT, 8 weeks	CSR	8	23	3.4 (SD: 2.4)	27	4.7 (SD: 2.0)	Partial eta squared=0.176 (mITT) 0.188 (ITT)	0.002 (mITT) 0.001 (ITT)
	Donovan et al, 2014[83]	4.1	Online individual parent-focused CBT, 8 weeks	PAS	8	19	30.0 (SD: 14.7)	29	40.2 (SD: 17.0)	Partial eta-squared=0.131 0.066 (mITT)	0.011 (mITT) 0.66 (ITT)
	Stjerneklar et al, 2019[141]	15	Internet CBT based on Cool Kids and Chilled anxiety management program, 14 weeks	ADIS-DSM IV CSR (primary diagnosis) change from baseline	14	35	NR	35	NR	Cohen's d=0.65;	0.022
	Stjerneklar et al, 2019[141]	15	Internet CBT based on Cool Kids and Chilled anxiety management program, 14 weeks	ADIS-DSM-IV CSR (all anxiety diagnoses) change from baseline	14	35	NR	35	NR	Cohen's d=0.83	0.002
	Stjerneklar et al, 2019[141]	15	Internet CBT based on Cool Kids and Chilled anxiety management program, 14 weeks	SCAS-C change from baseline	14	35	NR	35	NR	Cohen's d=0.68	<0.001

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Internet CBT (continued)	Stjerneklar et al, 2019[141]	15	Internet CBT based on Cool Kids and Chilled anxiety management program, 14 weeks	SCAS-M change from baseline	14	35	NR	35	NR	Cohen's d=1.12	<0.001
	Stjerneklar et al, 2019[141]	15	Internet CBT based on Cool Kids and Chilled anxiety management program, 14 weeks	SCAS-F change from baseline	14	35	NR	35	NR	Cohen's d=0.46	0.011
	Waite et al, 2019[152]	14.7	Internet CBT with accompanying parent sessions for half the group and no parent sessions for the other half, 10 weeks	CSR change from baseline	17	30	3.89 (SD: 2.58)	30	4.86 (SD: 2.19)	Effect size=0.05 (95% CI, 0.00 to 0.19)	NR
	Waite et al, 2019[152]	14.7	Internet CBT with accompanying parent sessions for half the group and no parent sessions for the other half, 10 weeks	SCAS-C change from baseline	17	30	30.35 (SD: 19.17)	30	33.46 (SD: 15.01)	Effect size=0.05 (95% CI, 0.00 to 0.20)	NR

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Internet CBT (continued)	Waite et al, 2019[152]	14.7	Internet CBT with accompanying parent sessions for half the group and no parent sessions for the other half, 10 weeks	SCAS-P change from baseline	17	30	33.12 (SD: 21.70)	30	28.93 (SD: 15.79)	Effect size=0.06 (95% CI, 0.00 to 0.21)	NR
Parent-only CBT	Cobham et al, 2017[77]	9.3	Parent-only group-based CBT sessions, 6 weeks	ADIS-CSR	6	33	3.7 (SD: 2.6)	29	5.4 (SD: 1.1)	NR	<0.001
	Cobham et al, 2017[77]	9.3	Parent-only group-based CBT sessions, 6 weeks	SCAS-M	6	33	20.1 (SD: 4.9)	29	32.3 (SD: 11.9)	NR	<0.001
	Cobham et al, 2017[77]	9.3	Parent-only group-based CBT sessions, 6 weeks	SCAS-F	6	33	21.4 (SD: 14.4)	29	30.6 (SD: 15.2)	NR	0.53
	Cobham et al, 2017[77]	9.3	Parent-only group-based CBT sessions, 6 weeks	SCAS-C	6	33	34.4 (SD: 13.9)	29	42.1 (SD: 11.5)	NR	<0.01
Parent-only and parent-child CBT	Hirshfeld-Becker et al, 2010[98]	5.4	Being Brave manualized CBT intervention with parent-only and parent-child sessions, 6 months	CGI-I SocAD score	24	19	2.42 (SD: 0.96)	20	3.40 (SD: 1.05)	Hedge's g=0.95 (95% CI, 0.29 to 1.62)	<0.01

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Parent-only and parent-child CBT (continued)	Hirshfeld-Becker et al, 2010[98]	5.4	Being Brave manualized CBT intervention with parent-only and parent-child sessions, 6 months	CGI-I S SepAD score	24	12	1.67 (SD: 0.98)	13	2.46 (SD: 0.88)	Hedge's g=0.82 (95% CI, 0.01 to 1.64)	0.045
	Hirshfeld-Becker et al, 2010[98]	5.4	Being Brave manualized CBT intervention with parent-only and parent-child sessions, 6 months	CGI-I GAD score	24	12	2.17 (SD: 0.83)	12	2.58 (SD: 1.38)	NR	0.38
	Hirshfeld-Becker et al, 2010[98]	5.4	Being Brave manualized CBT intervention with parent-only and parent-child sessions, 6 months	CGI-I specific phobia score	24	15	1.87 (SD: 1.30)	15	2.87 (SD: 1.19)	Hedge's g=0.78 (95% CI, 0.04 to 1.52)	0.037
	Hirshfeld-Becker et al, 2010[98]	5.4	Being Brave manualized CBT intervention with parent-only and parent-child sessions, 6 months	CGI-I agoraphobia score	24	9	2.22 (SD: 0.83)	11	2.55 (SD: 1.45)	NR	0.58

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Parent-child CBT	Ishikawa et al, 2019[103]	10.9	Japanese Anxiety Children/ Adolescents Cognitive Behavior; Therapy program, 8 weeks, with up to 3 subsequent booster sessions until 6 months after completion of therapy	SCAS-C	8 or 16 (post-treatment)	25	28.28 (SE: 3.55)	24	35.95 (SE: 3.97)	NR	P=NS
	Ishikawa et al, 2019[103]	10.9	Japanese Anxiety Children/ Adolescents Cognitive Behavior; Therapy program, 8 weeks, with up to 3 subsequent booster sessions until 6 months after completion of therapy	ADIS-DSM-IV CSR on primary diagnosis	8 or 16 (post-treatment	25	3.08 (SE: 0.50)	24	6.0 (SE: 0.51)	NR	<0.001 favoring CBT

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Parent-child CBT (continued)	Ishikawa et al, 2019[103]	10.9	Japanese Anxiety Children/ Adolescents Cognitive Behavior; Therapy program, 8 weeks, with up to 3 subsequent booster sessions until 6 months after completion of therapy	SCAS-P	8 or 16 (post-treatment	25	25.42 (SE: 2.57)	24	27.57 (SE: 2.62)	NR	<0.01 favoring CBT
Parent-guided CBT supported by telephone	Lyneham et al, 2006[112]	9.4	Parent-guided CBT supported by telephone using self-help book (Helping Your Anxious Child: A Step by Step Guide for Parents) and a workbook companion, 12 weks	ADIS CSR (sum of all anxiety disorders)	12	IG1: 28 IG2: 21 IG3: 29	NR	22	NR	IG1 vs. CG: Effect size cohen's d=2.19 IG2 vs. CG: Effect size cohen's d=1.57 IG3 vs. CG: Effect size cohen's d=0.80 Across all groups: Eta squared=0.49	IG1 vs. CG: <0.01; IG2 vs. CG: <0.01; IG3 vs. CG: <0.01; Across all groups: <0.01

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Parent-guided CBT supported by telephone (continued)	Lyneham et al, 2006[112]	9.4	Parent-guided CBT supported by telephone using self-help book (Helping Your Anxious Child: A Step by Step Guide for Parents) and a workbook companion, 12 weks	SCAS-M	12	IG1: 28 IG2: 21 IG3: 29	IG1: 39.50 (SD: 14.94) pretreat-ment 20.36 (SD: 16.04) 12 weeks IG2: 36.00 (SD: 14.57) pretreat-ment; 21.29 (SD: 14.28) 12 weeks IG3: 34.97 (SD: 15.50) pretreat-ment 22.97 (SD: 15.20) 12 weeks	22	39.23 (SD: 13.89) pretreat-ment 37.77 (SD: 15.26) 12 weeks	NR	NR

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Parent-guided CBT supported by telephone (continued)	Lyneham et al, 2006[112]	9.4	Parent-guided CBT supported by telephone using self-help book (Helping Your Anxious Child: A Step by Step Guide for Parents) and a workbook companion, 12 weks	SCAS-F	12	IG1: 28 IG2: 21 IG3: 29	IG1: 32.46 (SD: 14.48) pretreat-ment 22.50 (SD: 13.48) 12 weeks IG2: 26.47 (SD: 9.91) pretreat-ment 18.76 (SD: 10.37) 12 weeks IG3: 29.80 (SD: 16.90) pretreat-ment 19.60 (SD: 13.45) 12 weeks	22	28.33 (SD: 17.68) pre-treatment 29.50 (SD: 18.39) 12 weeks	NR	NR

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Parent-guided CBT supported by telephone (continued)	Lyneham et al, 2006[112]	9.4	Parent-guided CBT supported by telephone using self-help book (Helping Your Anxious Child: A Step by Step Guide for Parents) and a workbook companion, 12 weks	SCAS-C	12	IG1: 28 IG2: 21 IG3: 29	IG1: 43.54 (SD: 16.65) pretreat-ment 23.79 (SD: 14.84) 12 weeks IG2: 35.90 (SD: 12.13) pretreat-ment 24.86 (SD: 12.94) 12 weeks IG3: 35.17 (SD: 20.66) pretreat-ment 25.79 (SD: 19.51) 12 weeks	22	37.77 (SD: 20.36) pretreat-ment 36.41 (SD: 21.87) 12 weeks	NR	NR
	Lyneham et al, 2006[112]	9.4	Parent-guided CBT supported by telephone using self-help book (Helping Your Anxious Child: A Step by Step Guide for Parents) and a workbook companion, 12 weks	RCMAS-C	12	IG1: 28 IG2: 21 IG3: 29	IG1: 17.25 (SD: 5.72) pretreat-ment 10.89 (SD: 6.55) 12 weeks IG2: 14.14 (SD: 6.35) pretreat-ment 8.67 (SD: 6.21) 12 weeks IG3: 14.17 (SD: 7.48) pretreat-ment 10.28 (SD: 7.66) 12 weeks	22	15.59 (SD: 7.57) pretreat-ment 15.73 (SD: 7.30) 12 weeks	NR	NR

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Parent-delivered CBT	Rudy et al, 2017[129]	5.36	Exposure therapy first led by a therapist and then led by a parent, 5 weeks	ADIS CSR	5	12	2.72 (SD: 1.56)	10	4.56 (SD: 1.81)	Effect size d=2.39	0.009
	Rudy et al, 2017[129]	5.36	Exposure therapy first led by a therapist and then led by a parent, 5 weeks	CGI-S	5	12	2.00 (SD: 0.89)	10	3.33 (SD: 0.71)	Effect size d=2.75	<0.001
	Rudy et al, 2017[129]	5.36	Exposure therapy first led by a therapist and then led by a parent, 5 weeks	PARS	5	12	9.72 (SD: 4.76)	10	15.78 (SD: 3.35)	Effect size d=3.18	0.046
	Thirlwall et al, 2013[145]	NR, partici-pants ages 7 to 12 years	Parent-delivered CBT with a self-help book, 8 weeks	SCAS-P	12	IG1: 38 IG2: 42	IG1: 24.16 (SD: 12.93) IG2: 20.45 (SD: 11.52)	46	24.15 (SD: 11.36)	NR	IG1 vs. CG: P=NS; IG2 vs. CG: P=NS
	Thirlwall et al, 2013[145]	NR, partici-pants ages 7 to 12 years	Parent-delivered CBT with a self-help book, 8 weeks	SCAS-C	12	IG1: 40 IG2: 47	IG1: 30.00 (SD: 12.6) IG2: 28.47 (SD: 20.0)	57	29.40 (SD: 16.28)	NR	IG1 vs. CG: P=NS; IG2 vs. CG: P=NS
Family-based CBT	Shortt et al, 2001[134]	7.9	Family Based Cognitive Behavioral therapy sessions termed "FRIENDS," adapted from Coping Koala Workbook, 10 weeks	RCMAS	10	53	8.6 (SD: 0.97)	12	9.8 (SD: 2.0)	Eta squared=0.10	<0.05

Appendix F Table 3. Anxiety CBT Interventions vs. Wait-List, Treatment as Usual, or Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo; N	Placebo; Score (SD/SE)	Between-Group Difference	Between-Group P Value
Family-based CBT (continued)	Shortt et al, 2001[134]	7.9	Family Based Cognitive Behavioral therapy sessions termed "FRIENDS," adapted from Coping Koala Workbook, 10 weeks	DISCAP CSR	10	48	1.06 (SD: 0.24)	16	4.13 (SD: 0.41)	Eta squared=0.46	<0.001

Abbreviations: ADIS-C/P=Anxiety Disorders Interview Schedule for DSM-IV for Children-Children/Parents; ADIS CSR=Anxiety Disorders Interview Schedule clinician severity ratings; ADIS-DSM=Anxiety and Related Disorders Interview Schedule--Diagnostic and Statistical Manual; CBT=cognitive behavioral therapy; CDI=Children's Depression Inventory; CG=control group; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; CI=confidence interval; CSR=Clinician Severity Rating; DISCAP=Diagnostic Interview Schedule for Children, Adolescents, and Parents; DSM IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; FSSCR=Fear Survey Schedule for Children-Revised; GAD=general anxiety disorder; IG=intervention group; ITT=intention to treat; LSAS-CA=Liebowitz Social Anxiety Scale for Children and Adolescents; MASC-child=Multidimensional Anxiety Scale for Children; MASC-parent=Multidimensional Anxiety Scale for Parents; mITT=modified intent to treat; N=number; NR=not reported; NS=not significant; PARS=Pediatric Anxiety Rating Scale; PAS=Preschool Anxiety Scale; PSWQ-C=Penn State Worry Questionnaire for Children; RCMAS=Revised Children's Manifest Anxiety Scale; RCMAS-C=Revised Children's Manifest Anxiety Scale; SASC-R=Social Anxiety Scale for Children-Revised; SCARED-C=Screen for Anxiety Related Emotional Disorders for Children; SCARED-P=Screen for Anxiety Related Emotional Disorders-Parents; SCAS-C=Spence Children's Anxiety Scale-Child-rated; SCAS-P=Spence Children's Anxiety Scale-Parent-rated; SCAS-R Child=Spence Children's Anxiety Scale Revised-Child-rated; SCAS-R=Spence Children's Anxiety Scale Revised-Parent-rated; SD=standard deviation; SE=standard error; SepAD=separation anxeity disorder; SMQ-P=Selective Mutism Questionnaire-Parent; SocAD=social anxiety disorder; SPAI-C=Social Phobia and Anxiety Inventory for Children; SPAI-P=Social Phobia and Anxiety Inventory for Children for Parents; vs.=versus.

Appendix F Table 4. Anxiety Pharmacotherapy Interventions vs. Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Duloxetine (GAD)	Strawn et al, 2015[142]	12.4	Flexibly dosed duloxetine (30–120 mg/d)	Change in PARS (severity for GAD)	10	135	-9.7 (SE: 0.5)	137*	-7.1 (SE: 0.5)	NR	≤0.001†
				Change in PARS severity total score	10	135	-9.2 (SE: 0.5)	137*	-6.4 (SE: 0.5)	NR	≤0.001†
				Change in CGI-S	10	135	-1.9 (SE: 0.1)	137*	-1.4 (0.1)	NR	≤0.001†
Escitalopram (GAD)	Strawn et al, 2020[143]	14.8	Forced titration to 15 mg/d, then flexible titration to 20 mg/d	Change in PARS	8	26	-8.65 (SD: 1.31)	25	-3.52 (SD: 1.06)	NR	0.005†
				CGI-S	8	26	2.8 (SD: 0.3)	25	3.6 (SD: 0.2)	NR	<0.001†
Fluoxetine (any anxiety disorder)	Birmaher et al, 2003[73]	11.8	10 mg/d, after first week, up to 20 mg/d	SCARED-C	12	37	11.7 (SD: 12.4)	37	12.10 (SD: 7.3)	NR	0.03†
				SCARED-P	12	37	16.3 (SD: 12.7)	37	22 (SD: 12.3)	NR	0.04†
				PARS	12	37	7.1 (SD: 5.9)	37	9.3 (SD: 4.8)	NR	0.007† (0.08 for post-test differences)
Fluvoxamine (GAD, SepAD, or SocAD)	Pine et al, 2001[124] Walkup et al, 2001[213] Ginsburg et al, 2006[214] Reinblatt et al, 2009[215]	10.4	50 mg/d, then increase 50 mg/w to max. 300 mg/d in adolescents (13-17 years) and 250 mg/d in children ≤12 years of age	PARS	8	63	9.0 (SD: 7.0)	65	15.9 (SD: 5.3)	NR	<0.001†
Sertraline (GAD)	Rynn et al, 2001[130]	11.7	25 mg/d for the first week and 50 mg/d for weeks 2 to 9	HAM-A	9	11	7.8 (SD: 5.7)	11	21.0 (SD: 7.8)	NR	<0.001†
				CGI-S	9	11	2.4 (SD: 0.8)	11	3.9 (SD: 0.3)	NR	<0.001†
				CGI-I	9	11	2.1 (SD: 1.1)	11	3.5 (SD: 0.7)	NR	0.001

Appendix F Table 4. Anxiety Pharmacotherapy Interventions vs. Placebo: Anxiety Symptoms

Treatment (Condition)	Author, Year	Mean Age (Years)	Dose	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Sertraline (GAD) (continued)				ADIS CSR-C	9	11	2.7 (SD: 2.0)	11	4.6 (SD: 2.0)	NR	0.11‡
				ADIS CSR-P	9	11	2.6 (SD: 1.7)	11	4.9 (SD: 2.0)	NR	<0.007‡
				RCMAS	9	11	8.9 (SD: 7.0)	11	14.6 (SD: 8.2)	NR	<0.02‡
				MASC	9	11	35.7 (SD: 17.2)	11	56.4 (SD: 16.3)	NR	<0.03‡
Sertraline (GAD, SepAD, or SocAD)	Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Caporino et al, 2017[216]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	25mg/d, up to 200 mg/d by 8th week	PARS	12	133	9.8 (SD: 6.2)	76	12.6 (SD: 6.3)	Hedge's g (95% CI): 0.45 (0.17 to 0.74)	NS
				CGI-S	12	133	3.0 (SD: 1.3)	76	3.8 (1.4)	NR	CIs of individual treatments do not overlap
				MASC-C	12	133	38.2 (SD: 10.7)	76	42.9 (11.8)	b=−4.68, t=−2.80	0.03
				MASC-P	12	133	37.9 (SD: 17.3)	76	49.1 (16.9)	b=−11.1, t=−4.4	<0.001
				SCARED-C	12	133	9.3 (SD: 11.9)	76	13.8 (12.1)	NR	p=NS, p=NR
				SCARED-P	12	133	11.0 (SD: 11.7)	76	19.5 (11.8)	NR	<0.001

* N randomized=137, N analyzed=133. Conversion of standard error to standard deviation based on N analyzed.

† Difference in change from baseline to followup.

‡ Difference at followup.

Appendix F Table 4. Anxiety Pharmacotherapy Interventions vs. Placebo: Anxiety Symptoms

Abbreviations: ADIS=Anxiety Disorders Interview Schedule; ADIS-CSR=Anxiety Disorders Interview Schedule Clinician Severity Rating CGI=Clinical Global Impressions; CI=confidence interval; CSR-C=clinical severity score-child-rated; CSR-P= clinical severity score-parent-rated; GAD=generalized anxiety disorder; HAM-A=Hamilton Anxiety Rating Scale; MASC=Multidimensional Anxiety Scale for Children; N=number; NR=not reported; NS=not statistically significant; PARS=Pediatric Anxiety Rating Scale; RCMAS=Revised Children's Manifest Anxiety Scale; SCARED-C=Screen for Anxiety Related Emotional Disorders Child version; SCARED-P=Screen for Anxiety Related Emotional Disorders – Parent version; SD=standard deviation; SE=standard error; SepAD=separation anxiety disorder; SocAD=social anxiety disorder; vs.=versus.

Appendix F Table 5. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Response

Treatment (Condition)	Author, Year, Trial Number	Mean Age	Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect measure (95% CI), p value
Group child+parent in-person CBT	Cornacchio et al, 2019[79]	6.6	5 days	CGI-I≤2	4	14	7 (50)	15	0 (0)	(-0.58), P≤0.01
Individual child-focused in-person CBT	Ginsburg et al, 2020[92]	10.9	12 weeks	CGI-I≤2	12	148	NR (42.1)	68	NR (36.7)	P=0.34
Individual child-focused in-person CBT	Salzer et al, 2018[42] ISRCTN 22752528	17.4	31 weeks	LSAS-CA ≥31% reduction in total score	Post-treatment	34	NR (66)	39	NR (20)	(2.17 to 28.86), P=0.006
Individual child-focused in-person CBT	Walkup et al, 2008[153]; Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Caporino et al, 2017[216]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	12 weeks	CGI-I ≤2	12	139	83 (59.7)	76	18 (23.7)	(2.5 to 9.0), P<0.001
Individual child-focused internet CBT	Stjerneklar et al, 2019[141] NCT02535403	15	14 weeks	Clinically reliable change in SCAS-C	14	32	22 (69)	31	8 (26)	P=0.001

Appendix F Table 5. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Response

Treatment (Condition)	Author, Year, Trial Number	Mean Age	Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect measure (95% CI), p value
	Stjerneklar et al, 2019[141] NCT02535403	15	14 weeks	Clinically reliable change in SCAS-M	14	35	24 (69)	32	7 (22)	P<0.001
	Stjerneklar et al, 2019[141] NCT02535403	15	14 weeks	Clinically reliable change in SCAS-F	14	25	9 (35)	27	5 (19)	P=0.156
Individual child+parent in-person CBT	Hirshfeld-Becker et al, 2010[98]	5.4	6 months	CGI-I ≤2	6 months	34	20 (59)	30	9 (30)	P=0.016
Individual parent-led in-person CBT	Rudy et al, 2017[129] NCT02051192	5.36	5 weeks	CGI-I ≤2	5	12	10 (83.3)	10	0 (0.0)	P<0.001
Internet delivered CBT with and without parent sessions	Waite et al, 2019[152] ISRCTN79652741	14.7	10 weeks	CGI ≤2	17	30	12 (40.0)	30	9 (30.0)	(0.53-4.53)

Abbreviations: CBT=cognitive behavioral therapy; CGI-I=Clinical Global Impressions-Improvement; CI=confidence interval; LSAS-CA=Liebowitz Social Anxiety Scale for Children and Adolescents; NR=not reported; SCAS-C=Spence Children's Anxiety Scale-Child-rated; SCAS-F=Spence Children's Anxiety Scale -Father; SCAS-M=Spence Children's Anxiety Scale -Mother; vs.=versus.

Appendix F Table 6. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Remission

Treatment (Condition)	Author, Year	Mean Age	Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p value
Individual child-focused in-person CBT	Salzer et al, 2018[42] ISRCTN 22752528	17.4	31 weeks	LSAS-CA ≤30	Post-treatment	32	NR (47)	36	NR (6)	(1.85 to 114.95), P=0.0009
Individual child-focused in-person CBT	Walkup et al, 2008[153]; Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Caporino et al, 2017[216]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	12 weeks	CGI-S ≤2	12	139	50 (35.9)	76	21 (27.1)	(0 to 3.53), P=0.49
	Walkup et al, 2008[153]; Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Caporino et al, 2017[216]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	12 weeks	CGI-I=1	12	139	28 (20.4)	76	11 (15.0)	(0 to 4.78), P=0.61
Individual child+parent in-person CBT	Ishikawa et al, 2019[103]	10.9	8 weeks	SCAS-C; clinically significant change	2 or 4 months	25	14 (56.0)	24	9 (37.5)	P=0.20
	Ishikawa et al, 2019[103]	10.9	8 weeks	SCAS-P; clinically significant change	2 or 4 months	25	8 (32.0)	24	5 (20.83)	P=0.38

Appendix F Table 6. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Remission

Treatment (Condition)	Author, Year	Mean Age	Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p value
Individual child+parent in-person CBT (continued)	Ishikawa et al, 2019[103]	10.9	8 weeks	DSRS; clinically significant change	2 or 4 months	25	9 (36.0)	24	5 (20.83)	P=0.24
	Ishikawa et al, 2019[103]	10.9	8 weeks	CDI; clinically significant change	2 or 4 months	25	10 (40.0)	24	4 (16.67)	P=0.07
Individual child-focused internet CBT	Stjerneklar et al, 2019[141] NCT02535403	15	14 weeks	SCAS-C; Clinically significant change	14	32	14 (44)	31	2 (6)	P=0.001
	Stjerneklar et al, 2019[141] NCT02535403	15	14 weeks	SCAS-M; Clinically significant change	14	35	9 (26)	32	2 (6)	P=0.032
	Stjerneklar et al, 2019[141] NCT02535403	15	14 weeks	SCAS-F; Clinically significant change	14	25	1 (4)	27	2 (7)	P=1.00
IG1: Individual child+parent telephone CBT IG2: Individual child+parent email CBT IG3: Individual child+parent client-initiated CBT	Lyneham et al, 2006[112] NR	9.4	12 weeks	SCAS-C normal range	12	IG1: 28 IG2: 21 IG3: 29	IG1: NR (62) IG2: NR (57) IG3: NR (50)	22	NR (23)	Any IG vs. CG: P<0.05
Individual parent-led in-person CBT	Rudy et al, 2017[129] NCT02051192	5.36	5 weeks	ADIS-CSR <4	5	12	8 (66.7)	10	1 (10.0)	P=0.011
Group child+parent in-person CBT	Arendt et al, 2016[65]	11.8	10 weeks	Clinically significant change in SCAS-C	10	56	24 (42.9)	53	6 (11.3)	P≤0.001
	Arendt et al, 2016[65]	11.8	10 weeks	Clinically significant change in SCAS-M	10	56	29 (51.8)	53	6 (11.3)	P≤0.001
	Arendt et al, 2016[65]	11.8	10 weeks	Clinically significant change in SCAS-F	10	56	23 (41.8)	53	5 (9.8)	P≤0.001

Abbreviations: ADIS=Anxiety Disorders Interview Schedule for DSM-IV for Children; ADIS-CSR=Anxiety Disorders Interview Schedule for DSM-IV for Children Clinician Severity Rating; CBT=cognitive behavioral therapy; CDI=Children's Depression Inventory; CG=control group; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; CI=confidence interval; DSRS=Depression Self-Rating Scale; IG=intervention group; LSAS-CA=Liebowitz Social Anxiety Scale for Children and Adolescents; N=number; NR=not reported; SCAS-C=Spence Children's Anxiety Scale-Child-rated; SCAS-F=Spence Children's Anxiety Scale-Child-rated-Female; SCAS-M=Spence Children's Anxiety Scale-Child-rated-Male; SCAS-P=Spence Children's Anxiety Scale-Parent-rated; vs.=versus.

Appendix F Table 7. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age	Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p value
Group child-focused in-person CBT	Holmes et al, 2014[99] ACTRN12612000061831	9.6	10 weeks	ADIS-C/P; absence of GAD diagnosis	10	17	NR (52.9)	19	NR (0)	P<0.001
	Holmes et al, 2014[99] ACTRN12612000061831	9.6	10 weeks	ADIS-C/P; absence of any anxiety diagnosis	10	17	NR (17.6)	19	NR (0)	P=0.056
Group child+parent in-person CBT	Arendt et al, 2016[65]	11.8	10 weeks	ADIS-C/P; free of primary diagnosis	10	56	37 (66.1)	53	4 (7.5)	P<0.001
	Arendt et al, 2016[65]	11.8	10 weeks	ADIS-C/P; free of all anxiety diagnoses	10	56	27 (48.2)	53	3 (5.7)	P<0.001
Group child+parent in-person CBT	Cornacchio et al, 2019[79]	6.6	5 days	ADIS/C-P; Loss of selective mutism diagnosis	4	14	1 (7.1)	15	0 (0)	(0.19), P=1.00
Group child+parent in-person CBT	Lau et al, 2010[110] NR	8 years 7 months	11 weeks	K-SADS; presence of anxiety diagnosis or symptoms	13	24	16 (67)	21	21 (100)	P<0.01
	Lau et al, 2010[110] NR	8 years 7 months	11 weeks	K-SADS; absence of anxiety diagnosis or subclinical symptoms	13	24	8 (33)	21	0 (0)	NR
Group child+parent in-person CBT	Shortt et al, 2001[134]	7.9	10 weeks	DISCAP; anxiety free diagnosis	10	48	33 (69)	16	1 (6)	P<0.001
Individual child-focused in-person CBT	Barrett et al, 1996[70]	9.4	12 weeks	ADIS; no longer meeting criteria for current anxiety disorder	12	IG1/2: 53	37 (69.8)	23	6 (26.0)	P<0.05
Individual child-focused in-person CBT	Ginsburg et al, 2020[92]	10.9	12 weeks	ADIS; no anxiety disorder	12	148	NR (34.9)	68	NR (35.0)	P=0.67

Appendix F Table 7. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age	Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p value
Individual child-focused in-person CBT (continued)	Ginsburg et al, 2020[92]	10.9	12 weeks	ADIS; loss of primary anxiety disorder	12	148	NR (40.5)	68	NR (43.4)	P=0.61
Individual child-focused in-person CBT	Walkup et al, 2008[153]; Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Caporino et al, 2017[216]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	12 weeks	ADIS-C/P; loss of anxiety diagnosis	12	139	64 (46.2)	76	18 (23.7)	(1.03 to 4.79), P=0.05
Individual child-focused internet CBT	Stjerneklar et al, 2019[141] NCT02535403	15	14 weeks	ADIS; free of primary anxiety diagonsis	14	35	14 (40)	32	5 (16)	P=0.027
	Stjerneklar et al, 2019[141] NCT02535403	15	14 weeks	ADIS; free of any anxiety diagnosis	14	35	10 (29)	32	1 (3)	P=0.005
Individual child + parent in-person + internet CBT	Perrin et al, 2019[122] ISRCTN50951795	13.4	10 weeks	ADIS; presence of GAD	10	20	4 (20)	20	20 (100)	P<0.001
	Perrin et al, 2019[122] ISRCTN50951795	13.4	10 weeks	ADIS; presence of comorbid disorder	10	20	1 (5)	20	11 (55)	P<0.001
	Perrin et al, 2019[122] ISRCTN50951795	13.4	10 weeks	ADIS; recovery from all disorders	10	20	16 (80)	20	0 (0)	P<0.000
Individual child + parent in-person CBT	Hirshfeld-Becker et al, 2010[98]	5.4	6 months	SCID; absence of anxiety diagnosis	6 months	34	17 (50)	30	5 (17)	P<0.01
Individual child + parent in-person CBT	Ishikawa et al, 2019[103]	10.9	8 weeks	ADIS; free of principal diagnosis	2 or 4 months	26	13 (50.0)	25	3 (12.0)	P<0.01
	Ishikawa et al, 2019[103]	10.9	8 weeks	ADIS; free of any diagnosis	2 or 4 months	26	4 (15.38)	25	1 (4.0)	NS
Individual child+parent internet CBT	Waite et al, 2019[152] ISRCTN79652741	14.7	10 weeks	ADIS-C/P; remission of primary anxiety diagnosis	17 weeks	30	12 (40.0)	30	7 (23.3)	(0.72 to 6.70)

Appendix F Table 7. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age	Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p value
Individual child+parent internet CBT (continued)	Waite et al, 2019[152] ISRCTN79652741	14.7	10 weeks	ADIS-C/P; remission of all anxiety diagnoses	17 weeks	30	8 (26.7)	30	4 (13.3)	(0.63 to 8.92)
Parent-guided CBT supported by telephone	Lyneham et al, 2006[112] NR	9.4	12 weeks	ADIS; loss of prinicpal anxiety disorder	12	IG1: 28 IG2: 21 IG3: 29	NR	22	NR	Any IG vs. CG, P<0.01
	Lyneham et al, 2006[112] NR	9.4	12 weeks	ADIS; loss of any anxiety disorder	12	IG1: 28 IG2: 21 IG3: 29	NR	22	NR	Any IG vs. CG, P<0.01
Individual and group CBT, parent training	Ost et al, 2015[120]	11.6	12 weeks	ADIS; no longer fufilling criteria for social phobia	12 months	IG1: 16 IG2: 16	IG1: 9 (56) IG2: 10 (62)	23	2 (9)	IG1 vs. CG: P≤0.001 IG2 vs. CG: P≤0.001
Individual CBT	Villabo et al, 2018[150] NR	10.5	12 weeks	ADIS; loss of primary anxiety diagnosis	12	IG1: 44 IG2: 52	IG1: NR (52) IG2: NR (65)	51	NR (14)	IG1 vs CG: (21 to 56), P<0.001 IG2 vs CG: (35 to 68), P<0.001
	Villabo et al, 2018[150] NR	10.5	12 weeks	ADIS; loss of all anxiety disorders	12	IG1: 44 IG2: 52	IG1: NR (38) IG2: NR (56)	51	NR (6)	IG1 vs CG: (16 to 47), P<0.001 IG2 vs CG: (34 to 65), P<0.001
Parent-delivered CBT full CBT	Thirlwall et al, 2013[145] ISRCTN92977593	NR; partici-pants ages 7 to 12 years	8 weeks	ADIS; loss of primary diagnosis	12	46	IG1: 18 (39) IG2: 25 (50)	63	16 (25)	IG1 vs. CG: (0.89 to 2.74), P=0.119 IG2 vs. CG: (1.14 to 2.99), P=0.013
	Thirlwall et al, 2013[145] ISRCTN92977593	NR; partici-pants ages 7 to 12 years	8 weeks	ADIS; loss of any diagnosis	12	46	IG1: 7 (15) IG2: 17 (34)	63	7 (11)	IG1 vs CG: (0.56 to 3.88), P=0.433 IG2 vs CG: (1.40 to 7.01), P=0.006
Group parent-only in-person CBT	Cobham et al, 2017[77] ACTRN12615000514505	9.3	6 weeks	ADIS; absence of primary diagnosis	6	31	20 (64.5)	29	5 (16.2)	(0.259 to 0.709), P<0.001
	Cobham et al, 2017[77] ACTRN12615000514505	9.3	6 weeks	ADIS; absence of any diagnosis	6	31	12 (38.7)	29	1 (3.4)	(0.47 to 0.82), P<0.001

Appendix F Table 7. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age	Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p value
Individual parent-focused internet CBT	Donovan et al, 2014[83] ACTRN12612000139875	4.1	8 weeks	ADIS; absence of primary diagnosis	8	23	9 (39)	27	7 (26)	P=0.318
	Donovan et al, 2014[83] ACTRN12612000139875	4.1	8 weeks	ADIS; absencse of any diagnosis	8	23	8 (35)	27	7 (26)	P=0.496

Abbreviations: ADIS=Anxiety Disorders Interview Schedule for DSM-IV for Children; ADIS-C/P=Anxiety Disorders Interview Schedule for DSM-IV for Children-Children/Parents; CBT=cognitive behavioral therapy; CG=control group; CI=confidence interval; DISCAP=Diagnostic Interview Schedule for Children, Adolescents, and Parents; GAD=general anxiety disorder; IG=intervention group; K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; lifetime version; N=number; NR=not reported; NS=not significant; SCID=structured clinical interview; vs.=versus.

Appendix F Table 8. Anxiety Pharmacotherapy vs. Placebo for Anxiety in Children: Response

Treatment (Condition)	Author, Year	Mean Age	Dose (md/day)	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p Value
Escitalopram (GAD)	Strawn et al, 2020[143]	14.8	Forced titration to 15 mg/d, then flexible titration to 20 mg/d, 8 weeks	CGI-I score ≤2	8	26	16 (62)	25	6 (24)	NR P=0.0039
Fluoxetine (GAD, SepAD, or social phobia)	Birmaher et al, 2003[73]	11.8	Fluoxetine 10 mg/day, after first week increasing to 20 mg/day if tolerated	CGI-I score ≤2	12	36	22 (61)	37	13 (35)	Effect size=0.26 P=0.03
Fluoxetine (selective mutism)	Black et al, 1994[74]	8.5	Fluoxetine 0.2 mg/kg for 1 week, then 0.4 mg/kg for 1 week, then 0.6 mg/kg for 10 weeks	CGI-I score ≤2	12	6	3 (50)	9	4 (44.4)	NR P=NS
Sertraline (GAD)	Rynn, 2001[130]	11.7	25 mg for the first week and 50 mg for weeks 2 to 9, 9 weeks	CGI-I score ≤2	9	11	10 (91)	11	1 (9)	NR P<0.0001
Sertraline (GAD, SepAD, or SocAD)	Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Caporino et al, 2017[216]; Sanchez, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211] NCT00052078	10.7	25 mg/day, up to 200 mg/day by 8th week, for 12 weeks	CGI-I score ≤2	12	133	73 (54.9)	76	18 (23.7)	OR: 3.9 (3.0 to 5.9), P<0.001

Abbreviations: CGI-I=Clinical Global Impressions-Improvement; CI=confidence interval; GAD=general anxiety disorder; N=number; NR=not reported; NS=not significant; OR=odds ratio; SepAD=separation anxiety disorder; SocAD=social anxiety disorder; vs.=versus.

Appendix F Table 9. Anxiety Pharmacotherapy Interventions vs. Placebo: Remission

Treatment (Condition)	Author, Year	Mean Age	Dose (md/day)	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p Value
Duloxetine (GAD)	Strawn et al, 2015[142]	12.4	Flexibly dosed duloxetine (30–120 mg/d)	CGI-S score ≤2	10	135	(54)	133	(35)	NR P≤0.02
	Strawn et al, 2015[142]	12.4	Flexibly dosed duloxetine (30–120 mg/d)	CGI-I score=1	10	135	(50)	133	(34)	NR P≤0.05
Sertraline (GAD)	Rynn et al, 2001[130]	11.7	25 mg for the first week and 50 mg for weeks 2 to 9, 9 weeks	CGI-I score=1	9	11	2 (18)	11	0 (0)	NR P=0.28
Sertraline (GAD, SepAD, or SocAD)	Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Caporino et al, 2017[216]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211] NCT00052078	10.7	25 mg/day, up to 200 mg/day by 8th week, for 12 weeks	CGI-S score ≤2	12	133	62 (46.3)	76	21 (27.1)	OR: 2.55 (0 to 5.48), P=0.29
	Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Caporino et al, 2017[216]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211] NCT00052078	10.7	25 mg/day, up to 200 mg/day by 8th week, for 12 weeks	CGI-I score=1	12	133	45 (33.9)	76	11 (15.0)	OR: 3.56 (0 to 9.53), P=0.39
Sertraline (GAD, SepAD, or SocAD) (continued)	Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Caporino et al, 2017[216]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211] NCT00052078	10.7	25 mg/day, up to 200 mg/day by 8th week, for 12 weeks	Loss of anxiety diagnosis	12	133	61 (45.9)	76	18 (23.7)	OR: 2.84 (1.01 to 4.67), P=0.05

Appendix F Table 9. Anxiety Pharmacotherapy Interventions vs. Placebo: Remission

Abbreviations: CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; CI=confidence interval; GAD=general anxiety disorder; N=number; NR=not reported; OR=odds ratio; SepAD=separation anxiety disorder; SocAD=social anxiety disorder; vs.=versus.

Appendix F Table 10. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Functioning or Quality of Life

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Group CBT	Arendt et al, 2016[65]	11.8	Manualized group CBT program (Cool Kids), 10 weeks	CALIS youth	10	56	7.55 (SD: 6.46)	53	10.94 (SD: 7.20)	Partial eta squared=0.06	0.008
	Arendt et al, 2016[65]	11.8	Manualized group CBT program (Cool Kids), 10 weeks	CALIS mother	10	56	10.61 (SD: 7.28)	53	17.94 (SD: 9.07)	Partial eta squared=0.14	<0.001
	Arendt et al, 2016[65]	11.8	Manualized group CBT program (Cool Kids), 10 weeks	CALIS father	10	56	10.96 (SD: 7.72)	53	17.14 (SD: 9.16)	Partial eta squared=0.11 F=12	<0.001
	Cornacchio et al, 2019[79]	6.6	Group CBT program that relies on the early child format of Parent Child Interaction Therapy, 5 days	CGAS	4	14	53.6 (SD: 4.6)	15	52.5 (SD: 4.9)	Effect size Cohen's d=0.73	<0.1
	Holmes et al, 2014[99]	9.6	Group CBT program termed "No Worries!" that utilizes the A-B-C model, 10 weeks	CGAS	10	17	63.82 (SD: 11.03)	19	51.05 (SD: 7.66)	Partial eta squared=0.15	0.02
	Holmes et al, 2014[99]	9.6	Group CBT program termed "No Worries!" that utilizes the A-B-C model, 10 weeks	Pediatric QOL Inventory-C	10	17	76.09 (SD: 15.17)	19	66.88 (SD: 12.03)	NR	NS
	Holmes et al, 2014[99]	9.6	Group CBT program termed "No Worries!" that utilizes the A-B-C model, 10 weeks	Pediatric QOL Inventory-P	10	17	79.17 (SD: 14.16)	19	75.34 (SD: 11.74)	NR	NS
Individual CBT	Ginsburg et al, 2020[92]	10.9	Individual CBT consisting of 7 core modules, 12 weeks	CGAS	12	148	55.98	68	54.22	NR	0.42
	Ginsburg et al, 2020[92]	10.9	Individual CBT consisting of 7 core modules, 12 weeks	CGAS	52	148	58.92	68	59.22	NR	0.63
	Perrin et al, 2019[122]	13.4	Individual, GAD-specific CBT, 10 weeks	CGAS	10	20	82.1 (SD: 8.9)	20	59.4 (SD: 6.7)	Effect size partial eta squared=0.70	<0.001
	Perrin et al, 2019[122]	13.4	Individual, GAD-specific CBT, 10 weeks	PQ-LES-Q	10	20	60.8 (SD: 10.7)	20	48.7 (SD: 9.4)	Effect size partial eta squared=0.23	<0.01

Appendix F Table 10. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Functioning or Quality of Life

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual CBT (continued)	Villabo et al, 2018[150]	10.5	Individual CBT using the Coping Cat manual, 12 weeks	CGAS	12	IG1: 44 IG2: 52	IG1: 62.52 (SE: 1.17) IG2: 62.81 (SE: 1.10)	51	53.05 (SE: 1.09)	Effect size Hedge's g (95% CI) IG1 vs CG: 1.01 (0.68 to 1.35) IG2 vs CG: 1.04 (0.72 to 1.37)	IG1 vs CG <0.001 IG2 vs CG <0.001
Individual CBT, Sertraline, Individual CBT + Sertraline	Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	Individual CBT using Coping Cat program adapted for child's age and length of the study, 12 weeks	CGAS	12	IG1: 139 IG2: 133 IG3: 140	IG1: 63.8 (SD: 10.2) IG2: 65.0 (SD: 10.7) IG3: 68.6 (SD: 10.4)	76	60.1 (SD: 10.9)	All active treatments noted to be superior to placebo	NR
	Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	Individual CBT using Coping Cat program adapted for child's age and length of the study, 12 weeks	CAIS-C	12	IG1: 139 IG2: 133 IG3: 140	IG1: 9.1 (SD: 10.7) IG2: 7.7 (SD: 11.3) IG3: 8.1 (SD: 11.0)	76	11.2 (SD: 11.5)	No statistically significant differences between arms	NR

Appendix F Table 10. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Functioning or Quality of Life

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual CBT, Sertraline, Individual CBT + Sertraline (continued)	Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	Individual CBT using Coping Cat program adapted for child's age and length of the study, 12 weeks	CAIS-P	12	IG1: 139 IG2: 133 IG3: 140	IG1: 13.5 (SD: 10.0) IG2: 9.1 (SD: 10.5) IG3: 7.4 (SD: 10.2)	76	15.2 (SD: 10.7)	IG2 vs. CG: b=−6.1, t=−4.0 IG3 vs. CG: b=−7.7, t=−5.2	IG1 vs. CG: adjusted P=0.27 IG2 vs. CG: adjusted P<0.001 IG3 vs. CG: adjusted P<0.001
	Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211]	10.7	Individual CBT using Coping Cat program adapted for child's age and length of the study, 12 weeks	Sleep-related problems	12	IG1: 139 IG2: 133 IG3: 140	NR	76	NR	Active treatments resulted in significantly greater reductions in sleep problems than placebo related to separation, as reported by parents (F=6.52, p=0.01, η^2=0.01) but not by children No significant treatment type x time interactions for parent- or child-rated dysregulated Sleep	Significantly greater reductions in sleep problems than placebo related to separation, P=0.01

Appendix F Table 10. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Functioning or Quality of Life

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Individual and group CBT, parent training	Ost et al, 2015[120]	11.6	Individual weekly sessions and social skills group weekly sessions for the child and parent training about SocAD, 12 weeks	Change in QOLI-C from baseline	12	IG1: 16 IG2: 16	IG1: 3.85 (SD: 1.84) IG2: 3.46 (SD: 1.63)	23	2.89 (SD: 1.40)	F=4.1	<0.05 IG1 vs. CG=NS IG2 vs. CG=NS
Internet CBT	Donovan et al, 2014[83]	4.1	Online individual parent-focused CBT, 8 weeks	CGAS	8	23	66.9 (SD: 10.6)	27	61.9 (SD: 10.0)	Partial eta squared=0.115	0.016
	Stjerneklar et al, 2019[141]	15	Internet CBT based on Cool Kids and Chilled anxiety management program, 14 weeks	WHO-5 change from baseline	14	35	NR	35	NR	Effect size Cohen's d=0.04	0.945
	Stjerneklar et al, 2019[141]	15	Internet CBT based on Cool Kids and Chilled anxiety management program, 14 weeks	CALIS-C change from baseline	14	35	NR	35	NR	Effect size Cohen's d=0.21	0.254
	Stjerneklar et al, 2019[141]	15	Internet CBT based on Cool Kids and Chilled anxiety management program, 14 weeks	CALIS-M change from baseline	14	35	NR	35	NR	Effect size Cohen's d=0.93	<0.001
	Stjerneklar et al, 2019[141]	15	Internet CBT based on Cool Kids and Chilled anxiety management program, 14 weeks	CALIS-F change from baseline	14	35	NR	35	NR	Effect size Cohen's d=0.20	0.227
	Waite et al, 2019[152]	14.7	Internet CBT with accompanying parent sessions for half the group and no parent sessions for the other half, 10 weeks	CGAS change from baseline	17	30	59.48 (SD: 14.87)	30	55.18 (SD: 12.48)	Effect size (95% CI) 0.04 (0.00 to 0.18)	NR
	Waite et al, 2019[152]	14.7	Internet CBT with accompanying parent sessions for half the group and no parent sessions for the other half, 10 weeks	CAIS-C change from baseline	17	30	18.04 (SD: 16.97)	30	17.59 (SD: 13.09)	Effect size (95% CI) 0.01 (0.00 to 0.12)	NR

Appendix F Table 10. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Functioning or Quality of Life

Treatment (Condition)	Author, Year	Mean Age (Years)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Internet CBT (continued)	Waite et al, 2019[152]	14.7	Internet CBT with accompanying parent sessions for half the group and no parent sessions for the other half, 10 weeks	CAIS-P change from baseline	17	30	23.60 (SD: 21.81)	30	19.63 (SD: 16.34)	Effect size (95% CI) 0.04 (0.00 to 0.19)	NR
Parent-delivered CBT	Thirlwall et al, 2013[145]	NR, partici-pants ages 7 to 12 years	Parent-delivered CBT with a self-help book, 8 weeks	CAIS-P	12	IG1: 39 IG2: 41	IG1: 13.97 (SD: 14.64) IG2: 6.39 (SD: 6.29)	48	15.56 (SD: 12.31)	IG1 vs. CG: NR IG2 vs. CG: difference in change from baseline, -5.56 (95% CI, -9.40 to -1.73)	IG1 vs. CG: P=NS; IG2 vs. CG=0.0045

Abbreviations: CAIS-C=Child Anxiety Impact Scale; CAIS-P=Child Anxiety Impact Scale-Parent; CALIS=Child Anxiety Life Interference Scale; CALIS-C=Child Anxiety Life Interference Scale-Child; CALIS-F=Child Anxiety Life Interference Scale-Father; CALIS-M=Child Anxiety Life Interference Scale-Mother; CBT=cognitive behavioral therapy; CG=control group; CGAS=Children's Global Assessment Scale; CI=confidence interval; GAD=general anxiety disorder; IG=intervention group; N=number; NR=not reported; NS=not significant; PQ-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire ; QOL=quality of life; SD=standard deviation; SocAD=social anxiety disorder; vs.=versus; WHO-5=World Health Organization Five Item Well-being Index.

Appendix F Table 11. Anxiety Interventions: Subgroup Analyses for Benefits

Author, Year, Registry Number	Treatment Interventions and Comparators	Qualitative Results
Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211] NCT00052078	IG1: Individual child-focused in-person CBT (N=139) IG2: Sertraline (N=133) IG3: CBT + sertraline (N=140) CG: Placebo (N=76)	At post-treatment, anxiety severity as measured by independent evaluators (PARS) was significantly higher for participants of Hispanic ethnicity receiving CBT. Parent-rated anxiety severity (SCARED-P) was significantly higher for participants of Hispanic ethnicity receiving sertraline. After accounting for treatment engagement and other demographic factors, there were no statistically significant differences in response, remission, or relapse based on race. At post-treatment, parent-reported anxiety-related school impairment (CAIS) was significantly lower among male participants receiving either sertraline or sertraline in combination with CBT. There were no statistically significant sex effects based on youth-reported anxiety-related school impairment (CAIS). At post-treatment, age was not a statistically significant moderator of the effect of treatment on any outcome. The rate of overall AEs was significantly higher in children than in adolescents who received sertraline. The rate of total psychiatric AEs was significantly higher in children compared with adolescents across all treatment arms. The rate of total physical AEs was not significantly different between children and adolescents.
Shortt et al, 2001[134]	IG1: Group child+parent in-person CBT (N=54) CG: Wait-list (N=17)	Age and sex were not significant moderators of clinician's severity ratings (DISCAP) or self-report measures (RCMAS).
Ginsburg et al, 2020[92]	IG1: Individual child-focused in-person CBT (N=148) CG: TAU (N=68)	At post-treatment, age significantly moderated the effect of treatment on response status, indicating that beneficial effects of treatment were strongest for older participants. No moderation effects were observed at 1-year followup.
Strawn et al, 2015[142] NCT01226511	IG1: Duloxetine (N=135) CG: Placebo (N=137)	Age and sex were not significant moderators of GAD severity (PARS).
Pine et al, 2001[124] Walkup et al, 2001[213] Ginsburg et al, 2006[214] Reinblatt et al, 2009[215]	IG1: Fluvoxamine (N=63) CG: Placebo (N=65)	Age, sex, and race were not significant moderators of treatment effects on any outcome.
Barrett et al, 1996[70]	IG1: Individual child-focused CBT (N=28) IG2: Child+Parent CBT (N=25) CG: Wait-list (N=26)	At post-treamtment and 1-year followup, female and younger (7 to 10 years) participants who received child and parent-focused CBT had significantly higher rates of loss of diagnosis (ADIS) compared with those who received child-focused CBT.There were no significant differences across treament conditions at post-treatment or followup for male or older (11 to 14 years) participants.

Abbreviations: ADIS=Anxiety Disorders Interview Schedule; AE=adverse event; CAIS=Child Anxiety Impact Scale; CBT=cognitive behavioral therapy; CG=control group; DISCAP=Diagnostic Interview Schedule for Children, Adolescents, and Parents; GAD=general anxiety disorder; IG=intervention group; PARS=Pediatric Anxiety Rating Scale; RCMAS=Revised Children's Manifest Anxiety Scale; SCARED-P=Screen for Anxiety Related Emotional Disorders-Parents; TAU=treatment as usual.

Appendix F Table 12. Anxiety Interventions: Suicide-Related Harms for Anxiety Pharmacotherapy Studies (KQ 5)

Treatment (Condition)	Author, Year	Mean Age	Dose (md/day)	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), P-Value
Duloxetine (GAD)	Strawn et al, 2015[142]	12.4	Flexibly dosed duloxetine (30–120 mg/d)	Suicidal ideation	10	135	1 (1)	137	0 (0)	p=NR
Escitalopram (GAD)	Strawn et al, 2020[143]	14.8	Forced titration to 15 mg/d, then flexible titration to 20 mg/d, 8 weeks	Aborted suicide attempt	8	26	1 (3.8)	25	0 (0)	p=NR
				Self-injurious behavior	8	26	2 (7.7)	25	1 (4.0)	p=NR
				Worsening of suicide-related harms	8	26	6 (23.1)	25	2 (8.0)	p=NR
				Emergence or worsening of suicidality	8	26	NR	25	NR	p=0.449
Sertraline (GAD, separation anxiety disorder, social anxiety disorder)	Walkup et al, 2008[153]	10.7	25 mg/day, up to 200 mg/day by 8th week, for 12 weeks	Suicidal attempts	12	133	0 (0)	76	0 (0)	p=NR
				Suicidal ideation	12	133	0 (0)	76	1 (1.3)	p=NR
				Self-harm behavior without suicidal attempt	12	133	1 (0.8)	76	0 (0)	p=NR

Abbreviations: CI=confidence interval; GAD=general anxiety disorder; KQ=key question; N=number; NR=not reported

Appendix F Table 13. Anxiety Interventions: Other Adverse Events for Anxiety Pharmacotherapy Studies (KQ 5)

Treatment (Condition)	Author, Year	Mean Age	Dose (md/day)	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), P-Value
Fluoxetine (Any)	Birmaher et al, 2003[73]	11.8	10 mg/d, after first week, up to 20 mg/d, 12 weeks	GI events	12	35	Not calculable (44)	32	Not calculable (22)	p=0.04
				Neurological complaints (headaches, drowsiness),	2	36	16 (44)	36	5 (14)	p=0.04
				Excitement, giddiness, or disinhibition	12	36	7 (19)	36	4 (11)	p=NS
Fluvoxamine (GAD, separation anxiety disorder, or social anxiety disorder)	Pine et al, 2001[124] Walkup et al, 2001[213] Ginsburg et al, 2006[214] Reinblatt et al, 2009[215]	10.4	50 mg/d, then 50 mg/w to max. 300 mg/d in adolescents and 250 mg/d in children <12 years of age, 8 weeks	Abdominal discomfort	8	63	31 (49)	65	18 (28)	p=0.02
				Headache, increased motor activity, insomnia, nasal congestion, drowsiness, nausea, diarrhea, influenza, or upper respiratory infection	8	63	NR	65	NR	p=NS
Sertraline (GAD)	Rynn, 2001[130]	11.7	25 mg for the first week and 50 mg for weeks 2 to 9, 9 weeks	Dizziness	9	11	2 (18)	11	7 (64.4)	p<0.08
				Nausea	9	11	Not calculable (5)	11	6 (55)	p<0.06
				Stomach pain	9	11	2 (18)	11	7 (64)	p<0.08
				Dry mouth	9	11	6 (55)	11	3 (27)	p=0.39
				Drowsiness	9	11	8 (73)	11	5 (45)	p=0.39
				Leg spasms	9	11	4 (36)	11	1 (9)	p=0.31
				Restlessness	9	11	6 (55)	11	3 (27)	p=0.39
Duloxetine (GAD)	Strawn et al, 2015[142]	12.4	Flexibly dosed duloxetine (30–120 mg/d)	Treatment-emergent AEs	10	135	106 (78.5)	137	90 (65.7)	p=0.22
Escitalopram (GAD)	Strawn et al, 2020[143]	14.8	Forced titration to 15 mg/d, then flexible titration to 20 mg/d, 8 weeks	Bruising	8	26	4 (15)	25	0 (0)	p=0.06
				Other AEs reported by system organ class	8	26	Varies by outcome	25	Varies by outcome	p=NS

Appendix F Table 13. Anxiety Interventions: Other Adverse Events for Anxiety Pharmacotherapy Studies (KQ 5)

Treatment (Condition)	Author, Year	Mean Age	Dose (md/day)	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), P-Value
Sertraline (GAD, separation anxiety disorder, or social anxiety disorder)	Walkup et al, 2008[153]	10.7	25 mg/day, up to 200 mg/day by 8th week, for 12 weeks.	Homicidal ideation	12	133	2 (1.5)	76	0 (0)	p=NS
				Homidical attempts	12	133	0 (0)	76	0 (0)	p=NS
				Any physical AEs	12	133	56 (50.4)	76	35 (46.1)	p=NS
				Any psychiatric AEs	12	133	23 (17.3)	76	10 (13.2)	p=NS

Abbreviations: AE=adverse event; CI=confidence interval; GAD=general anxiety disorder; GI=gastrointestinal; KQ=key question; N=number; NR=not reported; NS=not significant.

Appendix F Table 14. Depression Psychotherapy Interventions vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo: Depression Symptoms

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Mean Score (SD)	Between-Group Difference	Between-Group P Value
Individual in-person youth CBT vs. TAU	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist delivered sessions (duration not specified)	CDRS-R	52 weeks	106	30.14 (11.26)	106	28.24 (10.54)	-2.25*	P=0.04
	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist delivered sessions (duration not specified)	CDRS-R	104 weeks	106	28.11 (9.88)	106	29.17 (10.79)	-1.30*	P=0.36
	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist delivered sessions (duration not specified)	CES-D (youth reported)	52 weeks	106	22.59 (7.00)	106	22.51 (7.43)	-2.88*	P<0.005
	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist delivered sessions (duration not specified)	CES-D	104 weeks	106	21.46 (7.44)	106	21.91 (6.95)	-0.32*	P=0.62
	Clarke et al, 2005[76]	15.3 (1.6)	5 to 9 therapist delivered sessions (duration not specified)	CES-D	52 weeks	53	11.5 (11.0)	50	14.9 (10.1)	-3.40	p=0.07
	Clarke et al, 2005[76]	15.3 (1.6)	5 to 9 therapist delivered sessions (duration not specified)	HAM-D	52 weeks	53	4.9 (7.1)	50	6.5 (6.6)	-1.60	p=0.32
Individual in-person CBT vs. Placebo	March et al, 2004[113]	14.6 (1.5)	15 therapist delivered sessions plus 2 parent-only sessions over 12 weeks	CDRS-R	6 weeks	111	44.63 (8.30)	112	44.90 (7.32)	-0.27	NR
	March et al, 2004[113]	14.6 (1.5)	15 therapist delivered sessions plus 2 parent-only sessions over 12 weeks	CDRS-R	12 weeks	111	42.06 (9.18)	112	41.77 (7.99)	0.29	P=0.97
	March et al, 2004[113]	14.6 (1.5)	15 therapist delivered sessions plus 2 parent-only sessions over 12 weeks	RADS	6 weeks	111	69.10 (13.59)	112	69.43 (10.94)	-0.33	NR
	March et al, 2004[113]	14.6 (1.5)	15 therapist delivered sessions plus 2 parent-only sessions over 12 weeks	RADS	12 weeks	111	67.96 (14.18)	112	66.68 (11.41)	1.28	P=0.94

Appendix F Table 14. Depression Psychotherapy Interventions vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo: Depression Symptoms

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Mean Score (SD)	Between-Group Difference	Between-Group P Value
Family CBT vs. Placebo	Fristad et al, 2019[90]	IG1: 11.7 (2.1) CG: 11.1 (2.4)	Family-based therapy with CBT techniques with parent at beginning and end of session over 12 weeks	CDRS-R	12 weeks	18	30 (9)	18	31 (11)	-1.00	p=0.88
Group in-person CBT vs. wait-list	Clarke et al, 1999[45]	16.2 (1.3) Completers	Group CBT (Adolescent Coping with Depression Course), over 8 weeks plus weekly meetings	BDI	8 weeks	37	10.1 (9.1)	27	16.0 (11.2)	-5.90	P<0.01
	Clarke et al, 1999[45]	16.2 (1.3) Completers	Group CBT (Adolescent Coping with Depression Course), over 8 weeks plus weekly meetings	HAM-D	8 weeks	37	4.6 (4.8)	27	7.7 (7.0)	-3.10	P=NS
Group in-person CBT + parent sessions vs. wait-list	Clarke et al, 1999[45]	16.2 (1.3) Completers	Group CBT (Adolescent Coping with Depression Course), plus 8 weekly 2-hour parent sessions (6 separate, 2 held jointly with adolescent group) over 8 weeks	BDI	8 weeks	32	13.3 (10.9)	27	16.0 (11.2)	-2.70	P<0.01
	Clarke et al, 1999[45]	16.2 (1.3) Completers	Group CBT (Adolescent Coping with Depression Course), plus 8 weekly 2-hour parent sessions (6 separate, 2 held jointly with adolescent group) over 8 weeks	HAM-D	8 weeks	32	6.7 (7.1)	27	7.7 (7.0)	-1.00	P=NS

Appendix F Table 14. Depression Psychotherapy Interventions vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo: Depression Symptoms

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Mean Score (SD)	Between-Group Difference	Between-Group P Value
Internet-based individual CBT vs. attention control	Topooco et al, 2018[147]	IG1: 17.2 (1.0) CG: 16.9 (1.1)	Internet-based CBT with 8 skill-based modules plus weekly 30-minute chat sessions with therapist over 8 weeks	BDI-II	8 weeks	33	19.9 (7.2)	37	25.2 (7.8)	-5.30	p<0.05
	Topooco et al, 2018[147]	IG1: 17.2 (1.0) CG: 16.9 (1.1)	Internet-based CBT with 8 skill-based modules plus weekly 30-minute chat sessions with therapist over 8 weeks	PHQ-9	8 weeks	33	9.7 (2.9)	37	10.8 (3.0)	-1.10	p=NS
	Topooco et al, 2019[148]	IG1: 17.5 (1.1) CG: 17.5 (1.2)	Internet-based CBT with 8 skill-based modules plus weekly 45-minute chat sessions with therapist over 8 weeks	BDI-II	8 weeks	35	16.0 (11.3)	35	24.8 (10.4)	-8.80	p<0.001
	Topooco et al, 2019[148]	IG1: 17.5 (1.1) CG: 17.5 (1.2)	Internet-based CBT with 8 skill-based modules plus weekly 45-minute chat sessions with therapist over 8 weeks	MFQ	8 weeks	35	24.3 (12.8)	35	31.0 (9.8)	-6.70	p<0.01
Interpersonal psychotherapy vs. TAU	Mufson et al, 2004[118]	15.1 (1.9)	Manualized IPT-A during 12 sessions in a 12- to 16-week period	BDI	12 weeks	34	8.4 (11.0)	29	12.3 (9.7)	-3.90	p=0.04
	Mufson et al, 2004[118]	15.1 (1.9)	Manualized IPT-A during 12 sessions in a 12- to 16-week period	CGI-I	12 weeks	34	2.3 (1.3)	29	3.1 (1.6)	-0.80	p=0.03
	Mufson et al, 2004[118]	15.1 (1.9)	Manualized IPT-A during 12 sessions in a 12- to 16-week period	CGI-S	12 weeks	34	2.4 (1.3)	29	3.0 (1.4)	-0.60	p=0.03

Appendix F Table 14. Depression Psychotherapy Interventions vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo: Depression Symptoms

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Mean Score (SD)	Between-Group Difference	Between-Group P Value
Interpersonal psychotherapy vs. TAU (continued)	Mufson et al, 2004[118]	15.1 (1.9)	Manualized IPT-A during 12 sessions in a 12- to 16-week period	HAM-D	12 weeks	34	8.7 (8.0)	29	12.8 (8.4)	-4.10	p=0.01
	Mufson et al, 2004[118]	15.1 (1.9)	Manualized IPT-A during 12 sessions in a 12- to 16-week period	HAM-D	16 weeks	34	6.9 (NR)	29	10.6 (NR)	-3.70	P=0.01
Parent Child Interaction Therapy-Emotion Development (PCIT-ED) vs. wait-list	Luby et al, 2018[111]	IG1: 5.1 (1.0) CG: 5.3 (1.1)	Manualized PCIT-ED sessions to teach parent followed by coaching parent-child interactions using a bug-in-the-ear device over 18 weeks	K-SADS-EC MDD core score	Change at 18 weeks	114	NR	115	NR	Mean difference (SE) -2.34 (0.26)	p<0.0001
	Luby et al, 2018[111]	IG1: 5.1 (1.0) CG: 5.3 (1.1)	Manualized PCIT-ED sessions to teach parent followed by coaching parent-child interactions using a bug-in-the-ear device over 18 weeks	PFC-scale	Change at 18 weeks	114	NR	115	NR	Adjusted mean difference (SE) -11.91 (1.29)	p<0.0001

* Across 0 to 52 weeks, not a comparison at 52 weeks.

Abbreviations: BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory, version 2; CBT=cognitive behavioral therapy; CDRS-R=Children's Depression Rating Scale-Revised; CES-D=Center for Epidemiological Studies-Depression; CG=control group; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; HAM-D=Hamilton Depression Rating Scale; IG=intervention group; IPT-A=interpersonal psychotherapy for depressed adolescents; K-SADS-EC=Schedule For Affective Disorders And Schizophrenia For School-Age Children-Early Childhood version; MDD=major depressive disorder; MFQ=mood & feelings questionnaire; N=number; NR=not reported; NS=not significant; PCIT-ED=Parent Child Interaction Therapy-Emotion Development; PFC=Preschool Feelings Checklist; PHQ-9=Patient Health Questionnaire, 9 question; RADS=Reynolds Adolescent Depression Scale; SD=standard deviation; TAU=treatment as usual; vs.=versus.

Appendix F Table 15. Depression Pharmacotherapy Interventions vs. Placebo: Depression Symptoms

Treatment (Condition)	Author, Year	Mean Age (SD)	Dose (md/day)	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Mean Score (SD)	Between-Group Difference	Between-Group P Value
Escitalopram vs. placebo	Emslie, 2009[86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	Change in CDRS-R	8 weeks	129	-22.1 (SEM: 1.22)	132	-18.8 (SEM: 1.27)	-3.3	0.022
	Emslie, 2009[86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	Change in CGI-I	8 weeks	129	2.2 (SEM: 0.11)	132	2.6 (SEM: 0.11)	-0.4	0.008
	Emslie, 2009[86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	CGI-S	8 weeks	129	-1.8 (SEM: 0.11)	132	-1.4 (SEM: 0.12)	-0.4	0.007
	Wagner, 2006[151]	12.3 (3.0)	10 to 20 mg	Change in CDRS-R	8 weeks	154	-21.9 (NR)	157	-20.2 (NR)	-1.7	0.31
	Wagner, 2006[151]	12.3 (3.0)	10 to 20 mg	Change in CGI-I	8 weeks	154	2.3 (NR)	157	2.5 (NR)	-0.2	0.169
	Wagner, 2006[151]	12.3 (3.0)	10 to 20 mg	Change in CGI-S	8 weeks	154	-1.6 (NR)	157	-1.3 (NR)	-0.3	0.057
Fluoxetine vs. placebo	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in CDRS-R	6 weeks	109	39.8 (7.37)	112	44.9 (7.32)	-5.1	NR
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in CDRS-R	12 weeks	109	36.3 (8.18)	112	41.8 (7.99)	-5.5	0.10
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in RADS	6 weeks	109	63.4 (12.44)	112	69.4 (10.94)	-6.0	NR
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in RADS	12 weeks	109	60.6 (13.07)	112	66.7 (11.41)	-6.1	0.34

Abbreviations: CDRS-R=Children's Depression Rating Scale-Revised; CG=control group; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; IG=intervention group; N=number; NR=not reported; RADS=Reynolds Adolescent Depression Scale; SD=standard deviation; SEM=standard error of the mean; vs.=versus.

Appendix F Table 16. Depression Pharmacotherapy + Psychotherapy Intervention vs. Placebo: Depression Symptoms

Treatment (condition)	Author, Year	Mean Age (SD)	Dose (md/day)	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Fluoxetine vs. placebo	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in CDRS-R	6 weeks	107	38.10 (7.78)	112	44.9 (7.32)	-6.80	NR
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in CDRS-R	12 weeks	107	33.79 (8.24)	112	41.8 (7.99)	-8.01	P=0.001
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in RADS	6 weeks	107	60.90 (11.59)	112	69.4 (10.94)	-8.50	NR
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in RADS	12 weeks	107	56.95 (12.24)	112	66.7 (11.41)	-9.75	P=0.001

Abbreviations: CDRS-R=Children's Depression Rating Scale-Revised; N=number; NR=not reported; SD=standard deviation; SE=standard error; vs.=versus.

Appendix F Table 17. Depression Collaborative Care Intervention vs. Treatment as Usual: Depression Symptoms

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (95% CI)	Placebo N	Placebo Mean Score (95% CI)	Between-Group Difference	Between-Group P Value
Collaborative care vs. enhanced usual care	Richardson et al, 2014[127]	15.3 (1.3)	Choice of treatment (antidepressant, brief CBT, or both), and followup over 12 months	CDRS-R	6 months	50	NR	51	NR	Mean difference between groups (95% CI) -8.5 (-13.4 to -3.6)	P=0.001
	Richardson et al, 2014[127]	15.3 (1.3)	Choice of treatment (antidepressant, brief CBT, or both), and followup over 12 months	CDRS-R	12 months	50	27.5 (23.8 to 31.1)	51	34.6 (30.6 to 38.6)	Mean difference between groups (95% CI) -9.4 (-15.0 to -3.8)	P=0.001

Abbreviations: CBT=cognitive behavioral therapy; CDRS-R=Children's Depression Rating Scale-Revised; CI=confidence interval; N=number; SD=standard deviation vs.=versus.

Appendix F Table 18. Depression Psychotherapy Interventions vs. Wait-List Control, Treatment as Usual, Attention Control, or Placebo: Response, Remission, and Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Effect Measure (95% CI), p value
Individual in-person youth CBT vs. TAU	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist delivered sessions (duration not specified)	MDD response*	52 weeks	106	90 (90.9)	106	87 (87.9)	OR: 1.39 (95% CI, 1.03 to 1.87)
	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist delivered sessions (duration not specified)	MDD Response*	104 weeks	106	93 (93.9)	106	93 (93.9)	OR: 1.38 (95% CI, 1.03 to 1.84)
	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist delivered sessions (duration not specified)	MDD Recovery†	52 weeks	106	79 (79.8)	106	68 (68.7)	OR: 1.60 (95% CI, 1.15 to 2.21)
	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist delivered sessions (duration not specified)	MDD Recovery†	104 weeks	106	88 (88.9)	106	78 (78.8)	OR: 1.59 (95% CI, 1.17 to 2.17)
Individual in-person CBT vs. Placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	15 therapist delivered sessions plus 2 parent-only sessions over 12 weeks	CGI ≥2	12 weeks	111	43.2 (34 to 52)	112	34.8 (26 to 44)	p=0.20
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	15 therapist delivered sessions plus 2 parent-only sessions over 12 weeks	CDRS-R score ≤28	12 weeks	111	14 (16)	112	19 (17)	OR: 0.9 (0.44 to 1.88); P=0.80

Appendix F Table 18. Depression Psychotherapy Interventions vs. Wait-List Control, Treatment as Usual, Attention Control, or Placebo: Response, Remission, and Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Effect Measure (95% CI), p value
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	Loss of MDD diagnosis based on K-SADS-P/L	12 weeks	NR	(61.1)	NR	(60.4)	OR: 1.0 (0.52 to 1.77); P=0.89
Family CBT vs. placebo	Fristad et al, 2019[90]	IG1: 11.7 (2.1) CG: 11.1 (2.4)	Family-based therapy with CBT techniques with parent at beginning and end of session over 12 weeks	CDRS-R score ≤28	12 weeks	18	11 (61)	18	10 (56)	p=NS
Group in-person CBT vs. wait-list	Clarke et al, 1999[45]	16.2 (1.3) Completers	Group CBT (Adolescent Coping With Depression Course), over 8 weeks plus weekly meetings	Absence of MDD/ dysthymia diagnoses	8 weeks	37	24 (64.9)	27	13 (48.1)	IG1/IG2 vs. CG, 1 tailed P<0.05 Cohen's h=0.38 OR: 2.15 (90% CI, 1.01 to 4.59)
Group in-person CBT + parent sessions vs. wait-list	Clarke et al, 1999[45]	16.2 (1.3) Completers	Group CBT (Adolescent Coping With Depression Course), plus 8 weekly 2-hour parent sessions (6 separate, 2 held jointly with adolescent group) over 8 week	Absence of MDD/ dysthymia diagnoses	8 weeks	32	22 (68.8)	27	13 (48.1)	
Internet-based individual CBT vs. attention control	Topooco et al, 2018[147]	IG1: 17.2 (1.0) CG: 16.9 (1.1)	Internet-based CBT with 8 skill-based modules plus weekly 30-minute chat sessions with therapist over 8 weeks	BDI-II ≥30% decrease	8 weeks	33	20 (60.6)	37	12 (32.4)	p<0.05
	Topooco et al, 2018[147]	IG1: 17.2 (1.0) CG: 16.9 (1.1)	Internet-based CBT with 8 skill-based modules plus weekly 30-minute chat sessions with therapist over 8 weeks	BDI-II ≥50% decrease	8 weeks	33	14 (42.4)	37	5 (13.5)	p<0.01

Appendix F Table 18. Depression Psychotherapy Interventions vs. Wait-List Control, Treatment as Usual, Attention Control, or Placebo: Response, Remission, and Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Effect Measure (95% CI), p value
	Topooco et al, 2018[147]	IG1: 17.2 (1.0) CG: 16.9 (1.1)	Internet-based CBT with 8 skill-based modules plus weekly 30-minute chat sessions with therapist over 8 weeks	Loss of MDD diagnosis	8 weeks	33	20 (71.4)	37	4 (16.0)	p<0.001
	Topooco et al, 2019[148]	IG1: 17.5 (1.1) CG: 17.5 (1.2)	Internet-based CBT with 8 skill-based modules plus weekly 45-minute chat sessions with therapist over 8 weeks	BDI-II ≥30% decrease	8 weeks	35	NR	35	NR	p=0.004
Internet based individual CBT vs. attention control (continued)	Topooco et al, 2019[148]	IG1: 17.5 (1.1) CG: 17.5 (1.2)	Internet-based CBT with 8 skill-based modules plus weekly 45-minute chat sessions with therapist over 8 weeks	BDI-II ≥13	8 weeks	35	NR	35	NR	p=0.004
	Topooco et al, 2019[148]	IG1: 17.5 (1.1) CG: 17.5 (1.2)	Internet-based CBT with 8 skill-based modules plus weekly 45-minute chat sessions with therapist over 8 weeks	BDI-II ≥10	8 weeks	35	NR	35	NR	p=0.004
	Topooco et al, 2019[148]	IG1: 17.5 (1.1) CG: 17.5 (1.2)	Internet-based CBT with 8 skill-based modules plus weekly 45-minute chat sessions with therapist over 8 weeks	Clinically significant improvement (2 SD below pre-treatment BDI-II mean)	8 weeks	35	16 (46)	35	4 (11)	p=0.001
	Topooco et al, 2019[148]	IG1: 17.5 (1.1) CG: 17.5 (1.2)	Internet-based CBT with 8 skill-based modules plus weekly 45-minute chat sessions with therapist over 8 weeks	No longer met MDD criteria	8 weeks	27	15 (56)	26	7 (27)	p=0.03
Interpersonal psychotherapy vs. TAU	Mufson et al, 2004[118]	15.1 (1.9)	Manualized IPT-A during 12 sessions in a 12- to 16-week period	HAM-D score ≤6	12 weeks	34	17 (50)	29	10 (34)	p=NR
	Mufson et al, 2004[118]	15.1 (1.9)	Manualized IPT-A during 12 sessions in a 12- to 16-week period	BDI score ≤9	12 weeks	34	25 (74)	29	15 (52)	p=0.048

Appendix F Table 18. Depression Psychotherapy Interventions vs. Wait-List Control, Treatment as Usual, Attention Control, or Placebo: Response, Remission, and Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Effect Measure (95% CI), p value
Parent Child Interaction Therapy-Emotion Development (PCIT-ED) vs. wait-list	Luby et al, 2018[111]	IG1: 5.1 (1.0) CG: 5.3 (1.1)	Manualized PCIT-ED sessions to teach parent followed by coaching parent-child interactions using a bug-in-the-ear device over 18 weeks	K-SADS-EC MDD diagnosis for all participants, multiply imputed	Change at 18 weeks	114	NR	115	NR	aOR‡ (95% CI) CG vs. IG1: 9.52 (8.44 to 10.74); P<0.0001
	Luby et al, 2018[111]	IG1: 5.1 (1.0) CG: 5.3 (1.1)	Manualized PCIT-ED sessions to teach parent followed by coaching parent-child interactions using a bug-in-the-ear device over 18 weeks	K-SADS-EC MDD diagnosis for completers	Change at 18 weeks	100	68 (75)	91	22 (22)	aOR (95% CI), CG vs. IG1: 12.15 (5.95 to 24.82); P<0.0001

* Major depression diagnostic response defined as ≥8 weeks below the threshold of 5 or more MD symptoms necessary for full diagnosis but where full recovery has not yet occurred.

† Recovery defined as ≥8 weeks of no or minimal symptoms (K-SADS Diagnostic Status Rating ≤1-2) and little or no impairment.

ǂ Controlled for baseline characteristics, gender, and baseline externalizing disorder.

Abbreviations: aOR=adjusted odds ratio; BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory, version 2; CBT=cognitive behavioral therapy; CDRS-R=Children's Depression Rating Scale-Revised; CG=control group; CGI=Clinical Global Impressions; CI=confidence interval; IG=intervention group; HAM-D=Hamilton Rating Scale for Depression; IG=intervention group; IPT-A=interpersonal psychotherapy for depressed adolescents; K-SADS-EC=Schedule for Affective Disorders and Schizophrenia for School-Age Children-version; K-SADS-PL=Schedule For Affective Disorders And Schizophrenia For School-Age Children-Present and Lifetime Version; MDD=major depressive disorder; N=number; NR=not reported; NS=not significant; PCIT-ED=Parent Child Interaction Therapy-Emotion Development; SD=standard deviation; TAU=treatment as usual; vs=versus.

Appendix F Table 19. Depression Pharmacotherapy Interventions vs. Placebo for Depression in Children: Remission and Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age	Dose (mg/day)	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Effect Measure (95% CI), p Value
Escitalopram vs. placebo	Emslie, 2009[86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	CDRS-R ≤28	8 weeks	154	64 (41.6)	157	56 (35.7)	0.15
	Wagner, 2006[151]	12.3 (3.0)	10 to 20 mg	CDRS-R ≤28	8 weeks	129	59 (45.7)	132	50 (37.9)	0.32
	Wagner, 2006[151]	12.3 (3.0)	10 to 20 mg	CGI-I ≤2	8 weeks	129	81 (62.8)	132	69 (52.3)	0.14
Fluoxetine vs. placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	CDRS-R score ≤28	12 weeks	109	25 (23)	112	19 (17)	1.5 (0.74 to 2.88); P=0.28
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	CGI-I ≤2	12 weeks	109	60.6 (51 to 70)	112	34.8 (26 to 44)	P=0.001
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Loss of MDD diagnosis based on K-SADS-P/L	12 weeks	NR	78.6%	NR	60.4%	P=0.007

Abbreviations: CDRS-R=Children's Depression Rating Scale-Revised; CG=control group; CGI-I=Clinical Global Impressions-Improvement; CI=confidence interval; IG=intervention group; K-SADS-PL=Schedule For Affective Disorders And Schizophrenia For School-Age Children-Present and Lifetime Version; MDD=major depressive disorder; N=number; NR=not reported; vs.=versus.

Appendix F Table 20. Depression Pharmacotherapy + Psychotherapy Intervention vs. Placebo: Response, Remission, and Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age	Dose (mg/day)	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Effect Measure (95% CI), p Value
Fluoxetine	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	CDRS-R score ≤28	12 weeks	107	40 (37)	112	19 (17)	3.0 (1.58 to 5.79); P=0.0009
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	CGI-I ≤2	12 weeks	107	71.0 (62 to 80)	112	34.8 (26 to 44)	P=0.001
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Loss of MDD diagnosis based on K-SADS-P/L	12 weeks	NR	85.3%	NR	60.4%	4.1 (2.00 to 8.44); P=0.0001

Abbreviations: CDRS-R=Children's Depression Rating Scale-Revised; CGI-I=Clinical Global Impressions-Improvement; CI=confidence interval; K-SADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children-present and lifetime version; MDD=major depressive disorder; N=number; NR=not reported; vs.=versus.

Appendix F Table 21. Depression Collaborative Care Intervention vs. Treatment as Usual: Response, Remission, and Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Effect Measure (95% CI), p Value
Collaborative care vs. enhanced usual care	Richardson et al, 2014[127]	15.3 (1.3)	Choice of treatment (antidepressant, brief CBT, or both), and followup over 12 months	≥50% reduction in CDRS-R	6 months	50	NR (48.4*)	51	NR (23.4*)	OR (95% CI): 3.1 (1.2 to 7.9), P=0.02
	Richardson et al, 2014[127]	15.3 (1.3)	Choice of treatment (antidepressant, brief CBT, or both), and followup over 12 months	≥50% reduction in CDRS-R	12 months	50	NR (67.6*)	51	NR (38.6*)	OR (95% CI): 3.3 (1.4 to 8.2), P=0.009
	Richardson et al, 2014[127]	15.3 (1.3)	Choice of treatment (antidepressant, brief CBT, or both), and followup over 12 months	PHQ-9 <5	6 months	50	NR (36.6*)	51	NR (10.2*)	OR (95% CI): 5.2 (1.6 to 17.3), P=0.007
	Richardson et al, 2014[127]	15.3 (1.3)	Choice of treatment (antidepressant, brief CBT, or both), and followup over 12 months	PHQ-9 <5	12 months	50	NR (50.4*)	51	NR (20.7*)	OR (95% CI): 3.9 (1.5 to 10.6), P=0.007

* Imputed % based on 20 multiple imputations.

Abbreviations: CBT=cognitive behavioral therapy; CDRS-R=Children's Depression Rating Scale-Revised; CI=confidence interval; N=number; NR=not reported; OR=odds ratio; PHQ-9=Patient Health Questionnaire-9; SD=standard deviation; vs.=versus.

Appendix F Table 22. Depression Collaborative Care Intervention vs. Treatment as Usual: Response, Remission, and Loss of Diagnosis

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Between-Group Difference	Between-Group P Value
Collaborative care vs. enhanced usual care	Richardson et al, 2014[127]	15.3 (1.3)	Choice of treatment (antidepressant, brief CBT, or both), and followup over 12 months	CIS	6 months	50	NR	51	NR	-4.4 (-8.4 to -0.5)	p=0.03 (A priori threshold for secondary outcomes of P ≤0.01)
	Richardson et al, 2014[127]	15.3 (1.3)	Choice of treatment (antidepressant, brief CBT, or both), and followup over 12 months	CIS	12 months	50	16.3 (13.8 to 18.8)	51	13.4 (10.8 to 15.9)	-4.3 (-8.3 to -0.3)	p=0.04 (A priori threshold for secondary outcomes of P ≤0.01)

Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; CIS=Columbia Impairment Scale; N=number;=standard deviation; vs.=versus.

Appendix F Table 23. Depression Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo: Functioning or Quality of Life (Continuous)

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Mean Score (SD)	Between-Group Difference	P value
Individual in-person youth CBT vs. TAU	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist-delivered sessions (duration not specified)	CGAS	52 weeks	106	72.33 (9.97)	106	74.10 (10.81)	4.2 (95% CI, 1.55 to 6.86)	P<0.007 favoring CBT
	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist-delivered sessions (duration not specified)	CGAS	104 weeks	106	76.86 (11.03)	106	76.45 (11.09)	0.13 (95% CI, -2.08 to 2.34)	P=0.21
	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist-delivered sessions (duration not specified)	PEDS-QL	52 weeks	106	75.40 (14.57)	106	76.94 (12.43)	0.55 (95% CI, -3.21 to 4.31)	P=0.73
	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist-delivered sessions (duration not specified)	PEDS-QL	104 weeks	106	75.40 (14.57)	106	76.94 (12.43)	1.05 (95% CI, -2.27 to 4.36)	P=0.90
	Clarke et al, 2005[76]	15.3 (1.6)	5 to 9 therapist-delivered sessions (duration not specified)	CGAS	52 weeks	53	71.4 (8.7)	50	68.4 (7.6)	NR	P=0.22
	Clarke et al, 2005[76]	15.3 (1.6)	5 to 9 therapist-delivered sessions (duration not specified)	SF-12 MCS	52 weeks	53	45.4 (9.3)	50	43.1 (10.2)	NR	P=0.04
	Clarke et al, 2005[76]	15.3 (1.6)	5 to 9 therapist-delivered sessions (duration not specified)	SF-12 PCS	52 weeks	53	49.0 (5.8)	50	48.1 (8.5)	NR	P=0.84
Individual in-person CBT vs. placebo pill	March et al, 2004[113]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	CGAS	6 weeks	111	56.7 (9.66)	112	57.0 (9.22)	NR	NR

Appendix F Table 23. Depression Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo: Functioning or Quality of Life (Continuous)

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Mean Score (SD)	Between-Group Difference	P value
Individual in-person CBT vs. placebo pill (continued)	March et al, 2004[113]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	CGAS	12 weeks	111	60.0 (11.47)	112	59.3 (12.72)	NR	P=0.3805
	March et al, 2004[113]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	CGAS	Change at 12 weeks	111	9.7 (12.12)	112	9.9 (12.38)	NR	P=NS
	March et al, 2004[113]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	HoNOSCA	12 weeks	111	11.7 (6.09)	112	11.2 (6.15)	NR	p=0.3344
	March et al, 2004[113]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	HoNOSCA	Change in 12 weeks	111	-3.6 (5.58)		-4.2 (5.71)	NR	p=NR
	March et al, 2004[113]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	PQ-LES-Q	12 weeks	111	47.4 (10.84)	112	48.2 (9.91)	NR	p=0.4630
	March et al, 2004[113]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	PQ-LES-Q	Change in 12 weeks	111	4.2 (10.01)	112	5.2 (10.16)	NR	p=NS
Group in-person CBT vs. wait-list	Clarke et al, 1999[45]	16.2 (1.3) Complet-ers	Group CBT (Adolescent Coping with Depression Course), over 8 weeks plus weekly meetings	GAF	8 weeks	37	71.0 (11.7)	27	64.5 (11.8)	NR	IG1/IG2 vs. CG P<0.05; effect size=0.54

Appendix F Table 23. Depression Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo: Functioning or Quality of Life (Continuous)

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Mean Score (SD)	Between-Group Difference	P value
Group in-person CBT + parent sessions vs. wait-list	Clarke et al, 1999[45]	16.2 (1.3) Complet-ers	Group CBT (Adolescent Coping with Depression Course), plus 8 weekly 2-hour parent sessions (6 separate, 2 held jointly with adolescent group) over 8 weeks	GAF	8 weeks	32	69.9 (14.9)	27	64.5 (11.8)	NR	IG1/IG2 vs. CG P<0.05; effect size=0.54
Interpersonal psycho-therapy vs. TAU	Mufson et al, 2004[118]	15.1 (1.9)	Manualized IPT-A during 12 sessions in a 12- to 16-week period	CGAS	12 weeks	34	66.7 (13.0)	29	59.5 (13.5)	NR	p=0.04, effect size 0.54
	Mufson et al, 2004[118]	15.1 (1.9)	Manualized IPT-A during 12 sessions in a 12- to 16-week period	CGAS	16 weeks	33	NR	29	NR	NR	p=0.06, effect size NR
	Mufson et al, 2004[118]	15.1 (1.9)	Manualized IPT-A during 12 sessions in a 12- to 16-week period	SAS-SR Overal	12 weeks	34	2.23 (0.66)	29	2.59 (0.67)	NR	p=0.01, effect size 0.55 Repeated measures ANOVA time x treatment interaction P=0.003
PCIT-ED vs. wait-list	Luby et al, 2018[111]	IG1: 5.1 (1.0) CG: 5.3 (1.1)	Manualized PCIT-ED sessions to teach parent followed by coaching parent-child interactions using a bug-in-the-ear device over 18 weeks	CGAS	Change to 18 weeks	114	NR	115	NR	Adjusted* mean difference (SE) 20.5 (2.3)	p<0.0001

Appendix F Table 23. Depression Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo: Functioning or Quality of Life (Continuous)

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Mean Score (SD)	Between-Group Difference	P value
	Luby et al, 2018[111]	IG1: 5.1 (1.0) CG: 5.3 (1.1)	Manualized PCIT-ED sessions to teach parent followed by coaching parent-child interactions using a bug-in-the-ear device over 18 weeks	PECFAS/ CAFAS	Change to 18 weeks	114	NR	115	NR	Adjusted mean difference (SE) 3.19 (0.46)	p<0.0001

* Controlled for baseline characteristics, gender, and baseline externalizing disorder.

Abbreviations: ANOVA=analysis of variance; CAFAS=Child and Adolescent Functional Assessment Scale; CBT=cognitive behavioral therapy; CG=control group; CGAS=Children's Global Assessment Scale; CI=confidence interval; GAF=Global Assessment of Functioning; HoNOSCA=Health of the Nation Outcome Scales for Children and Adolescents; IG=intervention group; IPT-A=intensive interpersonal psychotherapy for depressed adolescents; N=number; NR=not reported; NS=not significant; PCIT-ED=Parent Child Interaction Therapy-Emotion Development; PFC=Preschool Feelings Checklist; Preschool and Early Childhood Functional Assessment Scale/Child and Adolescent Functional Assessment Scale; PEDS-QL= Pediatric Quality of Life Inventory; PQ-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; SAS-SR=Social Adjustment Scale–Self-Report; SD=standard deviation; SE=standard error; SF-12 MCS=Short-Form 12 Mental Component Score; SF-12 PCS=Short-Form 12 Physical Component Score; TAU=treatment as usual; vs.=versus.

Appendix F Table 24. Depression Psychotherapy vs. Placebo: Functioning (Categorical)

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Effect Measure (95% CI), p Value
Individual in-person CBT vs. placebo pill	March et al, 2004[113]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	C-GAS >70	12 weeks	111	15 (13.5)	112	21 (18.7)	P=NS

Abbreviations: CBT=cognitive behavioral therapy; CGAS=Children's Global Assessment Scale; CI=confidence interval; N=number; NS=not significant; SD=standard deviation; vs.=versus.

Appendix F Table 25. Depression Pharmacotherapy Interventions vs. Placebo: Functioning (Continuous)

Treatment (Condition)	Author, Year	Mean Age (SD)	Dose (mg/day)	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Escitalopram vs. placebo	Emslie, 2009[86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	Change in CGAS	8 weeks	154	14.9 (SE: 1.11)	157	12.7 (SE: 1.15)	LSMD=2.169 (-0.439 to 4.777)	0.103
	Wagner, 2006[151]	12.3 (3.0)	10 to 20 mg	Change in CGAS	8 weeks	129	15.6	132	12.7	2.9	0.065
Fluoxetine vs. placebo	March, 2004[113]	14.6 (1.5)	10 to 40 mg	CGAS	6 weeks	109	59.9 (SD: `10.58)	112	57.0 (SD: 9.22)	2.9	NR
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	CGAS	12 weeks	109	62.1 (SD: 11.91)	112	59.3 (SD: 12.72)	2.8	P=0.0381
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in CGAS	12 weeks	109	12.6 (SD: 12.31)	112	9.9 (SD: 12.38)	2.7	P=NS
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	HoNOSCA	12 weeks	109	10.9 (SD: 6.35)	112	11.2 (SD: 6.15)	-0.3	P=0.3344
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in HoNOSCA	12 weeks	109	-5.1 (SD: 5.74)	112	-4.2 (SD: 5.71)	-0.9	P=NS
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	PQ-LES-Q	12 weeks	109	51.2 (SD: 10.43)	112	48.2 (SD: 9.91)	3.0	0.7215
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in PQ-LES-Q	12 weeks	109	6.6 (SD: 10.23)	112	5.2 (SD: 10.16)	1.4	P=NS

Abbreviations: CG=control group; CGAS=Children's Global Assessment Scale; HoNOSCA=Health of the Nation Outcome Scales for Children and Adolescents; IG=intervention group; LSMD=least-square mean difference; NR=not reported; NS=not significant; PQ-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; SD=standard deviation; SE=standard error; vs.=versus.

Appendix F Table 26. Depression Pharmacotherapy Intervention vs. Placebo: Functioning (Categorical)

Treatment	Author, Year	Mean Age	Dose (mg/day)	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Effect Measure (95% CI), p Value
Fluoxetine vs. placebo	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Rate of nonimpaired patients (C-GAS >70)	12 weeks	109	22 (20.2)	112	21 (18.7)	P=NS

Abbreviations: CGAS=Children's Global Assessment Scale; CI=confidence interval; N=number; NS=not significant; vs.=versus.

Appendix F Table 27. Depression Pharmacotherapy + Psychotherapy Intervention vs. Placebo: Functioning (Continuous)

Treatment	Author, Year	Mean Age (SD)	Dose (mg/day)	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Fluoxetine + CBT vs. placebo	March, 2004[113]	14.6 (1.5)	10 to 40 mg	CGAS	6 weeks	107	62.4 (11.2)	112	57.0 (9.22)	5.4	NR
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	CGAS	12 weeks	107	66.6 (11.91)	112	59.3 (12.72)	7.3	P<0.0001
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in CGAS	12 weeks	107	16.7 (12.31)	112	9.9 (12.38)	6.8	P<0.0001
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	HoNOSCA	12 weeks	107	9.5 (5.97)	112	11.2 (6.15)	-1.7	P=0.0393
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in HoNOSCA	12 weeks	107	-6.3 (5.69)	112	-4.2 (5.71)	-2.1	P<0.01
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	PQ-LES-Q	12 weeks	107	54.7 (11.21)	112	48.2 (9.91)	6.5	P<0.0001
	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Change in PQ-LES-Q	12 weeks	107	9.6 (10.14)	112	5.2 (10.16)	4.4	p<0.0001

Abbreviations: CBT=cognitive behavioral therapy; CGAS=Children's Global Assessment Scale; HoNOSCA=Health of the Nation Outcome Scales for Children and Adolescents; N=number; NR=not reported; PQ-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; SD=standard deviation; SE=standard error; vs.=versus.

Appendix F Table 28. Depression Pharmacotherapy + Psychotherapy Intervention vs. Placebo: Functioning (Categorical)

Treatment	Author, Year	Mean Age	Dose (mg/day)	Outcome Measure	Time Point (Weeks)	Treatment N	N (%; 95% CI)	Placebo N	N (%; 95% CI)	Effect Measure (95% CI), p Value
Fluoxetine + CBT vs. placebo	March, 2004[113]	14.6 (1.5)	10 to 40 mg	Rate of nonimpaired patients (C-GAS >70)	12 weeks	107	37 (34.6)	112	19 (17)	P=0.009

Abbreviations: CBT=cognitive behavioral therapy; CGAS=Children's Global Assessment Scale; CI=confidence interval; N=number; vs.=versus.

Appendix F Table 29. Depression Interventions: Subgroup Analyses for Benefits

Author, Year, Registry Number	Treatment Interventions and Comparators	Qualitative Results
Clarke et al, 1999[45]	IG1: Child-focused Group CBT (N=45) IG2: Child + Parent Group CBT (N=42) CG: Wait-list (N=36)	At posttreatment, sex was not a significant moderator of recovery rates.
March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286	IG1: Fluoxetine+CBT (N=107) IG2: Fluoxetine (N=109) IG3: Child + Parent CBT (N=111) CG: Placebo (N=112)	At posttreatment, age was significant moderator of clinician-rated symptom severity (CDRS-R), indicating adolescents younger than 16 years of age improved more than adolescents who were 16 or older across treatment conditions. At posttreatment, age, gender, and race/ethnicity were not significant moderators of clinician-rated (CGAS, HoNOSCA) and self-reported (PQ-LES-Q) functioning.
Wagner et al, 2006[151]	IG1: Escitalopram (N=132) CG: Placebo (N=136)	At posttreatment, age significantly moderated the effect of treatment on clinician-rated symptom severity (CGI-S), symptom improvement (CGI-I), and overall functioning (CGAS), indicating that treatment was effective in adolescents (12 to 17 years) but not in children (6 to 11 years).

Abbreviations: CBT=cognitive behavioral therapy; CG=control group; CGAS=Children's Global Assessment Scale; CGI-I=Clinical Global Impressions-Improvement; IG=intervention group; N=number; PQ-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.

Appendix F Table 30. Depression Psychotherapy Interventions vs. Placebo: Suicide-Related Outcomes (Continuous)

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point	Treatment N	Treatment Score (SD)	Placebo N	Placebo Score (SD/SE)	Between-Group P Value
Individual in-person CBT vs. placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	SIQ-Jr	6 weeks	111	13.18 (11.34)	112	16.85 (11.70)	NR
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006 [220]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	SIQ-Jr	12 weeks	111	11.40 (10.44)	112	15.01 (11.05)	P=0.76

Abbreviations: CBT=cognitive behavioral therapy; N=number; NR=not reported; SD=standard deviation; SE=standard error; SIQ-Jr=Suicidal Ideation Questionnaire-Junior; vs.=versus.

Appendix F Table 31. Depression Psychotherapy Interventions vs. Treatment as Usual or Placebo: Suicide-Related Outcomes (Categorical)

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p Value
Individual in-person youth CBT vs. TAU	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist-delivered sessions (duration not specified)	Suicidal behavior assessed by K-SADS interview	52 weeks	106	5 (5.8)	106	2 (2.4)	RR: 2.50 (0.50 to 12.60)
	Clarke et al, 2016[75]	14.6 (1.7)	4 to 8 therapist-delivered sessions (duration not specified)	Suicidal behavior assessed by K-SADS interview	104 weeks	106	1 (1.1)	106	1 (1.1)	RR: 1.00 (0.06 to 15.78)
Individual in-person CBT vs. placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	Suicide-related AEs determined by Columbia Classification Algorithm	12 weeks	111	5 (4.50)	112	4 (3.57)[113] Also reported as 3 (2.7%)[218]	RR: 1.26 (0.35 to 4.57) RR: 1.68 (0.41 to 6.87)
Individual in-person CBT vs. placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	Suicide attempts	12 weeks	111	1 (0.90%)	112	0 (0)	NR

Abbreviations: AE=adverse event; CBT=cognitive behavioral therapy; CI=confidence interval; K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; N=number; NR=not reported; RR=relative risk; SD=standard deviation; TAU=treatment as usual; vs.=versus.

Appendix F Table 32. Depression Pharmacotherapy Interventions vs. Placebo: Suicide-Related Outcomes (Continuous)

Treatment (Condition)	Author, Year	Mean Age (SD)	Dose (mg/day)	Outcome Measure	Time Point	Treatment N	Treatment Score (SD)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Effect Measure (95% CI), p Value
Escitalopram vs. placebo	Emslie, 2009[86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	Change in SIQ-Jr	8 weeks	155	-4.6 (SEM, 12.0)	157	-2.9 (10.2)	-1.7	0.29
	Emslie, 2009[86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	Change in MC-SSRS (worsening suicidal behavior)	8 weeks	155	2 (SEM, 1.5)	157	3 (2.3)	-1.0	NR
	Emslie, 2009[86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	Change in MC-SSRS (increase in suicidal ideation)	8 weeks	155	12 (SEM, 9.4)	157	12 (9.2)	0	NR
Fluoxetine vs. placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Change in SIQ-Jr	6 weeks	109	16.20 (12.42)	112	16.85 (11.70)	-0.65	NR
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Change in SIQ-Jr	12 weeks	109	14.44 (11.13)	112	15.01 (11.05)	-0.57	0.36*

* Means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model.

Abbreviations: CG=placebo group; CI=confidence interval; IG1=active drug group; MC-SSRS= Modified Columbia Suicide Severity Rating Scale; N=number; SD=standard deviation; SE=standard error; SEM=standard error of the mean; SIQ-Jr=Suicidal Ideation Questionnaire-Junior; vs.=versus.

Appendix F Table 33. Depression Pharmacotherapy Interventions vs. Placebo: Suicide-Related Outcomes (Categorical)

Treatment (Condition)	Author, Year	Mean Age (SD)	Dose (mg/day)	Outcome Measure	Time Point	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p Value
Escitalopram vs. placebo	Emslie, 2009 [86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	Self-harm related AE (other than suicidality)	8 weeks	155	6 (3.9)	157	6 (3.8)	NR
	Wagner, 2006 [151]	12.3 (3.0)	10 to 20 mg	Potential suicide-related events	8 weeks	131	1 (7.8)	133	2 (1.5)	NR
Fluoxetine vs. placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Suicide-related AEs determined by Columbia Classification Algorithm	12 weeks	109	9 (8.26)[113] Also reported as 10 (9.2)[218]	112	4 (3.57)[113] Also reported as 3 (2.7)[218]	RR: 2.31 (0.73 to 7.29) RR: 3.43 (0.97 to 12.11)
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Suicide attempts	12 weeks	109	2 (1.83)	112	0 (0)	NR

Abbreviations: AE=adverse event; CG=placebo group; CI=confidence interval; IG1=active drug group; N=number; NR=not reported; RR=relative risk; SD=standard deviation; vs.=versus.

Appendix F Table 34. Depression Pharmacotherapy + Psychotherapy Intervention vs. Placebo: Suicide-Related Outcomes (Continuous)

Treatment (Condition)	Author, Year	Mean Age (SD)	Dose (mg/day)	Outcome Measure	Time Point	Treatment N	Treatment Score (SD/SE)	Placebo N	Placebo Score (SD/SE)	Between-Group Difference	Between-Group P Value
Fluoxetine + CBT vs placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Change in SIQ-Jr	6 weeks	107	14.31 (12.58)	112	16.85 (11.70)	-0.65	NR
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Change in SIQ-Jr	12 weeks	107	11.79 (11.69)	112	15.01 (11.05)	-0.57	0.02*

* Supplemental between-group comparisons of means at 12 weeks; P=NS.

Abbreviations: CBT=cognitive behavioral therapy; N=number; NS=not significant; SD=standard deviation; SE=standard error; SIQ-Jr=Suicidal Ideation Questionnaire-Junior; vs.=versus.

Appendix F Table 35. Depression Pharmacotherapy + Psychotherapy Intervention vs. Placebo: Suicide-Related Outcomes (Categorical)

Treatment (Condition)	Author, Year	Mean Age (SD)	Dose (mg/day)	Outcome Measure	Time Point	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p Value
Fluoxetine + CBT vs placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Suicide-related AEs determined by Columbia Classification Algorithm	12 weeks	107	6 (5.61)[113] Also reported as 5 (4.7)[218]	112	4 (3.57)[113] Also reported as 3 (2.7)[218]	RR (95% CI): IG vs. CG: 1.57 (0.46 to 5.41) RR (95% CI): IG vs. CG: 1.75 (0.43 to 7.12)
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Suicide attempts	12 weeks	107	4 (3.7%)	112	0 (0)	NR

Abbreviations: AE=adverse event; CBT=cognitive behavioral therapy; CG=control group; CI=confidence interval; IG=intervention group; N=number; NR=not reported; RR=relative risk; SD=standard deviation; vs.=versus.

Appendix F Table 36. Depression Psychotherapy vs. Placebo Intervention: Adverse Events and Serious Adverse Events

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Effect Measure (95% CI), p Value
Individual in-person CBT vs. placebo	March et al, 2004[113] Curry et al, 2006 [217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	Physical AEs requiring medical attention or causing dysfunction	12 weeks	111	9 (8.1)	112	34 (30.4)	NR
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	Any psychiatric-related AEs	12 weeks	111	1 (1)	112	9 (9.8)	NR
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	Serious AEs	12 weeks	111	5 (4.50)	112	6 (5.36)	OR (95% CI): 0.8 (0.25 to 2.81)
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	15 therapist-delivered sessions plus 2 parent-only sessions over 12 weeks	Serious psychiatric-related AEs	12 weeks	111	0 (0)	112	1 (0.89), mania	NR

Abbreviations: AE=adverse event; CBT=cognitive behavioral therapy; CI=confidence interval; N=number; NR=not reported; OR=odds ratio; SD=standard deviation; vs.=versus.

Appendix F Table 37. Depression Pharmacotherapy Interventions vs. Placebo: Adverse Events and Serious Adverse Events

Treatment (Condition)	Author, Year	Mean Age (SD)	Dose (mg/day)	Outcome Measure	Time Point (Weeks)	Treatment N	N (%)	Placebo N	N (%)	Between-Group P Value
Escitalopram vs. placebo	Emslie, 2009[86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	Total AEs	8 weeks	155	121 (78.1)	157	118 (75.2)	NR
	Emslie, 2009[86]	IG1: 14.7 (1.6) CG: 14.5 (1.5)	10 to 20 mg	SAEs	8 weeks	155	4 (2.6), 1 sexual assault, 1 self-injurious behavior, 1 suicidal ideation, 1 irritability	157	2 (1.3) (1 suicidal tendency, 1 aggravated depression)	NR
	Wagner, 2006[151]	12.3 (3.0)	10 to 20 mg	Any AE	8 weeks	131	90 (68.7)	133	90 (67.7)	p=0.90
Fluoxetine vs. placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006 [220]	14.6 (1.5)	10 to 40 mg	Physical AEs requiring medical attention or causing dysfunction	12 weeks	109	35 (32.1)	112	34 (30.4)	NR
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Any psychiatric-related AEs	12 weeks	109	20 (21.0)	112	9 (9.8)	NR
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	SAEs	12 weeks	109	13 (11.93)	112	6 (5.36)	OR (95% CI): 2.4 (0.87 to 6.54)
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Serious psychiatric-related AEs	12 weeks	109	1 (0.92), worsening depression	112	1 (0.89), mania	NR

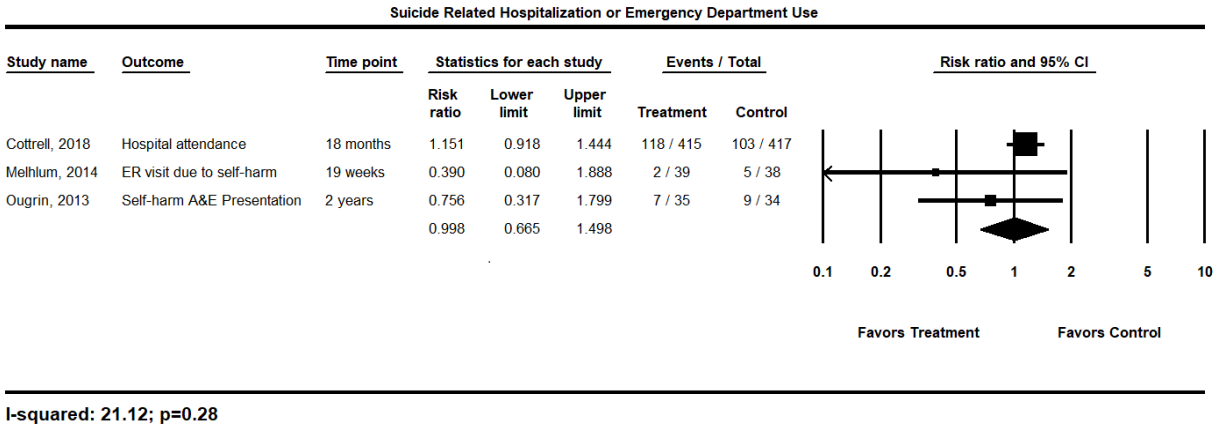
Abbreviations: AE=adverse event; CBT=cognitive behavioral therapy; CI=confidence interval; N=number; NR=not reported; OR=odds ratio; SAE=serious adverse event; SD=standard deviation; vs.=versus.

Appendix F Table 38. Depression Pharmacotherapy + Psychotherapy Intervention vs. Placebo: Adverse Events and Serious Adverse Events

Treatment (Condition)	Author, Year	Mean Age (SD)	Dose (mg/day)	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Score (SD)	Placebo N	Placebo Score (SD/SE)	Between-Group P Value
Fluoxetine + CBT vs. placebo	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Physical AEs requiring medical attention or causing dysfunction	12 weeks	107	37 (34.5)	112	34 (30.4)	NR
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Any psychiatric-related AEs	12 weeks	107	12 (15)	112	9 (9.8)	NR
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	SAEs	12 weeks	107	9 (8.41)	112	6 (5.36)	OR (95% CI): 1.6 (0.56 to 4.72)
	March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220]	14.6 (1.5)	10 to 40 mg	Serious psychiatric-related AEs	12 weeks	107	0 (0)	112	1 (0.89), mania	NR

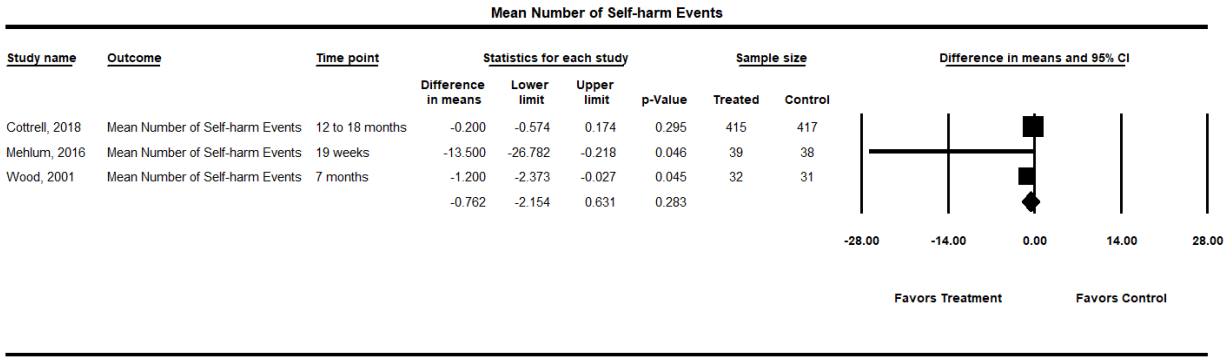
Abbreviations: AE=adverse event; CBT=cognitive behavioral therapy; CI=confidence interval; N=number; NR=not reported; OR=odds ratio; SD=standard deviation; SE=standard error; vs.=versus.

Appendix G Figure 1. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide-Related Hospitalization or Emergency Department Use



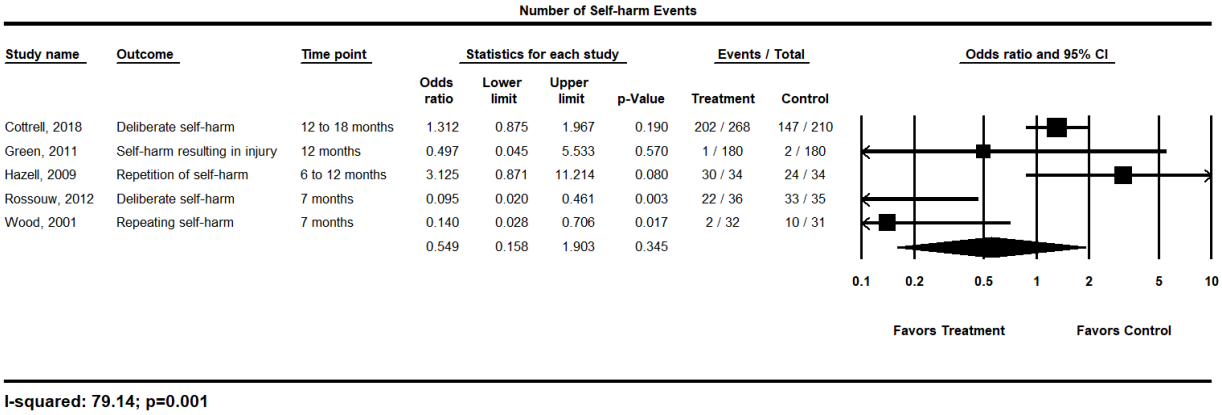
Abbreviations: A&E=accident and emergency; CI=confidence interval; ER=emergency room; vs. versus.

Appendix G Figure 2. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Mean Number of Self-Harm Events



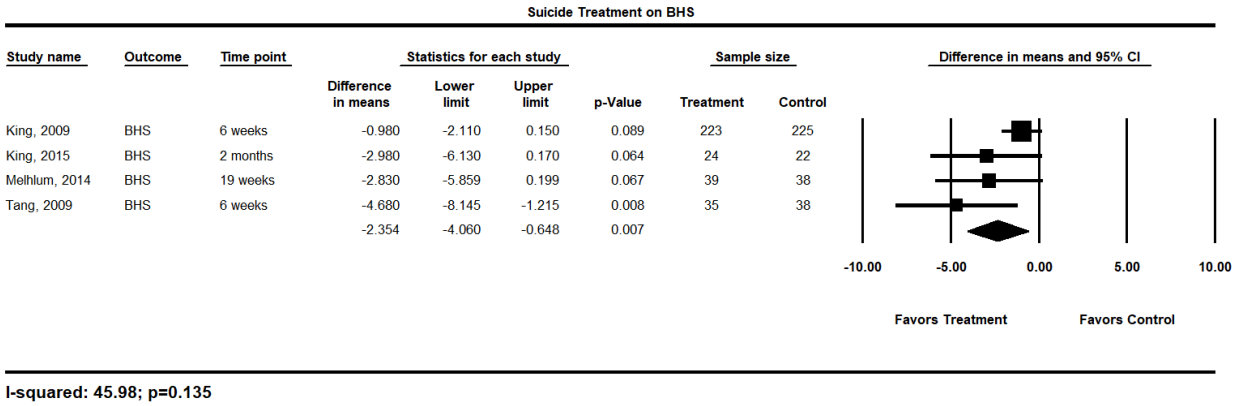
Abbreviations: CI=confidence interval; vs. versus.

Appendix G Figure 3. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Proportion With Self-Harm Events



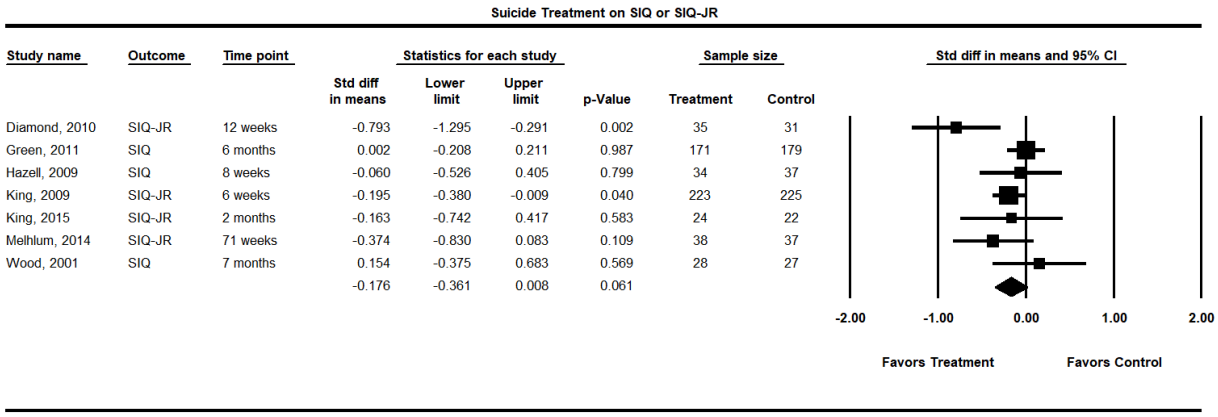
Abbreviations: CI=confidence interval; vs. versus.

Appendix G Figure 4. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms (Beck Hopelessness Scale)



Abbreviations: BHS=Beck Hopelessness Scale; CI=confidence interval; vs. versus.

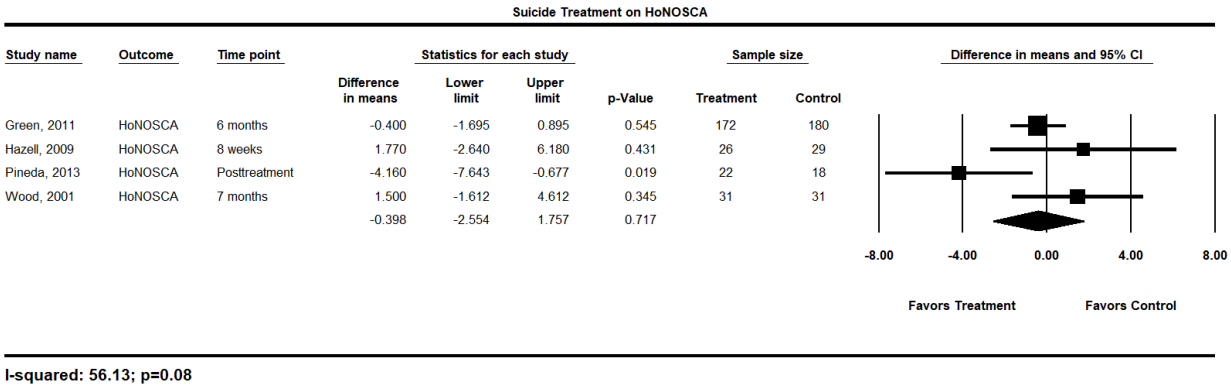
Appendix G Figure 5. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Suicide Symptoms (Suicidal Ideation Questionnaire or Suicidal Ideation Questionnaire-Junior)



I-squared: 44.80; p=0.092

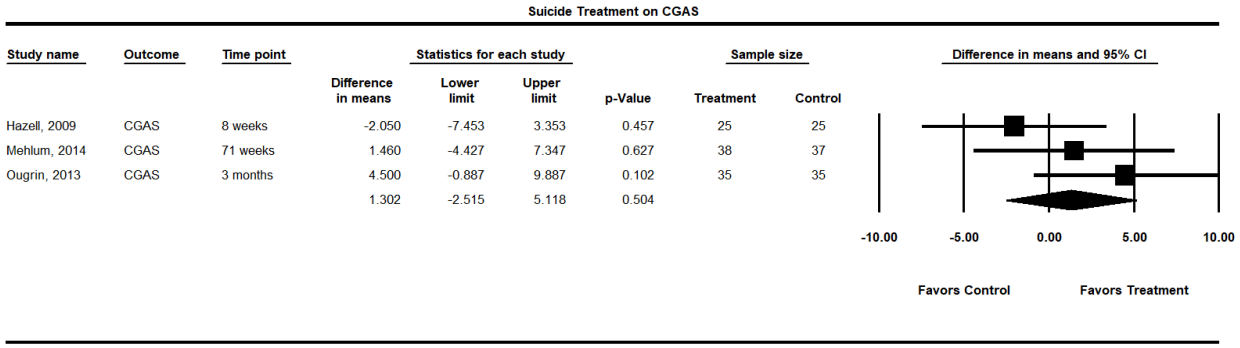
Abbreviations: CI=confidence interval; SIQ=Suicidal Ideation Questionnaire; SIQ-Jr=Suicidal Ideation Questionnaire-Junior; vs. versus.

Appendix G Figure 6. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Functional Status (Health of the Nation Outcome Scales for Children and Adolescents)



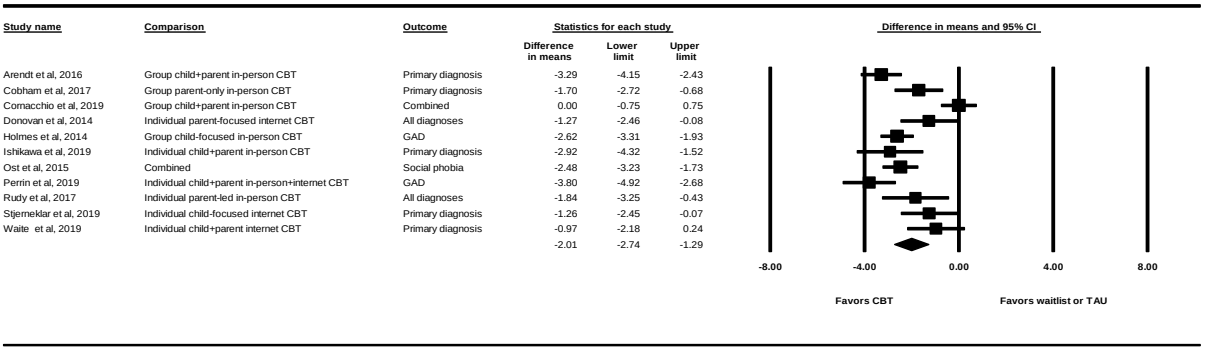
Abbreviations: CI=confidence interval; HoNOSCA=Health of the Nation Outcome Scales for Children and Adolescents; vs. versus.

Appendix G Figure 7. Suicide Risk Interventions vs. Treatment as Usual or Attention Control: Functional Status (Clinical Global Assessment Scale)



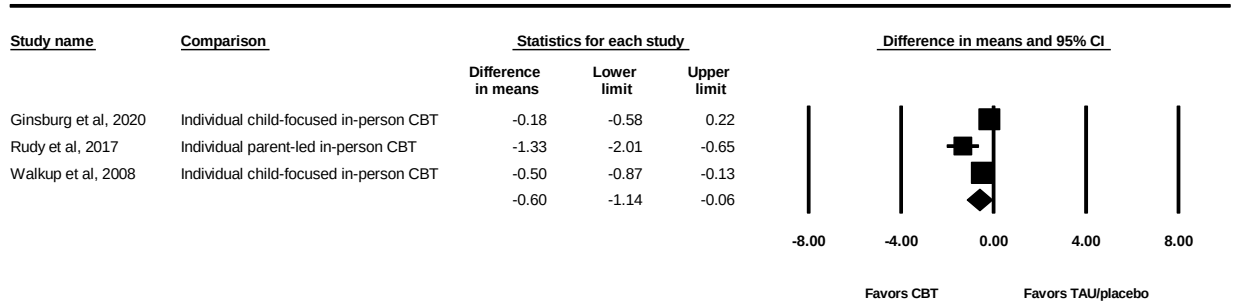
Abbreviations: CGAS=Children's Global Assessment Scale; CI=confidence interval; vs. versus.

Appendix G Figure 8. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Anxiety Symptoms (ADIS-Clinician Severity Ratings)



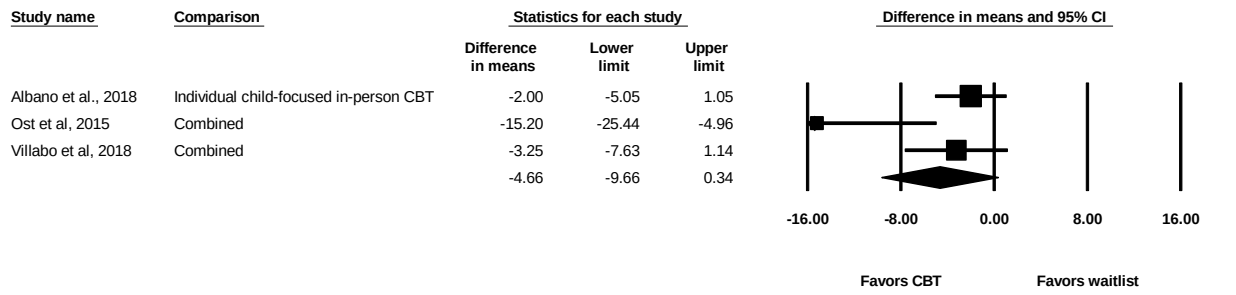
Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; GAD=general anxiety disorder; TAU=treatment as usual; vs. versus.

Appendix G Figure 9. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Anxiety Symptoms (Clinical Global Impressions-Severity)



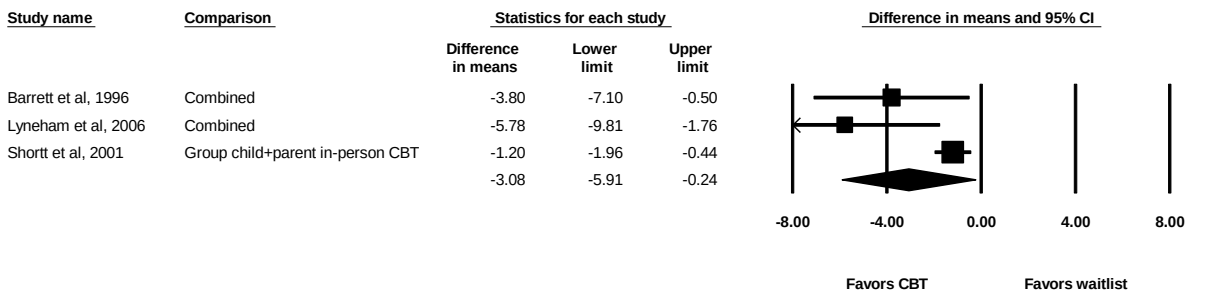
Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; TAU=treatment as usual; vs. versus.

Appendix G Figure 10. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Anxiety Symptoms (Multidimensional Anxiety Scale)



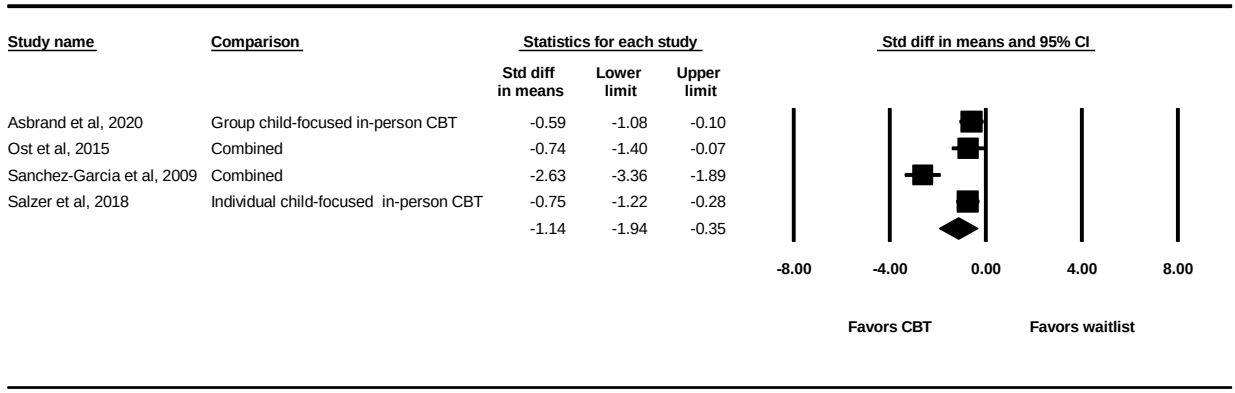
Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; vs. versus.

Appendix G Figure 11. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Anxiety Symptoms (Revised Children's Manifest Anxiety Scale)



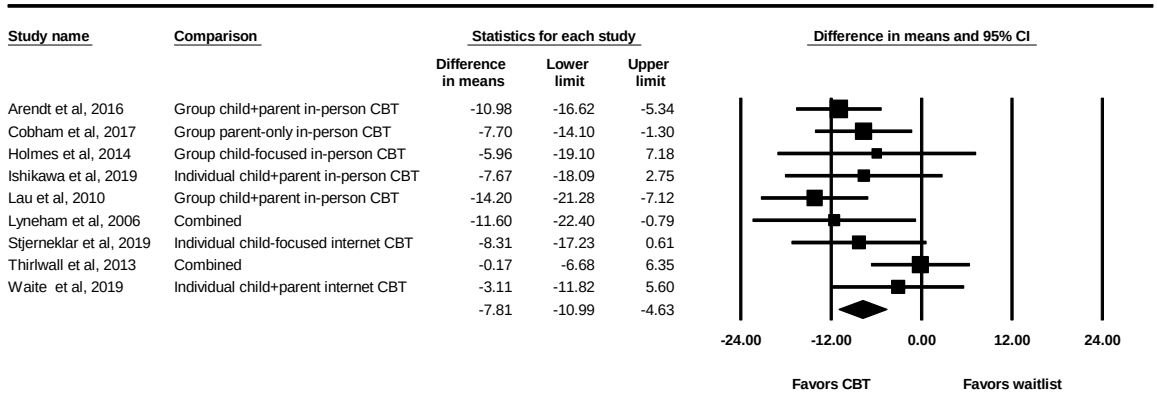
Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; vs. versus.

Appendix G Figure 12. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Anxiety Symptoms (Social Phobia and Anxiety Inventory for Children)



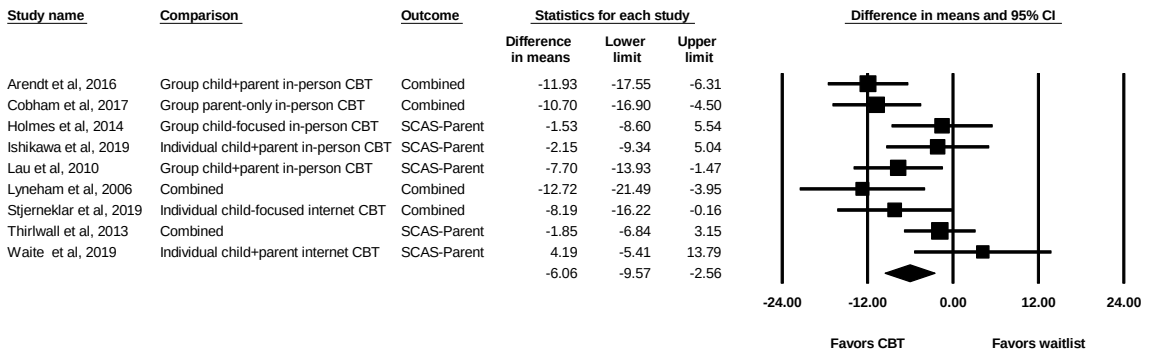
Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; vs. versus.

Appendix G Figure 13. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Anxiety Symptoms (Spence Children's Anxiety Scale-Child Rating)



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; vs. versus.

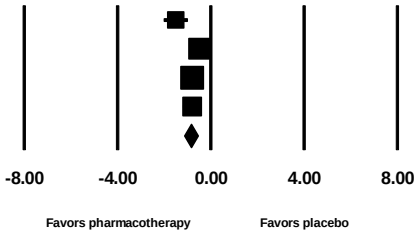
Appendix G Figure 14. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Anxiety Symptoms (Spence Children's Anxiety Scale-Parent Rating)



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; SCAS-Parent=Spence Children's Anxiety Scale-Parent-rated; vs. versus.

Appendix G Figure 15. Anxiety Pharmacotherapy Interventions vs. Placebo: Anxiety Symptoms (Clinical Global Impressions-Severity)

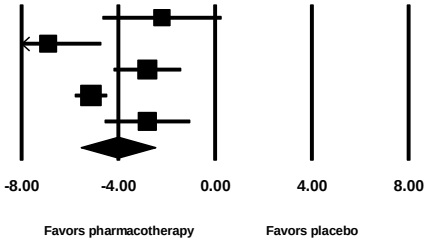
Study name	Comparison	Statistics for each study			Sample size		Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	Pharmacotherapy	Placebo	
Rynn et al, 2001	Sertraline	-1.50	-2.00	-1.00	11	11	
Strawn et al, 2015	Duloxetine	-0.50	-0.78	-0.22	135	133	
Strawn et al, 2020	Escitalopram	-0.80	-0.94	-0.66	26	25	
Walkup et al, 2008	Sertraline	-0.80	-1.18	-0.42	133	76	
		-0.84	-1.13	-0.55	305	245	



Abbreviation: CI=confidence interval; vs. versus.

Appendix G Figure 16. Anxiety Pharmacotherapy Interventions vs. Placebo: Anxiety Symptoms (Pediatric Anxiety Rating Scale)

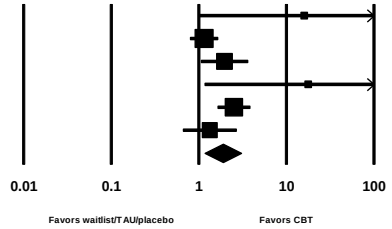
Study name		Statistics for each study			Sample size	
		Difference in means	Lower limit	Upper limit	Pharmacotherapy	Placebo
Birmaher et al, 2003	Fluoxetine	-2.20	-4.65	0.25	37	37
Pine et al, 2001	Fluvoxamine	-6.90	-9.08	-4.72	61	63
Strawn et al, 2015	Duloxetine	-2.80	-4.19	-1.41	135	133
Strawn et al, 2020	Escitalopram	-5.13	-5.79	-4.47	26	25
Walkup et al, 2008	Sertraline	-2.80	-4.56	-1.04	133	76
		-4.00	-5.54	-2.46	392	334



Abbreviation: CI=confidence interval; vs. versus.

Appendix G Figure 17. Anxiety CBT Interventions vs. Treatment as Usual: Response (Clinical Global Impressions-Improvements Scores ≤2)

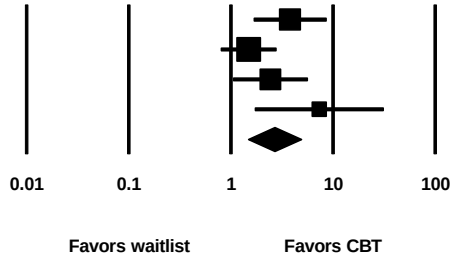
Study name	Comparison	Statistics for each study			Events / Total		Risk ratio and 95% CI
		Risk ratio	Lower limit	Upper limit	CBT	Waitlist	
Cornacchio et al, 2019	Group child+parent in-person CBT	16.00	1.00	256.54	7 / 14	0 / 15	
Ginsburg et al, 2020	Individual child-focused in-person CBT	1.15	0.80	1.65	62 / 148	25 / 68	
Hirshfeld-Becker et al, 2010	Individual child+parent in-person CBT	1.97	1.06	3.63	20 / 34	9 / 30	
Rudy et al, 2017	Individual parent-led in-person CBT	17.76	1.17	269.93	10 / 12	0 / 10	
Walkup et al, 2008	Individual child-focused in-person CBT	2.52	1.65	3.86	83 / 139	18 / 76	
Waite et al, 2019	Individual parent-led in-person CBT	1.33	0.66	2.69	12 / 30	9 / 30	
		1.89	1.17	3.05	194 / 377	61 / 229	



Abbreviation: CI=confidence interval; TAU=treatment as usual; vs. versus.

Appendix G Figure 18. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Remission (Clinically Significant Change in Spence Children's Anxiety Scale)

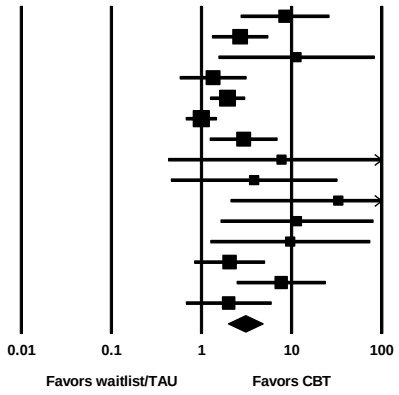
Study name	Comparison	Statistics for each study		
		Risk ratio	Lower limit	Upper limit
Arendt et al, 2016	Group child+parent in-person CBT	3.80	1.68	8.56
Ishikawa et al, 2019	Individual child+parent in-person CBT	1.49	0.80	2.78
Lyneham et al, 2006	Combined	2.44	1.06	5.64
Stjerneklar et al, 2019	Individual child-focused internet CBT	7.33	1.73	31.17
		2.68	1.48	4.88



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; vs. versus.

Appendix G Figure 19. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Loss of All Anxiety Diagnoses

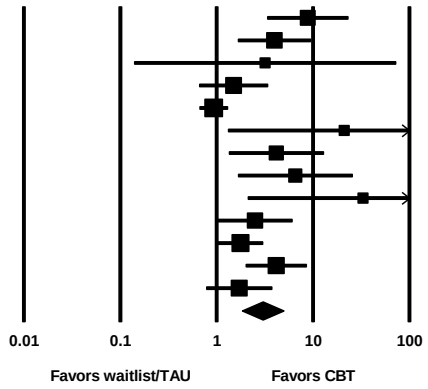
Study name	Comparison	Statistics for each study		
		Risk ratio	Lower limit	Upper limit
Arendt et al, 2016	Group child+parent in-person CBT	8.46	2.74	26.13
Barrett et al, 1996	Individual child-focused or child+family in-person CBT	2.68	1.32	5.47
Cobham et al, 2017	Individual+group child + parent in-person CBT	11.38	1.56	83.26
Donovan et al, 2014	Individual+group child in-person CBT	1.35	0.58	3.14
Ginsburg et al, 2011	Individual child-focused in-person CBT	1.95	1.25	3.03
Ginsburg et al, 2020	Individual child-focused internet CBT	1.00	0.67	1.48
Hirshfeld-Becker et al, 2010	Individual parent-guided in-person+telephone brief CBT	2.94	1.25	6.94
Holmes et al, 2014	Group child+parent in-person CBT	7.76	0.43	140.24
Ishikawa et al, 2019	Individual parent-guided in-person+telephone full CBT	3.85	0.46	32.08
Perrin et al, 2019	Individual child+parent internet CBT	33.00	2.11	515.02
Shortt et al, 2001	Individual child+parent in-person CBT	11.50	1.64	80.72
Stjerneklar et al, 2019	Individual child+parent in-person CBT	9.67	1.26	74.13
Thirlwall et al, 2013	Combined	2.05	0.84	5.03
Villabo et al, 2018	Combined	7.69	2.48	23.84
Waite et al, 2019	Group parent-only in-person CBT	2.01	0.68	5.97
		3.09	1.98	4.80



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; TAU=treatment as usual; vs. versus.

Appendix G Figure 20. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Loss of Primary Anxiety Diagnosis

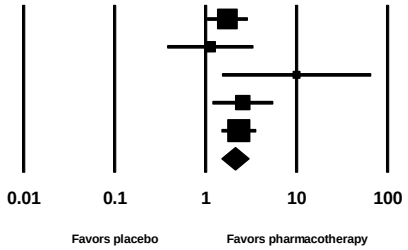
Study name	Comparison	Statistics for each study		
		Risk ratio	Lower limit	Upper limit
Arendt et al, 2016	Group child+parent in-person CBT	8.81	3.36	23.11
Cobham et al, 2017	Group parent-only in-person CBT	3.98	1.67	9.48
Cornacchio et al, 2019	Group child+parent in-person CBT	3.19	0.14	72.45
Donovan et al, 2014	Individual parent-focused internet CBT	1.50	0.66	3.39
Ginsburg et al, 2020	Individual child-focused in-person CBT	0.93	0.67	1.30
Holmes et al, 2014	Group child-focused in-person CBT	21.10	1.32	337.22
Ishikawa et al, 2019	Individual child+parent in-person CBT	4.17	1.35	12.89
Ost et al, 2015	Combined	6.55	1.68	25.57
Perrin et al, 2019	Individual child+parent in-person+internet CBT	33.00	2.11	515.02
Stjerneklar et al, 2019	Individual child-focused internet CBT	2.50	1.03	6.10
Thirlwall et al, 2013	Combined	1.77	1.03	3.02
Villabo et al, 2018	Combined	4.15	2.02	8.56
Waite et al, 2019	Individual child+parent internet CBT	1.72	0.78	3.76
		3.02	1.84	4.95



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; TAU=treatment as usual; vs. versus.

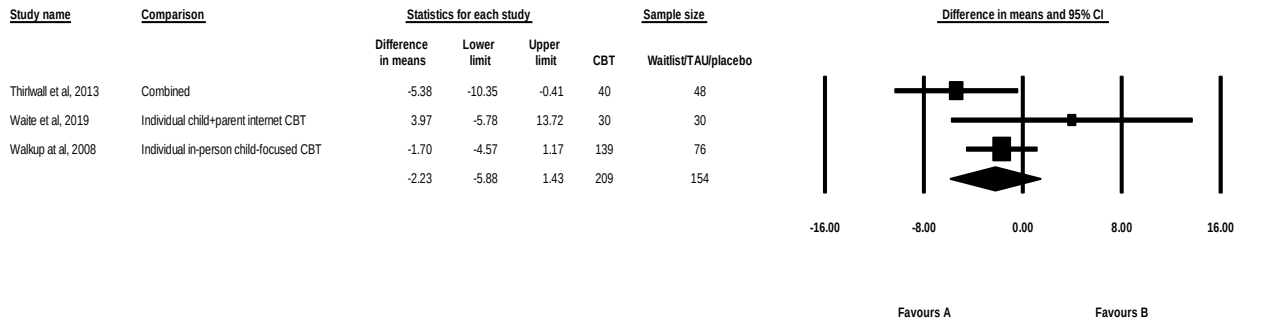
Appendix G Figure 21. Anxiety Pharmacotherapy Interventions vs. Placebo: Response (Clinical Global Impressions-Improvements Scores ≤2)

Study name	Comparison	Statistics for each study			Events / Total		Risk ratio and 95% CI
		Risk ratio	Lower limit	Upper limit	Pharmacotherapy	Placebo	
Birmaher et al, 2003	Fluoxetine	1.74	1.04	2.89	22 / 36	13 / 37	
Black et al, 1994	Fluoxetine	1.13	0.38	3.32	3 / 6	4 / 9	
Rynn et al, 2001	Sertraline	10.00	1.53	65.41	10 / 11	1 / 11	
Strawn et al, 2020	Escitalopram	2.56	1.20	5.49	16 / 26	6 / 25	
Walkup et al, 2008	Sertraline	2.32	1.50	3.57	73 / 133	18 / 76	
		2.11	1.50	2.98	124 / 212	42 / 158	



Abbreviations: CI=confidence interval; vs.=versus.

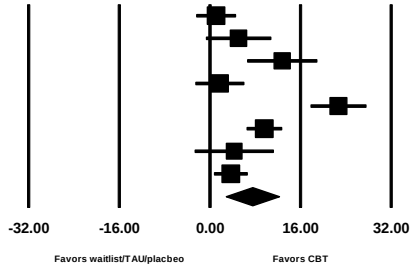
Appendix G Figure 22. Anxiety CBT Intervention vs. Treatment as Usual or Attention Control: Functioning (Children's Anxiety Impact Scale)



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; TAU=treatment as usual; vs.=versus.

Appendix G Figure 23. Anxiety CBT Interventions vs. Treatment as Usual or Attention Control: Functioning (Children's Global Assessment Scale)

Study name	Comparison	Statistics for each study		
		Difference in means	Lower limit	Upper limit
Cornacchio et al, 2019	Group child+parent in-person CBT	1.10	-2.37	4.57
Donovan et al, 2014	Individual parent-focused internet CBT	5.06	-0.66	10.78
Holmes et al, 2014	Group child-focused in-person CBT	12.77	6.62	18.92
Ginsburg et al, 2020	Individual in-person child-focused CBT	1.76	-2.51	6.03
Perrin et al, 2019	Individual child+parent in-person+internet CBT	22.70	17.82	27.58
Villabo et al, 2018	Combined	9.62	6.53	12.70
Waite et al, 2019	Individual child+parent internet CBT	4.30	-2.65	11.25
Walkup at al, 2008	Individual in-person child-focused CBT	3.70	0.78	6.62
		7.54	2.84	12.23



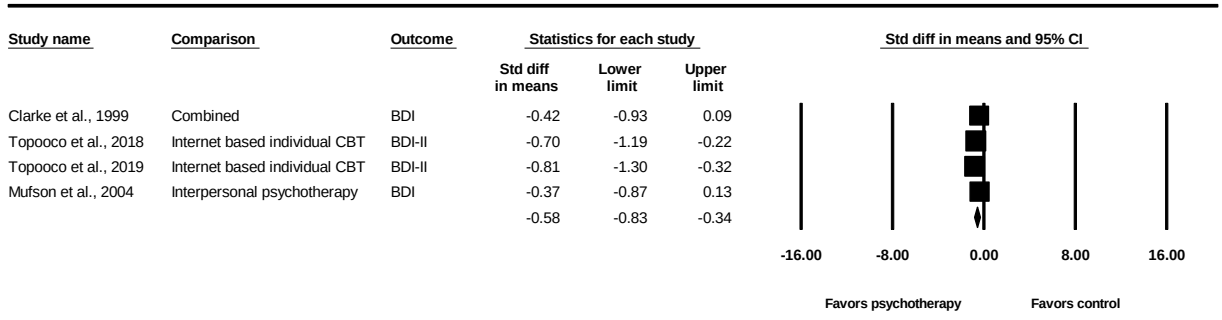
Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; TAU=treatment as usual; vs.=versus.

Appendix G Figure 24. Anxiety Pharmacotherapy Intervention vs. Placebo: Functioning (Children's Global Assessment Scale)

Study name	Comparison	Statistics for each study			Sample size		Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	Pharmacotherapy	Placebo	
Birmaher et al, 2003	Fluoxetine	9.10	3.13	15.07	37	37	
Walkup et al, 2008	Sertraline	4.90	1.86	7.94	133	76	
Strawn et al, 2015	Duloxetine	4.50	1.73	7.27	135	133	
		5.14	3.21	7.08	305	246	

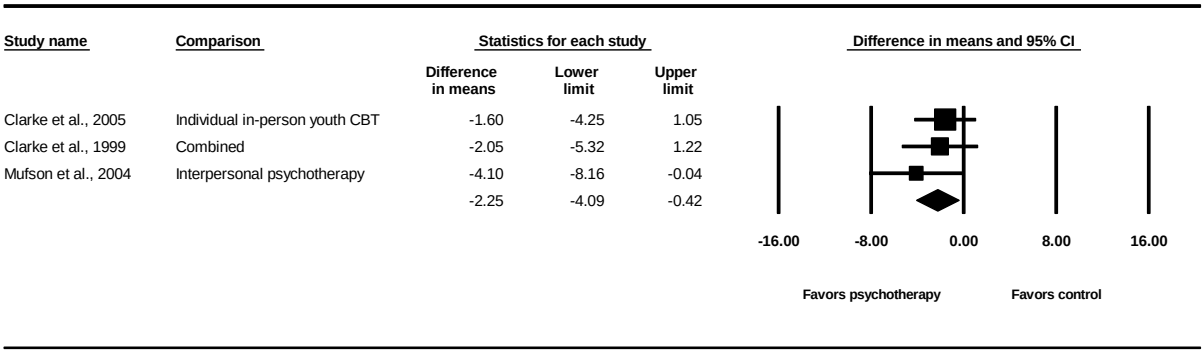
Abbreviation: CI=confidence interval; vs.=versus.

Appendix G Figure 25. Depression Psychotherapy Interventions vs. Attention Control, Treatment as Usual, or Wait-List: Depression Symptoms (Beck Depression Inventory [BDI] or BDI II)



Abbreviations: BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory, version 2; CBT=cognitive behavioral therapy; CI=confidence interval; vs.=versus.

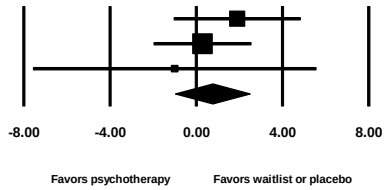
Appendix G Figure 26. Depression Psychotherapy Interventions vs. Treatment as Usual or Wait-List: Depression Symptoms (Hamilton Depression Rating Scale)



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; vs.=versus.

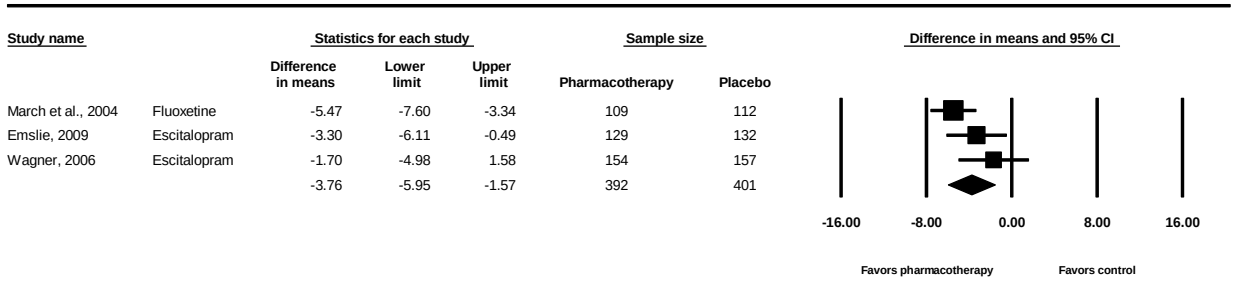
Appendix G Figure 27. Depression Psychotherapy Interventions vs. Treatment as Usual, Placebo, or Wait-List: Depression Symptoms (Children's Depression Rating Scale-Revised)

Study name	Comparison	Statistics for each study			Sample size	
		Difference in means	Lower limit	Upper limit	Psychotherapy	Control
Clarke et al., 2016	Individual in-person youth CBT	1.90	-1.04	4.84	106	106
March et al., 2004	Individual in-person CBT	0.29	-1.97	2.55	111	112
Fristad et al., 2019	Family CBT	-1.00	-7.57	5.57	18	18
		0.76	-0.97	2.48	235	236



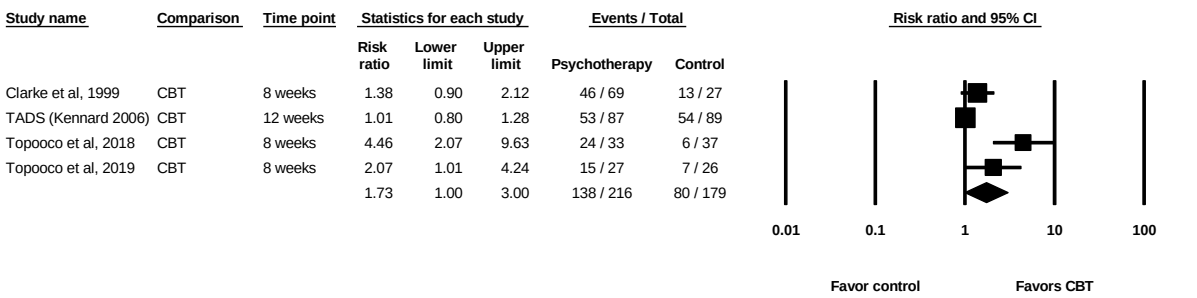
Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; vs.=versus.

Appendix G Figure 28. Depression Pharmacotherapy Interventions vs. Placebo: Depression Symptoms (Children's Depression Rating Scale-Revised)



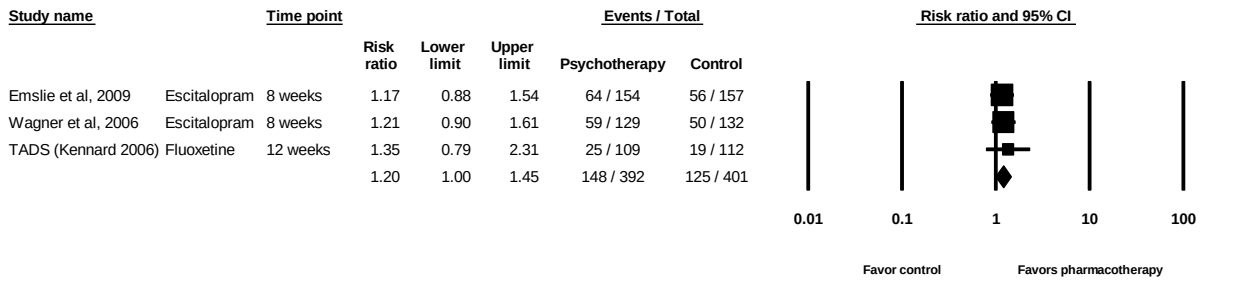
Abbreviation: CI=confidence interval; vs.=versus.

Appendix G Figure 29. Depression Psychotherapy Interventions vs. Attention Control, Wait-List, or Placebo: Loss of Diagnosis



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; vs.=versus.

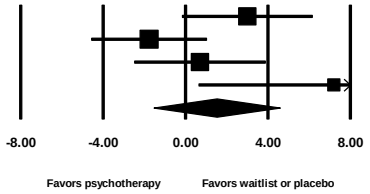
Appendix G Figure 30. Depression Pharmacotherapy Interventions vs. Placebo: Remission (Children's Depression Rating Scale-Revised ≤28)



Abbreviation: CI=confidence interval; vs.=versus.

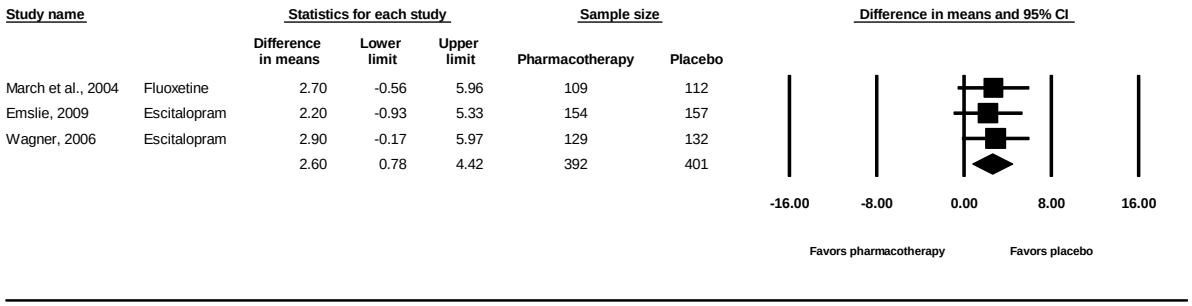
Appendix G Figure 31. Depression Psychotherapy Interventions vs. Wait-List or Placebo: Functioning (Children's Global Assessment Scale)

Study name	Comparison	Statistics for each study			Sample size		Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	Pharmacotherapy	Placebo	
Clarke et al., 2005	Individual in-person youth CBT	3.00	-0.16	6.16	53	50	
Clarke et al., 2016	Individual in-person youth CBT	-1.77	-4.57	1.03	106	106	
March et al., 2004	Individual in-person CBT	0.70	-2.48	3.88	111	112	
Mufson et al., 2004	Interpersonal psychotherapy	7.20	0.64	13.76	34	29	
		1.52	-1.54	4.58	304	297	



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; vs.=versus.

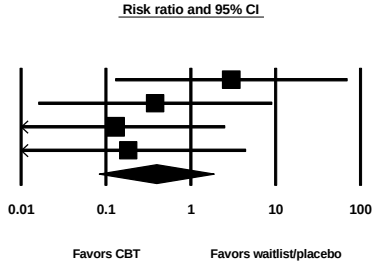
Appendix G Figure 32. Depression Pharmacotherapy Interventions vs. Placebo: Functioning (Children's Global Assessment Scale)



Abbreviation: CI=confidence interval; vs.=versus.

Appendix G Figure 33. Anxiety CBT Interventions vs. Wait-List or Placebo: Withdrawal Due to Adverse Events

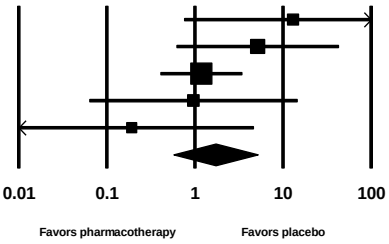
Study name	Comparison	Statistics for each study			Events / Total	
		Risk ratio	Lower limit	Upper limit	CBT	Waitlist or placebo
Perrin et al, 2019	Individual child+parent in-person+internet+CBT	3.00	0.13	69.52	1 / 20	0 / 20
Stjerneklar et al, 2019	Individual internet child-focused CBT	0.38	0.02	9.05	0 / 34	1 / 39
Waite et al, 2019	Individual child+parent internet CBT	0.13	0.01	2.53	0 / 27	2 / 17
Walkup et al, 2008	Individual in-person CBT	0.18	0.01	4.45	0 / 139	1 / 76
		0.39	0.08	1.87	1 / 220	4 / 152



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval; vs.=versus.

Appendix G Figure 34. Anxiety Pharmacotherapy Interventions vs. Placebo: Withdrawal Due to Adverse Events

Study name		Statistics for each study			Events / Total		Risk ratio and 95% CI
		Risk ratio	Lower limit	Upper limit	Pharmacotherapy	Placebo	
Birmaher et al, 2003	Fluoxetine	13.00	0.76	222.75	6 / 37	0 / 37	
Pine et al, 2001	Fluvoxamine	5.16	0.62	42.93	5 / 63	1 / 65	
Strawn et al, 2015	Duloxetine	1.18	0.41	3.43	7 / 135	6 / 137	
Strawn et al, 2020	Escitalopram	0.96	0.06	14.55	1 / 26	1 / 25	
Walkup et al, 2008	Sertraline	0.19	0.01	4.64	0 / 133	1 / 76	
		1.72	0.57	5.18	19 / 394	9 / 340	



Abbreviation: CI=confidence interval; vs.=versus.

Overview

Appendix H includes a synthesis of results for symptoms other than those directly targeted by the intervention, specifically, anxiety and depression for suicide risk interventions; depression for anxiety interventions; and anxiety for depression interventions.

Suicide Risk

Results: Anxiety Symptoms

Psychotherapy vs. Treatment as Usual or Attention Control

Three studies reported on the effects of suicide or self-harm interventions on anxiety symptoms at the end of treatment (1 month to 12 weeks).[94, 100, 144] Studies compared MBT,[94] IPT-A-IN,[144] child interview with counseling,[100] parent sessions,[100] or child interview with counseling plus parent sessions[100] with TAU. Two of the interventions[94, 144] were high contact (>3 sessions), and one intervention[100] was low contact (<3 sessions). The results could not be pooled because of differences in measures; the findings were mixed. Reported anxiety measures included the RCADS,[94] BAI,[144] and four individual anxiety items (e.g., "I feel uneasy or anxious").[100] Study sample sizes ranged from 53 to 615. Statistically significant improvement in anxiety symptoms was reported for the treatment arms of the IPT-A-IN (11.94 vs. 25.45, $p<0.001$),[144] child interview with counseling (rate of change: -0.683 vs. -0.440, $p<0.05$), and child interview with counseling plus parent sessions (rate of change at 1 month: -0.849 vs. -0.440, $p<0.001$)[100] at the end of treatment. No significant differences were reported on the RCADS at the end of treatment between MBT and TAU.[94] One study of child interview with counseling plus parent sessions continued to report statistically significant differences between arms at 1 month in addition to 2.5 months and continued to find statistically significant differences between arms.[100]

Results: Depression Symptoms

Psychotherapy vs. Treatment as Usual or Attention Control

Thirteen studies reported on the effects of suicide or self-harm interventions on depression symptoms at the end of treatment (2 weeks to 12 months).[80, 82, 93-95, 97, 100, 107, 108, 115, 128, 144, 159, 199-203] Included studies compared family therapy,[80, 199, 200] attachment-based therapy,[82] group psychotherapy,[93, 95] MBT,[94] internet-based CBT,[97] child interview with counseling,[100] parent sessions,[100] child interview with counseling plus parent sessions,[100] youth-nominated support team,[108] motivational interviewing,[107] DBT,[115, 201-203] mentalization-based treatment,[128] IPT-A-IN,[144] and developmental group therapy.[159] Overall nine trials[80, 82, 93-95, 115, 128, 144, 159, 199-203] examined high-contact interventions (>3 sessions), and four trials[97, 100, 107, 108] examined limited-contact interventions (<3 sessions). Twelve studies compared intervention with TAU,[80, 82, 93-95, 100, 107, 108, 115, 128, 144, 159, 199-203] and one study compared intervention with attention control.[97] Studies reported on a variety of instruments including the BDI-II, CDRS-R, CES-D, MADRS, MFQ, RCADS, RCADS-2-SF, and SMFQ. Study sample sizes ranged from 49 to 832. The most commonly reported measure was the MFQ.

Five studies reported on the MFQ[93, 95, 128, 159] or SMFQ at the end of treatment. The MFQ is a 13-item self-report measure with a range of 0 to 68. A cutoff of 28/29 discriminates between adolescents with major depression and those with subthreshold depression or with no depressive disorder. Posttreatment MFQ scores in the intervention arms ranged from 21.9 to 30.91, while scores in the control arm ranged from 23.4 to 32.38. The SMFQ is a 13-item self-report measure with a range of 0 to 26. A general cutoff of 8 discriminates between children and adolescents with clinical depression. For one study that reported an SMFQ score, the posttreatment mean score in the intervention arm was 10.2, while the mean score in the control arm was 12.6. Of these five studies, the standardized mean difference was -0.17 (**Appendix H Figure 1**, 95% CI, -0.43 to 0.09; N=633, I^2=52%). One study of group psychotherapy continued to find no statistically significant differences between group psychotherapy and routine care at 12 months.[93] A study of group therapy continued to find no statistically significant differences between group therapy and routine care at 12 months.[95]

Seven studies reported on other depression measures (BDI-II, CDRS-R, RCADS, RCADS-2-SF, and MFQ) at the end of treatment (2 weeks to 12 months).[80, 82, 94, 97, 107, 108, 128, 144, 199, 200, 221] Three studies reported statistically significant differences between groups; one on the BDI-II (19.97 vs. 31.58, p<0.001),[144] one on the MFQ (9.26 vs. 11.54, p<0.05),[128] and one on RADS-2-SF (25.38 vs. 30.87, p<0.01) favoring intervention.[107] One study[100] reported that child interview with counseling and the combination of child interview with counseling plus parent sessions significantly improved CES-D scores compared with TAU (rate of change: -0.951 vs. -0.685, p<0.01; rate of change: -1.021 vs. -0.685, p<0.01). Within the same study, parent-only sessions did not significantly improve depression scores. Six studies reported no statistically significant differences between intervention and TAU; of these, two reported on the CDRS-R;[80, 108, 199, 200] one each reported on the BDI-II,[82] RCADS-MD,[94] and RADS-2.[97] Five studies reported on the CDRS-R,[80, 199, 200] BDI-II,[82] MFQ,[93] RCADS-MD,[94] and RADS-2[97] at posttreatment and additional followups (8 weeks to 18 months) and continued to find no statistically significant differences between intervention and TAU.

One study reported on remission of depression symptoms based on the BDI-II.[82] Remission was defined as a BDI-II score $\leq$ 9. The study reported no statistically significant differences between attachment-based therapy and enhanced usual care at the end of treatment (12 weeks, OR 2.70; 95% CI, 1.03 to 17.07; p=0.06) or at 24 weeks (OR, 2.21; 95% CI, 0.76 to 6.42; p=0.14).

Anxiety

Results: Depression Symptoms

Psychotherapy vs. Wait-List Controls, Treatment as Usual, or Placebo

In addition to reporting on anxiety symptom outcomes, 10 studies reported on depression symptoms.[65, 70, 103, 112, 120, 122, 141, 145, 152, 153, 205-211] Four studies reported CDI outcomes at the end of treatment (data were reported at 8 to 16 weeks from baseline).[70, 103, 112, 120] CDI total scores ranged from 0 to 54 with a cutoff of 17 to 19 indicating a clinically relevant level of depressive symptoms.[222] Three studies had two active arms compared with the wait-list condition: telephone vs. email vs. client initiated "on their own,"[112] child focused vs. child and parent focused[120, 212] or child plus family focused.[70] Posttreatment scores in the CBT arms ranged from 4.1 to 14.6, while

scores in the wait-list arm ranged from 6.8 to 19.1. The pooled mean difference, averaging across multiple study arms in studies with more than one active arm, was -2.80 (**Appendix H Figure 2,** 95% CI, -4.74 to -0.86; N=280; k=4; I^2=0%).

Four studies reported child-rated short-MFQ scores at the end of treatment (data were reported at 10 to 17 weeks from baseline).[65, 141, 145, 152] Child-rated short-MFQ scores ranged from 0 to 26[223] with a cutoff of 10 to 12 commonly used to indicate the presence of depression. One study had two active arms compared with a wait-list condition: brief vs. full CBT.[145] Posttreatment scores in the CBT arms ranged from 3.0 to 8.1, while scores in the wait-list arm ranged from 5.2 to 7.8. The pooled mean difference, averaging across multiple study arms with more than one active arm,[145] was -1.14 (**Appendix H Figure 3,** 95% CI, -2.35 to 0.06; N=379; k=4; I^2=4%).

The same four studies also reported on parent-rated short-MFQ measures, but the respondent (mother vs. father) varied by study.[65, 141, 145, 152] Two studies reported separately on ratings from mothers and fathers,[65, 141] and two reported a single rating for parents.[145, 152] Posttreatment scores in the CBT arm ranged from 2.0 to 7.2, while scores in the wait-list arm ranged from 4.9 to 9.5. The pooled mean difference, averaging across multiple study arms with more than one active arm and across parental measures, was -1.89 (**Appendix H Figure 4,** 95% CI, -3.04 to -0.74; N=367; k=4; I^2=0%).

Two studies reported child-rated MFQ outcomes at the end of treatment (data were reported at 10 to 12 weeks from baseline).[122, 153, 205-211] Child-rated MFQ[224] scores ranged from 0 to 66 with a cutoff score of 27 to 29 commonly used to indicate the presence of depression. Posttreatment scores ranged from 4.6 to 6.9 in the CBT arms, while scores in the wait-list arms ranged from 6.4 to 25.4. One study[122] reported a statistically significant difference between arms favoring CBT (effect size partial eta squared=0.40, p<0.001). The other study did not find a statistically significant difference.[153, 205-211, 216] The same two studies reported parent-rated MFQ outcomes at the end of treatment.[122, 153, 205-211] Posttreatment scores ranged from 4.1 to 10.1 in the CBT arm, while scores in the wait-list arm ranged from 8.0 to 20.9. One study reported statistically significant differences between arms favoring CBT (effect size partial eta squared=0.19, p<0.01).[122] The second study did not report a statistically significant difference.[153, 205-211]

One study reported DSRS outcomes at the end of treatment (data were reported at 8 or 16 weeks from baseline).[103] Child-rated DSRS scores ranged from 0 to 36 with a cutoff score of 16 used to indicate depression.[225] No statistical difference was found on the DSRS.

Pharmacotherapy vs. Placebo

In addition to reporting on anxiety symptom outcomes, two sertraline studies (N=22 and N=209) reported on three different measures of depression symptoms at the end of treatment: clinician-rated HAM-D, parent-rated MFQ, and child-rated MFQ.[130, 153, 205-211, 216] The results were consistent for HAM-D and parent-rated MFQ in reporting statistically significant benefits for sertraline. One study found a statistically significant difference in HAM-D scores at 9 weeks from baseline when compared with placebo (4.0 vs. 11.5, p<0.001).[130] A HAM-D score of less than 8 is generally[226] considered to be within the normal range. The second study found a statistically significant difference in parent-rated MFQ scores at 12 weeks from baseline when compared with placebo (5.0 vs. 8.0, p<0.001) but no differences in child-rated MFQ scores. An

MFQ score of 12 or higher may indicate depression.[205] Both arms reported MFQ scores of 13 or higher in both arms at baseline and scores below 12 at followup.[205]

Combination Therapy (Sertraline Plus CBT) vs. Placebo

One study reported on outcomes comparing sertraline plus CBT with placebo.[153, 205-211, 216] The study reported parent and youth-reported MFQ scores.[205] Results varied by respondent. Parent-reported measures at followup favored combination therapy (4.1±7.2 vs. 8.0 ±7.5, adjusted $p<0.001$); youth measures were not statistically significantly different.

Depression

Results: Anxiety Symptoms

Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo

Two studies of internet-delivered CBT compared with placebo reported two measures of anxiety symptoms, the BAI and SIAS. Neither found a statistically significant difference between internet-delivered CBT and placebo at 8 weeks.[147, 148]

Pharmacotherapy vs. Placebo

None of the included studies reported anxiety outcomes.

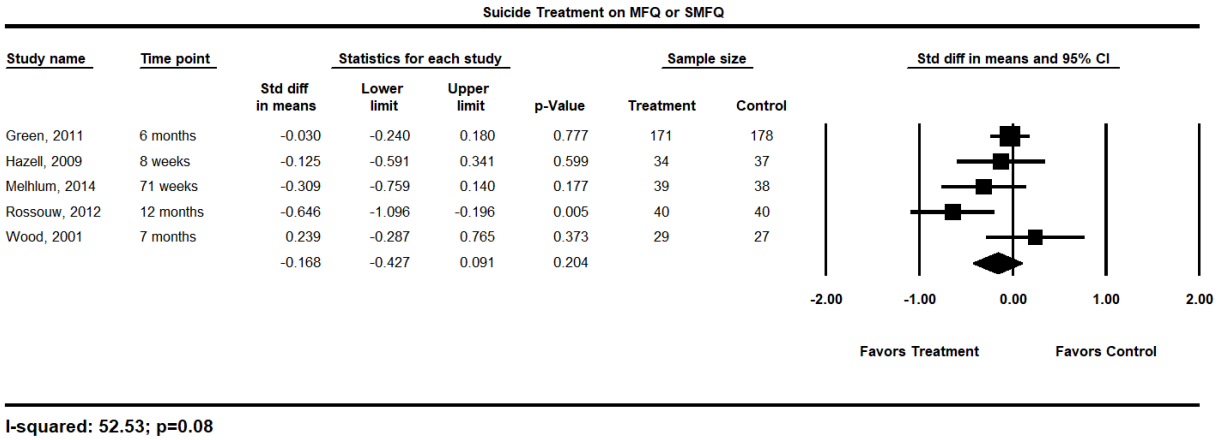
Combination Therapy (Fluoxetine Plus CBT) vs. Placebo

The study did not report anxiety outcomes.

Collaborative Care vs. Treatment as Usual

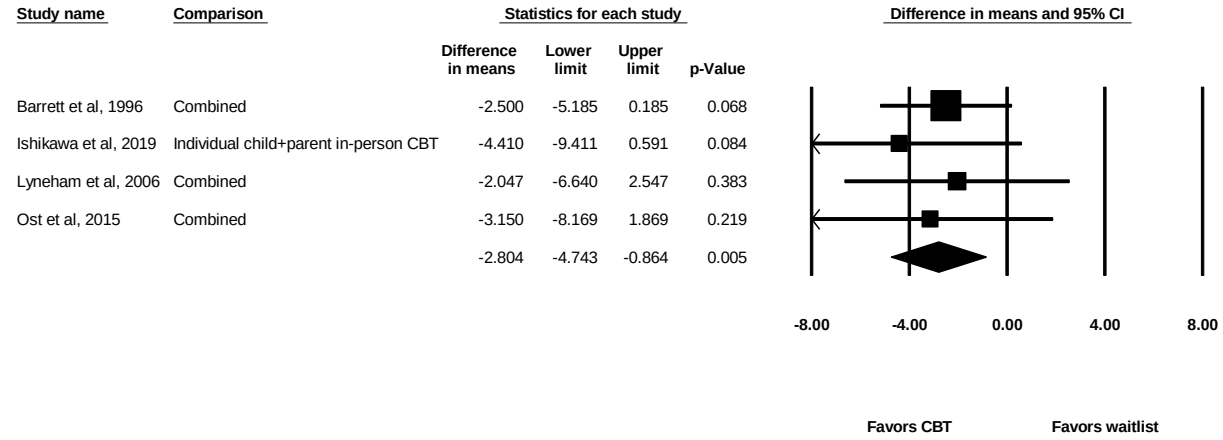
The study did not report anxiety outcomes.

Appendix H Figure 1. Depression Symptoms for Suicide and Self-Harm Interventions: Pooled Estimates of Effect



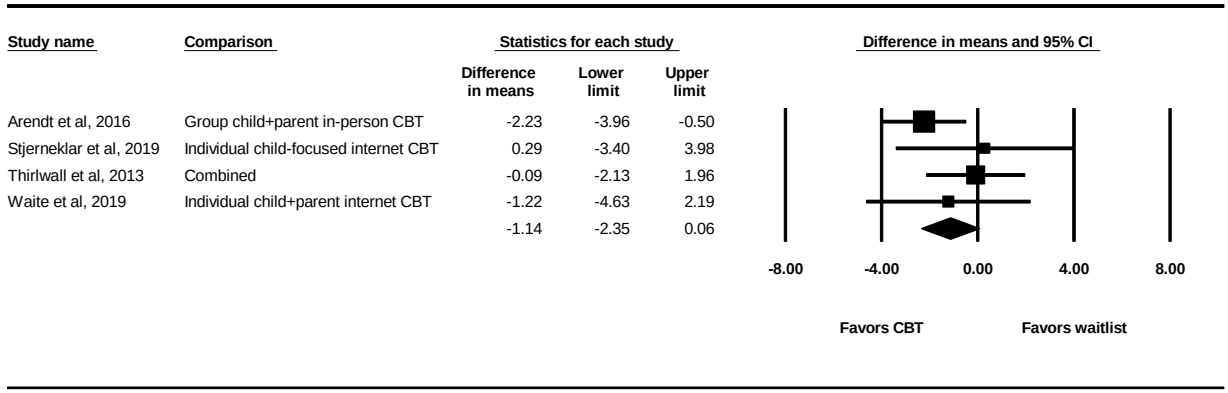
Abbreviations: CI=confidence interval; MFQ=Mood and Feelings Questionnaire; SMFQ=Short Mood and Feelings Questionnaire.

Appendix H Figure 2. Children's Depression Inventory Scores for CBT for Anxiety in Children and Adolescents



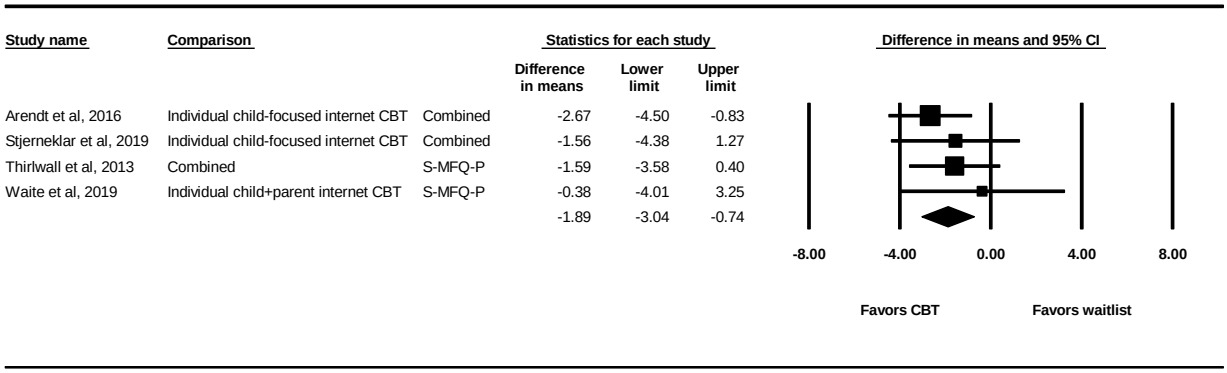
Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval.

Appendix H Figure 3. Short Mood and Feelings Questionnaire-Child for CBT for Anxiety in Children and Adolescents



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval.

Appendix H Figure 4. Short Mood and Feelings Questionnaire-Parent, Mother, or Father for CBT for Anxiety in Children and Adolescents



Abbreviations: CBT=cognitive behavioral therapy; CI=confidence interval.

Appendix H Table 1. Psychotherapy vs. Wait-List Controls, Treatment as Usual, Attention Control, or Placebo for Depression in Children: Anxiety Symptom Improvement Scales

Treatment (Condition)	Author, Year	Mean Age (SD)	Intervention and Duration	Outcome Measure	Time Point (Weeks)	Treatment N	Treatment Mean Score (SD)	Placebo N	Placebo Mean Score (SD)	Between-Group Difference	Between-Group P-Value
Internet-based individual CBT vs. attention control	Topooco et al, 2018[147]	IG1: 17.2 (1.0) CG: 16.9 (1.1)	Internet-based CBT with 8 skill-based modules plus weekly 30-minute chat sessions with therapist over 8 weeks	BAI	8 weeks	33	20.6 (9.0)	37	19.4 (8.6)	1.20	N=NS
	Topooco et al, 2018[147]	IG1: 17.2 (1.0) CG: 16.9 (1.1)	Internet-based CBT with 8 skill-based modules plus weekly 30-minute chat sessions with therapist over 8 weeks	SIAS	8 weeks	33	39.3 (13.8)	37	41.4 (11.8)	-2.10	N=NS
	Topooco et al, 2019[148]	IG1: 17.5 (1.1) CG: 17.5 (1.2)	Internet-based CBT with 8 skill-based modules plus weekly 45-minute chat sessions with therapist over 8 weeks	BAI	8 weeks	35	16.6 (10.3)	35	20.0 (9.3)	-3.40	p=NS
	Topooco et al, 2019[148]	IG1: 17.5 (1.1) CG: 17.5 (1.2)	Internet-based CBT with 8 skill-based modules plus weekly 45-minute chat sessions with therapist over 8 weeks	SIAS	8 weeks	35	35.4 (19.0)	35	35.1 (14.3)	0.30	p=NS

Abbreviations: BAI=Beck Anxiety Inventory; CBT=cognitive behavioral therapy; CG=control group; IG=intervention group; N=number; NS=not significant; SD=standard error; SIAS=Social Interaction Anxiety Scale; vs.=versus.

Appendix I Table 1. Anxiety Diagnostic Test Accuracy Studies: Study Characteristics (KQ 2)

Author, Year Quality	Country Funding	Recruitment and Setting	Age Range, Years	Total N Sex (% Female)	Index Test(s)	Reference Measure	Time Between Index Test and Reference Measure
Bailey et al, 2006[21] Fair	U.S. NIMH	Random sample of families from a southern California university-affiliated pediatric primary care service	8 to 17	190 (49)	SAS-C/P SAS-A/P SCARED-P SP SWQ-P	ADIS-C/P	NR
Canals et al, 2012[162] Fair	Spain Spanish Ministry of Health and Consumption	Recruited from 7 state and 6 state-subsidized private schools in one medium sized city in Catalonia, Spain	9 to 13	562 (55)	SCARED-C SCARED-C Short SCARED-P SCARED-P Short	MINI Kid	Within a week
Garcia-Lopez et al, 2015[164] NR Fair	Spain Spanish Ministry of Higher Education and the European Regional Development Fund	Recruited from public and private schools in a medium-size state in the south of Spain	12 to 18	1,034 (54)	EDAS* LSAS-CA* SAS-A* SASA SoPhI* SPAI-B SPIN* Mini SPIN*	ADIS-C/P	NR
Johnson et al, 2002[13] Fair	U.S. Aaron Diamond Foundation, Hibbard E. Williams Research Fund, University of California, Davis School of Medicine, Pfizer U.S. Pharmaceuticals	Primary care and school nurses' offices in California, Ohio, New Jersey, and New York; rural, urban, and suburban sites	13 to 18	403 (63)	PHQ-A	Clinical interview	NR
Muris et al, 2001[169] Fair	The Netherlands NR	Recruited from 10 primary schools in one region; 5 each from urban and rural communities	7 to 14	82 (61)	SCARED	KSCID	NR
O'Connor et al, 2016[14] Fair	U.K. GL Assessment	Recruited from 8 hospital pediatric outpatient departments. Clinical samples from a child and adolescent mental health service and hospital-based pediatric psychology service, all in Scotland	8 to 17	100 (48†)	PI-ED	C-DISC	Same time

Appendix I Table 1. Anxiety Diagnostic Test Accuracy Studies: Study Characteristics (KQ 2)

Author, Year Quality	Country Funding	Recruitment and Setting	Age Range, Years	Total N Sex (% Female)	Index Test(s)	Reference Measure	Time Between Index Test and Reference Measure
Queen et al, 2012[23] Fair	U.S. University of Miami, Department of Psychology; Fred C. and Helen Flipse Research Support Fund	Recruited from 2 pediatric primary care clinics in a large urban area in southeastern U.S.	12 to 17	71 (43)	ANS-2 questions ANS-3 questions ANS-5 questions	ADIS-IV-C	Within 1 month
Ranta et al, 2007[170] Fair	Finland NR	Recruited from 2 secondary schools in Ylojarvi, Finland	12 to 17	350 (49)	SPIN	K-SADS-PL	Within 1 month
Ranta et al, 2012[171] Fair	Finland NR	Recruited from 2 secondary schools in Ylojarvi, Finland	12 to 17	350 (49)	Mini SPIN	K-SADS-PL K-SADS (subclinical)	Within 1 month
Tsai et al, 2009[173] Fair	Taiwan National Science Council, Taiwan	Recruited from 3 public junior high schools in 3 rural areas of Taiwan (randomly invited)	13 to 15	144 (50†)	SPIN	MINI-Kid	4 weeks

*No accuracy data provided, so not included in summary of evidence.
†Percentage of those in Phase 1.

Abbreviations: ADIS-IV-C=Anxiety Disorders Interview Schedule for DSM-IV for Children; ADIS-C/P=Anxiety Disorders Interview Schedule for DSM-IV for Children-Children/Parents; ANS=Autonomic Nervous System Questionnaire; C-DISC=computerized diagnostic schedule for children; EDAS=escala para la deteccion de ansiedad socia; KQ=key question; K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; K-SADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children-present and lifetime version; KSCID-child edition of the structured clinical interview for DSM-IV; LSAS-CA=Social Anxiety Scale for Children and Adolescents; MINI-Kid=MINI international neuropsychiatric interview for kids; N=number; NUMH=National Institute of Mental Health; NR=not reported; PHQ-A=Patient Health Questionnaire-Adolescent; PI-ED=Pediatric Index of Emotional Distress; SAS-A/SASA=social anxiety scale-adolescents; SAS-A/P=social anxiety scale-adolescents/parents; SAS-C/P=social anxiety scale children/parents; SCARED=Screen for Anxiety Related Emotional Disorders; SCARED-C=Screen for Anxiety Related Emotional Disorders for Children; SCARED-P=Screen for Anxiety Related Emotional Disorders-Parents; SP=social phobia; SoPhI=social phobia inventory; SPAI-B=Brief form of the Social Phobia and Anxiety Inventory; SPIN=Social Phobia Inventory; SWQ-P=social worries questionnaire-parents; U.K.=United Kingdom; U.S.=United States.

Appendix I Table 2. Suicide Risk Harms of Screening Studies: Study Characteristics (KQ 3)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Gould et al, 2005[63] None	U.S. Cluster-RCT NIMH	181 classes in 6 high schools in New York State (Nassau, Suffolk, and Westchester counties)	Mental health screening that included questions on suicidal ideation and behaviors on two surveys administered 2 days apart.	Mental health screening that did not include questions on suicidal ideation and behaviors on the first of two surveys administered 2 days apart.	Fair
Robinson et al, 2011[64] None	Australia Cross-over RCT Bennelong Foundation; Lord Mayor Foundation, Rotary Club of Camberwell, Australian Rotary Health Research Fund	All-boys selective-entry government school in Melbourne	Case-detection tool embedded in an online questionnaire used to evaluate a depression awareness and education workshop. The intervention group received the embedded tool on Day 1.	Case-detection tool embedded in an online questionnaire used to evaluate a depression awareness and education workshop. The control group received the embedded tool on Day 2.	Fair

Abbreviations: KQ=key question; RCT=randomized, controlled trial; NIMH=National Institute of Mental Health; U.S.=United States.

Appendix I Table 3. Suicide Risk Harms of Screening Studies: Population Characteristics (KQ 3)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Gould et al, 2005[63] None	Age, mean: 14.8 (1.2) Female: 981 (41.9) Race/ethnicity: 80.3% White, 5.1% Black, 7.3% Hispanic, 3.8% Asian, and 3.5% other	Students ages 13 to 19 years in a participating high school	Students/parents "opting out" of participation	NR
Robinson et al, 2011[64] None	Age: NR (all were Year 10 students) Female: 0 (0) Race/ethnicity: NR	Year 10 student at Melbourne High	Did not consent to participate	NR

Abbreviations: KQ=key question; N=number; NR=not reported; SD=standard deviation.

Appendix I Table 4. Suicide Risk Harms of Screening Studies: Outcomes (KQ 3)

Author, Year Registry Number	Harm Outcomes
Gould et al, 2005[63] None	*Distress as measured by POMS-A subscale, mean (SD)* At baseline Intervention: 6.9 (10.0) Control: 6.4 (9.7); P=0.25 Immediately after first survey Intervention: 5.5 (9.7) Control: 5.1 (10.0); P=0.66 Before second survey 2 days later Intervention: 4.3 (9.0) Control: 3.9 (9.4); P=0.41 *Suicidal ideation as measured by SIQ-Jr, mean (SD)* On second survey 2 days later Intervention: 6.5 (11.5) Control: 6.6 (10.5), P=0.86 *Interim suicidality thoughts between 1st and 2nd surveys, %* Intervention: 4.7% Control: 3.9%; OR, 1.20 (95% CI, 0.72 to 2.00)
Robinson et al, 2011[64] None	*Distress as measured by POMS-A* Day 1 questionnaire No significant difference between groups on 5 subscales (Anger, Confusion, Depression, Fatigue, Tension); significant difference on the vigor subscale (P=0.0001) Change between Day 1 and Day 2 questionnaire No significant difference between groups on 5 subscales (Anger, Confusion, Depression, Fatigue, Tension); significant difference on the vigor subscale (P=0.000) *Distress as measured by the item "How distressing did you find answering questions about self-harm and suicidal ideation?," N (%)* Overall (not reported by group): Not at all distressing: 135 (50) A little distressing: 85 (31.5) Moderately distressing: 14 (5.2) Very distressing: 10 (3.7) Not sure: 26 (9.6)

Abbreviations: CI=confidence interval; KQ=key question; N=number; OR=odds ratio; POMS-A=Profile of Mood States in Adolescents; SD=standard deviation; SIQ-Jr=Suicidal Ideation Questionnaire Junior.

Appendix I Table 5. Suicide Risk Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Asarnow et al, 2017[66] NCT00692302	U.S. RCT National Institute of Mental Health, American Foundation for Suicide Prevention	Recruited through ED, inpatient/partial hospitalization, and outpatient services	IG1: CBT (N=20) Description: SAFETY is a family-centered treatment. Two therapists work with each family—one focuses on the youth, the other on the parents/caregivers. Sessions began with simultaneous individual youth and parent components and concluded with all participants coming together to practice skills and address identified issues. Provided linkage to followup care and resources at end of treatment Duration: 12 weeks	CG: TAU (N=22) An in-clinic parent session, followed by ≤3 telephone calls aimed at supporting motivation/actions to obtain followup treatment	Fair
Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200] ISRCTN59793150	Other very high HDI United Kingdom RCT National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme	Direct community referrals to CAMHS and hospital referrals following emergency attendance resulting from self-harm	IG1: Family therapy (N=415) Description: Between six and eight 75-minute family therapy sessions occurred over the course of 6 months (Self-harm Intervention Family Therapy [SHIFT]). Family therapists worked in groups of 3 with one therapist interviewing and two observing the family during each session. Sessions followed the Leeds Family Therapy & Research Centre manual. The theoretical approach was flexible and allowed for integration of different approaches and models other than SHIFT family therapy (e.g., supportive therapy/counseling, CBT, family work). Sessions emphasized the relational context of problems that families bring to therapy and that language, meaning, behavior, and emotions are part of the change process. Duration: 6 months	CG: TAU (N=417) TAU involved a range of individual and family-oriented work delivered by local CAMHS teams with various theoretical orientations (e.g., supportive therapy/counseling, CBT, family work)	Good

Appendix I Table 5. Suicide Risk Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Diamond et al, 2010[82] NCT00604097	U.S. RCT Centers for Disease Control and Prevention	Recruited from primary care offices and emergency room of children's hospital in Philadelphia, Pennsylvania	IG1: Attachment-Based Family Therapy (N=35) Description: Between 5 and 8 sessions of ABFT. Started with treatment to reframe the relationship with relevant family members as the initial treatment goal. Included 1 to 2 sessions with adolescent alone, to identify family conflicts linked to suicide. Included 1 to 2 sessions with parent alone to amplify parental love and empathy, and to teach emotionally focused parenting. Included 3 to 4 family sessions to discuss identified problems and practice new communication, problem solving, and affect regulation skills. Also received received weekly monitoring and access to a 24-hour crisis phone. Duration: 12 weeks	CG: Enhanced Usual Care (N=31) Facilitated referral process with ongoing clinical monitoring and received weekly monitoring and access to a 24-hour crisis phone	Fair
Green et al, 2011[93] ISRCTN 20496110	Other very high HDI United Kingdom RCT Health Foundation; University of Manchester	Recruited from child and adolescent mental health services teams in northwest England	IG1: Group psychotherapy (N=183) Description: Manual-based developmental group psychotherapy designed for self-harming adolescents based on techniques from CBT, DBT, and other group psychotherapy; groups were rolling entry and included 6 weekly sessions in the acute treatment phase followed by boosters that continued until participant felt better. Mean (SD) number of sessions attended was 10.2 (10.1). Duration: 6 weekly sessions followed by boosters that continued until participants felt better	CG: Routine care (N=183) Standard psychotherapy care excluding any group intervention. Mean (SD) number of sessions was 9.7 (10.4)	Good

Appendix I Table 5. Suicide Risk Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Griffiths et al, 2019[94] NCT02771691	Other very high HDI United Kingdom RCT Edinburgh and Lothians Health Foundation	Recruited from NHS Child and Adolescent Mental Health Services, which provides outpatient and specialist mental health services	IG1: MBT (N=26) Description: Up to 12 75-minute sessions of mentalization based therapy (MBT) delivered by trained MBT therapists under the supervision of an MBT-accredited supervisor, up to 10 participants per group. Duration: 12 weeks	CG: TAU (N=27) Treatment as usual, receiving tier 3 or tier 4 of usual CAMHS services, which could include psychosocial treatment or medication by team of multidisciplinary providers in outpatient settings (tier 3) or intensive community treatment, day programs, or an inpatient unit.	Fair
Hazell et al, 2009[95] ACTRN12608000532303	Other very high HDI Australia RCT NR	Recruited from child and adolescent mental health service in Newcastle, Brisbane North, or Logan, Australia	IG1: Group therapy (N=35) Description: Initially six 1-hour weekly sessions focused on relationships, school and peer relationships, family problems, anger management, depression and self-harm, and hopelessness and feelings about the future. After completion of initial 6 sessions, adolescents could attend group sessions for up to 12 months. Continued to receive routine care from their adolescent mental health service. Routine care generally consisted of individual counseling, family sessions, medication assessment and review, and other care coordination activities. Duration: Up to 12 months	CG: Routine care (N=37) Routine care generally consisted of individual counseling, family sessions, medication assessment and review, and other care coordination activities.	Good
Hill et al, 2019[97] NR	U.S. RCT American Psychological Foundation; Florida International University Doctoral Evidence Acquisition Award	Recruited from a large urban area via distribution of flyers at schools and public gathering places frequented by adolescents	IG1: Internet CBT (N=40) Description: Two 20- to 30-minute web-based sessions drawing on interpersonal-psychological theory of suicide and CBT, called LEAP by study authors. Also received email regarding psychoeducational information about mental health, suicide risk factors, and local and national resources for mental health treatment and suicide/crisis counseling. Duration: 2 sessions 1 week apart	CG: Information-only control (N=40) Received email regarding psychoeducational information about mental health, suicide risk factors, and local and national resources for mental health treatment and suicide/crisis counseling.	Good

Appendix I Table 5. Suicide Risk Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Hooven et al, 2012[100]	U.S. RCT NR	Recruited from 20 public high schools—14 traditional and 6 alternative in Seattle area.	IG1: C-Care (N=153) Description: 2-hour computerized interview and brief counseling intervention with child to facilitate motivation to access support. Connection to school resources and parent telephone call. Duration: 1 session, 2 hours IG2: P-CARE (N=155) Description: Two 2-hour parent sessions including reviewing suicide risk, support and communications skills, conflict reduction, youth mood management, and connection to resources. Two home visits and a followup parent booster telephone call at 2.5 months. Duration: 2 sessions, 2 hours each IG3: Counselors Care, Assess, Respond, Empower (C-Care) plus Parents-Counselors Care, Assess, Respond, Empower(P-CARE) (N=164) Description: 2-hour computerized interview and brief counseling with child to facilitate motivation to access support. Also connection to school resources and parent telephone call. Two 2-hour parent sessions including reviewing suicide risk, support and communications skills, conflict reduction, and youth mood management. Two home visits and a followup parent booster telephone call at 2.5 months. Duration: One 2-hour child session; two 2-hour parent sessions; one brief 30-minute interview	CG: TAU (N=143) One brief 30-minute interview including addressing suicide risk factors. Received connection to school resources and parent telephone call.	Fair

Appendix I Table 5. Suicide Risk Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
King et al, 2015[107] NR	U.S. RCT NR	Recruited from a hospital emergency department in a relatively underserved, low-income community	IG1: Teen Option to Change (Motivational Interviewing) (N=27) Description: Teen Option to Change, received same intervention as enhanced TAU plus personalized feedback regarding their suicide screening responses. Participated in an adapted motivational interview (approximately 35-45 minutes) with a mental health professional that involved development of a personalized action plan. Participants also received hand-written followup note and telephone check-in 2 to 5 days after ED visit. Duration: 35-45 minutes	CG: Enhanced TAU (N=22) Enhanced TAU included provision of a crisis card with suicide emergency phone numbers and written information about depression, suicide risk, firearm safety, and local mental health services.	Fair
King et al, 2009[108] NCT00071617	U.S. RCT NIMH	NR	IG1: Youth-Nominated Support Team (N=223) Description: Adolescents were asked to nominate caring adults with whom they would like to have regular supportive contact following their hospitalization for suicidal ideation or attempt. Individual or group psychoeducation sessions were conducted with each adolescent's support persons (mean length of session was 63.6 minutes). After the session, intervention specialist had weekly telephone contact with support person. Support person was also encouraged to have weekly contact with adolescents. Adolescents also received treatment as usual which could have included psychotherapy sessions, psychoactive medication, medication followup, alcohol/drug treatment, psychiatric hospitalization, and/or residential treatment. Duration: One initial psychoeducation session and weekly telephone contact over a flexibly-defined time period.	CG: TAU (N=225) TAU could have included psychotherapy sessions, psychoactive medication, medication followup, alcohol/drug treatment, psychiatric hospitalization, and/or residential treatment.	Fair

Appendix I Table 5. Suicide Risk Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203] NCT00675129	Other very high HDI Norway RCT Norwegian Directorate of Health, the South Eastern Regional Health Authority, Extra Foundation for Health and Rehabilitation, University of Oslo	Recruited from child and adolescent psychiatric outpatient clinics in Oslo	IG1: DBT (N=39) Description: DBT included 1 weekly session of individual therapy (60 minutes), 1 weekly session of multifamily skills training (120 minutes), and family therapy sessions and telephone coaching with individual therapists outside therapy sessions as needed over 19 weeks. Duration: 19 weeks	CG: Enhanced usual care (N=38) Standard care (required EUC therapists to provide on average no less than 1 weekly treatment session per patient throughout the trial) delivered by therapists who were not trained in or practicing DBT. Therapy was psychodynamically oriented or CBT combined with medication but was not manualized or checked for fidelity.	Good
Ougrin et al, 2013[121] Ougrin, 2011[204] ISRCTN 81605131	Other very high HDI United Kingdom RCT Psychiatry Research Fund (Institute of Psychiatry, King's College London), Maudsley Charitable Funds (South London and Maudsley NHS Trust) and West London Research Consortium	Recruited from emergency departments of four inner-London hospitals or following an urgent general practitioner's referral to the child and adolescent mental health services in two London National Health Service Trusts	IG1: Therapeutic Assessment (N=35) Description: 1-hour standard psychosocial evaluation, standard disposition planning plus a brief 30-minute therapeutic intervention Duration: 1 session	CG: Assessment as usual (N=35) 1-hour standard psychosocial evaluation and standard disposition planning	Fair

Appendix I Table 5. Suicide Risk Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Pineda et al, 2013[125] ACTRN12613000668707	Other very high HDI Australia RCT Rotary Health Research Fund Australia (M.R.D.)	Recruited from emergency departments of 2 hospitals and the community mental health service in the Blacktown–Mount Druitt Local Government Area (LGA) of Sydney, Australia	IG1: RAP-P (Family Intervention) (N=24) Description: Interactive psychoeducation program for parents of adolescents implemented over four 2-hour sessions (held once a week or once every 2 weeks). Parents were provided information to enhance their understanding of suicidal or self-injurious behavior, practical strategies to help their adolescent avoid or minimize their self-injurious behavior, and information to facilitate access to appropriate support services. Also received crisis management and safety planning. Duration: 4 to 8 weeks (4 sessions, held once a week or once every 2 weeks)	CG: Routine care (N=24) Any intervention deemed necessary by the adolescent's treatment team other than the family intervention program trialed. Family intervention limited to crisis management and safety planning. No structured intervention.	Fair
Rossouw et al, 2012[128] ISRCTN95266816	Other very high HDI United Kingdom RCT NR	Recruited individuals presenting with self-harm to community mental health services or acute hospital emergency rooms	IG1: Mentalization-based treatment for adolescents (MBT-A) (N=40) Description: Weekly 50-minute individual MBT-A sessions and monthly 50-minute mentalization-based family therapy (MBT-F) with a focus on impulsivity and affect regulation. Duration: 12 months	CG: TAU (N=40) TAU treatments were delivered by fully qualified child mental health professionals, not manualized but based on U.K. National Institute for Health and Clinical Excellence guidance.	Fair
Tang et al, 2009[144]	Other very high HDI Taiwan RCT NR	Recruited from a high school located in a city in southern Taiwan	IG1: Interpersonal psychotherapy (N=35) Description: Two 50-minute face-to-face weekly sessions of interpersonal psychotherapy and a 30-minute weekly telephone followup provided by trained school counselors Duration: 6 weeks	CG: TAU (N=38) Received school-based psychoeducation and irregular individual supportive counseling one or two times per week in the 6-week period. Supportive sessions were 30 to 60 minutes each and parents were invited to join sessions if needed.	Fair

Appendix I Table 5. Suicide Risk Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Wood et al, 2001[159]	Other very high HDI United Kingdom RCT Mental Health Foundation and the National Health Service Executive North West	Recruited from child and adolescent mental health service in South Manchester, England	IG1: Developmental Group Therapy (N=32) Description: Designed to meet the needs of adolescents and focus on the adolescent growing through difficulties by using positive corrective therapeutic relationships. Based on principles of problem-solving and CBT, DBT, and psychodynamic group therapy. Structured as 6 acute group sessions, followed by weekly long-term groups. Individual sessions usually done when extra cognitive behavioral work was needed. Participants had access to routine care that included family sessions, nonspecific counseling with the adolescent, and psychotropic medication. Duration: Median of 8 group sessions (range, 0 to 19) and 2.5 individual sessions (range, 0 to 10) over 6 months.	CG: Treatment as usual (N=31) TAU included routine care that would normally be provided including a variety of interventions including family sessions, nonspecific counseling with the adolescent, and psychotropic medication.	Good

Abbreviations: ABFT=Attachment-based Family Therapy; CAMHS=Child and Adolescent Mental Health Services; C-CARE=Counselors Care, Assess, Respond, Empower; CBT=cognitive behavioral therapy; CG=control group; DBT=dialectical behavior therapy; ED=emergency department; EUC=enhanced usual care; HDI=Human Development Index; HTA=health technology assessment; IG=intervention group; KQ=key question; LEAP=Learn, Explore, Assess you options, Plan; LGA=local government area; MBT=mentalization-based treatment; MBT-A=mentalization-based treatment for adolescents; MBT-F= mentalization-based treatment-family; N=number; NHS=National Health Service; NIHR=National Institute for Health Research; NIMH=National Institute of Mental Health; NR=not reported; P-CARE=Parents-Counselors Care, Assess, Respond, Empower; RAP-P=Resourceful Adolescent Parent Program; RCT=randomized, controlled trial; SAFETY=Safe Alternatives for Teens and Youths; SD=standard deviation; SHIFT=self-harm intervention family therapy; TAU=treatment as usual; U.K.=United Kingdom; U.S.=United States.

Appendix I Table 6. Suicide Risk Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Asarnow et al, 2017[66] NCT00692302	Mean age (SD): 14.6 (1.8) N (%) Female: 37 (88) Race/Ethnicity: White: 35 (83) Black: 2 (5) Hispanic/Latino: 9 (21) Asian: 5 (12) Other: 3 (7)	Children and adolescents ages 11 to 18 years living in stable family situation with a recent (past 3 months) SA or NSSI as primary problem, with the additional requirement of repetitive SH (≥3 lifetime SH episodes).	Symptoms interfering with participation in assessments/intervention (e.g. psychosis, substance dependence); not English speaking.	SA, past 3 months: 50% Nonsuicidal self-injury, past 3 months: 50% >1 Lifetime SA: 21% Major depression, past year: 55% Problematic substance abuse: 48%
Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200] ISRCTN59793150	Mean age (SD): 14.3 (1.4) N (%) Female: 737 (89) Race/Ethnicity: NR	Ages 11 to 17 years, self-harmed at least twice before being referred to CAMHS, and living with a primary caregiver who was willing to participate.	Serious risk of suicide, an ongoing child protection investigation in the family, pregnancy at time of trial entry, usual treatment by a specific specialist service within CAMHS, residence in a short-term foster home, moderate to severe learning disabilities, involvement in another study within the 6 months before entry to the current trial, sibling participation in the trial or treatment within CAMHS, and insufficient proficiency in English (participant or caregiver) to complete study questionnaires.	Primary/target condition % Known self-harm episodes: Two: 11% At least three: 89%
Diamond et al, 2010[82] NCT00604097	Mean age (SD): 15.1 (1.5) N (%) Female: 55 (83) Race/Ethnicity: African American: 49 (74)	Ages 12 to 17 years, having suicidal thoughts, scores above 31 on the SIQ-Jr, above 20 on the BDI-II, and a parent or guardian willing to participate.	Needed psychiatric hospitalization, recently discharged from a psychiatric hospital, had current psychosis, or had mental retardation or history of borderline intellectual functioning.	Depressive disorder: 47% Anxiety disorder: 67% Externalizing disorder: 57%

Appendix I Table 6. Suicide Risk Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Green et al, 2011[93] ISRCTN 20496110	Mean age (SD): 12 to 14 years, N (%) IG1: 69 (38) CG: 70 (38) 15 to 17 years, N (%) IG1: 114 (62) CG: 113 (62) N (%) Female: IG1: 171 (93) CG: 172 (94) Race/Ethnicity: Black and ethnic minority IG1: 12 (7) CG: 11 (6)	Ages 12 to 16 years with 2 or more episodes of self-harm during previous 12 months	Non-English speakers, severe low weight anorexia nervosa, current psychotic illness, attendance at special learning disability school, or current containment in secure care	Depressive disorder: 62% Behavioral disorder: 33%
Griffiths et al, 2019[94] NCT02771691	Mean age (SD): IG1: 15.4 (1.3) CG: 15.7 (1.4) N (%) Female: 38 (79) Race/Ethnicity: White Scottish: 33 (69)	Ages 12 to 18 years, self-harm behavior in the past 6 months, receiving CAMHS treatment, competent, and willing to provide written, informed consent	Severe learning disability or pervasive developmental disorder, acute psychotic episode, eating disorder in the absence of self-harm, non-English speaking, or current involvement in other ongoing treatment research	NR
Hazell et al, 2009[95] ACTRN12608000532303	Mean age (SD): IG1: 14.6 (1.1) CG: 14.4 (1.2) N (%) Female: IG1: 32 (91) CG: 33 (89) Race/Ethnicity: NR	Ages 12 to 16 years, had been referred to a child and adolescent mental health service, and reported at least two episodes of self-harm in the past year, one of which had occurred in the past 3 months	Required more intensive treatment, could not attend groups, experiencing acute psychosis, or unlikely to benefit from group intervention (e.g., intellectual disability)	Alcohol problems: 4% Substance misuse: 0% Depression: 57% Conduct/oppositional defiant disorder: 7%

Appendix I Table 6. Suicide Risk Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Hill et al, 2019[97] NR	Mean age (SD): 16.9 (1.66) N (%) Female: 55 (69) Race/Ethnicity: White: 55 (68) Black: 13 (16) Asian: 6 (8) American Indian/Alaskan Native: 1 (1) Other: 7 (9)	Ages 13 to 19 years, perceived burdensomeness score of 17 or greater on the Interpersonal Needs Questionnaire Perceived Burdensomeness subscale, and having available Internet access	Current psychosocial treatment or use of psychoactive medications (unless on a stable dose for 8 weeks or more)	NR
Hooven et al, 2012[100]	Mean age (SD): 16 (NR) N (%) Female: 369 (60) Race/Ethnicity: White: 406 (66) Mixed ethnicity: 86 (14) Asian American: 49 (8) African American: 25 (4) Latino/Hispanic: 18 (3)	Teens at risk for suicide based on Suicide Risk Screen (SRS) criteria	NR	NR
King et al, 2015[107] NR	Mean age (SD): 17.7 (1.7) N (%) Female: 39 (80) Race/Ethnicity: African American: 57 (28) Caucasian: 19 (39) American Indian/Alaska Native: 4 (2) Native Hawaiian/Pacific Islander: 2 (1) Hispanic: 2 (1) Other: 2 (1)	Adolescents ages 14 to 19 years with a positive suicide risk screen (C-SSRS) defined as suicidal ideation, a recent suicide attempt, or positive screens for both depression and alcohol or drug abuse, and presenting with a non-psychiatric chief complaint	Level one trauma (critically ill, medically unstable), significant cognitive impairment, or disposition of psychiatric hospitalization	Recent suicidal ideation or attempt: 35% Current depressive symptoms with comorbid alcohol or drug abuse: 53%

Appendix I Table 6. Suicide Risk Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
King et al, 2009[108] NCT00071617	Mean age (SD): 15.6 (1.3) N (%) Female: 319 (71) Race/Ethnicity: Caucasian: 376 (84) African American: 27 (6) Hispanic: 9 (2) Other: 36 (8)	Ages 13 to 17 years with significant suicidal ideation or suicide attempt within the past 4 weeks, all of whom had been psychiatrically hospitalized. Significant ideation or attempt was defined by parent or youth report on the NIMH DISC-IV.	Severe cognitive impairment (mental retardation or acute psychosis), direct transfer to medical unit, direct transfer to residential placement, or no legal guardian available	Comorbid diagnoses Depressive disorder: 88% PTSD or acute stress disorder: 25% Anxiety disorder: 29% Disruptive behavior disorder: 42% Alcohol or substance use disorder: 21%
Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203] NCT00675129	Mean age (SD): 15.6 (1.5) N (%) Female: 68 (88) Race/Ethnicity: Norwegian: 62 (85)	Ages 12 to 18 years, history of at least 2 episodes of self-harm, at least 1 within the last 16 weeks; at least 2 criteria of DSM-IV BPD (plus the self-destructive criterion), or, at least 1 criterion of DSM-IV BPD plus at least 2 subthreshold-level criteria	Bipolar disorder (except bipolar II), schizophrenia, schizoaffective disorder, another psychotic disorder, intellectual disability, or Asperger syndrome	Mean (SD) suicide attempts, lifetime: 1.7 (4.2) Attempted suicide last 4 months: 26% MDD: 22% Other depressive disorder: 38% Panic disorder: 9% PTSD: 17% Any anxiety disorder: 43% Any SUD: 3% Any eating disorder: 8% BPD: 20%

Appendix I Table 6. Suicide Risk Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Ougrin et al, 2013[121] Ougrin, 2011[204] ISRCTN 81605131	Mean age (SD): IG1: 15.5 (1.2) CG: 15.6 (1.5) N (%) Female: IG1: 28 (80) CG: 28 (80) Race/Ethnicity: White IG1: 20 (57) CG: 17 (49) Black IG1: 7 (20) CG: 7 (20) Asian IG1: 1 (3) CG: 7 (20) Mixed IG1: 6 (17) CG: 3 (9) Other IG1: 1 (3) CG: 1 (3)	Ages 12 to 18 years, not currently engaged with psychiatric services, who had self-harmed and been referred for a psychosocial assessment	Gross reality distortion, moderate or severe learning disability, lack of fluent English, immediate risk of violence or suicide, and the need for inpatient psychiatric admission	Emotional disorder IG1: 20 (57) CG: 22 (63) Disruptive disorder IG1: 5 (14) CG: 4 (11)

Appendix I Table 6. Suicide Risk Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Pineda et al, 2013[125] ACTRN12613000668707	Mean age (SD): IG1: 15.0 (1.3) CG: 15.3 (1.2) N (%) Female: IG1: 16 (73) CG: 14 (78) Race/Ethnicity: Anglo-Saxon IG1: 14 (64) CG: 9 (50) Culturally and linguistically diverse/non–English-speaking background IG1: 6 (27) CG: 8 (44) Aboriginal IG1: 2 (9) CG: 1 (6)	Ages 12 to 17 years, engaged in at least 1 episode of suicidal behavior within the last 2 months before referral to hospital/ health service using the Mental Health Outcomes and Assessment Tools (MH-OAT); resided with at least 1 parent; primary diagnosis	Psychoses, developmental disorders, or presented with poisoning from excessive use of recreational drugs	NR
Rossouw et al, 2012[128] ISRCTN95266816	Mean age (SD): IG1: 15.4 (1.3) CG: 14.8 (1.2) N (%) Female: 68 (85) Race/Ethnicity: White: 60 (75) Black: 4 (5) Asian: 8 (10) Mixed race: 6 (7.5) Other: 2 (3)	Ages 12 to 17 years who presented with at least 1 episode of confirmed self-harm within the past month, and for whom self-harm was the primary reason for referral and was confirmed as intentional	Comorbid diagnosis of psychosis, severe learning disability (IQ <65), pervasive developmental disorder, chemical dependence, or eating disorder in the absence of self-harm	Attempted suicide: 80% Taken overdose: 64% History of cutting: 95% Alcohol problems: 44% Substance misuse: 28% Depression: 97% Borderline personality disorder: 73%

Appendix I Table 6. Suicide Risk Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Tang et al, 2009[144]	Mean age (SD): IG1: 15.3 (1.7) CG: 15.2 (1.7) N (%) Female: IG1: 23 (66) CG: 25 (66) Race/Ethnicity: NR	Ages 12 to 18 years who had moderate–severe depression (BDI score >19), suicide ideation or previous suicidal attempt (BSS score >0), moderate–severe anxiety (BAI score >16), or significant hopelessness (BHS ≥9) in the preceding 2 weeks followed by structured clinical interview to confirm pyshicatric diagnosis on the DSM-IV-TR	Acute stage of psychosis, suspected axis II personality disorder, drug abuse, serious medication condition, acted out lethal suicidal behaviors, lacked proper care for suicidal risk by their family, or needed hospital emergency management	NR
Wood et al, 2001[159]	Mean age (SD): IG1: 14.2 (1.1) CG: 14.3 (2.1) N (%) Female: IG1: 25 (78) CG: 24 (77) Race/Ethnicity: NR	Ages 12 to 16 years, referred to child and adolescent mental health service following an incident of deliberate self-harm, and deliberately harmed themselves on at least one other occasion during the previous year	Judged too suicidal for ambulatory care, could not attend the groups, suffered from a psychotic disorder, or was unlikely to benefit from a group intervention (e.g., learning problems)	MDD: 83% Conduct or oppositional disorder: 67% Used drugs at least weekly: 44% Intoxicated at least weekly: 36%

Abbreviations: BAI=Beck Anxiety Inventory; BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory, version 2; BHS=Beck Hopelessness Scale; BPD=borderline personality disorder; BSS=Beck Scale for Suicide Ideation; CAMHS=Child and Adolescent Mental Health Services; CG=control group; C-SSRS=Columbia Suicide Severity Rating Scale; DISC-IV=Diagnostic Interview Schedule for Children-Version IV; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; IG=intervention group; IQ=intelligence quotient; KQ=key question; MDD=major depressive disorder; MH-OAT=Mental Health Outcomes and Assessment Tools; N=number; NIMH=National Institute of Mental Health; NR=not reported; NSSI=non-suicidal self-injury; PTSD=post-traumatic stress disorder; SA=suicide attempt; SD=standard deviation; SH=self-harm; SIQJR=Suicidal Ideation Questionnaire-Junior; SRS=suicide risk screen; SUD=substance use disorder.

Appendix I Table 7. Suicide Risk Treatment Studies: Suicide Death Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Outcome
Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203] NCT00675129	IG1: DBT (N=39) CG: Enhanced usual care (N=38)	Suicides, 19 weeks (posttreatment), ITT (IG1=39; CG=38), N (%) IG1: 0 (0) CG: 0 (0) Suicides, 3 years, mITT (IG1=37; CG=34), N (%) IG1: 0 (0) CG: 0 (0)
King et al, 2009[108] NCT00071617	IG1: Youth-Nominated Support Team (N=223) CG: TAU (N=225)	Suicide deaths, 12 months, analyzed (IGI=175; CG=171), N IG1: 0 CG: 1 P=NR
Green et al, 2011[93] ISRCTN 20496110	IG1: Group psychotherapy (N=183) CG: Routine care (N=183)	Suicide deaths, 12 months, analyzed (IG1=180; CG=180), N (%) IG1: 0 (0) CG: 0 (0)

Abbreviations: CG=control group; DBT=dialectical behavior therapy; IG=intervention group; KQ=key question; mITT=modified intent to treat; N=number; ITT=intent to treat; NR=not reported; TAU=treatment as usual.

Appendix I Table 8. Suicide Risk Treatment Studies: Suicide Attempts or Episode of Deliberate Self-Harm Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Outcome
Asarnow et al, 2017[66] NCT00692302	IG1: CBT (N=20) CG: TAU (N=22)	% of participants with suicide attempt, 3 months, ITT (IG1=20; CG: 22), n (%) IG1: 0 (0) CG: 4 (18.2) Z=2.45; p=0.01 favoring CBT (based on survival analysis) % of participants with suicide attempt, 5 months, ITT (IG1=20; CG: 22), n (%) IG1: 1 (5.0) CG: 4 (18.2) p=NR NSSI, 3 months, ITT (IG1=20; CG: 22), probabilities of survival without (SE) IG1: 0.55 (0.11) CG: 0.43 (0.14) p=0.054 favoring CBT (based on survival analyses)
Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200] ISRCTN59793150	IG1: Family therapy (N=415) CG: TAU (N=417)	Self-harm events per participant, 36 months, ITT (IG=415; CG=417), mean (SD) IG1: 1.0 (2.19) CG: 1.2 (3.22) P NR SASII self-harm event, 12 to 18 months; mITT (IG=268; CG=210), n (%) IG1: 202 (75) CG: 147 (70) P NR

Appendix I Table 8. Suicide Risk Treatment Studies: Suicide Attempts or Episode of Deliberate Self-Harm Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Outcome
Green et al, 2011[93] ISRCTN 20496110	IG1: Group psychotherapy (N=183) CG: Routine care (N=183)	Frequency of self-harm, 0 to 6 months, analyzed (IG1=181; CG=181), geometric mean IG1: 4.6 CG: 4.4 Ratio: 1.01 (95% CI, 0.80 to 1.29); P=0.91 Frequency of self-harm, 6 to 12 months, analyzed (IG1=179; CG=180), geometric mean IG1: 2.0 CG: 2.1 Ratio: 0.94 (95% CI, 0.73 to 1.18); P=0.60 Severity of self-harm, 0 to 6 months and 6 to 12 months, analyzed (IG1=181; CG=181), N No problem IG1: 37, 75 CG: 40, 70 Mild problem IG1: 96, 68 CG: 79, 76 Marked problem IG1: 27, 24 CG: 37, 21 Severe problem IG1: 21, 11 CG: 25, 13 Proportional OR, 0 to 6 months (95% CI): 0.81 (0.54 to 1.20); P=0.29 Proportional OR, 6 to 12 months (95% CI): 0.94 (0.63 to 1.40); P=0.75 Both adjusted for site, sex, age, frequency and severity of self-harm at baseline, psychosocial risk, behavioral disorder, and depressive disorder Self-harm resulting in injury, 12 months, analyzed (IG1=180; CG=180), N (%) IG1: 1 (0.05) CG: 2 (1.1) Time to self-harm, 0 to 12 months, N analyzed NR, median (IQR) IG1: 37 days (15 to 123) CG: 49 days (17 to 184) HR (95% CI): 1.07 (0.85 to 1.34); P=0.58

Appendix I Table 8. Suicide Risk Treatment Studies: Suicide Attempts or Episode of Deliberate Self-Harm Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Outcome
Griffiths et al, 2019[94] NCT02771691	IG1: MBT (N=26) CG: TAU (N=27)	Self-harm subscale (RTSHI), 12 weeks (posttreatment), ITT (IG1=22; CG=26), mean (SD) IG1: 26.00 (12.57) CG: 23.12 (12.28) Self-harm subscale (RTSHI), 24 weeks (12 week posttreatment) ITT (IG1=22; CG=26), mean (SD) IG1: 24.41 (12.52) CG: 22.93 (12.35) Self-harm subscale (RTSHI), 36 weeks (24 week posttreatment), ITT (IG1=22; CG=26), mean (SD) IG1: 24.50 (13.88) CG: 22.74 (13.04) Time x Group interaction (presumably across all 3 followup timepoints): P=NS RTSHI total, 12 weeks (posttreatment), ITT (IG1=22; CG=26), mean (SD) IG1: 38.78 (19.65) CG: 36.00 (18.80) RTSHI total, 24 weeks (12 week posttreatment) ITT (IG1=22; CG=26), mean (SD) IG1: 37.24 (20.22) CG: 36.14 (19.67) Time x Treatment interaction: P=NS RTSHI total, 36 weeks (24 week posttreatment), ITT (IG1=22; CG=26), mean (SD) IG1: 37.16 (21.90) CG: 36.03 (19.91) Time x Treatment interaction: P=NS Time x Group interaction (presumably across all 3 followup timepoints): P=NS
Hazell et al, 2009[95] ACTRN12608000532303	IG1: Group therapy (N=35) CG: Routine care (N=37)	Engaged in repetition of self-harm, 6 to 12 months, analyzed (IG1=34; CG=34), N (%) IG1: 30 (88) CG: 24 (71) Chi-square=3.24 P=0.07
King et al, 2009[108] NCT00071617	IG1: Youth-Nominated Support Team (N=223) CG: TAU (N=225)	Suicide attempt, 12 months, analyzed (IGI=175; CG=171), N IG1: 29 CG: 35 Chi-square=0.44 P=0.51

Appendix I Table 8. Suicide Risk Treatment Studies: Suicide Attempts or Episode of Deliberate Self-Harm Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Outcome
Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203] NCT00675129	IG1: DBT (N=39) CG: Enhanced usual care (N=38)	Self-harm episodes, 19 weeks (posttreatment), ITT (IG1=39; CG=38), mean (95% CI) IG1: 9.0 (4.8 to 13.2) CG: 22.5 (11.4 to 33.5) Between-group difference NR; P<0.05 Self-harm episodes, posttreatment to 1 year, mITT (IG1=38; CG=37), mean (95% CI) IG1: 5.5 (1.7 to 9.1) CG: 14.8 (7.3 to 22.3) Between-group difference NR; P<0.05 Self-harm episodes, between 1 and 3 years, mITT (IG1=37; CG=34), mean (SD) IG1: 6.32 (12.35) CG: 18.94 (42.74) P=NR Self-harm episodes, between 1 and 3 years, mITT(IG1=37; CG=34), median (range, IQR) IG1: 1 (0 to 65, 18) CG: 5 (0 to 226, 7) P<0.001 for comparison of ranges Self-harm episodes, 3 years, mITT(IG1=37; CG=34), IRR (95% CI) IRR, 0.32 (0.13 to 0.80); P=0.015 (favoring intervention) Adjusted IRR, 0.46 (0.18 to 1.19); P=0.108 adjusting for gender, suicide attempt in last 4 months at baseline, and presence of a depressive order at baseline
Rossouw et al, 2012[128] ISRCTN95266816	IG1: Mentalization-based treatment for adolescents (MBT-A) (N=40) CG: TAU (N=40)	Self-harm (RTSHI), 12 months, ITT (IG1=40; CG=40), log mean (SE) IG1: 1.33 (0.22) CG: 2.01 (0.21) Group differences from mixed-effects random regression model at 12 months, P<0.01 favoring MBT-A Odds of reporting at least one incident of self-harm, 12 months, completers (IG1=36; CG=35), n (%) IG1: 22 (56) CG: 33 (83) P=0.01, favoring MBT-A

Appendix I Table 8. Suicide Risk Treatment Studies: Suicide Attempts or Episode of Deliberate Self-Harm Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Outcome
Wood et al, 2001[159]	IG1: Developmental Group Therapy (N=32) CG: Treatment as usual (N=31)	Number of episodes of deliberate self-harm, 7 months (posttreatment), ITT (IGI=32; CG=31), mean (95% CI) IG1: 0.6 (0.3 to 0.9) CG: 1.8 (0.6 to 3.0) P=NR Number of persons repeating self-harm, 7 months (posttreatment), ITT (IG1=32; CG=31), N (%) IG1: 2 (6) CG: 10 (32) OR: 6.3 (1.4 to 28.7) Mean time in weeks to first repeated episode of self-harm, 7 months (posttreatment), ITT (IG1=32; CG=31), Mean (SD) IG1: 11.9 (7.2) CG: 7 (6.3) Mean difference, 4.9 (95% CI, 0.0 to 9.8); P<0.05

Abbreviations: CBT=cognitive behavioral therapy; CG=control group; CI=confidence interval; DBT=dialectical behavior therapy; HR=hazard ratio; IG=intervention group; IQR=interquartile ratio; ITT=intent to treat; KQ=key question; MBT=mentalization-based treatment; MBT-A=mentalization-based treatment for adolescents; mITT=modified intent to treat; NR=not reported; NS=not significant; NSSI=non-suicidal self-injury; OR=odds ratio; RTSHI=Risk-Taking and Self-Harm Inventory for Adolescents; SASII=Suicide Attempt Self-Injury Interview; SD=standard deviation; SE=standard error; TAU=treatment as usual.

Appendix I Table 9. Suicide Risk Treatment Studies: Suicide-Related Hospitalization or Emergency Department Use Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200] ISRCTN59793150	IG1: Family therapy (N=415) CG: TAU (N=417)	Hospital attendance for self-harm event, 18 months, ITT (IG=415; CG=417), N (%) IG1: 118 (28) CG: 103 (25) HR (95% CI): 1.14 (0.87 to 1.49); P=0.33 Hospital attendance for self-harm event, 12 months, ITT (IG=415; CG=417), N (%) IG1: NR CG: NR HR (95% CI): 1.09 (0.81 to 1.48); P=0.56 Hospital attendance for self-harm event, 36 months, ITT (IG=415; CG=417), N (%) IG1: 168 (40.5) CG: 166 (39.8) HR (95% CI): 1.03 (0.83 to 1.28); P=0.78
Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203] NCT00675129	IG1: DBT (N=39) CG: Enhanced usual care (N=38)	Admitted to hospital due to self-harm, 19 weeks (posttreatment), ITT (IG1=39; CG=38), N (%) IG1: 1 (2) CG: 2 (5) P=NS ER visit due to self-harm, 19 weeks (posttreatment), ITT (IG1=39; CG=38), N (%) IG1: 2 (5) CG: 5 (13) P=NS
Ougrin et al, 2013[121] Ougrin, 2011[204] ISRCTN 81605131	IG1: Therapeutic Assessment (N=35) CG: Assessment as usual (N=35)	One or more presentation to A&E with self-harm, 2 years, ITT (IG1=35; CG=34), N (%) IG1: 7 (20) CG: 9 (26) OR: 0.69 (0.23 to 2.13); P=0.53

Appendix I Table 9. Suicide Risk Treatment Studies: Suicide-Related Hospitalization or Emergency Department Use Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
Griffiths et al, 2019[94] NCT02771691	IG1: MBT (N=26) CG: TAU (N=27)	Self-harm ED presentation, 12 weeks (posttreatment), ITT (IG1=22; CG=26), mean number (range) IG1: 0.36 (0 to 2) CG: 0.23 (0 to 2) Self-harm ED presentation, 24 weeks (12 week posttreatment), ITT (IG1=22; CG=26), mean number (range) IG1: 0.23 (0 to 2) CG: 0.54 (0 to 3) Self-harm ED presentation, 36 weeks (24 week posttreatment), ITT (IG1=22; CG=26), mean number (range) IG1: 0.09 (0 to 1) CG: 0.35 (0 to 4) Time x Group interaction (presumably across all 3 followup timepoints): P=NS

Abbreviations: A&E=accident and emergency; CG=control group; CI=confidence interval; DBT=dialectical behavior therapy; ED=emergency department; ER=emergency room; HR=hazard ratio; IG=intervention group; ITT=intent to treat; KQ=key question; MBT=mentalization-based treatment; NR=not reported; NS=not significant; OR=odds ratio; TAU=treatment as usual.

Appendix I Table 10. Suicide Risk Treatment Studies: Measures of Suicide Risk Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200] ISRCTN59793150	IG1: Family therapy (N=415) CG: TAU (N=417)	BSS, 12 months, analyzed (IG=257; CG=202), mean (SD) IG1: 4.6 (7.25) CG: 5.7 (7.91) BSS, 18 months, analyzed (IG=212; CG=180), mean (SD) IG1: 4.6 (7.76) CG: 5.2 (7.76) BSS, 12 months, analyzed (IG=257; CG=202), proportion with ideation, N (%) IG1: 111 (43.2) CG: 98 (48.5) BSS, 18 months, analyzed (IG=212; CG=180), proportion with ideation, N (%) IG1: 85 (40.1) CG: 80 (44.4) BSS, 12 months, ITT (IG=415; CG=417), proportion with ideation (SE %) IG1: 0.26 (0.05) CG: 0.36 (0.05) OR (95% CI): 0.64 (0.44 to 0.94); P=0.024 BSS, 18 months, ITT (IG=415; CG=417), proportion with ideation (SE %) IG1: 0.22 (0.04) CG: 0.28 (0.05) OR (95% CI): 0.76 (0.49 to 1.16); P=0.20 HSFC, 12 months, ITT (IG=415; CG=417) mean (SE) IG1: 4.8 (0.40) CG: 5.1 (0.43) Difference, mean (95% CI), SE: -0.3 (-1.1 to 0.4), 0.37; P=0.38 HSFC, 18 months, ITT (IG=415; CG=417) mean (SE) IG1: 4.4 (0.42) CG: 4.6 (0.43) Difference, mean (95% CI), SE: -0.2 (-0.9 to 0.5), 0.36; P=0.63

Appendix I Table 10. Suicide Risk Treatment Studies: Measures of Suicide Risk Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
Diamond et al, 2010[82] NCT00604097	IG1: Attachment-Based Family Therapy (N=35) CG: Enhanced Usual Care (N=31)	SIQ-Jr, 12 weeks, ITT (IG1=35; CG=31), mean (95% CI) IG1: 5.2 (1.6 to 8.8) CG: 16.2 (10.1 to 22.2) P=NR SIQ-Jr, 24 weeks, ITT (IG1=35; CG=31), mean (95% CI) IG1: 10.4 (5.6 to 15.2) CG: 23.0 (15.6 to 30.4) P=NR Difference in difference from baseline to followup: 2.03 (SE=0.59), effect size=0.97, in favor of IG1, (t(64=-3.45, p=0.001) SSI, 12 weeks, ITT (IG1=35; CG=31), mean (95% CI) IG1: 69.2 (50.2 to 88.2) CG: 34.6 (15.0 to 54.2) P=NR SSI, 24 weeks, ITT (IG1=35; CG=31), mean (95% CI) IG1: 82.1 (67.0 to 97.3) CG: 46.2 (25.6 to 66.7) P=NR Difference in difference from baseline to followup: 2.07 (SE=0.80), effect size=0.64, in favor of IG1, (t(64=2.58, p=0.012)
Green et al, 2011[93] ISRCTN 20496110	IG1: Group psychotherapy (N=183) CG: Routine care (N=183)	SIQ, mean difference at 6 months, analyzed (IGI=171; CG=179), mean difference (95% CI) 0.07 (-8.60 to 8.75), P=0.99 SIQ, mean difference at 12 months, analyzed (IGI=169; CG=174), mean difference (95% CI) -2.37 (-11.11 to 6.36), P=0.59
Hazell et al, 2009[95] ACTRN12608000532303	IG1: Group therapy (N=35) CG: Routine care (N=37)	SIQ, 8 weeks, analyzed (IG1=34; CG=37), mean (SD) IG1: 74.11 (41.75) CG: 76.40 (54.28) SIQ, 12 months, analyzed (IG1=34; CG=37), mean (SD) IG1: 59.78 (42.07) CG: 61.68 (49.62) F=0.07 P=0.80 (for group differences from baseline)

Appendix I Table 10. Suicide Risk Treatment Studies: Measures of Suicide Risk Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
Hill et al, 2019[97] NR	IG1: Internet CBT (N=40) CG: Information-only control (N=40)	BSS 2 weeks (posttreatment), mITT (IG1=41; CG=39), mean (SD) IG1: 2.05 (3.27) CG: 4.49 (6.01) P=0.12 BSS, 8 weeks, mITT (IG1=41; CG=39), mean (SD) IG1: 1.69 (3.01) CG: 2.57 (4.40) P=0.92 Perceived Burdensomeness, 2 weeks (posttreatment), mITT (IG1=41; CG=39), mean (SD) IG1: 17.76 (6.37) CG: 18.81 (6.26) P=0.26 Perceived Burdensomeness, 8 weeks, mITT (IG1=41; CG=39), mean (SD) IG1: 13.90 (6.86) CG: 15.85 (6.25) P=0.10 Thwarted Belongingness, 2 weeks (posttreatment), mITT (IG1=41; CG=39), mean (SD) IG1: 31.78 (7.32) CG: 35.22 (8.60) P=0.12 Thwarted Belongingness, 8 weeks, mITT (IG1=41; CG=39), mean (SD) IG1: 27.30 (8.42) CG: 31.76 (8.09) P=0.03
Hooven et al, 2012[100]	IG1: C-Care (N=153) IG2: P-CARE (N=155) IG3: C-Care + P-Care (N=164) CG: TAU (N=143)	Suicide ideation, change from baseline to 1 month, ITT (IG1=153; CG=143), rate of change coefficients IG1: -1.131 CG: -0.917 P=NS, 1 tailed test Suicide ideation, change from baseline to 1 month, ITT (IG2=155; CG=143), rate of change coefficients IG2: -1.033 CG: -0.917 P=NS, 1 tailed test

Appendix I Table 10. Suicide Risk Treatment Studies: Measures of Suicide Risk Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
Hooven et al, 2012[100] (continued)		Suicide ideation, change from baseline to 1 month, ITT (IG3=164; CG=143), rate of change coefficients IG3: -1.451 CG: -0.917 P<0.001, 1 tailed test, favoring IG3 (C+P care) Suicide ideation, change from baseline to 9 months, ITT (IG3=164; CG=143), rate of change coefficients IG3: NR CG: NR P <0.005, 1 tailed test, favoring IG3 (C+P care) Direct suicide threats, change from baseline to 1 month, ITT (IG1=153; CG=143), rate of change coefficients IG1: -0.443 CG: -0.318 P=NS, 1 tailed test Direct suicide threats, change from baseline to 1 month, ITT (IG2=155; CG=143), rate of change coefficients IG2: -0.294 CG: -0.318 P=NS, 1 tailed test Direct suicide threats, change from baseline to 1 month, ITT (IG3=164; CG=143), rate of change coefficients IG3: -0.556 CG: -0.318 P<0.05, 1 tailed test Direct suicide threats, change from baseline to 9 months, ITT (IG3=164; CG=143), rate of change coefficients IG3: NR CG: NR P <0.01, 1 tailed test, favoring IG3 (C+P care)

Appendix I Table 10. Suicide Risk Treatment Studies: Measures of Suicide Risk Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
King et al, 2009[108] NCT00071617	IG1: Youth-Nominated Support Team (N=223) CG: TAU (N=225)	BHS, 6 weeks, analyzed (IGI=NR; CG=NR), adjusted mean IG1: 6.82 CG: 7.80 Main effects mixed model, P=0.09 BHS, 3 months, analyzed (IGI=168; CG=174), adjusted mean IG1: 6.72 CG: 6.53 Main effects mixed model, P=0.98 BHS, 12 months, analyzed (IGI=175; CG=171), adjusted mean IG1: 4.37 CG: 5.08 Main effects mixed model, P=0.14 SIQ-Jr, 6 weeks, analyzed (IGI=NR; CG=NR), adjusted mean IG1: 25.55 CG: 29.71 Main effects mixed model, P=0.04, Cohen's d=0.21 SIQ-Jr, 3 months, analyzed (IGI=168; CG=174), adjusted mean IG1: 23.62 CG: 21.57 Main effects mixed model, P=0.26 SIQ-Jr, 12 months, analyzed (IGI=175; CG=171), adjusted mean IG1: 16.71 CG: 17.14 Main effects mixed model, P=0.77 All of the above means were adjusted for baseline CDRS-R score, alcohol and drug use problem severity, and baseline scores for the outcome being measured
King et al, 2015[107] NR	IG1: Teen Option to Change (Motivational Interviewing) (N=27) CG: Enhanced TAU (N=22)	SIQ-Jr, 2 months, ITT (IG1=24; CG=22), mean (SD) IG1: 21.46 (17.4) CG: 24.28 (17.3) Cohen's d=0.22 P for time x treatment interaction=NS BHS, 2 months, ITT (IG1=24; CG=22), mean SD IG1: 5.66 (5.2) CG: 8.64 (5.7) Cohen's d=0.40 P for time x treatment interaction=NS

Appendix I Table 10. Suicide Risk Treatment Studies: Measures of Suicide Risk Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203] NCT00675129	IG1: DBT (N=39) CG: Enhanced usual care (N=38)	SIQ-Jr, 71 weeks, mITT (IG1=38; CG=37), mean (SD) IG1: 20.45 (19.15) CG: 22.05 (21.86) Between-group difference in slope=0.15; P=0.110 SIQ-Jr, 3.1 years, mITT(IG1=37; CG=34), mean (SD) IG1: 19.64 (18.54) CG: 23.15 (18.12) Between-group difference in slope=0.099; P=0.111 Between-group difference in mean change=NR; P=0.430 BHS, 19 weeks (posttreatment), ITT (IG1=39; CG=38), mean (SD) IG1: 6.23 (5.30) CG: 9.06 (6.53) Between-group difference in slope=-0.13; P=0.071 BHS, 71 weeks, mITT (IG1=38; CG=37), mean (SD) IG1: 6.97 (5.66) CG: 7.26 (6.57) Between-group difference in slope=0.02; P=0.446 BHS, 3.1 years, mITT (IG1=37; CG=34), mean (SD) IG1: 6.16 (5.24) CG: 8.10 (5.76) Between-group difference in slope=0.006; P=0.762 Between-group difference in mean change=NR; P=0.154
Pineda et al, 2013[125] ACTRN12613000668707	IG1: RAP-P (Family Intervention) (N=24) CG: Routine care (N=24)	ASQ-R, posttreatment, completers (IG1=22; CG=18), mean (SD) IG1: 8.73 (4.88) CG: 11.89 (5.47) ASQ-R, 6 months, completers (IG1=22; CG=18), mean (SD) IG1: 6.77 (4.06) CG: 10.83 (5.33) Time x Group interaction (presumably across both timepoints): P=0.05, favoring RAP-P

Appendix I Table 10. Suicide Risk Treatment Studies: Measures of Suicide Risk Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
Tang et al, 2009[144]	IG1: IPT-A-IN (N=35) CG: TAU (N=38)	BHS, 6 weeks, ITT (IG1=35; CG=38), mean (SD) IG1: 7.74 (5.29) CG: 12.42 (4.08) P<0.01 for post comparison controlling for baseline score BSS, 6 weeks, ITT (IG1=35; CG=38), mean (SD) IG1: 8.97 (10.77) CG: 16.29 (7.99) P<0.01 for post comparison controlling for baseline score
Wood et al, 2001[159]	IG1: Developmental Group Therapy (N=32) CG: Treatment as usual (N=31)	SIQ, change from baseline to 7 months (posttreatment), analyzed (IG1=28; CG=27), mean (SD) IG1: 47.3 (50.5) CG: 39.7 (46.7) Mean difference (95% CI): 7.5 (-18.8 to 33.9)

Abbreviations: ASQ-R=Adolescent Suicide Questionnaire–Revised; BHS=Beck Hopelessness Scale; BSS=Beck Scale for Suicide Ideation; CBT=cognitive behavioral therapy; C-CARE=Counselors Care, Assess, Respond, Empower; CDRS-R=Children's Depression Rating Scale-Revised; CG=control group; CI=confidence interval; DBT=dialectical behavior therapy; HR=hazard ratio; HSFC=Hopelessness Scale for Children; IG=intervention group; IPT-A-IN=intensive interpersonal psychotherapy for depressed adolescents with suicidal risk; ITT=intent to treat; KQ=key question; mITT=modified intent to treat; N=number; NR=not reported; NS=not significant; OR=odds ratio; P-CARE=Parents-Counselors Care, Assess, Respond, Empower; RAP-P=Resourceful Adolescent Parent Program; SD=standard deviation; SE=standard error; SIQ=Suicidal Ideation Questionnaire; SIQ JR=Suicidal Ideation Questionnaire-Junior; SSI=Scale for Suicidal Ideation; TAU=treatment as usual.

Appendix I Table 11. Suicide Risk Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Griffiths et al, 2019[94] NCT02771691	IG1: MBT (N=26) CG: TAU (N=27)	RCADS Anx, 12 weeks (posttreatment), ITT (IG1=22; CG=26), mean (SD) IG1: 78.21 (21.48) CG: 65.42 (22.4) RCADS Anx, 24 weeks (12 week posttreatment), ITT (IG1=22; CG=26), mean (SD) IG1: 76.56 (25.24) CG: 67.14 (22.05) RCADS Anx, 36 weeks (24 week posttreatment), ITT (IG1=22; CG=26), mean (SD) IG1: 77.55 (24.91) CG: 68.4 (21.61) Time x Group interaction (presumably across all 3 followup timepoints): P=NS
Hooven et al, 2012[100]	IG1: C-Care (N=153) IG2: P-CARE (N=155) IG3: C-Care + P-Care (N=164) CG: TAU (N=143)	4 anxiety items, change from baseline to 1 month, ITT (IG1=153; CG=143), rate of change coefficients IG1: -0.683 CG: -0.440 P<0.05, 1 tailed test, favoring IG1 (C care) 4 anxiety items, change from baseline to 1 month, ITT (IG2=155; CG=143), rate of change coefficients IG2: -0.515 CG: -0.440 P=NS, 1 tailed test 4 anxiety items, change from baseline to 1 month, ITT (IG3=164; CG=143), rate of change coefficients IG3: -0.849 CG: -0.440 P<0.001, 1 tailed test, favoring IG3 (C+P care) 4 anxiety items, change from baseline to 2.5 months, ITT (IG3=164; CG=143), rate of change coefficients IG3: NR CG: NR P <0.006, 1 tailed test, favoring IG3 (C+P care)
Tang et al, 2009[144]	IG1: IPT-A-IN (N=35) CG: TAU (N=38)	BAI, 6 weeks, ITT (IG1=35; CG=38), mean (SD) IG1: 11.94 (10.34) CG: 25.45 (14.35) F=21.79 P<0.001 (favoring intervention)

Abbreviations: BAI=Beck Anxiety Inventory; C-CARE=Counselors Care, Assess, Respond, Empower; CG=control group; IG=intervention group; IPT-A-IN=intensive interpersonal psychotherapy for depressed adolescents with suicidal risk; ITT=intent to treat; KQ=key question; MBT=mentalization-based treatment; NR=not reported; NS=not significant; P-CARE=Parents-Counselors Care, Assess, Respond, Empower; RCADS=Revised Children's Anxiety and Depression Scale; SD=standard deviation; TAU=treatment as usual.

Appendix I Table 12. Suicide Risk Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200] ISRCTN59793150	IG1: Family therapy (N=415) CG: TAU (N=417)	CDRS-R, posttreatment 12 months, analyzed (IG=244; CG=187), mean (SE) IG1: 36.5 (14.33) CG: 37.2 (13.09) CDRS-R, posttreatment 18 months, analyzed (IG=204; CG=165), mean (SE) IG1: 33.8 (14.77) CG: 35.0 (14.39) CDRS-R, posttreatment 12 months, ITT (IG=248; CG=189), mean (SE) IG1: 33.2 (1.46) CG: 33.9 (1.57) Difference, mean (95% CI), SE=-0.6 (-3.1 to 1.9), 1.27 P=0.62 CDRS-R, posttreatment 18 months, ITT (IG=204; CG=165), mean (SE) IG1: 30.6 (1.50) CG: 31.6 (1.46) Difference, mean (95% CI), SE=-1.0 (-3.5 to 1.5), 1.26 P=0.43
Diamond et al, 2010[82] NCT00604097	IG1: Attachment-Based Family Therapy (N=35) CG: Enhanced Usual Care (N=31)	BDI-II, 12 weeks, ITT (IG1=35; CG=31), mean (95% CI) IG1: 12.6 (8.0 to 17.2) CG: 18.5 (12.9 to 24.0) P=NR BDI-II, 24 weeks, ITT (IG1=35; CG=31), mean (95% CI) IG1: 12.4 (7.8 to 16.9) CG: 16.2 (10.4 to 21.9) P=NR BDI-II <9, 12 weeks, analyzed (IG1=31; CG=29), N (%) IG1: 17 (55) CG: 9 (31) OR: 2.70 (0.94 to 7.71); P=0.06 BDI-II <9, 24 weeks, analyzed (IG1=31; CG=26), N (%) IG1: 18 (58) CG: 10 (38) OR: 2.21 (0.76 to 6.42); P=0.14

Appendix I Table 12. Suicide Risk Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Green et al, 2011[93] ISRCTN 20496110	IG1: Group psychotherapy (N=183) CG: Routine care (N=183)	MFQ, mean difference at 6 months, analyzed (IGI=171; CG=178), mean difference (95% CI) -0.44 (-3.49 to 2.61), P=0.78 MFQ mean difference at 12 months, analyzed (IGI=170; CG=174), mean difference (95% CI) -1.45 (-4.90 to 1.99), P=0.41
Griffiths et al, 2019[94] NCT02771691	IG1: MBT (N=26) CG: TAU (N=27)	RCADS MD, 12 weeks (posttreatment), ITT (IG1=22; CG=26), mean (SD) IG1: 20.39 (4.74) CG: 18.15 (6.57) RCADS MD, 24 weeks (12 week posttreatment), ITT (IG1=22; CG=26), mean (SD) IG1: 19.89 (5.64) CG: 17.81 (6.65) RCADS MD, 36 weeks (24 week posttreatment), ITT (IG1=22; CG=26), mean (SD) IG1: 20.07 (5.72) CG: 18.49 (6.96) Time x Group interaction (presumably across all 3 followup timepoints): P=NS
Hazell et al, 2009[95] ACTRN12608000532303	IG1: Group therapy (N=35) CG: Routine care (N=37)	MFQ, 8 weeks, analyzed (IG1=34; CG=37), mean (SD) IG1: 30.91 (17.25) CG: 32.38 (19.94) MFQ, 12 months, analyzed (IG1=34; CG=37), mean (SD) IG1: 27.40 (17.16) CG: 31.76 (18.91) F=0.27 P=0.60 (presumably across 2 timepoints)
Hill et al, 2019[97] NR	IG1: Internet CBT (N=40) CG: Information-only control (N=40)	RADS-2, 2 weeks (posttreatment), mITT (IG1=41; CG=39), mean (SD) IG1: 23.12 (4.50) CG: 24.64 (5.90) P=0.45 RADS-2, 8 weeks (posttreatment), mITT (IG1=41; CG=39), mean (SD) IG1: 20.93 (4.49) CG: 23.00 (5.41) P=0.07

Appendix I Table 12. Suicide Risk Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Hooven et al, 2012[100]	IG1: C-Care (N=153) IG2: P-CARE (N=155) IG3: C-Care + P-Care (N=164) CG: TAU (N=143)	CES-D, change from baseline to 1 month, ITT (IG1=153; CG=143), rate of change coefficients IG1: -0.951 CG: -0.685 P<0.01, 1 tailed test, favoring IG1 (C-care) CES-D, change from baseline to 1 month, ITT (IG1=155; CG=143), rate of change coefficients IG2: -0.815 CG: -0.685 P=NS, 1 tailed test CES-D, change from baseline to 1 month, ITT (IG1=164; CG=143), rate of change coefficients IG3: -1.021 CG: -0.685 P<0.01, 1 tailed test, favoring IG3 (C+P care)
King et al, 2009[108] NCT00071617	IG1: Youth-Nominated Support Team (N=223) CG: TAU (N=225)	CDRS-R, 6 weeks, analyzed (IGI=NR; CG=NR), adjusted mean IG1: 39.69 CG: 40.80 Main effects mixed model, P=0.40 CDRS-R, 3 months, analyzed (IGI=168; CG=174), adjusted mean IG1: 38.27 CG: 38.55 Main effects mixed model, P=0.84 CDRS-R, 12 months, analyzed (IGI=175; CG=171), adjusted mean IG1: 33.16 CG: 33.96 Main effects mixed model, P=0.52
King et al, 2015[107] NR	IG1: Teen Option to Change (Motivational Interviewing) (N=27) CG: Enhanced TAU (N=22)	RADS-2-SF, 2 months, ITT (IG1=24; CG=22), mean (SD) IG1: 25.38 (4.7) CG: 30.87 (4.0) Cohen's d=1.07 P<0.01 for time x treatment interaction

Appendix I Table 12. Suicide Risk Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203] NCT00675129	IG1: DBT (N=39) CG: Enhanced usual care (N=38)	SMFQ, 19 weeks (posttreatment), ITT (IG1=39; CG=38), mean (SD) IG1: 10.19 (5.04) CG: 12.58 (6.62) Between-group difference in slope=-0.10; P=0.179 SMFQ, 71 weeks, mITT (IG1=38; CG=37), mean (SD) IG1: 9.88 (5.53) CG: 9.19 (6.57) Between-group difference in slope=0.04; P=0.240 SMFQ, 3.1 years, mITT (IG1=37; CG=34), mean (SD) IG1: 9.54 (5.3) CG: 10.56 (6.3) Between-group difference in slope=0.011; P=0.556 Between-group difference in mean change=NR; P=0.471 MADRS, 19 weeks (posttreatment), ITT (IG1=39; CG=38), mean (SD) IG1: 12.29 (7.52) CG: 15.76 (8.14) Between-group difference in change in slope=-0.22; P=0.019 MADRS, 71 weeks, mITT (IG1=38; CG=37), mean (SD) IG1: 15.09 (8.08) CG: 15.73 (9.06) Between-group difference in slope=0.06; P=0.199 MADRS, 3.1 years, mITT (IG1=37; CG=34), mean (SD) IG1: 11.7 (7.2) CG: 10.33 (7.03) Between-group difference in slope=0.044; P=0.089 Between-group difference in mean change=NR; P=0.429
Rossouw et al, 2012[128] ISRCTN95266816	IG1: Mentalization-based treatment for adolescents (MBT-A) (N=40) CG: TAU (N=40)	MFQ, 12 months, ITT (IG1=40; CG=40), log mean (SE) IG1: 9.26 (1.27) CG: 11.54 (1.14) Group differences from mixed-effects random regression model at 12 months, P<0.05 favoring MBT-A
Tang et al, 2009[144]	IG1: IPT-A-IN (N=35) CG: TAU (N=38)	BDI-II, 6 weeks, ITT (IG1=35; CG=38), mean (SD) IG1: 19.97 (14.68) CG: 31.58 (12.01) F=15.64 P<0.001 (favoring intervention)

Appendix I Table 12. Suicide Risk Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Wood et al, 2001[159]	IG1: Developmental Group Therapy (N=32) CG: Treatment as usual (N=31)	MFQ, change from baseline to 7 months (posttreatment), analyzed (IG1=29; CG=27), mean (SD) IG1: 18.8 (16.0) CG: 15.3 (13.0) Mean difference (95% CI): 3.5 (-4.4 to 11.3)

Abbreviations: BDI-II=Beck Depression Inventory, version 2; CBT=cognitive behavioral therapy; C-CARE=Counselors Care, Assess, Respond, Empower; CDRS-R=Children's Depression Rating Scale-Revised; CES-D=Center for Epidemiological Studies-Depression; CG=control group; CI=confidence interval; DBT=dialectical behavior therapy; IG=intervention group; IPT-A-IN=intensive interpersonal psychotherapy for depressed adolescents with suicidal risk; ITT=intent to treat; KQ=key question; MADRS=Montgomery–Åsberg Depression Rating Scale; MBT=mentalization-based treatment; MBT-A=mentalization-based treatment for adolescents; MFQ=mood & feelings questionnaire; mITT=modified intent to treat; N=number; NR=not reported; NS=not significant; P-CARE=Parents-Counselors Care, Assess, Respond, Empower; RADS-2=Reynolds Adolescent Depression Scale, 2nd Edition; RADS-2-SF=Reynolds Adolescent Depression Scale, 2nd Edition: Short Form; RCADS MD=Revised Children's Anxiety and Depression Scale-Depression; SD=standard deviation; SE=standard error; SMFQ=Short Mood & Feelings Questionnaire; TAU=treatment as usual.

Appendix I Table 13. Suicide Risk Treatment Studies: Response and Remission Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Presence/Absence of Diagnosis
Diamond et al, 2010[82] NCT00604097	IG1: Attachment-Based Family Therapy (N=35) CG: Enhanced Usual Care (N=31)	SIQ-Jr, clinical response defined as ≤13 SSI, clinical response defined as 0 vs. 1 suicide attempt BDI-II, clinical response defined as ≤9 SIQ-Jr <13, 12 weeks, analyzed (IG1=31; CG=29), N (%) IG1: 27 (87) CG: 15 (52) OR: 6.30 (1.76 to 22.61); P=0.003 (favoring intervention) SIQ-Jr <13, 24 weeks, analyzed (IG1=30; CG=26), N (%) IG1: 21 (70) CG: 9 (35) OR: 4.41; P=0.008 (favoring intervention) SSI (0 vs. 1), 12 weeks, analyzed (IG1=26; CG=26), N (%) IG1: 18 (69) CG: 9 (35) OR: 4.45 (1.33 to 13.56); P=0.013 (favoring intervention) SSI (0 vs. 1), 24 weeks, analyzed (IG1=28; CG=26), N (%) IG1: 23 (82) CG: 12 (46) OR: 5.37 (1.56 to 18.49); P=0.006 (favoring intervention)
Hill et al, 2019[97] NR	IG1: Internet CBT (N=40) CG: Information-only control (N=40)	Meeting reliable change criteria (Jacob and Truax, 1991) with clinically significant improvement based on perceived burdensomeness scores closer to that of the healthy population mean (≤14.61) Treatment response, 8 weeks, mITT (IG1=41; CG=39), N (%) IG1: 10 (24.4) CG: 4 (10.2)

Abbreviations: BDI-II=Beck Depression Inventory, version 2; CBT=cognitive behavioral therapy; CG=control group; IG=intervention group; KQ=key question; mITT=modified intent to treat; N=number; NR=not reported; OR=odds ratio; SIQ-Jr=Suicidal Ideation Questionnaire-Junior; SSI=Scale for Suicidal Ideation.

Appendix I Table 14. Suicide Risk Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes
Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200] ISRCTN59793150	IG1: Family therapy (N=415) CG: TAU (N=417)	PQ-LES, 12 months, analyzed (IG=259; CG=201), mean (SD) IG1: 48.5 (10.57) CG: 47.3 (10.26) PQ-LES, 18 months, ITT (IG=204; CG=165), mean (SD) IG1: 49.1 (11.14) CG: 48.7 (11.25) PQ-LES, 12 months, ITT (IG=415; CG=417), mean (SE) IG1: 49.9 (1.12) CG: 48.8 (1.13) Difference, mean (95% CI), SE: 1.1 (-0.5 to 2.7), 0.82; P=0.18 PQ-LES, 18 months, ITT (IG=415; CG=417), mean (SE) IG1: 50.6 (1.12) CG: 50.4 (1.20) Difference, mean (95% CI), SE: 0.1 (-1.9 to 2.1), 1.02; P=0.90 GHQ-12-Caregiver, 12 months, ITT (IG=415; CG=417), mean (SE) IG1: 12.8 (0.61) CG: 13.5 (0.65) Difference, mean (95% CI), SE: -0.7 (-1.8 to 0.3), 0.54; P=0.19 GHQ-12-Caregiver, 18 months, ITT (IG=415; CG=417), mean (SE) IG1: 12.8 (0.61) CG: 13.5 (0.65) Difference, mean (95% CI), SE: -0.7 (-1.8 to 0.3), 0.54; P=0.19
Green et al, 2011[93] ISRCTN 20496110	IG1: Group psychotherapy (N=183) CG: Routine care (N=183)	HoNOSCA, 6 months, analyzed (IGI=172; CG=180), mean (SD), mean difference (95% CI) IG1: 12.2 (6.3) CG: 12.6 (6.1) Difference, mean (95% CI), -0.55 (-1.64 to 0.54), P=0.32 HoNOSCA, 12 months, analyzed (IGI=168; CG=178), mean (SD), mean difference (95% CI) IG1: 10.9 (5.9) CG: 11.7 (6.7) Difference, mean (95% CI), -0.79 (-1.98 to 0.40), P=0.19

Appendix I Table 14. Suicide Risk Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes
Hazell et al, 2009[95] ACTRN12608000532303	IG1: Group therapy (N=35) CG: Routine care (N=37)	CGAS, 8 weeks, analyzed (IG1=25; CG=25), mean (SD) IG1: 58.54 (8.70) CG: 60.59 (10.69) CGAS, 12 months, analyzed (IG1=25; CG=25), mean (SD) IG1: 60.36 (8.48) CG: 60.14 (9.47) F=0.89 P=0.35 (for group differences from baseline) HoNOSCA, 8 weeks, analyzed (IG1=26; CG=29), mean (SD) IG1: 16.77 (7.12) CG: 15.00 (9.28) HoNOSCA, 12 months, analyzed (IG1=26; CG=29), mean (SD) IG1: 13.80 (6.83) CG: 15.41(8.75) F=3.77 P=0.06 (for group differences from baseline) SDQ, 8 weeks, analyzed (IG1=33; CG=37), mean (SD) IG1: 17.66 (6.58) CG: 18.89 (7.16) SDQ, 12 months, analyzed (IG1=33; CG=37), mean (SD) IG1: 15.14 (7.15) CG: 18.35 (6.26) F=2.60 P=0.11 (for group differences from baseline)
King et al, 2009[108] NCT00071617	IG1: Youth-Nominated Support Team (N=223) CG: TAU (N=225)	CAFAS, 3 months, analyzed (IGI=168; CG=174), adjusted mean IG1: 15.20 CG: 15.77 Main effects mixed model, P=0.58 CAFAS, 12 months, analyzed (IGI=175; CG=171), adjusted mean IG1: 12.43 CG: 12.70 Main effects mixed model, P=0.70

Appendix I Table 14. Suicide Risk Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes
Mehlum et al, 2014[115] Mehlum et al, 2016[201] Mehlum et al, 2019[202] Haga et al, 2018[203] NCT00675129	IG1: DBT (N=39) CG: Enhanced usual care (N=38)	CGAS, 71 weeks, mITT(IG1=38; CG=37), mean (SD) IG1: 65.68 (11.81) CG: 64.22 (14.13) Between-group difference in slope=0.03; P=0.067 CGAS, 3.1 years, mITT(IG1=37; CG=34), mean (SD) IG1: 65.0 (11.8) CG: 66.1 (11.2) Between-group difference in slope= -0.012; P=0.747 Between-group difference in mean change= -1.1; P=0.678
Ougrin et al, 2013[121] Ougrin, 2011[204] ISRCTN 81605131	IG1: Therapeutic Assessment (N=35) CG: Assessment as usual (N=35)	CGAS, 3 months, ITT (IG1=35; CG=35), mean (SD) IG1: 64.6 (12.9) CG: 60.1 (9.9) Mean difference: 4.49 (95% CI, -0.98 to 9.96)
Pineda et al, 2013[125] ACTRN12613000668707	IG1: RAP-P (Family Intervention) (N=24) CG: Routine care (N=24)	HoNOSCA, posttreatment, completers (IG1=22; CG=18), mean (SD) IG1: 13.45 (5.89) CG: 17.61 (5.20) HoNOSCA, 6 months, completers (IG1=22; CG=18), mean (SD) IG1: 4.77 (4.45) CG: 12.72 (5.29) Time x Group interaction (presumably across both timepoints): P=0.01, favoring RAP-P
Wood et al, 2001[159]	IG1: Developmental Group Therapy (N=32) CG: Treatment as usual (N=31)	HoNOSCA, change from baseline to 7 months (posttreatment), analyzed (IG1=31; CG=31), mean (SD) IG1: 8.4 (6.4) CG: 6.9 (6.1) Mean difference (95% CI), 1.5 (-1.7 to 4.7)

Abbreviations: CAFAS=Child and Adolescent Functional Assessment Scale; CG=control group; CGAS=Children's Global Assessment Scale; CI=confidence interval; DBT=dialectical behavior therapy GHQ-12=General Health Questionnaire, 12 questions; HoNOSCA=Health of the Nation Outcome Scales for Children and Adolescents; IG=intervention group; ITT=intent to treat; KQ=key question; mITT=modified intent to treat; PQ-LES=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; RAP-P=Resourceful Adolescent Parent Program; SD=standard deviation; SDQ=Strengths and Difficulties Questionnaire; SE=standard error; TAU=treatment as usual.

Appendix I Table 15. Suicide Risk Treatment Studies: Subgroups (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Other Outcomes/ Subgroups
Diamond et al, 2010[82] NCT00604097	IG1: Attachment-Based Family Therapy (N=35) CG: Enhanced Usual Care (N=31)	Adolescents diagnosed with depression SIQ-Jr, 24 weeks, analyzed (IG1=19; CG=16), total change from baseline (SE) IG1: -4.35 (0.66) CG: -2.19 (0.62) Difference in difference from baseline to followup: 2.16 (SE=0.91), effect size=1.00, in favor of IG1 (t(64=-2.39, p=0.02)
Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200] ISRCTN59793150	IG1: Family therapy (N=415) CG: TAU (N=417)	Moderator analysis for repetition of self-harm leading to hospital attendance Age: chi-square=0.4730, P=0.49 Sex: chi-square=1.5219, P=0.2173

Abbreviations: CG=control group; IG=intervention group; KQ=key question; SE=standard error; SIQ-Jr=Suicidal Ideation Questionnaire-Junior; TAU=treatment as usual.

Appendix I Table 16. Suicide Risk Treatment Studies: Harms (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Incidence Any AEs	Incidence of SAEs	Other Harms
Cottrell et al, 2018[80] Cottrell et al, 2018[199] Cottrell et al, 2018[200] ISRCTN59793150	IG1: Family therapy (N=415) CG: TAU (N=417)	One or more AE, 12 to 18 months followup, ITT (IG1=415; CG=417), N% IG1: 226 (54) CG: 217 (52) One or more accident and emergency/MIU/WIC attendance, 12 to 18 months followup, ITT (IG1=415, CG=417), N% IG1: 258 (62) CG: 253 (61)	One or more SAE, 12 to 18 months followup, ITT (IG1=415; CG=417), N (%) IG1: 156 (38) CG: 141 (34)	Two respondents died between 3 and 4 years postrandomization. Both participants were assigned to the Family Therapy group, neither death was related to self-harm.
Griffiths et al, 2019[94] NCT02771691	IG1: MBT (N=26) CG: TAU (N=27)	5 AEs among 4 participants (not reported by group); none were considered to be trial related	NR	NR

Abbreviations: AE=adverse event; CG=control group; IG=intervention group; ITT=intent to treat; KQ=key question; MBT=mentalization-based treatment; MIU=minor injury unit; N=number; NR=not reported; SAE=serious adverse event; SIQ JR=Suicidal Ideation Questionnaire-Junior; TAU=treatment as usual; WIC=walk-in center.

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Arendt et al, 2016[65]	Other very high HDI Denmark RCT TrygFonden	Recruited from a training and research clinic at a University Department of Psychology and Behavioural Sciences	IG1: Group child+parent in-person CBT (N=56) Description: Manualized group CBT program (Cool Kids) with a focus on teaching youths to recognize their emotions, restructure negative automatic thinking, and gradually confront feared situations. The treatment consisted of 10 2-hour weekly group sessions with 6 to 7 youths and their parents in each group. Duration: 10 weeks	CG: Wait-list (N=53) 3-month wait-list. All participants in the wait-list condition were offered the Cool Kids treatment after the waiting period	Some concerns
Asbrand et al, 2020[67] TU 78/5-2, HE 3342/4-2	Other very high HDI Germany RCT German Research Foundation	Recruited through advertisements in schools and medical facilities and through newspaper articles in 2 midsized German cities	IG1: Group child-focused in-person CBT (N=31) Description: Exposure-based CBT with 12 sessions (100 minutes each, including a 10-minute break) in groups of 5 to 7 children. Intervention components consist of psychoeducation, cognitive restructuring, social skills training, exposure, and relapse prevention. Duration: 12 weeks	CG: WLC (N=36) Wait-list control group receiving therapy about 16 weeks later	Some concerns
Barrett et al, 1996[70]	Other very high HDI Australia RCT The National Health and Medical Research Council of Australia, The Myer Foundation of Australia	Recruited from referrals from community centers, schools, mental health professionals, and medical practitioners, or parents referred them after media releases	IG1: CBT (N=28) Description: Seen on a weekly basis for 60 to 80 minutes using Coping Koala Workbook, which included recognizing anxious feelings and somatic reactions to anxiety, cognitive restructuring in anxiety-provoking situations, coping self-talk, exposure to feared stimuli, evaluating performance, and administering self-reinforcement as appropriate. The first 4 sessions were training sessions in which anxiety management procedures were introduced, role-played by the therapist, and practiced by each child. For the remaining 8 sessions, each child practiced the anxiety coping skills by using in vivo exposure to feared situations, starting with the low-stress situations and gradually increasing to high-stress situations. IG2: CBT + Family Intervention (N=25)		

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Barrett et al, 1996[70] (continued)			Description: Same as IG1 plus parallel program called Family Anxiety Management (FAM) consisting of child/parent therapy sessions after each CBT session; therapy emphasized methods for empowering parents and children focusing on 1) how to reward courageous behavior and extinguish excessive anxiety, 2) teaching parents to deal with their own upsets and awareness of their own anxiety responses, and 3) brief training in communication and problem-solving. Duration: 12 weeks	CG: Wait-list (N=26) 12-week waiting period, participants still meeting criteria at followup were offered the family intervention treatment	Some concerns
Birmaher et al, 2003[73]	U.S. RCT NIMH. Eli Lily provided fluoxetine and placebo	Recruited through advertisements and from an outpatient clinic	IG1: Fluoxetine (N=37) Description: Fluoxetine (10 mg/day, after first week increasing to 20 mg/day if tolerated). Duration: 12 weeks	CG: Placebo (N=37) Placebo	Some concerns
Black et al, 1994[74]	U.S. RCT NR	Recruited through announcements to school counselors in all elementary schools in Maryland, Virginia, and the District of Columbia	IG1: Fluoxetine (N=6) Description: Fluoxetine 0.2 mg/kg for 1 week, then 0.4 mg/kg for 1 week, then 0.6 mg/kg for 10 weeks. Duration: 12 weeks	CG: Placebo (N=9) Placebo syrup for 12 weeks	Some concerns
Cobham et al, 2017[77] ACTRN12615000514505	Other very high HDI Australia RCT Triple P is owned and distributed by the University of Queensland	Recruited through media and schools	IG1: Group parent-only in-person CBT (N=33) Description: Six 90-minute parent-only group-based CBT sessions focused on psychoeducation about parents role in the maintenance of anxiety, promoting emotional resilience, understanding the role of thoughts in anxiety and how to challenge them, avoidance and exposure, comment parental responses to children's anxiety, promoting coping, and maintaining gains. Concepts are translated into homework tasks and parents are encouraged to apply these principles and instruct children in the content they are learning. Duration: 6 weeks	CG: Wait-list control (N=30) Families in the wait-list condition were reassessed following the 6-week wait and then received the intervention	Low/ some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Cornacchio et al, 2019[79] NA	U.S. RCT National Institute of Health; American Psychological Association Division 53 Society for Clinical Child and Adolescent Psychology	Selective mutism specialty treatment center in metropolitan region in the southeast U.S. Families were typically referred by other programs or professionals in the field, their school, or by reading about the program online or in the news.	IG1: Group child+parent in-person CBT (N=14) Description: 5 consecutive days of 6- to 8-hour treatment; intensive group CBT program centered around graduated exposure to verbal communication that relies on the early child format of Parent Child Interaction Therapy. Each group consisted of approximately 10 children of similar age with a ratio of 1 staff counselor to 1 child. Child group treatment sessions occurred Monday to Friday and focused on verbalizations and social strategies. Staff relied on Child Directed Interaction and Verbal Directed Interaction skills and employed reinforcement, prompting, shaping, stimulus fading, graduated exposure, social skills training, cognitive strategies, relaxation training, and modeling strategies. Parent group training sessions occurred Monday to Thursday for 2 hours each session and focused on psychoeducation about selective mutism, interaction strategies for optimizing positive relationships, and eliciting verbal behavior. Therapists coached parents in vivo with their child in the implementation of these skills. Duration: 5 days	CG: Wait-list control (N=15) Wait-list control, following a 4-week period group CBT was offered to wait-list families.	Some concerns
Donovan et al, 2014[83] ACTRN12612000139875	Other very high HDI Australia RCT Australian Rotary Health	Recruited through media releases, general practitioners, childcare, and school newsletters throughout Australia.	IG1: Individual parent-focused internet CBT (N=23) Description: Online individual parent-focused CBT; six 1-hour session and 2 boosters, one telephone call and weekly emails from online therapist. Content of sessions: psychoeducation about anxiety, strategies for managing anxious child behavior, relaxation, coping self-talk, exposure, and social problem-solving. Duration: 6 sessions (8 weeks)	CG: Wait-list (N=29) Wait-list	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Ginsburg et al, 2020[92]	U.S. Other Institute of Education Sciences, U.S. Department of Education	Recruited via referrals from clinicians, school personnel, parents, or self-referrals.	IG1: Individual child-focused in-person CBT (N=148) Description: Modular CBT consisted of 7 core modules: psychoeducation, exposure, rewards, cognitive restructuring, problem-solving, somatic/relaxation skills, and relapse prevention; an optional parental psychoeducation module was available. Treatments were administered individually over 12 sessions, with each session lasting 30 to 40 minutes. Duration: 12 weeks	CG: TAU (N=68) TAU reflected the therapeutic strategies that clinicians would typically provide to students with anxiety (e.g., supportive therapy).	Some concerns
Hirshfeld-Becker et al, 2010[98]	U.S. RCT NIH, Mass General Hospital Brandon Shedd Fund	Recruited from an outpatient child psychiatry clinic at a general hospital; through print advertisements in local newspapers and parent magazines, email advertisements to hospital employees, and posters at local pediatric practices	IG1: Individual child+parent in-person CBT (N=34) Description: Being Brave manualized CBT intervention included up to 20 sessions over 6 months. First 6 sessions and session 20 were parent only, with a flexible number of parent-child sessions ranging from 8 to 13 depending on number needed to complete exposure exercises to several feared situations. Content of sessions 1 to 3 includes learning about anger management and modeling coping skills; content of sessions 4 to 6 includes coaching the child in anxiety management; content of parent-child sessions 7 to 19 involves child anxiety management such as coping plans and graduated exposure. Parent-only session 20 covers maintaining gains. Duration: 6 months	CG: Wait-list control (N=30) Wait-list control, participants offered treatment after 6 months.	Some concerns
Holmes et al, 2014[99] ACTRN12612000061831	Other very high HDI Australia RCT Griffith University Behavioural Basis of Health	Referred by parents, teachers, guidance officer networks, school newsletters, child and youth mental health services, and social media forums.	IG1: Group child-focused in-person CBT (N=20) Description: 10 weekly group-based 90-minute sessions followed by two booster sessions, conducted 1 and 3 months after the completion of the initial program. Parents concurrently complete seven 90-minute sessions as well as the two booster sessions. The group CBT program termed "No Worries!" utilizes the A-B-C model and provides psychoeducation about anxiety and worry and relaxation training. The majority of the program targets children's intolerance of uncertainty, positive and negative beliefs about worry, negative problem orientation, cognitive avoidance, sleep issues associated with worry, and perfectionism. Duration: 10 weeks	CG: Wait-list control (N=22) After 12 weeks participants in the wait-list condition were reassessed and offered the treatment program.	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Ishikawa et al, 2019[103]	Other very high HDI Japan RCT Japan Society for the Promotion of Science	Recruited using advertisements displayed at schools, public mental health clinics, and in newspapers and websites.	IG1: Individual child+parent in-person CBT (N=26) Description: Japanese Anxiety Children/Adolescents Cognitive Behavior Therapy program (JACA-CBT) adapted over 4 phases to allow increased suitability for Japanese children. CBT was provided once per week for 8 sessions and homework was assigned between the sessions. Booster sessions mainly focused on the family's implementation of the in vivo exposures in their daily life and were provided once per 1 to 3 months and until 6 months after the completion of therapy depending on the needs of each participant. Duration: 8 weeks, with up to 3 subsequent booster sessions until 6 months after completion of therapy	CG: Wait-list (N=25) Wait-list participants visited the clinic 2 months after the pretreatment assessment for a second assessment session (mean [SD] 70.0 days [11.0]), after which they started to participate in the CBT program	Some concerns
Lau et al, 2010[110] NR	Other very high HDI Hong Kong, China RCT NR	Referred by physicians or psychologists to the Child Assessment Service for one or more of the following concerns: learning, behavior, mood-related, anxiety, and other developmental problems.	IG1: Group child+parent in-person CBT (N=26) Description: Nine 2-hour weekly sessions (8 sessions followed by a 2-week break and 1 final session) of the Coping Cat CBT group-treatment program. Sessions included the use of puppet play, competitive games, worksheets, and question-and-answer format to cover core CBT elements, including recognizing anxiety symptoms, combating cognitive bias with cognitive restructuring, practicing gradual exposure to anxiety-provoking stimuli, and evaluating and rewarding one's coping. Parents were invited to observe treatment to learn coaching techniques and asked to provide real-world practice opportunities for their children during the week. Children were asked to complete worksheets. Duration: 11 weeks	CG: Wait-list control (N=25) After completing the baseline and second assessment, children in the wait-list condition received the 9-session treatment followed by a posttreatment assessment.	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Lyneham et al, 2006[112] NR	Other very high HDI Australia RCT Financial Markets Foundation for Children	Self-referrals to clinic in response to recommendations from counselor, teacher, local community health services, or after seeing advertisement in school newsletter.	IG1: Parent-guided CBT supported by telephone (N=28) Description: Parents received a self-help book (Helping Your Anxious Child: A Step by Step Guide for Parents) and a workbook companion that broke the program into 12 weekly modules. A child's workbook was provided that described each anxiety management skill in child-friendly language and included example applications as well as practice exercises. Each week parents were directed to read sections of the self-help book and complete activities to apply what they learned, and to complete certain activities with their child. Daily practice tasks were provided to reinforce weekly activities. Parents received 9 telephone calls. Phone calls occurred weekly for the first 6 weeks and then biweekly for the last 6 weeks. IG2: Parent-guided CBT supported by email (N=21) Description: Parents received a self-help book (Helping Your Anxious Child: A Step by Step Guide for Parents) and a workbook companion that broke the program into 12 weekly modules. A child's workbook was provided that described each anxiety management skill in child-friendly language and included example applications as well as practice exercises. Each week parents were directed to read sections of the self-help book and complete activities to apply what they learned, and to complete certain activities with their child. Daily practice tasks were provided to reinforce weekly activities. Parents received 9 emails—emails occurred weekly for the first 6 weeks and then biweekly for the last 6 weeks.	CG: Wait-list (N=22) Families allocated to the wait-list condition were sent a confirmation letter indicating when their second assessment would take place. Families were given the choice of completing the treatment program by phone, email, or on their own.	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Lyneham et al, 2006[112] NR (continued)			IG3: Parent-guided CBT with as needed support (N=29) Description: Parents received a self-help book (Helping Your Anxious Child: A Step by Step Guide for Parents) and a workbook companion that broke the program into 12 weekly modules. A child's workbook was provided that described each anxiety management skill in child-friendly language and included example applications as well as practice exercises. Each week parents were directed to read sections of the self-help book and complete activities to apply what they learned, and to complete certain activities with their child. Daily practice tasks were provided to reinforce weekly activities. Parents were given the option to contact their therapist by phone or email as many times as they needed during the 12-week period. All contact with therapist was parent initiated. Duration: 12 weeks		
Ost et al, 2015[120]	Other very high HDI Sweden RCT Swedish Council for Working Life and Social Research; Swedish Research Council	Recruited through referrals from the child psychiatric services and school health services in Stockholm County, Sweden	IG1: Individual+group child (N=16) Description: 12 individual weekly sessions plus 12 social skills group weekly sessions. Individual sessions focused on exposure to situations causing anxiety. Group social skills training on topics such as introducing oneself, starting a conversation, making phone calls, and assertiveness training. Therapist introduced importance of topic, demonstrated the skill, and then youth practiced skill. IG2: Child+parent in-person CBT (N=16) Child Treatment same as IG1 Description: Parent training consisted of 8 sessions of 90 minutes run concurrently with child's treatment. First 4 sessions were weekly then last 4 were biweekly. Sessions designed to teach parents about SocAD and how they can help their children in general and with practicing skills learned in group sessions, not reinforcing anxious behavior, modeling socially proactive behavior, and encouraging youth to participate in social activities. Duration: 12 weeks	CG: Wait-list (N=23) Wait-list	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Perrin et al, 2019[122] ISRCTN50951795	Other very high HDI United Kingdom RCT National Institute of Health Research, Guy's & St Thomas' Charity, NIHR Biomedical Research Centre at the South London, Maudsley NHS Foundation Trust and King's College London	Recruited from referrals to child and adolescent mental health services and a specialist child anxiety disorders clinic in the United Kingdom	IG1: Individual child+parent in-person+internet CBT (N=20) Description: 10 sessions of individual, GAD-specific CBT. Sessions proceeded sequentially through 6 modules: worry awareness training, planned exposure to uncertainty; modification of dysfunctional beliefs about worry; modified problem-solving training; imaginal exposure to unpleasant images or worries; and relapse prevention. During each session the therapist would elicit a concrete episode of worry from the past week that was tied to behavioral experiments and imaginal exposures. Homework tasks were provided and included: pausing several times a day to reflect upon, write down, and distinguish between worries about current problems vs. hypothetical situations; plan daily confrontations with situations that involve uncertainty and normally trigger worries; reducing requests for reassurance from others; practicing behavioral experiments to test dysfunctional beliefs; engaging in self-guided exposures to the context of worries to test tolerance of uncertainty and distress. Duration: 10 weeks	CG: Wait-list control (N=20) Wait-listed participants were provided information about the prevalence of worry and GAD, 10 copies of the self-report measures of worry (PSWQ-C) and pre-paid envelopes. Wait-list participants were asked to complete and return the PSWQ-C at the end of each week for 10 weeks.	Low/ Some Concerns
Pine et al, 2001[124] Walkup et al, 2001[213] Ginsburg et al, 2006[214] Reinblatt et al, 2009[215]	U.S. RCT NIMH, Research Foundation for Mental Hygiene; National Center for Research Resources - NIH General Clinical Research Center	Recruited from clinics at 5 academic medical centers.	IG1: Fluvoxamine (N=63) Description: Fluvoxamine 50 mg daily to start, then increased 50 mg per week to a maximum of 300 mg per day in adolescents and 250 mg per day in children younger than 12 years of age. Duration: 8 weeks	CG: Placebo (N=65) Placebo	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Rudy et al, 2017[129] NCT02051192	U.S. RCT NR	Children who presented to a university-based clinic for inclusion in an RCT evaluating the effectiveness of a behaviorally-based, parent-led treatment approach	IG1: Individual parent-led in-person CBT, (N=12) Description: Ten 60- to 90-minute sessions, twice weekly over 5 weeks. The first session focused on psychoeducation and treatment preparation and only included parents. The subsequent 9 sessions consisted of exposure therapy using participant modeling and reinforced practice of behavioral techniques for alleviating anxiety. Sessions 2 to 5 were therapist-led while parents observed. Sessions 6 to 10 were parent-led with the therapist serving as a coach and providing in the moment feedback. Families were encouraged to complete daily home exercises that aligned with skills practiced in session. Duration: 5 weeks	CG: TAU (N=10) Patients randomized to the TAU condition were instructed to continue receiving any prior interventions as recommended by their providers (e.g., psychotherapy, social skills training, behavioral interventions, family participation in family therapy or a parenting class, or pharmacoligcal interventions). Treatment changes were not prohibited but monitored.	Some concerns
Rynn et al, 2001[130]	U.S. RCT University of Pennsylvania and NIMH	Referrals by psychiatrists and pediatricians	IG1: Sertraline (N=11) Description: Sertaline once daily, 25 mg for the first week and 50 mg for weeks 2 to 9. Duration: 9 weeks	CG: Placebo (N=11) Placebo	Some concerns
Salzer et al, 2018[42,] ISRCTN 22752528	Other very high HDI Germany RCT German Federal Ministry of Education and Research	Recruited from outpatient clinics at universities in 4 German cities via mass media announcements or referral by private practice therapists and physicians.	IG1: Individual child-focused in-person CBT (N=34) Description: 25 individual 50-minute treatment sessions as well as up to 5 preparatory sessions. CBT focused on reducing self-focused attentional and safety behaviors through use of role plays, attentional training, and behavioral experiments. Duration: 31 weeks	CG: Wait-list control (N=39) Wait-list; after a waiting period of 4 months, patients were offered an active treatment, either CBT or psychodynamic therapy	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Sanchez-Garcia et al, 2009[131] NR	Other very high HDI Spain RCT Ministry of Science and Education; Seneca Foundation	Recruitment occurred in two phases. In phase 1, 2,931 students in 17 public and semi-public educational centers in the Region of Murcia completed the Inventory of Anxiety and Social Phobia (SPAI-C) and the revised Social Anxiety Scale for Children (SASC)	IG1: Individual+group child-focused in-person CBT (N=28) Description: 12 weekly group sessions, each lasting 90 minutes, referred to as Intervencion en Adolescentes con Fobia Social (IAFS). Group sessions are designed to expose participants to feared social situations and consist of four components: 1) education (information on treatment is provided, explanatory model of social phobia is presented, objectives are planned); 2) training in social skills (starting and holding conversations, assertiveness, making and maintaining friends, public speaking); 3) exposure (exposure to situations listed above such as starting and maintaining conversations with audiovisual, video, and group feedback provided); and 4) cognitive restructuring (a combination of Beck's cognitive therapy and Ellis's rational emotional therapy are used). IG2: Group CBT without cognitive restructuring (N=29) Description: 12 weekly group sessions, each lasting 90 minutes, termed IAFS. Group sessions are designed to expose participants to feared social situations and consist of three components: 1) education (information on treatment is provided, explanatory model of social phobia is presented, objectives are planned); 2) training in social skills (starting and holding conversations, assertiveness, making and maintaining friends, public speaking); and 3) exposure (exposure to situations listed above such as starting and maintaining conversations with audiovisual, video, and group feedback provided). Duration: 12 weeks	CG: Wait-list control (N=25) Participants in the wait-list control began receiving treatment after the first followup evaluation at 6 months	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Shortt et al, 2001[134]	Other very high HDI Austrailia RCT NR	Recruited from child mental health centers, school guidance officers, and parents who responded to advertisements	IG1: Group child+parent in-person CBT (N=54) Description: 10 weekly Family Based Cognitive Behavioral therapy sessions termed "FRIENDS" with 5 to 13 children and 1 or more parents per family. Sessions included a 10-minute joint parent-child meeting to provide outline of session and homework; a 50- to 60-minute youth session; a 5-minute session after youth session with parents to review strategies to practice, and a 30- to 40-minute parent session. Booster sessions were given at 1 and 3 months following the end of treatment. Program adapted from Coping Koala Workbook, which was adapted from the Coping Cat Workbook. Duration: 10 weeks	CG: Wait-list (N=17) Wait-list	Some concerns
Stjerneklar et al, 2019[141] NCT02535403	Other very high HDI Denmark RCT Trygfonden and Edith and Godtfred Kirk Christiansens Fund	Families self-referred after reading announcements on website or learning about study from community health services	IG1: Individual child-focused internet CBT (N=35) Description: Based on Cool Kids and Chilled anxiety management program; 8 online sessions of CBT of approximately 30 minutes each plus homework practice that focuses on psychoeducation, cognitive restructuring, and graded exposure. Content includes goal setting, realistic thinking, problem-solving, and assertiveness and is presented using a variety of formats such as text, audio, illustration, cartoons, worksheets, and video vignettes. Youth rate the interference of anxiety in their lives weekly. Youth received a 20-minute weekly call from their therapist. Parents were given a resource describing their role in treatment and the treatment's core strategies; parents were encouraged to provide support and encouragement to their youth. Therapists called parents within first 2 weeks to answer questions. Duration: 14 weeks	CG: Wait list control group (N=35) Wait-list, participants asked not to engage in other forms of treatment or make changes to their use of psychiatric medication. Participants offered treatment after 14 weeks.	Low/ Some Concerns
Strawn et al, 2015[142] NCT01226511	Multicountry United States, Mexico, and South Africa RCT Eli Lilly and Company	NR	IG1: Duloxetine (N=135) Description: Flexibly dosed duloxetine (30 to 120 mg once daily). Duration: 10 weeks	CG: Placebo (N=137) Placebo	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Strawn et al, 2020[143] NCT02818751	U.S. RCT National Institute of Mental Health, NIH	Recruited from a single academic site	IG1: Escitalopram (N=26) Description: Escitalopram (forced titration to 15 mg/d, then flexible titration to 20 mg/d). Duration: 8 weeks	CG: Placebo (N=25) Placebo	Low/ Some Concerns
Thirlwall et al, 2013[145] ISRCTN92977593	Other very high HDI United Kingdom RCT Medical Research Council	Recruited from referrals made to community mental health services anxiety clinic from primary and secondary care	IG1: Parent-delivered brief CBT (N=61) Description: Parents were given a self-help book and received bimonthly therapist contact over 8 weeks, involving two 1-hour in-person sessions and two 20-minute phone sessions (2 hours and 40 minutes of therapist guidance). Sessions covered causal and maintaining factors of anxiety; how to identify and challenge child anxious thoughts; parental responses to child anxiety and graduated exposure; and problem-solving. Parents completed homework tasks between sessions independently and with their child. IG2: Parent-delivered full CBT (N=64) Description: Parents were given a self-help book and received weekly therapist contact over 8 weeks, involving four 1-hour in person sessions and four 20-minute phone sessions (5 hours and 20 minutes of therapist guidance). Sessions covered causal and maintaining factors of anxiety; how to identify and challenge child anxious thoughts; cognitive restructuring; graduated exposure; and problem-solving. Parents completed homework tasks between sessions independently and with their child. Duration: 8 weeks	CG: Wait-list control (N=69) Wait-list families were asked to refrain from starting any other intervention for children's anxiety for 12 weeks. Following posttest assessments at 12 weeks, wait-list families who still required treatment were offered guided parent-delivered CBT	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Villabo et al, 2018[150] NR	Other very high HDI Norway RCT NR	Recruited from child and adolescent mental health service clinics in southeastern Norway	IG1: Individual CBT (N=55) Description: Based on Norwegian translation of the CopingCat manual. 14 sessions (12 child sessions and 2 parent sessions) focused on anxiety management skills and tailored behavioral exposures to anxiety-provoking situations. IG2: Group CBT (N=55) Description: 14 sessions (12 child and 2 parent sessions) delivered in group format over 12 weeks consisting of CBT using the Coping Cat manual. Each child received training in anxiety management skills and behavioral exposure to anxiety provoking situations. Met individually with 1 of the 2 group therapists for the first 3 sessions, then sessions 4 to 14 in a group with 3 to 5 participants. Duration: 12 weeks	CG: Wait-list (N=55) Following the 12 week wait-list period participants were re-randomized to one of of the two treatment formats.	Some concerns
Waite et al, 2019[152] ISRCTN79652741	Other very high HDI United Kingdom RCT National Institute for Health Research (NIHR) Clinical Research Network, Medical Research Council (MRC) Clinical Research Training Fellowship	Recruitment from referrals to a child and adolescent mental health services clinic	IG1: Individual child+parent internet CBT (N=30) Description: A 10-week intervention with 10 treatment sessions and 2 booster sessions of internet-delivered CBT anxiety management strategies (psychoeducation, relaxation training, recognition of the physiological symptoms of anxiety, cognitive strategies of coping, self-talk and cognitive restructuring, graded exposure, and problem-solving) with accompanying parent sessions for half the group and no parent sessions for the other half. Duration: 10 weeks	CG: Wait-list control (N=30) Wait-list control for 10 weeks	Some concerns

Appendix I Table 17. Anxiety Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Walkup et al, 2008[153] Albano et al, 2018[205] Taylor et al 2018[206] Compton et al, 2014[207] Caporino et al, 2017[216] Sachez et al, 2019[208] Rynn et al, 2015[209] Gordon-Hollingsworth et al, 2015[210] Ginsburg et al, 2011[211] NCT00052078	U.S. RCT NIMH; Pfizer provided sertraline and matching placebo free of charge	Participants were recruited (not reported how) by investigators at medical centers in 6 cities (Durham, NC; New York, NY; Baltimore, MD; Philadelphia, PA, Los Angeles, CA; Pittsburgh, PA).	IG1: Individual child-focused in-person CBT (N=139) Description: 60-minute sessions of 12 individual CBT using Coping Cat program adapted for the child's age and length of the study and 2 parent-only sessions. Therapy included training in anxiety management skills and behavioral exposure to anxiety-provoking situations. Parents attended weekly check-ins and 2 parent-only sessions. IG2: Sertraline (N=133) Description: Sertraline, beginning with 25 mg/day, up to 200 mg/day by 8th week, for 12 weeks. IG3: CBT + Sertraline (N=140) Description: Sertraline, beginning with 25 mg/day, up to 200 mg/day by 8th week, for 12 weeks. Plus 12 sessions of 60-minute individual Coping Cat CBT, including training in anxiety management and exposure to anxiety-provoking situations as well as 2 parent-only sessions. IG3: CBT + Sertraline (N=140) Description: Sertraline, beginning with 25 mg/day, up to 200 mg/day by 8th week, for 12 weeks. Plus 12 sessions of 60-minute individual Coping Cat CBT, including training in anxiety management and exposure to anxiety-provoking situations as well as 2 parent-only sessions. Duration: 12 weeks	CG: Placebo (N=76) Pill placebo	Some concerns

Abbreviations: A-B-C= antecedents, behavior, consequences; CBT=cognitive behavioral therapy; CG=control group; FAM=Family Anxiety Management; GAD=generalized anxiety disorder; HDI=Human Development Index; IAFS=Intervencion en Adolescentes con Fobia Social; IG=intervention group; JACA-CBT=Japanese Anxiety Children/Adolescents Cognitive Behavior Therapy; KQ=key question; MRC=Medical Research Council; NA=not available; NHS=National Health Service; NIH=National Institutes of Health; NIHR=National Institute for Health Research; NIMH=National Institute of Mental Health; NR=not reported; PSWQ-C=Penn State Worry Questionnaire for Children; RCT=randomized, controlled trial; SASC=Social Anxiety Scale for Children; SD=standard deviation; SocAD=social anxiety disorder; SPAI-C=Social Phobia and Anxiety Inventory for Children; TAU=treatment as usual; U.S.=United States; WL=wait-list; WLC=waitlist control.

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Arendt et al, 2016[65]	Mean age (SD): 11.8 (2.7) N (%) Female: 62 (57) Race/Ethnicity: NR	An anxiety disorder as the primary diagnosis	Psychosis, untreated ADHD, intellectual disability and severe behavior disorders.	Primary diagnosis SepAD: 33.0% GAD: 23.9% SocAD: 15.6% Specific phobia: 14.7% OCD: 7.3% Panic disorder with agoraphobia: 0.9% Agoraphobia without panic disorder: 4.6% Comorbid diagnoses Anxiety disorders: 70.6% No comorbidity: 15.6% Externalizing disorders: 11.9% Mood disorder: 9.2% Other: 6.4%
Asbrand et al, 2020[67] TU 78/5-2, HE 3342/4-2	Mean age (SD): IG1: 11.5 (1.35) CG: 11.2 (1.33) N (%) Female: IG1: 16 (51.6) CG: 24 (67.6) Race/Ethnicity: NR	Ages 9 to 13 years with a primary diagnosis of SocAD	Health problems (e.g., asthma, cardiac arrhythmia) and medication (e.g., methylphenidate) that could have interfered with psychophysiological assessment.	SocAD: 100% Comorbid diagnoses: IG1: 41.9% CG: 45.9%
Barrett et al, 1996[70]	Mean age (SD): IG1: 9.7 (2.5) IG2: 10.1 (1.9) CG: 8.2 (1.9) N (%) Female: 34 (43) Race/Ethnicity: NR	Has a principal diagnosis of overanxiety disorder, separation anxiety disorder, or social phobia.	Intellectual or physical disabilities, currently taking antianxiety or depression medication, or parents were involved in acute marital breakdown.	Principal diagnosis Overanxiety disorder: 38% SepAD: 38% Social phobia: 24% Other comorbid conditions Depression: 6% Simple phobia: 22% Oppositional disorder: 2%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Birmaher et al, 2003[73]	Mean age (SD): 11.8 (2.8) N (%) Female: 40 (54) Race/Ethnicity: 71 (96) White 1 (1) Asian 2 (3) Biracial	Ages 7 to 17 years with DSM-IV GAD, SAD, and/or SP who had significant impairment in functioning	Current MDD; lifetime bipolar, OCD, PTSD, eating disorder, substance abuse, PDD, and mental retardation; significant medical and neurological illness; prior trials with SSRIs; current medications that may affect the central nervous system; or pregnancy.	Primary target conditions (participants could have more than 1 condition) SepAD: 47% GAD: 64% SocAD: 55% Other comorbid conditions (past or current, participants could have more than 1 condition) Past or current simple phobia: 24% Past MDD: 4% Past or current dysthymia: 4% Past of current ADHD: 5% Past or current ODD: 4%
Black et al, 1994[74]	Mean age (SD): 8.5 (NR) N (%) Female: 9 (60) Race/Ethnicity: NR	Ages 6 to 16 years meeting DSM-III criteria for selective mutism	Mental retardation, major medical illness, being treated with medication, mutism symptoms were improving rapidly, less than 14 weeks left in school term, or parents did not speak English.	Primary condition Selective mutism: 100% Comorbid conditions SocAD and/or avoidant disorder: 100% Simple phobia: 33% SepAD: 13% Overanxious disorder: 13% ODD: 13% OCD: 7%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Cobham et al, 2017[77] ACTRN12615000514505	Mean age (SD): 9.3 (2.0) N (%) Female: IG1: 19 (59) CG:11 (38) Race/Ethnicity: IG1: White: 28 (88) CG: White: 27 (93)	Ages 7 to 14 years meeting diagnostic criteria for a primary DSM-IV anxiety diagnosis and whose parents were able to attend treatment; participants with secondary non-anxiety diagnoses were not excluded	Ongoing treatment including psychological or medication for the child's anxiety.	IG1 Primary/target condition % GAD: 38% SocAD: 13% SepAD: 25% Specific phobia: 19% OCD: 3% Other comorbid conditions % ADHD: 13% ODD: 9% Dysthymia: 3% MDD: 3% Depression NOS: 3% CG Primary/target condition % GAD: 38% SocAD: 41% SepAD: 10% Specific phobia: 10% OCD: 0 Other comorbid conditions % ADHD: 14% ODD: 3% Dysthymia: 3% MDD: 3% Depression NOS: 0

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Cornacchio et al, 2019[79] NA	Mean age (SD): 6.6 (1.3) N (%) Female: 22 (76) Race/Ethnicity: White: 24 (83) Black: 2 (7) Asian: 2 (7) Other: 1 (3) Hispanic/Latino: 10 (35)	Ages 5 to 9 years who met DSM-5 criteria for selective mutism. Children with comorbid anxiety disorders, taking stable doses of psychotropic medication (no starting/stopping, dose changes 6 weeks prior to baseline through posttreatment assessment) were included (17% of sample reported taking stable does of psychotropic medication). Required to cease non-study psychotherapeutic activities before baseline assessment through posttreatment assessment.	Presence of comorbid mental health condition more impairing than selective mutism, or nonverbal with both parents.	Primary condition % Selective mutism: 100% Other comorbid conditions % SocAD: 72% SepAD: 28% GAD: 24% Specific phobia: 10% OCD: 7% ADHD: 7%
Donovan et al, 2014[83] ACTRN12612000139875	Mean age (SD): 4.1 (0.76) N (%) Female: 28 (54) Race/Ethnicity: NR	Ages 3 to 6 years, primary diagnosis of SocAD, SepAd, GAD, or specific phobia using parent version of Anxiety Disorders Interview Schedule-Child Version	PDD or already receiving psychological treatment.	Primary/target condition SocAD: 56% SepAD: 25% GAD: 2% Specific phobia: 12% Selective mutism: 6% Mean (SD) number of anxiety diagnoses: 2.02 (1.02)
Ginsburg et al, 2020[92]	Mean age (SD): 10.9 (3.3) N (%) Female: 105 (48.6) Race/Ethnicity: Non-Hispanic White: 138 (63.9) Other: 62 (28.7)	Ages 6 to 18 years meeting DSM-IV criteria for a primary anxiety disorder (disorder with the highest CSR). Participants could be on stable doses of medication for a psychiatric disorder.	Medical or psychiatric condition contraindicating study treatment, needing immediate or alternative treatment, receiving psychosocial treatment for anxiety, or in the custody of state social services.	Primary diagnosis % SepAD: 13% SocAD: 22% GAD: 62% Specific phobia: 1% Not otherwise specified: 2% % with comorbid diagnosis SepAD: 10% SocAD: 23% GAD: 17%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Hirshfeld-Becker et al, 2010[98]	Mean age (SD): 5.4 (1.0) N (%) Female: 34 (53) Race/Ethnicity: White: 41 (80) Latino: 2 (3) Asian: 5 (8) Biracial/unknown: 6 (9)	Ages 4 to 7 years with a current DSM-IV anxiety diagnosis.	Parental active psychosis, suicidality, or substance abuse; child mental retardation; current psychiatric treatment or past CBT; consensus of two senior clinicians that child was too uncooperative or distractible or too severely symptomatic to wait 6 months to receive treatment.	77% had more than 1 anxiety disorder GAD: 44% SocAD: 67% SepAD: 44% Agoraphobia: 36% Specific phobia: 48%
Holmes et al, 2014[99] ACTRN12612000061831	Mean age (SD): 9.6 (1.4) N (%) Female: 28 (67) Race/Ethnicity: NR	Ages 7 to 12 years meeting DSM-IV criteria for a primary diagnosis of GAD with an ADIS-C/P CSR of at least 4 and a minimum reading level of 7 years.	Diagnosis of behavioral problems more impairing than anxiety, PDD, intellectual handicap, learning disability, or presence of substance abuse, self-harm, or suicidal ideation, currently receiving psychological assistance or medical treatment.	Primary condition: GAD: 100% Other comorbid conditions: SepAD: 64% Specific phobia: 88% SocAD: 76% Dysthymia: 7% MDD: 5% ADHD: 21% ODD: 14%
Ishikawa et al, 2019[103]	Mean age (SD): 10.9 (2.0) N (%) Female: 29 (57) Race/Ethnicity: Asian (Japanese): 51 (100)	Ages 7 to 15 years with an anxiety disorder as determined through the ADIS for DSM-IV, agree to attend treatment with their parents, and discontinue other forms of therapy during the study.	PTSD, disruptive behavioral disorders, substance abuse, mental retardation, pervasive developmental disorder, or a psychotic disorder.	Principle diagnosis SepAD: 0% SocAD: 61% GAD: 14% Specific phobia: 18% Depression: 2% Dysthymia: 6% No. of comorbid disorders 1: 25% 2: 29% 3 or more: 45%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Lau et al, 2010[110] NR	Mean age (SD): 8 years 7 months (14 months) N (%) Female: 21 (47) Race/Ethnicity: NR	Ages 6 to 11 years with diagnosed anxiety disorder or with subclinical symptoms of anxiety	Presence of only specific phobia diagnosis or severe hyperactivity symptoms.	Primary condition % GAD: 38% SepAD: 24% SocAD: 51% Subclinical symptoms of anxiety disorders: 18% Other comorbid conditions % ADHD: 14% Developmental coordination disorder: 7% Selective mutism: 7%
Lyneham et al, 2006[112] NR	Mean age (SD): 9.4 (2.0) N (%) Female: 49 (49) Race/Ethnicity: Australian: 90 (90) European: 6 (6) Asian: 1 (1) Other: 3 (3)	Ages 6 to 12 years, living a minimum of 1-hour drive from a specialist anxiety service, and continued medications allowed if on stable doses for 1 month prior to entry	NR	Primary diagnosis % GAD: 40% SepAD: 22% SocAD: 21% OCD: 9% Specific phobia: 7% Panic disorder: 1% Comorbid conditions % Secondary anxiety diagnosis: 86% ODD: 8% Mood disorder: 6% ADHD: 3% Asperger's: 2% Tourette's disorder: 1%
Ost et al, 2015[120]	Mean age (SD): 11.6 (2.0) N (%) Female: 34 (62) Race/Ethnicity: NR	Ages 8 to 14 years meeting DSM-IV criteria for SocAD as the primary diagnosis; severity had to be at least 4 on the clinician severity scale of the ADIS-C/P; duration of the phobia ≥1 year; motivated for treatment; and parents and participants had to agree to discontinue any other therapy or treatment	Having another psychiatric disorder with a higher clinician severity than for SocAD; lack of motivation.	Primary target SocAD: 100% Comorbid conditions Specific phobias: 40% GAD: 21% SepAD: 12% OCD: 4% Panic disorder (±) agoraphobia: 3% MDD: 12% Neurodevelopmental disorders: 7% ODD: 2%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Perrin et al, 2019[122] ISRCTN50951795	Mean age (SD): IG1: 13.2 (2.4) CG: 13.6 (2.8) N (%) Female: IG1: 11 (55) CG: 14 (70) Race/Ethnicity: Ethnic minority IG1: 5 (25) CG: 6 (30)	Ages 10 to 18 years, referred for treatment of anxiety with a current and primary diagnosis of DSM-IV GAD with no other psychiatric problems in need of more urgent treatment, including self-injurious thoughts or behaviors or substances use/abuse, no concurrent psychological or pharmacological treatment for any disorders, and the absence of moderate to severe learning difficulties as evidenced in medical or school records or reported by the referrer or parent.	No other exclusion criteria were applied.	Primary Condition GAD % IG1: 100% CG: 100% Comorbid conditions % SepAD IG1: 40% CG: 10% SocAD IG1: 10% CG: 35% Specific phobia IG1: 5% CG: 0% MDD IG1: 15% CG: 15%
Pine et al, 2001[124] Walkup et al, 2001[213] Ginsburg et al, 2006[214] Reinblatt et al, 2009[215]	Mean age (SD): IG1: 10.4 (2.8) CG: 10.3 (3.1) N (%) ages 6 to 12 years IG1: 48 (76) CG: 47 (72) N (%) Female: 63 (49) Race/Ethnicity: White: 81 (63) Black: 9 (7) Hispanic: 24 (19) Other: 14 (11)	Ages 6 to 17 years, meet criteria for socAD, sepAD, or GAD using DSM-IV, clinically important anxiety symptoms as measured by the PARS, Children's Global Assessment Scale score <60, and willingness to attend clinic weekly.	Current psychopharmacotherapy; current diagnosis of major depression, Tourette's syndrome, OCD, PTSD, panic disorder, or ADHD that required drug therapy; history or current diagnosis of mania, psychosis, or PDD; current suicidal ideation; mental retardation; and previous treatment with an SSRI.	Diagnoses at baseline SepAD: 59% GAD: 57% SocAD: 66% Past or current comorbid conditions ADHD: 16% ODD: 5% MDD: 5% PTSD: 2%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Rudy et al, 2017[129] NCT02051192	Mean age (SD): 5.36 (1.14) N (%) Female: 9 (41) Race/Ethnicity: White: 14 (64) Hispanic: 3 (14) Black: 1 (5) Asian: 1 (5) Other: 3 (14)	Ages 4 to 7 years meeting DSM-IV-TR criteria for a diagnosis of an anxiety disorder or a minimum score of 12 on the PARS and a score ≥70 on the PPVT-IV. Participants taking prescribed psychotropic medication must have been stable (no change in dose or type) for 10 weeks prior to entering the study.	No additional criteria.	Target conditions: SocAD: 23% OCD: 23% SepAD: 14% Selective mutism: 9% Specific phobia: 9% GAD: 5% Anxiety NOS: 5%: Other comorbid conditions ADHD: 45% Disruptive behavioral disorder: 32%
Rynn et al, 2001[130]	Mean age (SD): 11.7 (3.9) N (%) Female: 5 (22.7) Race/Ethnicity: White: 18 (81)	Ages 5 to 17 years meeting DSM-IV criteria for GAD according to the ADIS for Children–Revised, and a Hamilton Anxiety Rating Scale score ≥16	Acute or unstable medical conditions such as diabetes, seizure disorder, severe asthma, or hyperthyroidism; additional axis I or axis II psychiatric disorder, such as MDD, OCD, mental retardation, PDD, eating disorder, schizophrenia, or other psychotic disorders; comorbid ADHD and oppositional defiant disorder; at risk for suicide and/or had abnormal results on the physical examination or laboratory tests.	GAD: 100% Subsyndromal sepAD: 27%
Salzer et al, 2018[42,] ISRCTN 22752528	Mean age (SD): 17.4 (2.0) N (%) Female: 71 (66) Race/Ethnicity: NR	Ages 14 to 20 years with a primary diagnosis of SocAD based on German edition of Kiddie-SADS-Present and Lifetime version.	Psychotic and acute substance-related disorders, organic mental disorders, severe medical conditions, ADHD, PTSD, suicidal ideation; IQ <80; or concurrent psychotherapeutic or psychopharmacological treatments.	Primary/target condition SocAD: 100% Other comorbid conditions Specific phobia: 27% MDD: 24% Dysthymia: 12% GAD: 8%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Sanchez-Garcia et al, 2009[131] NR	Mean age (SD): 11.91 (1.3) N (%) Female: 60 (73) Race/Ethnicity: NR	Age 10 to 14 years meeting ADIS-IV criteria for generalized social phobia	Failure to attend three consecutive sessions.	NR
Shortt et al, 2001[134]	Mean age (SD): 7.9 (1.2) N (%) Female: 42 (59) Race/Ethnicity: Australian: NR (92%) European: NR (7%) Asian: NR (1%)	Ages 6 to 10 years, with one or more of the following principal anxiety disorder diagnoses: GAD, SocAD, or SepAD	Intellectual or severe physical impairment, or currently receiving psychosocial or psychopharmacological interventions.	Primary target condition GAD: 59% SocAD: 14% SepAD: 27% Other comorbid conditions Comorbid GAD: 20% Comorbid specific phobia: 38% Comorbid Sep AD: 16% Comorbid SocAD: 13% Dysthymia: 3% Major depression: 1%
Stjerneklar et al, 2019[141] NCT02535403	Mean age (SD): 15 (1.3) N (%) Female: 55 (79) Race/Ethnicity: NR	Ages 13 to 17 years with diagnosis for primary anxiety disorder according to DSM-IV and who had direct access to a home computer with internet access	Severe comorbid depression, substance abuse, current severe self-harm or suicidal ideation, pervasive developmental disorder, learning disorder or intellectual disability, or psychotic symptoms.	Primary diagnosis SocAD: 40% GAD: 16% Specific phobia: 9% SepAD: 13% PD: 4% PD with agoraphobia: 3% Agoraphobia without PD OCD: 11% (considered as a primary anxiety diagnosis at time of study) Number of comorbid anxiety diagnoses: mean 2.11 (SD 0.93) Other comorbid diagnoses Other anxiety disorder: 73% Mood disorder: 9%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Strawn et al, 2015[142] NCT01226511	Mean age (SD): IG1: 12.6 (3.0) CG: 12.2 (2.9) N (%) Female: IG: 70 (51.9) CG: 75 (54.7) Race/Ethnicity: IG: White: 112 (83.0) Black: 9 (6.7) Multiracial: 6 (4.4) American Indian or Alaska Native: 7 (5.2) Asian: 1 (0.7) Hispanic or Latino: 37 (29.6) CG: White: 111 (81.0) Black: 10 (7.3) Multiracial: 9 (6.6) American Indian or Alaska Native: 6 (4.4) Asian: 1 (0.7) Hispanic or Latino: 40 (31.3)	Ages 7 to 17 years meeting DSM-IV-TR criteria for GAD, assessed using the MINI-Kid, and had a PARS severity for GAD score 15 at two screening visits; CGI-Severity score ≥4 at the two screening visits; and significant social, academic, and/or familial dysfunction as determined by CGAS score of ≤60 at two screening visits	Current MDD or history of bipolar disorder, psychotic disorder, eating disorder, OCD, posttraumatic stress disorder, or panic disorder, had a first-degree relative with bipolar I disorder, represented a serious suicide risk, or had a history of substance abuse/dependence within the past year or an unexplained positive urine drug screen. Current use of antidepressants, antipsychotics, anticonvulsants, anorexics, benzodiazepines, psychostimulants (excluding caffeine), and herbal preparations with central nervous system activity.	SepAD: 18.75% SocAD: 17.65%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Strawn et al, 2020[143] NCT02818751	Mean age (SD): IG1: 14.8 (1.7) CG: 14.9 (1.6) N (%) Female: IG1: 20 (77) CG: 19 (76) Race/Ethnicity: IG1: Asian: 0 (0) Black or African American: 1 (4) White: 23 (88) Other: 2 (8) Hispanic or Latino: 3 (12) CG: Asian: 2 (8) Black or African American: 1 (4) White: 20 (80) Other: 2 (8) Hispanic or Latino: 0 (0)	Ages 12 to 17 years, DSM-IV-TR criteria for GAD assessed using ADIS, PARS score ≥15 and a CGI-S score ≥4	Current MDD or any history of DSM-IV-TR bipolar disorder, psychotic disorder, OCD, or PTSD. Use of antidepressants, antipsychotics, anticonvulsants, stimulants, or benzodiazepines was prohibited.	Primary/target condition % GAD: 100% Comorbid conditions % SepAD: 17.6% Panic disorder: 56.9% Agoraphobia: 27.5% ADHD: 17.6% Specific phobia: 3.5%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Thirlwall et al, 2013[145] ISRCTN92977593	Mean age (SD): NR N (%) Female: IG1: 30 (49) IG2: 30 (47) CG: 34 (49) Race/Ethnicity: IG1 White: 53 (87) IG2 White: 55 (86) CG White: 58 (84)	Ages 7 to 12 years meeting DSM-IV criteria for GAD, SocAD, SepAD, panic disorder, agoraphobia, or specific phobia and primary caregiver available to attend treatment. If taking psychotropic medication, stable dosage for at least 1 month and agreement to maintain dose throughout study.	Significant physical or intellectual impairment (including ASD) in the participating child and significant intellectual impairment or current DSM-IV anxiety disorder or other severe mental health difficulties (MDD, psychosis, substance/alcohol dependence) in the primary caregiver.	Primary condition IG1 SepAD: 23% SocAD: 18% GAD: 26% Other: 33% IG2 SepAD: 25% SocAD: 20% GAD: 25% Other: 30% CG SepAD: 22% SocAD: 25% GAD: 22% Other: 32% Other comorbid conditions IG1 PDD: 2% MDD: 8% ADHD: 12% ODD: 15% IG2 PDD: 5% MDD: 3% ADHD: 8% ODD: 14% CG PDD: 6% MDD: 10% ADHD: 12% ODD: 16%

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Villabo et al, 2018[150] NR	Mean age (SD): 10.5 (1.5) N (%) Female: 75 (45.5) Race/Ethnicity: Caucasian: 163 (98.8) Asian: 1 (0.6) Hispanic: 1 (0.6)	Ages 7 to 13 years with a primary DSM-IV diagnosis of SepAD, GAD, or SocAD, significant functional impairment, an IQ of 70 or higher, and at least one parent proficient in Norwegian.	A mental health disorder with a higher treatment priority, PDD, psychosis, or current use of anxiolytic medication.	Other comorbid conditions % MDD: 3% Specific phobia: 27% ADHD: 19% ODD: 7%
Waite et al, 2019[152] ISRCTN79652741	Mean age (SD): 14.7 (1.42) N (%) Female: 39 (65) Race/Ethnicity: White: 55 (92)	Adolescents ages 13 to 18 years and their parents with a DSM-IV anxiety disorder diagnosis identified as the primary problem	Diagnosis of OCD, if on medication, on stable dose for 2 months and agree to remain on that dose for the trial, parent with no significant intellectual impairment, psychotic symptoms, substance dependence, conduct d/o, autism, learning problems, self-harm behaviors within previous month, or computer and internet access at home.	Primary/target condition % SocAD: 19 (32) GAD: 15 (25) SepAD: 5 (8) Panic with agoraphobia: 7 (12) Panic without agoraphobia: 1 (2) Agoraphobia: 2 (3) Specific phobia: 11 (18) Other comorbid conditions % Dysthymia: 10 (17) MDD: 3 (5) ADHD: 1 (2) ODD: 2 (3) School refusal: 7 (12)

Appendix I Table 18. Anxiety Treatment Studies: Population Characteristics (KQ 4)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/Behavioral Conditions
Walkup et al, 2008[153] Albano et al, 2018[205] Taylor et al 2018[206] Compton et al, 2014[207] Caporino et al, 2017[216] Sachez et al, 2019[208] Rynn et al, 2015[209] Gordon-Hollingsworth et al, 2015[210] Ginsburg et al, 2011[211] NCT00052078	Mean age (SD): 10.7 (2.8) N (%) Female: 242 (50) Race/Ethnicity: White: 385 (79) Black: 44 (9) Asian: 12 (3) American Indian: 6 (1) Pacific Islander: 2 (0) Other: 39 (8) Hispanic: 59 (12)	Ages 7 to 17 years with a primary diagnosis of SepAD, GAD, or SocAD using DSM-IV-TR criteria, substantial impairment, and an IQ ≥80. Children with comorbid psychiatric diagnosis of lesser severity than the target disorders were also included.	Unstable medical conditions; refusal to attend school because of anxiety; failure to have a response to two adequate trials of SSRIs or one adequate trial of CBT; pregnancy or unprotected sexual activity in females; psychoactive medications other than stable stimulant medication; psychiatric diagnosis such as MDD, substance use disorder, unmedicated ADHD, lifetime history of bipolar disease, psychotic disorders, or PDD; those who presented as acute risk to themselves or others.	Primary/target conditions SepAD: 3% SocAD: 11% GAD: 7% SepAD and SocAD: 7% SepAD and GAD: 8% SocAD and GAD: 28% SepAD, SocAD, and GAD: 36% Other comorbid conditions Other internalizing disorder: 44% ADHD: 12% ODD or conduct disorder: 9% Tic disorder: 3%

Abbreviations: ADHD=attention deficit hyperactivity disorder; ADHD= attention deficit–hyperactivity disorder; ADIS=Anxiety Disorders Interview Schedule; ADIS-C=Anxiety Disorders Interview Schedule for DSM-IV for Children-Children; ADIS-IV=Anxiety and Related Disorders Interview Schedule-IV?; ASD=autism spectrum disorder; CBT=cognitive behavioral therapy; CG=control group; CGAS=Children's Global Assessment Scale; CGI=Clinical Global Impressions; CGI-S= Clinical Global Impressions=Severity; CSR=Clinician Severity Rating; DSM=DSM-IV=Diagnostic and Statistical Manual of Mental Disorders; DSM-5=DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; GAD=generalized anxiety disorder; IG=intervention group; IQ=intelligent quotient; KQ=key question; MDD=major depressive disorder; MINI=Mini International Neuropsychiatric Interview; NA=not available; NOS=not otherwise specified; NR=not reported; OCD=obsessive compulsive disorder; ODD=oppositional defiant disorder; PARS=Pediatric Anxiety Rating Scale; PD=panic disorder; PDD=persistent depressive disorder; PPVT-IV= Peabody Picture Vocabulary Test; PTSD=post-traumatic stress disorder; SAD=suicide, anxiety, depression; SD=standard deviation; SepAD=separation anxiety disorder; SocAD=social anxiety disorder; SP=social phobia; SSRI=selective serotonin reuptake inhibitor

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Arendt et al, 2016[65]	IG1: Group child + parent in-person CBT (N=56) CG: Wait-list (N=53)	ADIS CSR primary diagnosis, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 2.16 (2.59) CG: 5.45 (1.90) Time-by-condition effect, P<0.001, partial eta squared=0.35 ADIS CSR all diagnosis, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 5.21 (5.19) CG: 10.75 (5.63) Time-by-condition effect, P<0.001, partial eta squared=0.22 SCAS-youth, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 21.57 (14.42) CG: 32.55 (15.64) Time-by-condition effect, P<0.001, partial eta squared=0.18 SCAS-P mother, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 22.25 (12.59) CG: 37.04 (16.95) Time-by-condition effect, P<0.001, partial eta squared=0.24 SCAS-P father, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 23.56 (13.87) CG: 32.63 (16.17) Time-by-condition effect, P<0.001, partial eta squared=0.19
Asbrand et al, 2020[67] TU 78/5-2, HE 3342/4-2	IG1: Group child-focused in-person CBT (N=31) CG: WLC (N=36)	SPAI-C, posttreatment (12 weeks), ITT (IG1=31; CG=36), Time x Group interaction No group effect, F(2,116.6)=5.87, p=0.899, but a significant interaction effect of Time x Group F(2,116.6)=5.87, p=0.004 favoring CBT SASC-R Child, posttreatment (12 weeks), ITT (IG1=31; CG=36), Time x Group interaction No main effect of Group, F(1,66)=0.39, p=0.534 or Time x Group interaction F(2,115.6)=1.16, p=0.316 SASC-R Parent, posttreatment (12 weeks), ITT (IG1=31; CG=36), Time x Group interaction No main effect of group, F(1,65.2)=0.27, p=0.608 or Time x Group interaction F(2,114.4)=1.01, p=0.366
Barrett et al, 1996[70]	IG1: CBT (N=28) IG2: CBT + family intervention (N=25) CG: Wait-list (N=26)	RCMAS, posttreatment (12 weeks), completer (IG1=28; CG=23), mean (SD) IG1: 9.0 (6.8) CG: 11.6 (6.0) Time x treatment interaction=NS RCMAS, posttreatment (12 weeks), completer (IG2=25; CG=23), mean (SD) IG2: 6.6 (4.6) CG: 11.6 (6.0) Time x treatment interaction=NS

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Barrett et al, 1996[70] (continued)		FSSCR, posttreatment (12 weeks), completer (IG1=28; CG=23), mean (SD) IG1: 119.9 (26.0) CG: 134.3 (32.6) Time x Treatment interaction=NS FSSCR, posttreatment (12 weeks), completer (IG2=25; CG=23), mean (SD) IG2: 114.2 (20.2) CG: 134.3 (32.6) Time x Treatment interaction=NS
Birmaher et al, 2003[73]	IG1: Fluoxetine (N=37) CG: Placebo (N=37)	SCARED-C, posttreatment (12 weeks), ITT (IG1=37, CG=37), mean (SD) IG1: 11.7 (12.4) CG: 14.6 (14.5) Time x Treatment baseline to 12 weeks p=0.03 SCARED-P, posttreatment (12 weeks), ITT (IG1=37, CG=37), mean (SD) IG1: 16.3 (12.7) CG: 22 (12.3) Time x Treatment baseline to 12 weeks p=0.04 PARS, posttreatment (12 weeks), ITT (IG1=37, CG=37), mean (SD) IG1: 7.1 (5.9) CG: 9.3 (4.8) Time x Treatment baseline to 12 weeks p=0.04 CGI-S ≤4, posttreatment (12 weeks) (IG1=37, CG=37), % (SD) IG1: 89.3 (0.06) CG: 83.9 (0.07) Time x Treatment baseline to 12 weeks p=0.007
Black et al, 1994[74]	IG1: Fluoxetine (N=6) CG: Placebo (N=9)	CGI anxiety parent-rated marked or much improved, posttreatment (12 weeks), ITT (IG1=6; CG=9), N (%) IG1: 2 (33.3) CG: 1 (11.1) p=NS CGI generalized anxiety clinician-rated marked or much improved; posttreatment (12 weeks), ITT (IG1=6; CG=9), N (%) IG1: 4 (66.7) CG: 3 (33.3) p=NS CGI social anxiety clinician-rated marked or much improved; posttreatment (12 weeks), ITT (IG1=6; CG=9), N (%) IG1: 4 (66.7) CG: 5 (55.6)

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
		p=NS
Black et al, 1994[74] (continued)		CGI anxiety teacher-rated marked or much improved; posttreatment (12 weeks), ITT (IG1=6; CG=9), N (%) IG1: 5 (83.3) CG: 6 (66.7) p=NS
Cobham et al, 2017[77] ACTRN12615000514505	IG1: Group parent-only in-person CBT (N=33) CG: Wait list control (N=30)	ADIS-CSR, posttreatment (6 weeks), mITT(IG1=33; CG=29), mean (SD) IG1: 3.7 (2.6) CG: 5.4 (1.1) Between-group difference in change from baseline; P<0.001 SCAS-M, posttreatment (6 weeks), mITT(IG1=33; CG=29), mean (SD) IG1: 20.1 (4.9) CG: 32.3 (11.9) Between-group difference in change from baseline; P<0.001 SCAS-F, posttreatment (6 weeks), mITT (IG1=33; CG=29), mean (SD) IG1: 21.4 (14.4) CG: 30.6 (15.2) Between-group difference in change from baseline; p=0.53 SCAS-C, posttreatment (6 weeks), mITT (IG1=33; CG=29), mean (SD) IG1: 34.4 (13.9) CG: 42.1 (11.5) Between-group difference in change from baseline; P<0.01
Cornacchio et al, 2019[79] NA	IG1: Group child+parent in-person CBT (N=14) CG: Wait list control (N=15)	ADIS CSR selective mutism, posttreatment (4 weeks), ITT (IG1=14; CG=15), Mean (SD) IG1: 4.2 (0.9) CG: 4.6 (0.7) Time x Condition interaction P>0.05 Effect size Cohen's d=-0.50 ADIS CSR social anxiety, posttreatment (4 weeks), ITT (IG1=14; CG=15), Mean (SD) IG1: 4.0 (0.8) CG: 3.6 (1.5) Time x Condition interaction P<0.05 Effect size Cohen's d=-0.50 SMQ-P home subscale, posttreatment (4 weeks), ITT (IG1=14; CG=15), Mean (SD) IG1: 2.2 (0.4) CG: 1.7 (0.7) P>0.05 Cohen's d=0.36

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Cornacchio et al, 2019[79] NA (continued)		SMQ-P social subscale, posttreatment (4 weeks), ITT (IG1=14; CG=15), Mean (SD) IG1: 1.2 (0.6) CG: 0.7 (0.7) P<0.05 Cohen's d=0.58
Donovan et al, 2014[83] ACTRN12612000139875	IG1: Individual parent-focused internet CBT (N=23) CG: Wait-list (N=29)	CSR, posttreatment (8 weeks), mITT (IG1=23; CG=27), Mean (SD) IG1: 3.4 (2.4) CG: 4.7 (2.0) Time x treatment p=0.002, partial eta squared 0.176 For ITT population: Time x Treatment p=0.001, partial eta squared=0.188 PAS, posttreatment (8 weeks), mITT (IG1=19; CG=29), Mean (SD) IG1: 30.0 (14.7) CG: 40.2 (17.0) Time x Treatment p=0.011, partial eta squared=0.131 For ITT population: Time x Treatment p=0.66, partial eta squared=0.066
Ginsburg et al, 2020[92]	IG1: Individual child-focused in-person CBT (N=148) CG: TAU (N=68)	CGI-S, posttreatment (12 weeks), ITT (IG=148; CG=68), mean IG: 3.97 CG: 4.15 p=0.38 CGI-S, 12 months, ITT (IG=148; CG=68), mean IG: 3.61 CG: 3.41 p=0.34 SCARED-P, posttreatment (12 weeks), ITT (IG=148; CG=68), mean IG: 20.25 CG: 21.72 Cohen's d=0.29; p=0.05 SCARED-P, 12 months, ITT (IG=148; CG=68), mean IG: 17.74 CG: 15.12 p=0.44 SCARED-C, posttreatment (12 weeks), ITT (IG=148; CG=68), mean IG: 22.82 CG: 23.65 p=0.87

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Ginsburg et al, 2020[92] (continued)		SCARED-C, 12 months, ITT (IG=148; CG=68), mean IG: 19.63 CG: 20.54 p=0.65
Hirshfeld-Becker et al, 2010[98]	IG1: Individual child + parent in-person CBT (N=34) CG: Wait-list control (N=30)	CGI-I SocAD score, posttreatment (6 months), completers (IG1=19, CG=20), mean (SD) IG1: 2.42 (0.96) CG: 3.40 (1.05) P<0.01; Hedge's g=0.95 (95% CI, 0.29 to 1.62) CGI-I SepAD score, posttreatment (6 months), completers (IG1=12; CG=13), mean (SD) IG1: 1.67 (0.98) CG: 2.46 (0.88) p=0.045; Hedge's g=0.82 (95% CI, 0.01 to 1.64) CGI-I GAD score, posttreatment (6 months), completers (IG1=12; CG=12), mean (SD) IG1: 2.17 (0.83) CG: 2.58 (1.38) p=0.38; Hedge's g=NR CGI-I specific phobia score, posttreatment (6 months), completers (IG1=15; CG=15), mean (SD) IG1: 1.87 (1.30) CG: 2.87 (1.19) p=0.037; Hedge's g=0.78 (95% CI, 0.04 to 1.52) CGI-I agoraphobia score, posttreatment (6 months), completers (IG1=9; CG=11), mean (SD) IG1: 2.22 (0.83) CG: 2.55 (1.45) p=0.58
Holmes et al, 2014[99] ACTRN12612000061831	IG1: Group child-focused in-person CBT (N=20) CG: Wait-list control (N=22)	ADIS-C/P CSR, posttreatment (10 weeks), completers (IG1=17, CG=19), mean (SD) IG1: 3.59 (1.3) CG: 6.21 (0.79) P<0.001, partial eta squared=0.43 SCAS-P GAD symptoms, posttreatment (10 weeks), ITT (IG1=20, CG=22), mean (SD) IG1: NR CG: NR Time x Group interaction: p=0.048, partial eta squared=0.09

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Holmes et al, 2014[99] ACTRN12612000061831 (continued)		SCAS-P GAD symptoms, posttreatment (10 weeks), completers (IG1=17, CG=19), mean (SD) IG1: 6.17 (2.71) CG: 6.84 (2.29) Time x Group interaction: p=0.053 SCAS-P total symptoms, posttreatment (10 weeks), completers (IG1=17, CG=19), mean (SD) IG1: 29.94 (12.70) CG: 31.47 (8.79) Time x Group interaction: p=NS SCAS-C GAD symptoms, posttreatment (10 weeks), completers (IG1=17, CG=19), mean (SD) IG1: 7.41 (4.65) CG: 8.42 (4.56) Time x Group interaction: p=NS SCAS-C total symptoms, posttreatment (10 weeks), completers (IG1=17, CG=19), mean (SD) IG1: 34.88 (20.25) CG: 40.84 (19.93) Time x Group interaction: p=NS
Ishikawa et al, 2019[103]	IG1: Individual child + parent in-person CBT (N=26) CG: Wait-list (N=25)	SCAS-C, posttreatment (2 or 4 months), completers (IG=25; CG=24), mean (SE) IG: 28.28 (3.55) CG: 35.95 (3.97) Time x Treatment interaction: p=NS ADIS-DSM-IV CSR, posttreatment (2 or 4 months), ITT (IG=25; CG=24), mean (SE) [on primary diagnosis] IG: 3.08 (0.50) CG: 6.0 (0.51) Time x Treatment interaction: P<0.001 favoring CBT SCAS-P, posttreatment (2 or 4 months), completers (IG=25; CG=24), mean (SE) IG: 25.42 (2.57) CG: 27.57 (2.62) Time x Treatment interaction: P<0.01 favoring CBT
Lau et al, 2010[110] NR	IG1: Group child + parent in-person CBT (N=26) CG: Wait-list control (N=25)	SCAS, posttreatment (13 weeks), mITT (IG1=24; CG=21), mean (SD) IG1: 24.6 (10.5) (9.7 decrease from baseline) CG: 38.8 (13.7) (1.8 increase from baseline) Effect size partial eta squared=0.27 Time x Condition interaction: P<0.001 PSCAS, posttreatment (13 weeks), mITT (IG1=24; CG=21), mean (SD) IG1: 28.8 (10.3) (4.2 decrease from baseline)

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
		CG: 36.5 (11.0) (1.3 increase from baseline) Effect size partial eta squared=0.11 Time x Condition interaction: P<0.05
Lyneham et al, 2006[112] NR	IG1: Parent-guided CBT supported by telephone (N=28) IG2: Parent-guided CBT supported by email (N=21) IG3: Parent-guided CBT with as needed support (N=29) CG: Wait-list (N=22)	ADIS CSR (sum of all anxiety disorders), posttreatment (12 weeks), ITT (IG1=28, IG2=21, IG3=29, CG=22) IG1 vs. CG: Effect size cohen's d: 2.19, P<0.01 IG2 vs. CG: Effect size cohen's d: 1.57, P<0.01 IG3 vs. CG: Effect size cohen's d: 0.80, P<0.01 Time x Treatment interaction across all groups: eta squared=0.49; P<0.01 SCAS-M, pretreatment, ITT (IG1=28, IG2=21, IG3=29, CG=22), mean (SD) IG1: 39.50 (14.94) IG2: 36.00 (14.57) IG3: 34.97 (15.50) CG: 39.23 (13.89) SCAS-M, posttreatment (12 weeks), ITT (IG1=28, IG2=21, IG3=29, CG=22), mean (SD) IG1: 20.36 (16.04) IG2: 21.29 (14.28) IG3: 22.97 (15.20) CG: 37.77 (15.26) SCAS-F, pretreatment, ITT (IG1=28, IG2=21, IG3=29, CG=22), mean (SD) IG1: 32.46 (14.48) IG2: 26.47 (9.91) IG3: 29.80 (16.90) CG: 28.33 (17.68) SCAS-F, posttreatment (12 weeks), ITT (IG1=28, IG2=21, IG3=29, CG=22), mean (SD) IG1: 22.50 (13.48) IG2: 18.76 (10.37) IG3: 19.60 (13.45) CG: 29.50 (18.39) SCAS-C, pretreatment, ITT (IG1=28, IG2=21, IG3=29, CG=22), mean (SD) IG1: 43.54 (16.65) IG2: 35.90 (12.13) IG3: 35.17 (20.66) CG: 37.77 (20.36)

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Lyneham et al, 2006[112] NR (continued)		SCAS-C, posttreatment (12 weeks), ITT (IG1=28, IG2=21, IG3=29, CG=22), mean (SD) IG1: 23.79 (14.84) IG2: 24.86 (12.94) IG3: 25.79 (19.51) CG: 36.41 (21.87) RCMAS-C, pretreatment, ITT (IG1=28, IG2=21, IG3=29, CG=22), mean (SD) IG1: 17.25 (5.72) IG2: 14.14 (6.35) IG3: 14.17 (7.48) CG: 15.59 (7.57) RCMAS-C, posttreatment (12 weeks), ITT (IG1=28, IG2=21, IG3=29, CG=22), mean (SD) IG1: 10.89 (6.55) IG2: 8.67 (6.21) IG3: 10.28 (7.66) CG: 15.73 (7.30)
Ost et al, 2015[120]	IG1: Individual + group child (N=16) IG2: Child + parent in-person CBT (N=16) CG: Wait-list (N=23)	Change in CSR from baseline to posttreatment (12 weeks), ITT (IG1=16; IG2=16; CG=23), mean (SD) IG1: 3.25 (0.39) IG2: 3.69 (1.66) CG: 5.95 (1.15) Time x Treatment: F=26.6, P<0.001. IG1 vs. CG: p=sig, NR, favoring IG1 IG2 vs. CG: p=sig, NR, favoring IG2 Change in SPAI-C from baseline to posttreatment (12 weeks), ITT (IG1=16; IG2=16; CG=23), mean (SD) IG1: 12.5 (8.9) IG2: 19.1 (12.0) CG: 22.8 (9.4) Time x Treatment: F=5.0, P<0.05 IG1 vs. CG: p=sig, NR, favoring IG1 IG2 vs. CG: p=sig, NR, favoring IG2 Change in MASC from baseline to posttreatment (12 weeks), ITT (IG1=16; IG2=16; CG=23), mean (SD) IG1: 35.8 (16.0) IG2: 43.2 (18.1) CG: 54.7 (15.3) Time x Treatment: F=4.6, P<0.05 IG1 vs. CG: p=sig, NR, favoring IG1 IG2 vs. CG: p=NS

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Ost et al, 2015[120] (continued)		Change in SPAI-P from baseline to posttreatment (12 weeks), ITT (IG1=16; IG2=16; CG=23), mean (SD) IG1: 19.8 (10.7) IG2: 24.6 (12.5) CG: 29.8 (8.7) Time x Treatment: F=4.2, P<0.05 IG1 vs. CG: p=sig, NR, favoring IG1 IG2 vs. CG: p=NS Change in FSSCR from baseline to posttreatment (12 weeks), ITT (IG1=16; IG2=16; CG=23), mean (SD) IG1: 109.1 (23.7) IG2: 117.3 (30.2) CG: 119.3 (32.6) Time x Treatment: F=0.8, P>0.05 IG1 vs. CG: p=NS IG2 vs. CG: p=NS
Perrin et al, 2019[122] ISRCTN50951795	IG1: Individual child + parent in-person + internet CBT (N=20) CG: Wait-list control (N=20)	ADIS GAD severity, posttreatment (10 weeks), ITT (IG1=20, CG=20), mean (SD) IG1: 1.9 (2.3) CG: 5.7 (1.1) Effect size partial eta squared=0.54 p<0.001 SCARED-R-C (anxiety), posttreatment (10 weeks), ITT (IG1=20, CG=20), mean (SD) IG1: 15.2 (12.5) CG: 46.3 (15.9) Effect size partial eta squared=0.53 p<0.001 SCARED-R-P (anxiety), posttreatment (10 weeks), ITT (IG1=20, CG=20), mean (SD) IG1: 18.9 (12.4) CG: 38.2 (14.9) Effect size partial eta squared=0.37 p<0.001 SCARED-R-C (GAD), posttreatment (10 weeks), ITT (IG1=20, CG=20), mean (SD) IG1: 4.6 (5.2) CG: 12.9 (4.2) Effect size partial eta squared=0.47 p<0.001 SCARED-R-P (GAD), posttreatment (10 weeks), ITT (IG1=20, CG=20), mean (SD) IG1: 6.5 (4.3) CG: 11.2 (4.7)

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
		Effect size partial eta squared=0.24 p<0.001 PSWQ-C, posttreatment (10 weeks), ITT (IG1=20, CG=20), mean (SD) IG1: 10.6 (12.2) CG: 31.1 (7.2) Effect size partial eta squared=0.54 P<0.001
Pine et al, 2001[124] Walkup et al, 2001[213] Ginsburg et al, 2006[214] Reinblatt et al, 2009[215]	IG1: Fluvoxamine (N=63) IG2: Sertraline (N=133) IG3: CBT + sertraline (N=140) CG: Placebo (N=65)	PARS change in score, baseline to posttreatment (8 weeks), mITT (IG1=61; CG=63), mean (SD) IG1: 9.0 (7.0) CG: 15.9 (5.3) Time x Treatment interaction: P<0.001
Rudy et al, 2017[129] NCT02051192	IG1: Individual parent-led in-person CBT (N=12) CG: TAU (N=10)	ADIS CSR, posttreatment (5 weeks), ITT (IG1=12; CG=10), mean (SD) IG1: 2.72 (1.56) CG: 4.56 (1.81) Time x Treatment interaction: effect size d=2.39, p=0.009 CGI-S, posttreatment (5 weeks), ITT (IG1=12; CG=10), mean (SD) IG1: 2.00 (0.89) CG: 3.33 (0.71) Time x Treatment interaction: effect size d=2.75, P<0.001 PARS, posttreatment (5 weeks), ITT (IG1=12; CG=10), mean (SD) IG1: 9.72 (4.76) CG: 15.78 (3.35) Time x Treatment interaction: effect size d=3.18, p=0.046
Rynn et al, 2001[130]	IG1: Sertraline (N=11) CG: Placebo (N=11)	HAM-A, posttreatment (week 9), ITT (IG=11; CG=11), mean (SD) IG: 7.8 (5.7) CG: 21.0 (7.8) P<0.001 Time x Treatment interaction: baseline to posttreatment P<0.001 CGI-S, posttreatment (week 9), ITT (IG=11; CG=11), mean (SD) IG: 2.4 (0.8) CG: 3.9 (0.3) P<0.001 Time x Treatment interaction: baseline to posttreatment P<0.001

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Rynn et al, 2001[130] (continued)		CGI-I, posttreatment (week 9), ITT (IG=11; CG=11), mean (SD) IG: 2.1 (1.1) CG: 3.5 (0.7) p=0.001 Time x Treatment interaction: baseline to posttreatment P<0.001 ADIS CSR-C posttreatment (week 9), ITT (IG=11; CG=11), mean (SD) IG: 2.7 (2.0) CG: 4.6 (2.0) p=0.11 ADIS CSR-P, posttreatment (week 9), ITT (IG=11; CG=11), mean (SD) IG: 2.6 (1.7) CG: 4.9 (2.0) P<0.007 RCMAS, posttreatment (week 9), ITT (IG=11; CG=11), mean (SD) IG: 8.9 (7.0) CG: 14.6 (8.2) P<0.02 MASC total score, posttreatment (week 9), ITT (IG=11; CG=11), mean (SD) IG: 35.7 (17.2) CG: 56.4 (16.3) P<0.03
Salzer et al, 2018[42,] ISRCTN 22752528	IG1: Individual child-focused in-person CBT (N=34) CG: Wait-list control (N=39)	LSAS-CA, change in score from baseline to posttreatment, ITT (IG1=34; CG=39), effect size Cohen's d=0.61 (95% CI, 0.14 to 1.08); p=0.0112 SPAI, change in score from baseline to posttreatment, ITT (IG1=34; CG=39), effect size Cohen's d=0.75 (95% CI, 0.27 to 1.22); p=0.0021
Sanchez-Garcia et al, 2009[131] NR	IG1: Individual + group child-focused in-person CBT (N=28) IG2: Group CBT without cognitive restructuring (N=29) CG: Wait-list control (N=25)	SPAI-C, posttreatment (12 weeks), mITT (IG1=28, IG2=29, CG=25), mean (SD) IG1: 15.45 (7.77) IG2: 12.75 (8.03) CG: 30.80 (5.75) IG1 vs. CG P<0.001, effect size 2.23 (unclear what type of ES this is) IG2 vs. CG P<0.001, effect size 2.51 (unclear what type of ES this is)

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Sanchez-Garcia et al, 2009[131] NR (continued)		SPAI-C, 6 months, mITT (IG1=28, IG2=29, CG=25), mean (SD) IG1: 11.91 (6.03) IG2: 13.21 (8.55) CG: 27.64 (4.01) IG1 vs. CG P<0.001, effect size 3.04 (unclear what type of ES this is) IG2 vs. CG P<0.001, effect size 2.08 (unclear what type of ES this is) SASC-R, posttreatment (12 weeks), mITT (IG1=28, IG2=29, CG=25), mean (SD) IG1: 15.89 (6.81) IG2: 11.45 (6.48) CG: 35.36 (5.33) IG1 vs. CG P<0.001, effect size 3.16 (unclear what type of ES this is) IG2 vs. CG P<0.001, effect size 3.94 (unclear what type of ES this is) SASC-R, 6 months, mITT (IG1=28, IG2=29, CG=25), mean (SD) IG1: 12.14 (6.86) IG2: 12.24 (7.34) CG: 38.80 (6.71) IG1 vs. CG P<0.001, effect size 2.44 (unclear what type of ES this is) IG2 vs. CG P<0.001, effect size 2.90 (unclear what type of ES this is)
Shortt et al, 2001[134]	IG1: Group child + parent in-person CBT (N=54) CG: Wait-list (N=17)	RCMAS posttreatment (10 weeks), completers (IG1=53 CG=12), mean (SD) IG1: 8.6 (0.97) CG: 9.8 (2.0) Time x Treatment, eta squared=0.10, P<0.05 DISCAP CSR, posttreatment (10 weeks), completers (IG1-48, CG-16), mean (SD) IG1: 1.06 (0.24) CG: 4.13 (0.41) Time x Treatment, eta squared=0.46, P<0.001
Stjerneklar et al, 2019[141] NCT02535403	IG1: Individual child-focused internet CBT (N=35) CG: Wait-list control group (N=35)	ADIS-DSM-IV CSR (primary diagnosis), change in score from baseline to posttreatment (14 weeks), ITT (IG1=35; CG=35), between-group effect size Cohen's d=0.65; p=0.022 ADIS-DSM-IV CSR (all anxiety diagnoses), change in score from baseline to posttreatment (14 weeks), ITT (IG1=35; CG=35), between-group effect size Cohen's d=0.83; p=0.002 SCAS-C, change in score from baseline to posttreatment (14 weeks), ITT (IG1=35; CG=35), between-group effect size Cohen's d=0.68; P<0.001

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
		SCAS-M change in score from baseline to posttreatment (14 weeks), ITT (IG1=35; CG=35), between-group effect size Cohen's d=1.12; P<0.001 SCAS-F change in score from baseline to posttreatment (14 weeks), ITT (IG1=35; CG=35), between-group effect size Cohen's d=0.46; p=0.011
Strawn et al, 2015[142] NCT01226511	IG1: Duloxetine (N=135) CG: Placebo (N=137)	PARS severity for GAD, mean change from baseline to post acute treatment (10 weeks), ITT (IG=135; CG=133), mean (SE) IG: -9.7 (0.5) CG: -7.1 (0.5) d=0.5 P≤0.001, favoring duloxetine PARS severity total score, mean change from baseline to post acute treatment (10 weeks), ITT (IG=135; CG=133), mean (SE) IG: -9.2 (0.5) CG: -6.4 (0.5) P≤0.001, favoring duloxetine CGI-S mean change from baseline to post acute treatment (10 weeks), ITT (IG=135; CG=133), mean (SE) IG: -1.9 (0.1) CG: -1.4 (0.1) P≤0.001, favoring duloxetine
Strawn et al, 2020[143] NCT02818751	IG1: Escitalopram (N=26) CG: Placebo (N=25)	PARS, score from baseline to posttreatment (8 weeks), ITT/LOCF (IG=26; CG=25), mean change (SD) IG: -8.65 (1.31) CG: -3.52 (1.06) Difference in mean change NR (95% CI, -8.57 to -1.70); p=0.005 CGI-S, mean improvement in score, posttreatment (8 weeks), ITT (IG=26; CG=25) Significantly greater for IG compared with CG P<0.001 CGI-S, mean score, posttreatment (8 weeks), ITT (IG=26; CG=25), mean (SD) IG: 2.8 (0.3) CG: 3.6 (0.2) p=0.032

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Thirlwall et al, 2013[145] ISRCTN92977593	IG1: Parent-delivered brief CBT (N=61) IG2: Parent-delivered full CBT (N=64) CG: Wait-list control (N=69)	SCAS-P, posttreatment (12 weeks), unclear (IG1=38; IG2=42; CG=46), mean (SD) IG1: 24.16 (12.93) IG2: 20.45 (11.52) CG: 24.15 (11.36) IG1 vs. CG difference in change from baseline NR; P=NS IG2 vs. CG difference in change from baseline NR; P=NS SCAS-C, posttreatment (12 weeks), unclear (IG1=40; IG2=47; CG=57), mean (SD) IG1: 30.00 (12.6) IG2: 28.47 (20.0) CG: 29.40 (16.28) IG1 vs. CG difference in change from baseline NR; P=NS IG2 vs. CG difference in change from baseline NR; P=NS CGI-I, improvement at posttreatment (12 weeks), unclear (IG1=46; CG=63), N (%) IG1: 25 (54) IG2: 38 (76) CG: 16 (25) IG1 vs. CG adjusted RR: 1.89 (95% CI, 1.16 to 3.09); p=0.011 IG2 vs. CG adjusted RR: 2.64 (95% CI, 1.70 to 4.11); P<0.0001
Villabo et al, 2018[150] NR	IG1: Individual CBT (N=55) IG2: Group CBT (N=55) CG: Wait-list (N=55)	MASC-C, posttreatment (12 weeks), ITT (IG1=44, IG2=52, CG=51), mean (SE) IG1: 48.61 (1.48) IG2: 48.80 (1.65) CG: 51.95 (1.60) IG1 vs. CG: effect Size Hedge's g (95% CI): 0.28 (0.10 to 0.65), p=NS IG2 vs. CG: effect Size Hedge's g (95% CI): 0.26 (0.12 to 0.64), p=NS Means adjusted for age, gender, number of comorbid conditions, and baseline ADIS CSR for each target anxiety disorder MASC-P, posttreatment (12 weeks), ITT (IG1=44, IG2=52, CG=51), mean (SE) IG1: 47.25 (2.58) IG2: 49.72 (2.46) CG: 50.86 (2.45) IG1 vs. CG: effect Size Hedge's g (95% CI): 0.20 (0.18 to 0.61), p=NS IG2 vs. CG: effect Size Hedge's g (95% CI): 0.06 (-0.34 to 0.48), p=NS Means adjusted for age, gender, number of comorbid conditions, and baseline ADIS CSR for each target anxiety disorder

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Waite et al, 2019[152] ISRCTN79652741	IG1: Individual child + parent internet CBT (N=30) CG: Wait-list control (N=30)	ADIS C/P change from baseline to 17 weeks, primary diagnosis, ITT (IG1=30; CG=30), N (%) IG1: 12 (40) CG: 7 (23.3) OR=2.19 (95% CI, 0.72 to 6.70) ADIS C/P change from baseline to 17 weeks, remission of all ADs, ITT (IG1=30; CG=30), N (%) IG1: 8 (26.7) CG: 4 (13.3) OR=2.36 (95% CI, 0.63 to 8.92) CGI-I change from baseline to 17 weeks, ITT (IG1=30; CG=30), N (%) IG1: 12 (40) CG: 5 (16.7) OR=3.33 (95% CI, 1.00 to 11.14) CSR change from baseline to 17 weeks, ITT (IG1=30; CG=30), mean (SD); effect size (95% CI) IG1: 3.89 (2.58) CG: 4.86 (2.19) ES=0.05 (95% CI, 0.00 to 0.19) SCAS-C change from baseline to 17 weeks, ITT (IG1=30; CG=30), mean (SD); effect size (95% CI) IG1: 30.35 (19.17) CG: 33.46 (15.01) ES=0.05 (95% CI, 0.00 to 0.20) SCAS-P change from baseline to 17 weeks, ITT (IG1=30; CG=30), mean (SD); effect size (95% CI) IG1: 33.12 (21.70) CG: 28.93 (15.79) ES=0.06 (95% CI, 0.00 to 0.21)
Walkup et al, 2008[153] Albano et al, 2018[205] Taylor et al 2018[206] Compton et al, 2014[207] Caporino et al, 2017[216] Sachez et al, 2019[208] Rynn et al, 2015[209] Gordon-Hollingsworth et al, 2015[210] Ginsburg et al, 2011[211] NCT00052078	IG1: Individual child-focused in-person CBT (N=139) IG2: Sertraline (N=133) IG3: CBT + sertraline (N=140) CG: Placebo (N=76)	PARS change in score from baseline to 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), mean (SD) IG1: 10.8 (5.9) IG2: 9.8 (6.2) IG3: 7.4 (6.0) CG : 12.6 (6.3) IG1 vs. CG: effect size Hedge's g (95% CI): 0.31 (0.02 to 0.59) IG2 vs. CG: effect size Hedge's g (95% CI): 0.45 (0.17 to 0.74) IG3 vs. CG: effect size Hedge's g (95% CI): 0.86 (0.56 to 1.15) IG1 vs. CG: Time vs. Intervention: p=0.01 IG2 vs. CG: Time vs. Intervention: p=NS IG3 vs. CG: Time vs. Intervention: p=NS

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Walkup et al, 2008[153] Albano et al, 2018[205] Taylor et al 2018[206] Compton et al, 2014[207] Caporino et al, 2017[216] Sachez et al, 2019[208] Rynn et al, 2015[209] Gordon-Hollingsworth et al, 2015[210] Ginsburg et al, 2011[211] NCT00052078 (continued)		CGI-S change in score from baseline to 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), mean (SD) IG1: 3.3 (1.3) IG2: 3.0 (1.3) IG3: 2.4 (1.3) CG: 3.8 (1.4) No statistics reported, CIs of individual treatments do not overlap MASC-C IG1: 40.9 (10.4) IG2: 38.2 (10.7) IG3: 39.5 (10.8) CG: 42.9 (11.8) IG2 vs. CG: b=-4.68, t=-2.80, adjusted p=0.03, all other comparisons not statistically significant, P=NR MASC-P IG1: 42.1 (16.1) IG2: 37.9 (17.3) IG3: 33.4 (16.9) CG: 49.1 (16.9) IG1 vs. CG: b=-7.0, t=-2.9, adjusted P<0.001 IG2 vs. CG: b=-11.1, t=-4.4, adjusted P<0.001 IG3 vs. CG: b=-15.7, t=-6.4, adjusted P<0.001 SCARED-C IG1: 12.4 (11.4) IG2: 9.3 (11.9) IG3: 9.4 (11.6) CG: 13.8 (12.1) No statistically significant differences between arms, P=NR SCARED-P IG1: 16.9 (11.2) IG2: 11.0 (11.7) IG3: 9.6 (11.4) CG: 19.5 (11.8) IG1 vs. CG: adjusted p=0.26 IG2 vs. CG: b=-7.9, t=-4.7, adjusted P<0.001 IG3 vs. CG: b=-9.8, t=-5.9, adjusted P<0.001

Abbreviations: ADIS=Anxiety Disorders Interview Schedule; ADIS-C=Anxiety Disorders Interview Schedule for DSM-IV for Children-Children; ADIS-CSR=Anxiety Disorders Interview Schedule Clinician Severity Ratings; ADIS-DSM=Anxiety and Related Disorders Interview Schedule; ADIS-DSM-IV= Anxiety and Related Disorders Interview Schedule-Diagnostic and Statistical Manual-IV; CBT=cognitive behavioral therapy; CG=control group; CGI=Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; CI=confidence interval; CSR=Clinician Severity Ratings; CSR-C=clinical rating scale-child-rated; CSR-P=clinical rating scale-parent rated; DISCAP=Diagnostic

Appendix I Table 19. Anxiety Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Interview Schedule for Children, Adolescents, and Parents; ES=effect size; FSSCR=Fear Survey Schedule for Children-Revised; GAD=generalized anxiety disorder; HAM-D=HAM-D=Hamilton Depression Rating Scale; IG=intervention group; ITT=intent to treat; KQ=key question; LOCF=last observation carried forward; MASC=Multidimensional Anxiety Scale for Children; MASC=C=Multidimensional Anxiety Scale for Children-child; MASC-P= Multidimensional Anxiety Scale for Children-parent; mITT=modified intent to treat; NA=not available; NR=not reported; NS=not significant; OR=odds ratio; PARS=Pediatric Anxiety Rating Scale; PSCAS=Spence Children's Anxiety Scale-Parent; PSWQ-C=Penn State Worry Questionnaire for Children; RCMAS=Revised Children's Manifest Anxiety Scale; RCMAS-C=Revised Children's Manifest Anxiety Scale RR=relative risk; SASC-R=Social Anxiety Scale for Children-Revised; SCARED-C=Screen for Anxiety Related Emotional Disorders-Children; SCARED-P=Screen for Anxiety Related Emotional Disorders-Parent; SCARED-R-C=Screen for Anxiety Related Emotional Disorders-R-Children; SCARED-R-P Screen for Anxiety Related Emotional Disorders R-Parents; SCAS= Spence Children's Anxiety Scale; SCAS-C=Spence Children's Anxiety Scale-Child; SCAS-F=Spence Children's Anxiety Scale-Father; SCAS-M=Spence Children's Anxiety Scale-Child-Mother; SCAS-P=Spence Children's Anxiety Scale-Parent; SD=standard deviation; SE=standard error; SepAD=separation anxiety disorder; SMQ-P=Selective Mutism Questionnaire-Parent; SocAD=social anxiety disorder; SPAI=Social Phobia and Anxiety Inventory; SPAI-C=Social Phobia and Anxiety Inventory for Children; SPAI-P=Social Phobia and Anxiety Inventory for Parents; TAU=treatment as usual; WLC=waitlist control.

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Arendt et al, 2016[65]	IG1: Group child + parent in-person CBT (N=56) CG: Wait-list (N=53)	S-MFQ youth, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 2.96 (3.84) CG: 5.19 (5.32) Time-by-condition effect, p=0.020; partial eta squared=0.05 S-MFQ mother, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 3.34 (3.78) CG: 5.79 (5.51) Time-by-condition effect, p=0.044; partial eta squared=0.04 S-MFQ father, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 2.85 (4.03) CG: 5.73 (5.92) Time-by-condition effect, F=3.82; p=0.053; partial eta squared=0.04
Barrett et al, 1996[70]	IG1: CBT (N=28) IG2: CBT + family intervention (N=25) CG: Wait-list (N=26)	CDI, posttreatment (12 weeks), completers (IG1=28; CG=23), mean (SD) IG1: 4.5 (3.8) CG: 6.8 (5.3) Time x Treatment interaction=NS CDI, posttreatment (12 weeks), completers (IG2=25; CG=23), mean (SD) IG2: 4.1 (4.8) CG: 6.8 (5.3) Time x Treatment interaction=NS
Ishikawa et al, 2019[103]	IG1: Individual child + parent in-person CBT (N=26) CG: Wait-list (N=25)	DSRS, posttreatment (2 or 4 months), completers (IG=25; CG=24), mean (SE) IG: 14.00 (1.54) CG: 16.50 (1.50) Time x Treatment interaction p=NS CDI, posttreatment (2 or 4 months), completers (IG=25; CG=24), mean (SE) IG: 14.64 (1.75) CG: 19.05 (1.86) Time x Treatment interaction P<0.05 favoring CBT

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Lyneham et al, 2006[112] NR	IG1: Parent-guided CBT supported by telephone (N=28) IG2: Parent-guided CBT supported by email (N=21) IG3: Parent-guided CBT with as needed support (N=29) CG: Wait-list (N=22)	CDI, pretreatment, ITT (IG1=28, IG2=21, IG3=29, CG=22), mean (SD) IG1: 14.41 (9.79) IG2: 11.38 (3.79) IG3: 11.86 (9.75) CG: 10.33 (8.75) CDI, posttreatment (12 weeks), ITT (IG1=28, IG2=21, IG3=29, CG=22), mean (SD) IG1: 7.44 (7.99) IG2: 9.24 (3.86) IG3: 8.62 (9.95) CG: 10.48 (8.44)
Ost et al, 2015[120]	IG1: Individual + group child (N=16) IG2: Child + parent in-person CBT (N=16) CG: Wait-list (N=23)	Change in CDI from baseline to posttreatment (12 weeks), ITT (IG1=16; IG2=16; CG=23), mean (SD) IG1: 6.4 (6.1) IG: 9.3 (9.7) CG: 11.0 (7.7) Time x Treatment: F=1.2, p=NS
Perrin et al, 2019[122] ISRCTN50951795	IG1: Individual child + parent in-person + internet CBT (N=20) CG: Wait-list control (N=20)	MFQ-P, posttreatment (10 weeks), ITT (IG1=20, CG=20), mean (SD) IG1: 10.1 (9.7) CG: 20.9 (14.9) Effect size partial eta squared=0.19 P<0.01 MFQ-C, posttreatment (10 weeks), ITT (IG1=20, CG=20), mean (SD) IG1: 6.9 (9.8) CG: 25.4 (14.4) Effect size partial eta squared=0.40 P<0.001
Rynn et al, 2001[130]	IG1: Sertraline (N=11) CG: Placebo (N=11)	HAM-D, posttreatment (week 9), ITT (IG=11; CG=11), mean (SD) IG: 4.0 (3.6) CG: 11.5 (4.2) P<0.001

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Stjerneklar et al, 2019[141] NCT02535403	IG1: Individual child-focused internet CBT (N=35) CG: Wait-list control group (N=35)	S-MFQ-C, change from baseline to posttreatment (14 weeks), ITT (IG1=35, CG=35), between-group change effect size Cohen's d=0.11; p=0.932 S-MFQ-M, change from baseline to posttreatment (14 weeks), ITT (IG1=35, CG=35), between-group change effect size Cohen's d=0.60; p=0.008 S-MFQ-F, change from baseline to posttreatment (14 weeks), ITT (IG1=35, CG=35), between-group change effect size Cohen's d=0.07; p=0.813
Thirlwall et al, 2013[145] ISRCTN92977593	IG1: Parent-delivered brief CBT (N=61) IG2: Parent-delivered full CBT (N=64) CG: Wait-list control (N=69)	SMFQ-P, posttreatment (12 weeks), unclear (IG1=39; IG2=43; CG=49), mean (SD) IG1: 4.54 (5.19) IG2: 2.00 (2.77) CG: 4.86 (5.28) IG1 vs. CG difference in change from baseline: NR IG2 vs. CG difference in change from baseline: -1.44 (95% CI, -2.82 to -0.07), p=0.0395 SMFQ-C, posttreatment (12 weeks), unclear (IG1=42; IG2=48; CG=57), mean (SD) IG1: 5.57 (5.06) IG2: 3.94 (5.04) CG: 4.84 (5.38) IG1 vs. CG difference in change from baseline: NR IG2 vs. CG difference in change from baseline: NR
Waite et al, 2019[152] ISRCTN79652741	IG1: Individual child + parent internet CBT (N=30) CG: Wait-list control (N=30)	Short MFQ-C change from baseline to 17 weeks, ITT (IG1=30; CG=30), mean (SD); effect size (95% CI) IG1: 6.48 (6.4) CG: 7.70 (7.05) ES=0.00 (95% CI, 0.00 to 0.10) Short MFQ-P change from baseline to 17 weeks, ITT (IG1=30; CG=30), mean (SD); effect size (95% CI) IG1: 6.73 (6.91) CG: 7.11 (7.44) ES=0.00 (95% CI, 0.00 to 0.07)

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Walkup et al, 2008[153] Albano et al, 2018[205] Taylor et al 2018[206] Compton et al, 2014[207] Caporino et al, 2017[216] Sachez et al, 2019[208] Rynn et al, 2015[209] Gordon-Hollingsworth et al, 2015[210] Ginsburg et al, 2011[211] NCT00052078	IG1: Individual child-focused in-person CBT (N=139) IG2: Sertraline (N=133) IG3: CBT + sertraline (N=140) CG: Placebo (N=76)	MFQ-Youth, 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), mean (SD) IG1: 5.3 (7.9) IG2: 4.6 (8.3) IG3: 4.8 (8.1) CG: 6.4 (8.5) No statistically significant differences between arms, P=NR MFQ-P, 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), mean (SD) IG1: 8.1 (7.1) IG2: 5.0 (7.4) IG3: 4.1 (7.2) CG: 8.0 (7.5) IG1 vs. CG: adjusted p=0.91 IG2 vs. CG: b=-3.0, t=-2.8, adjusted P<0.001 IG3 vs. CG: b=-3.9, t=-3.7, adjusted P<0.001

Abbreviations: CBT=cognitive behavioral therapy; CDI=Children's Depression Inventory; CG=control group; CI=confidence interval; DSRS=Depression Self-Rating Scale; ES=effect size; HAM-D=Hamilton Depression Rating Scale; IG=intervention group; ITT=intent to treat; KQ=key question; MFQ=Mood & Feelings Questionnaire; MFQ-C=Mood and Feelings Questionnaire for Children; MFQ-P=Mood and Feelings Questionnaire for Parents; NR=not reported; NS=not significant; SD=standard deviation; SE=standard error; S-MFQ=Short Mood and Feelings Questionnaire for Parents; S-MFQ-C= Mood and Feelings Questionnaire for Children; S-MFQ-F= Mood and Feelings Questionnaire-Fathers; S-MFQ-M= Mood and Feelings Questionnaire-Mothers.

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Arendt et al, 2016[65]	IG1: Group child + parent in-person CBT (N=56) CG: Wait-list (N=53)	**Response** Clinically significant change based on SCAS-Child using method of Jacobson and Truax Clinically significant change based on SCAS-Mother using method of Jacobson and Truax Clinically significant change based on SCAS-Father using method of Jacobson and Truax Clinically significant change based on SCAS-Child, posttreatment (10 weeks), ITT (IG1=56; CG=53), N (%) IG1: 24 (42.9) CG: 6 (11.3) P<0.001 Clinically significant change based on SCAS-Mother, posttreatment (10 weeks), ITT (IG1=56; CG=53), N (%) IG1: 29 (51.8) CG: 6 (11.3) P<0.001 Clinically significant change based on SCAS-Father, posttreatment (10 weeks), ITT (IG1=56; CG=53), N (%) IG1: 23 (41.8) CG: 5 (9.8) P<0.001 **Loss of Diagnosis** Free of primary diagnosis (ADIS) Free of all anxiety diagnoses (ADIS) Free of primary diagnosis, posttreatment (10 weeks), ITT (IG1=56; CG=53), N (%) IG1: 37 (66.1) CG: 4 (7.5) P<0.001 Free of all anxiety diagnoses, posttreatment (10 weeks), ITT (IG1=56; CG=53), N (%) IG1: 27 (48.2) CG: 3 (5.7) P<0.001
Barrett et al, 1996[70]	IG1: CBT (N=28) IG2: CBT + family intervention (N=25) CG: Wait-list (N=26)	**Loss of Diagnosis** No longer meeting DSM-III-R criteria for a current anxiety disorder No longer meeting DSM-III-R criteria for a current anxiety disorder, posttreatment (12 weeks), completers (IG1/2=53, CG=23), N (%) IG1/2: 37 (69.8) CG: 6 (26.0) P<0.05
Birmaher et al, 2003[73]	IG1: Fluoxetine (N=37) CG: Placebo (N=37)	**Response** CGI-I ≤2 at end of treatment (12 weeks) CGI-I ≤2, posttreatment (12 weeks), mITT (IG1=36, CG=37), N% IG1: 22 (61) CG: 13 (35) p=0.03, ES=0.26

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Black et al, 1994[74]	IG1: Fluoxetine (N=6) CG: Placebo (N=9)	**Response** CGI response (markedly or much improved vs. minimally improved, no change, or worse) with respect to mutism CGI mutism parent rated marked or much improved, posttreatment (12 weeks), ITT (IG1=6; CG=9), N (%) IG1: 4 (66.7) CG: 1 (11.1) p=0.03 CGI mutism clinician rated marked or much improved, posttreatment (12 weeks), ITT (IG1=6; CG=9), N (%) IG1: 3 (50) CG: 4 (44.4) p=NS CGI mutism teacher rated marked or much improved; posttreatment (12 weeks), ITT (IG1=6; CG=9), N (%) IG1: 4 (66.6) CG: 4 (44.4) p=NS
Cobham et al, 2017[77] ACTRN12615000514505	IG1: Group parent-only in-person CBT (N=33) CG: Wait-list control (N=30)	**Loss of Diagnosis** Absence of any anxiety diagnosis based on diagnostic interview (ADIS) ADIS, absence of any anxiety diagnosis, posttreatment (6 weeks), mITT (IG1=31, CG=29), N% IG1: 12 (38.7) CG: 1 (3.4) P<0.001 RR (95% CI): 0.56 (0.47 to 0.82) ADIS, absence of primary anxiety diagnosis, posttreatment (6 weeks), mITT (IG1=31, CG=29), N% IG1: 20 (64.5) CG: 5 (16.2) P<0.001 RR (95% CI): 0.43 (0.259 to 0.709)

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Cornacchio et al, 2019[79] NA	IG1: Group child + parent in-person CBT (N=14) CG: Wait-list control (N=15)	**Response** CGI-I score of 1 ("very much improved") or 2 ("much improved") CGI-I ≤2, posttreatment (4 weeks), ITT (IG1=14; CG=15), N (%) IG1: 7 (50) CG: 0 (0) Fisher's p=0.006 Effect size phi=-0.58 **Loss of Diagnosis** Loss of selective mutism diagnosis based on ADIS/C-P Loss of selective mutism diagnosis ADIS C/P, 4 weeks, ITT (IG1=14; CG=15), N (%) IG1: 1 (7.1) CG: 0 (0) Fisher's p=1.00 Effect size phi=0.19
Donovan et al, 2014[83] ACTRN12612000139875	IG1: Individual parent-focused internet CBT (N=23) CG: Wait-list (N=29)	**Loss of Diagnosis** Absence of primary anxiety diagnosis, absence of any anxiety diagnosis (ADIS) Absence of primary diagnosis, posttreatment (8 weeks), mITT (IG1=23, CG=27), N (%) IG1: 9 (39.1) CG: 7 (25.9) p=0.318 Absence of any diagnosis, posttreatment (8 weeks), mITT (IG1=23, CG=27), N (%) IG1: 8 (34.8) CG: 7 (25.9) p=0.496

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Ginsburg et al, 2020[92]	IG1: Individual child-focused in-person CBT (N=148) CG: TAU (N=68)	**Response** Responder (receiving a CGI-I score of 1 or 2) Responder, posttreatment (12 weeks), ITT (IG=148; CG=68), N (%) IG: NR (42.1) CG: NR (36.7) p=0.34 Responder, 12 months, ITT (IG=148; CG=68), N (%) IG: NR (47.7) CG: NR (57.1) p=0.24 **Loss of Diagnosis** No anxiety disorder (loss of all study entry anxiety diagnosis) using ADIS Loss of primary anxiety disorder using ADIS No anxiety disorder, posttreatment (12 weeks), ITT (IG=148; CG=68), N (%) IG: NR (34.9) CG: NR (35.0) p=0.67 No anxiety disorder, 12 months, ITT (IG=148; CG=68), N (%) IG: NR (48.6) CG: NR (53.1) p=0.69 Loss of primary anxiety disorder, posttreatment (12 weeks), ITT (IG=148; CG=68), N (%) IG: NR (40.5) CG: NR (43.3) p=0.61 Loss of primary anxiety disorder, 12 months, ITT (IG=148; CG=68), N (%) IG: NR (53.2) CG: NR (59.2) p=0.44

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Hirshfeld-Becker et al, 2010[98]	IG1: Individual child + parent in-person CBT (N=34) CG: Wait-list control (N=30)	**Response** CGI-I ≤2 (much improved or very much improved) CGI-I score ≤2, posttreatment (6 months), ITT (IG1=34; CG=30), n (%) IG1: 20 (59) CG: 9 (30) p=0.016 NNT 3.5 (95% CI NR) **Loss of Diagnosis** Absence of anxiety diagnosis based on clinical interview Absence of anxiety diagnosis, posttreatment (6 months), ITT (G1=34; CG=30), n (%) IG1: 17 (50) CG: 5 (17) P<0.01
Holmes et al, 2014[99] ACTRN12612000061831	IG1: Group child-focused in-person CBT (N=20) CG: Wait-list control (N=22)	**Loss of Diagnosis** No longer meeting criteria for diagnosis (any anxiety, GAD) ADIS-C/P absence of GAD diagnosis, posttreatment (10 weeks), ITT (IG1=20, CG=22), % IG1: 45 CG: 0 P<0.001 ADIS-C/P absence of GAD diagnosis, posttreatment (10 weeks), completers (IG1=17, CG=19), % IG1: 52.9 CG: 0 P<0.001 ADIS-C/P absence of any anxiety diagnosis, posttreatment (10 weeks), ITT (IG1=20, CG=22), % IG1: 15 CG: 0 p=0.059 ADIS-C/P absence of any anxiety diagnosis, posttreatment (10 weeks), completers (IG1=17, CG=19), % IG1: 17.6 CG: 0 p=0.056

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Ishikawa et al, 2019[103]	IG1: Individual child + parent in-person CBT (N=26) CG: Wait-list (N=25)	**Response** A clinically significant change was examined based on a Reliable Change Index (RCI) and a nondysfunctional range. The RCI was calculated based on standard errors of pretreatment scores. When the RCI was greater than 1.96, the children were considered to show clinically meaningful change. Clinical cutoff points were applied to set a non-dysfunctional range when obtained Proportion of participants showing clinical significance change, SCAS-C Proportion of participants showing clinical significance change, DSRS Proportion of participants showing clinical significance change, CDI Proportion of participants showing clinical significance change, SCAS-P Proportion of participants showing clinical significance change in SCAS-C, posttreatment (2 or 4 months), completer (IG=25; CG=24), N (%) IG: 14 (56.0) CG: 9 (37.5) p=0.20 Proportion of participants showing clinical significance change in DSRS, posttreatment (2 or 4 months), completer (IG=25; CG=24), N (%) IG: 9 (36.0) CG: 5 (20.83) p=0.24 Proportion of participants showing clinical significance change in CDI, posttreatment (2 or 4 months), completer (IG=25; CG=24), N (%) IG: 10 (40.0) CG: 4 (16.67) p=0.07 Proportion of participants showing clinical significance change in SCAS-P, posttreatment (2 or 4 months), completer (IG=25; CG=24), N (%) IG: 8 (32.0) CG: 5 (20.83) p=0.38 **Remission** Proportion free of principal diagnosis, posttreatment (2 or 4 months), ITT (IG=26; CG=25), N (%) IG: 13 (50.0) CG: 3 (12.0) P<0.01 Proportion free of any diagnosis, posttreatment (2 or 4 months), ITT (IG=26; CG=25), N (%) IG: 4 (15.38) CG: 1 (4.0) p=NS

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Lau et al, 2010[110] NR	IG1: Group child + parent in-person CBT (N=26) CG: Wait-list control (N=25)	**Loss of Diagnosis** K-SADS anxiety diagnostic status Presence of anxiety diagnosis of symptoms, posttreatment (13 weeks), mITT (IG1=24; CG=21), N (%) IG1: 16 (67) CG: 21 (100) P<0.01 Absence of anxiety diagnosis or subclinical symptoms, posttreatment (13 weeks), mITT (IG1=24; CG=21), N (%) IG1: 8 (33) CG: 0 (0)
Lyneham et al, 2006[112] NR	IG1: Parent-guided CBT supported by telephone (N=28) IG2: Parent-guided CBT supported by email (N=21) IG3: Parent-guided CBT with as needed support (N=29) CG: Wait-list (N=22)	**Remission** Return to normal range for SCAS-C (overall or for any subscales) SCAS-C normal range, posttreatment (12 weeks), ITT (IG1=28, IG2=21, IG3=29, CG=22), % IG1: 62 IG2: 57 IG3: 50 CG: 23 Any IG: 57 Any IG vs. CG: P<0.05 **Loss of Diagnosis** ADIS, no longer met criteria for principal anxiety disorder and/or any anxiety disorder ADIS loss of principal anxiety disorder, posttreatment (12 weeks), ITT (IG1=28, IG2=21, IG3=29, CG=22) Any IG vs. CG, P<0.01 ADIS loss of any anxiety disorder, posttreatment (12 weeks), ITT (IG1=28, IG2=21, IG3=29, CG=22) Any IG vs. CG, P<0.01
Ost et al, 2015[120]	IG1: Individual + group child (N=16) IG2: Child + parent in-person CBT (N=16) CG: Wait-list (N=23)	**Loss of Diagnosis** No longer fulfilling criteria for social phobia (ADIS) ADIS absence of social phobia (12 months), ITT (IG1=16; IG2=16; CG=23), N (%) IG1: 9 (56) IG2: 10 (62) CG: 2 (9) IG1 vs. CG: p≤0.001, favoring IG1 IG2 vs. CG: p≤0.001, favoring IG2

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Perrin et al, 2019[122] ISRCTN50951795	IG1: Individual child + parent in-person + internet CBT (N=20) CG: Wait-list control (N=20)	**Loss of Diagnosis** Presence of GAD based on ADIS Presence of comorbid disorders based on ADIS Recovery from all disorders based on ADIS ADIS GAD diagnosis present, posttreatment (10 weeks), ITT (IG1=20, CG=20), N (%) IG1: 4 (20) CG: 20 (100) p<0.001 ADIS comorbid disorder diagnosis present, posttreatment (10 weeks), ITT (IG1=20, CG=20), N (%) IG1: 1 (5) CG: 11 (55) p<0.001 ADIS recovery from all disorders, posttreatment (10 weeks), ITT (IG1=20, CG=20), N (%) IG1: 16 (80) CG: 0 (0) p<0.000
Pine et al, 2001[124] Walkup et al, 2001[213] Ginsburg et al, 2006[214] Reinblatt et al, 2009[215]	IG1: Fluvoxamine (N=63) IG2: Sertraline (N=133) IG3: CBT + sertraline (N=140) CG: Placebo (N=65)	**Response** Response to treatment defined as CGI-I <4 CGI-I score <4, posttreatment (8 weeks), ITT (IG1=63: CG=65), N (%) IG1: 48 (76) CG: 19 (29) P<0.001
Rudy et al, 2017[129] NCT02051192	IG1: Individual parent-led in-person CBT (N=12) CG: TAU (N=10)	**Response** CGI-I scores of much improved or very much improved CGI-I much improved/very much improved, 5 weeks, ITT (IG1=12; CG=10), N% IG1: 10 (83.3) CG: 0 (0.0) P<0.001 **Remission** ADIS-CSR scores <4 ADIS CSR <4, 5 weeks, ITT (IG1=12; CG=10), N% IG1: 8 (66.7) CG: 1 (10.0) p=0.011

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Rynn et al, 2001[130]	IG1: Sertraline (N=11) CG: Placebo (N=11)	**Response** Moderately or markedly improved (CGI-I scale scores=1 or 2) CGI-I=1 or 2, posttreatment (week 9), ITT (IG=11; CG=11), N (%) IG: 10 (91) CG: 1 (9) P<0.001 **Remission** Remission rate "markedly improved" based on CGI=1 CGI=1, posttreatment (week 9), ITT (IG=11; CG=11), N (%) IG: 2 (18) CG: 0 (0)
Salzer et al, 2018[42,] ISRCTN 22752528	IG1: Individual child-focused in-person CBT (N=34) CG: Wait-list control (N=39)	**Response** LSAS-CA ≥31% reduction in total score LSAS-CA response, posttreatment, ITT (IG1=34; CG=39), N (%) IG1: NR (66) CG: NR (20) OR: 7.91 (95% CI, 2.17 to 28.86); p=0.0056 **Remission** LSAS-CA total score ≤30 LSAS-CA remission, posttreatment, mITT (IG1=32; CG=36), N (%) IG1: 47 CG: 6 OR: 14.6 (95% CI, 1.85 to 114.95); p=0.0009
Shortt et al, 2001[134]	IG1: Group child + parent in-person CBT (N=54) CG: Wait-list (N=17)	**Loss of Diagnosis** Anxiety-free diagnosis based on clinical interview with parent Anxiety-free diagnosis, 10 weeks, ITT (IG1=54, CG=17), N (%) IG1: NR CG: NR IG1 vs. CG: P<0.001 Anxiety-free diagnosis, 10 weeks, completers (IG1=48, CG=16), N (%) IG1: 33 (69) CG: 1 (6) P<0.001

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Stjerneklar et al, 2019[141] NCT02535403	IG1: Individual child-focused internet CBT (N=35) CG: Wait-list control group (N=35)	**Response** Improved SCAS scores that were statistically reliable according to the reliable change index 14 weeks Improved by SCAS-C, at posttreatment (14 weeks), (IG1=32; CG=31), N (%) IG1: 22 (69) CG: 8 (26) p=0.001 Improved by SCAS-M scores, at posttreatment (14 weeks), (IG1=35; CG=32), N (%) IG1: 24 (69) CG: 7 (22) P<0.001 Improved by SCAS-F scores, at posttreatment (14 weeks), (IG1=25; CG=27), N (%) IG1: 9 (35) CG: 5 (19) p=0.156 **Remission** SCAS scores that were statistically reliable according to the reliable change index and were deemed a clinical change were considered recovered, but specific score thresholds not reported. Recovered by SCAS-C, at posttreatment (14 weeks), mITT (IG1=32; CG=31), N (%) IG1: 14 (44) CG: 2 (6) p=0.001 Recovered by SCAS-M, at posttreatment (14 weeks), mITT (IG1=35; CG=32), N (%) IG1: 9 (26) CG: 2 (6) p=0.032 Recovered by SCAS-F, at posttreatment (14 weeks), mITT (IG1=25; CG=27), N (%) IG1: 1 (4) CG: 2 (7) p=1.00 **Loss of Diagnosis** Free of diagnosis based on ADIS-IV Free of primary anxiety diagnosis, at posttreatment (14 weeks), mITT (IG1=35; CG=32), N (%) IG1: 14 (40) CG: 5 (16) OR: 3.6 (95% CI NR); p=0.027 Free of any anxiety diagnosis, at posttreatment (14 weeks), mITT (IG1=35; CG=32), N (%) IG1=10 (29) CG: 1 (3) OR: 12.4 (95% CI NR); p=0.005

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Strawn et al, 2015[142] NCT01226511	IG1: Duloxetine (N=135) CG: Placebo (N=137)	**Response** Response: 50% improvement on PARS severity for GAD 50% improvement on PARS severity for GAD, post acute treatment (10 weeks), ITT (IG=135; CG=133), % IG: 59 CG: 42 P≤0.05, favoring duloxetine **Remission** Remission: CGI-Severity ≤2 Remission: PARS severity for GAD ≤8 CGI-Severity ≤2, post acute treatment (10 weeks), ITT (IG=135; CG=133), % IG: 54 CG: 35 P≤0.01, favoring duloxetine PARS severity for GAD ≤8, post acute treatment (10 weeks), ITT (IG=135; CG=133), % IG: 50 CG: 34 P≤0.05, favoring duloxetine
Strawn et al, 2020[143] NCT02818751	IG1: Escitalopram (N=26) CG: Placebo (N=25)	**Response** CGI-I score ≤2, posttreatment (8 weeks), ITT/LOCF (IG=26; CG=25), N (%) IG: 16 (62) CG: 6 (24) RR: NR (95% CI, 0.578 to 0.95); p=0.0039
Thirlwall et al, 2013[145] ISRCTN92977593	IG1: Parent-delivered brief CBT (N=61) IG2: Parent-delivered full CBT (N=64) CG: Wait-list control (N=69)	**Loss of Diagnosis** Loss of diagnosis based on ADIS ADIS loss of primary diagnosis, 12 weeks, unclear (IG1=46; IG2=50; CG=63), N (%) IG1: 18 (39) IG2: 25 (50) CG: 16 (25) IG1 vs. CG adjusted RR: 1.56 (0.89 to 2.74); p=0.119 IG2 vs. CG adjusted RR: 1.85 (1.14 to 2.99); p=0.013 ADIS loss of any diagnosis, 12 weeks, unclear (IG1=46; IG2=50; CG=63) N (%) IG1: 7 (15) IG2: 17 (34) CG: 7 (11) IG1 vs. CG adjusted RR: 1.47 (0.56 to 3.88); p=0.433 IG2 vs. CG adjusted RR: 3.13 (1.40 to 7.01); p=0.006

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Villabo et al, 2018[150] NR	IG1: Individual CBT (N=55) IG2: Group CBT (N=55) CG: Wait-list (N=55)	**Loss of Diagnosis** Loss of all anxiety disorders based on ADIS, loss of primary anxiety diagnosis based on ADIS ADIS loss all anxiety diagnosis, posttreatment (12 weeks), ITT (IG1=44, IG2=52 CG=51), % (95% CI) IG1: 38 (24 to 52) IG2: 56 (43 to 69) CG: 6 (-1 to 0.14) IG1 vs. CG: ARD 31 (16 to 47), P<0.001 IG2 vs. CG: ARD 50 (34 to 65), P<0.001 ADIS loss primary anxiety diagnosis, posttreatment (12 weeks), ITT (IG1=44, IG2=52 CG=51), % (95% CI) IG1: 52 (38 to 67) IG2: 65 (52 to 78) CG: 14 (4 to 23) IG1 vs. CG: ARD 38 (21 to 56), P<0.001 IG2 vs. CG: ARD 51 (35 to 68), P<0.001
Waite et al, 2019[152] ISRCTN79652741	IG1: Individual child + parent internet CBT (N=30) CG: Wait-list control (N=30)	**Response** Clinical improvement: CGI-I ≤2 CGI-I ≤2, baseline to 17 weeks, ITT (IG1=30; CG=30), N (%) IG1: 12 (40.0) CG: 9 (30.0) OR=1.56 (95% CI, 0.53 to 4.53) **Loss of Diagnosis** Loss of AD diagnosis based on ADIS Loss of AD diagnosis, 17 weeks, ITT (IG1=30; CG=30), N (%) ADIS C/P Remission of primary AD: IG1: 12 (40) CG: 7 (23.3) OR=2.19 (95% CI, 0.72 to 6.70) Remission of all ADs IG1: 8 (26.7) CG: 4 (13.3) OR=2.36 (95% CI, 0.63 to 8.92)

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Walkup et al, 2008[153] Albano et al, 2018[205] Taylor et al 2018[206] Compton et al, 2014[207] Caporino et al, 2017[216] Sachez et al, 2019[208] Rynn et al, 2015[209] Gordon-Hollingsworth et al, 2015[210] Ginsburg et al, 2011[211] NCT00052078	IG1: Individual child-focused in-person CBT (N=139) IG2: Sertraline (N=133) IG3: CBT + sertraline (N=140) CG: Placebo (N=76)	**Response** Response score on CGI-I ≤2 CGI-I ≤2, 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 83 (59.7) IG2: 73 (54.9) IG3: 113 (80.7) CG: 18 (23.7) IG1 vs. CG: OR: 4.8 (95% CI, 2.6 to 9.0), P<0.001 IG2 vs. CG: OR: 3.9 (95% CI, 3.0 to 5.9), P<0.001 IG3 vs. CG: OR: 13.6 (95% CI, 6.9 to 26.8), P<0.001 Numbers needed to treat, 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), N (CI) IG1 vs. CG: 2.8 (2.7 to 3.0) IG2 vs. CG: 3.2 (3.2 to 3.5) IG3 vs. CG: 1.7 (1.7 to 1.9) **Remission** 1. CGI-S score ≤2 2. CGI-I score=1 CGI-S ≤2, 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 50 (35.9) IG2: 62 (46.3) IG3: 91 (64.9) CG: 21 (27.1) IG1 vs. CG: OR: 1.65 (0 to 3.53), p=0.49 IG2 vs. CG: OR: 2.55 (0 to 5.48), p=0.29 IG3 vs. CG: OR: 5.59 (0 to 12.07), p=0.16 CGI-I=1, 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 28 (20.4) IG2: 45 (33.9) IG3: 64 (45.6) CG: 11 (15.0) IG1 vs. CG: OR: 1.77 (0 to 4.78), p=0.61 IG2 vs. CG: OR: 3.56 (0 to 9.53), p=0.39 IG3 vs. CG: OR: 5.97 (0 to 15.82), p=0.31

Appendix I Table 21. Anxiety Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Walkup et al, 2008[153] Albano et al, 2018[205]; Taylor et al 2018[206]; Compton et al, 2014[207]; Caporino et al, 2017[216]; Sachez et al, 2019[208]; Rynn et al, 2015[209]; Gordon-Hollingsworth et al, 2015[210]; Ginsburg et al, 2011[211] NCT00052078 (continued)		**Loss of Diagnosis** Loss of anxiety diagnosis (AD) using clinical interview Loss of ADs at 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 64 (46.2) IG2: 61 (45.9) IG3: 96 (68.3) CG: 18 (23.7) IG1 vs. CG: OR: 2.91 (1.03 to 4.79), p=0.05 IG2 vs. CG: OR: 2.84 (1.01 to 4.67), p=0.05 IG3 vs. CG: OR: 7.47 (2.63 to 12.64), p=0.01

Abbreviations: ADIS=Anxiety and Related Disorders Interview Schedule; ADIS-C=Anxiety and Related Disorders Interview Schedule for DSM-IV -Children; ADIS-CSR=Anxiety and Related Disorders Interview Schedule Clinical Rating Scale; ADIS-IV= Anxiety and Related Disorders Interview Schedule IV; ARD=absolute risk difference; CBT=cognitive behavioral therapy; CDI=Children's Depression Inventory; CG=control group; CGI=Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; CI=confidence interval; CSR=Clinician Severity Ratings; DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition-Revised; DSRS=Depression Self-Rating Scale; ES=effect size; G=group; GAD=generalized anxiety disorder; IG=intervention group; ITT=intent to treat; KQ=key question; K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; LOCF=last observation carried forward; LSAS-CA=Liebowitz Social Anxiety Scale for Children and Adolescents; mITT=modified intent to treat; NA=not available; NNT=number needed to treat; NR=not reported; NS=not significant; OR=odds ratio; PARS=Pediatric Anxiety Rating Scale; RCI=Reliable Change Index; RR=relative risk; SCAS=Spence Children's Anxiety Scale; SCAS-C=Spence Children's Anxiety Scale-Child-rated; SCAS-F=Spence Children's Anxiety Scale-Father; SCAS-M=Spence Children's Anxiety Scale-Mother-rated; SCAS-P=Spence Children's Anxiety Scale-Parent-rated; TAU=treatment as usual.

Appendix I Table 22. Anxiety Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes
Arendt et al, 2016[65]	IG1: Group child + parent in-person CBT (N=56) CG: Wait-list (N=53)	CALIS youth, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 7.55 (6.46) CG: 10.94 (7.20) Time-by-condition effect, p=0.008, partial eta squared=0.06 CALIS mother, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 10.61 (7.28) CG: 17.94 (9.07) Time-by-condition effect, P<0.001, partial eta squared=0.14 CALIS father, posttreatment (10 weeks), ITT (IG1: 56; CG: 53), mean (SD) IG1: 10.96 (7.72) CG: 17.14 (9.16) Time-by-condition effect, F=12.45, P<0.001, partial eta squared=0.11	
Asbrand et al, 2020[67] TU 78/5-2, HE 3342/4-2	IG1: Group child-focused in-person CBT (N=31) CG: Wait-list control (N=36)	NR	Severity of diagnosis, posttreatment (12 weeks), ITT (IG1=31; CG=36), group effect, F(1)=7.24, p=0.007, Time x Group interaction F(1)=16.23, p <0.001 favoring CBT No subgroups of interest reported
Birmaher et al, 2003[73]	IG1: Fluoxetine (N=37) CG: Placebo (N=37)	CGAS, posttreatment (12 weeks), ITT (IG1=37, CG=37), mean (SD) IG1: 70.3 (15.0) CG: 61.2 (10.9) Treatment x Time baseline to 12 weeks p=0.0001 CGAS ≥70, posttreatment (12 weeks), ITT (IG1=37, CG=37), N (%) IG1: 15 (40.5) CG: 10 (27.0) p=0.20; ES=0.14	NR
Cornacchio et al, 2019[79] NA	IG1: Group child + parent in-person CBT (N=14) CG: Wait-list control (N=15)	CGAS, posttreatment (4 weeks), ITT (IG1=14; CG=15), mean (SD) IG1: 53.6 (4.6) CG: 52.5 (4.9) P<0.01 Effect size Cohen's d=0.73	NR

Appendix I Table 22. Anxiety Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes
Donovan et al, 2014[83] ACTRN12612000139875	IG1: Individual parent-focused internet CBT (N=23) CG: Wait-list (N=29)	CGAS, posttreatment (8 weeks), mITT (IG1=23; CG=27), mean (SD) IG1: 66.91 (10.63) CG: 61.85 (9.98) Time x Treatment p=0.016, partial eta squared=0.115 For ITT population: Time x Treatment p=0.010, partial eta squared=0.125	NR
Ginsburg et al, 2020[92]	IG1: Individual child-focused in-person CBT (N=148) CG: TAU (N=68)	CGAS, posttreatment (12 weeks), ITT (IG=148; CG=68), mean IG: 55.98 CG: 54.22 p=0.42 CGAS, 12 months, ITT (IG=148; CG=68), mean IG: 58.92 CG: 59.22 p=0.63	NR
Holmes et al, 2014[99] ACTRN12612000061831	IG1: Group child-focused in-person CBT (N=20) CG: Wait-list control (N=22)	CGAS, posttreatment (10 weeks), completers (IG1=17, CG=19), mean (SD) IG1: 63.82 (11.03) CG: 51.05 (7.66) p=0.02; partial eta squared=0.15 Pediatric QOL Inventory-C, posttreatment (10 weeks), completers (IG1=17, CG=19), mean (SD) IG1: 76.09 (15.17) CG: 66.88 (12.03) Time x Group interaction p=NS Pediatric QOL Inventory-P, posttreatment (10 weeks), completers (IG1=17, CG=19), mean (SD) IG1: 79.17 (14.16) CG: 75.34 (11.74) Time x Group interaction p=NS	NR
Ost et al, 2015[120]	IG1: Individual + group child (N=16) IG2: Child + parent in-person CBT (N=16) CG: Wait-list (N=23)	Change in QOLI-C from baseline to posttreatment (12 weeks), ITT (IG1=16; IG2=16; CG=23), mean (SD) IG1: 3.85 (1.84) IG2: 3.46 (1.63) CG: 2.89 (1.40) Time x Treatment: F=4.1, P<0.05 IG1 vs. CG: p=NS IG2 vs. CG: p=NS	NR

Appendix I Table 22. Anxiety Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes
Perrin et al, 2019[122] ISRCTN50951795	IG1: Individual child + parent in-person + internet CBT (N=20) CG: Wait-list control (N=20)	CGAS, posttreatment (10 weeks), ITT (IG1=20, CG=20), mean (SD) IG1: 82.1 (8.9) CG: 59.4 (6.7) Effect size partial eta squared=0.70 p<0.001 PQ-LES-Q, posttreatment 10 weeks), ITT (IG1=20, CG=20), mean (SD) IG1: 60.8 (10.7) CG: 48.7 (9.4) Effect size partial eta squared=0.23 P<0.01	NR
Thirlwall et al, 2013[145] ISRCTN92977593	IG1: Parent-delivered brief CBT (N=61) IG2: Parent-delivered full CBT (N=64) CG: Wait-list control (N=69)	CAIS-P, posttreatment (12 weeks), unclear (IG1=39; IG2=41; CG=48), mean (SD) IG1: 13.97 (14.64) IG2: 6.39 (6.29) CG: 15.56 (12.31) IG1 vs. CG difference in change from baseline NR, P=NS IG2 vs. CG difference in change from baseline, -5.56 (95% CI, -9.40 to -1.73), p=0.0045	NR
Salzer et al, 2018[42,] ISRCTN 22752528	IG1: Individual child-focused in-person CBT (N=34) CG: Wait-list control (N=39)	NR	LSAS-CA deterioration, posttreatment, ITT (IG1=34; CG=39), N (%) IG1: NR (9.4) CG: NR (11.3)
Stjerneklar et al, 2019[141] NCT02535403	IG1: Individual child-focused internet CBT (N=35) CG: Wait-list control group (N=35)	WHO-5, change in score from baseline to posttreatment (14 weeks), ITT (IG1=35; CG=35), between-group effect size Cohen's d=0.04; p=0.945 CALIS-C change in score from baseline to posttreatment (14 weeks), ITT (IG1=35; CG=35), between-group effect size Cohen's d=0.21; p=0.254 CALIS-M change in score from baseline to posttreatment (14 weeks), ITT (IG1=35; CG=35), between-group effect size Cohen's d=0.93; P<0.001 CALIS-F change in score from baseline to posttreatment (14 weeks), ITT (IG1=35; CG=35), between-group effect size Cohen's d=0.20; p=0.227	NR

Appendix I Table 22. Anxiety Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes
Strawn et al, 2015[142] NCT01226511	IG1: Duloxetine (N=135) CG: Placebo (N=137)	CGAS mean change from baseline to post acute treatment (10 weeks), ITT (IG=135; CG=133), mean (SE) IG: 17.1 (1.2) CG: 12.2 (1.2) P≤0.01, favoring duloxetine CGAS >70 (functional remission), post acute treatment (10 weeks), ITT (IG=135; CG=133), % IG: 59 CG: 42 P≤0.05, favoring duloxetine	NR
Villabo et al, 2018[150] NR	IG1: Individual CBT (N=55) IG2: Group CBT (N=55) CG: Wait-list (N=55)	CGAS, posttreatment (12 weeks), ITT (IG1=44, IG2=52, CG=51), mean (SE) IG1: 62.52 (1.17) IG2: 62.81 (1.10) CG: 53.05 (1.09) IG1 vs. CG: effect size Hedge's g (95% CI): 1.01 (0.68 to 1.35), P<0.001 IG2 vs. CG: effect size Hedge's g (95% CI): 1.04 (0.72 to 1.37)	NR
Waite et al, 2019[152] ISRCTN79652741	IG1: Individual child + parent internet CBT (N=30) CG: Wait-list control (N=30)	CGAS change from baseline to 17 weeks, ITT (IG1=30; CG=30), mean (SD); effect size (95% CI) IG1: 59.48 (14.87) CG: 55.18 (12.48) ES: 0.04 (95% CI, 0.00 to 0.18) CAIS-C change from baseline to 17 weeks, ITT (IG1=30; CG=30), mean (SD); effect size (95% CI) IG1: 18.04 (16.97) CG: 17.59 (13.09) ES=0.01 (95% CI, 0.00 to 0.12) CAIS-P change from baseline to 17 weeks, ITT (IG1=30; CG=30), mean (SD); effect size (95% CI) IG1: 23.60 (21.81) CG: 19.63 (16.34) ES=0.04 (95% CI, 0.00 to 0.19)	CGI-I change from baseline to 17 weeks, ITT (IG1=30; CG=30), N (%) IG1: 12 (40) CG: 5 (16.7) OR=3.33 (95% CI, 1.00 to 11.14) Short MFQ-C change from baseline to 17 weeks, ITT (IG1=30; CG=30), mean (SD); effect size (95% CI) IG1: 6.48 (6.4) CG: 7.70 (7.44) ES=0.00 (95% CI, 0.00 to 0.07)

Appendix I Table 22. Anxiety Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes
Walkup et al, 2008[153] Albano et al, 2018[205] Taylor et al 2018[206] Compton et al, 2014[207] Caporino et al, 2017[216] Sachez et al, 2019[208] Rynn et al, 2015[209] Gordon-Hollingsworth et al, 2015[210] Ginsburg et al, 2011[211] NCT00052078	IG1: Individual child-focused in-person CBT (N=139) IG2: Sertraline (N=133) IG3: CBT + sertraline (N=140) CG: Placebo (N=76)	CGAS, 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), mean (SD) IG1: 63.8 (10.2) IG2: 65.0 (10.7) IG3: 68.6 (10.4) CG: 60.1 (10.9) No statistics reported, all active treatments noted to be superior to placebo CAIS-C IG1: 9.1 (10.7) IG2: 7.7 (11.3) IG3: 8.1 (11.0) CG: 11.2 (11.5) No statistically significant differences between arms, P NR CAIS-P IG1: 13.5 (10.0) IG2: 9.1 (10.5) IG3: 7.4 (10.2) CG: 15.2 (10.7) IG1 vs. CG: adjusted p=0.27 IG2 vs. CG: b=−6.1, t=−4.0, adjusted P<0.001 IG3 vs. CG: b=−7.7, t=−5.2, adjusted P<0.001 Sleep-related problems, 12 weeks, ITT (IG1=139; IG2=133; IG3=140; CG=76), mean (SD) NR by arm, active treatments (IG1, IG2, IG3) resulted in significantly greater reductions in sleep problems than placebo related to separation, as reported by parents (F=6.52, p=0.01, η^2=0.01) but not by children. No significant treatment type x time interactions for parent- or child-rated dysregulated sleep. Effect sizes were small to medium and differed somewhat by treatment type and informant.	NR

Abbreviations: CAIS-C=Child Anxiety Impact Scale; CAIS-P=Child Anxiety Impact Scale-Parent; CALIS=Child Anxiety Life Interference Scale; CALIS-C=Child Anxiety Life Interference Scale-Child; CALIS-F=Child Anxiety Life Interference Scale-Father; CALIS-M=Child Anxiety Life Interference Scale-Mother; CBT=cognitive behavioral therapy; CG=control group; CGAS=Children's Global Assessment Scale; CGI-I=Clinical Global Impressions-Improvement; CI=confidence interval; ES=effect size; IG=intervention group; ITT=intent to treat; KQ=key question; LSAS-CA=Liebowitz Social Anxiety Scale for Children and Adolescents; MFQ-C=Mood and Feelings Questionnaire for Children; mITT=modified intent to treat; NA=not available; NR=not reported; NS=not significant; OR=odds ratio; PQ-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; QOL=quality of life; QOLI-C= Quality of Life Inventory for Children; SD=standard deviation; SE=standard error; TAU=treatment as usual; WHO-5=World Health Organization Five Item Well-being Index.

Appendix I Table 23. Anxiety Treatment Studies: Suicide-Related Harms and Suicide-Related Withdrawal (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide Related Symptoms
Perrin et al, 2019[122] ISRCTN50951795	IG1: Individual child + parent in-person +internet CBT (N=20) CG: Wait-list control (N=20)	NR One participant withdrew because of the onset of suicidal thoughts in response to a family crisis that began after treatment commenced. The crisis was unrelated to the participant's GAD or treatment.
Strawn et al, 2015[142] NCT01226511	IG1: Duloxetine (N=135) CG: Placebo (N=137)	Suicidal ideation, 10 weeks (event occurred at 3 weeks), ITT (IG=135; CG=137), N (%) IG: 1 (1) CG: 0 NA
Strawn et al, 2020[143] NCT02818751	IG1: Escitalopram (N=26) CG: Placebo (N=25)	Aborted suicide attempt, posttreatment (8 weeks), ITT (IG=26; CG=25), N (%) IG: 1 (3.8) CG: 0 (0) Self-injurious behavior, posttreatment (8 weeks), ITT (IG=26; CG=25), N (%) IG: 2 (7.7) CG: 1 (4.0) Worsening of suicidality, posttreatment (8 weeks), ITT (IG=26; CG=25), N (%) IG: 6 (23.1) CG: 2 (8.0) Emergence or worsening of suicidality did not significantly differ between IG and CG (p=0.449) NR
Waite et al, 2019[152] ISRCTN79652741	IG1: Individual child + parent internet CBT (N=30) CG: Wait-list control (N=30)	Risk of suicide, 17 weeks, completers (IG1=27; CG=17), N (%) IG: 0 (0) CG: 2 (4.54) withdrew due to risk of suicide
Walkup et al, 2008[153] Albano et al, 2018[205] Taylor et al 2018[206] Compton et al, 2014[207] Caporino et al, 2017[216] Sachez et al, 2019[208] Rynn et al, 2015[209] Gordon-Hollingsworth et al, 2015[210] Ginsburg et al, 2011[211] NCT00052078	IG1: Individual child-focused in-person CBT (N=139) IG2: Sertraline (N=133) IG3: CBT + sertraline (N=140) CG: Placebo (N=76)	Self-harm behavior without suicidal attempt, across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 1 (0.7) IG2: 1 (0.8) IG3: 2 (1.4) CG: 0 Suicidal ideation across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 5 (3.6) IG2: 0 IG3: 5 (3.6) CG: 1 (1.3) Suicidal attempts, across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 0 IG2: 0 IG3: 0 CG: 0

A**bbreviations**: CBT=cognitive behavioral therapy; CG=control group; GAD=generalized anxiety disorder; IG=intervention group; ITT=intent to treat; KQ=key question; NR=not reported.

Appendix I Table 24. Anxiety Treatment Studies: Harms (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Incidence Any AEs	Incidence of SAEs	Withdrawal due to AE	Other Harms
Birmaher et al, 2003[73]	IG1: Fluoxetine (N=37) CG: Placebo (N=37)	Time x Treatment for total side effects between groups p=NS Gastrointestinal events, 2 weeks (IG1=35; CG=32), N (%) IG1: 16 (46) CG: 7 (22) p=0.04 Gastrointestinal events, 12 weeks (IG1=35; CG=32), % IG1: 44 CG: 22 p=0.04 Neurological complaints (headaches, drowsiness), 2 weeks (IG1=36; CG=36), N (%) IG1: 16 (44) CG: 5 (14) p=0.04 Excitement, giddiness, or disinhibition, posttreatment (12 weeks) (IG1=36, CG=36), N IG1: 7 CG: 4 p=NS	NR	Patient-initiated withdrawal (behavioral disinhibition and non-specified adverse event), 12 weeks (IG1=37; CG=37), N (calculated %) IG1=6 (16) CG=0 p=NR NR	NR
Black et al, 1994[74]	IG1: Fluoxetine (N=6) CG: Placebo (N=9)	NR	NR	Dosage reductions due to perceived side effects, 12 weeks (end of treatment), ITT (IG1=6; CG=9), N (%) IG1: 0 (0) CG: 2 (22.2) NR	Global side effect severity, 12 weeks (end of treatment), ITT (IG1=6; CG=9), mean (SD) IG1: 1.40 (0.55) CG: 1.00 (0.0) p=NS No subgroups of interest reported

Appendix I Table 24. Anxiety Treatment Studies: Harms (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Incidence Any AEs	Incidence of SAEs	Withdrawal due to AE	Other Harms
Perrin et al, 2019[122] ISRCTN50951795	IG1: Individual child + parent in-person + internet CBT (N=20) CG: Wait-list control (N=20)	NR	NR	One participant withdrew because of the onset of suicidal thoughts in response to a family crisis that began after treatment commenced. The crisis was unrelated to the participant's GAD or treatment. Withdrawal due to AE, 8 weeks, ITT (IG1=20; CG=20), N (%) IG1: 1 (5) CG: 0 (0)	NR
Pine et al, 2001[124] Walkup et al, 2001[213] Ginsburg et al, 2006[214] Reinblatt et al, 2009[215]	IG1: Fluvoxamine (N=63) CG: Placebo (N=65)	NR	NR	Withdrawal due to AE, 8 weeks, ITT (IG1=63; CG=65), N (%) IG1: 5 (8) CG: 1 (2)	Abdominal discomfort IG1: 31 (49) CG: 18 (28) p=0.02 The following other harms were reported but findings were not significant between groups: headache, increased motor activity, insomnia, nasal congestion, drowsiness, nausea, diarrhea, influenza, or URI No subgroups of interest reported

Appendix I Table 24. Anxiety Treatment Studies: Harms (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Incidence Any AEs	Incidence of SAEs	Withdrawal due to AE	Other Harms
Rynn et al, 2001[130]	IG1: Sertraline (N=11) CG: Placebo (N=11)	Total AEs NR: Fisher's exact tests (p<0.05) showed no statistically significant differences in adverse events between the sertraline group and the placebo group Dizziness, 9 weeks, ITT (IG=11; CG=11), N (%) IG: 2 (18) CG: 7 (64.4) P<0.08 Nausea, 9 weeks, ITT (IG=11; CG=11), N (%) IG: NR (5) CG: 6 (55) P<0.06 Stomach pain, 9 weeks, ITT (IG=11; CG=11), N (%) IG: 2 (18) CG: 7 (64) P<0.08 Dry mouth, 9 weeks, ITT (IG=11; CG=11), N (%) IG: 6 (55) CG: 3 (27) p=0.39 Drowsiness, 9 weeks, ITT (IG=11; CG=11), N (%) IG: 8 (73) CG: 5 (45) p=0.39 Leg spasms, 9 weeks, ITT (IG=11; CG=11), N (%) IG: 4 (36) CG: 1 (9) p=0.31 Restlessness, 9 weeks, ITT (IG=11; CG=11), N (%) IG: 6 (55) CG: 3 (27) p=0.39	NR	NR	NR

Appendix I Table 24. Anxiety Treatment Studies: Harms (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Incidence Any AEs	Incidence of SAEs	Withdrawal due to AE	Other Harms
Salzer et al, 2018[42,] ISRCTN 22752528	IG1: Individual child-focused in-person CBT (N=34) CG: Wait-list control (N=39)	Any AE, posttreatment, ITT (IG1=34; CG=39), N (%) IG1: 1 (3) CG: 3 (8) P=NS	Any SAE, posttreatment, ITT (IG1=34; CG=39), N (%) IG1: 0 CG: 1 (3) Note: the article calls this an SAE, it was hospitalization due to the need to remove a dental brace	NR	NR
Stjerneklar et al, 2019[141] NCT02535403	IG1: Individual child-focused internet CBT (N=35) CG: Wait-list control group (N=35)	Any AE, 14 weeks—study only reports that 1 participant in CG dropped out due to worsening of symptoms	NR	Patient-initiated dropout, 14 weeks, 1 participant in CG due to worsening in symptoms and offered treatment through the municipality NR	NR
Strawn et al, 2015[142] NCT01226511	IG1: Duloxetine (N=135) CG: Placebo (N=137)	Treatment-emergent AEs, 10 weeks, ITT (IG=135; CG=137), N (%) IG: 106 (78.5) CG: 90 (65.7) p=0.22	Serious adverse event, 10 weeks, ITT (IG=135; CG=137), N (%) IG: 1 (0.7) CG: 0 (0)	Discontinuation because of an AE, 10 weeks, ITT (IG=135; CG=137), N (%) IG: 7 (5.2) CG: 6 (4.4) p=0.784 NA	Mortality, 10 weeks, ITT (IG=135; CG=137), N (%) IG: 0 CG: 0
Strawn et al, 2020[143] NCT02818751	IG1: Escitalopram (N=26) CG: Placebo (N=25)	NR for overall, only reported by system organ class; "did not differ between groups with the exception of bruising."	Serious adverse event, 8 weeks, ITT (IG=26; CG=23), N (%) IG: 1 (3.8) CG: 1 (4.0)	Discontinued due to serious adverse event, posttreatment (8 weeks), ITT (IG=26; CG=25), N (%) IG: 1 (3.8) CG: 1 (4.0) NR	C-SSRS–defined worsening, posttreatment (8 weeks), ITT (IG=26; CG=25), N (%) IG: 6 (23.1) CG: 2 (8.0) No subgroups of interest reported
Waite et al, 2019[152] ISRCTN79652741	IG1: Individual child + parent internet CBT (N=30) CG: Wait-list control (N=30)	NR	NR	Risk of suicide, 17 weeks, completers (IG1=27; CG=17), N (%) IG: 0 (0) CG: 2 (4.54) withdrew due to risk of suicide	NR

Appendix I Table 24. Anxiety Treatment Studies: Harms (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Incidence Any AEs	Incidence of SAEs	Withdrawal due to AE	Other Harms
Walkup et al, 2008[153] Albano et al, 2018[205] Taylor et al 2018[206] Compton et al, 2014[207] Caporino et al, 2017[216] Sachez et al, 2019[208] Rynn et al, 2015[209] Gordon-Hollingsworth et al, 2015[210] Ginsburg et al, 2011[211] NCT00052078	IG1: Individual child-focused in-person CBT (N=139) IG2: Sertraline (N=133) IG3: CBT + sertraline (N=140) CG: Placebo (N=76)	Any physical AE, across 12 weeks, (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 51 (36.7) IG2: 67 (50.4) IG3: 58 (41.4) CG: 35 (46.1) Any psychiatric adverse events, across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 13 (9.4) IG2: 23 (17.3) IG3: 41 (29.3) CG: 10 (13.2) Harm-related adverse events (i.e., self-injurious behavior, homicidal ideation)* across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 8 (5.8) IG2: 3 (2.3) IG3: 14 (10.0) CG: 1 (1.3)	Serious adverse events Psychiatric hospitalization, across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 0 IG2: 1 (0.8) IG3: 1 (0.7) CG: 0 Medical hospitalization, across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 0 IG2: 1 (0) IG3: 0 CG: 0	Withdrawal from treatment due to worsening symptoms, across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 0 IG2: 0 IG3: 1 (0.7) CG: 1 (1.3) Withdrawal from study due to worsening symptoms, across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 0 IG2: 1 (0.8) IG3: 1 (0.7) CG: 0	Homicidal ideation, across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 0 IG2: 2 (1.5) IG3: 0 CG: 0 Homicidal attempts, across 12 weeks (IG1=139; IG2=133; IG3=140; CG=76), N (%) IG1: 0 IG2: 0 IG3: 0 CG: 0

* There were no instances of suicidal behavior.

Abbreviations: AE=adverse event; CBT=cognitive behavioral therapy; CG=control group; C-SSRS=Columbia Suicide Severity Rating Scale (C-SSRS; GAD=generalized anxiety disorder; IG=intervention group; ITT=intent to treat; KQ=key question; NA=not applicable; NR=not reported; NS=not significant; SAE=serious adverse event; SD=standard deviation; URI=upper respiratory illness.

Appendix I Table 25. Depression Treatment Studies: Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Clarke et al, 2016 [75] NCT00523081	U.S. RCT Kaiser Permanente Center for Health Research	Reviewed HMO Electronic Medical Record then sought primary care provider permission	IG1: CBT + TAU (N=106) Description: Two, 4-session modules: CT (cognitive therapy) and BA (behavioral activation). Intervention terminates after first module if nearly or completely recovered Duration: 4 to 8 sessions of CBT (duration not specified)	CG: TAU (N=106) Participants permitted to continue and or initiate any nonresearch mental health or general medical treatment	Some concerns
Clarke et al, 2005 [76] R01-HS10535, HS13854	U.S. RCT AHRQ and Garfield Memorial Fund	Pediatric clinics in a health maintenance organization	IG1: Brief CBT + TAU SSRI (N=77) Description: Between five and nine 60-minute sessions of individual CBT in initial phase, if recovered, did not receive the 2nd module. If not recovered, progressed to remaining module of sessions 6 to 9. Also acute phase aimed to maximize SSRI benefits through targeting medication adherence and consultation with PCP about dosing. Monthly informational parent meetings. There was a continuation phase CBT with brief check-in phone calls at 1, 2, 3, 5, 7, and 9 months following acute phase Duration: 5 to 9 60-minute sessions	CG: TAU + SSRI (N=75) Treatment as Usual SSRIs - permitted to receive any nonstudy healthcare services or medications including the index SSRI medication	Some concerns
Clarke et al, 1999 [45]	U.S. RCT NIMH	Recruited at 2 sites via announcements to health professionals and school counselors, television and newspaper stories, and advertisements	IG1: Group CBT (N=45) Description: Group CBT (Adolescent Coping With Depression Course) for adolescents only; no family involvement; mixed-gender groups of 10 adolescents; 16 sessions, each session 2 hours, delivered over 8 weeks; delivered by advanced graduate psychology or social work students or masters- or doctoral-level clinicians, plus 40 hours of specialized training and weekly supervision meetings IG2: Group CBT Plus Parent Sessions (N=42) Description: Group CBT same as IG1 plus 8 weekly 2-hour parent sessions (6 separate, 2 held jointly with adolescent group) over 8 weeks Duration: 8 weeks	CG: Wait-list (N=36) At the end of the 8 weeks, participants were offered nonexperimental treatment	Some concerns

Appendix I Table 25. Depression Treatment Studies: Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Emslie et al, 2009[86] Findling, 2013[227] NCT00107120	U.S. RCT Forest Laboratories	NR	IG1: Escitalopram (N=158) Description: Escitalopram dose was fixed at 10 mg/day for the first 3 weeks of double-blind treatment; dose could be increased to 20 mg/day at the end of week 3 or 4. Dosage could be returned to 10 mg/day if limited by adverse events. Duration: 8 weeks	CG: Placebo (N=158) Placebo	Some concerns
Fristad et al, 2019[90] NCT01341925	U.S. RCT NIMH and National Center for Research Resources	Recruited from community advertisements and clinical referrals	IG1: Family CBT (N=19) Description: Family-based therapy incorporating psychoeducation and CBT techniques into weekly 45- to 50-minute parent and child individual sessions. Parents join for the beginning and end of each child session. Sessions with siblings or school professionals provided as relevant. Duration: 12 weeks	CG: Placebo (N=18) Two placebo pills twice daily and a multivitamin/mineral tablet.	Low/some concerns
Luby et al, 2018[111] NCT02076425	U.S. RCT NIMH	Recruited from preschools, daycares, primary care, and mental health facilities	IG1: PCIT-ED (N=114) Description: Parent Child Interaction Therapy-Emotion Development (PCIT-ED) is a dyadic parent-child psychotherapy that includes an Emotion Development module after the standard 12 PCIT sessions. Both the standard PCIT and the add-on ED module use the technique of teaching of the parent followed by coaching the parent in interactions with the child in vivo using a bug-in-the-ear device. Therapy is manualized with therapist training and fidelity monitoring procedures. Duration: 20 sessions over 18 weeks	CG: Wait-list (N=115) Wait-list control	Some concerns

Appendix I Table 25. Depression Treatment Studies: Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286	U.S. RCT NIMH, study drug and placebo provided by Lilly Inc.	Recruited from clinics; newspaper, TV, and radio advertisements; primary care physicians; other mental health clinicians; and schools and juvenile justice facilities at 13 academic and community clinics	IG1: Fluoxetine + CBT (N=107) Description: Combination of fluoxetine and CBT as described in the other study arms. IG2: Fluoxetine + CBT (N=107) Description: Combination of fluoxetine and CBT as described in the other study arms. IG3: Fluoxetine (N=109) Description: Flexible dose of 10 to 40 mg/d based on pharmacotherapist-assigned CGI-S score and assessment of clinically significant AEs. Medication management took place during 6 medication visits lasting 20 to 30 minutes each, and pharmacotherapist offered general encouragement about effectiveness of pharmacotherapy for MDD. Duration: 12 weeks	CG: Placebo (N=112) Placebo for fluoxetine	Some concerns
Mufson et al, 2004[118] McGlinchey et al, 2017[228]	U.S. RCT SAMHSA	Five school-based mental health clinics in New York City, NY	IG1: Interpersonal psychotherapy (N=34) Description: Interpersonal psychotherapy modified for depressed adolescents (IPT-A) was manualized treatment to reduce depressive symptoms and improve interpersonal functioning administered during 12 sessions in a 12- to 16-week period. Therapists provided 8 consecutive 35-minute weekly sessions followed by 4 sessions scheduled at any frequency during the ensuing 8 weeks. Duration: 16 weeks	CG: TAU (N=29) The psychological treatment the adolescents would have received in the school-based clinic if the study had not been in place, varied but closely resembled supportive counseling. Most adolescents in the TAU group received individual psychotherapy, 8 received 1 to 3 additional family/parent sessions, and 5 participated in group therapy.	Some concerns

Appendix I Table 25. Depression Treatment Studies: Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Richardson et al, 2014[127] NCT01140464	U.S. RCT NIMH	Recruited from 9 pediatric and family care clinics in 3 urban areas in Washington State	IG1: Collaborative care (N=50) Description: ROAD, adapted collaborative care intervention based on the IMPACT Team Care model. Included developmentally sensitive materials and structured involvement of adolescent and parent in the initial education and engagement session, the choice of treatment (antidepressant, brief CBT, or both), and followup contacts. Delivered by master's-level clinicians. Adolescents with a less than 50% decrease in PHQ-9 at 4 to 8 weeksld increase medication dose, add CBT to medication, add medication to CBT, or switch treatments. Those who needed specialty mental health care could be referred at any time. Duration: 12 months	CG: Enhanced Usual Care (N=51) Adolescents and parents received a letter summarizing test results and encouraging followup to initiate depression care. Primary care clinicians received letters summarizing the results and recommending treatment. Group health coverage includes primary care, mental health care, and medications. All patients could self-refer to mental health care through a centralized behavioral health intake line.	Low
Topooco et al, 2018[147] NCT02363205	Other very high HDI Sweden RCT Queen Silvia's Jubilee Fund, Swedish Central Bank	Recruited from the community through social media, schools, and organizations for youth mental health	IG1: Internet CBT (N=33) Description: Internet-based CBT consisting of 8 skill-based modules including reading assignments and videos plus 8 weekly 30-minute chat sessions with therapist highly structured to correspond to modules. Techniques included psychoeducation, behavioral activation, cognitive restructuring, affect regulation, anxiety management, and relapse prevention. Duration: 8 weeks	CG: Attention control (N=37) Therapist monitoring and nonspecific counseling to control for time and nonspecific treatment factors. Participants had access to the treatment platform to view depression scores and message their therapist. Participants were instructed to contact their therapist due to deterioration and received nonspecific support. Therapists were instructed not to use specific CBT techniques.	Some concerns

Appendix I Table 25. Depression Treatment Studies: Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Topooco et al, 2019[148] NCT02363205	Other very high HDI Sweden RCT The Swedish Central Bank	Recruited from the community through social media, schools, youth centers, and clinics across Sweden	IG1: Internet CBT (N=35) Description: Internet-based CBT consisting of 8 skill-based modules including reading assignments and videos plus 8 weekly 45-minute chat sessions with therapist highly structured to correspond to modules. Techniques included psychoeducation, behavioral activation, cognitive restructuring, affect regulation, anxiety management, and relapse prevention. Therapist chat sessions each week conducted within the platform. Duration: 8 weeks	CG: Attention control (N=35) Assigned a therapist, received an introductory personal platform in-mail from therapist, weekly assessments viewed by therapist, informed that therapist might contact them to follow-up on their wellbeing. Participants were allowed to seek regular care, which in Sweden is for free for adolescents.	Some Concerns
Wagner et al, 2006[151]	U.S. RCT Forest Laboratories	25 sites in the U.S.	IG1: Escitalopram (N=132) Description: Escitalopram, flexible dose, 10 to 20 mg/day based on clinical response and tolerability. Duration: 8 weeks	CG: Placebo (N=136) Placebo	Some concerns

Abbreviations: AE=adverse event; AHRQ=Agency for Healthcare Research and Quality; BA=behavioral activation; CBT=cognitive behavioral therapy; CG=control group; CGI-S=Clinical Global Impressions-Severity; CT=cognitive therapy; ED=emergency department; HDI=Human Development Index; HMO=health maintenance organization; IG=intervention group; IMPACT= Improving Mood-Promoting Access to Collaborative Treatment; IPT-A=Intensive Interpersonal Psychotherapy for Depressed Adolescents with Suicidal Risk; KQ=key question; MDD=major depressive disorder; NIMH=National Institute of Mental Health; NR=not reported; PCIT=Parent Child Interaction Therapy; PCIT-ED=Parent Child Interaction Therapy-Emotion Development; PCP=primary care provider; PHQ-9=Patient Health Questionnaire-9 question; RCT=randomized, controlled trial; ROAD= Reaching Out to Adolescents in Distress; SAMHSA=Substance Abuse and Mental Health Services Administration; SSRI=selective serotonin reuptake inhibitor; TAU=treatment as usual; U.S.=United States.

Appendix I Table 26. Depression Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Clarke et al, 2016[75] NCT00523081	Mean age (SD): 14.6 (1.7) N (%) Female: 145 (68.4) Race/Ethnicity: Hispanic: 34 (16) Racial minority status: 25 (11.8)	Ages 12 to 18 years meeting DSM-IV criteria for major depression and recently declined antidepressants or discontinued prematurely (<30 days)	Current antidepressant use, bipolar disorder, any psychotic disorder, mental retardation (IDD), autism spectrum disorder, imminent suicide risk, or received >/=CBT	MDD: 100%
Clarke et al, 2005[76] R01-HS10535, HS13854	Mean age (SD): 15.3 (1.6) N (%) Female: 120 (79) Race/Ethnicity: NR	Ages 12 to 18 years with a confirmed DSM episode of major depression who had been dispensed SSRIs	Chart indication of schizophrenia or significant developmental or intellectual disability	MDD: 100%
Clarke et al, 1999[45] None NA	Mean age (SD): 16.2 (1.3) completers N (%) Female: 87 (71) completers Race/Ethnicity: NR	Ages 14 to 18 years with a current DSM-III-R diagnosis of major depressive disorder or dysthymia	Current mania/hypomania, panic disorder, GAD, conduct disorder, psychoactive substance abuse/dependence, lifetime organic brain syndrome, mental retardation, or schizophrenia; receiving other treatment for depression and unwilling to discontinue; or needed immediate, acute treatment.	Primary diagnosis (% completers) MDD: 76% Dysthymia: 13% Comorbid MDD/Dysthymia: 11% Other comorbid disorders Current anxiety disorder: 24% History of nonaffective psychiatric disorder: 24% Recurrent affective disorder: 47%

Appendix I Table 26. Depression Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Emslie et al, 2009[86] Findling, 2013[227] NCT00107120	Mean age (SD): IG1: 14.7 (1.6) CG: 14.5 (1.5) N (%) Female: IG1: 92 (59) CG: 92 (59) Race/Ethnicity: White IG1: 113 (73) CG: 123 (78)	Ages 12 to 17 years meeting diagnostic criteria for MDD (DSM-IV) with duration of current episode at least 12 weeks based on K-SADS-PL; score ≥45 on the CDRS-R at screening and baseline; CGI-S score ≥4, Kaufman Brief Intelligence Test score ≥80; normal physical examination, laboratory tests, and ECG at screening. Caregiver capable of providing information about patient's condition. Family support to guarantee adequate safety monitoring.	Principal diagnosis meeting DSM-IV criteria for an Axis I disorder other than MDD; or met DSM-IV criteria at screening for ADD/ADHD, OCD, PTSD, bipolar disorder, pervasive developmental disorder, mental retardation, conduct disorder, or oppositional defiant disorder; history of any psychotic disorder, as defined by DSM-IV or seizures; personality disorder of sufficient severity to interfere with participation, past year history of anorexia nervosa, bulimia, or substance abuse or dependence (including alcohol); first-degree relative with bipolar disorder, considered suicide risk by investigators, positive test for alcohol or other prohibited medication on urine drug screen, not been treated with any antidepressant or anxiolytic medication within 2 weeks of baseline (4 weeks for fluoxetine), any neuroleptic or stimulant within 6 months of screening, or any investigational drug within 30 days or 5 half-lives before screening; been in a previous clinical study of citalopram or escitalopram, history of hypersensitivity reaction to any SSRI; failed to respond to an adequate trial of escitalopram or citalopram or to adequate trials of two other SSRIs; pregnant women or nursing mothers; and female subjects of childbearing potential not practicing a reliable birth control method.	Recurrent MDD: 29% Previous and/or ongoing secondary psychiatric disorders: 15% Antidepressant naive: 83%

Appendix I Table 26. Depression Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Fristad et al, 2019[90] NCT01341925	Mean age (SD): IG1: 11.7 (2.1) CG: 11.1 (2.4) N (%) Female: IG1: 10 (52) CG: 5 (27) Race/Ethnicity: Black IG1: 5 (26) CG: 4 (22) White IG1: 11 (58) CG: 12 (67) Asian IG1: 0 CG: 0 Biracial IG1: 3 (15) CG: 2 (11) Hispanic IG1: 2 (11) CG: 1 (6)	Ages 7 to 14 years diagnosed with MDD, DD, or DDNOS based on the DSM-IV-TR and a CDRS-R score ≥40 and at least 1 caregiver able to participate in followup procedures	Inability to swallow capsules, DSM-IV-TR autistic disorder, psychosis warranting antipsychotic medication, active suicidal concern, active psychotherapy or pharmacotherapy other than stable doses, ADHD or sleep aid medication, IQ <70, or lack of access to a phone	Anxiety disorder IG1: 79% CG: 78% ADHD IG1: 63% CG: 72% Disruptive behavior disorder IG1: 32% CG: 33% PTSD IG1: 16% CG: 11%

Appendix I Table 26. Depression Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Luby et al, 2018[111] NCT02076425	Mean age (SD): IG1: 5.1 (1.0) CG: 5.3 (1.1) N (%) Female: IG1: 38 (33) CG: 42 (36) Race/Ethnicity: African American IG1: 9 (8) CG: 17 (15) Caucasian IG1: 94 (82) CG: 82 (72) Asian IG1: 1 (1) CG: 0 More than 1 race IG1: 10 (9) CG: 16 (14)	Ages 3 to 6 years meeting early-onset MDD symptoms on the Preschool Age Psychiatric Assessment and subsequently diagnosed with MDD using K-SADS-EC by clinician.	Autism spectrum disorder, a serious neurological or chronic medical disorder; significant developmental delay; taking antidepressant medications or in ongoing psychotherapy; on unstable doses of other psychotropic medications; unstable caregiving; or depression judged as too severe to wait for 18 weeks for treatment	Anxiety IG1: 40% CG: 43% ADHD IG1: 46% CG: 33% Mania/hypomania IG1: 2 CG: 2 ODD IG1: 51 CG: 49 Conduct disorder IG1:3 CG: 3
March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286	Mean age (SD): 14.6 (1.5) N (%) Female: 236 (54.4) Race/Ethnicity: White: 320 (73.8) Black: 57 (12.5) Hispanic: 40 (8.9)	Ages 12 to 17 years meeting DSM-IV criteria for MDD, CDRS-R score of ≥45, IQ of ≥80, and not taking antidepressants. Stable ADHD medications were permitted.	Current or past diagnosis of bipolar disorder, severe conduct disorder, current substance abuse or dependence, PDD, thought disorder, concurrent treatment with psychotropic medication or psychotherapy outside the study, 2 failed SSRI trials, a poor response to clinical treatment containing CBT for depression, intolerance to fluoxetine, confounding medical condition, non-English speaking patient or parent, or pregnancy or refusal to use birth control	Primary/target condition MDD: 100% Other comorbid conditions Anxiety: 27% Disruptive behavior: 24% ADHD: 14% OCD: 3% Substance use: 2%

Appendix I Table 26. Depression Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Mufson et al, 2004[118] McGlinchey et al, 2017[228]	Mean age (SD): 15.1 (1.9) N (%) Female: 53 (84) Race/Ethnicity: Hispanic IG1: 26 (76.5) CG: 19 (65.5)	Ages 12 to 18 years, referred to mental health clinics in 1 of 5 school-based health clinics with a HAM-D score ≥10 and a CGAS store ≤64 at screening, DSM-IV diagnosis of MDD, dysthymia, adjustment disorder with depressed mood, or DDNOS.	Actively suicidal or mentally retarded, life threatening medical condition, substance use disorder diagnosis, psychosis, schizophrenia, current treatment for depression, or taking antidepressants.	Primary/target condition % Major depression IG1: 53% CG: 48% Dysthymic disorder IG1: 15% CG: 21% Double depression IG1: 6% CG: 7% DDNOS IG1: 12% CG: 10% Adjustment disorder with depressed mood IG1: 15% CG: 14% Other comorbid conditions % Anxiety disorders: 32% ODD: 16% Substance use: 16% ADHD: 6%
Richardson et al, 2014[127] NCT01140464	Mean age (SD): 15.3 (1.3) N (%) Female: 73 (72) Race/Ethnicity: White: 70 (69) Black: 5 (5) Asian/Pacific Islander: 2 (2) Other/multiracial: 24 (24)	Ages 13 to 17 years meeting MDD criteria on the K-SADS or a PHQ-9 ≥10 on 2 occasions with a CDRS-R score of >42. Adolescents taking antidepressants or receiving psychotherapy who were still symptomatic were eligible to participate.	Non-English speaking, suicidal plan or recent attempt, bipolar, drug/alcohol misuse (CRAFFT score ≥5), seeing a psychiatrist, or developmental delay.	Primary/target condition % Major depression K-SADS scale: 60% Treatment for depression/anxiety in prior 6 months: 39% Antidepressants in 6 months prior to baseline: 25% Undergoing active treatment at start of study: 17% Other comorbid conditions % Brief SCARED score ≥3: 72%

Appendix I Table 26. Depression Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Topooco et al, 2018[147] NCT02363205	Mean age (SD): IG1: 17.2 (1.0) CG: 16.9 (1.1) N (%) Female: IG1: 31 (94) CG: 35 (95) Race/Ethnicity: NR	Ages 15 to 19 years with a score of 14 or more on the BDI-II; at least 5 MDD symptoms or meeting MDD diagnosis on the MINI 6.0 (cut-off ≤16); adolescents with comorbid anxiety disorders included if depression was the primary concern; adolescents on medication for ADHD, anxiety, or depression included if dose was fixed in the past month and constant through study.	Severe suicidal ideation; severe comorbid psychiatric condition that might interfere with the treatment (e.g., bipolar disorder or schizophrenia); currently undergoing psychotherapy treatment; other medical problems that would require other treatments; or currently meeting diagnostic criteria for alcohol or substance misuse	Primary/target diagnosis MDD IG1: 85% CG: 68% Other comorbid conditions Anxiety IG1: 73% CG: 78%
Topooco et al, 2019[148] NCT02363205	Mean age (SD): IG1: 17.5 (1.1) CG: 17.5 (1.2) N (%) Female: IG1: 32 (91) CG: 35 (100) Race/Ethnicity: NR	Ages 15 to 19 years with a score of 14 or more on the BDI-II; at least 4 symptoms including 1 core symptom, or fulfilled criteria for MDD according to the MINI clinical interview; adolescents with comorbid anxiety disorders included if depression was the primary concern; adolescents on medication for ADHD, anxiety, or depression included if dose was stable for the previous month.	Adolescents receiving psychological therapy, were alcohol or drug dependent, showed severe suicidal ideation, or who had severe comorbid psychiatric conditions (e.g., bipolar disorder or psychotic symptoms).	Primary/target condition % MDD IG1: 77 CG: 74 Other comorbid conditions % Anxiety IG1: 71 CG: 69

Appendix I Table 26. Depression Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Wagner et al, 2006[151]	Mean age (SD): 12.3 (3.0) N (%) Female: 137 (52) Race/Ethnicity: White IG1: 93 (71) CG: 95 (71) Black IG1: 19 (15) CG: 17 (13) Asian IG1: 1 (1) CG: 2 (2) Other IG1: 18 (14) CG: 19 (14)	Ages 6 to 17 years, DSM-IV criteria for MDD, current episode at least 4 weeks duration, normal physical examination, laboratory tests, and EKG	Any primary psychiatric diagnosis other than MDD, any psychotic features, any severe personality disorder, ADHD, PTSD, bipolar disorder, PDD, mental retardation, conduct disorder, oppositional defiant disorder, eating disorder, substance abuse including alcohol within the past year; not practicing birth control, pregnant, or nursing; no psychotherapy or behavioral therapy within previous 3 months; hospitalized because of a suicide attempt or serious suicide attempts within the past year; treated with any antidepressant or anxiolytic medication within 2 weeks of baseline (4 weeks for fluoxetine), treatment with an antipsychotic or stimulant within 6 months before screening, receipt of an investigational drug 30 days before study entry, failure of adequate trial of escitalopram or citalopram or adequate trials of 2 other SSRIs, concomitant treatment with any psychotropic drug other than zolpidem or zaleplon for insomnia	Primary/target condition: MDD: 100%

Abbreviations: ADD=attention deficit disorder; ADHD=attention deficit hyperactivity disorder; BDI-II=Beck Depression Inventory, version 2; CBT=cognitive behavioral therapy; CDRS-R=Children's Depression Rating Scale-Revised; CG=control group; CGAS=Children's Global Assessment Scale; CGI-S=Clinical Global Impressions-Severity; DD=depressive disorder; DDNOS=depressive disorders not otherwise specified; DSM=Diagnostic and Statistical Manual of Mental Disorders; DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders-3rd edition-Revised; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders-4th edition-Revised; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders-4th edition-Revised, Text Revision; ECG=electrocardiogram; EKG=electrocardiogram; GAD=generalized anxiety disorder; HAM-D=Hamilton Depression Rating Scale; IDD=intellectual and developmental disability; IG=intervention group; IQ=intelligence quotient; KQ=key question; K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; K-SADS-EC=Schedule For Affective Disorders And Schizophrenia For School-Age Children-Early Childhood version; K-SADS-PL= Schedule For Affective Disorders And Schizophrenia For School-Age Children-Present and Lifetime version; MDD=major depressive disorder; MINI=Mini International Neuropsychiatric Interview; NA=not available; NR=not reported; OCD=obsessive compulsive disorder; ODD=oppositional defiant disorder; PDD=persistent depressive disorder; PHQ-9=Patient Health Questionnaire-9 question; PTSD=post-traumatic stress disorder; SCARED=Screen for Anxiety Related Emotional Disorders; SD=standard deviation; SSRI=selective serotonin reuptake inhibitor.

Appendix I Table 27. Depression Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Clarke et al, 2016[75] NCT00523081	IG1: CBT + TAU (N=106) CG: TAU (N=106)	CDRS, posttreatment (52 weeks and 104 weeks), ITT (IG1=106; CG=106), mean (SD) 52 weeks IG1: 30.14 (11.26) CG: 28.24 (10.54) Effect size d=0.278; mean difference: 2.25 (95% CI, -4.45 to 0.05) P<0.04 favoring CBT 104 weeks IG1: 28.11 (9.88) CG: 29.17 (10.79) Effect size d=0.145; mean difference: -1.30 (95% CI, -3.73 to 1.14) P<0.36 CES-D, posttreatment (52 weeks and 104 weeks), ITT (IG1=106; CG=106), mean (SD) 52 weeks IG1: 22.59 (7.00) CG: 22.51 (7.43) Effect size d=0.394; mean difference: -2.88 (95% CI: -4.87 to -0.89) P<0.005 favoring CBT 104 weeks IG1: 21.46 (7.44) CG: 21.91 (6.95) Effect size d=0.055; mean difference: -0.32 (95% CI: -1.91 to 1.27) P=0.62
Clarke et al, 2005[76] R01-HS10535, HS13854	IG1: Brief CBT + TAU SSRI (N=77) CG: TAU + SSRI (N=75)	CES-D scores posttreatment change from baseline to followup at week 52, completers (IG=53; CG=50), mean (SD) IG1: 11.5 (11.0) CG: 14.9 (10.1) Effect size=0.17, F=3.2 Time x Treatment interaction p=0.07 (no differences between CBT+SSRI vs. TAU+SSRI) HAM-D scores posttreatment change from baseline to followup at week 52, completers (IG1=53; CG=50), mean (SD) IG1: 4.9 (7.1) CG: 6.5 (6.6) Effect size=0.054, F=1.0 Time x Treatment interaction p=0.32 (no differences between CBT+SSRI vs. TAU+SSRI)

Appendix I Table 27. Depression Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Clarke et al, 1999[45] None NA	IG1: Group CBT (N=45) IG2: Group CBT plus parent sessions (N=42) CG: Wait-list (N=36)	BDI, posttreatment (8 weeks), completers (IG1=37; IG2=32; CG=27), mean (SD) IG1: 10.1 (9.1) IG2: 13.3 (10.9) CG: 16.0 (11.2) IG1/IG2 vs. CG P<0.01; effect size=0.61 HAM-D, posttreatment (8 weeks), completers (IG1=37; IG2=32; CG=27), mean (SD) IG1: 4.6 (4.8) IG2: 6.7 (7.1) CG: 7.7 (7.0) IG1/IG2 vs. CG P NS
Emslie et al, 2009[86] Findling, 2013[227] NCT00107120	IG1: Escitalopram (N=158) CG: Placebo (N=158)	CDRS-R, change from baseline to 8 weeks, ITT (IG1=154; CG=157), mean difference (SE) IG1: -22.1 (1.22) CG: -18.8 (1.27) LSMD (95% CI): -3.356 (-6.226 to -0.486); P=0.022, ES=0.27 CGI-I, 8 weeks, ITT (IG1=154; CG=157), mean difference (SE) IG1: 2.2 (0.11) CG: 2.6 (0.11) LSMD (95% CI): -0.344 (-0.595 to -0.092); P=0.008 CGI-S, change from baseline to 8 weeks, ITT (IG1=154; CG=157), mean difference (SE) IG1: -1.8 (0.11) CG: -1.4 (0.12) LSMD (95% CI): -0.37 (-0.64 to -0.10); P=0.007
Fristad et al, 2019[90] NCT01341925	IG1: Family CBT (N=19) CG: Placebo (N=18)	CDRS-R, posttreatment (12 weeks), ITT (IG1=18; CG=18), mean (SD) IG1: 30 (9) CG: 31 (11) Between-group change Cohen's d=0.04; P=0.880
Luby et al, 2018[111] NCT02076425	IG1: PCIT-ED (N=114) CG: Wait-list (N=115)	K-SADS-EC MDD core score, change from baseline to post-assessment, ITT (IG1=114; CG=115), adjusted mean difference (SE) 2.34 (0.26) Cohen's d=1.01; P<0.0001 PFC-scale, change from baseline to post-assessment, ITT (IG1=114; CG=115), adjusted mean difference (SE) 11.91 (1.29) Cohen's d=1.04; P<0.0001 Controlling for baseline characteristics, gender, and baseline externalizing disorder.

Appendix I Table 27. Depression Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
March et al, 2004[113] Curry et al, 2006 [217] Emslie et al, 2006 [218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286	IG1: Fluoxetine + CBT (N=107) IG2: Fluoxetine + CBT (N=107) IG3: Fluoxetine (N=109) CG: Placebo (N=112)	CDRS-R, 6 weeks, ITT (IG1=107; IG2=109; IG3=111; CG=112), adjusted mean (SD) IG1: 38.10 (7.78) IG2: 39.80 (7.37) IG3: 44.63 (8.30) CG: 44.90 (7.32) CDRS-R total, 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112), adjusted mean (SD) IG1: 33.79 (8.24) IG2: 36.30 (8.18) IG3: 42.06 (9.18) CG: 41.77 (7.99) Across 12 weeks time-by-treatment interaction P=0.001 based on linear random coefficient regression; planned pairwise comparisons IG1 vs. CG; P=0.001 IG2 vs. CG; P=0.10 IG3 vs. CG; P=0.40 Supplemental between-group comparisons of means at 12 weeks IG1 vs. CG; P=0.001 IG2 vs. CG; P=0.002 IG3 vs. CG; P=0.97 RADS, 6 weeks, ITT (IG1=107; IG2=109; IG3=111; CG=112), adjusted mean (SD) IG1: 60.90 (11.59) IG2: 63.41 (12.44) IG3: 69.10 (13.59) CG: 69.43 (10.94) RADS, 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112), adjusted mean (SD) IG1: 56.95 (12.24) IG2: 60.58 (13.07) IG3: 67.96 (14.18) CG: 66.68 (11.41)

Appendix I Table 27. Depression Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
March et al, 2004[113] Curry et al, 2006 [217] Emslie et al, 2006 [218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286 (continued)		Across 12 weeks time-by-treatment interaction P=0.001; based on linear random coefficient regression, planned pairwise comparisons IG1 vs. CG; P=0.001 IG2 vs. CG; P=0.34 IG3 vs. CG; P=0.21 Supplemental between-group comparisons of means at 12 weeks IG1 vs. CG; P=0.001 IG2 vs. CG; P=0.003 IG3 vs. CG; P=0.94 NOTE: Means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model
Mufson et al, 2004[118] McGlinchey et al, 2017 [228]	IG1: Interpersonal psychotherapy (N=34) CG: TAU (N=29)	BDI, posttreatment (week 12), ITT (IG1=34; CG=29), mean (SD) IG1: 8.4 (11.0) CG: 12.3 (9.7) P=0.14, effect size=0.37 Repeated measures ANOVA Time x Treatment interaction P=0.04 CGI-I, posttreatment (week 12), ITT (IG1=34; CG=29), mean (SD) IG1: 2.3 (1.3) CG: 3.1 (1.6) P=0.03, effect size=0.59 (95% CI, 0.24 to 0.94) CGI-S, posttreatment (week 12), ITT (IG1=34; CG=29), mean (SD) IG1: 2.3 (1.3) CG: 3.0 (1.4) P=0.03, effect size=0.48 (95% CI, 0.15 to 0.81) HAM-D, posttreatment (week 12), ITT (IG1=34; CG=29), mean (SD) IG1: 8.7 (8.0) CG: 12.8 (8.4) P=0.04, effect size=0.50 Repeated measures ANOVA Time x Treatment interaction P=0.003 HAM-D, week 16, mITT (IG1=33; CG=29), mean (SD) IG1: 6.9 (NR) CG: 10.6 (NR) P=0.04, effect size=0.51 (95% CI, 0.003 to 1.02)

Appendix I Table 27. Depression Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Richardson et al, 2014[127] NCT01140464	IG1: Collaborative care (N=50) CG: Enhanced usual care (N=51)	Modified CDRS-R, 6 months, ITT (IG1=50; CG=51), mean difference between groups (95% CI) -8.5 (-13.4 to -3.6), P=0.001 Modified CDRS-R, posttreatment (12 months), ITT (IG1=50; CG=51), mean (95% CI) IG1: 27.5 (23.8 to 31.1) CG: 34.6 (30.6 to 38.6) Modified CDRS-R, posttreatment (12 months), ITT (IG1=50; CG=51), mean difference between groups (95% CI) -9.4 (-15.0 to -3.8), P=0.001
Topooco et al, 2018[147] NCT02363205	IG1: Internet CBT (N=33) CG: Attention control (N=37)	BDI-II, posttreatment (8 weeks), ITT (IG1=33; CG=37), mean (SD) IG1: 19.9 (7.2) CG: 25.2 (7.8) Between-group Cohen's d (95% CI), baseline to 8 weeks: 0.71 (0.22 to 1.19), P<0.05 PHQ-9, posttreatment (8 weeks), ITT (IG1=33; CG=37), mean (SD) IG1: 9.7 (2.9) CG: 10.8 (3.0) Between-group Cohen's d (95% CI), baseline to 8 weeks: 0.36 (-0.10 to -0.84), P=NS
Topooco et al, 2019[148] NCT02363205	IG1: Internet CBT (N=35) CG: Attention control (N=35)	BDI-II, posttreatment (week 8), ITT (IG1=35; CG=35), mean (SD) IG1: 16.0 (11.3) CG: 24.8 (10.4) Between-group change from baseline ES NR; P<0.001 MFQ, posttreatment (week 8), ITT (IG1=35; CG=35), mean (SD) IG1: 24.3 (12.8) CG: 31.0 (9.8) Between-group change from baseline ES NR; P<0.01

Appendix I Table 27. Depression Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Wagner et al, 2006[151]	IG1: Escitalopram (N=132) CG: Placebo (N=136)	CDRS-R, baseline to posttreatment (8 weeks), ITT/LOCF (IG1=129; CG=132), adjusted mean change IG1: -21.9 CG: -20.2 P=0.31 CGI-S, baseline to posttreatment (8 weeks), ITT/LOCF (IG1=129; CG=132), adjusted mean change IG1: -1.6 CG: -1.3 P=0.057 CGI-I, posttreatment (8 weeks), ITT/LOCF (IG1=129; CG=132), adjusted mean IG1: 2.3 CG: 2.5 P=0.169

Abbreviations: ANOVA=analysis of variance; BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory, version 2; CBT=cognitive behavioral therapy; CDRS=Children's Depression Rating Scale; CDRS-R=Children's Depression Rating Scale-Revised; CES-D=Center for Epidemiological Studies-Depression; CG=control group; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; CI=confidence interval; ES=effect size; HAM-D=Hamilton Depression Rating Scale; IG=intervention group; ITT=intent to treat; KQ=key question; K-SADS-EC=Schedule For Affective Disorders And Schizophrenia For School-Age Children-Early Childhood version; LOCF=last observation carried forward; LSMD=least-square mean difference; MDD=major depressive disorder; MFQ=Mood & Feelings Questionnaire; mITT=modified intent to treat; NA=not available; NR=not reported; NS=not significant; PCIT-ED=Parent Child Interaction Therapy-Emotion Development; PFC=Preschool Feelings Checklist; PHQ-9=Patient Health Questionnaire-9 question; RADS=Reynolds Adolescent Depression Scale; SD=standard deviation; SE=standard error; SSRI=selective serotonin reuptake inhibitor; TAU=treatment as usual.

Appendix I Table 28. Depression Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Topooco et al, 2018[147] NCT02363205	IG1: Internet CBT (N=33) CG: Attention control (N=37)	BAI, posttreatment (8 weeks), ITT (IG1=33; CG=37), mean (SD) IG1: 20.6 (9.0) CG: 19.4 (8.6) Between-group Cohen's d (95% CI), baseline to 8 weeks: 0.14 (-0.33 to -0.60) SIAS, posttreatment (8 weeks), ITT (IG1=33; CG=37), mean (SD) IG1: 39.3 (1)
Topooco et al, 2019[148] NCT02363205	IG1: Internet CBT (N=35) CG: Attention control (N=35)	BAI, posttreatment (week 8), ITT (IG1=35; CG=35), mean (SD) IG1: 16.6 (10.3) CG: 20.0 (9.3) Between-group change from baseline ES NR; P NS SIAS, week 8, ITT (IG1=35; CG=35), mean (SD) IG1: 35.4 (19.0) CG: 35.1 (14.3) Between-group change from baseline ES NR; P NS

Abbreviations: BAI=Beck Anxiety Inventory; CBT=cognitive behavioral therapy; CG=control group; CI=confidence interval; ES=effect size; IG=intervention group; ITT=intent to treat; KQ=key question; NR=not reported; NS=not significant; SD=standard deviation; SIAS=Social Interaction Anxiety Scale.

Appendix I Table 29. Depression Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Clarke et al, 2016[75] NCT00523081	IG1: CBT + TAU (N=106) CG: TAU (N=106)	**Response** Major depression diagnostic response defined as ≥8 weeks below the threshold of 5 or more major depressive symptoms necessary for full diagnosis, but where full recovery has not yet occurred Time to response MDD response, 52 weeks, ITT (IG1=106; CG=106), mean (SD) 52 weeks IG1: 90 (90.9) CG: 87 (87.9) NNT: 34, OR: 1.39 (95% CI, 1.03 to 1.87) MDD response, 104 weeks, ITT (IG1=106; CG=106), mean (SD) IG1: 93 (93.9) CG: 91 (91.9) NNT: 50, OR: 1.38 (95% CI, 1.03 to 1.84) NNT ranged from 5 at posttreatment to 50 at the final followup point (week 102) Time to response IG1: Average of 13.3 weeks until response (95% CI, 10.6 to 15.9 [median, 9 weeks]) CG: Average of 18 weeks until response (95% CI, 14.7 to 21.3 [median, 12 weeks]) **Remission** Recovery defined as ≥8 weeks of no or minimal symptoms (K-SADS Diagnostic Status Rating ≤1-2) and little or no impairment Time to recovery MDD recovery, 104 weeks, ITT (IG1=106; CG=106), mean (SD) IG1: 79 (79.8) CG: 68 (68.7) NNT: 10, OR: 1.60 (95% CI, 1.15 to 2.21) MDD recovery, 104 weeks, ITT (IG1=106; CG=106), mean (SD) IG1: 88 (88.9) CG: 78 (78.8) NNT: 10, OR: 1.59 (95% CI, 1.17 to 2.17) Time to recovery IG1: Average of 22.6 weeks to recovery (95% CI ,18.8 to 26.5 [median, 15 weeks]) CG: Average of 30 weeks to recovery (95% CI, 25.3 to 34.7 [median, 23 weeks])

Appendix I Table 29. Depression Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Clarke et al, 2005[76] R01-HS10535, HS13854	IG1: Brief CBT + TAU SSRI (N=77) CG: TAU + SSRI (N=75)	**Response** Number of cases that moved over time from the disordered to the nondisordered CES-D ranges, using "moderately depressed" cutoff score of ≥16 and a "seriously depressed" score ≥24 Loss of depression (from moderately depressed to nondisordered range) CES-D ≥16 at 52 weeks, completers (IG1=53; CG=50), N (%) IG1: 13 (25) CG: 22 (44) Chi square=4.3, p=0.04 favoring CBT No differences at higher cut off level of ≥24 (scores not reported) **Remission** Number of cases that moved over time from the disordered to the nondisordered CES-D ranges Same as above **Other outcomes** Recurrence: Recurrence within 52 weeks among those who had recovered from their depression episode Recurrence of depression among those who had recovered 32 (24%) of 135, N by group NR IG1: 16 (not calculable) CG: 16 (not calculable) Chi squared=0.01, p=0.76
Clarke et al, 1999[45] None NA	IG1: Group CBT (N=45) IG2: Group CBT plus parent sessions (N=42) CG: Wait-list (N=36)	**Loss of diagnosis** No longer meeting DSM-III-R criteria for MDD or dysthymia Absence of MDD/dysthymia diagnoses, posttreatment (8 weeks), completers (IG1=37; IG2=32; CG=27), N (%) IG1: 24 (64.9) IG2: 22 (68.8) Combined IG1/IG2: 46 (66.7) CG: 13 (48.1) IG1/IG2 vs. CG, 1 tailed P<0.05; Cohen's h=0.38 OR: 2.15 (90% CI, 1.01 to 4.59)

Appendix I Table 29. Depression Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Emslie et al, 2009[86] Findling et al, 2013[227] NCT00107120	IG1: Escitalopram (N=158) CG: Placebo (N=158)	**Response** CGI-I ≤2 CDRS-R (40% decrease) CGI-I ≤2, 8 weeks, ITT (IG1=154; CG=157), N (%) IG1: 99 (64.3) CG: 83 (52.9) P=0.03 CDRS-R (40% decrease), 8 weeks, ITT (IG1=154; CG=157), N (%) IG1: 91 (59.1) CG: 76 (48.4) P=0.06 **Remission** Defined as CDRS-R ≤28 CDRS-R ≤28, 8 weeks, ITT (IG1=154; CG=157), N (%) IG1: 64 (41.6) CG: 56 (35.7) P=0.15
Fristad et al, 2019[90] NCT01341925	IG1: Family CBT (N=19) CG: Placebo (N=18)	**Remission** Defined as CDRS-R score ≤28 CDRS-R score ≤28, 12 weeks, ITT (IG1=18; CG=18), N (%) IG1: 11 (61) CG: 10 (56)
Luby et al, 2018[111] NCT02076425	IG1: PCIT-ED (N=114) CG: Wait-list (N=115)	**Loss of diagnosis** MDD diagnosis K-SADS-EC MDD diagnosis, change from baseline to post assessment (18 weeks), ITT (IG1=114; CG=115), aOR (95% CI) CG vs. IG1: 9.52 (8.44 to 10.74); P<0.0001 K-SADS-EC MDD diagnosis, change from baseline to post assessment, completers (IG1=100; CG=91), N (%), aOR (95% CI) IG1: 68 (75) CG: 22 (22) CG vs. IG1: 12.15 (5.95 to 24.82); P<0.0001 Both analyses controlling for baseline characteristics, gender, and baseline externalizing disorder. K-SADS-EC MDD diagnosis for all participants, multiply imputed.

Appendix I Table 29. Depression Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286	IG1: Fluoxetine + CBT (N=107) IG2: Fluoxetine + CBT (N=107) IG3: Fluoxetine (N=109) CG: Placebo (N=112)	**Response** CGI improvement score of 1 (very much improved) or 2 (much improved) CGI-I positive response, 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112), % with response (95% CI) adjusted for clinical site IG1: 71.0 (62 to 80) IG2: 60.6 (51 to 70) IG3: 43.2 (34 to 52) CG: 34.8 (26 to 44) P<0.001 Planned pairwise comparisons IG1 vs. CG; P=0.001 IG2 vs. CG; P=0.001 IG3 vs. CG; P=0.20 **Remission** CDRS-R score ≤28 CDRS-R score ≤28, 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112), % IG1: 40 (37) IG2: 25 (23) IG3: 14 (16) CG: 19 (17) OR (95% CI) IG1 vs. CG: 3.0 (1.58 to 5.79); P=0.0009 IG2 vs. CG: 1.5 (0.74 to 2.88); P=0.28 IG3 vs CG: 0.9 (0.44 to 1.88); P=0.80 **Loss of diagnosis** Loss of MDD diagnosis based on K-SADS-P/L Loss of MDD diagnosis, 12 weeks (posttreatment), completers (n=379), % IG1: 85.3 IG2: 78.6 IG3: 61.1 CG: 60.4 Overall treatment effect: P<0.0001 OR (95% CI) IG1 vs. CG: 4.1 (2.00 to 8.44); P=0.0001 IG2 vs. CG: 2.4 (1.27 to 4.67); P=0.007 IG3 vs. CG: 1.0 (0.52 to 1.77); P=0.89

Appendix I Table 29. Depression Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Mufson et al, 2004[118] McGlinchey et al, 2017[228]	IG1: Interpersonal psychotherapy (N=34) CG: TAU (N=29)	**Remission** HAM-D ≤6, posttreatment (week 12), ITT (IG1=34; CG=29), N (%) IG1: 17 (50) CG: 10 (34) P=NR BDI ≤9, posttreatment (week 12), ITT (IG1=34; CG=29), N (%) IG1: 25 (74) CG: 15 (52) P=0.048
Richardson et al, 2014[127] NCT01140464	IG1: Collaborative care (N=50) CG: Enhanced usual care (N=51)	**Response** ≥50% reduction in CDRS-R ≥50% reduction in CDRS-R, 6 months, ITT (IG1=50; CG=51), imputed % based on 20 multiple imputations IG1: 48.4 CG: 23.4 OR (95% CI): 3.1 (1.2 to 7.9), P=0.02 ≥50% reduction in CDRS-R, posttreatment (12 months), ITT (IG1=50; CG=51), imputed % based on 20 multiple imputations IG1: 67.6 CG: 38.6 OR (95% CI): 3.3 (1.4 to 8.2), P=0.009 **Remission** PHQ-9 <5 PHQ-9 <5, 6 months, ITT (IG1=50, CG=51), imputed % based on 20 multiple imputations IG1: 36.6 CG: 10.2 OR: 5.2 (1.6 to 17.3), P=0.007 PHQ-9 <5, posttreatment (12 months), ITT (IG1=50, CG=51), imputed % based on 20 multiple imputations IG1: 50.4 CG: 20.7 OR: 3.9 (1.5 to 10.6), P=0.007

Appendix I Table 29. Depression Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Richardson et al, 2014[127] NCT01140464 (continued)		**Other outcomes** Satisfaction with care (moderately to very satisfied) Satisfaction with care (moderately to very satisfied), 6 months, ITT (IG1=50; CG=51), imputed % based on 20 multiple imputations IG1: 85.8 CG: 52.2 OR (95% CI): 5.6 (1.9 to 16.0), P=0.001 Satisfaction with care (moderately to very satisfied), posttreatment (12 months), ITT (IG1=50; CG=51), imputed % based on 20 multiple imputations IG1: 82.2 CG: 68.5 OR (95% CI): 2.1 (0.7 to 6.1), P=0.001
Topooco et al, 2018[147] NCT02363205	IG1: Internet CBT (N=33) CG: Attention control (N=37)	**Response** A 30% or more decrease in symptoms on the BDI-II BDI-II ≥30% decrease, posttreatment (8 weeks), ITT (IG1=33; CG=37), N (%) IG1: 20 (60.6) CG: 12 (32.4) P<0.05 **Remission** 50% or more decrease in symptoms on the BDI-II BDI-II ≥50% decrease, posttreatment (8 weeks), ITT (IG1=33; CG=37), N (%) IG1: 14 (42.4) CG: 5 (13.5) P<0.01 **Loss of diagnosis** Loss of MDD diagnosis based on DSM-IV criteria Loss of diagnosis DSM-IV criteria for MDD, posttreatment (8 weeks), ITT (IG1=33; CG=37), N (%) IG1: 20 (71.4) CG: 4 (16.0) P<0.001 **Other outcomes** Deterioration of 30% or more in BDI-II score Deterioration of 30% or more in BDI-II score, completers (IG1=30; CG=36), N (%) IG1: 1 (3) CG: 3 (8) Deterioration of 30% or more in BDI-II score, ITT (IG1=33; CG=37), N (%) IG1: 4 (12) CG: NR

Appendix I Table 29. Depression Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Topooco et al, 2019[148] NCT02363205	IG1: Internet CBT (N=35) CG: Attention control (N=35)	**Response** Various definitions based on BDI-II criteria BDI-II ≥30% decrease, posttreatment (8 weeks), ITT (IG1=35; CG=35), N (%) IG1: NR CG: NR P=0.004 BDI-II ≥13, posttreatment (8 weeks), ITT (IG1=35; CG=35), N (%) IG1: NR CG: NR P=0.004 BDI-II ≥10, posttreatment (8 weeks), ITT (IG1=35; CG=35), N (%) IG1: NR CG: NR P≤0.001 **Remission** Clinically significant improvement defined as scoring 2 SD below the pretreatment mean for both conditions on the BDI-II, while also fulfilling the reliable change index criteria Clinically significant improvement, posttreatment (8 weeks), ITT (IG1=35, CG=35), N (%) IG1: 16 (46) CG: 4 (11) P=0.001 **Loss of diagnosis** No longer met DSM-5 criteria for MDD among those who met DSM-5 criteria at baseline No longer met MDD criteria, posttreatment (8 weeks), ITT (IG1=27; CG=26), N (%) IG1: 15 (56) CG: 7 (27) P=0.03 **Other outcomes** Deterioration defined as an increase of 30% or more on the BDI-II Deterioration BDI-II ≥30% increase, 8 weeks, completers (IG1=26; CG=31), N (%) IG1: 1 (3) CG: 0 (0)

Appendix I Table 29. Depression Treatment Studies: Response, Remission, and Loss of Diagnosis (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Wagner et al, 2006[151]	IG1: Escitalopram (N=132) CG: Placebo (N=136)	**Response** CDRS-R total score ≤28 CGI-I ≤2 CDRS-R response, posttreatment (8 weeks), ITT (IG1=129; CG=132), N (%) IG: 59 (45.7) CG: 50 (37.9) P=0.32 CGI-I response, posttreatment (8 weeks), ITT (IG1=129; CG=132), N (%) IG: 81 (62.8) CG: 69 (52.3) P=0.14

Abbreviations: aOR=adjusted odds ratio; BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory, version 2; CBT=cognitive behavioral therapy; CDRS-R=Children's Depression Rating Scale-Revised; CES-D=Center for Epidemiological Studies-Depression; CG=control group; CGI=Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CI=confidence interval; DSM-5=Diagnostic and Statistical Manual of Mental Disorders-5th edition; DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders-3rd edition-Revised; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders-4th edition; HAM-D=Hamilton Depression Rating Scale; IG=intervention group; ITT=intent to treat; KQ=key question; K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; K-SADS-EC=Schedule For Affective Disorders And Schizophrenia For School-Age Children-Early Childhood version; K-SADS-P=Schedule for Affective Disorders and schizophrenia for School-Age Children-Parent; MDD=major depressive disorder; NA=not available; NNT=number needed to treat; NR=not reported; OR=odds ratio; PCIT-ED=Parent Child Interaction Therapy-Emotion Development; PHQ-9=Patient Health Questionnaire-9 question; SD=standard deviation; SSRI=selective serotonin reuptake inhibitor; TAU=treatment as usual.

Appendix I Table 30. Depression Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes/ Subgroups
Clarke et al, 2016[75] NCT00523081	IG1: CBT + TAU (N=106) CG: TAU (N=106)	CGAS, 52 weeks, ITT (IG1=106; CG=106), mean (SD) IG1: 72.33 (9.97) CG: 74.10 (10.81) Effect size: d=0.431; mean difference: 4.2 (95% CI, 1.55 to 6.86) P<0.007 favoring CBT CGAS, 104 weeks, ITT (IG1=106; CG=106), mean (SD) IG1: 76.86 (11.03) IG2: 76.45 (11.09) Effect size: d=0.016; mean difference: 0.13 (95% CI, -2.08 to 2.34) P=0.21 PEDS-QL, 104 weeks, ITT (IG1=106; CG=106), mean (SD) 52 weeks IG1: 75.40 (14.57) CG: 76.94 (12.43) Effect size: d=0.04; mean difference: 0.55 (95% CI, -3.21 to 4.31) P=0.73 PEDS-QL, 104 weeks, ITT (IG1=106; CG=106), mean (SD) IG1: 75.40 (14.57) CG: 76.94 (12.43) Effect size: d=0.09; mean difference: 1.05 (95% CI, -2.27 to 4.36) P=0.90	
Clarke et al, 2005[76] R01-HS10535, HS13854	IG1: Brief CBT + TAU SSRI (N=77) CG: TAU + SSRI (N=75)	CGAS, 52 weeks, completer (IG1=53, CG=50), mean (SD) IG1: 71.4 (8.7) CG: 68.4 (7.6) Time x Treatment interaction p=0.22, F=1.52 Effect size=0.09; no detectable advantage of CBT SF-12 Mental Component Scale IG1: 45.4 (9.3) CG: 43.1 (10.2) Time x Treatment interaction p=0.04, F=4.25 Effect size=0.20 favoring CBT condition SF-12 Physical Component Scale IG1: 49.0 (5.8) CG: 48.1 (8.5) Time x Treatment interaction p=0.84, F=0.04 Effect size=0.11; no detectable advantage	Recurrence of depression among those who had recovered 32 (24%) of 135, N by group NR IG1: 16 (not calculable) CG: 16 (not calculable) Chi squared=0.01, p=0.76, No subgroups of interest reported

Appendix I Table 30. Depression Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes/ Subgroups
Clarke et al, 1999[45] None NA	IG1: Group CBT (N=45) IG2: Group CBT plus parent sessions (n=42) CG: Wait-list (N=36)	GAF, posttreatment (8 weeks), completers (IG1=37; IG2=32; CG=27), mean (SD) IG1: 71.0 (11.7) IG2: 69.9 (14.9) CG: 64.5 (11.8) IG1/IG2 vs. CG: P<0.05; effect size=0.54	
Emslie et al, 2009[86] Findling, 2013[227] NCT00107120	IG1: Escitalopram (N=158) CG: Placebo (N=158)	CGAS, change from baseline to 8 weeks, ITT (IG1=154; CG=157), mean difference (SE) IG1: 14.9 (1.11) CG: 12.7 (1.15) LSMD (95% CI): 2.169 (-0.439 to 4.777); P=0.103	
Luby et al, 2018[111] NCT02076425	IG1: PCIT-ED (N=114) CG: Wait-list (N=115)	CGAS core score, change from baseline to post assessment, ITT (IG1=114; CG=115), adjusted mean difference (SE) -20.5 (2.3) Cohen's d=1.2; P<0.0001 PECFAS/CAFAS, change from baseline to post assessment, ITT (IG1=114; CG=115), adjusted mean difference (SE) 3.19 (0.46) Cohen's d=0.78; P<0.0001 Controlling for baseline characteristics, gender, and baseline externalizing disorder	

Appendix I Table 30. Depression Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes/ Subgroups
March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286	IG1: Fluoxetine + CBT (N=107) IG2: Fluoxetine + CBT (N=107) IG3: Fluoxetine (N=109) CG: Placebo (N=112)	CGAS, 6 weeks, ITT (IG1=107; IG2=109; IG3=111; CG=112), unadjusted mean (SD) IG1: 62.4 (11.2) IG2: 59.9 (10.58) IG3: 56.7 (9.66) CG: 57.0 (9.22) CGAS, 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112), unadjusted mean (SD) IG1: 66.6 (11.91) IG2: 62.1 (11.91) IG3: 60.0 (11.47) CG: 59.3 (12.72) Across 12 weeks time-by-treatment interaction P<0.001; based on linear random coefficient regression, pairwise comparisons IG1 vs. CG: P<0.0001 IG2 vs. CG: P=0.0381 IG3 vs. CG: P=0.3805 CGAS, 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112) GLM mean change from baseline (SD) IG1: 16.7 (12.31) IG2: 12.6 (12.31) IG3: 9.7 (12.12) CG: 9.9 (12.38) IG1 vs. CG: P<0.0001 IG2 vs. CG: P=NS IG3 vs. CG: P=NS Rate of nonimpaired patients (CGAS >70), 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112), % IG1: 37 (34.6) IG2: 22 (20.2) IG3: 15 (13.5) CG: 21 (18.7) Between-group difference: p=0.002 IG1 vs. CG: P=0.009 IG2 vs. CG: P=NS IG3 vs. CG: P=NS	

Appendix I Table 30. Depression Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes/ Subgroups
March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286 (continued)		HoNOSCA, 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112), unadjusted mean (SD) IG1: 9.5 (5.97) IG2: 10.9 (6.35) IG3: 11.7 (6.09) CG: 11.2 (6.15) Across 12 weeks time-by-treatment interaction P=0.0234; based on linear random coefficient regression, pairwise comparisons IG1 vs. CG: P=0.0393 IG2 vs. CG: p=0.5861 IG3 vs. CG: p=0.3344 HoNOSCA, 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112), GLM mean change from baseline (SD) IG1: -6.3 (5.69) IG2: -5.1 (5.74) IG3: -3.6 (5.58) CG: -4.2 (5.71) IG1 vs. CG: P<0.01 IG2 vs. CG: P=NS IG3 vs. CG: P=NR PQ-LES-Q, 12 weeks, ITT (IG1=107; IG2=109; IG3=111; CG=112), unadjusted mean (SD) IG1: 54.7 (11.21) IG2: 51.2 (10.43) IG3: 47.4 (10.84) CG: 48.2 (9.91) Across 12 weeks time-by-treatment interaction P<0.001; based on linear random coefficient regression, pairwise comparisons IG1 vs. CG: P<0.0001 IG2 vs. CG: P=0.7215 IG3 vs. CG: P=0.4630	

Appendix I Table 30. Depression Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes/ Subgroups
March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286 (continued)		PQ-LES-Q, 12 weeks, ITT (IG1=107; IG2=109; IG3=111; CG=112), GLM mean change from baseline (SD) IG1: 9.6 (10.14) IG2: 6.6 (10.23) IG3: 4.2 (10.01) CG: 5.2 (10.16) IG1 vs. CG: P<0.001 IG2 vs. CG: P=NS IG3 vs. CG: P=NS IG3: -3.6 (5.58) CG: -4.2 (5.71) IG1 vs. CG: P<0.01 IG2 vs. CG: P=NS IG3 vs. CG: P=NR PQ-LES-Q, 12 weeks, ITT (IG1=107; IG2=109; IG3=111; CG=112), unadjusted mean (SD) IG1: 54.7 (11.21) IG2: 51.2 (10.43) IG3: 47.4 (10.84) CG: 48.2 (9.91) Across 12 weeks time-by-treatment interaction P<0.001; based on linear random coefficient regression, pairwise comparisons IG1 vs. CG: P<0.0001 IG2 vs. CG: P=0.7215 IG3 vs. CG: P=0.4630 PQ-LES-Q, 12 weeks, ITT (IG1=107; IG2=109; IG3=111; CG=112), GLM mean change from baseline (SD) IG1: 9.6 (10.14) IG2: 6.6 (10.23) IG3: 4.2 (10.01) CG: 5.2 (10.16) IG1 vs. CG: P<0.001 IG2 vs. CG: P=NS IG3 vs. CG: P=NS	

Appendix I Table 30. Depression Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes/ Subgroups
Mufson et al, 2004[118] McGlinchey et al, 2017[228]	IG1: Interpersonal psychotherapy (N=34) CG: TAU (N=29)	CGAS, posttreatment (week 12), ITT (IG1=34; CG=29), mean (SD) IG1: 66.7 (13.0) CG: 59.5 (13.5) P=0.04, effect size=0.54 CGAS, week 16, mITT (IG1=33; CG=29), mean (SD) IG1: NR CG: NR P=0.06, effect size NR SAS-SR Overall, posttreatment (week 12), ITT (IG1=34; CG=29), mean (SD) IG1: 2.23 (0.66) CG: 2.59 (0.67) P=0.01, effect size=0.55 Repeated measures ANOVA Time x Treatment interaction P=0.003	
Richardson et al, 2014[127] NCT01140464	IG1: Collaborative care (N=50) CG: Enhanced usual care (N=51)	CIS, posttreatment (12 months), ITT (IG1=50; CG=51), mean (95% CI) IG1: 16.3 (13.8 to 18.8) CG: 13.4 (10.8 to 15.9) CIS, 6 months, ITT (IG1=50; CG=51), mean difference between groups (95% CI) -4.4 (-8.4 to -0.5), P=0.03 CIS, posttreatment (12 months), ITT (IG1=50; CG=51), m ean difference between groups(95% CI) -4.3 (-8.3 to -0.3), P=0.04	Satisfaction with care (moderately to very satisfied), 6 months, ITT (IG1=50; CG=51), imputed % based on 20 multiple imputations IG1: 85.8 CG: 52.2 OR (95% CI): 5.6 (1.9 to 16.0), P=0.001 Satisfaction with care (moderately to very satisfied), posttreatment (12 months), ITT (IG1=50; CG=51), imputed % based on 20 multiple imputations IG1: 82.2 CG: 68.5 OR (95% CI): 2.1 (0.7 to 6.1), P=0.001

Appendix I Table 30. Depression Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes/ Subgroups
Topooco et al, 2018[147] NCT02363205	IG1: Internet CBT (N=33) CG: Attention control (N=37)	NR	Deterioration of 30% or more in BDI-II score, completers (IG1=30; CG=36), N (%) IG1: 1 (3) CG: 3 (8) Deterioration of 30% or more in BDI-II score, ITT (IG1=33; CG=37), N (%) IG1: 4 (12) CG: NR
Topooco et al, 2019[148] NCT02363205	IG1: Internet CBT (N=35) CG: Attention control (N=35)	NR	Deterioration BDI-II ≥30% increase, 8 weeks, completers (IG1=26; CG=31), N (%) IG1: 1 (3) CG: 0 (0)
Wagner et al, 2006[151]	IG1: Escitalopram (N=132) CG: Placebo (N=136)	CGAS, baseline to posttreatment (8 weeks), ITT/LOCF (IG1=129; CG=132), adjusted mean change IG1: 15.6 CG: 12.7 P=0.065	NR

Abbreviations: ANOVA=analysis of variance; BDI-II=Beck Depression Inventory, version 2; CAFAS=Child and Adolescent Functional Assessment Scale; CBT=cognitive behavioral therapy; CG=control group; CGAS=Children's Global Assessment Scale; CI=confidence interval; CIS=Columbia Impairment Scale; GAF=Global Assessment of Functioning; GLM=general linear model; HoNOSCA=Health of the Nation Outcome Scales for Children and Adolescents; ITT=intent to treat; KQ=key question; LOCF=last observation carried forward; LSMD=least-square mean difference; mITT=modified intent to treat; NA=not available; NR=not reported; NS=not significant; OR=odds ratio; PCIT-ED=Parent Child Interaction Therapy-Emotion Development; PECFAS= Preschool and Early Childhood Functional Assessment Scale/Child and Adolescent Functional Assessment Scale; PEDS-QL= Pediatric Quality of Life Inventory; PQ-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; SAS-SR=Social Adjustment Scale-Self Report; SD=standard deviation; SE=standard error; SF-12=Short Form-12; SSRI=selective serotonin reuptake inhibitor; TAU=treatment as usual.

Appendix I Table 31. Depression Treatment Studies: Suicide-Related Harms and Suicide-Related Withdrawal (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
Clarke et al, 2016[75] NCT00523081	IG1: CBT + TAU (N=106) CG: TAU (N=106)	K-SADS suicidal behavior, 52 weeks, ITT (IG1=106; CG=106), n (%) IG1: 5 (5.8) CG: 2 (2.4) Effect size NNT=37, OR: 1.03 (95% CI, 0.47 to 2.27) P=0.27 K-SADS suicidal behavior, 104 weeks, ITT (IG1=106; CG=106), n (%) IG1: 1 (1.1) CG: 1 (1.1) Effect size NNT=11, OR: 1.21 (95% CI, 0.32 to 3.78) P=0.51
Emslie et al, 2009[86] Findling, 2013[227] NCT00107120	IG1: Escitalopram (N=158) CG: Placebo (N=158)	Self-harm related AE (other than suicidality), baseline to 8 weeks, ITT (IG1=155; CG=157), N (%) IG1: 6 (3.9) CG: 6 (3.8) See efficacy section for additional measures related to suicidality IG: 0 CG: 1 (withdrawal from study for insufficient therapeutic response and initiation of commercially available escitalopram)
March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286	IG1: Fluoxetine + CBT (N=107) IG2: Fluoxetine + CBT (N=107) IG3: Fluoxetine (N=109) CG: Placebo (N=112)	See suicide outcomes in efficacy section for SIQ-Jr scores Suicide-related AEs, 12 weeks, ITT (IG1=107; IG2=109; IG3=111; CG=112), N (%) IG1: 6 (5.61) reported in March et al; 5 (4.7%) reported in Emslie et al IG2: 9 (8.26) reported in March et al; 10 (9.2%) reported in Emslie et al IG3: 5 (4.50) CG: 4 (3.57) reported in March et al; 3 (5.2%) reported in Emslie et al Suicide-related AEs, OR (95% CI) vs. CG IG1: 1.6 (0.44 to 5.85) IG2: 2.4 (0.73 to 8.14) IG3: 1.3 (0.33 to 4.87) CG: NA Suicide attempts, ITT (IG1=107; IG2=109; IG3=111; CG=112), N (calculated %) IG1: 2 (1.9%) reported in Emslie et al; 4 (3.7%) reported in March et al IG2: 2 (1.83%) IG3: 1 (0.90%) CG: 0 N of events too small to allow statistical comparison of suicide events No completed suicides

Appendix I Table 31. Depression Treatment Studies: Suicide-Related Harms and Suicide-Related Withdrawal (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Suicide-Related Symptoms
Wagner et al, 2006[151]	IG1: Escitalopram (N=132) CG: Placebo (N=136)	Potential suicide-related events, posttreatment (8 weeks), safety (IG1=131; CG=133), N (%) IG1: 1 (7.8) CG: 2 (1.5) Withdrawal due to suicidal ideation, posttreatment (8 weeks), safety (IG1=131; CG=133), N (%) IG1: 0 (0) CG: 0 (0)

Abbreviations: AE=adverse event; CBT=cognitive behavioral therapy; CG=control group; CI=confidence interval; IG=intervention group; ITT=intent to treat; KQ=key question; K-SADS=Schedule for Affective Disorders and schizophrenia for School-Age Children; NA=not available; NNT=number needed to treat; OR=odds ratio; SIQ=Suicidal Ideation Questionnaire; TAU=treatment as usual.

Appendix I Table 32. Depression Treatment Studies: Harms (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Incidence Any AEs	Incidence of SAEs	Withdrawal Due to AE	Other Harms
Emslie et al, 2009[86] Findling, 2013[227] NCT00107120	IG1: Escitalopram (N=158) CG: Placebo (N=158)	Total adverse events, baseline to 8 weeks, safety population (IG=155; CG=157), N (%) IG1: 121 (78.1) CG: 118 (75.2)	SAEs, baseline to 8 weeks, safety population (IG1=155; CG=157), N (%) IG1: 4 (2.6) (1 sexual assault, 1 self-injurious behavior, 1 suicidal ideation, 1 irritability) CG: 2 (1.3) (1 suicidal tendency, 1 aggravated depression)	Discontinued due to AEs, baseline to 8 weeks, safety population (IG1=155; CG=157), N (%) IG1: 4 (2.6) CG: 1 (0.6) P=0.21 IG: 0 CG: 1 (withdrawal from study for insufficient therapeutic response and initiation of commercially available escitalopram)	NR
March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286	IG1: Fluoxetine + CBT (N=107) IG2: Fluoxetine + CBT (N=107) IG3: Fluoxetine (N=109) CG: Placebo (N=112)	Physical AEs requiring medical attention or causing dysfunction, 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112), N patients [N events] (%) IG1: 37 [61] (34.5) IG2: 35 [81] (32.1) IG3: 9 [NR] (8.1) CG: 34 [60] (30.4) Any psychiatric-related AEs, 12 weeks (posttreatment), ITT (IG1=107; IG2=109; IG3=111; CG=112), N patients [N events] (%) IG1: 12 [16] (15) IG2: 20 [23] (21) IG3: 1 [1] (1) CG: 9 [11] (9.8)	Serious AEs, 12 weeks, ITT (IG1=107; IG2=109; IG3=111; CG=112), N (%) IG1: 9 (8.41) IG2: 13 (11.93) IG3: 5 (4.50) CG: 6 (5.36) Serious AEs, OR (95% CI) vs. CG: IG1: 1.6 (0.56 to 4.72) IG2: 2.4 (0.87 to 6.54) IG3: 0.8 (0.25 to 2.81) CG: NA Between-group P=0.15 NOTE: ORs ≤2 reflect little or no increased risk	NR	NR

Appendix I Table 32. Depression Treatment Studies: Harms (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Incidence Any AEs	Incidence of SAEs	Withdrawal Due to AE	Other Harms
March et al, 2004[113] Curry et al, 2006[217] Emslie et al, 2006[218] Kennard et al, 2006[219] Vitiello et al, 2006[220] NCT00006286 (continued)			Serious psychiatric-related AEs, 12 weeks, ITT (IG1=107; IG2=109; IG3=111; CG=112), N patients [N events], (calculated %) IG1: 0 IG2: 1 [1] (0.92) (worsening depression, also captured below) IG3: 0 CG: 1 [1] (0.89) (mania, also captured below) These events more frequent in fluoxetine arms (IG1 and IG2) than CBT (IG3) or placebo (CG), but P=NR		
Richardson et al, 2014[127] NCT01140464	IG1: Collaborative care (N=50) CG: Enhanced usual care (N=51)	NR	NR	NR	Psychiatric Hospitalization, ITT (IG1=50; CG=51), N(%) IG: 3 (6) CG: 2 (4) Emergency Department Visit with a Primary Psychiatric Diagnosis, ITT (IG1=50; CG=51), N(%) IG: 1 (2) CG: 5 (10)

Appendix I Table 32. Depression Treatment Studies: Harms (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Incidence Any AEs	Incidence of SAEs	Withdrawal Due to AE	Other Harms
Wagner et al, 2006[151]	IG1: Escitalopram (N=132) CG: Placebo (N=136)	Any AE, posttreatment (8 weeks), safety (IG1=131; CG=133), N (%) IG1: 90 (68.7) CG: 90 (67.7) P=0.90	Any SAE, posttreatment (8 weeks), safety (IG1=131; CG=133), N (%) IG1: 2 (1.5), pneumonia, accidental injury CG: 3 (2.3) (allergic reaction, manic reaction, worsening depression)	Withdrawal due to any AE, posttreatment (8 weeks), safety (IG1=131; CG=133), N (%) IG1: 2 (1.5) CG: 2 (1.5) Withdrawal due to suicidal ideation, posttreatment (8 weeks), safety (IG1=131; CG=133), N (%) IG1: 0 (0) CG: 0 (0)	NR

Abbreviations: AE=adverse event; CBT=cognitive behavioral therapy; CG=control group; CI=confidence interval; IG=intervention group; ITT=intent to treat KQ=key question; NA=not available; NR=not reported; OR=odds ratio; SAE=serious adverse event.

Appendix I Table 33. Depression Studies: Characteristics of Systematic Reviews, Meta-Analyses, or Network Meta-Analyses (KQ 5)

Author, Year	Study Design	Search Dates Covered	Study Selection Criteria	Included Studies (Participants)
Cipriani et al, 2016[161]	Network meta-analysis	Database inception through May 3015	• Double-blind RCTs comparing any antidepressant with placebo or another antidepressant as oral therapy for the acute treatment of children and adolescents with MDD, without restrictions on language. • Eligible medications (as long as administered within the therapeutic dose range) included amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, and venlafaxine. • Studies were excluded if they focused on treatment-resistant depression, had a duration less than 4 weeks, or had fewer than 10 patients.	34 RCTs (5,260) Mean (range) sample size: 159 (23 to 463) % Female: 53 Mean (SD) age: 13.6 (2.87) Median (range) duration of treatment: 8 weeks (5 to 12) % conducted in North America: 50 % high risk of bias: 29 % moderate risk of bias: 59 % low risk of bias: 12

Abbreviations: KQ=key question; MDD=major depressive disorder; RCT=randomized controlled trial; SD=standard deviation.

Appendix I Table 34. Depression Studies: Results of Systematic Reviews, Meta-Analyses, or Network Meta-Analyses (KQ 5)

Author, Year	Adverse Event Findings	Suicidality Findings
Cipriani et al, 2016[161]	Discontinuations due to AEs, OR (95% CI) Clomipramine vs. placebo: 1.01 (0.43 to 2.38) Duloxetine vs. placebo: 2.75 (1.18 to 6.44) Escitalopram vs. placebo: 1.90 (0.44 to 8.28) Fluoxetine vs. placebo: 1.09 (0.44 to 2.72) Sertraline vs. placebo: 3.60 (1.40 to 10.63) Surface under the cumulative ranking curve (larger values indicate more tolerable medications) Placebo: 82.5% Fluoxetine: 75.7% Clomipramine: 57.2% Escitalopram: 47.3% Duloxetine: 33.9% Sertraline: 29.6%	Suicide behavior or ideation (measures not specified) Clomipramine vs. placebo: 0.82 (0.29 to 2.38) Duloxetine vs. placebo: 0.90 (0.55 to 1.48) Escitalopram vs. placebo: 0.99 (0.47 to 2.08) Fluoxetine vs. placebo: 1.12 (0.72 to 1.73) Sertraline vs. placebo: 1.92 (0.33 to 11.06) Surface under the cumulative ranking curve (larger values indicate safer interventions with respect to suicide behavior or ideation) Placebo: 65.6% Duloxetine: 65.3% Escitalopram: 60.4% Clomipramine: 59.7% Fluoxetine: 53.3% Sertraline: 28.0%

Abbreviations: AE=adverse event; CI=confidence interval; KQ=key question; MDD=major depressive disorder; OR=odds ratio; RCT=randomized, controlled trial; SD=standard deviation.

Appendix I Table 35. Anxiety or Depression Treatment Studies: Study Characteristics (KQ 4 & KQ 5)

Author, Year Registry Number	Country Study Design Funding	Setting	Intervention(s)	Comparator	Quality
Ehrenreich-May et al, 2017[84]	U.S. RCT National Institute of Mental Health	Potential participants and their parents were referred to the clinic by teachers, school counselors, pediatricians, psychiatrists, other mental health and health care professionals, or were self-referred through community flyers or online program information	IG1: UP-A (N=27) Description: Unified Protocol for the Treatment of Emotional Disorders in Adolescents (UP-A) with 5 core modules (Getting to Know Your Emotions and Behaviors; Awareness of Emotions; Being Flexible in Your Thinking; Emotion Exposure; and Keep it Going: Maintaining Your Gains) and 3 supplemental modules (Building and Keeping Motivation; Keeping Safe/Dealing with Difficult Times; and Parenting the Emotional Adolescent) Duration: 8 to 21 weeks, average participant received 14.86 weeks of treatment	CG: Wait-list (N=24) Delayed treatment wait-list lasting 8 weeks	Some concerns
Weersing et al, 2017[156] Brent et al, 2019[229] NCT01147614	U.S. RCT National Institute of Mental Health	Nine pediatric primary care settings in San Diego and Pittsburgh. Participants were clinically referred by pediatrics staff or self-referred from flyers in practices.	IG1: Brief behavioral therapy (N=95) Description: 8 to 12 weekly 45-minute sessions completed over 16 weeks. Exposure and behavioral activation were combined through graded engagement in avoided activities and supplemented by relaxation to manage somatic symptoms and problem-solving skills to aid in stress management. Duration: 16 weeks	CG: Assisted referral (N=90) Participants in the assisted referral condition received feedback about symptoms and benefits of services, referrals, and education about obtaining services and problems-solving barriers to treatment. The study coordinator contacted the youth's primary caregiver at least every 2 weeks during the acute treatment phase to check in and problem solve obstacles to care. ARC coordinators connected 82.2% of families with specialty mental health care for a mean of 6.5 outpatient sessions.	Some concerns

Abbreviations: ARC=assisted referral to care; CG=control group; IG=intervention group; KQ=key question; RCT=randomized, controlled trial; UP-A=Unified Protocol for the Treatment of Emotional Disorders in Adolescents.

Appendix I Table 36. Anxiety or Depression Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Ehrenreich-May et al, 2017[84]	Mean age (SD): 15.77 (1.66) N (%) Female: 29 (56.9) Race/Ethnicity: Hispanic/Latino: 30 (59) Non-Hispanic White: 12 (24) African American: 4 (8) Asian American: 1 (2) Other: 4 (8)	Ages 12 to 17 years with a primary diagnosis of any DSM-IV anxiety disorder (including obsessive compulsive disorder) and/or depression diagnosis. Adolescents currently on psychotropic medication were required to have been on a stable dosage of an SSRI for 3 months, or 1 month for a benzodiazepine, prior to enrolling in the study.	Bipolar disorder, recent psychiatric hospitalization or severe suicidal ideation, significant cognitive impairment (suspected IQ below 80), or with treatment-interfering substance abuse. Had previously received CBT for anxiety or depression.	Principal diagnosis % Generalized anxiety disorder: 41.2% Social phobia: 31.4% Major depressive disorder: 21.6% Obsessive compulsive disorder: 5.9% Anxiety disorder, NOS: 5.9% Panic disorder without agoraphobia: 3.9% Specific phobia: 3.9% Dysthymic disorder: 3.9% Posttraumatic stress disorder: 3.9% Panic disorder with agoraphobia: 2.9% Depressive disorder, NOS: 2.9% Trichotillomania: 2% Comorbid diagnosis % Generalized anxiety disorder: 27.5% Social phobia: 19.6% Major depressive disorder: 29.4% Obsessive compulsive disorder: 7.8% Anxiety disorder, NOS: 17.6% Panic disorder without agoraphobia: 3.9% Specific phobia: 21.6% Dysthymic disorder: 3.9% Posttraumatic stress disorder: 2% Depressive disorder, NOS: 15.7% Trichotillomania: 2% Attention deficit/hyperactivity disorder: 15.7% Separation anxiety disorder: 2% Eating disorder, NOS: 2% Learning disorder: 2% Substance-related disorder: 2% Communication disorder: 2%

Appendix I Table 36. Anxiety or Depression Treatment Studies: Population Characteristics (KQ 4 & KQ 5)

Author, Year, Registry Number	Patient Characteristics: Age, Mean (SD) Female, N (%) Race/Ethnicity	Inclusion Criteria	Exclusion Criteria	Prevalence of Psychiatric/ Behavioral Conditions
Weersing et al, 2017[156] Brent et al, 2019[229]	Mean age (SD): 11.3 (2.6) N (%) Female: 107 (57.8) Race/Ethnicity: White: 144 (77.8) Hispanic: 38 (20.7)	Ages 8 to 16 years meeting DSM-IV criteria for full or probable diagnoses of SepAD, GAD, SocAD, MDD, dysthymic disorder, or minor depression and living with a consenting legal guardian for at least 6 months.	Concurrent active treatment for anxiety or depression, current suicidal plan, bipolar disorder, psychosis, PTSD, substance dependence, current abuse, intellectual disability, school placement below 2nd grade, or unstable serious physical illness	Primary/target condition One or more anxiety disorders: 62% Anxiety and clinically elevated depression: 32% Clinically significant depression without anxiety: 6%

Abbreviations: CBT=cognitive behavioral therapy; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; GAD=generalized anxiety disorder; IQ=intelligence quotient; KQ=key question; MDD=major depressive disorder; NOS=not otherwise specified; PTSD=post-traumatic stress disorder; SD=standard deviation; SepAD=separation anxiety disorder; SocAD=social anxiety disorder; SSRI=selective serotonin reuptake inhibitor.

Appendix I Table 37. Anxiety or Depression Treatment Studies: Anxiety-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Anxiety Symptoms
Ehrenreich-May et al, 2017[84]	IG1: UP-A (N=27) CG: Wait-list (N=24)	Principal diagnosis ADIS CSR, 8 weeks, ITT (IG1=21; CG=16), mean (SD) IG1: 4.1 (1.53) CG: 5.4 (1.27) Time x Treatment interaction P<0.006 CGI-Severity, ITT, (IG1=21; CG=16), mean (SD) IG1: 4.1 (1.31) CG: 5.1 (1.02) Time x Treatment interaction P<0.006 CGI-Improvement, ITT, (IG1=21; CG=16), mean IG1: 3.04 CG: 4.00 t(36)=2.55, p=0.016, d=0.85
Weersing et al, 2017[156] Brent et al, 2019	IG1: Brief behavioral therapy (N=95) CG: Assisted referral (N=90)	CGI-I, posttreatment 16 weeks, ITT (IG=95; CG=90), mean (SD) IG1: 2.3 (1.1) CG: 3.1 (1.3) CGI-S, posttreatment 16 weeks, ITT (IG=95; CG=90), mean (SD) IG1: 2.6 (1.2) CG: 3.4 (1.3) PARS, posttreatment 16 weeks, ITT (IG=95; CG=90), mean (SD) IG1: 8.6 (5.0) CG: 11.4 (6.4) Treatment x Time P=0.01, Cohen's f=0.28 PARS, 32 weeks, ITT (IG=95; CG=90), mean (SD) IG1: NR CG: NR Treatment x Time P=0.003, Cohen's f=0.21

Abbreviations: ADIS=Anxiety Disorders Interview Schedule; CG=control group; CGI=Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; CSR=Clinician Severity Ratings; IG=intervention group; ITT=intent to treat; KQ=key question; NR=not reported; PARS=Pediatric Anxiety Rating Scale; SD=standard deviation; UP-A=Unified Protocol for the Treatment of Emotional Disorders in Adolescents.

Appendix I Table 38. Anxiety or Depression Treatment Studies: Depression-Related Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Depression Symptoms
Ehrenreich-May et al, 2017[84]	IG1: UP-A (N=27) CG: Wait-list (N=24)	RCADS, 8 weeks, ITT (IG1=21; CG=16), mean (SD) IG1: 105.9 (29.51) CG: 102.5 (27.53) Time x Treatment interaction P>0.40 RCADS-P, 8 weeks, ITT (IG1=21; CG=16), mean (SD) IG1: 130.3 (24.68) CG: 129.8 (23.32) Time x Treatment interaction P>0.40
Weersing et al, 2017[156] Brent et al, 2019[229]	IG1: Brief behavioral therapy (N=95) CG: Assisted referral (N=90)	CDRS-R, posttreatment 16 weeks, ITT (IG=95; CG=90), mean (SD) IG1: 22.6 (7.3) CG: 25.2 (9.4) Treatment x Time P=0.38, Cohen's f=0.07 CDRS-R, 32 weeks, ITT (IG=95; CG=90), mean (SD) IG1: NR CG: NR Treatment x Time P=0.64, Cohen's f=0.05

Abbreviations: CDRS-R=Children's Depression Rating Scale-Revised; CG=control group; IG=intervention group; ITT=intent to treat; KQ=key question; NR=not reported; RCADS=Revised Children's Anxiety and Depression Scale; RCADS-P=Revised Children's Anxiety and Depression Scale-Parent; SD=standard deviation; UP-A=Unified Protocol for the Treatment of Emotional Disorders in Adolescents.

Appendix I Table 39. Anxiety or Depression Treatment Studies: Response, Remission, and Loss of Diagnosis Outcomes (KQ 5)

Author, Year, Registry Number	Treatment Interventions and Comparators	Response Remission Loss of Diagnosis
Weersing et al, 2017[156] Brent et al, 2019[229] NCT01147614	IG1: Brief behavioral therapy (N=95) CG: Assisted referral (N=90)	Response CGI-I scores ≤2 for anxiety and depression CGI-I ≤2, posttreatment (16 weeks), completers (IG1=88; CG=71), N (%) IG1: 50 (56.8) CG: 20 (28.2) P<0.001 CGI-I ≤2, 32 weeks, ITT (IG1=95; CG=90), N (%) IG1: NR (67.5) CG: NR (43.1) P=0.002 Remission CGI-I score=1 for anxiety and depression CGI-I score=1, 32 weeks, ITT (IG1=95; CG=90), N (%) IG: NR (36.3) CG: NR (22.2) P=0.06 Loss of diagnosis NR Other outcomes NR

Abbreviations: CG=control group; CGI-I=Clinical Global Impressions-Improvement; IG=intervention group; ITT=intent to treat; KQ=key question; NR=not reported.

Appendix I Table 40. Anxiety or Depression Treatment Studies: Functioning Outcomes (KQ 4)

Author, Year, Registry Number	Treatment Interventions and Comparators	Functioning Outcomes	Other Outcomes/ Subgroups
Ehrenreich-May et al, 2017[84]	IG1: UP-A (N=27) CG: Wait-list (N=24)	ALIS, 8 weeks, ITT (IG1=21; CG=16), mean (SD) IG1: 28.2 (24.18) CG: 37.3 (27.31) Time x Treatment interaction P>0.40	Ethnicity moderated response, with Hispanic youths having a heightened response and greater improvements in functioning
Weersing et al, 2017[156] Brent et al, 2019[229]	IG1: Brief behavioral therapy (N=95) CG: Assisted referral (N=90)	CGAS, posttreatment 16 weeks, ITT (IG=95; CG=90), mean (SD) IG1: 68.5 (10.7) CG: 61.9 (11.9) Time x Treatment P=0.001, Cohen's d=0.58 CGAS, 32 weeks, ITT (IG=95; CG=90), mean (SD) IG1: 70.9 (11.4) CG: 65.0 (13.1) Time x Treatment P=0.004, Cohen's d=0.49	No subgroups of interest reported

Abbreviations: ALIS= adolescent life interference scale; CG=control group; CGAS=Children's Global Assessment Scale; IG=intervention group; ITT=intent to treat; KQ=key question; SD=standard deviation; UP-A=Unified Protocol for the Treatment of Emotional Disorders in Adolescents.

Appendix J. List of Excluded Studies

List of Exclusion Codes:

X1: Non-English

X2: Ineligible population

X3: Ineligible intervention

X4: Ineligible comparator

X5: Ineligible setting

X6: Ineligible country

X7: Ineligible study design

X8: Ineligible publication type

X9: Ineligible outcome

X10: Duplicate

X11: Relevant protocol or ongoing study

X12: Superseded by full publication

X13: Poor quality

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2. Children with anxiety do best on combination therapy. Drug Benefit Trends. 2008;20(12):504-. PMID: 2008-19322-002. Exclusion Code: X8.
3. Corrections: (The Lancet Psychiatry (2017) 4 (2)(109-119) (S2215036616303789) (10.1016/S2215-0366(16)30378-9)). The lancet psychiatry. 2017;4(8):582. doi: 10.1016/S2215-0366%2817%2930283-3. PMID: CN-01475235. Exclusion Code: X4.
4. Re: "Desvenlafaxine versus placebo in a Fluoxetine-referenced study of children and adolescents with major depressive disorder: design, definitions, and ongoing challenges for child and adolescent psychopharmacology research" by Strawn JR and Croarkin PE (J Child Adolesc Psychopharmacol 2018;28: (5)363). J Child Adolesc Psychopharmacol. 2019;29(3):245-6. doi: 10.1089/cap.2018.0163. PMID: CN-02001995. Exclusion Code: X2.
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6. Changes in firearm and medication storage practices in homes of youths at risk for suicide: results of the SAFETY Study, a clustered, emergency department–based, multisite, stepped-wedge trial. Ann Emerg Med. 2020doi: 10.1016/j.annemergmed.2020.02.007. PMID: CN-02147046. Exclusion Code: X2.
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9. Abbasi Z, Amiri S, Talebi H. The effective comparison between modular cognitive behavioral therapy (MCBT) and child-parent relationship training (CPRT) in children with separation anxiety symptoms. Social Sciences (Pakistan). 2016;11(6):890-902. Exclusion Code: X6.
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Appendix J. List of Excluded Studies

professional training: a feasibility randomised controlled trial study protocol. Pilot Feasibility Stud. 2020 Dec 10;6(1):191. doi: 10.1186/s40814-020-00733-8. PMID: 33298193. Exclusion Code: X2.

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12. Afshari A, Neshat-Doost HT, Maracy MR, et al. The effective comparison between emotion-focused cognitive behavioral group therapy and cognitive behavioral group therapy in children with separation anxiety disorder. J Res Med Sci. 2014 Mar;19(3):221-7. PMID: 24949029. Exclusion Code: X6.
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62. Bernstein GA, Borchardt CM, Perwien AR, et al. Imipramine plus cognitive-behavioral therapy in the treatment of school refusal. J Am Acad Child Adolesc Psychiatry. 2000 Mar;39(3):276-83. doi: 10.1097/00004583-200003000-00008. PMID: 10714046. Exclusion Code: X3.
63. Bhatta S, Champion JD, Young C, et al. Outcomes of depression screening among adolescents accessing school-based pediatric primary care clinic services. J Pediatr Nurs. 2018 Jan-Feb;38:8-14. doi: 10.1016/j.pedn.2017.10.001. PMID: 29167086. Exclusion Code: X3.
64. Biederman J. Clonazepam in the treatment of prepubertal children with panic-like symptoms. J Clin Psychiatry. 1987 Oct;48 Suppl:38-42. PMID: 3667548. Exclusion Code: X3.
65. Bierman KL, Heinrichs BS, Welsh JA, et al. Reducing adolescent psychopathology in socioeconomically disadvantaged children with a preschool intervention: a randomized controlled trial. The American Journal of Psychiatry. 2020 December 10, 2020;178(4):305-12. doi: 10.1176/appi.ajp.2020.20030343. Exclusion Code: X2.
66. Bilek EL, Ehrenreich-May J. An open trial investigation of a transdiagnostic group treatment for children with anxiety and depressive symptoms. Behav Ther. 2012;43(4):887-97. doi: 10.1016/j.beth.2012.04.007. PMID: 2012-27520-008. Exclusion Code: X7.
67. Birmaher B, Waterman GS, Ryan N, et al. Fluoxetine for childhood anxiety disorders. J Am Acad Child Adolesc Psychiatry. 1994 Sep;33(7):993-9. doi: 10.1097/00004583-199409000-00009. PMID: 7961355. Exclusion Code: X2.
68. Blom EH, Larsson JO, Serlachius E, et al. The differentiation between depressive and anxious adolescent females and controls by behavioural self-rating scales. J Affect Disord. 2010 May;122(3):232-40. doi:

Appendix J. List of Excluded Studies

10.1016/j.jad.2009.07.006. PMID: 19695710. Exclusion Code: X7.

69. Blossom JB, Ginsburg GS, Birmaher B, et al. Parental and family factors as predictors of threat bias in anxious youth. Cognit Ther Res. 2013;37(4):812-9. doi: 10.1007/s10608-012-9513-0. PMID: 2013-00135-001. Exclusion Code: X7.
70. Bodden DH, Bögels SM, Muris P. The diagnostic utility of the Screen for Child Anxiety Related Emotional Disorders-71 (SCARED-71). Behav Res Ther. 2009 May;47(5):418-25. doi: 10.1016/j.brat.2009.01.015. PMID: 19230863. Exclusion Code: X4.
71. Bodden DH, Dirksen CD, Bögels SM, et al. Costs and cost-effectiveness of family CBT versus individual CBT in clinically anxious children. Clin Child Psychol Psychiatry. 2008 Oct;13(4):543-64. doi: 10.1177/1359104508090602. PMID: 18927140. Exclusion Code: X4.
72. Bottelier MA, Schrantee AGM, Van Wingen GA, et al. Treatment with fluoxetine in adolescents may aggravate emotional dysregulation: a power analysis for future studies. European neuropsychopharmacology. 2015;25:S461-S2. PMID: CN-01163210. Exclusion Code: X9.
73. Boudreaux ED, Camargo CA, Jr., Arias SA, et al. Improving suicide risk screening and detection in the emergency department. Am J Prev Med. 2016 Apr;50(4):445-53. doi: 10.1016/j.amepre.2015.09.029. PMID: 26654691. Exclusion Code: X2.
74. Boylan C, Morgan S, Carthy A, et al. A randomised controlled trial of a programme for parents and full-time carers of young people with self-harm or suicidal behaviour. Eur Child Adolesc Psychiatry. 2013;22(2):S184-. doi: 10.1007/s00787-013-0423-9. PMID: CN-01006221. Exclusion Code: X2.
75. Boyle MH, Cunningham CE, Georgiades K, et al. The Brief Child and Family Phone Interview (BCFPI): 2. Usefulness in screening for child and adolescent psychopatholog. J Child Psychol Psychiatry. 2009 Apr;50(4):424-31. doi: 10.1111/j.1469-7610.2008.01971.x. PMID: 19175807. Exclusion Code: X5.
76. Bredemeier K, Spielberg JM, Silton RL, et al. Screening for depressive disorders using the Mood and Anxiety Symptoms Questionnaire Anhedonic Depression Scale: a receiver-operating characteristic analysis. Psychol Assess. 2010 Sep;22(3):702-10. doi: 10.1037/a0019915. PMID: 20822283. Exclusion Code: X2.
77. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. JAMA. 2008 Feb 27;299(8):901-13. doi: 10.1001/jama.299.8.901. PMID: 18314433. Exclusion Code: X2.
78. Brent DA, Brunwasser SM, Hollon SD, et al. Effect of a cognitive-behavioral prevention program on depression 6 years after implementation among at-risk adolescents: a randomized clinical trial. JAMA Psychiatry. 2015 Nov;72(11):1110-8. doi: 10.1001/jamapsychiatry.2015.1559. PMID: 26421861. Exclusion Code: X2.
79. Brent DA, Emslie GJ, Clarke GN, et al. Predictors of spontaneous and systematically assessed suicidal adverse events in the treatment of SSRI-resistant depression in adolescents (TORDIA) study. Am J Psychiatry. 2009 Apr;166(4):418-26. doi: 10.1176/appi.ajp.2008.08070976. PMID: 19223438. Exclusion Code: X2.
80. Brent DA, Holder D, Kolko D, et al. A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. Arch Gen Psychiatry. 1997 Sep;54(9):877-85. PMID: 9294380. Exclusion Code: X13.
81. Brent DA, Kennard BD. Impact of a brief inpatient intervention and suicide safety planning app to decrease suicidal behavior after hospital discharge. J Am Acad Child Adolesc Psychiatry. 2018;57(10):S33-. doi: 10.1016/j.jaac.2018.07.142. PMID: CN-01654953. Exclusion Code: X12.
82. Brent DA, Kolko DJ, Birmaher B, et al. Predictors of treatment efficacy in a clinical trial of three psychosocial treatments for adolescent depression. J Am Acad Child Adolesc Psychiatry. 1998 Sep;37(9):906-14. doi: 10.1097/00004583-199809000-00010. PMID: 9735610. Exclusion Code: X4.
83. Britton JC, Bar-Haim Y, Clementi MA, et al. Training-associated changes and stability of attention bias in youth: Implications for Attention Bias Modification Treatment for pediatric anxiety. Dev Cogn Neurosci. 2013;4:52-64. doi: 10.1016/j.dcn.2012.11.001. PMID: 2013-09450-006. Exclusion Code: X4.
84. Brunoni AR, Sampaio-Junior B, Moffa AH, et al. The Escitalopram versus Electric Current Therapy for Treating Depression Clinical Study (ELECT-TDCS): rationale and study design of a non-inferiority, triple-arm, placebo-controlled clinical trial. Sao Paulo Med J. 2015 May-Jun;133(3):252-63. doi: 10.1590/1516-3180.2014.00351712. PMID: 26176930. Exclusion Code: X2.
85. Brunshaw JM, Szatmari P. The agreement between behaviour checklists and structured psychiatric interviews for children. Can J Psychiatry. 1988 Aug;33(6):474-81. doi: 10.1177/070674378803300608. PMID: 3196999. Exclusion Code: X2.
86. Bunnell BE, Mesa F, Beidel DC. A two-session hierarchy for shaping successive approximations of speech in selective mutism: pilot study of mobile apps and mechanisms of behavior change.

Behav Ther. 2018 Nov;49(6):966-80. doi: 10.1016/j.beth.2018.02.003. PMID: 30316494. Exclusion Code: X3.

87. Burke TA, Jacobucci R, Ammerman BA, et al. Using machine learning to classify suicide attempt history among youth in medical care settings. J Affect Disord. 2020 May 1;268:206-14. doi: 10.1016/j.jad.2020.02.048. PMID: 32174479. Exclusion Code: X3.
88. Busby DR, King CA, Brent D, et al. Adolescents' engagement with crisis hotline risk-management services: a report from the Emergency Department Screen for Teen Suicide Risk (ED-STARS) Study. Suicide Life Threat Behav. 2020 Feb;50(1):72-82. doi: 10.1111/sltb.12558. PMID: 31152463. Exclusion Code: X9.
89. Bushnell GA, Stürmer T, Swanson SA, et al. Dosing of Selective Serotonin Reuptake Inhibitors among children and adults before and after the FDA black-box warning. Psychiatr Serv. 2016 Mar;67(3):302-9. doi: 10.1176/appi.ps.201500088. PMID: 26567938. Exclusion Code: X3.
90. Canals J DE, Carbajo G, Blade J. Prevalence of DSM-III-R and ICD-10 psychiatric disorders in a Spanish population of 18-year-olds. Acta Psychiatr Scand. 1997;96:287-94. Exclusion Code: X3.
91. Canals J M-HC, Fernandez-Ballart J, Domenech E. A longitudinal study of depression in an urban Spanish pubertal population. Eur Child Adolesc Psychiatry. 1995;4:102-11. Exclusion Code: X9.
92. Caporino N. Child/adolescent anxiety multimodal extended long-term study: depression and suicide outcomes. J Am Acad Child Adolesc Psychiatry. 2017;56(10):S318-. doi: 10.1016/j.jaac.2017.07.639. PMID: CN-01452306. Exclusion Code: X9.
93. Caporino NE, Brodman DM, Kendall PC, et al. Defining treatment response and remission in child anxiety: signal detection analysis using the pediatric anxiety rating scale. J Am Acad Child Adolesc Psychiatry. 2013 Jan;52(1):57-67. doi: 10.1016/j.jaac.2012.10.006. PMID: 23265634. Exclusion Code: X10.
94. Caporino NE, Sakolsky D, Brodman DM, et al. Establishing clinical cutoffs for response and remission on the Screen for Child Anxiety Related Emotional Disorders (SCARED). J Am Acad Child Adolesc Psychiatry. 2017 Aug;56(8):696-702. doi: 10.1016/j.jaac.2017.05.018. PMID: 28735699. Exclusion Code: X3.
95. Caron EB, Drake KL, Stewart CE, et al. Intervention adherence and self-efficacy as predictors of child outcomes in school nurse-delivered interventions for anxiety. J Sch Nurs. 2020 May 15:1059840520925522. doi: 10.1177/1059840520925522. PMID: 32410495. Exclusion Code: X4.
96. Cartwright-Hatton S, McNally D, Field AP, et al. A new parenting-based group intervention for young anxious children: Results of a randomized controlled trial. J Am Acad Child Adolesc Psychiatry. 2011;50(3):242-51. doi: 10.1016/j.jaac.2010.12.015. PMID: 2011-04926-006. Exclusion Code: X3.
97. Cederlund R, Öst L-G. Psychometric properties of the Social Phobia and Anxiety Inventory-Child version in a Swedish clinical sample. J Anxiety Disord. 2013;27(5):503-11. doi: 10.1016/j.janxdis.2013.06.004. PMID: 2013-31517-009. Exclusion Code: X2.
98. Cervin M, Storch EA, Piacentini J, et al. Symptom-specific effects of cognitive-behavioral therapy, sertraline, and their combination in a large randomized controlled trial of pediatric anxiety disorders. J Child Psychol Psychiatry. 2020 Apr;61(4):492-502. doi: 10.1111/jcpp.13124. PMID: 31471911. Exclusion Code: X7.
99. Cervin M, Storch EA, Piacentini J, et al. Symptom-specific effects of cognitive-behavioral therapy, sertraline, and their combination in a large randomized controlled trial of pediatric anxiety disorders. Journal of child psychology & psychiatry. 2020;61(4):492-502. doi: 10.1111/jcpp.13124. PMID: CN-02127722. Exclusion Code:
100. Chanen AM, Jackson HJ, McCutcheon LK, et al. Early intervention for adolescents with borderline personality disorder using cognitive analytic therapy: randomised controlled trial. Br J Psychiatry. 2008 Dec;193(6):477-84. doi: 10.1192/bjp.bp.107.048934. PMID: 19043151. Exclusion Code: X4.
101. Chang SW, Kuckertz JM, Bose D, et al. Efficacy of attention bias training for child anxiety disorders: a randomized controlled trial. Child Psychiatry Hum Dev. 2019 Apr;50(2):198-208. doi: 10.1007/s10578-018-0832-6. PMID: 30051155. Exclusion Code: X3.
102. Chapdelaine A, Carrier JD, Fournier L, et al. Treatment adequacy for social anxiety disorder in primary care patients. PLoS One. 2018;13(11):e0206357. doi: 10.1371/journal.pone.0206357. PMID: 30395608. Exclusion Code: X2.
103. Charkhandeh M, Talib MA, Hunt CJ. The clinical effectiveness of cognitive behavior therapy and an alternative medicine approach in reducing symptoms of depression in adolescents. Psychiatry Res. 2016 May 30;239:325-30. doi: 10.1016/j.psychres.2016.03.044. PMID: 27058159. Exclusion Code: X6.
104. Chavira DA, Stein MB. Combined psychoeducation and treatment with selective serotonin reuptake inhibitors for youth with generalized social anxiety disorder. J Child Adolesc Psychopharmacol. 2002 Spring;12(1):47-54. doi: 10.1089/10445460252943560. PMID: 12014595. Exclusion Code: X3.

Appendix J. List of Excluded Studies

105. Chavira DA, Stein MB, Bailey K, et al. Child anxiety in primary care: prevalent but untreated. Depress Anxiety. 2004;20(4):155-64. doi: 10.1002/da.20039. PMID: 15643639. Exclusion Code: X9.
106. Chen H, Upadhyay N, Lyu N, et al. Association of primary and behavioral health integrated care upon pediatric mental disorder treatment. Acad Pediatr. 2021 Jun 1doi: 10.1016/j.acap.2021.05.021. PMID: 34087480. Exclusion Code: X7.
107. Chen S. An online solution focused brief therapy for adolescent anxiety during the novel coronavirus disease (COVID-19) pandemic: a structured summary of a study protocol for a randomised controlled trial. Trials. 2020;21(1)doi: 10.1186/s13063-020-04355-6. PMID: CN-02120850. Exclusion Code: X2.
108. Chiappini EA, Gosch E, Compton SN, et al. In-session involvement in anxious youth receiving CBT with/without medication. J Psychopathol Behav Assess. 2020;42(4):615-26. doi: 10.1007/s10862-020-09810-x. PMID: 2020-39041-001. Exclusion Code: X9.
109. Chorpita BF, Moffitt CE, Gray J. Psychometric properties of the Revised Child Anxiety and Depression Scale in a clinical sample. Behav Res Ther. 2005 Mar;43(3):309-22. doi: 10.1016/j.brat.2004.02.004. PMID: 15680928. Exclusion Code: X5.
110. Chowdhury T, Champion JD. Outcomes of depression screening for adolescents accessing pediatric primary care-based services. J Pediatr Nurs. 2020 Mar 2;52:25-9. doi: 10.1016/j.pedn.2020.02.036. PMID: 32135479. Exclusion Code: X7.
111. Christensen KS, Haugen W, Sirpal MK, et al. Diagnosis of depressed young people--criterion validity of WHO-5 and HSCL-6 in Denmark and Norway. Fam Pract. 2015 Jun;32(3):359-63. doi: 10.1093/fampra/cmv011. PMID: 25800246. Exclusion Code: X8.
112. Chu BC, Carpenter AL, Wyszynski CM, et al. Scalable options for extended skill building following Didactic training in Cognitive-Behavioral Therapy for anxious youth: A Pilot Randomized Trial. J Clin Child Adolesc Psychol. 2017 May-Jun;46(3):401-10. doi: 10.1080/15374416.2015.1038825. PMID: 25984590. Exclusion Code: X2.
113. Chu BC, Crocco ST, Esseling P, et al. Transdiagnostic group behavioral activation and exposure therapy for youth anxiety and depression: Initial randomized controlled trial. Behav Res Ther. 2016 Jan;76:65-75. doi: 10.1016/j.brat.2015.11.005. PMID: 26655958. Exclusion Code: X5.
114. Chutko L, Surushkina SY, Nikishena I, et al. Treatment of anxiety disorders in school maladaptation with adaptol. Neurosci Behav Physiol. 2011;41(5):520-4. Exclusion Code: X3.
115. Cianchetti C, Faedda N, Pasculli M, et al. Predictive validity for the clinical diagnosis of a new parent questionnaire, the CABI, compared with CBCL. Clin Child Psychol Psychiatry. 2020 Apr;25(2):507-19. doi: 10.1177/1359104519895056. PMID: 31894698. Exclusion Code: X2.
116. Clarke G, Sheppler CR, Firemark AJ, et al. Augmenting usual care SSRIs with cognitive behavioral therapy for insomnia to improve depression outcomes in youth: Design of a randomized controlled efficacy-effectiveness trial. Contemp Clin Trials. 2020 Feb 28;91:105967. doi: 10.1016/j.cct.2020.105967. PMID: 32114185. Exclusion Code: X4.
117. Clarke GN, Hornbrook M, Lynch F, et al. Group cognitive-behavioral treatment for depressed adolescent offspring of depressed parents in a health maintenance organization. J Am Acad Child Adolesc Psychiatry. 2002 Mar;41(3):305-13. doi: 10.1097/00004583-200203000-00010. PMID: 11886025. Exclusion Code: X2.
118. Clément C, Lin J, Stangier U. Efficacy of behavioral experiments in Cognitive Therapy for social anxiety disorder: study protocol for a randomized controlled trial. Trials. 2019 Dec 19;20(1):748. doi: 10.1186/s13063-019-3905-3. PMID: 31856903. Exclusion Code: X4.
119. Cobham VE. Do anxiety-disordered children need to come into the clinic for efficacious treatment? J Consult Clin Psychol. 2012;80(3):465-76. doi: 10.1037/a0028205. PMID: 2012-10793-001. Exclusion Code: X13.
120. Cobham VE, Dadds MR, Spence SH. The role of parental anxiety in the treatment of childhood anxiety. J Consult Clin Psychol. 1998 Dec;66(6):893-905. doi: 10.1037//0022-006x.66.6.893. PMID: 9874902. Exclusion Code: X3.
121. Cohen JR, So FK, Young JF, et al. Youth depression screening with parent and self-reports: assessing current and prospective depression risk. Child Psychiatry Hum Dev. 2019 Aug;50(4):647-60. doi: 10.1007/s10578-019-00869-6. PMID: 30737605. Exclusion Code: X7.
122. Coker TR, Porras-Javier L, Zhang L, et al. 4.57 Improved Access to Mental Health Care Using a Telehealth-Enhanced Referral Process in Pediatric Primary Care: a Cluster Randomized Trial. J Am Acad Child Adolesc Psychiatry. 2018;57(10):S222-. doi: 10.1016/j.jaac.2018.09.282. PMID: CN-01653032. Exclusion Code: X2.
123. Colins O, Grisso T, Vahl P, et al. Standardized screening for mental health needs of detained youths from various ethnic origins: the Dutch Massachusetts Youth Screening Instrument-Second Version (MAYSI-2). Journal of Psychopathology & Behavioral Assessment. 2015;37(3):481-92. doi: 10.1007/s10862-014-9476-4. PMID: 109827440. Language: English. Entry Date: 20150812. Revision Date: 20160831.

Appendix J. List of Excluded Studies

Publication Type: Journal Article. Exclusion Code: X9.

124. Comer JS, Furr JM, del Busto C, et al. Therapist-led, internet-delivered treatment for early child social anxiety: a waitlist-controlled evaluation of the iCALM Telehealth Program. Behav Ther. 2021doi: 10.1016/j.beth.2021.01.004. PMID: CN-02276119. Exclusion Code: X3.
125. Compton SN, Grant PJ, Chrisman AK, et al. Sertraline in children and adolescents with social anxiety disorder: an open trial. J Am Acad Child Adolesc Psychiatry. 2001 May;40(5):564-71. doi: 10.1097/00004583-200105000-00016. PMID: 11349701. Exclusion Code: X4.
126. Conner OL, Siegle GJ, McFarland AM, et al. Mom—It helps when you're right here! Attenuation of neural stress markers in anxious youths whose caregivers are present during fMRI. PLoS One. 2012;7(12)doi: 10.1371/journal.pone.0050680. PMID: 2013-12066-001. Exclusion Code: X3.
127. Conway PM, Erlangsen A, Teasdale TW, et al. Predictive validity of the Columbia-Suicide Severity Rating Scale for short-term suicidal behavior: a Danish study of adolescents at a high risk of suicide. Arch Suicide Res. 2017 Jul 3;21(3):455-69. doi: 10.1080/13811118.2016.1222318. PMID: 27602917. Exclusion Code: X2.
128. Cooper WO, Callahan ST, Shintani A, et al. Antidepressants and suicide attempts in children. Pediatrics. 2014 Feb;133(2):204-10. doi: 10.1542/peds.2013-0923. PMID: 24394688. Exclusion Code: X4.
129. Cornwall E, Spence SH, Schotte D. The effectiveness of emotive imagery in the treatment of darkness phobia in children. Behav Change. 1996;13(4):223-9. Exclusion Code: X3.
130. Cortez AB, Wilkins J, Handler E, et al. Multistage adolescent depression screening: a comparison of 11-year-olds to 12-year-olds. Perm J. 2021 May;25doi: 10.7812/tpp/20.233. PMID: 33970080. Exclusion Code: X7.
131. Cosi S, Canals J, Hernández-Martinez C, et al. Parent-child agreement in SCARED and its relationship to anxiety symptoms. J Anxiety Disord. 2010 Jan;24(1):129-33. doi: 10.1016/j.janxdis.2009.09.008. PMID: 19864109. Exclusion Code: X9.
132. Costello LH, Suh C, Burnett B, et al. Addressing adolescent depression in primary care: building capacity through psychologist and pediatrician partnership. J Clin Psychol Med Settings. 2019 Nov 20doi: 10.1007/s10880-019-09680-w. PMID: 31749100. Exclusion Code: X4.
133. Cotton S, Kraemer KM, Sears RW, et al. Mindfulness-based cognitive therapy for children and adolescents with anxiety disorders at-risk for bipolar disorder: A psychoeducation waitlist controlled pilot trial. Early Intervention in Psychiatry. 2020;14(2):211-9. doi: 10.1111/eip.12848. PMID: 2019-37562-001. Exclusion Code: X7.
134. Courtney-Seidler EA, Burns K, Zilber I, et al. Adolescent suicide and self-injury: deepening the understanding of the biosocial theory and applying dialectical behavior therapy. International Journal of Behavioral Consultation and Therapy. 2014;9(3):35-40. doi: 10.1037/h0101638. PMID: 2019-11792-008. Exclusion Code: X8.
135. Crane ME, Norris LA, Frank HE, et al. Impact of treatment improvement on long-term anxiety: results from CAMS and CAMELS. J Consult Clin Psychol. 2021 Feb;89(2):126-33. doi: 10.1037/ccp0000523. PMID: 33705168. Exclusion Code: X9.
136. Creswell C, Cruddace S, Gerry S, et al. Treatment of childhood anxiety disorder in the context of maternal anxiety disorder: a randomised controlled trial and economic analysis. Health Technol Assess. 2015 May;19(38):1-184, vii-viii. doi: 10.3310/hta19380. PMID: 26004142. Exclusion Code: X7.
137. Cuijpers P, Smits N, Donker T, et al. Screening for mood and anxiety disorders with the five-item, the three-item, and the two-item Mental Health Inventory. Psychiatry Res. 2009 Aug 15;168(3):250-5. doi: 10.1016/j.psychres.2008.05.012. PMID: 19185354. Exclusion Code: X2.
138. Cunha M, Gouveia JP, do Céu Salvador M. Social fears in adolescence: the social anxiety and avoidance scale for adolescents. Eur Psychol. 2008;13(3):197-213. doi: 10.1027/1016-9040.13.3.197. PMID: 2008-13222-006. Exclusion Code: X13.
139. Cwik M, Jay S, Ryan TC, et al. Lowering the Age Limit in Suicide Risk Screening: Clinical Differences and Screening Form Predictive Ability. J Am Acad Child Adolesc Psychiatry. 2021 May;60(5):537-40. doi: 10.1016/j.jaac.2020.11.025. PMID: 33667604. Exclusion Code: X4.
140. da Costa CZ, de Morais RM, Zanetta DM, et al. Comparison among clomipramine, fluoxetine, and placebo for the treatment of anxiety disorders in children and adolescents. J Child Adolesc Psychopharmacol. 2013 Dec;23(10):687-92. doi: 10.1089/cap.2012.0110. PMID: 24350814. Exclusion Code: X6.
141. D'Amato G. Chlordiazepoxide in management of school phobia. Dis Nerv Syst. 1962 May;23:292-5. PMID: 13882945. Exclusion Code: X2.
142. Dams J, Kronmuller KT, Leibing E, et al. Direct costs of social phobia in adolescents and cost-effectiveness of psychotherapy. Psychiatr Prax. 2019;46(3):148-55. doi: 10.1055/a-0733-4999. PMID: CN-01937705. Exclusion Code: X1.
143. Dardas LA. Family functioning moderates the impact of depression treatment on adolescents' suicidal ideations. Child & Adolescent Mental

Health. 2019;24(3):251-8. doi: 10.1111/camh.12323. PMID: 138125078. Language: English. Entry Date: 20190821. Revision Date: 20200122. Publication Type: Article. Exclusion Code: X9.

144. de Groot J, Cobham V, Leong J, et al. Individual versus group family-focused cognitive-behaviour therapy for childhood anxiety: pilot randomized controlled trial. Aust N Z J Psychiatry. 2007 Dec;41(12):990-7. doi: 10.1080/00048670701689436. PMID: 17999271. Exclusion Code: X3.
145. de Haan A, Petermann F, Meiser-Stedman R, et al. Psychometric properties of the German version of the Child Post-Traumatic Cognitions Inventory (CPTCI-GER). Child Psychiatry Hum Dev. 2016;47(1):151-8. doi: 10.1007/s10578-015-0552-0. PMID: 2015-23379-001. Exclusion Code: X3.
146. De Lijster JM, Dieleman GC, Utens E, et al. Online Attention Bias Modification in Combination with Cognitive-Behavioural Therapy for Children and Adolescents with Anxiety Disorders: a Randomised Controlled Trial. Behav Change. 2019doi: 10.1017/bec.2019.8. PMID: CN-01937771. Exclusion Code: X4.
147. de Wilde EJ, van de Looij P, Goldschmeding J, et al. Self-report of suicidal thoughts and behavior vs. school nurse evaluations in Dutch high-school students. Crisis. 2011;32(3):121-7. doi: 10.1027/0227-5910/a000064. PMID: 21616760. Exclusion Code: X9.
148. Deas D, Randall CL, Roberts JS, et al. A double-blind, placebo-controlled trial of sertraline in depressed adolescent alcoholics: a pilot study. Hum Psychopharmacol. 2000 Aug;15(6):461-9. doi: 10.1002/1099-1077(200008)15:6<461::aid-hup209>3.0.co;2-j. PMID: 12404308. Exclusion Code: X2.
149. DelBello MP, Hochadel TJ, Portland KB, et al. A double-blind, placebo-controlled study of selegiline transdermal system in depressed adolescents. J Child Adolesc Psychopharmacol. 2014 Aug;24(6):311-7. doi: 10.1089/cap.2013.0138. PMID: 24955812. Exclusion Code: X3.
150. Desousa DA, Salum GA, Isolan LR, et al. Sensitivity and specificity of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a community-based study. Child Psychiatry Hum Dev. 2013 Jun;44(3):391-9. doi: 10.1007/s10578-012-0333-y. PMID: 22961135. Exclusion Code: X6.
151. DeVylder JE, Ryan TC, Cwik M, et al. Screening for suicide risk among youths with a psychotic disorder in a pediatric emergency department. Psychiatr Serv. 2020 Feb 1;71(2):205-8. doi: 10.1176/appi.ps.201900290. PMID: 31795855. Exclusion Code: X5.
152. DeVylder JE, Ryan TC, Cwik M, et al. Assessment of selective and universal screening for suicide risk in a pediatric emergency department. JAMA Netw Open. 2019 Oct 2;2(10):e1914070. doi: 10.1001/jamanetworkopen.2019.14070. PMID: 31651971. Exclusion Code: X4.
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Appendix J. List of Excluded Studies

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Appendix J. List of Excluded Studies

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466. Ollendick TH, Öst L-G, Reuterskiöld L, et al. One-session treatment of specific phobias in youth: A randomized clinical trial in the United States and Sweden. J Consult Clin Psychol. 2009;77(3):504-16. doi: 10.1037/a0015158. PMID: 2009-08093-012. Exclusion Code: X2.

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Appendix J. List of Excluded Studies

479. Parikh R, Michelson D, Malik K, et al. The effectiveness of a low-intensity problem-solving intervention for common adolescent mental health problems in New Delhi, India: protocol for a school-based, individually randomized controlled trial with an embedded stepped-wedge, cluster randomized controlled recruitment trial. Trials. 2019 Sep 18;20(1):568. doi: 10.1186/s13063-019-3573-3. PMID: 31533783. Exclusion Code: X6.
480. Park CH, Kim GS. A validation study on DAS in the prediction of suicidal risk for adolescents. The Arts in Psychotherapy. 2013;40(1):108-14. doi: 10.1016/j.aip.2012.11.006. PMID: 2013-09132-013. Exclusion Code: X9.
481. Parker AG, Hetrick SE, Jorm AF, et al. The effectiveness of simple psychological and physical activity interventions for high prevalence mental health problems in young people: A factorial randomised controlled trial. J Affect Disord. 2016 May 15;196:200-9. doi: 10.1016/j.jad.2016.02.043. PMID: 26926659. Exclusion Code: X2.
482. Parr CJ, Cartwright-Hatton S. Social anxiety in adolescents: the effect of video feedback on anxiety and the self-evaluation of performance. Clin Psychol Psychother. 2009 Jan-Feb;16(1):46-54. doi: 10.1002/cpp.599. PMID: 19123484. Exclusion Code: X2.
483. Paschall MJ, Bersamin M. School-based health centers, depression, and suicide risk among adolescents. Am J Prev Med. 2018 Jan;54(1):44-50. doi: 10.1016/j.amepre.2017.08.022. PMID: 29132951. Exclusion Code: X3.
484. Patel A, Watts C, Shiddell S, et al. Universal adolescent suicide screening in a pediatric urgent care center. Arch Suicide Res. 2018 Jan-Mar;22(1):118-27. doi: 10.1080/13811118.2017.1304303. PMID: 28281893. Exclusion Code: X4.
485. Pauschardt J, Remschmidt H, Mattejat F. Assessing child and adolescent anxiety in psychiatric samples with the Child Behavior Checklist. J Anxiety Disord. 2010 Jun;24(5):461-7. doi: 10.1016/j.janxdis.2010.03.002. PMID: 20362414. Exclusion Code: X5.
486. Pergamin-Hight L, Pine DS, Fox NA, et al. Attention bias modification for youth with social anxiety disorder. J Child Psychol Psychiatry. 2016;57(11):1317-25. doi: 10.1111/jcpp.12599. PMID: 2016-53125-007. Exclusion Code: X3.
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489. Perloe A, Esposito-Smythers C, Curby TW, et al. Concurrent trajectories of change in adolescent and maternal depressive symptoms in the TORDIA study. J Youth Adolesc. 2014 Apr;43(4):612-28. doi: 10.1007/s10964-013-9999-0. PMID: 23975354. Exclusion Code: X2.
490. Perrin S, Last CG. Do childhood anxiety measures measure anxiety? J Abnorm Child Psychol. 1992 Dec;20(6):567-78. doi: 10.1007/bf00911241. PMID: 1487597. Exclusion Code: X5.
491. Peterson BS, West AE, Weisz JR, et al. A Sequential Multiple Assignment Randomized Trial (SMART) study of medication and CBT sequencing in the treatment of pediatric anxiety disorders. BMC Psychiatry. 2021 Jun 30;21(1):323. doi: 10.1186/s12888-021-03314-y. PMID: 34193105. Exclusion Code: X4.
492. Pettit JW, Bechor M, Rey Y, et al. A Randomized Controlled Trial of Attention Bias Modification Treatment in Youth With Treatment-Resistant Anxiety Disorders. J Am Acad Child Adolesc Psychiatry. 2020 Jan;59(1):157-65. doi: 10.1016/j.jaac.2019.02.018. PMID: 30877049. Exclusion Code: X2.
493. Phillips R, Spears MR, Montgomery AA, et al. Could a brief assessment of negative emotions and self-esteem identify adolescents at current and future risk of self-harm in the community? A prospective cohort analysis. BMC Public Health. 2013 Jun 22;13:604. doi: 10.1186/1471-2458-13-604. PMID: 23800153. Exclusion Code: X4.
494. Piacentini J, Bennett S, Compton SN, et al. 24- and 36-week outcomes for the Child/Adolescent Anxiety Multimodal Study (CAMS). J Am Acad Child Adolesc Psychiatry. 2014;53(3):297-310. doi: 10.1016/j.jaac.2013.11.010. PMID: CN-00982077. Exclusion Code:
495. Pina AA, Silverman WK, Fuentes RM, et al. Exposure-based cognitive-behavioral treatment for phobic and anxiety disorders: Treatment effects and maintenance for Hispanic/Latino relative to European-American youths. J Am Acad Child Adolesc Psychiatry. 2003;42(10):1179-87. doi: 10.1097/00004583-200310000-00008. PMID: 2003-08377-006. Exclusion Code: X4.
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497. Posner K, Oquendo MA, Gould M, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035-43. doi:

10.1176/appi.ajp.164.7.1035. PMID: CN-01772061. Exclusion Code: X2.

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499. Prochaska JD, Le VD, Baillargeon J, et al. Utilization of Professional Mental Health Services Related to Population-Level Screening for Anxiety, Depression, and Post-traumatic Stress Disorder Among Public High School Students. Community Ment Health J. 2016 Aug;52(6):691-700. doi: 10.1007/s10597-015-9968-z. PMID: 26733335. Exclusion Code: X3.

500. Putwain DW, Pescod M. Is reducing uncertain control the key to successful test anxiety intervention for secondary school students? Findings from a randomized control trial. Sch Psychol Q. 2018 Jun;33(2):283-92. doi: 10.1037/spq0000228. PMID: 29094957. Exclusion Code: X2.

501. Radomski AD, Bagnell A, Curtis S, et al. Examining the Usage, User Experience, and Perceived Impact of an Internet-Based Cognitive Behavioral Therapy Program for Adolescents With Anxiety: Randomized Controlled Trial. JMIR Ment Health. 2020 Feb 7;7(2):e15795. doi: 10.2196/15795. PMID: 32022692. Exclusion Code: X2.

502. Randell BP, Eggert LL, Pike KC. Immediate post intervention effects of two brief youth suicide prevention interventions. Suicide Life Threat Behav. 2001 Spring;31(1):41-61. doi: 10.1521/suli.31.1.41.21308. PMID: 11326768. Exclusion Code: X9.

503. Rapee RM. Group treatment of children with anxiety disorders: Outcome and predictors of treatment response. Aust J Psychol. 2000;52(3):125-9. Exclusion Code: X7.

504. Rapee RM, Abbott MJ, Lyneham HJ. Bibliotherapy for children with anxiety disorders using written materials for parents: a randomized controlled trial. J Consult Clin Psychol. 2006 Jun;74(3):436-44. doi: 10.1037/0022-006x.74.3.436. PMID: 16822101. Exclusion Code: X13.

505. Rasing SPA, Stikkelbroek YAJ, den Hollander W, et al. Pragmatic Quasi-Experimental Controlled Trial Evaluating the Outcomes of Blended CBT Compared to Face-to-Face CBT and Treatment as Usual for Adolescents with Depressive Disorders. Int J Environ Res Public Health. 2021 Mar 17;18(6)doi: 10.3390/ijerph18063102. PMID: 33802913. Exclusion Code: X2.

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514. Rinke ML, German M, Azera B, et al. Effect of Mental Health Screening and Integrated Mental Health on Adolescent Depression-Coded Visits. Clin Pediatr (Phila). 2019 Apr;58(4):437-45. doi: 10.1177/0009922818821889. PMID: 30623684. Exclusion Code: X9.

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516. Rizo Martínez LE, Guevara Pérez MÁ, Hernández González M, et al. A preliminary study of the prevalence of post-traumatic stress disorder, depression and anxiety symptoms in female adolescents maltreatment victims in Mexico. Salud Mental. 2018;41(3):139-44. doi: 10.17711/SM.0185-3325.2018.018. PMID: 2019-01689-005. Exclusion Code: X6.
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Appendix J. List of Excluded Studies

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Appendix J. List of Excluded Studies

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Appendix J. List of Excluded Studies

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