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Screening for Child and Adolescent Depression In Primary Care Settings: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract:

Background: Depression among youth is a relatively common, disabling condition that is associated with serious long-term morbidities and risk of suicide. The majority of depressed youth, however, are undiagnosed and untreated, despite opportunities for identification in settings such as primary care.

Purpose: We sought to assess the health effects of routine primary care screening for Major Depressive Disorder (MDD) among children and adolescents ages 7 to 18 years, including evaluating the accuracy of screening tests and the risks and benefits of treatment with psychotherapy and/or SSRIs.

Methods: We developed an analytic framework and five key questions to represent the logical evidence connecting primary care screening to improved health outcomes. We conducted a series of literature searches for each key question in Medline, the Cochrane Central Registry of Controlled Trials, PsycInfo, and the Cochrane Database of Systematic Reviews through May 2007. We also reviewed studies included in recent systematic evidence reviews and meta-analyses, contacted experts, and reviewed bibliographies from relevant studies. We examined 5,737 abstracts and 480 full text articles. One reviewer abstracted relevant information from each included article into standardized evidence tables. A second reviewer checked key elements. Two reviewers quality graded each article using US Preventive Services Task Force criteria. Due to heterogeneity among studies, we conducted qualitative syntheses for studies of screening test accuracy and for the benefits and harms of psychotherapeutic treatment interventions. For SSRI trials, we quantitatively pooled results for absolute risk differences for response rates and suicide-related adverse effects, using random effects models, and describe findings of other systematic reviews.

Results: No controlled trials compared health outcomes in screened and unscreened pediatric populations. Data from six fair-quality studies evaluating the accuracy of screening instruments among 2,781 adolescents in primary care or school settings report sensitivity of 73 to 100 percent and specificity of 65 to 94 percent. Three studies including participants less than 12 years old yielded sensitivities of 53 to 90 percent and specificities of 49 to 96 percent. Pooled risk difference (RD) for response rates among nine fair- or good-quality, double-blinded, placebo-controlled RCTs evaluating short-term efficacy of SSRIs among 1,972 children and adolescents yielded a higher response rate among treated youth (RD 12 percent, 95 percent confidence interval (CI) 7, 16). Ten fair- or good-quality RCTs evaluated short-term efficacy of psychotherapy among 757 children or adolescents aged 9 to 18 years. Most psychotherapy trials demonstrated an improvement in depression symptoms based on proportion achieving remission, change in mean depression score, or improved global functioning. Treatment with SSRIs was associated with a small increased risk of suicidality (RD 1 percent, 95 percent CI 0, 2). Suicidality includes suicidal ideation, preparatory acts, or attempts. No suicide deaths have occurred in controlled trials of SSRIs. Observational data are inconclusive.

Conclusions: Although no trials of screening for pediatric MDD were identified, limited available data suggest that primary care feasible screening tools may be accurate in identifying depressed adolescents, and treatment can improve depression outcomes. Treating depressed youth with SSRIs may be associated with a small increased risk of suicidality and therefore should only be considered if judicious clinical monitoring is possible. Specific treatment should be based on the individual's needs and mental health treatment guidelines.

Contents

Contents, continued

Figures

Tables

Appendixes

Contents, continued

Chapter 1. Introduction

Scope and Purpose

We conducted this systematic review to aid the United States Preventive Services Task Force (USPSTF) in updating its 2002 recommendation on screening for child and adolescent depression among average-risk, primary care populations. This report summarizes the evidence for the benefits and harms of screening, the accuracy of primary care feasible screening tests, and the benefits and risks of treating depression using psychotherapy and/or selective serotonin reuptake inhibitors (SSRIs) among patients aged 7 to 18 years. We focus on Major Depressive Disorder (MDD) and do not address screening or treatment for minor depression or dysthymia. This review summarizes the current state of the evidence relevant to primary care clinicians and identifies key gaps in this scientific literature.

Condition Definition

Clinical depression is a condition characterized by persistent unhappiness or a loss of interest or pleasure in most activities. Among children and adolescents, irritability, rather than sadness, may be the predominant mood and can be accompanied by tantrums or verbal outbursts. Additional accompanying behavior patterns may include social isolation, deterioration in schoolwork, and expression of anger. Sleep and appetite disturbances can occur and may manifest as complaints of tiredness or nonspecific pain, such as stomach aches or headaches. When symptoms cluster together and persist for two weeks or more, major depressive disorder (MDD) may be present.

The American Psychiatric Association has established diagnostic criteria for depressive disorders among youth (Table 1).[1] While dysthymic disorder (DD) is similar to MDD, it is generally longer lasting and less severe. A variety of terms are used for people with depressive symptoms whose depression does not meet criteria for MDD or DD, such as subthreshold depression, subsyndromal depression, and minor depression. Bipolar disorder, a mutually exclusive clinical entity from MDD, is characterized by episodes of abnormally elevated mood in addition to depression. Compared to younger pre-pubertal children, adolescents with MDD are more likely to experience an inability to gain pleasure from enjoyable experiences (that is, anhedonia), hopelessness, increased sleeping, weight change, use of alcohol or illicit drugs, and have more lethal suicide attempts. In contrast, children are more likely to experience somatic complaints, psychomotor agitation, separation anxiety, phobias, and hallucinations than adolescents.[2]

Prevalence and Burden of Disease/Illness

MDD has been increasingly recognized among youth and is surprisingly common, particularly among adolescents (Table 2). A recent meta-analysis estimated the prevalence of MDD among adolescents aged 13 to 18 years to be 5.6 percent. Prevalence estimates were based on psychiatric interviews for nearly 60,000 youth from varying time frames (1, 3, 6, and 12 months).[3] Gender differences in prevalence are present among adolescents, with higher prevalence among girls than boys (5.9 vs. 4.6 percent).[3] Lifetime prevalence among adolescents may be as high as 20 percent.[4-6] Depression is less common among children younger than 13 years, among whom prevalence of MDD is estimated to be 2.8 percent.[3] Point prevalence of MDD among adolescents in primary care settings has ranged from 9 to 21 percent.[7-9]

As many as 8 percent of youth with adolescent-onset depression are estimated to have completed suicide by young adulthood.[10] Such youth may also have a five-fold increase in risk of attempting suicide compared to non-depressed adolescents.[10] Suicide is the third leading cause of death among those aged 15 to 24 years and the sixth leading cause among those aged 5 to 14 years.[11] The majority of adolescents who have completed suicide had longer-term MDD.[12]

MDD is also associated with substantial long-term morbidity, including decreased school performance, poor social functioning, early pregnancy, increased physical illness, and increased risk of substance abuse.[10,13,14] Depressed adolescents have more psychiatric and medical hospitalizations than adolescents who are not depressed.[10] Additionally, the cost of medical care (general medical combined with mental health care) is higher for children with depressive disorders than children without mental health diagnoses and children with other mental health diagnoses (other than conduct disorder).[15] Young adults who have adolescent-onset MDD are at increased risk of impairment in work, social interactions, and family functioning.[10,16]

Natural History

While depression can begin at any age, a substantial proportion of patients have their first episode of MDD during childhood or adolescence. Cumulative Kaplan-Meier curves for age-at-onset show that risk is fairly low until the early teens, at which time it rises in a roughly linear fashion.[17] One study of adult primary care patients (40.5 years of age, on average) found that 38 percent of depressed patients' initial onset of MDD was before age 18.[18] The average length of a major depressive episode in children and adolescents is approximately 7 to 9 months.[19] Factors associated with longer time to recovery in children and adolescents include earlier age of onset, greater severity of illness, suicidality, presence of comorbid dysthymia, anxiety, disruptive disorders, maladaptive cognitive patterns, and adverse family environment.[20] Like adult depression, depression in children and adolescents is often recurrent, with estimates of recurrence ranging from 40 to 70 percent.[19] These rates may overestimate the general risk, however, as they are based on small, non-community-based samples.

Adolescent MDD is particularly associated with increased risk of MDD occurrence in early adulthood in both clinical and community samples.[10,14,21] Among a school-based sample of

adolescents with MDD, 46 percent experienced a major depressive episode between the ages of 19 and 23 years, and an additional 22 percent had a non-mood-related psychiatric disorder between the ages of 19 and 23 years.[21] Among adolescents with an MDD diagnosis, risk factors for MDD in young adulthood include high levels of emotional reliance, multiple major depressive episodes in adolescence, higher proportion of family members with recurrent MDD, high levels of antisocial or borderline personality disorder symptoms, negative attributional style (males only),[14] and low SES.[22] The relationship between onset of MDD prior to adolescence and MDD in adulthood, however, is not clear.[23]

An additional outcome of concern is that MDD may convert to a bipolar disorder, which involves episodes of mania or hypomania and often also includes psychosis. The rate of conversion to a bipolar illness is higher in adolescents than in adults. Twenty to thirty percent of clinically referred youth with a diagnosis of MDD will develop a bipolar illness during the subsequent 5 to 10 years.[19] This is a considerably higher rate than that of adults, which is estimated at less than 10 percent.[19] Another complicating factor of MDD is that it frequently co-occurs with other mental health disorders. One study of adolescents with MDD from mental health clinic and school populations found that 76 to 78 percent had an additional mental health disorder, most commonly anxiety disorders.[24]

Etiology

A variety of factors contribute to the development of depression, with most people who develop MDD having multiple risk factors.[25] Researchers have identified several familial and personal factors that appear to increase the risk of depression, such as parental depression, sub-syndromal depression, anxiety, neurobiology, temperament/personality, negative cognitions, stress, and interpersonal conflict.[26] In addition, negative life events[27] and health issues, such as chronic pain,[28] may increase the likelihood of depression. The role of genetics in the development of depression is unclear. Twin studies support the heritability of depressive symptomatology,[29] and one twin study of adolescent girls reported moderate heritability (41 percent) of a depressive disorder meeting DSM-IV criteria.[30] In contrast, two adoption studies do not support a genetic component of depression.[31,32]

These risk factors may contribute directly to the development of depression or may increase the likelihood that a young person who is faced with negative life events or chronic stressors will become depressed. Several of these factors have multiple presumptive pathways for increasing the risk of depression. Having a depressed parent, for example, may increase risk due to both genetic predisposition to depression inherited from the parent and the effects of the depressed parent's behavior, who are more likely to be irritable and inconsistent and less warm and interactive than parents who are not depressed.[33] Similarly, many of these factors are likely to interact with each other to increase depression risk. Genes may contribute to a child's neurochemistry, personality, and ability to self-regulate, which may cause others to react more negatively to them, thus creating a more depressogenic environment.

Prevalence in Subgroups with Risk Factors

As risk factors for depression are difficult to assess, researchers have focused on identifying subgroups of youth who have an increased risk of developing depression. Some examples of factors that can be assessed relatively accurately and reliably include being an offspring of depressed parents, having comorbid mental health or chronic medical conditions, and having suffered a major negative life event. Prevalence of depression is considerably higher among some of these subgroups than in the general population (Table 3). For example, a study identified 20 to 33 percent of obese youth as having depression.[34] Among youth with psychiatric comorbidities, the majority of studies from several reviews found that 10 to 30 percent of youth with an anxiety disorder also had a depressive disorder,[35-37] with individual studies reporting prevalence as high as 69.2 percent.[36] Offspring of depressed parents also have a high prevalence of depression. By the age of 18 years, 40 to 67 percent of these youth are estimated to have met criteria for depression at some point during their lives.[38]

Rationale for Screening/Screening Strategies

Mass screening in primary care could help clinicians identify missed depression cases and initiate appropriate treatment. Screening could also help clinicians identify patients earlier in their course of depression. In both cases, it would be necessary to deliver effective treatment that would improve patients' depression and more quickly alleviate suffering.

Current tools for assessing children and adolescents for depression include diagnostic interviews and symptom rating scales.[39] Several of these tools are long and complex and have primarily been evaluated in non-primary care settings. Diagnostic screening tools, however, have been developed which are feasible for use in primary care (Table 4). In some cases, tools designed for adults have been used directly with, or adapted for, adolescents. Some tools have been developed specifically for younger children and consider developmental differences. Relatively few available tools have been designed for use with children or adolescents specifically in the primary care setting.

Mass depression screening was feasible and acceptable from the provider's perspective in a recent pilot study.[40] In this study, adolescents presenting to a pediatric primary care practice for health maintenance or urgent care visits were asked to complete a paper and pencil screening tool prior to their office visit. Front desk staff were involved in administering the tool and providers underwent special training in depression assessment. At the end of the study, providers reported that the burden of the program was low and that the patients were generally satisfied with the screening process. All 11 providers wanted to continue the screening program after the 6-month study period. The 13- to 17-year-old primary care patients in their study were able to complete a paper and pencil screening tool in less than 5 minutes. Few details were provided regarding the type of clinic or characteristics of the patients, therefore it is not clear how well the results would generalize to different types of clinical settings.

Interventions/Treatment

Available modes of treatment for MDD in youth include pharmacotherapy (Table 5) and psychotherapy, delivered singly or in combination. Trials demonstrating the efficacy of drug treatments and time-limited psychotherapies among pediatric populations were first published during the 1990s.[2] Presently, fluoxetine, an SSRI, is the only pharmacologic agent that the FDA has approved for the treatment of pediatric MDD. The term "psychotherapy" refers to a broad range of psychological interventions that may employ a variety of techniques, over different periods of time, and be based on different theoretical assumptions. Psychotherapeutic interventions may be very structured and manual-based or may be relatively unstructured. They may involve a variety of techniques, such as identifying and changing maladaptive behaviors or thought patterns, improving social or life skills, and empathetic listening and reflection on a patient's thoughts.

Recent Controversies Regarding Treatment

In 2004, the FDA released a black box warning about suicidality and antidepressant use in pediatric patients. A blinded analysis of suicidality outcomes by suicidology researchers from Columbia University played an early role in the ultimate release of an FDA black box warning. There have subsequently been numerous publications discussing this issue, including the publications of the findings from the FDA meta-analyses evaluating risk of suicidality among pediatric patients treated with antidepressants. The FDA's analyses included a total of 4,582 patients from 24 trials. We describe their methodology and findings as part of our results.[21]

Current Clinical Practice

Identification of Depression

Current, reliable data describing pediatric depression screening practices among primary care providers are lacking. Available information from the past decade is based on clinician self-report. Providers in community health centers have reported screening 64 percent of their patients for depression, though they only documented their screening efforts in 3 percent of the patients.[41] Providers in an HMO estimated screening an average of 46 percent of their patients for depression.[42] Data based on direct observation or provider- and/or patient-report after specific clinical encounters would be more reliable. We are not aware of recent data describing the proportion of depressed children or adolescents who have been seen by a primary care provider but were not identified by the provider as depressed (i.e., missed cases). One older (1988) study found that pediatricians identified only 17 percent of children with behavioral or emotional problems.[43]

When asked to recall the identification methods used with their last depression patient, only one of 245 providers reported using a structured screening questionnaire.[44] Providers in this same study reported that in 68 percent of their cases the presenting problem indicates that depression is a likely concern. This is concerning because depressed youth may not directly seek help with their depression from their provider. A recent Norwegian study found that youth with anxiety and depressive symptoms rarely sought treatment—only 34 percent of those in the 99th percentile for symptom severity sought treatment—despite a health care system with free services that are relatively easy to access.[45] Other commonly used clues for identifying depression in youth are the patient's appearance, reports or observations of family dynamics, and family members' concern for identifying a patient as possibly depressed.[44]

Once they identified depression as a likely problem, 50 percent of pediatricians based their diagnosis on their overall impression and inquiry about one to two symptoms. Only 17 percent used formal DSM-IV criteria for assigning a diagnosis. Once depression was diagnosed, 92 percent of pediatricians reported further assessment of specific symptoms and contributing factors.

This same study reporting on identification practices also queried providers regarding their beliefs about their role in identifying depression and their confidence in their ability to identify depression.[44] They found that 90 percent of pediatricians believe that recognition of child and adolescent depression is their responsibility, but 46 percent lacked confidence that they could recognize depression.

Treatment of Depression

Among youth identified in primary care as being depressed, the majority appear to receive treatment.[46-48] During the year 1998, 69.7 percent of youth with visits in primary care for newly identified episodes of depression were either seen by a mental health specialist or received one or more dispensing of psychotropic medication in an HMO[46] in the subsequent 30 to 90 days. Similarly, data from the National Ambulatory Medical Care Survey (NAMCS) and the outpatient component of the National Hospital Ambulatory Medical Care Survey (NHAMCS) showed that of adolescent primary care visits in which depression is reported, antidepressants were prescribed 52 percent of the time, and 68 percent of the visits included psychotherapy or counseling.[47]

Provider beliefs and perceptions. Despite these high rates of treatment reported in primary care visits where depression is noted, a survey of pediatricians found that only about a quarter of pediatricians believe that treating child and adolescent depression is their responsibility.[44] Further, 86 percent of pediatricians were not confident that they could successfully treat child and adolescent depression with medication,[44] and 90 percent of pediatricians were not confident that they could successfully treat child or adolescent depression with counseling.[44] According to this survey, the main barriers to treating depression in youth for pediatricians are: inadequate time to provide counseling or education (endorsed as a barrier by 68 percent of surveyed pediatricians), inadequate time to collect an adequate history (56 percent), incomplete training to diagnose or counsel (56 percent), and incomplete knowledge of treatment for depression (44 percent).[44]

Modes of depression treatment. Psychotherapy is the most common mode of treating depressed youth. Of children treated for depression identified by a large community survey, 79 percent received psychotherapy.[48] Although pediatric providers' use of counseling may be declining,[47] they report using counseling in 68 percent of visits involving depression, and 35 percent of youth identified with a new episode of depression in primary care were seen by a mental health specialist within 90 days.[46]

Antidepressant use is also an important treatment modality for adolescents. In the US during 2002, 17/1000 (1.7 percent) of all children (0 to 18 years old) used antidepressants.[49] Of children treated for depression identified by a large community survey, 57 percent received antidepressants.[48] In primary care settings, over half of those treated for depression are prescribed antidepressants.[46,47] The most commonly used medications are SSRIs: among all youth dispensed a psychotropic medication for a new episode of depression in an HMO in 1998, 78.8 percent received an SSRI, 3.6 percent received a TCA, 13.9 percent received another antidepressant (bupropion, nefazodone, trazodone, or venlafaxine), 2.3 percent received a mood stabilizer, and 1.3 percent received a benzodiazepine.[46]

Trends in the use of antidepressants. Several studies show that antidepressant use in youth increased steadily from the early- to mid-1990s until concerns about suicidality appeared in the early 2000s.[47,50-52] From 1997 to 2002, antidepressant use went from 21/1000 (2.1 percent) to 39/1000 (3.9 percent) in those aged 13 to 18 years and stayed steady in younger children: 15/1000 to 14/1000 in those aged 6 to 12 years old and 1/1000-1/10,000 in those 0 to 5 years old according to a Medical Expenditure Panel Survey (MEPS) database.[52] The use of SSRIs in particular have increased since the early- to mid-1990s.[47,52] SSRI use was documented in 1.35 million outpatient child and adolescent visits in the 2001 to 2002 NHAMCS and NAMCS, which is a 2.6-fold increase from 1995 to 1996. Fluoxetine increased by 100 percent, sertraline by 62 percent, and paroxetine by 269 percent between 1995 to 1996 and 2001 to 2002. At the same time, TCA antidepressant use declined from 16 percent to 2 percent.[47]

The number of children and adolescents prescribed antidepressants in the US declined after the 2004 FDA public health advisory of black box warning.[53,54] From April 2002 to February 2004, the number of prescriptions increased by a monthly average of 0.79 percent. From February 2004 (when there was an FDA hearing on SSRI safety that was widely covered by the media) through July 2004, there was a monthly decrease of an average of 4.23 percent.[53] The same change in prescribing trends has been observed when including data through September 2005 and restricting to pediatric patients who have received a newly documented diagnosis of depression.[55]

In contrast to the increase in antidepressant use in adolescents from the early 1990s through early 2000s, suicide trends in adolescents and young adults steadily declined from 1994 through 2002.[56] The downward trend, however, may be reversing: suicide rates in children and adolescents increased by 14 to 18 percent between 2003 and 2004 (when the black box warning appeared).[57,58]

Recommendations of Other Groups

Routine screening for emotional and behavioral problems has been recommended by Medicaid's Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program, the American Academy of Pediatrics, and the American Medical Association. The Canadian Task Force on Preventive Health Care concluded in 2004 that there was insufficient evidence to recommend for or against screening for depression among children or adolescents in primary care settings.[59] The Society for Adolescent Medicine supports the initiation and continued use of antidepressant medications for adolescents when clinically warranted with close monitoring for emergent suicidality, hostility, agitation, mania, or unusual changes in behavior.[60]

Previous USPSTF Recommendation

In 2002, the USPSTF concluded there was insufficient evidence to recommend for or against routine screening of children or adolescents for depression (I Recommendation).[61] At the time of the 2002 review, no evidence was available describing the direct health outcomes among children or adolescents identified with MDD through primary care screening. While a small number of studies evaluated screening test performance in ambulatory, non-psychiatric pediatric populations, most of the data were from adolescent populations. Trials evaluating MDD treatment among children or adolescents indicated that tricyclic antidepressants were not effective and cognitive-behavioral therapy was efficacious among school populations. Only two controlled trials had been published describing the efficacy of SSRIs among youth, and these demonstrated mixed results.[62,63] For both screening and treatment, it was unclear whether available results were generalizable to children or primary care settings. The previous report did not specifically search for literature on the harms of screening or the adverse effects of treatment.

Chapter 2. Methods

Using the methods of the USPSTF (detailed in Appendix B),[64] we developed an analytic framework (Figure 1) and five key questions (KQ) to guide our literature search. KQ1 assessed direct evidence that screening programs for depression among average-risk child and adolescent primary care patients reduce morbidity and/or mortality. KQ1a examined whether screening increases the proportion of patients identified with and/or treated for depression. KQ2 addressed the accuracy of depression screening instruments for children and adolescents in identifying depression in primary care or school-based clinics. KQ3 examined the harms of screening for depression in children and adolescents. KQ4 addressed the effectiveness of treating screen-detected children and adolescents with SSRIs and/or psychotherapy. KQ5 assessed serious adverse effects of SSRI and/or psychotherapy treatments for depression in children and adolescents. In conjunction with members of the USPSTF, we restricted the scope of this report to include only SSRIs. Fluoxetine is currently the only agent FDA-approved to treat pediatric depression. We broadened the scope to include all SSRIs because they act through a similar mechanism to fluoxetine and are most commonly prescribed.[46] Tricyclic antidepressants were demonstrated to lack efficacy in previous evidence reviews and newer atypical antidepressants are not approved for treating depression among youth.

For all key questions, we searched for systematic reviews, meta-analyses, and evidence-based guidelines on depression screening, treatment, or associated harms in children and adolescents in the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews (CDSR), MEDLINE, and PsycINFO from 1998 through May 2006. We also conducted a series of searches for each key question and reviewed the search results for applicability to all key questions. For KQs 1-3, addressing screening outcomes, accuracy, and harms, we searched for depression screening in children and adolescents in primary care to cover the time period since the previous USPSTF review (1998 through May 2007) in MEDLINE, PsycINFO, and the Cochrane Collaboration Registry of Clinical Trials (CCRCT) without restrictions on study designs. For KQ4, we searched for RCTs/CCTs of psychotherapy and SSRI treatment in children and adolescents in MEDLINE, PsycINFO, and CCRCT in two separate searches covering 1998 through May 2007 for psychotherapy and 2004 through May 2007 for SSRIs. For KQ5, we searched for adverse effects of SSRIs and psychotherapeutic treatment, without restrictions on study designs, in two separate searches covering 1990 through May 2007 for psychotherapy and 2004 through May 2007 for SSRIs. The search period for SSRI treatment trials (safety and efficacy) began in 2004 because several previous systematic reviews provided good coverage through 2004.[65,66] Our search period for adverse effects of psychotherapy began in 1990 because harms of treatment were not addressed in the previous USPSTF review. Articles were also obtained from outside experts and through reviewing bibliographies of other relevant articles and systematic reviews. In addition to these searches for published trials, we searched pharmaceutical company and federal agency trial registries for unpublished trials of SSRIs. All searches were limited to articles in English. Inclusion and exclusion criteria specific to each question are detailed in Appendix B.

Two investigators independently reviewed all abstracts for KQs 4 and 5. The initial search for KQs 1-3 produced a very high yield (3,418 abstracts). Therefore, we used a modified approach to reviewing these abstracts, detailed in Appendix B. Two investigators evaluated

abstracts against a set of inclusion/exclusion criteria, including independent review using design-specific quality criteria based on the USPSTF methods, supplemented by NICE[67] criteria for quality of systematic reviews (Appendix B, Table B3). Two investigators critically appraised all studies excluded for quality reasons. Data from included studies were abstracted into evidence tables by one investigator and checked by a second. We found no data for KQs 1, 1a, and 3. Data synthesis for KQ2, psychotherapy (KQ4 & 5), combined psychotherapy and SSRI interventions (KQ4 and 5), and observational data on harms of SSRIs (KQ5) were qualitative because heterogeneity in the interventions, samples, and settings did not allow for quantitative synthesis. For evidence on the efficacy and adverse effects of SSRIs, we calculated pooled absolute risk differences using random effects models and narratively describe data from other meta-analyses. Details of our quantitative synthesis approach and rationale are described in detail in Appendix B.

Chapter 3. Results

Key Question 1. Does screening for depression among children and adolescents in the primary care setting improve health outcomes?

Summary of findings. No trials were found that examined health outcomes of depression screening programs in youth.

Study details. None.

Key Question 1a. Does screening increase the proportion of patients identified with and/or treated for depression?

Summary of findings. No trials were found that examined whether screening led to an increased proportion of children or adolescents identified with and/or treated for depression.

Study details. None.

Key Question 2. Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?

Summary of findings. We identified nine fair-quality studies (reported in 12 publications) of depression screening instrument accuracy in children and adolescents, covering six different depression instruments (Table 6). Two of these studies were conducted in primary care samples, one in a community sample, and six in school samples. Only one study included children younger than ten years of age, and the majority included adolescents 12 years or older. While the large number of instruments and heterogeneity in samples and settings makes generalization across studies difficult, it may explain the wide range of performance characteristics reported (sensitivity ranged from 18 to 100 percent and specificity ranged from 38 to 97 percent).

Studies involving younger children tended to have poorer performance. One study highlighted the fact that optimal cutoffs may differ for boys and girls. All of the studies had methodological limitations, such as samples with high levels of attrition or nonrandom selection, excessive delays between screening and diagnostic interviews, poor reporting of methods or attrition, small samples, and less-than-ideal reference standards.

Sensitivity in the two primary care studies ranged from 73 percent for the Patient Health Questionnaire for Adolescents (PHQ-A) to 90 percent for the Beck Depression Inventory-Primary Care Version (BDI-PC). Specificity ranged from 91 percent (BDI-PC) to 94 percent (PHQ-A). As both of these studies examined only adolescents, no information was found that is directly applicable to younger children. The single study involving a community sample

reported sensitivities ranging from 33 to 63 percent for the Strengths and Difficulties Questionnaire (SDQ), examining various combinations of child-, parent-, and teacher- report with two different age ranges. The 33 percent sensitivity in the SDQ for child-only report in those 11 to 15 years old improved to 63 percent when both parent- and child-report were used. Sensitivity for those 5 to 10 years old (parent-report only) was 53 percent.

Most data were gathered in school settings, which included four studies examining the Beck Depression Inventory (BDI), two examining the Center for Epidemiologic Study-Depression Scale (CES-D), and one examining the Revised Clinical Interview Scale (CIS-R). Cutoffs of both 11 and 16 performed reasonably to very well on the BDI, with sensitivity ranging from 84 to 100 percent (BDI ≥11) or 77 to 100 percent (BDI ≥16), and specificity ranging from 77 to 86 percent (BDI ≥11) or 65 to 96 percent (BDI ≥16). Confidence in these results is quite limited, however, because of methodological problems within each study.

Study Details.

Primary care settings. Two fair-quality studies examining the quality of depression instruments were conducted in primary care settings,[7,9] one of which was included in the 2002 review.[9]

Johnson et al., 2002:[7] This most recent study examined the properties of the Patient Health Questionnaire for Adolescents (PHQ-A), which was designed to assess mood disorders, anxiety, eating disorders, and substance use disorders in adolescent primary care patients. The sample includes 403 adolescents, aged 13 to 18 years, showing no evidence of mental retardation or organic mental disorders, recruited from urban, rural, and suburban primary care sites in California, Ohio, New Jersey, and New York. This study included both office-based and school-based clinics.

After receiving the PHQ-A, a PhD-level psychologist, who was blinded to the results of the PHQ-A, completed a diagnostic interview by phone. Procedures differed between the California sites and the other sites, which resulted in 241 (60 percent) of the 403 completed phone interviews at non-California sites being completed more than 18 days after the PHQ-A. These interviews, therefore, were dropped from the analysis. In contrast, 95 percent of the California sites' phone interviews were completed within one week of the PHQ-A. No data were presented comparing those with complete data, and were subsequently dropped due to this time lag.

This sample was 63.3 percent female, with an average age of 15.9 years. Over three-fourths of the sample was White (77 percent White, 4.2 percent African American, 12.4 percent Hispanic), 9.4 percent of this sample met criteria for MDD according to the diagnostic interview, and 12.4 percent screened positive on the PHQ-A. This study reported sensitivity of 73 percent, specificity of 94 percent, and overall accuracy of 92 percent.

Winter et al., 1999:[9] A 1999 study examined the psychometric properties of the Beck Depression Inventory of Primary Care (BDI-PC) in a sample of 12- to 17-year-olds scheduled for routine health maintenance appointments. Investigators recruited 50 boys and 50 girls to complete the BDI-PC in the waiting room prior to an appointment, which required 10 months of recruitment. Pediatricians administered the mood module of the PRIME-MD without seeing BDI-PC responses. The accuracy of pediatricians in assigning mental health diagnoses is unknown, but is likely only fair: kappas of 0.61 and 0.63 have been observed in other studies

using similar methodology in adult, primary care providers comparing primary care providers with mental health clinicians, according to the study authors.

The sample in this study was 50 percent female, 73 percent White, 19 percent African American, and 4 percent Hispanic, with an average age of 13.9 years. Eleven percent met criteria for MDD according to the PRIME-MD interview. Using a cutoff of 4, the BDI-PC had both sensitivity and specificity of 91 percent.

Community settings. One fair-quality study examined depression screening instruments in a community sample.[68] This study was not included in the previous USPSTF review.

Goodman et al., 2003:[68] This 2003 study examined the Strengths and Difficulties Questionnaire (SDQ) through the British Office of National Statistics.[68] A sample of 10,438 children was recruited, and parent and teacher reports were attempted for all children. Children were only included if data were complete for all three sources (self, parent, teacher) in 11- to 15-year-olds, and two sources (parent, teacher) in 5- to 10-year-olds (n = 7,984, 76 percent of the children recruited). The SDQ covers common areas of emotional and behavioral difficulties and results in summary scores of "unlikely," "possible," and "probable" for conduct-oppositional disorders, hyperactivity-inattention disorders, and anxiety-depressive disorders. After completion of the SDQ, nonclinical interviewers administered a structured diagnostic interview, the Development and Well-Being Assessment (DAWBA). An experienced clinician reviewed the DAWBA and assigned a clinical diagnosis.

Participants were an average age of 10.2 years, and 50.3 percent were female. Children with complete data had slightly lower rates of psychiatric disorders than the full sample. Among those 5 to 10 years old who did not complete a self-report instrument, the sensitivity was 53.9 percent for parent-report SDQ and 69.2 percent when the parent and teacher reports were combined. Specificity was not reported. Among children aged 11 to 15 years, sensitivity for self-report SDQ was 33.3 percent; parent-report was 44.4 percent; parent- and child-report combined was 63 percent; and self-, parent-, and teacher-report combined was 75.9 percent. This study did not report specificity.

School settings. Six fair-quality studies in nine publications examined the psychometric properties of depression screening instruments in school settings. Four of the studies examined the Beck Depression Index (BDI),[6,69-73] two examined the Center for Epidemiologic Studies Depression Scale (CES-D),[73-75] and one examined the Revised Clinical Interview Schedule (CIS-R).[76] One of the studies examined both the BDI and CES-D.[73]

Canals et al., 2002:[69-71] The most recent study to examine the BDI was conducted in Spain in a sample of children who had been part of a study 7 years before the current study. Children attending local schools were identified through census records of an urban commercial area of 96,000 inhabitants in Reus, Catalan. Seven years later, they found 304 of the original 579 children and had them complete the Spanish version of the BDI. Of the 304 who completed the BDI, 290 (95 percent) also completed the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) within one week. Participants were not blinded to the BDI results.

The average age of the youth was 18 (range 17.5 to 18.5), and 50 percent were female. The sample had low prevalence of depressive disorders: 3.4 percent were diagnosed with MDD, and 13.1 percent of participants were diagnosed with a depressive disorder of some kind. Researchers reported instrument characteristics using four different cutoffs and assessed accuracy for four different depressive disorders: MDD, DD, adjustment disorder with depressed mood, and depressive disorder not otherwise specified. At the highest cutoff of 16, which had the best PPV, sensitivity was 90 percent, specificity was 96 percent, PPV was 47 percent, and NPV was 99.6 percent for MDD. Although the sensitivity and specificity were very high in this study, confidence in the generalizability of the results is limited by the fact that they only had data on a nonrandom sample of 52 percent of students who had participated in a different study 7 years previous.

Berrera et al., 1988:[72] Another study examined the BDI in samples drawn from a school and from youth with inpatient psychiatric admissions. They report results separately for the two samples. We only report the results of the school sample here. Forty-nine youth from a secondary school near the psychiatric facility completed the BDI and, within one week, the semi-structured Child Assessment Schedule (CAS). The authors did not report whether diagnostic interviewers were blinded to BDI results, nor did they describe how the sample was selected from the school.

The school sample had an average age of 14.6 years (range 12 to 17) and was 54 percent female. Five of the 49 participants (10 percent) met criteria for a major depressive episode. They reported instrument characteristics at five different cutoffs for a major depressive episode. At a cutoff of 16, the authors reported a sensitivity of 100 percent and specificity of 93.2 percent, with 6.1 percent false positives. Although sensitivity and specificity were very high in this sample, confidence in the results is limited by the very small sample size, potential lack of blinding, and the lack of description about how the school sample was selected and how many recruited participants refused or were ineligible.

Whitaker et al., 1999:[6] The next study to examine the BDI in a school sample looked at performance characteristics in predicting lifetime MDD in the entire enrollment of 9th through 12th grades in a single New Jersey county during October, 1984. Of the 5,596 students enrolled, 5,108 (91 percent) completed the BDI and instruments screening for several other psychiatric disorders during the fall. A stratified random sample of 468 students was selected to complete a semi-structured diagnostic interview the subsequent winter and spring, 356 (76.1 percent) of whom completed the interview. Interviewers did not have access to screening results. Because they oversampled potential cases of several different types of psychiatric disorders, specificity may be underestimated. To adjust for this, they report specificity after excluding all cases of other disorders identified by the screening tool from the false positive results, in addition to the specificity using the entire sample, as it is traditionally calculated.

Characteristics of the larger screening sample were reported. The authors also reported that diagnostic interview completion was not related to sex, age, social class, or BMI. The screening sample was 49.8 percent female, 94 percent White, and 92 percent were between ages 14 and 17. High school was the highest level of educational attainment for 42 percent of the mothers, and 34 percent of the fathers completed high school and had no schooling beyond high school. For lifetime MDD, the BDI had a sensitivity of 77 percent, specificity of 65 percent using the usual methods, and specificity of 72 percent using their modified method. Although they did not report the time lag between the screening instrument and the diagnostic interview, it

is possible that over two months elapsed in many, if not most, cases. This explains why they compared the BDI with lifetime MDD rather than current MDD. Lifetime MDD, unfortunately, is of limited clinical utility in the primary care setting.

Roberts et al., 1991:[73] One study examined both the BDI and the CES-D in a stratified random sample of students from five high schools in rural and urban west-central Oregon. Study authors report that approximately 61 percent (n = 1,704) of selected students participated in the study. They did not describe why they only reported an approximate number of participants, and they also did not report the number of youth invited to participate. Our interpretation is that these 1,704 youth completed at least one of the screening instruments and a diagnostic interview using the K-SADS. They did not report whether the interviewers were blinded to the screening results.

The youth in this study were an average of 16.6 years old, 53 percent female, and 91 percent white. Fifty-three percent of the students lived with both of their natural parents and 42 percent of the fathers had completed four or more years of college. The authors did not report the prevalence of depression in their sample. Using a BDI cutoff of 11, they report sensitivity of 83.7 percent, specificity of 80.9 percent, PPV of 10.2 percent, and NPV of 99.5 percent for current MDD. CES-D had similar performance characteristics: sensitivity of 83.7 percent, specificity of 75.2 percent, PPV of 8.0 percent and NPV of 99.4 percent for current MDD using a cutoff of 24. Questions about the sample's characteristics, low participation rate, and potential lack of blinding limit confidence in this study's results.

Garrison et al., 1991:[74,75] The study recruited all 7th graders enrolled in four middle schools in a suburban school district in the southeastern US during 1985. Students joining those four classes during either of the subsequent two years were also recruited. A total of 2,488 students completed the CES-D. A stratified (based on CES-D results) random sample of 332 students completed a diagnostic interview using the K-SADS. Interviewers were blinded to the students' screening scores. The authors did not report the number of students invited to complete the interview. Because of the two-step, stratified sampling procedure, weighted estimates, rather than raw data, were used to calculate instrument accuracy. The time between the CES-D and the diagnostic interview was not reported.

Forty-two percent of the students completing the interview were aged 12 years or younger at baseline, and an additional 38 percent were 13 years old. Fifty-seven percent of the students were female, 75 percent were White, 25 percent were African American, 49 percent lived with both natural parents, and 36 percent of the fathers completed high school but not college. Educational attainment of an additional 35 percent of fathers was unknown. The prevalence of depression in this sample was 8.2 percent in males and 8.7 percent in females, based on the diagnostic interview. This study reported instrument characteristics for males and females separately at four different cutoffs: 12, 16, 20, and 22. The CES-D performed more poorly in boys than in girls at all cutoffs but the lowest, 12. Their highest cutoff of 22 is most comparable to the previous study and demonstrated fairly good performance characteristics in girls: sensitivity was 83 percent, specificity was 77 percent, and PPV was 25 percent for MDD. For boys, however, the CES-D performed poorly at a cutoff of 22, with sensitivity of 18 percent, specificity of 83 percent, and PPV of 9 percent.

Patton et al., 1999:[76] The study used a two-stage cluster sampling procedure to first select 45 schools in Victoria, Australia for participation. Two classrooms were then selected

from each school. After completing the CIS-R as a screening tool, all those who screened positive and a random sample of those screening negative were invited to complete a diagnostic interview within three weeks using the depression and hypomania modules of the CIDI. Because of the sampling strategy, weighted estimates were used to calculate CIS-R performance characteristics. Eighty-five percent (n = 1,729) of the 2,032 students invited to participate completed the screening instrument, and 170 completed the diagnostic interview.

Study participants had an average age of 15.7 years (SD 0.5), were 53 percent female, and had a 6.2 percent prevalence of current MDD, based on the diagnostic interview. The study reported a very low sensitivity of 18 percent, specificity of 97 percent, PPV of 49 percent, and NPV of 91 percent. The low sensitivity of the study bears further exploration of the psychometric properties of the screening instrument. The CIS-R was originally developed as a tool for lay interviewers to conduct diagnostic interviews. The original research on this instrument examined the consistency of results between two interviewers, but test-retest stability and the performance characteristics of the instrument relative to a gold standard were not reported.[77] Although the current authors designed and conducted the study fairly well, the instrument may have been flawed in its original form, or adaptation to a self-administered, computer-based format may have been untenable, or both.

Key Question 3. What are the harms of screening?

Summary of findings. No studies were found that examined harms of depression screening programs in youth.

Study details. None.

Key Question 4. Does treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?

Summary of findings. We identified 18 fair- or good-quality RCTs that reported health outcomes among children or adolescents with MDD treated with SSRIs and/or psychotherapy (Table 7). These trials evaluated the short-term efficacy of five different SSRIs against placebo control conditions, ten different group or individually-delivered psychotherapies compared with control conditions, and combined therapy including both cognitive-behavioral psychotherapy and an SSRI. Two of these trials were conducted in community- or school-based clinical settings (both good-quality RCTs),[78,79] and the remainder were conducted in academic research centers or in schools (e.g., classroom-based). The majority of SSRI trials (6/9) included children at least as young as 8 years old in their study samples. The majority of trials testing psychotherapy interventions included only adolescents 12 to 14 years and older. Only two psychotherapy trials included 9- or 10-year-olds, and no completed trials included children 7 or 8 years of age. In total, nine of the SSRI or psychotherapy trials were good quality, according to USPSTF criteria, and nine were fair quality. Good-quality trials typically used a multigated screening procedure, including a clinical assessment, to identify depressed participants, measured outcomes through blinded clinical assessments (and often also self-reported depression symptoms), and analyzed

intention-to-treat populations, most often using LOCF data to replace missing values. Collaborative care interventions were outside the scope of this report, but are addressed in the discussion of our results. Depression outcomes were reported after 8 to 12 weeks of SSRI treatment or 4 to 16 weeks of psychotherapy. No controlled data were available for longer-term outcomes. Additional relevant outcomes were reported regarding global functioning.

We calculated that for the nine SSRI trials, the pooled absolute risk difference in the response between treatment and intervention groups was 12 percent (95 percent CI 7, 16; random-effects analysis), indicating higher response rates among those treated with SSRIs. When considering individual SSRIs, fluoxetine and citalopram both yielded statistically significant higher response rates. Data from meta-analyses of efficacy among children and adolescents analyzed separately in a recent systematic review by Bridge and colleagues (2007) suggested that overall, SSRIs were less effective among children. When restricting the analysis to only fluoxetine trials, however, results were similar for both children (RD 21 percent, 95 percent CI 4, 37) and adolescents (RD 20 percent, 95 percent CI 7, 33). These results were statistically significant for both groups.

Nine out of the ten psychotherapy trials found that treated patients had higher response rates or a greater reduction in depression symptoms after interventions, compared with a variety of control conditions. Two studies included children aged nine and ten years and both reported that mean clinician-rated depression scores improved more among treated patients than control group patients. No trials included children aged seven or eight years. One trial tested the effect of psychotherapy plus SSRI (TADS trial). Seventy-one percent (95 percent CI 62, 80) of adolescents treated with combination therapy achieved response criteria compared to 34.8 percent (95 percent CI 26, 44) of placebo control patients. This trial did not include any patients younger than 12 years of age.

Study details - SSRIs. We identified nine good-[78,80-87] or fair-quality,[63,88,89] double-blind, placebo-controlled RCTs evaluating the short-term health outcomes of five different types of SSRIs to treat MDD among children or adolescents (randomized total of 2,030 participants). Two separate RCTs evaluating sertraline were pooled and reported in one publication by the study authors and are discussed here as one trial.[81] Eight of the nine trials were published after the search window of the previous USPSTF report. We found no additional completed unpublished trials. We present the pooled risk difference and 95 percent confidence interval of the response rate to SSRI treatment for the nine trials that met our inclusion and exclusion criteria.

We also identified numerous recent systematic evidence reviews that included both published and unpublished results and examined the efficacy of SSRIs for treating MDD in youth.[65,66,90-92] We include results from the most recently published, good-quality systematic evidence review by Bridge and colleagues, which was the only review that included all of the trials that we identified through our searches.[92] This meta-analysis, however, also includes results from six trials of antidepressants for treating MDD that did not meet our inclusion and exclusion criteria. Two additional publications report *post hoc* analyses of efficacy by age subgroups.[93,94]

Trial characteristics. Trials evaluated the efficacy of fluoxetine, paroxetine, sertraline, citalopram, and escitalopram. Length of treatment ranged from eight to 12 weeks. Most trials involved multiple sites and were conducted in the United States or Canada in research/academic

settings. The TADS trial was the only one conducted predominantly in clinical settings located in the community and was described as an effectiveness trial. Trials included children and adolescents between the ages of 6 to 18 years of age; three exclusively enrolled adolescents.[78,80,82] Approximately half to two-thirds of included participants were females and 18 to 32 percent were racial or ethnic minorities.

All trials required patients to have MDD of at least moderate severity (baseline CDRS-R scores ranging from 55 to 65 points). The average duration of depressive illness at the time of study entry varied from 3 to 26 months. Trials also varied with respect to the prevalence of other psychiatric comorbidities in the study populations. Three trials reported that psychiatric comorbidities were common among the studied population (40 to 50 percent of population).[78,80,81] Four trials excluded patients who had other psychiatric disorders.[81,84,89] Few trials reported including patients with comorbid anxiety disorders (15 to 28 percent prevalence)[78,80,82] or ADHD (12 to 17 percent prevalence).[78,88] Trials generally excluded patients who reported a history of substance abuse. One trial did not describe whether patients with substance abuse issues were included.[81]

Trial quality. Overall, these trials were of good quality. Most of the trials described an adequate randomization method (e.g., computer-generated sequence). All trials were described as double-blind with the treatment allocation masked from participants and study staff; three reported that study drug and placebo were actually packaged identically to ensure blinding.[81,82,84] The remaining trials did not use any specific language describing how the allocation sequence was concealed from the researchers enrolling participants. Eligibility criteria were well described and appropriate. The characteristics of the baseline populations were also described in detail and indicated that randomization procedures were successful with regard to important potential confounding characteristics. Most of the trials excluded patients who were participating in any other specific psychotherapy, but allowed (or provided) some type of supportive psychotherapy. Attrition ranged from 18 to 38 percent and was similar between groups, except for two fair-quality trials in which attrition was higher in the control groups (38 to 46 percent) than the intervention groups (17 to 29 percent).[63,88] Most trials did not report how well patients adhered to taking study medications, except reporting those who discontinued completely. All trials conducted analyses on the intention-to-treat population, although most excluded patients who did not take at least one dose of study drug or placebo and complete at least one subsequent outcome assessment. In general, trials used the last observation carried forward method; some used either linear coefficient regression or rate of change methods to predict missing outcomes.

Outcomes. The definition of treatment response varied across trials. Trials reported binary response rates as well as changes in continuous scores over time between groups. Most trials defined the primary measurement of response to treatment using either the Clinical Global Inventory-Improvement scale[95] or a predefined level of change in the Children's Depression Rating Scale-Revised score.[96] The CDRS-R was the most common continuous depression scale used to report the mean change in symptoms over time. Outcomes were measured at post-treatment, which ranged from 8 to 12 weeks. Remission was defined as CDRS-R score of 28 or less, but was reported in only three trials.

Results. Response rates among treatment and placebo groups varied across all nine trials (Table 7). Thirty-six to 69 percent of patients in treatment groups met response criteria at post-intervention followup compared to 24 to 59 percent of patients in placebo control groups. Considering individual trials, the absolute risk differences were highest among two trials of

fluoxetine in which 56 to 61 percent of fluoxetine-treated patients met response criteria at 8 to12 weeks, in contrast with only 33 to 35 percent of placebo-treated patients. Notably, approximately 40 percent of patients treated with fluoxetine did not meet response criteria. These trials were also the only two in which differences in response rates between intervention and control group were statistically significant. The two trials in which the risk differences were lowest (2 to 3 percent) were both trials of paroxetine. Based on the outcomes reported in all nine RCTs (1,972 participants), the pooled absolute risk difference was 12 percent (95 percent CI 7, 16) (Figure 2; random effects model). These results indicate that a greater proportion of patients treated with an SSRI responded compared to patients treated with placebo.

Remission rates were reported for three of the trials.[83,85,88] Emslie and colleagues (2002) reported that 41.3 percent of patients in the fluoxetine treatment group met remission criteria compared to 19.8 percent of patients in the placebo control group ($p < 0.01$). Kennard and colleagues (2006) reported that among adolescents in the TADS trial, remission rates were similar between fluoxetine- and placebo-treated groups (23 percent vs. 17 percent, ns). Emslie and colleagues (2006) reported finding no difference in remission rates between paroxetine- and placebo-treated children and adolescents (results combined across age groups).

Mayes and colleagues analyzed the efficacy of fluoxetine for children (< 12 years; n = 134) compared to adolescents (≥ 12 years; n = 175), [94] using data from two of the published RCTs of fluoxetine.[63,88] In a random regression analysis of the CDRS-R score, they reported a significant treatment group by age group interaction ($p = 0.044$). Reductions in CDRS-R scores from baseline were significantly greater for those treated with fluoxetine versus placebo in both children ($p<.001$) and adolescents ($p = .011$). The effect sizes indicated that the treatment effect was larger among children (ES 0.71) than adolescents (ES 0.39). They reported that among children, response rates to fluoxetine were significantly better than placebo (56.9 percent vs. 33.3 percent; $p = 0.009$). Among adolescents, response rates were also higher to fluoxetine than placebo (51.1 percent vs. 38.6 percent) but were not statistically significant ($p = 0.128$). Data from one other trial of fluoxetine in adolescents with MDD (TADS trial) were not included in these analyses.

Donnelly and colleagues analyzed the efficacy of sertraline by age group,[93] using data from a previously published trial[81] that included 177 children and 199 adolescents. Among adolescents, mean change in CDRS-R scores favored sertraline treated patients over placebo ($p = 0.012$). In contrast, mean change in CDRS-R scores were not different between sertraline and placebo-treated children.

Bridge et al., 2007:[92] Bridge and colleagues recently published a good-quality systematic evidence review in which they conducted meta-analyses of efficacy and adverse effects for all antidepressants (including non-SSRI atypical antidepressants) to treat MDD, obsessive-compulsive disorder, or non-obsessive-compulsive anxiety disorders in children or adolescents. They present results separately for MDD trials and also calculated pooled outcomes for children and adolescents separately. In addition, they evaluated trial-level variables as potential moderators of outcome effects. Bridge and colleagues quality rated individual trials using Detsky scores, but did not exclude trials based on quality considerations. The review includes 15 MDD trials that randomized 3,430 participants overall. It included the nine RCTs that met our inclusion and exclusion criteria, two RCTs that we excluded due to poor quality (a fluoxetine

trial[62] and a citalopram trial[97]), and four additional trials evaluating atypical antidepressants. Based on data from 2,910 participants in 13 RCTs, they found that the pooled absolute rates of response were 61 percent (95 percent CI 58, 63) among participants treated with antidepressants and 50 percent (95 percent CI 47, 53) among participants treated with placebo, which yielded a pooled risk difference of 11 percent (95 percent CI 7, 15), and a number needed to treat (NNT) of 10 (95 percent CI 7, 15). These results were based on a random-effects model, which assumes that heterogeneity across trials is not fully accounted for by the observed covariates and provides a more conservative estimate of effect than a fixed-effect model because it incorporates within- and between-study heterogeneity. The authors also conducted pooled analyses of the continuous measures of mean improvement in depression symptom scores and found that those results demonstrated a consistent effect of greater response among treated participants compared to control groups (Hedges g = 0.20; 95 percent CI 0.12, 0.29). The Hedges g for individual trials ranged from -0.06 to 0.60. The Hedges g was statistically significant (the 95 percent confidence interval did not cross zero) for the results of five individual trials and ranged from 0.28 to 0.60 across those trials.[63,78,81,88,89]

Results of the pooled RD and NNT, stratified by type of SSRI, are presented in Table 8. The pooled RD was largest for the fluoxetine trials (RD 20, 95 percent CI 11, 29), and the NNT was 6 (4 to 10), indicating that an estimated six patients with MDD would need to be treated in order for one to benefit. Results of the data from citalopram and escitalopram were also statistically significant (RD 8 percent, 95 percent CI 1, 16), and the NNT was 13 (7 to 200). Results from trials testing these two drugs were pooled because escitalopram is the active component of citalopram. We excluded one trial of citalopram due to poor quality.[97] To understand this trial's impact on the pooled results among the citalopram and escitalopram trials, we recalculated the pooled RD for the citalopram trial[89] and the escitalopram trial[84] that met our inclusion criteria; the results remained statistically significant (RD 11 percent, 95 percent CI 2, 20).

Bridge and colleagues conducted numerous secondary analyses to explore the effects of potential moderating variables. They explored the role of continuous moderators (methodological quality, number of treatment sites, proportion of female participants, duration of illness at baseline) using regression analyses. Continuous variables that were associated with outcome were dichotomized by median split and analyzed as categorical variables. They also evaluated the role of trial-level categorical variables that could have had a moderating effect (publication status, primary funding source, study location, drug class, use of placebo run-in period). They assessed for publication bias visually using a funnel plot and quantitatively using an adjusted rank correlation test and a regression procedure to measure funnel plot asymmetry. They found that the number of trial sites and the duration of the MDD episode at intake to the study were both inversely associated with the risk difference in response and the scalar measure of efficacy. These results indicate that study drugs were less efficacious in trials with more study sites or that included patients who, on average, had had MDD for longer periods prior to the start of the trial. Study quality and proportion of females were not associated with the efficacy outcomes.

Age-grouped data were available for 10 of the 15 included MDD trials. The authors found that the pooled risk difference in response was lower among children than among adolescents and not statistically different than zero. Children generally had a higher placebo response. When restricting to the fluoxetine trials only, however, the pooled RDs were similar

for children (RD 21 percent, 95 percent CI 4, 37) and adolescents (RD 20 percent, 95 percent CI 7, 33). Other categorical trial-level variables (drug class, publication status, and placebo run-in period) were not significant. They did not evaluate the role of funding agency because the only two trials funded by the National Institutes of Mental Health were evaluating fluoxetine.[63,78] All other trials were funded by the drug industry.

Study details – psychotherapy interventions. Numerous systematic evidence reviews and meta-analyses focusing on the efficacy of psychotherapy for treating depression in youth have been published since the end of the previous USPSTF review's search window. The inclusion and exclusion criteria used in these reviews, however, only partially overlapped with our criteria. We used the five most recently published SERs as supplemental sources for identifying trials relevant for this report.[91,98-101] In total, we located ten good-[78,79,102,103] or fair-quality[104-109] RCTs evaluating psychotherapeutic interventions to treat children or adolescents with depression that met our inclusion and exclusion criteria. These trials randomized a total of 757 patients who ranged in age from 9 to 18 years old and included 16 different comparisons of depression outcomes between an intervention and control condition. A variety of group and individual therapies were tested. Group CBT, individual IPT-A, and individual CBT were the only interventions tested in multiple trials. Two studies were effectiveness trials (both good quality) conducted in actual community clinical settings (one of IPT-A and one of individual CBT). Other interventions were tested for efficacy in schools or research settings that were not specifically described.

Seven trials reported response to treatment based on clinician-rated measures.[78,79,102,103,105-107] These trials used a variety of different criteria to define response criteria, such as no longer meeting DSM-III-R criteria for depression based on a diagnostic interview,[102,103,105,106] or a change in Hamilton Rating Scale for Depression[79,105,107] or CGI-S score.[78,105,107] Of the three trials which didn't report response criteria based on clinician-rated measures, two reported the mean change in a clinician-rated measure,[104,109] and one trial only measured outcomes using self-reported measures.[108] Trials reported outcomes at post-intervention assessments at 5 to 16 weeks post-randomization. Only one trial reported usable followup data with controlled comparison observations.[109] One other trial that reported a controlled followup comparison had markedly differential attrition at 8-week followup.[105] These results are not included in this report. Four other trials measured outcomes at followup assessments, but waitlist control groups started (or completed) treatment, therefore the effect of the intervention could not be differentiated from the effect of time at the followup assessment. Four trials did not report followup data.[78,79,103,107]

Nine of ten trials reported a statistically positive difference indicating a higher response (either response rate or mean depression score) for the intervention group compared to the control group. Five trials reported that response rate was higher in the intervention group than control group. These statistically significant results were based on clinician-rated measures (four trials)[102,103,106,107] or self-reported measures.[79] Three others reported that mean values of depression scores were lower among intervention group participants compared to control group. These statistically significant results were also based on clinician-rated[104,105,109] or self-reported measures.[108] The only trial that reported no statistically significant difference between the intervention group and control group was the TADS trial. In that particular trial, however, the control group consisted of daily placebo pills and bi-weekly meetings with a clinician (20 to 30 minutes each) to monitor symptoms and deliver encouragement that the placebo pill would be

effective. Since this control condition was serving as control for fluoxetine interventions as well, it is unclear if the clinical monitoring could have improved depression symptoms.

Only two studies included children younger than 9 or 10 years of age, and both showed evidence that the interventions were efficacious.[105,109] These fair-quality trials randomized a total of 97 patients. While the absolute differences between the response rates in the intervention and control groups were quite high (41 to 67 percent; data not shown), p-values were not reported for response rates in either trial. Results from mean depression scores indicated that clinician-rated symptoms improved more in the intervention groups than control groups and were statistically significant. No trials included children 7 or 8 years old.

Primary Care Settings

Mufson et al., 2004:[79] This good-quality RCT (n = 64) measured the effectiveness of individual Interpersonal Therapy for Adolescents (IPT-A) delivered by clinicians in school-based health clinics. The study was set in impoverished areas of New York City. The population was predominantly Hispanic females. The intervention was delivered by school health clinicians (social workers and doctoral-level clinical psychologists) who received trial-specific training. Eligible patients were referred for treatment to the school health clinic and had to meet DSM-IV criteria for MDD, DD, adjustment disorder with depressed mood, or depressive disorder NOS. Patients were randomized to IPT-A for 16 weeks or treatment as usual (TAU) control. TAU was whatever care the students would have received in the school health clinic if the study hadn't been taking place. Most received individual psychotherapy, eight received family therapy, and five participated in group therapy. Recovery criteria for the trial were defined as HAMD ≤ 6 or BDI ≤ 9.

At post-intervention (week 12), a greater proportion of patients in the IPT-A group met HAM-D recovery criteria compared to the TAU group, although the difference was not statistically significant (50 vs. 34 percent, p–value NR). The recovery rate based on the BDI score was also higher among the IPT-A group compared to TAU (74 vs. 52 percent, $p = 0.048$). Mean clinician-rated depression scores (HAMD) showed greater improvement for the IPT-A group compared to TAU at post-treatment ($p = 0.04$; ES 0.50). The difference in HAMD scores between groups emerged at week 8, with a 4.1 point difference ($p = 0.003$). Random regression analysis indicated that the IPT-A group recovered at a significantly faster rate than the CG. Differences in BDI scores also emerged between the groups at week 8, favoring the IPT-A group by 5.42 points ($p = 0.001$). Two measures of global functioning also indicated statistically significant differences between groups, favoring the IPT-A group. Attrition was 11 percent, and the ITT population was analyzed using the LOCF method. Generalizability, however, is limited because of the predominantly low SES, Hispanic population.

TADS, 2004:[78] TADS is a good-quality RCT (n = 439) in which adolescent subjects ages 12 to 17 years with MDD were randomized to four different conditions, including individual CBT and a placebo control condition (n = 223 for these two groups). The patients were a volunteer sample recruited from clinical, community, and school settings and 13 different academic and community sites in the USA. The individual CBT condition involved 15 1-hour sessions over 12 weeks. The control condition for the CBT arm of the trial was designed to also serve as the control for the arms receiving fluoxetine alone or with CBT. Patients in this control group were treated with placebo pills. The patients had 6 20- to 30-minute visits with a physician to monitor clinical status and medication effects (of the placebo), adjust the dose of the

placebo, and to offer general encouragement about the effectiveness of pharmacotherapies. Patients and all study personnel were blinded to whether or not the pill was the study drug or not.

The primary depression outcome, response rate as measured by the CGI-I score, indicated no statistically significant difference between the CBT group and the placebo control group (43.2 vs. 34.8 percent, p = 0.20). CDRS and RADS scores also showed no difference. Suicide- and harms-related adverse events were also not different between groups. This good-quality trial included patients similar to those seen in primary care settings. The control condition, however, was not an ideal comparison to the intervention. The clinical monitoring could have improved depression symptoms, even though they were of lower intensity than the CBT. A placebo effect could have also increased response in the control group.

Research Clinic Settings

Clarke et al., 1999:[102] This good-quality RCT (n = 123) evaluated group CBT for adolescents and group CBT with separate parent sessions. Patients aged 14 to 18 years were recruited by health professionals, school counselors, and advertisements and were screened by diagnostic interview. Patients were required to meet DSM-III-R criteria for MDD or dysthymia to be eligible. Patients were randomized to two intervention groups or a control group. The group CBT intervention condition (adolescent-only) followed the Adolescent Coping with Depression Course, including 16 two-hour sessions delivered over eight weeks (mean attendance was 14 of 16 sessions). In the second intervention group (adolescent + parent), adolescents participated in the same group CBT course and their parents participated in eight weekly parent sessions. Nearly 90 percent of adolescents in the adolescent + parent group had at least one of their parents attend the sessions, with greater attendance by mothers than by fathers. The control group was a wait-list condition in which participants were offered treatment after the experiment.

After eight weeks, patients were assessed by blinded clinicians. Self- and parent-reported measures were also assessed. Recovery was defined as no longer meeting DSM-III-R criteria for either major depression or dysthymia for the two weeks preceding the post-treatment assessment. Recovery rates were higher in both the adolescent-only group (24/37, 64.9 percent) and the adolescent + parent group (22/32, 68.8 percent), compared to the waitlist control group (13/27, 48.1 percent). The results of the two intervention groups were combined and compared to the control group for statistical analyses, which yielded significant results (chi-squared, $p < 0.05$; Cohen's h = 0.38 – small to medium effect). The odds ratio for estimating the relative risk of recovery was 2.15 (95 percent CI 1.01, 4.59). Differences in clinician-rated HAM-D scores were not significant between intervention groups and the control group. Clinician-rated global assessment of function (GAF) scores were higher in the intervention groups compared to the control group ($p < 0.05$, change score effect size = 0.54). Attrition was 22 percent overall and outcomes were analyzed using intention-to-treat analyses using random effects regression to predict outcomes for subjects with missing data based on all available data.

Diamond et al., 2002:[103] This was a small, good-quality RCT (n = 32) conducted in a low socioeconomic, predominantly African-American sample of adolescents aged 13 to 17 years old. Patients with a primary diagnosis of MDD meeting DSM-III-R criteria were randomized to an Attachment Based Family Therapy (ABFT) intervention for 12 weeks or to a wait-list condition for 6 weeks. Outcomes at the post-intervention assessment at 12 weeks were compared to the post-waitlist assessment for the control condition at 6 weeks (a 12-week waitlist condition was considered to be unethical). Selected outcomes were also compared using the

mid-intervention (6 weeks) assessment results for the ABFT group in order to compare groups at an equivalent time point. Clinically significant response was defined as a self-reported BDI score ≤ 9. Depression severity was also assessed by clinician-rated HAM-D scores by blinded interviewers.

For comparisons between ABFT at post-intervention (12 weeks) and control group at post-waitlist (6 weeks), the ABFT group had a higher clinically significant response rate (62 vs. 19 percent, p = 0.01), and greater proportion no longer meeting criteria for MDD (81 vs. 47 percent, p = 0.04). The ABFT group also had a higher proportion with clinically significant reduction in symptoms when comparing outcomes measured at 6 weeks for both groups (56 vs. 19 percent (p = 0.03). Clinician-rated depression scores (HAM-D) and self-reported anxiety scores (STAIC) were also lower for the post-intervention ABFT group compared to CG (p = 0.005, effect size 1.21), but self-reported depression scores (BDI) were not statistically significant. Suicidal ideation and levels of hopelessness were reduced in the ABFT group compared to control group, but did not reach statistical significance (p = 0.09; ES 0.52 and p = 0.08; ES 0.78). No attrition occurred in this trial.

Mufson et al., 1999:[107] This fair-quality RCT (n = 48) evaluated the efficacy of 12 weeks of individual Interpersonal Psychotherapy for Depressed Adolescents (IPT-A) among adolescents aged 12 to 18 years who met DSM-III-R criteria for MDD. Patients in the study sample were predominantly Latino and of low socioeconomic status. Patients were recruited from two specialty mental health clinics to which they had mostly been self-referred by parents or mental health professionals in school-based mental health clinics. The control condition consisted of clinical monitoring (CM) on a monthly basis and therapist availability. Therapists were told to refrain from advice giving or skills training and mainly go over symptoms and listen supportively. This condition was used to create an ethical waitlist condition.

Recovery rates based on HRSD ≤ 6 indicated that more IPT-A group patients recovered compared to the CM control group (75 vs. 46 percent, p = 0.04). Results of the Clinical Global Impressions Severity rating demonstrated similar results with a higher proportion rated as improved in the IPT-A group (95.5 vs. 61.5 percent, p < 0.001). Depression scores, as measured by HRSD, BDI, and CGI-S, decreased more in the IPT-A group than in the control condition (p = 0.02, p = 0.05, p < 0.001). No statistically significant differences were present in CGAS scores or suicidality at post-intervention measures. This trial's ITT population was analyzed using the LOCF method to replace missing values and was otherwise similar in quality to those we rated as good quality. Attrition, however, was high overall (33 percent) and was differential between groups (12 percent in IPT-A group and 54 percent in CM control group). It is therefore unclear if groups remained comparable at post-intervention assessment and so the study was rated as fair quality. Generalizability is limited because the population was predominantly low income, Hispanic, and female. In addition, the sample included severely depressed individuals (50 percent with current suicidal ideation at initial assessment) and may not represent the spectrum of disease severity typical of primary care samples.

Rossello and Bernal, 1999:[108] This fair-quality RCT (n = 71) set in Puerto Rico evaluated the short-term efficacy of individual IPT (n = 19) and individual CBT (n = 21) compared to a waitlist control group (n = 18). Patients randomized to the IPT or CBT arm of the trial received 12 weekly, 1-hour sessions with a trained therapist. The trial included patients aged 13 to 17 years who were referred to the clinic by local schools and met DSM-III-R criteria for MDD. The study population was 100 percent Latino and 54 percent female. Patients were

not eligible if they were receiving any psychotropic medication or psychotherapy at the time of enrollment. At baseline, the three groups were similar on all outcome measures. Baseline demographic characteristics across groups, however, were not reported. Depression outcomes were based on self-reported measures, including the CDI. Adherence was fair, with 68 percent in the IPT arm and 52 percent in the CBT arm completing at least 8 of the 12 sessions. Pre- to post-treatment comparison of CDI scores showed that adolescents in the IPT ($F = 11.62$, $p < 0.002$) and CBT ($F = 2.58$, $p < 0.015$) groups had significantly lower depressive symptoms compared to those in the waitlist control group. In addition, moderate effect sizes were found for both IPT (0.73) and CBT (0.43). Using a cutoff of 17 on the CDI to separate functional from nonfunctional adolescents, 82 percent of adolescents in IPT and 59 percent of those in CBT showed a clinically significant change.

Ackerson et al., 1998:[104] This small, fair-quality RCT (n = 30) evaluated a directed self-help bibliotherapy intervention using Burns' book *Feeling Good*. Patients were aged 14 to 18 years and recruited through mental health, social service agencies, schools, and other community and clinical settings. Included patients were experiencing mild to moderate depressive symptomatology, as measured by a CDI score of ≥ 10 and an HRSD score of ≥ 10. The sample was 64 percent female and 36 percent nonwhite. Patients were ineligible if they were receiving other forms of psychotherapy, and no patients were being treated with SSRIs. Intervention subjects (n = 12) had 4 weeks to read the *Feeling Good* book and complete exercises in an accompanying workbook. Subjects were called weekly to collect data on pages read and exercises completed. No counseling was provided during these calls. The control group was a waitlist condition (n = 10). While these patients were also telephoned weekly, the authors do not report any data regarding the content of these calls or whether measures were taken to ensure no counseling occurred.

We rated the quality of this study as fair based on a number of issues. Outcome assessment was not blinded, and neither the details about the contents of the book nor the number of pages read by each participant were reported. Also, while attrition was 27 percent overall (20 percent in the intervention group and 33 percent in the control group), the reasons for dropouts were not provided. The efficacy of bibliotherapy in reducing depression severity was assessed using repeated measures ANOVAs for each outcome measure, comparing pre- and post-treatment scores for the immediate treatment and waitlist conditions. Results indicated that those in the immediate treatment condition had greater improvement in depression severity compared to the waitlist group, as measured by the HRSD ($F = 37.78$, $p < 0.05$), self-reported CDI ($F = 24.40$, $p < 0.05$), and parent-reported CBCL-D ($F = 4.98$, $p < 0.05$). One-month followup data for the immediate treatment condition showed no significant differences in CDI or CBCL-D scores between post-treatment and followup, indicating maintenance of positive treatment effects. HRSD scores were significantly lower at one-month followup compared to immediately after treatment ($F = 5.79$, $p < 0.05$), suggesting that some improvement in depressive symptoms continued beyond treatment end. Clinically-significant change was assessed for all 22 subjects who completed treatment (12 immediate treatment and 10 delayed treatment subjects), but was not reported separately by group. Using a cutoff score of <10 on the HRSD and a standardized measure of change greater than 1.96 to indicate clinically-significant change, 59 percent of the completers achieved remission. Using the same cutoffs for the CDI, 64 percent achieved remission.

School-based settings

Kahn et al., 1990:[105] This fair-quality RCT (N = 68) evaluated the efficacy of short-term group CBT, group relaxation training, or individual self-modeling compared to a waitlist control condition. Patients were latency age adolescents (ages 10 to 14) with moderate to severe depression and were identified by a multistage screening procedure of an entire middle school in a middle-SES neighborhood. Treatments were conducted in schools. Group CBT and relaxation were conducted in small groups of two to five students. These groups consisted of 12 50-minute sessions over a 6- to 8-week period. Post-treatment assessments were conducted by clinicians, approximately half (44 percent) of whom were blinded to the condition. The Group CBT was based on the Adolescent Coping with Depression Course. The self-modeling treatment involved repeated observation of oneself on edited or rehearsed videotape showing only desired target behaviors (e.g., smiling, verbalizing positive self-attributions). Post-intervention scores on the RADS and CDI were both significant for interaction effects between treatment and time ($p < 0.001$ for both). Pretreatment values were not different. At post-test assessment, a greater proportion of patients in each of the three intervention conditions moved from dysfunction to functional range on depression score measures. Using the RADS scores, 12 percent of CG participants moved to functional at post-treatment versus 88 percent, 65 percent, and 70 percent of CBT, relaxation, or self-modeling, respectively. Attrition was only three percent at post-treatment. At 8-week followup, however, attrition was quite different between groups (44 percent in CG vs. 10 to 11 percent in IGs). Therefore, we cannot be certain of whether the intervention groups differed from the CG in terms of possible confounding variables at the 8-week followup. Also, this study's results were compromised by the fact that only half of the clinicians assessing outcomes were blinded to treatment condition.

Stark et al., 1987:[109] This small, fair-quality RCT (n = 29) evaluated group self-control (SC) therapy (n = 9) and group behavioral problem-solving (BPS) therapy (n = 10) compared to a wait-list control condition (n = 9). Participants in the two intervention groups attended 12 45- to 50-minute sessions over 5 weeks. Material from missed sessions was covered individually by therapists. Patients aged 9 to 12 years were identified through a staged screening process at one middle school. Included patients had a CDI score of greater than 16 at first assessment and a CDI score of at least 13 at the second assessment. The population was 43 percent female, and race and ethnicity were not reported. Data regarding the percentage of participants in each group who received other treatment outside of the trial was not specifically reported, but two of the nine subjects on the waitlist were referred to the school psychologist by their teachers for behavior related to depression. These students met with the psychologist weekly. The outcome assessor was blind to treatment assignment.

Within-group comparisons showed that subjects in both the SC group and the BPS group scored significantly lower on the CDI (SC: mean difference = 13.56, SD = 7.76, $t = 5.24$, $p < 0.001$; BPS: MD = 12.80, SD = 9.68, $t = 4.18$, $p < 0.01$), the CDS (SC: MD = 19.89, SD = 10.94, $t = 5.46$, $p < 0.001$; BPS: MD = 15.10, SD = 12.45, $t = 3.84$, $p < 0.01$), and the CDRS-R (SC: MD = 13.22, SD = 7.89, $t = 5.03$, $p < 0.001$; BPS: MD = 9.40, SD = 9.32, $t = 3.19$, $p < 0.05$) at post-treatment compared to pre-treatment scores. The mean difference in pre-post treatment scores for the waitlist control group was not significant for the CDI or CDRS-R, but was significantly lower for the CDS (MD = 8.00, SD = 5.75, $t = 4.18$, $p < 0.01$). Results of an ANCOVA controlling for pretreatment scores showed significant differences between the three groups on the CDI ($p < 0.01$), and differences on the CDS ($p < 0.07$) and CDRS-R ($p < 0.11$)

approached significance. Using the Bryant-Paulson generalization of Tukey's HSD procedure, the mean post-treatment CDI score was significantly lower in the SC group than the waitlist control group ($Q = 4.55$, $p < 0.05$). In addition, change in depression severity was clinically significant. While all subjects scored over 13 on the CDI before treatment, 78 percent in the self-control condition, 60 percent in the behavioral problem-solving condition, and 11 percent in the waitlist condition scored below 13 on the CDI after treatment. Parent ratings on the depression, social withdrawal, and internalizing subscales of the CBCL showed no significant differences between groups at post-treatment. Eighty-two percent of subjects completed followup assessments 8 weeks after the end of treatment. Depression severity in both intervention groups was significantly lower on the CDI (SC: MD = 15.63, SD = 6.50, $t = 6.80$, $p < 0.001$; BPS: MD = 14.78, SD = 7.95, $t = 5.58$, $p < 0.001$), CDS (SC: MD = 24.25, SD = 13.38, $t = 5.13$, $p < 0.001$; BPS: MD = 20.44, SD = 13.67, $t = 4.49$, $p < 0.01$), and CDRS-R (SC: MD = 15.38, SD = 6.46, $t = 6.73$, $p < 0.001$; BPS: MD = 9.44, SD = 8.10, $t = 3.50$, $p < 0.01$) at followup, compared to pre-treatment scores. In addition, SC participants showed significant improvement in CDI (MD = 4.13, SD = 3.48, $t = 3.35$, $p < 0.01$) and CDRS-R (MD = 3.00, SD = 3.55, $t = 2.39$, $p < 0.05$) scores from post-treatment to 8-week followup, and BPS participants showed significant improvement in CDS scores (MD = 5.44, SD = 6.56, $t = 2.49$, $p < 0.05$). Eighty-eight percent of the SC participants and 67 percent of the BPS participants maintained a score below 13 on the CDI at 8-week followup.

Lewinsohn et al., 1990:[106] This fair-quality RCT tested the short-term efficacy of two different types of group CBT among adolescents aged 15 to 18 years meeting DSM-III criteria for MDD or RDC criteria for intermittent depression or minor depression (n = 69). Participants were recruited via letters and announcements to health professionals, school counselors, and the media. The sample was 61 percent female. The two intervention conditions were group CBT for the adolescent alone, based on the CWD course (n = 21), and group CBT for the adolescent plus additional separate sessions for the parents (n = 19). The control condition was a waitlist group (n = 19). Adolescents in both intervention groups attended 14 2-hour group CBT sessions twice a week for 7 weeks. Parents in the second intervention group attended 7 2-hour sessions once a week for 7 weeks. Adolescents were interviewed using the K-SADS-E to determine clinical diagnostic status. Only 20 percent of the interviews were dual rated by a blinded interviewer. Quality issues for this trial include lack of information about allocation concealment, blinding of outcomes assessors, and participant adherence to treatment.

At post-treatment, 52.4 percent of the adolescent-and-parent group and 57.1 percent of the adolescent-only group still met diagnostic criteria, whereas 94.7 percent of the control condition still met diagnostic criteria ($p < 0.01$), indicating greater improvement in the two group CBT intervention conditions. Depression severity was measured by the BDI and the CES-D. Comparison of post-treatment scores for both intervention groups combined, versus the waitlist group, showed significantly lower adolescent depression scores for the treatment groups (BDI: $F = 4.27$, $p < 0.001$; CES-D: $F = 4.85$, $p < 0.001$). Differences in post-treatment BDI and CES-D scores between the two treatment conditions were not statistically significant. Comparison data from post-treatment, 1-month followup, and 6-month followup was available for 16 participants in the adolescent-only group and 14 participants in the adolescent-and-parent group. There were no significant differences in CES-D or BDI scores between these three time points for either intervention group. Improvements in depression symptoms, therefore, were maintained over a 6-month period.

Study Details – SSRI + psychotherapy interventions.

TADS, 2004:[78] TADS is a good-quality RCT (n = 439) of adolescent subjects aged 12 to 17 years with MDD. This study is also described in the sections regarding SSRI or psychotherapy efficacy (monotherapies). In this same trial, some patients were randomized to a condition in which they received fluoxetine and individual CBT (n = 107) and were compared to the placebo control group (n = 112). The fluoxetine therapy allocation was known to the patient and CBT therapist and was meant to more closely resemble the patient-therapist relationship in a naturalistic setting, thus theoretically making results more generalizable. Outcomes were still assessed by blinded clinicians. The patients were a volunteer sample recruited from 13 different academic and community sites in the US. The group CBT condition involved 15 1-hour sessions over 12 weeks, and the fluoxetine was administered at 10 to 40 mg/day for 12 weeks. Patients in the control group were treated with placebo pills. Patients in both the CBT + fluoxetine group and the placebo control group had six 20- to 30-minute visits with a physician to monitor clinical status and medication effects, adjust the dose of fluoxetine or placebo, and offer general encouragement about the effectiveness of pharmacotherapies.

The primary depression outcome was response rate as measured by the CGI-I score, which indicated a higher proportion of patients receiving combined CBT + fluoxetine treatment improved compared to patients treated with the placebo control. Rates of response were 71.0 percent (95 percent CI 62, 80) for CBT + fluoxetine and 34.8 percent (95 percent CI 26, 44) for placebo (p = 0.001). Changes in CDRS-R and RADS scores over the 12 weeks of treatment also showed that CBT + fluoxetine was superior to placebo (p = 0.001). The effect size (Hedges *g*) on the CDRS-R for CBT + fluoxetine was 0.98, and on the CGI-I it was 0.84. The NNT on the CGI-I was 3 (95 percent CI 2, 4). Decrease in suicidal thinking over the 12 weeks of treatment, measured by the adjusted mean on the Suicidal Ideation Questionnaire-Junior High School Version (SIQ-Jr), was significantly greater in the CBT + fluoxetine group compared to placebo (p = 0.02).

Key Question 5. What are the adverse effects of treatment?

Summary of findings. Data describing the adverse effects of SSRIs were available from the nine RCTs included for KQ4 for which we calculated pooled absolute risk differences for suicide-related adverse events (SRE) using data for a subset of trials included in the Bridge 2007 review.[92] SRE includes suicidal ideation (i.e., passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior), suicide attempts, or preparatory actions toward imminent suicidal behavior (e.g., a person tries to hang themselves but is prevented from doing so by a family member). In addition, data were available from four meta-analyses that calculated the pooled relative risk or risk difference of suicide-related adverse events based on outcomes assessed using blinded suicidology experts,[92,110,111] or included other serious adverse events (SAE) in addition to SRE.[66] In addition, data from large retrospective cohort or case-control studies provided observational data describing risk of suicidality, suicide death, and manic conversion. Previous systematic reviews and meta-analyses did not exclude trials based on quality criteria and some did not report any quality rating procedure or results. In contrast, we were able to review published results from all currently completed trials and analyze them in detail using our typical USPSTF quality rating criteria. Bridge and colleagues conducted sensitivity analyses and determined that quality score did not alter the magnitude of their estimates of pooled risk difference. Previous reviews have also used

varying inclusion and exclusion criteria (e.g., MDD trials only, SSRIs only) and have used both fixed-effects and random-effects approaches to meta-analyses, as well as Bayesian methods of meta-analyses. The random-effects and Bayesian approaches assume additional sources of trial-related variation across studies and typically produce relative risk estimates that are smaller in magnitude and wider in confidence interval. The FDA researchers used fixed-effects methods, validated by results of heterogeneity tests, to calculate the more conservative estimate. Meta-analyses also differed in terms of calculating RR or RD. The FDA analysis focused on RR and therefore could not include data from four trials (non-SSRI MDD trials) that did not include SAE outcomes in either group.

Most conservative estimates indicate that treating any pediatric population with antidepressants for any indication doubles the relative risk of SAE (RR 1.95, 95 percent CI 1.28, 2.98).[110] The absolute risk difference between intervention and control populations was one percent (95 percent CI 1, 2). No other meta-analyses reported the pooled RD among SSRI trials for MDD and considered data from all currently available completed trials, including a recently published trial of escitalopram. We calculated the pooled RD of those trials, excluding two poor-quality RCTs, and found an RD of 1 percent (95 percent CI 0, 2). In total, even the most conservative estimates indicate that the risk of suicidality may increase absolutely by one or two percent.

The evidence linking antidepressants and suicidal behavior from two cohort studies (one good quality[112] and one fair quality[113]) contradicted the results of a good-quality case-control study.[114] The two cohort studies did not find a relationship between antidepressant use and suicide deaths (0 suicide deaths in youth taking antidepressants in the years 1995 to 1999) or attempts (Hazard ratio 1.59, 95 percent CL 0.89, 2.82), after controlling for a number of potential confounders. In fact, Valuk and colleagues found that youth who used antidepressants for 6 months or more were at reduced risk of suicide (HR 0.34, 95 percent CL 0.21, 0.55). The case-control study, however, did find an association between antidepressant use and suicide deaths (OR 15.62, 95 percent CI 1.65, ∞) and suicide attempts (OR 1.52, 95 percent CI 1.12, 2.07).[114] Olfson and colleagues linked 263 individuals attempting suicide and eight suicide death cases with comparable controls in separate analyses, matching on multiple demographic, severity, and utilization factors. Results for suicide deaths should be interpreted cautiously, however, given the small number of cases.

Antidepressant use increased the risk of conversion from a unipolar depressive disorder to a bipolar disorder in a large good-quality cohort study of individuals aged 5 to 29 years.[115] The conversion rate in patients using antidepressants was 7.7 percent per year, compared with 2.5 percent per year in those who did not use antidepressants. Further, there appeared to be a treatment-by-age interaction, where the difference in conversion rates between antidepressant users and nonusers was even larger in younger children—the rate ratio between users and nonusers was 2.9 in 5- to 14-year-olds (95 percent CI 2.8, 3.1) compared with 1.4 in 15-to 29-year-olds (95 percent CI 1.3, 1.5).

Study details. We systematically searched for data describing the risk of serious adverse events including death, psychiatric hospitalization, suicidal ideation, suicidal attempts, discontinuation of medication due to serious adverse events, and triggering symptoms of mania. We considered evidence from RCTs, meta-analyses of RCTs, and large observational studies with appropriate control groups. During the past few years, numerous systematic evidence reviews and regulatory

agency reports have synthesized available data from RCTs to estimate whether excess risk of suicide-related events occurs among depressed children or adolescents treated with SSRIs or atypical antidepressants.[65,66,90-92,110,111,116-124] These reviews were each limited to the quality and quantity of data that were available at the time these analyses were conducted. For this report, we included the most recently published reviews that used suicide-related outcome data that were blindly classified by suicidology experts at Columbia University (requested by the FDA Division of Neuropharmacological Drug Products).[92,110,111] Only one of these reports incorporated a recently published trial of escitalopram.[92] The body of available RCTs is the same as those that are described for KQ 4. In addition to providing results from published reviews, we present the pooled results of suicide-related events for the nine RCTs that met all inclusion and exclusion criteria.

Hammad et al., 2006:[110] This good-quality report describes the meta-analyses conducted by the FDA, Division of Neuropharmacological Products to assess the risk of suicidality for pediatric patients treated with antidepressants. Data were included from 23 placebo-controlled trials of antidepressants (SSRIs and atypical antidepressants) in pediatric patients conducted by nine drug development programs and one placebo-controlled, multicenter trial funded by the NIMH (the TADS trial), including data from a total of 4,582 patients. The review focused on suicide-related events (SREs), including suicidal ideation and suicidal behaviors. The FDA requested the nine drug manufacturers of antidepressants to have blinded personnel electronically search their trial databases for text strings (e.g., *suic-, overdos, self harm, attempt*). Drug manufacturers provided narrative summaries for each SRE and also for any adverse events during trials that were identified as serious, accidental injuries, or accidental overdoses. Regulatory agencies define "serious adverse event" during pharmaceutical trials as any event that results in death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of an existing hospitalization.

The FDA arranged for a group of 10 independent pediatric suicidology experts at Columbia University to blindly classify these potential SRE narratives. The experts categorized each event into one of five possible categories: suicide attempt, preparatory actions toward imminent suicidal behavior, suicidal ideation, self-injury with intent unknown, and injury events with not enough information to determine whether they represented self-injury or other injury. The first three categories most clearly represented suicidality and were the primary outcome of interest. The latter two categories were less certain and were included as a secondary outcome of "possible suicidal behavior or ideation". The exposure window for eligible SREs was: adverse events that occurred during the double-blind acute treatment period or within 1 day of the end of this period. For patients who left the study early, only events that occurred before discontinuation or on the day after the last dose of the assigned treatment were included. Events that occurred before randomization or after the double-blind period were excluded to avoid confounding from a wide array of possible subsequent treatment scenarios. The most serious event was selected for patients who had more than one eligible event. The researchers pooled the results from all available data to generate overall estimates of the drug effects. They calculated Mantel-Haenszel RR and RD using a fixed-effects approach. They also calculated results using a random-effects model as a sensitivity analysis. In addition, the FDA scientists had access to all individual-level data describing multiple demographic, trial-related, disease-related, drug-related, and psychiatric history-related data. They were able to conduct stratified analyses to evaluate for potential effect modification and confounding variables.

In total, the experts identified 109 SREs, and an additional 11 events were recorded in TADS (n = 89 for primary outcome, n = 120 for secondary outcome). No suicide deaths occurred in any trial. The incidence of the primary outcome varied from 0 to 8 percent across the 24 individual antidepressant trials. Relative risk estimates varied even within the same drug and same indication (e.g., MDD, OCD). Overall, the RR of suicidality was 1.95 (95 percent CI 1.28, 2.98) across all trials. Separate analyses for suicidal ideation (RR 1.74, 95 percent CI 1.06, 2.86) were similar to those for suicidal behavior (RR 1.90, 95 percent CI 1.00, 3.63). The only individual trial to show a statistically significant increase in risk of suicidality in the drug-treated group was TADS (RR 4.62, 95 percent CI 1.02, 20.92), although the RR was ≥2 in seven other trials. The authors examined trial designs and inclusion and exclusion criteria to explain heterogeneity within trials, but found no consistent explanations for heterogeneity.

The pooled RR of SRE are presented in the first column of Table 9. Among the MDD trials (in bold-faced type), the pooled RR of SRE for all SSRIs combined was 1.66 (95 percent CI 1.02, 2.68). The RR estimates of SRE for individual types of SSRIs in the MDD trials were not statistically significant. The only individual drug type that had a statistically significant RR of SRE, either within MDD trials or for any indication, was a non-SSRI, extended-release venlafaxine (not shown in the table), for which the RR among the MDD trials was 8.84 (95 percent CI 1.12, 69.51). Results of sensitivity analyses did not yield substantial differences in RR estimates. Across all trials for all indications, the results for the overall RR estimate using a random-effects model (RR 1.75, 95 percent CI 1.11, 2.76) was slightly lower than when using the fixed-effects approach (RR 1.95, 95 percent CI 1.28, 2.98). Findings for the secondary outcome (including less certain suicidal events) (RR 2.19, 95 percent CI 1.50, 3.19) were also similar to the results for the primary outcome. The absolute risk difference for the primary outcome across all 24 trials was 0.01 (95 percent CI 0.01, 0.02). The absolute risk difference for the secondary outcome was 0.02 (95 percent CI 0.01, 0.03).

Bridge et al., 2007:[92] As described for key question 4, this good-quality systematic evidence review included meta-analyses of efficacy and suicide-related events for all pediatric antidepressant trials for all indications, with results stratified by indication (MDD trials separate from other indications). SRE were obtained from Hammad and colleagues for all trials included in the FDA analyses of SRE. For newer trials, Bridge and colleagues used the same type of methodology (blinded expert review of case narratives) and outcome classification to determine SRE. Bridge and colleagues reported risk differences and used random-effects models. Pooled results are reported in Table 9, based on 5,310 patients who were in RCTs of any antidepressant for any indication and the subset of 3,430 patients who were treated for MDD. The authors did not report results for SSRIs separately from other newer atypical antidepressants. The RD for all antidepressants for MDD was one percent (95 percent CI -0.1, 2; NNH = 112). They also report results by antidepressant type. The RDs for individual types of antidepressants (e.g., fluoxetine) ranged from zero to two percent and were not statistically significant for any single type of antidepressant. Patient- and trial-level characteristics were examined and none were related to suicide-related events.

Data were also reported separately for children and adolescents. Data for suicide attempts or preparatory acts were reported separately from suicidal ideation. When considering all SRE among children, the risk difference was one percent (95 percent CI -1, 3). Among adolescents, the risk difference was one percent (95 percent CI -0, 2). Within each subgroup of age and outcome type, rates of suicide-related events ranged from one to two percent among

antidepressant-treated patients and from zero to one percent among placebo-treated patients. When SRE were separated into suicide attempts/preparatory acts and suicidal ideation, risk differences ranged from zero to one percent for children or adolescents separately and combined, and were not statistically significant within any subgroup.

Wallace et al., 2006:[66] This fair-quality meta-analysis assessed the efficacy and safety of SSRIs for pediatric MDD. Although this meta-analysis had several limitations, it assessed a broad range of adverse effects, beyond just suicide-related events, and thus was included in this review. The authors used a comprehensive search method through April 2005, but data from the escitalopram trial was not yet available. They assessed quality criteria and only included trials that met their quality criteria. Their sources of information for outcomes, however, were published results or, for unpublished trials, the Committee on Safety of Medicine website (UK regulatory agency subcommittee). Therefore, they did not use suicide-related outcomes based on the blinded Columbia review. Also, they did not have access to full published reports of trials, therefore their ability to conduct comprehensive quality rating may have been limited. The SAE outcomes they included were death; life-threatening symptoms including suicide attempts, hospitalization, significant disability or incapacity including mania; or events which jeopardize the patient and require medical intervention including study discontinuation. The authors used fixed-effects models for conducting meta-analyses. They lumped results from trials of newer atypical antidepressants with SSRIs. They included seven published RCTs and four unpublished RCTs. Their results are presented in Table 9. They report 108 SAEs among 1,129 SSRI- or atypical antidepressant-treated patients (9.6 percent) and 48 SAEs among 1,016 placebo-treated patients (4.7 percent). The relative risk was 1.97 (95 percent CI 1.42, 2.75), indicating that overall, patients treated with antidepressants had approximately twice the risk of having any type of serious adverse event. While results varied within drug types, results were not statistically significant for fluoxetine (RR 1.40, 95 percent CI 0.75, 2.68) or citalopram/escitalopram (RR 1.21 95 percent CI 0.62, 2.36). In contrast, RR were approximately three-fold higher and statistically significant among paroxetine- (RR 2.70, 95 percent CI 1.28, 5.71) or sertraline-treated (RR 3.31, 95 percent CI 1.25, 8.79) patients.

Our own pooled SRE results: For our own analyses, we used the trial-level SRE data reported in the Bridge SER, which were either the outcomes used by the FDA or outcomes ascertained using equivalent methodology. We did not have access to these original patient-level results, therefore we could not verify the accuracy of the trial-level results reported in Bridge. We calculated the RD across all SSRIs and within SSRI subtypes, pooling among the nine trials that met our inclusion criteria (n = 2,013; Table 9). We found that the RD was one percent (95 percent CI 0, 2) (Figure 3). Among individual drugs, risk differences ranged from negative one to three percent, and none were statistically significant. For fluoxetine, the RD was three percent (95 percent CI -2, 7). As a sensitivity analysis, we recalculated the risk difference among all nine RCTs using a fixed-effects model, and results were similar (RD 1 percent, 95 percent CI 0, 3).

Nillson and colleagues report on longer-term outcomes of one of the fluoxetine trials,[88] including data on adverse events for the entire 19-week study period.[125] After the 9-week acute treatment phase, participants were followed for an additional 10 weeks. Participants continued to take either fluoxetine or placebo medication during this 10-week period as originally assigned. Participants in the fluoxetine group not showing a response to treatment were further randomized either to receive a change in dose or to remain at the same dose for the continuation phase.

During the entire 19-week acute and continuation treatment, 11 participants in each group discontinued their medications due to adverse events (10.0 percent of fluoxetine group and 10.1 percent of the placebo group), and four participants in each group reported a suicide-related or self-harm event (3.7 percent of the fluoxetine group and 3.8 percent of the placebo group).

Harms: SSRI + psychotherapy treatment. The TADS trial was the only trial that reported adverse effects of combined SSRI and psychotherapy treatment.[78,126] In this study, several protocols were established across sites for assessing adverse events. An adverse event had to cause clinically significant interference with functioning, require medical attention, or be associated with impaired functioning and cause the patient to require a concomitant medication. Harm-related adverse events were those involving harm to the self, including non-suicidal events such as cutting oneself for relief of dysphoria. It also included worsening suicidal ideation without self-harm, suicide attempt of any lethality, or harm to others. Suicide-related adverse events required the patient to exhibit worsening suicidal ideation, make a suicide attempt, or both. Harmful behaviors without suicidal ideation or intent, such as cutting, are not included as suicide-related adverse events.

Although high-risk suicidality was an exclusion criteria for the TADS trial, 27 percent of patients had at least minimal suicidal ideation based on a suicide question on the CDRS-R, and two percent had severe suicidal ideation (across all four groups). When comparing the results for the suicidality outcomes, the suicide-related adverse event rate among the CBT + fluoxetine group was 6/107 (5.61 percent) compared with 4/112 (3.57 percent) in the placebo control group. The odds ratio was 1.60 (95 percent CI 0.44, 5.85), indicating that the rates were not statistically different from each other. Results of harm-related adverse events were slightly higher 9/107 (8.4 percent) for the fluoxetine + CBT group, but the odds ratio, comparing the risk with placebo control patients, was similar in magnitude and also not statistically significant. One patient in the CBT + fluoxetine group developed hypomania, while two patients in the placebo control group developed either hypomania or mania.

Emslie et al. (2006) have separately reported additional safety results from the TADS trial, restricting analyses to observed cases only and to patients who were still in their assigned treatment arm at the time of observation (i.e., did not receive any out-of-protocol treatments.[126] Seventy-eight to 86 percent of patients remained in their treatment arms at 12 weeks and these rates were not significantly different between groups. They present results of suicide-related events measured by 1) self-report of suicidal ideation on the Suicidal Ideation Questionnaire for grades 7 to 9 (SIQ-Jr), 2) clinician-rated suicidal behavior on CDRS-R, and 3) Columbia Classification System. Mean SIQ-Jr score was higher at baseline in the combined treatment group (although not statistically significant). Although the mean SIQ-Jr scores were not statistically different between groups, the overall improvement in suicidal ideation was greater for the combined treatment group compared to the placebo group ($p = 0.02$). Both self- and clinician-rated measures were also analyzed for worsening and emergence of suicidality. Results varied depending on which measure and criteria were used, but differences were not statistically significant. Results of suicide-related events using the Columbia Classification system yielded higher rates of suicide-related events among the combination therapy group than the placebo group (4.7 percent vs. 2.7 percent) but no statistically significant difference.

Kaizar et al., 2006:[111] Using Bayesian meta-analytic approaches, Kaizar and colleagues re-analyzed the data from the FDA meta-analysis that led to the black box warning on

antidepressant use for children. This series of meta-analyses examined variations in risk associated with drug formulation, drug class, study length, and indications for use. The authors also conducted a series of sensitivity analyses. In children and adolescents with MDD, use of any antidepressant was associated with a doubling of risk for suicidal behavior or ideation. Some, but not all, analyses suggested that risk was limited to use of any SSRI (as compared with atypical antidepressants such as bupropion). A commentary on this analysis notes that limited power complicates firm conclusions on lack of an effect on suicidality for non-SSRI antidepressants or for other psychiatric diagnoses,[127] which supports the FDA's conservative interpretation of general caution in the use of antidepressants in children and adolescents.

Observational studies.

Suicide deaths and attempts.

Valuck et al., 2006:[112] This good-quality, propensity-adjusted retrospective cohort study used data from a proprietary database of paid claims from 74 managed care plans in the US (covering the years 1997 to March, 2003) to examine whether antidepressant use increased the likelihood of a suicide attempt. They identified all members aged 12 to 18 years who received a diagnosis of MDD, an antidepressant dispensing, or both. The authors limited the sample to youth beginning new episodes of depression by eliminating those with claims indicative of depression or psychotherapy in the 12 months prior to the index claim. Suicide attempts were identified based on ICD-9 and ICD-10 codes, though suicide deaths, if any, were not reported. Antidepressant use was measured by dispensing claims and were categorized by type of antidepressant (TCA, SSRI (+ venlafaxine), other, multiple, or none), and measures of duration and compliance were calculated from the dispensing dates and days-supply dispensed. Their analyses included 24,119 youth and had an average of 1.36 years of followup data from the index claim, with a range of 6 months to 6 years with 3 months of followup.

Valuck and colleagues used a two-step approach to data analysis. First, they conducted a propensity analysis to address the fact that patients were not randomly assigned to the medication usage conditions. This is important because depression severity increases the likelihood of a suicide attempt and may also increase the likelihood that a youth would be given antidepressant medication, thus making it difficult to determine whether an increased rate of suicide attempts in antidepressant users would be due to the effects of the medication or due to the fact that they are more severely depressed than those who do not use medications. The propensity score quantifies the probability of receiving each type of treatment, given the following covariates: region, provider specialty, year of MDD diagnosis, age at time of first MDD diagnosis, gender, Medicaid status, number of chronic illnesses, presence of terminal diagnosis, presence of substance abuse diagnosis, presence of schizophrenia diagnosis, presence of other mental health diagnosis, and a log transform of the previous year's healthcare expenditures. Next, the propensity scores were used as continuous adjustment variables in a Cox proportional hazards model to model time until suicide attempt.

While this study did not find an increase in the risk of suicide attempts among those taking antidepressants, one model was adjusted with propensity scores and the covariates used to create the propensity scores. The medication group showing the largest effect was SSRIs (including venlafaxine), but the effect was not statistically significant (Hazard ratio 1.59, 95 percent CL 0.89, 2.82, $p = 0.116$). Further, this study found that those who used antidepressants

for 6 months or more had a reduced risk of a suicide attempt (HR 0.34, 95 percent CL 0.21, 0.55, $p < 0.001$).

Sondergard et al., 2006:[113] This large-scale, fair-quality retrospective cohort study identified all Danish children (aged 10 to 17 years) who had received antidepressants (covering 1995-1999) and all suicide deaths in children aged 10 to 17 during the years 1995-1999. Additionally, they identified a randomly-selected cohort of 50,000 youth who were 10 to 17 years old as of 1/1/1995, subsequently dropping youth who died or emigrated in the intervening years through 1999. It was not clear whether the study authors excluded youth who were exposed to antidepressants from this control cohort.

This study found 19 suicide deaths among the 51,731 youth followed (2,569 of whom had received antidepressants). None of the 19 youth who committed suicide were using antidepressants at the time of their death. Five of these 19 had received antidepressants at some point during the observation period. A multivariate model predicting suicide attempt from age at suicide (10 to 17 vs. 18 to 22), sex, history of antidepressant use, and history of psychiatric service use found that antidepressant use was not an independent predictor of suicide (Rate ratio 4.47, 95 percent CI 0.95, 20.96).

Olfson et al., 2006:[114] Olfson and colleagues conducted a good-quality matched case-control study of suicide attempts and suicide deaths using Medicaid utilization and administrative databases and the National Death Index database. They identified the sample of individuals aged 6 to 64 years with one or more inpatient stays for depression, excluding patients without pharmacy data or with comorbid diagnoses indicating that antidepressant medications might be inappropriate. From this sample, suicide attempt cases were identified as those with a suicide attempt preceded by psychiatric hospitalization based on claims data, and suicide death cases were those with a cause of death of suicide in a national death database. Cases were eliminated from the potential control pool and up to five controls were selected for each case by matching on: age (± 3 years); sex; race or ethnicity; state; date of hospital discharge (±30 days); presence of a claim for substance abuse; recent claim indicating a suicide attempt; and use of an antipsychotic, stimulant, anxiolytic, or mood-stabilizing medication during the 60 days preceding their event date. For suicide attempts they analyzed 263 cases and 1,241 controls. For suicide deaths, the authors analyzed 8 cases and 39 controls.

This study found that children and adolescents who attempted suicide were more likely to be treated with antidepressants than those who did not attempt suicide (45.6 percent of cases used antidepressants vs. 36.1 percent of controls, OR 1.52, 95 percent CI 1.12, 2.07). Looking at specific agents, those 6- to 18-year-olds taking sertraline, a tricyclic, or venlafaxine were more likely to have attempted suicide than those who did not take an antidepressant, but youth taking other agents did not have an increased likelihood of a suicide attempt. Similarly, there was an association between suicide deaths and treatment with an antidepressant medication (OR 15.62, 95 percent CI 1.65, ∞). Youth suicide cases were more likely than controls to be treated with an SSRI (37.5 percent of cases used an SSRI vs. 7.7 percent of controls, OR 11.26, 95 percent CI 0.97, ∞ , $p = 0.005$).

Conversion to Bipolar.

Martin et al., 2004:[115] This good-quality retrospective cohort analysis examined whether antidepressant use affected the rate at which people aged 5 to 29 years with depression or anxiety diagnoses developed a bipolar illness (termed “manic conversion”) and whether the relationship

between antidepressant use and manic conversion differed for people of different ages. Martin and colleagues used the MarketScan Research Database, a publicly available fee-for-service claims database with medical and pharmacy information from more than 200 different insurance companies covering more than 7 million people. After selecting all 5- to 29-year-olds with depression or anxiety diagnoses and pharmacy data available, they calculated start and end dates for antidepressant use, date of manic conversion (if any), and four indices of severity: (1) whether the primary diagnosis was for severe depression, mild depression, or anxiety; (2) the number of different psychiatric diagnoses in the year; (3) the presence of an inpatient psychiatric hospital stay; and (4) the total number of psychotropic medication categories used.

The study authors described two types of manic conversion: (1) early-onset (median 28 days), characterized by anxiety and akathisia, usually dissipating upon drug discontinuation; and (2) later-onset (median 91 days), more closely resembling classic mania and not dissipating as readily after medication discontinuation. This study focused only on the later-onset type and eliminated cases in which manic conversion occurred in the first 2 months of observation.

In their sample of 87,920 patients, 4,786 patients (5.4 percent overall, 6.0 percent per person-year) converted from depression or anxiety to a bipolar illness. The conversion rate among antidepressant-treated patients was 7.7 percent per year, compared with 2.5 percent per year in untreated patients (rate ratio 3.1, 95 percent CI 3.0, 3.2). Further, the conversion ratio between antidepressant users and nonusers was higher in the 5- to 14-year-olds (rate ratio 2.9, 95 percent CI 2.8, 3.1) than the 15- to 29-year-olds (rate ratio 1.4, 95 percent CI 1.3, 1.5). Number Needed to Treat to Harm (NNH) analyses showed that for SSRIs, 43 15-to 29-year-old patients would need to be treated to see one case of manic conversion while only 12 5-to 9-year-olds, 11 10-to14-year-olds, and 20 15-to 19-year-olds would need to be treated for one manic conversion.

Table 10 presents a summary of evidence for each key question.

Chapter 4. Discussion

Summary of Review Findings

KQ1

We found no studies that directly examined the efficacy of screening children and adolescents for depression in increasing recognition or treatment of depression, or improving patients' depression. Therefore, we cannot say whether the use of systematic screening improves identification, treatment, and outcomes of depression over standard identification methods.

KQ2

Although some instruments appear to have better performance characteristics than others, it is difficult to say the degree to which differences are due to the quality of the instrument or the characteristics of the population or study. None of the instruments have been studied in large numbers of patients from a variety of settings, including studies by investigators other than those who developed the questionnaires. Of primary importance to this review, two primary care studies reported sensitivities of 73 and 90 percent, and specificities of 91 and 94 percent, in instruments developed for primary care (the PHQ-A and BDI-PC). Both of these studies examined only adolescents, so no information was found that is directly applicable to younger children. More data were reported in other settings using a variety of instruments, some including younger children (though most were at least 10 years old), with sensitivities ranging from 18 to 100 percent and specificities ranging from 38 to 97 percent, and differed depending on what instrument, cutoff score, and informant source was used.

Data describing the accuracy of using depression screening instruments in younger children remain very limited. Only one study included children younger than ten and reported generally poor sensitivity and did not report specificity. Assessing depression is difficult in young children, who usually lack the reading skills for paper and pencil instruments and who may have difficulty verbalizing their inner experiences. Usually a parent or caregiver is required to assess a child for depression, but data with older children suggests that the addition of self-report instruments substantially improves the accuracy of depressive diagnoses.[68,128,129] A promising instrument is currently being assessed for use in younger children. This instrument uses a pictorial approach to assess the seven commonly seen disorders in young children, including depression. The Dominic involves a series of drawn pictures depicting a character of indeterminate gender named "Dominic" in situations representing the seven disorders assessed.[130,131] For example, one picture shows Dominic walking alone and crying, and the interviewer asks "Do you feel sad and depressed most of the time like Dominic?" It also includes 8 pictures that show "Dominic" feeling happy, in a normal situation. The tool takes 10 to 15 minutes to administer. Preliminary data demonstrate adequate test-retest reliability, internal consistency within the set of pictures targeting each disorder, and agreement with clinical

judgment. Information on sensitivity and specificity would be valuable on this instrument and other instruments using approaches requiring minimal verbal skills.

KQ3

We found no studies that examined potential harms of systematic, standardized screening for depression in any setting. One study, however, has examined iatrogenic distress of screening for suicidality and found that assessing suicidality does not increase distress in adolescents.[132] This is reassuring since screening for suicidality is often a part of depression screening. Another concerning harm would be if the screening test caused a clinician to miss a case of depression that would have otherwise been detected, perhaps by inappropriately lowering their level of clinical suspicion during the clinical encounter. The negative predictive values of the PHQ-A and BDI-PC, however, were 97 to 99 percent, indicating that a low percentage of adolescents with a negative screen would actually have undetected major depression.

The most likely harm of a systematic screening program in primary care would be the allocation of resources to depression screening that may provide more benefit elsewhere. The positive predictive values of the two tools tested in primary care were both 56 percent, indicating that nearly half of patients with positive screening results would actually not meet criteria for MDD. A positive screening test would be a prompt indicating that further diagnostic assessment by a clinician is needed. If the tool were administered in a waiting room setting, then the patient would already have a scheduled appointment and would receive further assessment immediately. The false positive test would therefore use some of the primary healthcare provider's time during the scheduled office visit but not necessarily require costly followup evaluation by a mental health specialist. Other costs to the healthcare system would be related to the time of office staff to administer the test and process results prior to the office visit. Theoretical harms are similar to those that have been discussed for suicide screening programs.[133] Until systematic depression screening is tested in a controlled manner, however, actual harms to patients or costs to healthcare systems, relative to undetected and untreated depression, cannot be measured.

KQ4

The quantity of efficacy data from RCTs of interventions treating pediatric MDD is also quite limited, particularly in comparison with the large body of evidence supporting efficacy among adults. Despite this limitation in quantity, good-quality RCTs have been conducted testing SSRIs and psychotherapies among pediatric populations and provide evidence that efficacious interventions are available, although long-term effects are not known. Meta-analyses have consistently found that fluoxetine is efficacious for treating pediatric populations. Fluoxetine has been studied among both children and adolescents aged 7 to 17 years and is the only drug that is approved by the FDA for treating MDD among youth. Available age-stratified meta-analysis results indicate that fluoxetine is efficacious for both children and adolescents. The absolute risk difference is approximately 20 percent for both age groups, which would mean that approximately five children or adolescents with MDD would need to be treated with fluoxetine in order for one to benefit. When combining data from trials of all SSRIs for treating MDD in youth, we found that patients treated with an SSRI were more likely to show a response to treatment than patients treated with placebo pills. These pooled results, however, must be interpreted cautiously. Baseline response rates among placebo-treated patients were quite

variable across the trials, and some individual SSRIs do not appear to be efficacious. Furthermore, not all SSRIs have been evaluated in pediatric clinical trials.

Another important clinical consideration is that the SSRI trials focused on response rates instead of remission rates. A lower percentage of patients would be expected to have a full remission from depression symptoms than the percentage that met response criteria. In the two fluoxetine trials that report remission rates, only 20 to 40 percent of patients in the fluoxetine groups met criteria for remission at the end of acute treatment. Thus, the majority of treated patients continued to have residual symptoms, even after treatment.

Efficacy trials were typically set in specialty research clinics and tested how well the interventions would work under closely controlled conditions. Effectiveness trials, set in more "real world" community clinics, provide information about whether the same intervention would work when implemented in more naturalistic settings. Fluoxetine has been studied in one effectiveness trial among adolescents (TADS) and was found to be more effective than placebo. This trial also evaluated combined therapy with fluoxetine plus individual cognitive-behavioral therapy and found that nearly three out of four patients responded to combined therapy, in contrast with only one in three who responded in the placebo group. These results indicate that two to three adolescents would need to be treated with combined CBT + fluoxetine therapy in order for one adolescent to benefit from the therapy.

Results of psychotherapy trials indicate that a variety of psychotherapy types are efficacious among adolescents, including group CBT and IPT-A. IPT-A has been demonstrated to be effective in a school-based health clinic when delivered by social workers and clinical psychologists, leading to greater improvements in clinician-rated depression scores compared to a treatment-as-usual control group. The difference between groups became apparent by the eighth week of the intervention period. This study was conducted among a low-income, Hispanic population. Several previous meta-analyses of psychotherapy trials that have had either broader or narrower inclusion and exclusion criteria than this review have also concluded that psychotherapies can effectively reduce depression symptoms, although they have differed in terms of the magnitude of the effect.

Numerous potential barriers may interfere with delivering effective treatments to depressed youth identified through primary care.[134] For example, patients and their families may not be receptive to treatment, and if they are, mental health services may not be available for referral. If mental health services are available, clinicians may not use them appropriately. Recent RCTs have evaluated collaborative care models or quality improvement (QI) interventions that try to reduce some of these barriers.[135,136] In the Youth Partners in Care Study (YPIC), Asarnow and colleagues tested a quality improvement intervention designed to increased access to evidence-based treatments for adolescents with depression through primary care.[135,137] The trial included patients ages 13 to 21 years with elevated depressive symptoms from five different healthcare organizations (42 percent met criteria for MDD). Patients were randomized either to a QI condition or to usual care. The QI condition included having an expert team leader at each site, care managers who supported primary care clinicians with patient evaluation, education, medication, psychosocial treatment, and linkage to specialty mental health services. Care managers were trained in delivering manual-based CBT. After six months, patients in the QI condition reported higher rates of receiving mental health care than patients in usual care (32 vs. 17 percent, $p < 0.001$), mostly due to increased rates of psychotherapy (32 vs.

21 percent, p = 0.007). Medication treatment was similar across groups (12 and 16 percent). Adolescents in the QI condition also reported lower depressive symptoms, higher mental health-related functioning, and greater satisfaction with mental care.

Clarke and colleagues have recently evaluated a collaborative care intervention that involved individual CBT, consultation between the CBT therapist and the PCP, and brief telephone contacts during a 12-month followup period.[136] Clarke and colleagues found a small improvement in mental health-related functioning. Youth in both intervention and control groups, however, showed similar rates of improvement in depressive symptoms from baseline. Interestingly, medication compliance was less among patients in the intervention condition.

All but two included trials had attrition, ranging from 3 to 38 percent of randomized patients. Attrition reduces confidence in the results by increasing susceptibility to confounding through loss of the effects of the initial randomization procedure. The most common method of handling missing data was the LOCF method. The LOCF method and other *ad hoc* approaches to handling missing data have been criticized in recent years.[136,138] LOCF is based on the unrealistic assumption that subjects' measurements don't change after dropout. This assumption is particularly problematic in diseases like depression where the effects of treatment may be expected to change over time. Molenberghs et al. show that the LOCF approach produces biased estimates of treatment effect, and the direction and magnitude of the bias depends on the true (but unknown) treatment effects. Since the direction of the bias can go either way, LOCF can't be assumed to be a conservative estimate. In addition, the bias from LOCF exists even if the reasons behind the missing data are completely random. Given these shortcomings of the LOCF method, many advocate for the use of more stable likelihood-based methods such as linear mixed models in combination with sensitivity analyses to test how the results change under various assumptions.[138,139]

KQ5

The most conservative estimates from the final results of the FDA analyses indicate that treating youth with antidepressants leads to a two percent absolute increase in risk of experiencing either suicidal ideation or behavior.[110] No completed suicides are associated with these trials. When data are pooled for individual drugs, they have not yielded statistically significant increases in suicide-related outcomes. That lack of statistically significant effects, however, may be due to lack of power. For fluoxetine, six percent (17/287) of treated patients and 4 percent (11/289) of placebo control patients experienced either suicidal ideation or behavior during a trial, yielding an absolute risk difference of two percent. This result, however, was not statistically significant.

Based on the estimate of increased absolute risk of two percent, in order for one patient to develop suicidality attributable to antidepressant therapy, approximately 50 patients would need to be treated. Authors of several meta-analyses have argued that additional sources of heterogeneity must be incorporated to more accurately assess the true risk of either efficacy or harms. The FDA analyses used fixed-effects models to calculate risk differences and risk ratios. In contrast, Bridge and colleagues used a random-effects model that incorporated additional sources of within and between meta-analysis heterogeneity. This study found that the absolute risk difference was one percent and that the number needed to harm was 112. In either case,

available data indicate that a patient is more likely to benefit from treatment than to develop suicidality. Nevertheless, suicidality is an extremely serious condition and could theoretically translate into an increased risk of suicide death (current trial data are insufficient to answer this question). As a result, the overall balance of risk and benefit of treatment with antidepressants is not yet clear.

We included results from large observational studies in our report. Those findings, however, are greatly limited by the potential for confounding by indication and residual confounding. The same patient and disease characteristics that are associated with increased risk of suicidality (e.g., depression severity) may also increase the likelihood that a clinician would choose to treat a patient with an antidepressant. Although the analyses in the observational studies that we included attempted to adjust for depression severity using different methods, the studies all used data from large administrative datasets and did not have precise clinical measurements of depression severity. Recent data reported by Simon and colleagues (2007) illustrate an additional problem of residual confounding.[140] They reported that patients aged 25 and younger who had been prescribed antidepressants by a psychiatrist have a much higher incidence of suicide attempts before and after starting treatment compared to patients prescribed antidepressants by primary care physicians. In contrast, their previous research demonstrated that depression severity as measured by conventional diagnostic interviews and symptom scales differed only slightly between patients treated by these different providers.[141] Therefore, even if depression severity can be documented in an observational data set, residual confounding may still be a problem.

Our report did not include findings from autopsy studies of cases of adolescent suicide.[142-145] These studies have documented low rates of antidepressant exposure among adolescents dying by suicide. However, toxicology analyses used in these studies only measure antidepressant levels from the days immediately prior to death, and data were not reported regarding whether or not these patients had been treated with antidepressants in the weeks or months prior to suicide death.

Data are also currently insufficient to determine the role of combined treatment (SSRI plus psychotherapy) on suicide-related adverse events. The TADS trial was the only RCT included in this review that evaluated combined therapy.[78] Suicide-related adverse events were less common among patients treated with combined therapy (fluoxetine and CBT; 5.6 percent) compared to fluoxetine alone (8.3 percent), and more common than among patients in the placebo control group (3.6 percent), but differences were not statistically significant. The trial was not powered sufficiently to detect differences of these magnitudes, therefore it is uncertain whether or not combined therapy would lead to a slight increase in suicidality compared to placebo if more data from larger numbers of patients were available . The additional TADS safety results reported by Emslie and colleagues (2006) indicate that the suicidality results vary depending on how it is measured.[126] Two recent comparative efficacy trials have compared combined therapy with SSRI treatment alone and neither found statistically significant differences between groups for suicidality measures.[146,147] The decision to treat an individual pediatric patient with an antidepressant should be based on the clinical situation and on guidelines from mental health specialists. Thus, careful consideration must be given to how closely a patient will be able to be monitored, either through the clinical setting or at home, after initiating a therapy.

Harms of psychotherapy have not been systematically reported in trials in the past. Recently, Bridge and colleagues highlighted the importance of assessing suicidality at baseline and during followup assessments in trials of psychotherapy.[148]

Some youth are believed to have an increased risk of becoming depressed, including those with depressed parents, those with chronic medical conditions, those with other mental health conditions, and those who have experienced significant negative life events. Comorbid familial depression may be particularly relevant when considering high-risk screening approaches in family practice settings. While we did identify a few studies that gave some information about depression treatment efficacy in youth with risk factors, a systematic examination of the efficacy of depression treatment in youth with risk factors was beyond the scope of this review. Most studies examining youth with risk factors were either very small,[149-151] or had other methodological problems, such as attrition.[152] Several studies included the presence of a risk factor in a multivariate model to determine if it influenced the intervention's effectiveness. Two studies examining the effect of anxiety found contradictory results using different interventions; anxiety was related to better depression outcomes with a CBT intervention[153] and to poorer outcomes with an IPT intervention.[154] Using a similar analytic approach, youth with a history of sexual abuse had poorer depression outcomes with a CBT intervention than those who did not.[155] Finally, we also found a study reporting that depressive symptomatology declined in youth with PTSD when they participated in a CBT intervention.[156]

Limitations

This review focuses on major depressive disorder and does not address evidence to support screening or treatment for dysthymia, minor depression, or other psychiatric disorders in children and adolescents.

Research addressing MDD in children and adolescents is less comprehensive and well developed than that for adults. Unlike the adult literature, no research directly evaluates the benefits of screening (e.g., increased diagnosis, greater treatment initiation, or improved health outcomes) for depression in children and adolescents in primary care. There is also a more limited volume of research on screening instruments, on pharmacological or psychotherapeutic treatments, and on community treatment patterns in children and adolescents compared to research in depressed adults. Research is particularly limited on screening instruments and treatments appropriate for children aged 10 years and younger.

A major concern for mental health care providers and researchers involves unintended adverse effects from depression-related treatment, and possibly screening, in children and adolescents. The majority of available evidence is focused on the impact of antidepressants on suicidality and is derived from short-term randomized controlled trials. These trials do not specifically focus on collecting adverse effects data and are often conducted in highly selected populations. Additionally, the number of patients studied is substantially smaller than studies in adults, which limits the ability to detect rare events such as suicide. Nonetheless, researchers and regulatory agencies have made considerable efforts to perform comprehensive quality analyses to inform the potential short-term risks of suicidality. Longer-term data on suicidality effects and information on other serious adverse effects, particularly mania precipitation, is quite

limited. We did not address more common adverse effects associated with antidepressant use that can affect the acceptability of pharmacological treatments and adherence.

While comorbidity is a common feature of depression in children and adolescents, data are too limited to comment on the impact of various comorbid states on treatment outcomes in children and adolescents, which could be important factors in treatment matching.

Emerging Issues/Next Steps

We have located trials relevant to this report that are not yet completed or published. These are described in Appendix D. We are not aware of any trials that are in progress or are planned that will assess the effect of screening programs on intermediate outcomes (e.g., disease remission). As mentioned in the summary for KQ2, Bergeron and colleagues are conducting a trial on the accuracy of the Dominic Interactive screening tool among 6- to 11-year-olds. Also, Stark and colleagues have conducted a school-based CBT trial among 9- to 13-year-old girls for which results are expected in 2008. Mufson and colleagues are conducting an ongoing trial of IPT versus usual treatment among 125 female adolescents aged 12 to 18 years that is set in a school-based health clinic. Finally, Hunkeler and colleagues are completing a large-scale observational study of 800,000 children and adolescents who were members of the Kaiser Permanente Medical Care program from 1995 to 2003. This study will assess the relationship between antidepressants and suicidal behavior, including completed suicides.

An expert steering committee is currently completing guidelines for assessing and treating adolescent depression in primary care (GLAD-PC). This guideline has used a combination of evidence- and consensus-based methodologies to develop these guidelines. These guidelines are expected to be published soon.

Future Research

- Large-scale, randomized controlled trials (or well-controlled clinical trials) of primary care or health care system depression screening programs documenting health outcomes (response, remission, and related health, psychological, and social improvements, as well as harms) and rates of diagnosis and treatment initiation would help guide clinicians as to the role of depression screening programs in caring for children and adolescents

- Descriptive epidemiological studies describing the prevalence of MDD (diagnosed and undiagnosed; treated and untreated) in children and adolescents in primary health care settings by age, sex, and race/ethnicity

- Trials comparing depression treatment adherence and outcomes (including benefits achieved and harms avoided or increased) from depression collaborative care management approaches compared with usual clinical care

- Analyses of predictors of treatment that may be relevant to the implementation and sustainability of interventions in primary care, such as patient treatment preference or level of provider training needed for delivering effective interventions

- Comparative effectiveness of pharmacological and non-pharmacological treatments for MDD in children and adolescents, particularly those at high risk for suicidality or non-adherence to pharmacotherapy

- Observational outcomes studies of risks for longer-term outcomes, including mania precipitation, with use of antidepressants, particularly SSRIs

Conclusions

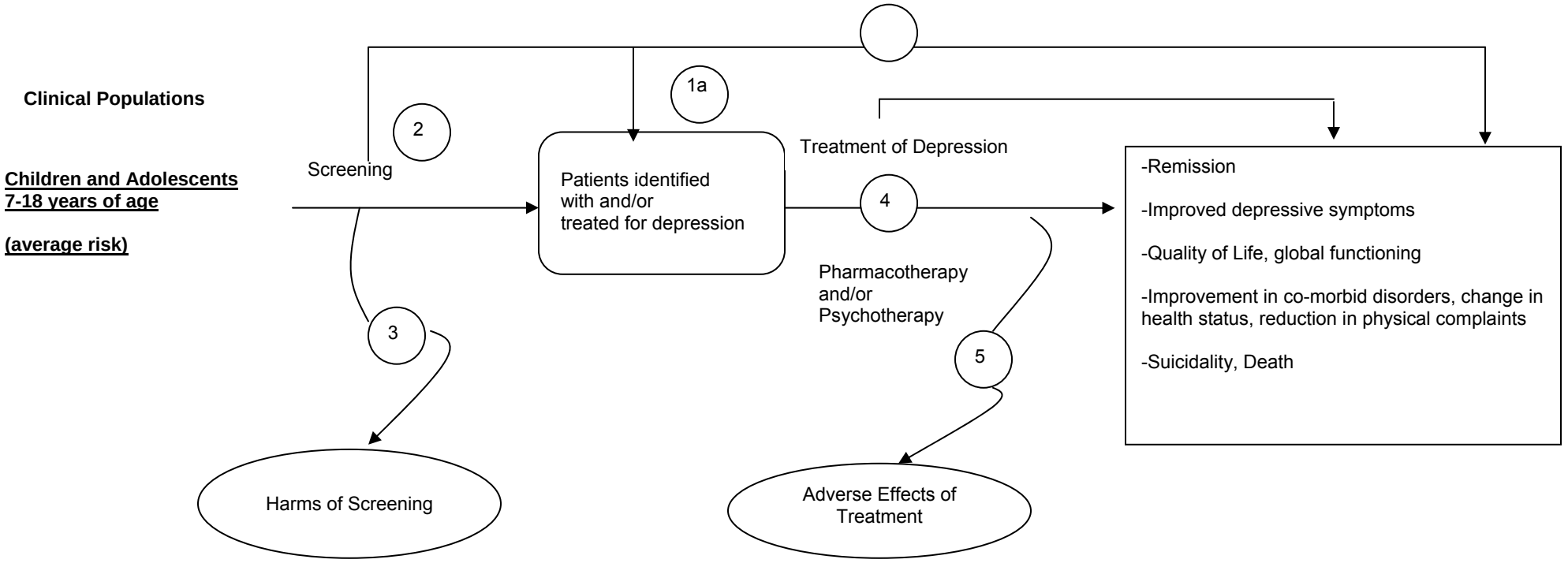
Although no trials of screening for pediatric MDD were identified, very limited available data suggest that primary care-feasible screening tools have been reasonably accurate in identifying depressed adolescents. Studies are needed to assess whether these findings can be replicated by other research groups in larger studies that include patients from a variety of primary care settings. Data are also limited regarding treatment of MDD among youth, but evidence from RCTs, including some effectiveness trials, indicate that available treatments are effective in improving depression outcomes among adolescents. Thus, it is possible that screening among adolescents could lead to increased detection of depression, earlier detection of depression, and greater or earlier improvement in depression symptoms than if patients had never been screened.

Data describing screening among children are inadequate. Effects of treatment among children also need to be understood better, as data indicate age is a modifier of treatment effects. Treatment of depressed youth with SSRIs is associated with a small increased risk of suicidality and therefore should only be considered if judicious clinical monitoring is possible. Specific treatment should be based on individual patients' needs and on mental health treatment guidelines.

Acknowledgments

We are grateful for the feedback and guidance provided by our expert consultant and reviewers: Amy Cheung, MD; Greg Clarke, PhD; Lisa Sharp, PhD; Craig Whittington, PhD; Robin Weersing, PhD, and Karen Wagner, MD, PhD.

Figure 1. Analytic framework



Key Questions: Screening and Treatment for Depression in Children and Adolescents

1. Does screening for depression among children and adolescents in the primary care setting improve health outcomes?
   1a. Does screening increase the proportion of patients identified with and/or treated for depression?

2. Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?

3. What are the harms of screening?

4. Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?

5. What are the adverse effects of treatment?

Figure 2. Response to SSRIs to treat MDD in RCTs including children and adolescents

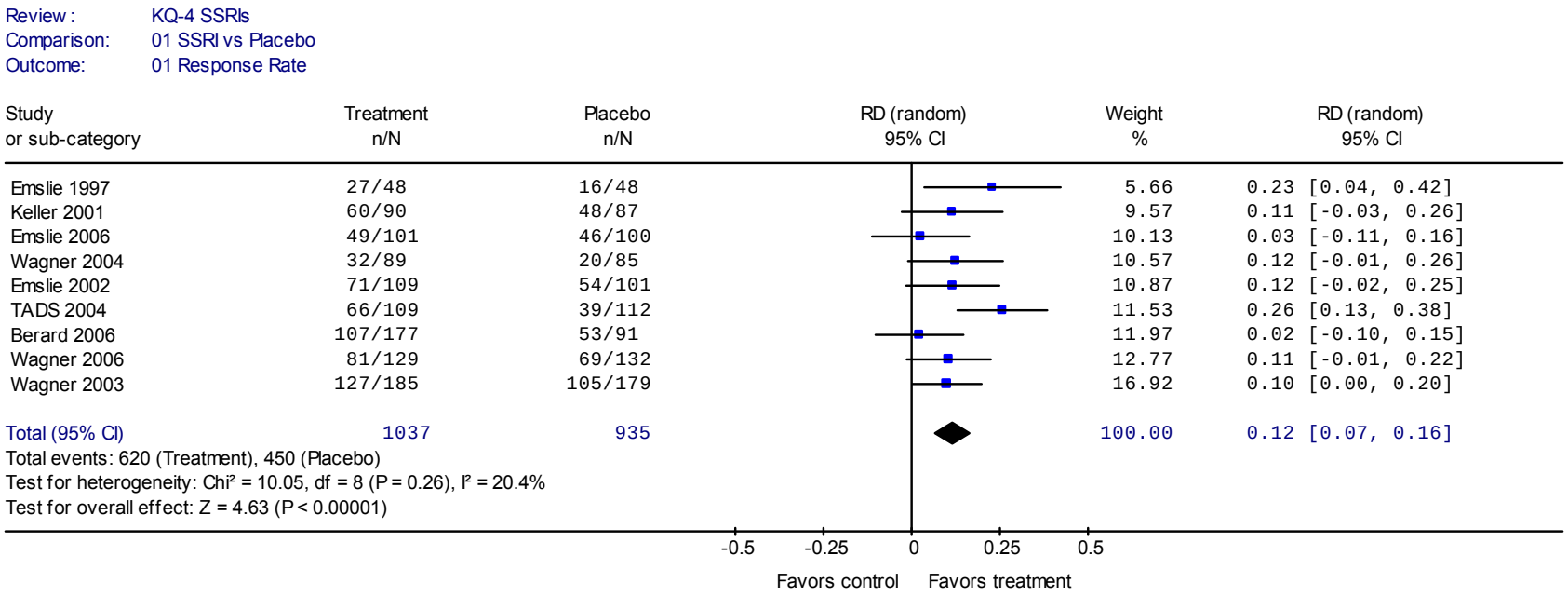


Figure 3. Suicidal ideation or behavior risk in children or adolescents treated with SSRIs for MDD

Review: KQ-4 SSRIs
Comparison: 01 SSRI vs Placebo
Outcome: 03 Suicidal ideation or behavior rate

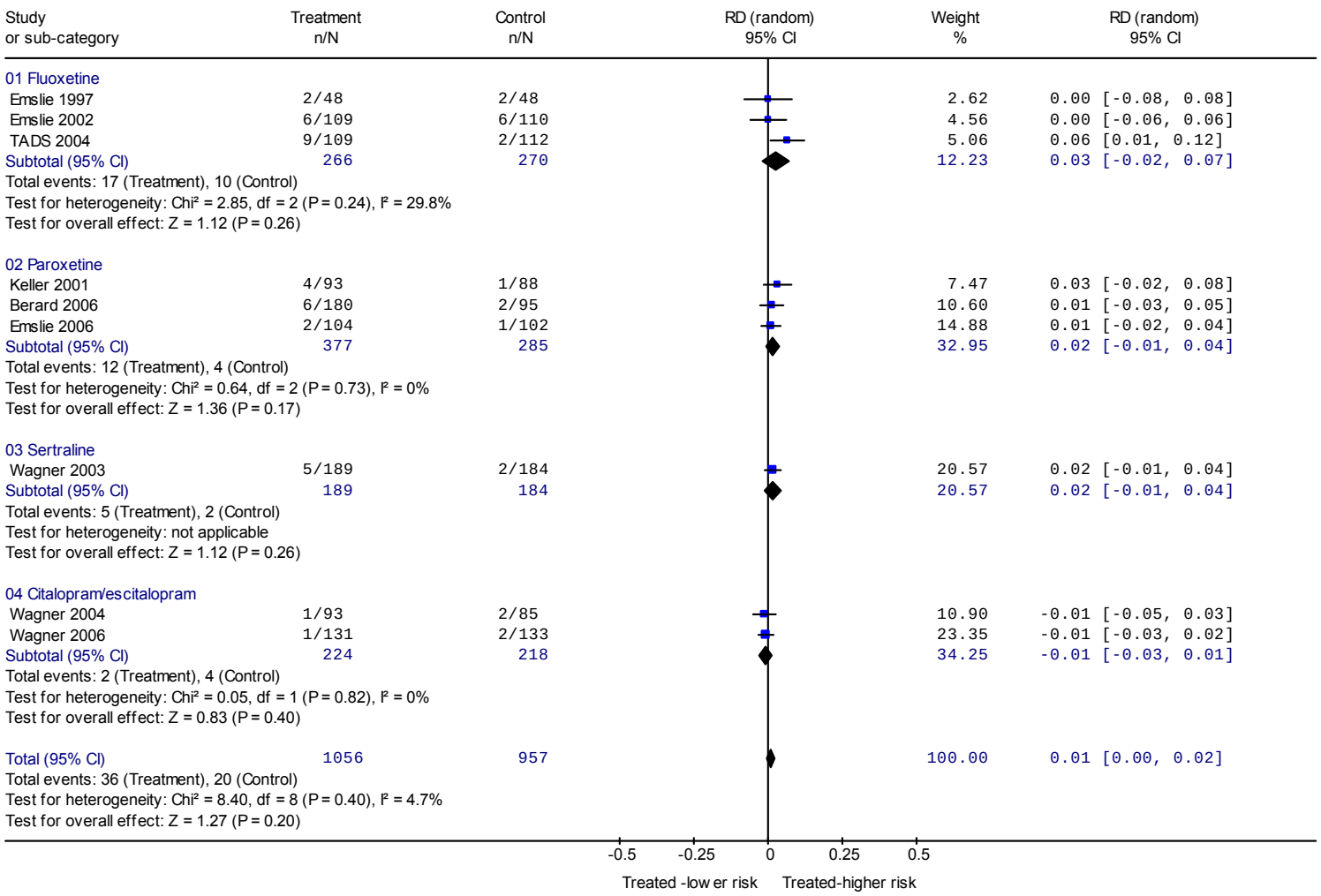


Table 1. Diagnostic criteria for primary DSM-IV depression disorders in children and adolescents[1]

A. Depressive Diagnoses	
Major Depressive Episode: - 5 or more depressive symptoms from column B for $\geq$ 2 weeks - Must have either depressed mood or loss of interest or pleasure - Symptoms must cause significant distress or impairment - No manic or hypomanic behavior ***Minor Depressive Episode:*** - 2-4 depressive symptoms from column B for $\geq$ 2 weeks - Must have either depressed mood or loss of interest or pleasure - Symptoms must cause significant distress or impairment - No manic or hypomanic behavior	1. Depressed mood or irritability 2. Markedly diminished interest or pleasure in most or all activities 3. Significant weight loss (or poor appetite) or weight gain, or failure to gain appropriate weight 4. Insomnia or hypersomnia 5. Psychomotor retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive or inappropriate guilt 8. Diminished ability to think or concentrate, or indecisiveness 9. Recurrent thoughts of death (not just fear of dying), or suicidal ideation, plan, or attempt
Dysthymic Disorder: - Depressed mood or irritability for most of the time for at least one year - Presence of 2 or more symptoms of dysthymia from column B - Never without symptoms for 2 months or more over a one year period - Symptoms must cause clinically significant distress or impairment - No major depressive disorder in first year; no manic, hypomanic, or mixed episodes	1. Significant weight loss (or poor appetite) or weight gain, or failure to gain appropriate weight 2. Insomnia or hypersomnia 3. Fatigue or loss of energy 4. Low self-esteem 5. Diminished ability to think or concentrate, or indecisiveness 6. Feelings of hopelessness

Table 2. Reported prevalence of Major Depressive Disorder (MDD) and Dysthymia in community and primary care samples

Sample (ages if provided)	
Current* MDD, community samples[3]	
Younger children (under age 13)	2.8%
Adolescents (13-18)	5.6%
Adolescent girls (13-18)	5.9%
Adolescent boys (13-18)	4.6%
Lifetime MDD, community samples[4-6]	
Adolescents (13-18)	4.0% - 24.0%
Adolescent girls (13-18)	4.5% - 31.6%
Adolescent boys (13-18)	2.9% - 15.2%
Current MDD, primary care samples	
Younger children (4-9)[157]	0.7%
Children and adolescents (6-18)[158]	11.0%
Current Dysthymia, community sample[159]	
Adolescents	3.1%
Lifetime Dysthymia, community sample[6]	
Adolescents	4.9%
Adolescent girls	5.3%
Adolescent boys	2.3%

*Data from a meta-analysis combining 1 to 12 month prevalence estimates

Table 3. Prevalence of depressive disorders in subgroups at risk for depression (chronic medical or mental health conditions)

	Depressive Disorder*	Prevalence	Ages (if provided)
Asthma[160.161]	MDD	2.7%	5 to 11
	Dysthymia	4.9%	8 to 15
Epilepsy[162]	Mood**	24.6%	5 to 16
Celiac Disease[163]	MDD	7.0%	
	Dysthymia	7.0%	
	Mood**	17.0%	
Recurrent Abdominal Pain[164]	MDD	31.0%	
	Dysthymia	9.5%	
	Mood**	42.9%	
Obesity (community setting)[34]	Mood**	20.0%	13 to 21
Obesity (clinical setting)[34]	Mood**	33.3%	13 to 21
Anxiety[35-37]	Mood**	10 - 30%	
Generalized Social Anxiety Disorder[165]	MDD	6.0%	8 to 17
CD/ODD[36]	Mood**	10.9 - 20.4%	
ADHD (general population)[36]	Mood**	7.2 - 13.2%	
ADHD (psychiatric setting)[158]	MDD	50%	6 to 18
ADHD (pediatric setting)[158]	MDD	42%	6 to 18
PTSD[166]	Lifetime MDD	41.7%	at 18
NYC post-9/11: Severe exposure[167]	MDD	11.0%	9 to 21
NYC post-9/11: Moderate exposure[167]	MDD	8.0%	9 to 21
Parental Depression[38]	Lifetime MDD	40.0% - 67.0%	at 15 to 20

*Meeting diagnostic criteria based on diagnostic interviews **Mood=Any mood disorder
MDD=Major Depressive Disorder; CD/ODD=Conduct Disorder/Oppositional Defiant Disorder; ADHD=Attention Deficit/Hyperactivity Disorder; PTSD=Post-traumatic Stress Disorder; NYC post 9/11=New York City residents after terrorist attack on 9/11/2001

Table 4. Screening instrument descriptions and diagnostic tools

Instrument	Abbreviation	Age (years)	Number of Items	Score Range	Typical Cutoff	Time to Complete (minutes)
Screening Instruments						
Beck Depression Inventory[168] (self-report)	BDI	≥14	21	0-63	11 (female adolescents) 15 (male adolescents)	5-10
Center for Epidemiological Studies-Depression Scale[169] (self-report)	CES-D	≥14	20	0-60	24 (female adolescents) 22 (male adolescents)	10
Center for Epidemiological Studies-Depression Scale for Children[170] (self-report)	CES-DC	12-18	20	0-60	None identified	5-10
Children's Depression Inventory[171] (self-report and/or parent/ other care-giver report)	CDI	7-17	27	0-54	19	10-15
Mood and Feelings Questionnaire[172] (self-report and parent-report)	MFQ	8-18	33 (child) 34 (parent)	0-66 0-68	29 None identified	5-10
Short Mood and Feelings Questionnaire[128] (self-report)	SMFQ	6-17	13	0-26	8 (child) 12 (child + parent)	5-7
Patient Health Questionnaire for Adolescent[7] (self-report)	PHQ-A	13-18	67	(n.a.)	Scoring algorithm	5-10
Revised Clinical Interview Schedule (computer-based)[77] (self-report)	CIS-R	unknown	varies	(n.a.)	Scoring algorithm	No data found
Reynolds Adolescent Depression Scale[173] (self-report)	RADS RADS-2	13-18 11-20	30 30	30-120 30-120	77 76	5-15
Reynolds Child Depression Scale[174] (self-report)	RCDS	8-12	30	30-121	None identified	10-15

Instrument	Abbreviation	Age (years)	Number of Items	Score Range	Typical Cutoff	Time to Complete (minutes)
Strengths and Difficulties Questionnaire[175] (self, parent, and teacher report available)	SDQ	unknown	25	(n.a.)	Scoring algorithm (combines available reports)	5-10

Instrument	Abbreviation
Structured Diagnostic Tools	
Child Assessment Schedule[176]	CAS
Composite International Diagnostic Interview [177]	CIDI
Development and Well-Being Assessment[178]	DAWBA
Diagnostic Interview for Children and Adolescents[179]	DICA
Revised Diagnostic Interview Schedule for Children[180]	DISC-R
Schedule for Affective Disorders and Schizophrenia for School-Aged Children[181]*	K-SADS

*Semi-structured

Table 5. Second-generation antidepressant drugs

Category	Drug Class	Generic Names
Second-generation	Selective Serotonin Re-uptake Inhibitors (SSRIs)	Fluoxetine*, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Escitalopram
Second-generation	Selective Norepinephrine Re-uptake Inhibitors	Venlafaxine, Mirtazapine, Duloxetine
Second-generation	5-HT2 Receptor Antagonists	Nefazodone
Second-generation	Dopamine Re-uptake Inhibitors	Bupropion

*Fluoxetine is the only antidepressant FDA-approved to treat pediatric depression

Table 6. Depression screening instrument accuracy summary for current major depressive disorder

Study	N (completing screen and diagnostic interview)	Instrument	Age range	Sensitivity	Specificity	PPV	NPV	USPSTF Study Quality[a]
Primary care samples								
Johnson, 2002[7]	241[b]	PHQ-A positive	13-18	73%	94%	56%	97%	Fair
Winter*, 1999[9]	100	BDI-PC ≥ 4	12-17	91%	91%	55.6%	98.8%	Fair
Community samples								
Goodman, 2003[68]	7,984	SDQ positive	5-10	54% (p)	NR	NR	NR	Fair
			11-15	33% (c)	NR	NR	NR	
			11-15	44% (p)	NR	NR	NR	
			11-15	63% (c + p)	NR	NR	NR	
School samples								
Canals, 2001,[69] 1997,[70] 1995[71]	290	BDI ≥ 11	17-18	90%	86%	20%	99.5%	Fair
		BDI ≥ 16		90%	96%	47%	99.6%	
Barrera*, 1988[72]	49	BDI ≥ 11	12-17	100%	77%	NR	NR	Fair
		BDI ≥ 16		100%	93%	NR	NR	
Whitaker*, 1990[6]	356	BDI ≥ 16	14-17	77%	65%	NR	NR	Fair
Roberts*, 1991[73]	1,704	BDI ≥ 11	Mean age 16.6	84%	81%	10%	99.5%	Fair
		CES-D ≥ 24		84%	75%	8%	99%	
Garrison*, 1991,[74] 1990[75]	332	CES-D ≥ 22	11-15	18% (male)	83% (male)	9%	NR	Fair
				83% (female)	77% (female)	25%	NR	
		CES-D ≥ 12	11-15	85% (male)	49% (male)	13%	NR	
				84% (female)	38% (female)	11%	NR	
Patton, 1999[76]	170	CIS-R positive	Mean age 15.7	18%	97%	49%	91%	Fair

*Included in 2002 USPSTF report

[a]USPSTF Quality Criteria are described in Appendix B, Table B3

[b]403 patients completed screen and diagnostic interviews, but 162 patients were excluded due to time lag between screen and interview

Abbreviations: c=child, p=parent; NR=not reported; MFQ=Mood and Feelings Questionnaire; SMFQ= Short Mood and Feelings Questionnaire; BDI-PC= Beck Depression Inventory-Primary Care Version; PHQ-A= Patient Health Questionnaire for Adolescents; SDQ= Strengths and Difficulties Questionnaire; CES-DC= Center for Epidemiological Studies-Depression Scale for Children; BDI= Beck Depression Inventory; CES-D= Center for Epidemiological Studies-Depression Scale; CIS-R= Revised Clinical Interview Schedule

Table 7. Characteristics of randomized controlled trials of depression treatment in children and adolescents (KQ 4)

Reference	Intervention	Age range, y	N patients randomized	Length of intervention, weeks	Response Criteria	Response rate		Risk Difference, % (95% CI)	USPSTF Quality[a]
						Treatment Group	Control Group		
SSRIs[a]									
Emslie, 1997[63,94]	IG: Fluoxetine CG: Placebo	7-17	96	8	CGI-I ≤ 2	27/48 (56)	16/48 (33)	23 (4 to 42)	Fair
Emslie, 2002[88,94]	IG: Fluoxetine CG: Placebo	8-17	219	9	≥ 30% decrease in CDRS-R	71/109 (65)	54/101 (54)	12 (-2 to 25)	Fair
TADS, 2004[78]	IG1: Fluoxetine CG: Placebo	12-17	221	12	CGI-I ≤ 2	66/109 (61)	39/112 (35)	26 (13 to 39)	Good
Keller, 2001[80]	IG: Paroxetine CG: Placebo	12-18	180[a]	8	HAM-D ≤ 8 or ≥ 50% reduction from baseline	60/90 (67)	48/87 (55)	12 (-3 to 26)	Good
Berard, 2006[82]	IG: Paroxetine CG: Placebo	13-18	286	12	≥ 50% decrease in MADRS	107/177 (61)	53/91 (58)	2 (-10 to 15)	Good
Emslie, 2006[83]	IG: Paroxetine CG: Placebo	7-17	206	8	CGI-I ≤ 2	49/101 (49)	46/100 (46)	3 (-11 to 16)	Good
Wagner, 2003[81,93]	IG: Sertraline CG: Placebo	6-17	376	10	≥ 40% decrease in adjusted CDRS-R	127/185 (69)	105/179 (59)		Good
Wagner, 2004[89]	IG: Citalopram CG: Placebo	7-17	178	8	CDRS-R score ≤ 28	32/89 (36)	20/85 (24)	12 (-1 to 26)	Fair
Wagner, 2006[84]	IG: Escitalopram CG: Placebo	6-17	268	8	CGI-I ≤ 2	81/129 (63)	69/132 (52)	11 (-1 to 22)	Good
Psychotherapy Interventions									

Reference	Intervention	Age range, y	N patients randomized	Length of intervention, weeks	Response Criteria	Response rate		Risk Difference, % (95% CI)	USPSTF Quality[a]
						Treatment Group	Control Group		
Clarke, 1999[102]	IG1: Group CBT IG2: Group CBT + Parent CG: Waitlist	14 – 18	123	8	No longer meeting DSM-III-R criteria for 2 weeks based on LIFE clinical interview	IG1: 24/37 (64.9%) IG2: 22/32 (68.8%)	13/27 (48.1%)	P < 0.05 (IG1 and IG2 combined vs. CG)	Good
Kahn, 1990[105]	IG1: Group CBT IG2: Group relaxation IG3: Individual self-modeling CG: Waitlist	10-14	68	6-8	Moved from dysfunctional to functional BID score	IG1: 13/17 (76%) IG2: 11/17 (65%) IG3: 10/17 (59%)	3/17 (18%)	p-values NR	Fair
Lewinsohn, 1990[106]	IG1: Group CBT IG2: Group CBT + Parent CG: Waitlist	14-18	69	7	No longer meet DSM-III-R criteria based on K-SADS-E	IG1: 42.9% IG2: 47.6%	5.3%	P < 0.01 (IG1 and IG2 combined vs. CG)	Fair
Stark, 1987[109]	IG1: Group Self-Control IG2: Group Behavioral Problem Solving CG: Waitlist	9-12	29	5	CDI < 13	IG1: 7/9 (78%) IG2: 6/10 (60%)	1/9 (11%)	NR	Fair
Rosello, 1999[108]	IG1: Individual IPT IG2: Individual CBT CG: Waitlist	13-17	71	12	CDI ≤ 17	IG1: 82% IG2: 59%	NR	NR	Fair
Mufson, 1999[107]	IG1: Individual IPT CG: Clinical Monitoring	12-18	48	12	HRSD < 6 CGI-S	75% 20/21(95.5%)	46% 7/11 (61.5%)	p = 0.04 p < 0.001	Fair
Mufson, 2004[79]	IG1: Individual IPT CG: Treatment as Usual	12-18	64	16	HAMD ≤ 6	17/34 (50%)	10/29 (34%)	p-value NR	Good

Reference	Intervention	Age range, y	N patients randomized	Length of intervention, weeks	Response Criteria	Response rate		Risk Difference, % (95% CI)	USPSTF Quality[a]
						Treatment Group	Control Group		
Diamond, 2002[103]	IG1: Attachment-Based Family Therapy CG: Waitlist	13-17	32	12	No longer meet criteria for MDD on K-SADS-P	13/16 (81%)	7/15 (47%)	P = 0.04	Good
Ackerson, 1998[104]	IG1: Cognitive bibliotherapy CG: Waitlist	14-18	30	4	NR	NR	NR	N/A	Fair
TADS, 2004[78]	IG2: Individual CBT CG: Placebo + clinical monitoring	12-17	223	12	CGI improvement score of 1 or 2	43.2% (95% CI 34 – 52)	34.8% (95% CI 26 – 44%)	P = 0.20	Good
Psychotherapy and SSRI									
TADS, 2004[78]	IG3: Individual CBT + fluoxetine CG: Placebo + clinical monitoring	12-17	209	12	CGI improvement score of 1 or 2	71% (95% CI 62% - 80%)	34.8% (95% CI 26 – 44%)		Good

[a]USPSTF Quality Criteria are described in Appendix B, Table B3
[b]Source of SSRI summary data: Bridge et al., 2007
Abbreviations: y-year; N-number; CI-confidence interval; USPSTF-United States Preventive Services Task Force; IG-intervention group; CG-control group; CGI-I-Clinical Global Impression-Improvement scale; CDRS-R-Children's Depression Rating Scale-Revised; HAM-D-Hamilton Rating Scale for Depression; MADRS- Montgomery-Asberg Depression Rating Scale; DSM-III-R-Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised; CBT-cognitive-behavioral therapy; LIFE-Longitudinal Interval Followup Evaluation; BID- Bellevue Index of Depression; K-SADS-E- Kiddie-Schedule for Affective Disorders and Schizophrenia-Epidemiological edition; IPT-interpersonal therapy; HRSD-Hamilton Rating Scale for Depression; CGI-S-Clinical Global Impression-Severity of Illness; NR-not reported; K-SADS-P-Kiddie-Schedule for Affective Disorders and Schizophrenia-Present Version

Table 8. Pooled estimates of efficacy outcomes in randomized controlled trials of SSRIs in Major Depressive Disorder among children and adolescents[92]

	Response Rate[a] No. Response/Total (%)		Risk Difference, % (95% CI)	NNT (95% CI)
	Treatment	Placebo		
Fluoxetine	164/266 (62)	109/261 (42)	20 (11 to 29)	6 (4 to 10)
Paroxetine	216/368 (59)	147/278 (53)	5 (-3 to 13)	…
Sertraline	127/185 (69)	105/179 (59)	10 (0 to 20)	10 (6 to 500)
Citalopram/ Escitalopram	163/301 (54)	136/294 (46)	8 (1 to 16)	13 (7 to 200)

[a]Criteria for response to treatment varied across individual trials

SSRI-selective serotonin reuptake inhibitor; No.-number; NNT-number needed to treat; CI-confidence interval

Table 9. Summary of suicide-related adverse events among children and adolescents treated with antidepressants (KQ 5)

Drug/Indication	RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)
	Outcome			
	Suicide-related events[a]	***Suicide-related events[b]***	***Serious adverse events[c]***	***Suicide-related events[d]***
Citalopram or Escitalopram/MDD	1.37 (0.53 to 3.50)	-0% (-3% to 2%)	1.21 (0.62 to 2.36)	-1% (-3% to 1%)
Fluvoxamine/MDD	No MDD trials	No MDD trials	No MDD trials	No MDD trials
Paroxetine/MDD	2.15 (0.71 to 6.52)	2% (-1% to 4%)	2.70 (1.28 to 5.71)	2% (-1% to 4%)
Fluoxetine/MDD	1.53 (0.74 to 3.16)	2% (-3% to 6%)	1.40 (0.75 to 2.68)	3 (-2% to 7%)
Sertraline/MDD	2.16 (0.48 to 9.62)	2% (-1% to 4%)	3.31 (1.25 to 8.79)	2% (-1% to 4%)
Focus of this report: **All SSRIs/MDD**	**1.66 (1.02 - 2.68)**	**NR**	**NR**	**1% (0% to 2%)**
All antidepressants/MDD	NR	1% (-0.1% to 2%) NNH = 112	2.00 (1.43 to 2.79)	
All newer antidepressants/any indication	1.95 (1.28 to 2.98)[e]	0.7% (0.1% to 1.3%) NNH = 143		
Source	Hammad, 2006[110]	Bridge, 2007[92]	Wallace, 2006[66]	Primary analyses conducted for this report
Methods	Fixed-effects model meta-analyses	Random-effects model meta-analyses	Fixed-effects model meta-analyses	Random-effects model meta-analyses
All antidepressants N *MDD N* *SSRI for MDD N*	4,582 NR NR	5,310 3,430 NR	N/A 2,145 N/A	N/A N/A 2,013
Comments	Missing one escitalopram trial[84]		Missing one escitalopram trial[84]	Restricted to fair- or good-quality RCTs

MDD = Major depressive disorder, SSRI = selective serotonin reuptake inhibitor, RR = risk ratio, RD = risk difference, OR = odds ratio

[a]Assessed by independent blinded suicidology experts at Columbia University

[b]Assessed by independent blinded suicidology experts at Columbia University for trials included in Hammad et al. 2006 and using similar methodology for trials not included in that report

[c]Serious adverse events include death, life-threatening symptoms including suicide attempts, hospitalization, significant disability or incapacity including mania, or events which jeopardize the patient and require medical intervention including study discontinuation. These were assessed from individual trial data.

[d]Using trial-level outcomes published in Bridge et al., 2007

[e]Excludes data from four trials in which no SRE occurred in either treatment or placebo control group

Table 10: Summary of evidence quality by key question

No. of studies	Design	Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
KQ 1. Does screening for depression among children and adolescents in the primary care setting improve health outcomes?						
No evidence						
KQ1a. Does screening increase the proportion of patients identified with and/or treated for depression?						
No evidence						
KQ2. Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?						
9	Screening accuracy studies using a valid reference standard	Younger ages poorly represented, majority of studies in school settings, few instruments examined in more than one study	Fair	Fair. Two studies conducted in primary care settings, one in community setting, six in school settings.	Fair	Two instruments demonstrated good sensitivity and specificity in primary care settings in adolescents. Only one study (in a community setting) included children younger than ten years of age, and the majority included adolescents 12 years or older. The large number of instruments and heterogeneity in samples and settings makes generalization across studies difficult and may explain the wide range of performance characteristics reported (sensitivity ranged from 18 to 100 percent and specificity ranged from 38 to 97 percent).
KQ3. What are the harms of screening?						
No evidence						
KQ4. Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?						
SSRIs						
9	RCTs	No long-term outcomes; trials excluded patients with many comorbid disorders	Fair	Fair. Primarily conducted in research or specialty settings.	Good. (3 fair, 6 good)	SSRI users had higher response rates than those taking placebo medication, with an absolute risk difference between treatment and control groups of 12 percent (95 % CI 7, 16). Fluoxetine and citalopram both yielded statistically significant higher response rates. Data from meta-analyses of efficacy among children and adolescents analyzed separately suggested that SSRIs were less effective among children.
KQ4. Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes? (continued)						
	Psychotherapy					

No. of studies	Design	Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
10	RCTs	No data ages 7-8; limited data ages 9-10; short-term outcomes only	Good	Fair; only 2 trials in community clinics	Fair (6 fair, 4 good)	Most of the psychotherapy trials found that treated patients had higher response rates, remission rates, or a greater reduction in depression symptoms after interventions compared to a variety of different types of control conditions.
KQ4. Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes? (continued)						
SSRI and Psychotherapy Combined						
1	RCT	Single study	N/A	Good	Fair (1 good-quality RCT)	Combined fluoxetine and individual CBT group showed a response rate of 71% vs. 35% in those taking placebo and receiving weekly clinical monitoring.
KQ 5. What are the serious adverse effects of treatments?						
SSRIs						
17	RCTs, meta-analyses, cohort studies, case-control study	Inadequate power to assess suicidality	Fair	Fair	Fair	Even the most conservative estimates indicate that the risk of suicidality may increase absolutely by 1 or 2 percent.
Psychotherapy						
No evidence						

RCT-randomized controlled trial; MDD-major depressive disorder; SSRI-selective serotonin reuptake inhibitor; CBT-cognitive-behavioral therapy

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Appendix A. Terminology and Abbreviations

Akathisia: A movement disorder characterized by a feeling of inner restlessness and a compelling need to be in constant motion as well as by actions such as rocking while standing or sitting, lifting the feet as if marching on the spot and crossing and uncrossing the legs while sitting.

Anhedonia: The inability to gain pleasure from enjoyable experiences.

Cognitive-behavioral therapy (CBT): A general term for a classification of therapies that focus on patterns of thinking and behavior that are maladaptive and the beliefs that underlie them. Specific techniques commonly include keeping a diary of significant events and associated feelings, thoughts and behaviors; questioning and testing assumptions or habits of thoughts that might be unhelpful and unrealistic; gradually facing activities which may have been avoided; and trying out new ways of behaving and reacting. Relaxation and distraction techniques are also commonly included.

Collaborative care: A range of specific components may be included in collaborative care interventions, but at minimum the care of the patient is shared by two providers, usually from different disciplines, in consultation with each other. Interventions may range from simple telephone interventions encouraging treatment plan compliance to complex interventions starting with systematic patient identification and including a team of providers from several disciplines.

Hypomania: A mild, less debilitating form of mania.

Interpersonal therapy (IPT): A short-term supportive psychotherapy that focuses on the connection between interactions between people and the development of a person's emotional well-being. IPT focuses on four general areas: grief, role disputes, role transitions, and interpersonal deficits, emphasizing the ways in which a person's current relationships and social context cause or maintain symptoms.

Mania: An abnormally elevated mood state characterized by such symptoms as inappropriate elation, increased irritability, severe insomnia, grandiose notions, increased speed and/or volume of speech, disconnected and racing thoughts, increased sexual desire, markedly increased energy and activity level, poor judgment, and inappropriate social behavior.

Non-directive supportive therapy: Focuses on establishing a trusting relationship with the therapist, empathy, and reflecting a client's feelings about topics and events discussed rather than teaching specific skills or urging clients to change behavioral patterns other than those the client is attempting to change him or herself.

Preparatory actions to suicidal behavior: The person takes steps to injure him or herself, but is stopped by self or others. This includes steps such as buying a gun with the intent of self-harm, but where no attempt has yet been made at self-harm.

Psychomotor retardation: A slowing down of thought and a reduction of physical movements.

Suicide attempt: Self-injurious behavior associated with some intent to die. Intent can be stated or inferred. No injury needed.

Suicidal behavior: Suicidal ideation, suicide attempt, preparatory act, or suicide death.

Suicidal ideation: Thoughts about wanting to be dead or thoughts about killing oneself, not accompanied by preparatory behavior.

List of acronyms and abbreviations

Abbreviation/Acronym	Phrase, term, name of instrument
ABFT	Attachment-Based Family Therapy
ADHD	Attention Deficit Hyperactive Disorder
AE	Adverse event
BDI	Beck Depression Inventory
BDI-PC	Beck Depression Inventory-Primary Care Version
BID	Bellevue Index of Depression
BMI	Body mass index

Abbreviation/Acronym	Phrase, term, name of instrument
CAS	Child Assessment Schedule
CBCL	Child Behavior Checklist
CBT	Cognitive-Behavioral Therapy
CDRS	Children's Depression Rating Scale
CRRS-R	Children's Depression Rating Scale-Revised
CES-D	Center for Epidemiologic Study-Depression Scale
CES-DC	Center for Epidemiologic Study-Depression Scale for Children
C-GAS	Children's Global Assessment Scale
CGI	Clinical Global Impression Scale
CGI-I	Clinical Global Impression-Improvement Scale
CGI-S	Clinical Global Impression-Severity of Illness
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
CIS-R	Revised Clinical Interview Scale
CM	Clinical monitoring
DAWBA	Development and Well-Being Assessment
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders-3rd Edition-Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-4th Edition
FDA	Food and Drug Administration
GAF	Global Assessment of Function
HAM-D	Hamilton Rating Scale for Depression
HRSD	Hamilton Rating Scale for Depression
ICD-10	International Classification of Diseases-10th revision
ICD-9	International Classification of Diseases-9th revision
IPT-A	Interpersonal Therapy for Adolescents
ITT	Intention to treat
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
K-SADS-E	Kiddie Schedule for Affective Disorders and Schizophrenia-Epidemiological edition
K-SADS-P	Kiddie Schedule for Affective Disorders and Schizophrenia-Present Version
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version
LIFE	Longitudinal Interval Followup Evaluation
LOCF	Last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
MFQ	Mood and Feelings Questionnaire
NARSD	National Alliance for Research on Schizophrenia and Depression
NIMH	National Institute of Mental Health
NNH	Number needed to harm
NNT	Number needed to treat
NPV	Negative predictive value
OCD	Obsessive compulsive disorder
OR	Odds ratio
PHQ-A	Patient Health Questionnaire for Adolescents
PPV	Positive predictive value
PRIME-MD	Primary Care Evaluation of Mental Disorders
RADS	Reynolds Adolescent Depression Scale
RCT	Randomized controlled trial
RD	Risk differential
RR	Relative risk
SAE	Serious adverse event
SAMHSA	Substance Abuse and Mental Health Services Administration
SAS-SR	Social Adjustment Scale-Self-Report
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SDQ	Strengths and Difficulties Questionnaire
SER	Systematic evidence review
SES	Socioeconomic status

Abbreviation/Acronym	Phrase, term, name of instrument
SMFQ	Short Mood and Feelings Questionnaire
SRE	Suicide-related event
SSRI	Selective serotonin reuptake inhibitor
TAU	Treatment as usual
TCA	Tricyclic antidepressant
USPSTF	United States Preventive Services Task Force

Appendix B. Detailed Methods

Literature Search Strategy

For all key questions (KQs), we used existing systematic evidence reviews and meta-analyses to the extent possible and supplemented with primary systematic literature searches bridging the time period covered by the prior review. Results are presented in a cumulative fashion, incorporating the relevant studies from the prior review. For all key questions, we initially searched for systematic reviews, meta-analyses, and evidence-based guidelines on depression screening, treatment, or associated harms in children and adolescents in the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews (CDSR), MEDLINE, and PsycINFO from 1998 through May 2006. Subsequent searches specific to each key question supplemented evidence found in the search of reviews and meta-analyses. Two reviewers independently examined all searches for relevance to all key questions.

For KQs 1-3 (addressing screening outcomes, accuracy, and harms), we found no systematic reviews or meta-analyses that met our inclusion criteria. Therefore, we conducted a primary literature search for depression screening in children and adolescents in primary care to cover the time period since the previous USPSTF review (1998 through May 2007) in MEDLINE, PsycINFO, and the Cochrane Collaboration Registry of Clinical Trials (CCRCT) without restrictions on study designs. Search terms are listed in Appendix B, Table B1.

For KQ4, we found one systematic review[1] and one meta-analysis[2] of SSRI treatment efficacy and adverse effects in children and adolescents that covered the years through 2004. We used these reviews as source documents and bridged their searches for SSRI treatment and harms. Therefore, for KQ4, we searched for RCTs/CCTs of psychotherapy and SSRI treatment in children and adolescents in MEDLINE, PsycINFO, and CCRCT in two separate searches covering 1998 through May 2007 for psychotherapy and 2004 through May 2007 for SSRIs.

For KQ5, we searched for adverse effects of SSRIs and psychotherapeutic treatment, without restrictions on study designs, in two separate searches covering 1990 through May 2007 for psychotherapy and 2004 through May 2007 for SSRIs. Our search period for adverse effects of psychotherapy began in 1990 because harms of treatment were not addressed in the previous USPSTF report.

We also obtained articles from outside experts and through reviewing bibliographies of other relevant articles and systematic reviews. In addition to these searches for published trials, the following sources were searched for unpublished trials of SSRIs: Robert Wood Johnson Foundation, Computer Retrieval of Information on Scientific Projects (CRISP), NARSAD: The Mental Health Research Association, ClinicalStudyResults.org, Current Controlled Trials, GlaxoSmithKline Clinical Trial Register, ClinicalTrials.gov, Eli Lilly and Company Clinical Trial Registry, Australian Clinical Trials Registry, NovartisClinicalTrials.com, Bristol-Myers Squibb Clinical Trial Registry, International Federation of Pharmaceutical Manufacturers and Associations Clinical Trials Portal, Drugs@FDA, European Medicines Agency, Education Resources Information Center (ERIC).

Inclusion and Exclusion Criteria

We developed the following set of inclusion/exclusion criteria that were applied to the key questions.

Populations: This review addresses children and adolescents aged 7 to 18 in the US and other similarly developed westernized populations (defined as Human Development Index > .90). Currently available screening tools are reported to be appropriate for children ages 7 and older.[3] Furthermore, the prevalence of depression among children younger than 6 is estimated to be less than one percent, thus the predictive value of a positive test is likely to be low.

Populations with Risk Factors: We addressed the prevalence of depression among populations with risk factors through a contextual question and also captured studies evaluating screening and treatment among populations with risk factors. We examined studies conducted among populations with the following clinically relevant risk factors recommended by experts who reviewed the work plan for this review: children of depressed parents, prior personal history of a major depressive episode, chronic medical conditions with high prevalence among primary care populations (e.g., asthma), substance abuse, and acute negative life events. After reviewing the evidence for depression screening and treatment in populations with risk factors, the USPSTF decided that the review should not address screening and treatment in high-risk populations separately due to the lack of relevant studies. In the discussion section of this review, however, we do consider this evidence in relation to our findings' applicability to these high-risk populations. We did not examine primary epidemiological studies that identify risk factors for childhood depression. We excluded studies focusing on patients with bipolar disorder or with psychotic disorders, including psychotic depression, as well as patients with severe medical conditions (e.g., cancer) that may interfere

with the performance of screening tools or treatment, or are not generally represented in primary care populations. We also excluded studies focusing on identifying parental depression, including post-partum maternal depression.

Diseases: This report includes studies focusing on Major Depressive Disorder or Depression Not Otherwise Specified, as defined by DSM-IV criteria. We also included studies that use a pre-determined cutoff on a screening test to define major depression. We did not address screening or treatment of dysthymia or minor depression, or prevention of depression. We did not address screening specifically for suicide prevention, which has been addressed by a separate USPSTF recommendation.[3,4]

Settings: We included studies conducted in primary care or in school-based clinics. In addition, we included studies conducted in nonclinic-based settings (e.g., church or after-school programs) if they were conducted in populations that are comparable to primary care patients. For key questions 4 and 5, which evaluate treatment efficacy and adverse effects, we included trials that were conducted in outpatient mental health clinic settings, but these settings were excluded for KQs 1-3. This report does not address depression screening or treatment in incarcerated populations, drug treatment programs, inpatient settings, or residential settings.

Screening interventions: This review includes only studies of screening instruments that are feasible for primary care settings. Specifically, a screening tool should take no longer than 15 minutes to complete if delivered prior to clinician and patient face-to-face contact (e.g., in the waiting room or in the exam room before clinician entrance), and no longer than five minutes or five questions if used during the face-to-face visit. More general mental health screening tools were included if they had a depression module or were being used to identify depressive illness and related outcomes.

Treatment interventions: We included studies of pharmacological interventions that evaluate SSRIs: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram. We excluded studies of tricyclic antidepressants (which were found to be ineffective among children and adolescents in the previous review), monoamine oxidase inhibitors (MAOIs), and electroconvulsive therapy (ECT) or other interventions that are not primary care feasible or referable. We also excluded atypical antidepressants since they are not currently FDA-approved for treating depression in children or adolescents and are not expected to be approved in the near future. This report includes studies evaluating the following types of psychotherapeutic interventions: cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT), pure or guided self-help, family support, and parental education. The scope of this review does not include health systems approaches to depression treatment such as collaborative care interventions; however, we consider these areas in the discussion of our findings.

Outcomes: We included the following outcomes if they were reported at six weeks followup time or later. The primary health outcomes of interest were remission from depression, improved depressive symptoms, and recurrence of depression. Additional outcomes of interest included quality of life, global functioning, psychosocial functioning, educational achievement, unplanned pregnancy, substance abuse, improvement in comorbid disorders, change in health status, and reduction in physical complaints. For harms, we focused on death, other serious psychiatric events (such as hospitalization, suicidal ideation, and suicide attempts), triggering symptoms of mania, and discontinuation of medication due to adverse events.

Study designs: For key questions 1 and 4, addressing outcomes of screening and treatment, we included RCTs, CCTs, systematic reviews, and meta-analyses. We excluded non-comparative study designs and comparative effectiveness studies. For psychotherapy trials, we included studies with no treatment, placebo pill, or waitlist control groups. We also accepted clinical monitoring as a control group if there was significantly less interaction time compared to the intervention arm(s) and it was restricted to non-therapeutic content. Nondirective supportive psychotherapy was considered to be a treatment group unless it was described as being significantly less intense (in total minutes of contact) than the intervention arm(s).

For key question 2, addressing the accuracy of screening, we included studies of diagnostic accuracy that reported sensitivity and specificity compared to an independently-assessed criterion standard for MDD or Depression NOS within two months of the screening test. For key questions 3 and 5, evaluating the harms of screening and treatment, we used evidence from RCTs preferentially, then well-designed non-randomized controlled trials and high-quality observational studies with sample sizes of at least 1,000.

Quality: We excluded studies that met criteria for "Poor" quality using the USPSTF design-specific criteria (Appendix B, Table B3).

Language: We excluded non-English language abstracts and articles.

Article Review and Data Abstraction

We reviewed a total of 5,737 abstracts and 480 complete articles for all KQs (Appendix B, Figure B1). While we conducted three searches to cover depression screening, depression treatment efficacy, and depression treatment harms, we reviewed all abstracts for potential inclusion for any of the KQs. Two investigators independently reviewed all abstracts for KQs 4 and 5. The initial search for KQs 1-3 produced a very high yield (3,418 abstracts). Therefore, we used a modified approach to reviewing these abstracts. One investigator reviewed all the abstracts for KQs 1-3. A second investigator independently reviewed all abstracts from the CCRCT search, the 500 most recently published abstracts from both MEDLINE and PsycINFO, and every fifth abstract in the remaining set for MEDLINE and PsycINFO, representing an additional random subset of 20% that were dual reviewed. Therefore, 1,562 of the 3,418 (46%) screening abstracts were dually reviewed for inclusion or exclusion. There were a total of 22 discrepancies between the two reviewers for the 1,562 dual-reviewed abstracts (1.4%). None of these 22 abstracts were included in the final review; therefore, we feel confident that no relevant articles were missed by having a second investigator dual review only a subset of the abstracts.

Two investigators independently reviewed articles against inclusion/exclusion criteria specific for each key question and marked articles for exclusion as soon as an exclusion criterion was met. Included studies that met all criteria were then independently rated for quality by two investigators, using the USPSTF's study design-specific criteria supplemented by the National Institute for Health and Clinical Excellence (NICE) criteria for quality assessment[5] (Appendix B, Table B3). The Methods Work Group of the USPSTF has defined a three-category rating of "good," "fair," and "poor" based on these criteria. In general, a good study meets all criteria well. A fair study does not meet, or it is not clear that it meets, at least one criterion, but has no known important limitation that could invalidate its results. A poor study has important limitations. Articles were rated as good, fair, or poor by each rater, and disagreements were settled by consensus. Studies receiving a poor final quality rating were excluded from the review. Listings of excluded articles for each key question, along with the reason for exclusion, are in Appendix C, Tables C1, C3, C4, C6, and C9. A list of all exclusion criteria is in Appendix B, Table B2.

There are 4 systematic reviews/meta-analyses and 31 trials (reported in 47 articles) included in this review. We found no studies for KQs 1, 1a, and 3. For KQ2, we found 9 studies reported in 12 articles, 5 of which were included in the previous USPSTF report. KQ4 includes 1 systematic review and 18 trials reported in 29 articles, 3 of which were included in the previous USPSTF report, and KQ5 includes 4 meta-analyses and 13 trials reported in 19 articles, none of which were included in the previous USPSTF report because harms were not addressed. One primary reviewer abstracted relevant information such as study setting, population, screening method, and outcomes into standardized evidence tables for each included article (Appendix C, Tables C2, C5, C7 and C8). A second reviewer checked the abstracted data for accuracy and completeness.

Data Synthesis

We found no data for KQs 1, 1a, and 3. Data synthesis for KQ2 was qualitative because heterogeneity in the instruments, samples and settings studied did not allow for quantitative synthesis. For psychotherapy trials included in KQs 4 and 5, we did not conduct meta-analyses due to the heterogeneity of the interventions. Instead, we qualitatively summarized our findings in the results text and summary tables. For evidence on the efficacy and adverse effects of SSRIs (KQ4 & 5), binary outcome data for response rate and suicide-related adverse events were pooled across the trials meeting our inclusion and exclusion criteria. We used a recent good-quality systematic review (Bridge et al, 2007) as a source of outcome data for response rate and suicide-related events. Bridge and colleagues used suicide-related event data based on the blinded review of outcomes by suicidology experts from Columbia (the same data used in analyses by the FDA). For newer trials, the authors used methodology similar to the Columbia review. We quality rated all individual trials and compared all data for response outcomes against outcomes reported in published versions of individual trials. This review revealed no discrepancies. We could not analyze the data for suicide-related events since the FDA provided these outcomes to Bridge and colleagues. Heterogeneity tests were performed on outcome results. Authors of previous meta-analyses of these data argued that fixed-effect models are not appropriate for this body of literature.[6,7] Commentators on these previous meta-analyses, however, argued that using this approach is appropriate for adverse event outcomes because the trials are already biased toward finding null effects due to lack of systematic measurement of adverse events, underreporting outcomes, and measurement error.

We agree with the assessment by Bridge and colleagues that these trials are likely to have heterogeneity across studies not accounted for by observed covariates. We used a random-effects model (method of DerSimonian and Laird[8]) to calculate the pooled risk difference. Random-effects approaches generally yield lower risk estimates and wider confidence intervals (resulting in more conservative estimates of efficacy and less conservative estimates of adverse events). In order to incorporate more conservative estimates of adverse events into the review, we included results from meta-analyses using fixed-effects models. We conducted sensitivity analyses recalculating

pooled risk differences using a fixed-effects model to understand how this difference in approach would affect results. We focused on the risk difference, instead of relative risk, as the data are more directly applicable to comparing risks and benefits (i.e., calculating and comparing numbers needed to treat or harm). All meta-analyses were conducted using RevMan software v4.2.

External Review Process

The USPSTF appointed three liaisons to guide the scope and reporting of this review. The work plan for the review was sent to five experts on childhood mental health, whom we asked to comment on the general proposed approach, scope of the review, and adequacy of the identified questions. In addition, five outside experts provided feedback on a draft version of this evidence synthesis.

USPSTF Involvement

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. The authors worked with three USPSTF liaisons at key points throughout the review process to develop and refine the scope, analytic framework, and key questions; to resolve issues around the review process; and to finalize the evidence synthesis. The AHRQ had no role in study selection, quality assessment, or synthesis, although AHRQ staff provided project oversight, reviewed the draft evidence synthesis, and distributed the initial evidence report for external review of content by outside experts, including representatives of professional societies and federal agencies. The final published systematic evidence review was revised based on comments from these external reviewers.

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Appendix B Table B1. Search Strategies

Systematic Reviews and Meta-Analyses
Databases: Database of Abstracts of Reviews (DARE), the Cochrane Database of Systematic Reviews (CDSR), MEDLINE, PsycINFO
1998 to 2006

1. Search "Depression" OR "Depressive Disorder" OR "Depression, Postpartum" OR "Depressive Disorder, Major" OR "Dysthymic Disorder" OR "Seasonal Affective Disorder" Limits: All Child: 0-18 years, English, Publication Date from 1998 to 2006
2. Search 1 AND systematic.sb
3. Search depression.ti.ab. OR depressed.ti.ab. OR depressive.ti.ab
4. Search child.ti.ab OR children.ti.ab. OR adolescen*.ti.ab. OR teen.ti.ab. OR teens.ti.ab. OR teenage*.ti.ab.
5. Search 3 AND 4
6. Search 5 AND (publisher.sb. OR in process.sb.)
7. Search 6 AND systematic.sb.
8. Search 6 AND (meta-analysis.ti.ab. OR medline.ti.ab. OR systematic*.ti.ab. OR search*.ti.ab.)
9. Search 7 OR 8
10. Search 7 OR 8 Limits: English, Publication Date from 1998 to 2006
11. Search 2 OR 10

Screening Outcomes, Screening Accuracy, and Screening Adverse Effects (Key Questions 1-3)
Databases: MEDLINE, PsycINFO, Cochrane Central Register of Controlled Trials
1998 to 2006

1. Depressive Disorder/
2. Depressive Disorder, Major/
3. Depression/
4. depress$.ti,ab.
5. 1 or 2 or 3 or 4
6. Mass Screening/
7. screen$.ti,ab.
8. case finding.ti,ab.
9. casefinding.ti,ab.
10. child$ depression inventory$.ti,ab.
11. child$ depression scale$.ti,ab.
12. child$ depression rating scale$.ti,ab.
13. child$ self report rating scale$.ti,ab.
14. "mood and feelings questionnaire$".ti,ab.
15. reynold$ child$ depression.ti,ab.
16. reynold$ adolesc$ depression.ti,ab.
17. kutcher$ adolesc$.ti,ab.
18. "depression scale for children$".ti,ab.
19. beck depression inventory$.ti,ab.
20. Center for Epidemiologic Studies Depression Scale$.ti,ab.
21. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 5 and 21
23. limit 22 to ("child (6 to 12 years)" or "adolescent (13 to 18 years)")
24. children$.ti,ab.
25. childhood.ti,ab.
26. teen.ti,ab.
27. teens.ti,ab.
28. teenage$.ti,ab.
29. pediatric$.ti,ab.
30. paediatric$.ti,ab.
31. adolescen$.ti,ab.
32. boys.ti,ab.
33. girls.ti,ab.
34. youth.ti,ab.
35. youths.ti,ab.
36. child.ti,ab.
37. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. 22 and 37
39. 23 or 38
40. limit 39 to english language
41. limit 40 to yr="1998 - 2006"

Treatment Efficacy (Key Question 4)
Databases: MEDLINE, PsycINFO, Cochrane Central Register of Controlled Trials
SSRIs: 2004 to 2006; Psychotherapy: 1998 to 2006

1. Depressive Disorder/
2. Depressive Disorder, Major/
3. Depression/
4. depress$.ti. or (depression or depressive or depressed).ab.
5. 1 or 2 or 3 or 4
6. Antidepressive Agents, Second-Generation/
7. Serotonin Uptake Inhibitors/
8. Antidepressive Agents/
9. antidepressant$.ti,ab.
10. antidepressives.ti,ab.
11. antidepressive agent$.ti,ab.
12. antidepressive drug$.ti,ab.
13. selective serotonin reuptake inhibitor$.ti,ab.
14. ssri.ti,ab.
15. ssris.ti,ab.
16. Fluoxetine/
17. fluoxetine.ti,ab.
18. prozac.ti,ab.
19. Fluvoxamine/
20. fluvoxamine.ti,ab.
21. luvox.ti,ab.
22. Paroxetine/
23. paroxetine.ti,ab.
24. paxil.ti,ab.
25. Sertraline/
26. sertraline.ti,ab.
27. zoloft.ti,ab.
28. Citalopram/
29. citalopram.ti,ab.
30. celexa.ti,ab.
31. escitalopram.ti,ab.
32. lexapro.ti,ab.
33. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. Psychotherapy/
35. Psychotherapy, Brief/
36. Psychotherapy, Group/
37. psychotherap$.ti,ab.
38. Cognitive Therapy/
39. (cognitive adj (therap$ or treatment$ or intervention$)).ti,ab.
40. Behavior Therapy/
41. (behavio$ adj (therap$ or treatment$ or intervention$)).ti,ab.
42. interpersonal therap$.ti,ab.
43. interpersonal intervention$.ti,ab.
44. Self-Help Groups/
45. self help.ti,ab.
46. Family Therapy/
47. family support.ti,ab.
48. parent$ education.ti,ab.
49. Parents/ed [Education]
50. Counseling/
51. Directive Counseling/
52. counsel$.ti,ab.

Appendix B Table B1. Search Strategies

53. Problem Solving/
54. problem solving.ti,ab.
55. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56. 5 and 33
57. limit 56 to yr="2004 - 2006"
58. 5 and 55
59. limit 58 to yr="1998 - 2006"
60. 57 or 59
61. limit 60 to ("child (6 to 12 years)" or "adolescent (13 to 18 years)")
62. children$.ti,ab.
63. child.ti,ab.
64. childhood.ti,ab.
65. teen.ti,ab.
66. teens.ti,ab.
67. teenage$.ti,ab.
68. pediatric$.ti,ab.
69. paediatric$.ti,ab.
70. adolescen$.ti,ab.
71. boys.ti,ab.
72. girls.ti,ab.
73. youth.ti,ab.
74. youths.ti,ab.
75. 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
76. 60 and 75
77. 61 or 76
78. limit 77 to (clinical trial or controlled clinical trial or randomized controlled trial)
79. clinical trials/ or controlled clinical trials/ or randomized controlled trials/
80. double-blind method/ or random allocation/ or single-blind method/
81. random$.ti,ab.
82. 79 or 80 or 81
83. 77 and 82
84. 78 or 83
85. limit 84 to english language
86. limit 85 to news
87. 85 not 86

Treatment Adverse Effects (Key Question 5)
Databases: MEDLINE, PsycINFO, Cochrane Central Register of Controlled Trials
SSRIs: 2004 to 2006; Psychotherapy: 1990 to 2006

1. Depressive Disorder/
2. Depressive Disorder, Major/
3. Depression/
4. depress$.ti. or (depression or depressive or depressed).ab.
5. 1 or 2 or 3 or 4
6. Antidepressive Agents, Second-Generation/
7. Serotonin Uptake Inhibitors/
8. Antidepressive Agents/
9. antidepressant$.ti,ab.
10. antidepressives.ti,ab.
11. antidepressive agent$.ti,ab.
12. antidepressive drug$.ti,ab.
13. selective serotonin reuptake inhibitor$.ti,ab.
14. ssri.ti,ab.
15. ssris.ti,ab.
16. Fluoxetine/
17. fluoxetine.ti,ab.
18. prozac.ti,ab.
19. Fluvoxamine/
20. fluvoxamine.ti,ab.
21. luvox.ti,ab.

Appendix B Table B1. Search Strategies

22. Paroxetine/
23. paroxetine.ti,ab.
24. paxil.ti,ab.
25. Sertraline/
26. sertraline.ti,ab.
27. zoloft.ti,ab.
28. Citalopram/
29. citalopram.ti,ab.
30. celexa.ti,ab.
31. escitalopram.ti,ab.
32. lexapro.ti,ab.
33. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 1 or 3 or 4
35. 33 and 34
36. limit 35 to yr="2004 - 2006"
37. Psychotherapy/
38. Psychotherapy, Brief/
39. Psychotherapy, Group/
40. psychotherap$.ti,ab.
41. Cognitive Therapy/
42. (cognitive adj (therap$ or treatment$ or intervention$)).ti,ab.
43. Behavior Therapy/
44. (behavio$ adj (therap$ or treatment$ or intervention$)).ti,ab.
45. interpersonal therap$.ti,ab.
46. interpersonal intervention$.ti,ab.
47. Self-Help Groups/
48. self help.ti,ab.
49. Family Therapy/
50. family support.ti,ab.
51. parent$ education.ti,ab.
52. Parents/ed [Education]
53. Counseling/
54. Directive Counseling/
55. counsel$.ti,ab.
56. Problem Solving/
57. problem solving.ti,ab.
58. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59. 5 and 58
60. limit 59 to yr="1990 - 2006"
61. 36 or 60
62. limit 61 to ("child (6 to 12 years)" or "adolescent (13 to 18 years)")
63. children$.ti,ab.
64. child.ti,ab.
65. childhood.ti,ab.
66. teen.ti,ab.
67. teens.ti,ab.
68. teenage$.ti,ab.
69. pediatric$.ti,ab.
70. paediatric$.ti,ab.
71. adolescen$.ti,ab.
72. boys.ti,ab.
73. girls.ti,ab.
74. youth.ti,ab.
75. youths.ti,ab.
76. 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75
77. 61 and 76
78. 62 or 77
79. harm$.ti,ab.
80. (adverse effects or chemically induced or drug effects or mortality or poisoning or toxicity).fs.
81. adverse effect$.ti,ab.

Appendix B Table B1. Search Strategies

82. adverse event$.ti,ab.
83. adverse reaction$.ti,ab.
84. Adverse Drug Reaction Reporting Systems/
85. Drug Toxicity/
86. Drug Hypersensitivity/
87. Death/
88. death.ti,ab.
89. death$.ti,ab.
90. Suicide/
91. Suicide, Attempted/
92. suicide.ti,ab.
93. suicidal$.ti,ab.
94. mania.ti,ab.
95. manic episode$.ti,ab.
96. overdos$.ti,ab,mh.
97. self damag$.ti,ab.
98. self injur$.ti,ab.
99. self injurious behavior/
100. self inflict$.ti,ab.
101. 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100
102. 78 and 101
103. Antidepressive Agents, Second-Generation/ae, po, to [Adverse Effects, Poisoning, Toxicity]
104. Serotonin Uptake Inhibitors/ae, po, to [Adverse Effects, Poisoning, Toxicity]
105. Fluoxetine/ae, po, to [Adverse Effects, Poisoning, Toxicity]
106. Fluvoxamine/ae, po, to [Adverse Effects, Poisoning, Toxicity]
107. Paroxetine/ae, po, to [Adverse Effects, Poisoning, Toxicity]
108. Sertraline/ae, po, to [Adverse Effects, Poisoning, Toxicity]
109. Citalopram/ae, po, to [Adverse Effects, Poisoning, Toxicity]
110. 103 or 104 or 105 or 106 or 107 or 108 or 109
111. limit 110 to yr="2004 - 2006"
112. limit 111 to ("child (6 to 12 years)" or "adolescent (13 to 18 years)"
113. 111 and 76
114. 112 or 113
115. 102 or 114
116. limit 115 to english language
117. limit 116 to humans
118. limit 116 to animals
119. 118 not 117
120. 116 not 119
121. limit 120 to news
122. 120 not 121

Appendix B Table B2. Exclusion Criteria for Key Questions

Exclusion Criteria Applied to All Key Questions

Population:
- Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
- Focus on patients with severe medical illnesses (e.g., cancer), bipolar disorder, or psychotic disorder
- Focus on identifying or treating maternal depression (e.g., during pregnancy or post-partum)
- Focus on identifying or treating parental depression
- Conducted in population that is not comparable to primary care (e.g., high risk conditions not prevalent in primary care populations)
- Focus on patients with minor depression or dysthymia or doesn't present MDD outcomes separately
- Conducted exclusively in high-risk populations
- Conducted in non-Westernized population

Setting:
- Not conducted in primary care, school-based clinics, or other setting with primary care-comparable population (e.g., church or after school program)
- Conducted with inpatients, or those in residential treatment or drug treatment programs
- Conducted with incarcerated populations

Design:
- Editorials
- Letters
- Non-comparative studies
- Non-systematic reviews
- Opinions
- Comparative effectiveness studies
- Abstracts

Quality:
- Does not meet quality criteria

No relevant outcomes
Precedes search period
Article covered by an included systematic review
Systematic review used as source document only
Non-English

Additional Exclusion Criteria Specific to Each Key Question

Key Question 1 - Does screening for depression among children and adolescents in the primary care setting improve health outcomes?

Relevance:
- Does not focus on screening and treatment of depression
- Reports on test that is not relevant to or feasible in primary care setting
- Focus on screening for suicide risk

Setting:
- Conducted in outpatient mental health clinic

Quality:
- Only short-term health outcomes less than six weeks are reported

Key Question 2 - Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?

Relevance:
- Does not focus on depression screening
- Does not use a credible reference standard or reports on test that is not relevant to or feasible in primary care setting
- Focus on screening for suicide risk

Setting:
- Conducted in outpatient mental health clinic

Design:
- Does not report sensitivity and specificity compared to an independently-assessed criterion standard for MDD or Depression NOS within two months of the screening test

Appendix B Table B2. Exclusion Criteria for Key Questions

Key Question 3 - What are the harms of screening?

Relevance:
- Does not focus on harms of depression screening
- Focus on screening for suicide risk

Setting:
- Conducted in outpatient mental health clinic

Key Question 4 - Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?

Relevance:
- Does not focus on depression treatment
- Focus on efficacy of tricyclic antidepressants, atypical antidepressants, MAOIs, ECT or other medications/procedures that are not primary care feasible or referable
- Focus on treatment comparison, matching, or fine-tuning
- Examination of non-demographic modifiers (e.g., genetics, personality characteristics)
- Focus on prevention of depression (either universal or among populations with risk factors)
- Focus on health systems approach to depression treatment such as collaborative care interventions

Setting:
- Intervention not primary care feasible or widely available for primary care referral

Design:
- Control group is not significantly less interaction time compared to intervention arm or has therapeutic content, including nondirective supportive therapy

Quality:
- Only short-term health outcomes less than six weeks are reported

Key Question 5 - What are the adverse effects of treatment?

Relevance:
- Does not focus on harms of depression treatment
- Focus on harms of tricyclic antidepressants, atypical antidepressants, MAOIs, ECT or other medications/procedures that are not primary care feasible or referable
- Focus on treatment comparison, matching, or fine-tuning
- Examination of non-demographic modifiers (e.g., genetics, personality characteristics)
- Focus on harms of prevention of depression (either universal or among populations with risk factors)

Setting:
- Focus on harms of intervention that is not primary care feasible or widely available for primary care referral

Design:
- High quality observational study with sample size less than 1,000

Appendix B Table B3. Quality Rating Criteria

Study Design	United States Preventive Services Task Force quality rating criteria[1]	National Institute for Health and Clinical Excellence methodology checklists[2]
Systematic reviews and meta-analyses	• Comprehensiveness of sources considered/search strategy used • Standard appraisal of included studies • Validity of conclusions • Recency and relevance are especially important for systematic reviews	• The study addresses an appropriate and clearly focused question • A description of the methodology used is included • The literature search is sufficiently rigorous to identify all the relevant studies • Study quality is assessed and taken into account • There are enough similarities between the studies selected to make combining them reasonable
Case-control studies	• Accurate ascertainment of cases • Nonbiased selection of cases/controls with exclusion criteria applied equally to both • Response rate • Diagnostic testing procedures applied equally to each group • Measurement of exposure accurate and applied equally to each group • Appropriate attention to potential confounding variables	• The study addresses an appropriate and clearly focused question • The cases and controls are taken from comparable populations • The same exclusion criteria are used for both cases and controls • Percentage of each group (cases and controls) that participated in the study is similar and participation is not unacceptably low • Comparison is made between participants and non-participants to establish their similarities or differences • Cases are clearly defined and differentiated from controls • Clearly established that controls are non-cases • Measures have been taken to prevent knowledge of primary exposure influencing case ascertainment • Exposure status is measured in a standard, valid, and reliable way • The main potential confounders are identified and taken into account in the design and analysis • Confidence intervals provided
Randomized controlled trials (RCTs)	• Initial assembly of comparable groups employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to followup or overall high loss to followup • Measurements are equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The assignment of subjects to treatment groups is randomized • An adequate concealment method is used • Subjects and investigators are kept blind about treatment allocation • The treatment and control groups are similar at the start of the trial • The only difference between groups is the treatment under investigation • All relevant outcomes are measured in a standard, valid, and reliable way • Percentage of the individuals or clusters recruited into each treatment arm of the study who dropped out before the study was completed is acceptable • All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis) • Where the study is carried out at more than one site, results are comparable for all sites

Appendix B Table B3. Quality Rating Criteria

Study Design	United States Preventive Services Task Force quality rating criteria[1]	National Institute for Health and Clinical Excellence methodology checklists[2]
Cohort studies	• Initial assembly of comparable groups employs 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, contamination) • Important differential loss to followup or overall high loss to followup • Measurements are equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation • The study indicates how many of the people asked to take part did so, in each of the groups being studied • The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis • Percentage of individuals or clusters recruited into each arm of the study who dropped out before the study was completed is acceptable • Comparison is made between full participants and those lost to follow-up, by exposure status • The outcomes are clearly defined • The assessment of outcome is made blind to exposure status • Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome • The measure of assessment of exposure is reliable • Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable • Exposure level or prognostic factor is assessed more than once • The main potential confounders are identified and taken into account in the design and analysis • Confidence intervals provided
Diagnostic accuracy studies	• Screening test relevant, available for primary care, adequately described • Study uses a credible reference standard, performed regardless of test results • Reference standard interpreted independently of screening test • Handles indeterminate result in a reasonable manner • Spectrum of patients included in study • Sample size • Administration of reliable screening test	• The nature of the test being studied is clearly specified • The test is compared with an appropriate gold standard • Where no gold standard exists, a validated reference standard is used as a comparator • Patients for testing are selected either as a consecutive series or randomly, from a clearly defined study population • The test and gold standard are measured independently (blind) of each other • The test and gold standard are applied as close together in time as possible • Results are reported for all patients that are entered into the study • A pre-diagnosis is made and reported

Appendix B Table B3. Quality Rating Criteria

Hierarchy of research design[1]

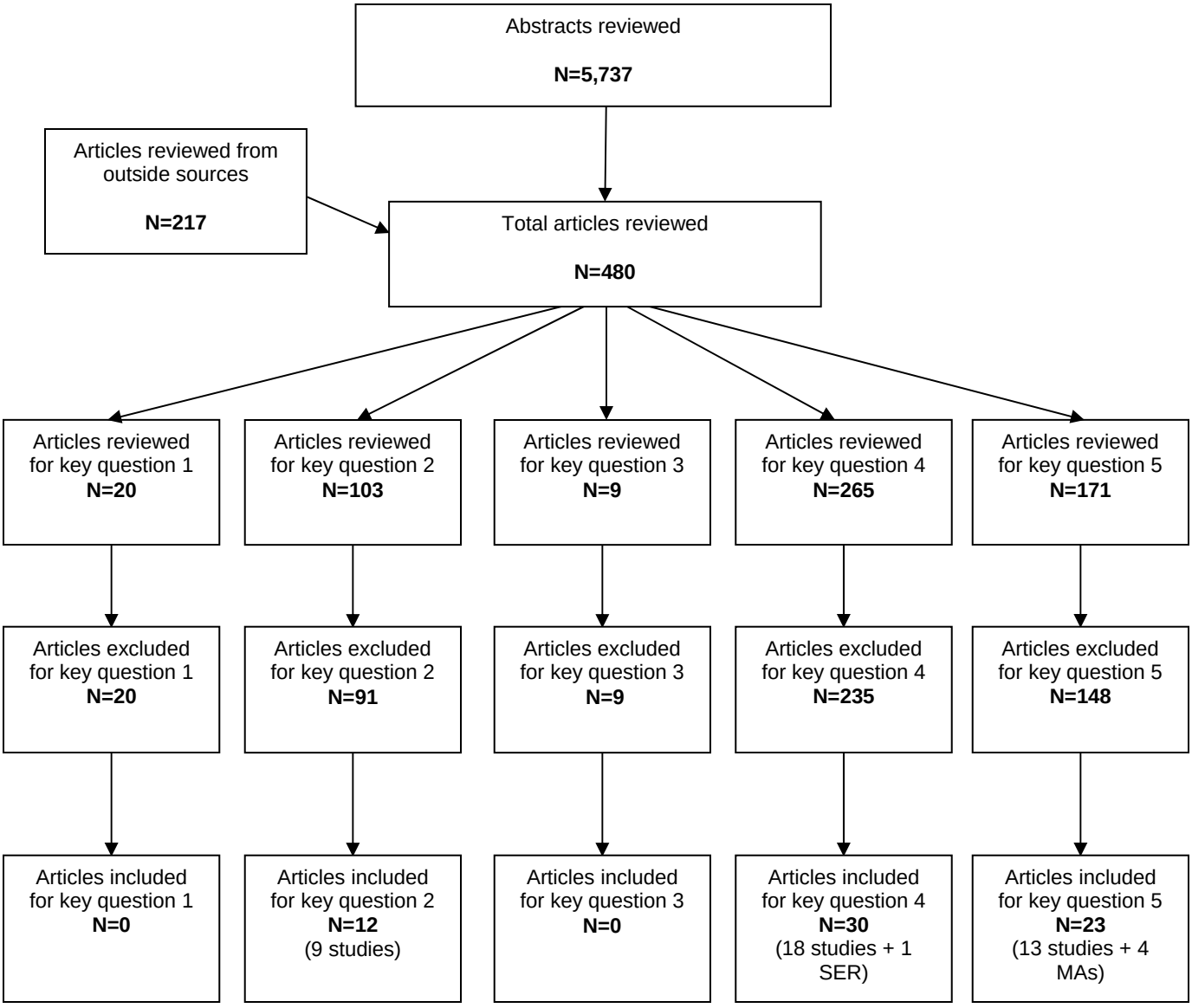
I	Properly conducted randomized controlled trial (RCT)
II-1:	Well-designed controlled trial without randomization
II-2:	Well-designed cohort or case-control analytic study
II-3:	Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
III:	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

References

1. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001; 20(3 Suppl):21-35.

2. National Institute for Health and Clinical Excellence. (April 2006). *'The guidelines manual'.* London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk.

Appendix B Figure B1: Search Results and Article Flow



Appendix C Table C1. Studies Excluded from the Review for Key Question 1

Key Question 1: Does screening for depression among children and adolescents in the primary care setting improve health outcomes?	
Reference	**Reason for exclusion***
Asarnow JR, Jaycox LH, Anderson M. Depression among youth in primary care models for delivering mental health services. *Child Adolesc Psychiatr Clin N Am.* 2002;11:477-97, viii.	Does not focus on depression screening or treatment or harms of either
Asarnow JR, Jaycox LH, Duan N et al. Effectiveness of a quality improvement intervention for adolescent depression in primary care clinics: a randomized controlled trial. *JAMA.* 2005;293:311-319.	Does not focus on depression screening or treatment or harms of either
Borowsky IW, Mozayeny S, Ireland M. Brief psychosocial screening at health supervision and acute care visits. *Pediatrics.* 2003;112:129-133.	Does not report outcomes listed in inclusion criteria
Chatterji P, Caffray CM, Crowe M, Freeman L, Jensen P. Cost assessment of a school-based mental health screening and treatment program in New York City. *Mental Health Services Research* 2004; 6(3):155-66.	Does not meet criteria for study design
Christensen H, Griffiths KM, Korten A. Web-based cognitive behavior therapy: analysis of site usage and changes in depression and anxiety scores. *J Med Internet Res.* 2002;4:e3.	Does not focus on depression screening or treatment or harms of either
Cuijpers P, van Straten A, Smits N, Smit F. Screening and early psychological intervention for depression in schools : Systematic review and meta-analysis. *Eur Child Adolesc Psychiatry* 2006; 15(5):300-7.	Does not meet criteria for study design
Geddes J, Butler R. Depressive disorders. *Clin Evid.* 2002;951-973.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Gilbody S, House AO, Sheldon TA. Screening and case finding instruments for depression. *Cochrane Database of Systematic Reviews.* 2006.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Hazell P. Depression in children and adolescents. *Evid Based Ment Health.* 2003;6:103-104.	Does not meet criteria for study design
Klein DN, Dougherty LR, Olino TM. Toward guidelines for evidence-based assessment of depression in children and adolescents. *J Clin Child Adolesc Psychol.* 2005;34:412-432.	Does not meet criteria for study design
Moor S, Ann M, Hester M et al. Improving the recognition of depression in adolescence: Can we teach the teachers? *J Adolesc.* 2007; 30(1):81-95.	Does not focus on depression screening or treatment or harms of either
Murphy K. Recognizing depression in children. *Nurse Practitioner* 2004;29(9):18-29; quiz 30-1.	Does not focus on depression screening or treatment or harms of either
Nelms BC. Childhood depression: Be on the alert. *Journal of Pediatric Health Care* 2003;17(4):161-2.	Does not focus on depression screening or treatment or harms of either
Pignone, M. P., Gaynes, B. N., Rushton, J. L., Mulrow, C. D., Orleans, C. T., Whitener, B. L., Mills, C., and Lohr, K. N. Screening for Depression. i-D-83. 2002. Rockville, MD, Agency for Healthcare Research and Quality.	Used as a source document only
Smith MS, Mitchell J, McCauley EA, Calderon R. Screening for anxiety and depression in an adolescent clinic. *Pediatrics.* 1990;85:262-266.	Does not report outcomes listed in inclusion criteria
Van Lang ND, Ferdinand RF, Verhulst FC. Predictors of future depression in early and late adolescence. *Journal of Affective Disorders.* 2007;97:137-144.	Does not meet criteria for study design
Weeks SK, Anderson MA, Harmon LS, Michaels TK. Getting inside depression and suicide ideation. *Nursing Management* 2004;35(10):42-6.	Does not meet criteria for study design

Appendix C Table C1. Studies Excluded from the Review for Key Question 1

Key Question 1: Does screening for depression among children and adolescents in the primary care setting improve health outcomes?	
Reference	**Reason for exclusion***
Winter LB, Steer RA, Jones-Hicks L, Beck AT. Screening for major depression disorders in adolescent medical outpatients with the Beck Depression Inventory for Primary Care. *J Adolesc Health.* 1999;24:389-394.	Does not focus on depression screening or treatment or harms of either
Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. *J Psychiatr Res.* 2004;38:577-582.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Zuckerbrot RA, Jensen PS. Improving recognition of adolescent depression in primary care. *Archives of Pediatrics & Adolescent Medicine* 2006; 160(7):694-704.	Does not meet criteria for study design

* See Appendix B, Table B2 for more detailed exclusion criteria

Appendix C Table C2. EvidenceTable for Screening Accuracy for Depression in Children and Adolescents: Key Question 2

Study ID	Setting	Prevalence of depression	Number of patients (CONSORT-type numbers) Exclusions (# and reason)	Patient characteristics	Primary screening test characteristics	Reference/Gold Standard
Canals, 2001[1] Canals, 1997[2] Canals, 1995[3]	**Location:** Urban Spain, school setting **Target population:** Original sample: boys aged 11 and girls aged 10 Current sample: all of original sample who could be found and consented (304/579) **Selection method:** All age-eligible children per municipal census recruited and completed assessments through schools	3.4% MDD (calc) 6.2% Dysthymia (calc) (per diagnostic interview, time frame NR)	579 original sample 304 found/recruited for current study 290 completed full baseline assessment **Exclusions:** 579-304=275 not found or did not consent	**Mean age:** 18 (range 17.5-18.5) **Female:** 49.7% of recruited (calc) **Ethnicity:** NR **SES**: "above average" **Risk factors**: NR	**Test:** BDI **Screening cutoff**: ≥10, 11, 14, 16	Schedules for Clinical Assessment in Neuropsychiatry (SCAN)
Winter, 1999[4]	**Location:** Outpatient pediatric practice in suburban area in New Jersey **Target population:** Adolescents (ages 12-17) **Selection method:** Adolescents attending a health maintenance appointment were recruited, all enrolled except three girls who refused	11% current MDD (calc) (per diagnostic interview)	103 approached, 100 enrolled (50 girls, 50 boys) **Exclusions:** none	**Mean age:** 13.9 (SD 1.6) **Female:** 50% **Ethnicity:** 73% White, 19% Black, 4% Hispanic, 4% Asian **SES:** "middle class" **Risk factors:** NR	**Test:** BDI-PC **Screening cutoff:** ≥4	Mood Module of PRIME-MD administered by pediatricians

Appendix C Table C2. EvidenceTable for Screening Accuracy for Depression in Children and Adolescents: Key Question 2

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Other performance characteristics	USPSTF Quality Score	Applicability
Canals, 2001[1] Canals, 1997[2] Canals, 1995[3]	10: 100% 11: 90% 14: 90% 16: 90% (MDD only)	10: 81.8% 11: 86% 14: 91.8% 16: 96% (MDD only)	10: 16.9% 11: 20% 14: 29% 16: 47% (MDD only)	10: 100% 11: 99.5% 14: 99% 16: 99.6% (MDD only)	NR	Fair	Fair. Participants still available for contact eight years after original sample more likely to be female, parents have higher levels of education and SES, but probably not problematic enough to disqualify.
Winter, 1999[4]	91% (MDD)	91% (MDD)	55.6% (MDD)	98.8% (MDD)	AUC=0.98	Fair--not sure why it took so long to recruit the subjects, less-than-ideal reference standard (kappa=0.63 reported in another study using this study's methodology)	Good-Excellent. Question why it took so long to recruit these cases. Few adolescents having health maintenance visits? If so, generalizability may be more limited, despite primary care setting.

Appendix C Table C2. EvidenceTable for Screening Accuracy for Depression in Children and Adolescents: Key Question 2

Study ID	Setting	Prevalence of depression	Number of patients (CONSORT-type numbers) Exclusions (# and reason)	Patient Characteristics	Primary screening test characteristics	Reference/ Gold Standard
Patton, 1999[5]	**Location:** Schools in Victoria, Australia Students of Government, Catholic, and Independent schools **Target population:** Forty-five schools selected with probability proportional to number of year nine students in each of three types of schools. Two classes randomly selected from each school **Selection method:** All CIS-R-positive youth and random sample of CIS-R-negative students selected for diagnostic interview	3.8% current depression (per screener) 6.2% current MDD (per diagnostic interview) 12.1% six months previous (per diagnostic interview)	2,032 selected 1,729 completed screener 65 positive screen, attempted diagnostic interview 53 positive screen, completed diagnostic interview 105 negative screen, completed diagnostic interview **Exclusions:** NR	**Mean age:** 15.7 (SD 0.5) **Female:** 53% **Ethnicity:** NR **SES:** NR **Risk factors:** NR	**Test:** CIS-R **Screening cutoff:** NR	CIDI
Johnson, 2002[6]	**Location:** Primary care and school nurses' offices in CA, OH, NJ, and NY; rural, urban, and suburban sites **Target population:** 13- to 18-year-old English-speaking youth with at least 9 years of education **Selection method:** CA: youth with recent primary care visit within specified network were invited via letter OH, NJ, NY: youth invited by their providers and given baseline questionnaire packet to mail in; only those whose diagnostic interview completed within 18 days included in analysis (162/403 completed diagnostic interviews)	9.4% MDD (per diagnostic interview, no time-frame specified)	CA: 900 invited 285 parental consent returned 254 youth completed baseline questionnaire 241 completed diagnostic interview within one week OH, NJ, NY: 442 invited and completed baseline questionnaire 403 completed diagnostic interview 162 diagnostic interview within 18 days Total sample: 241+162=403 **Exclusions:** Evidence of cognitive impairment (# NR)	**Mean age:** 15.9 (SD 1.2) **Female:** 63.3% **Ethnicity:** 77.2% White, 4.2% African American, 12.4% Hispanic **SES:** NR **Risk factors:** NR	**Test:** PHQ-A **Screening cutoff:** NR - used "diagnostic algorithm"	Diagnostic interview with mental health professional
Barrera, 1988[7]	**Location:** Private secondary school, assume in AZ (location of authors) **Target population:** Students ages 12-17 **Selection method:** NR	10.2% (per diagnostic interview)	49 (other CONSORT numbers NR) **Exclusions:** NR	**Mean age:** 14.9 (range 12-18) **Female:** 55% **Ethnicity:** NR **SES:** NR **Risk factors:** NR	**Test:** BDI **Screening cutoff**: 6, 11, 16, 21, 26	Child Assessment Schedule

Appendix C Table C2. EvidenceTable for Screening Accuracy for Depression in Children and Adolescents: Key Question 2

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Other performance characteristics	USPSTF Quality Score	Applicability
Patton, 1999[5]	18% (depressive episode) (used inverse probability weighting based on likelihood of selection/ participation since only followed up on subset)	97% (depressive episode) (used inverse probability weighting based on likelihood of selection/ participation since only followed up on subset)	49% (depressive episode)	91% (depressive episode)	NR	Fair--delay between screen and reference standard problematic but not fatal	Fair
Johnson, 2002[6]	73% (MDD)	94% (MDD)	56% (MDD)	97% (MDD)	NR	Fair--dropped 60% of non-CA site participants from analysis because lag between screen and reference test >18 days; no reliability information on this form of PHQ	Fair. Excellent except for the large nonrandom group of the OH/NJ/NY sample dropped from analysis, which may have biased results
Barrera, 1988[7]	6: 100% 11: 100% 16: 100% 21: 80% 26: 80% (major depressive episode)	6: 52.3% 11: 77.3% 16: 93.2% 21: 95.5% 26: 97.7% (major depressive episode)	NR	NR	False positive/negative: 6: 42.9% / 0% 11: 20.4% / 0% 16: 6.1% / 0% 21: 4.1% / 2.0% 26: 2.0% / 2.0% (major depressive episode)	Fair	Fair. No information about refusal rate, drop-out between screen and interview, so could be problematic but we wouldn't be able to tell

Appendix C Table C2. EvidenceTable for Screening Accuracy for Depression in Children and Adolescents: Key Question 2

Study ID	Setting	Prevalence of depression	Number of patients (CONSORT-type numbers) Exclusions (# and reason)	Patient Characteristics	Primary screening test characteristics	Reference/ Gold Standard
Whitaker, 1990[8]	**Location:** Schools in NJ **Target population:** Entire enrollment of grades 9-12 in one NJ semi-rural county **Selection method:** All students in private or public schools invited for screening, random stratified (based on screening results) sample selected for interview	4.0% (weighted prevalence for population per diagnostic interview)	5,596 identified as eligible 5,108 completed screen 468 selected for interview 356 completed interview **Exclusions:** None reported, likely had none	**Age:** 92% ages 14-17 **Female:** 49.8% **Ethnicity:** 94% White **SES:** 42% mothers and 34% fathers high school graduates and no more schooling **Risk factors:** NR	**Test:** BDI **Screening cutoff**: 16	Semi-structured diagnostic interview, depression section modeled after Columbia Clinical Interview
Garrison, 1991[9] Garrison, 1990[10]	**Location:** Middle and high schools in southeastern metropolitan school district **Target population:** Students in or transferring to designated schools for middle or high school **Selection method:** Earliest assessment, at 7th, 8th, or 9th grade	8.2% males 8.7% females (per diagnostic interview)	2,488 completed screening 2,465 data presented (NR why 23 cases dropped) 348 selected for diagnostic interview 332 completed diagnostic interview **Exclusions:** None reported, likely had none	**Age:** 93% ages 12-14 **Female:** 57% **Ethnicity:** 75% White, 25% African American **SES:** 36% fathers completed high school and no further schooling **Risk factors:** NR	**Test:** CES-D **Screening cutoff:** 12, 16, 20, 22	K-SADS
Roberts, 1991[11]	**Location:** High schools in west-central OR **Target population:** High school students **Selection method:** Random sample of nine schools in five communities (stratified by school); rural oversampled to get equal proportion urban/rural	NR	1,710 completed at least one of screeners and K-SADS data **Exclusions:** Parental refusal (# NR)	**Mean age:** 16.6 **Female:** 52.9% **Ethnicity:** 91.1% White **SES:** 42.8% fathers and 30.1% mothers completed 4+ years college **Risk factors:** NR	**Test:** BDI and CESD **Screening cutoff**: BDI: 11 for total sample, 11 for females, 15 for males CESD: 24 for total sample, 24 for females, 22 for males	K-SADS

Appendix C Table C2. EvidenceTable for Screening Accuracy for Depression in Children and Adolescents: Key Question 2

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Other performance characteristics	USPSTF Quality Score	Applicability
Whitaker, 1990[8]	76.9% (lifetime MDD)	64.8% (lifetime MDD)	NR	NR	NR	Fair--due to apparent long time span between screen and interview, which they handled by assessing lifetime MDD	Fair
Garrison, 1991[9] Garrison, 1990[10]	Males: 12: 85% 16: 59% 20: 19% 22: 18% Females: 12: 84% 16: 83% 20: 84% 22: 83% (MDD)	Males: 12: 49% 16: 66% 20: 78% 22: 83% Females: 12: 38% 16: 53% 20: 70% 22: 77% (MDD)	Males: 12: 13% 16: 13% 20: 7% 22: 9% Females: 12: 11% 16: 14% 20: 21% 22: 25% (MDD)	NR	AUC 0.61 (males) 0.77 (females)	Fair--fairly high attrition rate, time between screen and interview NR	Fair
Roberts, 1991[11]	BDI: 83.7 CESD: 83.7 (Current MDD)	BDI: 80.9 CESD: 75.2 (Current MDD)	BDI: 10.2 CESD: 8.0 (Current MDD)	BDI: 99.5 CESD: 99.4 (Current MDD)	NR	Fair	Fair. Only 61% of recruited youth participated

Appendix C Table C2. EvidenceTable for Screening Accuracy for Depression in Children and Adolescents: Key Question 2

Study ID	Setting	Prevalence of depression	Number of patients (CONSORT-type numbers) Exclusions (# and reason)	Patient Characteristics	Primary screening test evaluated Screening cutoff	Reference/Gold Standard
Goodman, 2003[12]	**Location:** UK **Target population:** General population of 5- to 15-year-olds **Selection method:** Sample selected from child benefit records, which represents 98% of British children	NR	10,438 recruited 7,984 (76%) had complete data: parent-, teacher-, and self-report **Exclusions** NR, likely had none	**Mean age:** 10.2 **Female:** 50.3% **Ethnicity**: NR **SES:** NR **Risk factors:** NR	**Test:** SDQ **Screening cutoff**: No cut-off specified, used scoring algorithm for anxiety-depressive disorders to categorize as unlikely, possible, or probable. "Probable" was considered positive screen, "unlikely" and "possible" were considered negative screens.	Clinical raters reviewed parent and child interview records, teacher questionnaires and assigned diagnosis (but did not review SDQ data)

Appendix C Table C2. EvidenceTable for Screening Accuracy for Depression in Children and Adolescents: Key Question 2

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Other performance characteristics	USPSTF Quality Score	Applicability
Goodman, 2003[12]	5- to 10-year-olds Parent-report: 53.9% 11- to 15-year-olds Self-report: 33.3% Parent-report: 44.4% Self+Parent: 63.0% (any depressive disorder)	NR	NR	NR	NR	Fair--did not provide specificity, instrument measured probability of depression ***or*** anxiety diagnosis	Fair-Good, but they used teacher report which would not be feasible for primary care

SES-socio-economic status; MDD-Major Depressive Disorder; calc-calculated; NR-not reported; SD-standard deviation; BDI-Beck Depression Inventory; BDI-PC- Beck Depression Inventory for Primary Care; PRIME-MD-Primary Care Evaluation of Mental Disorders; AUC-Area under the curve; CIS-R-Clinical Interview Schedule; CIDI-Composite International Diagnostic Interview; PHQ-A- Patient Health Questionnaire for Adolescents; CESD-Center for Epidemiologic Studies Depression Scale; CESD-C-Center for Epidemiologic Studies Depression Scale for Children; K-SADS-Kiddie Schedule for Affective Disorders and Schizophrenia; psych-psychiatric; ped-pediatric; SMFQ-Short Mood and Feeling Questionnaire; DISC- Diagnostic Interview Schedule for Children; DSM-Diagnostic and Statistical Manual of Mental Disorders; SDQ-Strengths and Difficulties Questionnaire; MFQ-C/P- Mood and Feeling Questionnaire, Child and Parent versions

References

1. Canals, Josepa, Blade, J., Carbajo, G., and Domenech-Llaberia, E. The Beck Depression Inventory: Psychometric characteristics and usefulness in nonclinical adolescents. European Journal of Psychological Assessment 17[1], 63-68. 2001.

2. Canals J, Domenech E, 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;96:287-294.

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4. Winter LB, Steer RA, Jones-Hicks L, Beck AT. Screening for major depression disorders in adolescent medical outpatients with the Beck Depression Inventory for Primary Care. *J Adolesc Health.* 1999;24:389-394.

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5. Patton GC, Coffey C, Posterino M, Carlin JB, Wolfe R, Bowes G. A computerised screening instrument for adolescent depression: population-based validation and application to a two-phase case-control study. *Social Psychiatry & Psychiatric Epidemiology 34(3):166-72.* 1999.

6. Johnson JG, Harris ES, Spitzer RL, Williams JB. The patient health questionnaire for adolescents: validation of an instrument for the assessment of mental disorders among adolescent primary care patients. *J Adolesc Health.* 2002;30:196-204.

7. Barrera M, Jr., Garrison-Jones CV. Properties of the Beck Depression Inventory as a screening instrument for adolescent depression. *J Abnorm Child Psychol.* 1988;16:263-273.

8. Whitaker A, Johnson J, Shaffer D et al. Uncommon troubles in young people: prevalence estimates of selected psychiatric disorders in a nonreferred adolescent population. *Arch Gen Psychiatry.* 1990;47:487-496.

9. Garrison CZ, Addy CL, Jackson KL, McKeown RE, Waller JL. The CES-D as a screen for depression and other psychiatric disorders in adolescents. *J Am Acad Child Adolesc Psychiatry.* 1991;30:636-641.

10. Garrison CZ, Jackson KL, Marsteller F, McKeown R, Addy C. A longitudinal study of depressive symptomatology in young adolescents. *J Am Acad Child Adolesc Psychiatry.* 1990;29:581-585.

11. Roberts RE, Lewinsohn PM, Seeley JR. Screening for adolescent depression: a comparison of depression scales. *J Am Acad Child Adolesc Psychiatry.* 1991;30:58-66.

12. Goodman R, Ford T, Simmons H, Gatward R, Meltzer H. Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. *International Review of Psychiatry 15(1-2):166-72.* 2003;-May.

Appendix C Table C3. Studies Excluded from the Review for Key Question 2

Key Question 2: Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?	
Reference	**Reason for exclusion***
Abela, John R. Z., Zuroff, David C., Ho, Moon Ho, Adams, Philippe, and Hankin, Benjamin L. Excessive Reassurance Seeking, Hassles, and Depressive Symptoms in Children of Affectively Ill Parents: A Multiwave Longitudinal Study. *Journal of Abnormal Child Psychology* 2006;34(2), 171-187.	Does not focus on depression screening or treatment or harms of either
Ailey SH. Screening adolescents with mental retardation for depression. *Journal of School Nursing* 2000; 16(1):6-11.	Screening test results do not use a credible reference standard or test is not relevant to or feasible in primary care setting
Ambrosini PJ, Metz C, Bianchi MD, Rabinovich H, Undie A. Concurrent validity and psychometric properties of the Beck Depression Inventory in outpatient adolescents. *J Am Acad Child Adolesc Psychiatry.* 1991;30:51-57.	Conducted exclusively in high-risk populations
Angold A, Costello EJ, Messer SC, Pickles A, Winder F, Silver D. Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *Int J Methods Psychiatr Res.* 1995;5:237-249.	Does not meet criteria for population
Aragones E, Pinol JL, Labad A, Folch S, Melich N. Detection and management of depressive disorders in primary care in Spain. *International Journal of Psychiatry in Medicine* 2004;34(4):331-43.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Arroll, Bruce, Khin, Natalie, and Kerse, Ngaire. Screening for depression in primary care with two verbally asked questions: Cross sectional study. *BMJ: British Medical Journal* 2003;327(7424), 1144-1146.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Baillie AJ. Predictive gender and education bias in Kessler's psychological distress Scale (k10). *Social Psychiatry & Psychiatric Epidemiology* 2005;40(9):743-8.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Bauman, Sheri, Merta, Rod, and Steiner, Robert. Further validation of the adolescent form of the SASSI. *Journal of Child & Adolescent Substance Abuse* 1999;9(1), 51-71.	Does not focus on depression screening or treatment or harms of either
Beck AT, Steer RA, Ball R, Ciervo CA, and Kabat M. Use of the Beck Anxiety and Depression Inventories for Primary Care with medical outpatients. Psychological Assessment 4, 211-219. 1997.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Bennett DS, Ambrosini PJ, Kudes D, Metz C, Rabinovich H. Gender differences in adolescent depression: do symptoms differ for boys and girls? *Journal of Affective Disorders* 2005;89(1-3):35-44.	Does not focus on depression screening or treatment or harms of either
Bidaut-Russell, Michelle, Valla, Jean Pierre, Thomas, Jean M., Begeron, Lise, and Lawson, Erma. Reliability of the Terry: A mental health cartoon-like screener for African-American children. *Child Psychiatry & Human Development* 1998; 28(4), 249-263.	Screening test results do not use a credible reference standard or test is not relevant to or feasible in primary care setting
Biederman J, Monuteaux MC, Kendrick E, Klein KL, Faraone SV. The CBCL as a screen for psychiatric comorbidity in paediatric patients with ADHD. *Archives of Disease in Childhood* 2005;90(10):1010-5.	Conducted exclusively in high-risk populations

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Key Question 2: Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?	
Reference	**Reason for exclusion***
Borowsky IW, Mozayeny S, Ireland M. Brief psychosocial screening at health supervision and acute care visits. *Pediatrics.* 2003;112:129-133.	Does not report outcomes listed in inclusion criteria
Brooks SJ KSK. The Kutcher Adolescent Depression Scale: assessment of its evaluative properties over the course of an 8-week pediatric pharmacotherapy trial. *Journal of child and adolescent psychopharmacology* 2003;13(3):337-49.	Does not meet criteria for study design
Brugha, T. S., Bebbington, P. E., Jenkins, R., Meltzer, H., Taub, N. A., Janas, M., and Vernon, J. Cross validation of a general population survey diagnostic interview: A comparison of CIS-R with SCAN ICD-10 diagnostic categories. *Psychological Medicine* 1999;29(5), 1029-1042.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Boyd JH, Weissman MM, Thompson WD, Myers JK. Screening for depression in a community sample. Understanding the discrepancies between depression symptom and diagnostic scales. *Arch Gen Psychiatry.* 1982;39:1195-1200.	Does not meet population criteria
Cairney J, Veldhuizen S, Wade TJ, Kurdyak P, Streiner DL. Evaluation of 2 measures of psychological distress as screeners for depression in the general population. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie.* 2007;52:111-120	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Canning EH, Kelleher K. Performance of screening tools for mental health problems in chronically ill children. *Arch Pediatr Adolesc Med.* 1994;148:272-278.	Conducted exclusively in high-risk populations
Caplan, Rochelle, Siddarth, Prabha, Gurbani, Suresh, Hanson, Rebecca, Sankar, Ramen, and Shields, W. Donald. Depression and Anxiety Disorders in Pediatric Epilepsy. *Epilepsia* 2005; 46(5), 720-730.	Screening test results do not use a credible reference standard or test is not relevant to or feasible in primary care setting
Center for Epidemiological Studies. Innovations in clinical practice: Focus on children & adolescents. 105-107. 2003.	Does not focus on depression screening or treatment or harms of either
Chorpita, Bruce F., Moffitt, Catherine E., and Gray, Jennifer. Psychometric properties of the Revised Child Anxiety and Depression Scale in a clinical sample. *Behaviour Research and Therapy* 2005;43(3), 309-322.	Conducted exclusively in high-risk populations
Chrisman, Allan, Egger, Helen, Compton, Scott N., Curry, John, and Goldston, David B. Assessment of Childhood Depression. *Child and Adolescent Mental Health* 2006; 11(2), 111-116.	Does not meet criteria for study design
Christensen H, Griffiths KM, Korten A. Web-based cognitive behavior therapy: analysis of site usage and changes in depression and anxiety scores. *J Med Internet Res.* 2002;4:e3.	Does not focus on depression screening or treatment or harms of either
Comer JS, Kendall PC. High-end specificity of the children's depression inventory in a sample of anxiety-disordered youth. *Depression & Anxiety* 2005;22(1):11-9.	Conducted exclusively in high-risk populations
Cuffe SP, McKeown RE, Addy CL, Garrison CZ. Family and psychosocial risk factors in a longitudinal epidemiological study of adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry* 2005;44(2):121-9.	Does not focus on depression screening or treatment or harms of either
Cuijpers P, van Straten A, Smits N, Smit F. Screening and early psychological intervention for depression in schools : Systematic review and meta-analysis. *Eur Child Adolesc Psychiatry.* 2006; 15(5):300-7.	Does not meet criteria for study design
Daviss, W. Burleson, Birmaher, Boris, Melhem, Nadine A., Axelson, David A., Michaels, Shana M., and Brent, David A. Criterion validity of the Mood and Feelings Questionnaire for depressive episodes in clinic and non-clinic subjects. Journal of Child Psychology and Psychiatry 2006;47(9), 927-934.	Does not meet criteria for population

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Key Question 2: Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?	
Reference	**Reason for exclusion***
de Ross, Raelene, Gullone, Eleonora, and Chorpita, Bruce F. The Revised Child Anxiety and Depression Scale: A psychometric investigation with Australian youth. *Behaviour Change* 2002;19(2), 90-101.	Screening test results do not use a credible reference standard or test is not relevant to or feasible in primary care setting
Dierker LC, Albano AM, Clarke GN et al. Screening for anxiety and depression in early adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry* 2001;40(8):929-36.	Does not meet quality criteria: rate of participation different within strata, small final sample unlikely to be representative of primary care population
Fendrich M, Weissman MM, Warner V. Screening for depressive disorder in children and adolescents: validating the Center for Epidemiologic Studies Depression Scale for Children. *Am J Epidemiol.* 1990;131:538-551.	Does not meet population criteria
Friedman RJ and Butler LF. Development and validation of a test battery to assess childhood depression. 606-1533-44, 1-27. 6-15-1979. Ontario, Canada, The Ontario Institute for Studies in Education. Final Report to Health and Welfare, Canada.	Does not meet quality criteria: outcome assessment not blinded, inadequate reference standard
Gardner W, Lucas A, Kolko DJ, Campo JV. Comparison of the PSC-17 and alternative mental health screens in an at-risk primary care sample. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2007;46:611-618.	Conducted exclusively in high-risk populations
Gardner W, Shear K, Kelleher KJ et al. Computerized adaptive measurement of depression: a simulation study. *BMC Psychiatry.* 2004;4:13.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Gardner, W., Murphy, M, and Childs, G. The PSC-17: a brief pediatric symptom checklist including psychosocial problem subscales: a report from PROS and ASPN. *Ambulatory Child Health* 1999;5, 225-236.	Does not report outcomes listed in inclusion criteria
Geddes J, Butler R. Depressive disorders. *Clin Evid.* 2002;951-973.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Goncalves, Bruno and Fagulha, Teresa. The Portuguese Version of the Center for Epidemiologic Studies Depression Scale (CES-D). *European Journal of Psychological Assessment* 2004;20(4), 339-348.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Gupta S, Crawford SG, Mitchell I. Screening children with asthma for psychosocial adjustment problems: a tool for health care professionals. *J Asthma.* 2006;43:543-548.	Conducted exclusively in high-risk populations
Hazell P. Depression in children and adolescents. *Evid Based Ment Health.* 2003;6:103-104.	Does not meet criteria for study design
Holcomb SS. Identification and treatment of depression. *Nurse Pract.* 2006;31:42-44.	Does not meet criteria for study design
Jellinek M, Little M, Murphy JM, Pagano M. The Pediatric Symptom Checklist. Support for a role in a managed care environment. *Arch Pediatr Adolesc Med.* 1995;149:740-746.	Does not report outcomes listed in inclusion criteria
Jellinek MS, Murphy JM, Burns BJ. Brief psychosocial screening in outpatient pediatric practice. *J Pediatr.* 1986;109:371-378.	Does not report outcomes listed in inclusion criteria

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Key Question 2: Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?	
Reference	**Reason for exclusion***
Jellinek MS, Murphy JM, Little M, Pagano ME, Comer DM, Kelleher KJ. Use of the Pediatric Symptom Checklist to screen for psychosocial problems in pediatric primary care: a national feasibility study. *Arch Pediatr Adolesc Med.* 1999;153:254-260.	Does not report outcomes listed in inclusion criteria
Jellinek MS, Murphy JM, Robinson J, Feins A, Lamb S, Fenton T. Pediatric Symptom Checklist: screening school-age children for psychosocial dysfunction. *J Pediatr.* 1988;112:201-209.	Does not report outcomes listed in inclusion criteria
Kanner AM, Dunn DW. Diagnosis and management of depression and psychosis in children and adolescents with epilepsy. *J Child Neurol.* 2004;19:Suppl-72.	Conducted exclusively in high-risk populations
Kashani JH, Sherman DD, Parker DR, Reid JC. Utility of the Beck Depression Inventory with clinic-referred adolescents. *J Am Acad Child Adolesc Psychiatry.* 1990;29:278-282.	Conducted exclusively in high-risk populations
Katon, Wayne J., Richardson, Laura, Russo, Joan, Lozano, Paula, and McCauley, Elizabeth. Quality of Mental Health Care for Youth with Asthma and Comorbid Anxiety and Depression. [References]. Medical Care 44[12], 1064-1072. 2006.	Conducted exclusively in high-risk populations
Killeen MR. Screening for major depression disorders in adolescent medical outpatients with the Beck Depression Inventory for Primary Care. *Journal of Child & Family Nursing* 2000;3(1):51-3.	Does not meet criteria for study design
Klein DN, Dougherty LR, Olino TM. Toward guidelines for evidence-based assessment of depression in children and adolescents. *J Clin Child Adolesc Psychol.* 2005;34:412-432.	Does not meet criteria for study design
Kresanov K, Tuominen J, Piha J, Almqvist F. Validity of child psychiatric screening methods. *European Child & Adolescent Psychiatry* 1998;7(2):85-95.	Does not focus on depression screening or treatment or harms of either
LeBlanc JC, Almudevar A, Brooks SJ, Kutcher S. Screening for adolescent depression: comparison of the Kutcher Adolescent Depression Scale with the Beck depression inventory. *Journal of Child & Adolescent Psychopharmacology 12(2):113-26.* 2002.	Conducted in population that is not comparable to primary care (e.g., high risk conditions not prevalent in primary care populations)
Matthey S, Petrovski P. The Children's Depression Inventory: error in cutoff scores for screening purposes. *Psychological Assessment* 2002;14(2):146-9.	Does not focus on depression screening or treatment or harms of either
McClusky J. Data need to be accurate when screening for depression in teenagers. *BMJ* 2005;331(7521):906.	Does not focus on depression screening or treatment or harms of either
McCue P, Buchanan T, Martin CR. Screening for psychological distress using internet administration of the Hospital Anxiety and Depression Scale (HADS) in individuals with chronic fatigue syndrome. *British Journal of Clinical Psychology.* 2006;45:4-98.	Conducted exclusively in high-risk populations
Means-Christensen AJ, Sherbourne CD, Roy-Byrne PP, Craske MG, Stein MB. Using five questions to screen for five common mental disorders in primary care: diagnostic accuracy of the Anxiety and Depression Detector. *General Hospital Psychiatry* 2006;28(2):108-18.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Monga S, Birmaher B, Chiappetta L et al. Screen for Child Anxiety-Related Emotional Disorders (SCARED): convergent and divergent validity. *Depression & Anxiety* 2000;12(2):85-91.	Does not focus on depression screening or treatment or harms of either
Moor S, Ann M, Hester M et al. Improving the recognition of depression in adolescence: Can we teach the teachers? *J Adolesc.* 2007; 30(1):81-95.	Does not focus on depression screening or treatment or harms of either

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Key Question 2: Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?	
Reference	**Reason for exclusion***
Murphy JM, Ichinose C, Hicks RC et al. Utility of the Pediatric Symptom Checklist as a psychosocial screen to meet the federal Early and Periodic Screening, Diagnosis, and Treatment (EPSDT) standards: a pilot study. *J Pediatr.* 1996;129:864-869.	Does not report outcomes listed in inclusion criteria
Murphy JM, Reede J, Jellinek MS, Bishop SJ. Screening for psychosocial dysfunction in inner-city children: further validation of the Pediatric Symptom checklist. *J Am Acad Child Adolesc Psychiatry.* 1992;31:1105-1111.	Does not report outcomes listed in inclusion criteria
Osman A, Kopper BA, Barrios F, Gutierrez PM, Bagge CL. Reliability and validity of the Beck depression inventory--II with adolescent psychiatric inpatients. *Psychological Assessment* 2004;16(2):120-32.	Does not meet criteria for study design
Pandya R, Metz L, Patten SB. Predictive value of the CES-D in detecting depression among candidates for disease-modifying multiple sclerosis treatment. *Psychosomatics* 2005;46(2):131-4.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Pavuluri M, Birmaher B. A practical guide to using ratings of depression and anxiety in child psychiatric practice. *Current Psychiatry Reports* 2004;6(2):108-16.	Does not meet criteria for study design
Pellegrino, Joseph F., Singh, Nirbhay N., and Carmanico, Sharon J. Concordance among three diagnostic procedures for identifying depression in children and adolescents with EBD. *Journal of Emotional and Behavioral Disorders* 1999;7(2), 118-127.	Does not meet setting criteria
Perreira, Krista M., eb-Sossa, Natalia, Harris, Kathleen Mullan, and Bollen, Kenneth. What Are We Measuring? An Evaluation of the CES-D Across Race/Ethnicity and Immigrant Generation. *Social Forces* 2005; 83(4), 1567-1602.	Screening test results do not use a credible reference standard or test is not relevant to or feasible in primary care setting
Pignone, M. P., Gaynes, B. N., Rushton, J. L., Mulrow, C. D., Orleans, C. T., Whitener, B. L., Mills, C., and Lohr, K. N. Screening for Depression. i-D-83. 2002. Rockville, MD, Agency for Healthcare Research and Quality.	Used as a source document only
Prescott CA, McArdle JJ, Hishinuma ES et al. Prediction of major depression and dysthymia from CES-D scores among ethnic minority adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry* 1998;37(5):495-503.	Does not meet criteria for study design
Puertas G, Patel V, Marshall T. Are visual measures of mood superior to questionnaire measures in non-Western settings? Social Psychiatry & Psychiatric Epidemiology 2004; 39(8):662 -6.	Does not focus on depression screening or treatment or harms of either
Puura K, Almqvist F, Tamminen T et al. Psychiatric disturbances among prepubertal children in southern Finland. *Social Psychiatry & Psychiatric Epidemiology* 1998;33(7):310-8.	Does not focus on depression screening or treatment or harms of either
Revah-Levy A, Birmaher B, Gasquet I, Falissard B. The Adolescent Depression Rating Scale (ADRS): a validation study. *BMC Psychiatry.* 2007;7:2.	Conducted in population that is not comparable to primary care (e.g., high risk conditions not prevalent in primary care populations)
Reynolds, William M. and Mazza, James J. Reliability and validity of the Reynolds Adolescent Depression Scale with young adolescents. *Journal of School Psychology* 1998; 36(3), 295-312.	Screening test results do not use a credible reference standard or test is not relevant to or feasible in primary care setting
Reynolds, William M. The Reynolds Adolescent Depression Scale-Second Edition (RADS-2). 224-236. 2004.	Does not focus on depression screening or treatment or harms of either

Appendix C Table C3. Studies Excluded from the Review for Key Question 2

Key Question 2: Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?	
Reference	**Reason for exclusion***
Rieffe, Carolien, Terwogt, Mark Meerum, Petrides, K. V., Cowan, Richard, Miers, Anne C., and Tolland, Abigail. Psychometric properties of the Emotion Awareness Questionnaire for children. Personality and Individual Differences 43(1), 95-105. 2007.	Screening test results do not use a credible reference standard or test is not relevant to or feasible in primary care setting
Saylor CF, Finch AJ, Jr., Spirito A, Bennett B. The children's depression inventory: a systematic evaluation of psychometric properties. *Journal of Consulting & Clinical Psychology* 1984;52(6):955-67.	Does not report outcomes listed in inclusion criteria
Schubiner H, Tzelepis A, Wright K, Podany E. The clinical utility of the Safe Times Questionnaire. *J Adolesc Health.* 1994;15:374-382.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Shaffer D, Scott M, Wilcox H et al. The Columbia Suicide Screen: validity and reliability of a screen for youth suicide and depression. *Journal of the American Academy of Child & Adolescent Psychiatry* 2004;43(1):71-9.	Does not focus on depression screening or treatment or harms of either
Shemesh E, Yehuda R, Rockmore L et al. Assessment of depression in medically ill children presenting to pediatric specialty clinics. *Journal of the American Academy of Child & Adolescent Psychiatry 2005;44(12):1249-57.*	Conducted exclusively in high-risk populations
Sitarenios, Gill and Kovacs, Maria. Use of the Children's Depression Inventory. 267-298. 1999.	Does not focus on depression screening or treatment or harms of either
Snijders AH, Robertson MM, Orth M. Beck Depression Inventory is a useful screening tool for major depressive disorder in Gilles de la Tourette syndrome. *Journal of Neurology, Neurosurgery & Psychiatry* 2006;77(6):787-9.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Sorensen MJ, Frydenberg M, Thastum M, Thomsen PH. The Children's Depression Inventory and classification of major depressive disorder: validity and reliability of the Danish version. *European Child & Adolescent Psychiatry* 2005;14(6):328-34.	Conducted exclusively in high-risk populations
Taylor EH. Advances in the diagnosis and treatment of children with serious mental illness. *Child Welfare* 1998; 77(3):311-32.	Does not focus on depression screening or treatment or harms of either
Thapar A, McGuffin P. Validity of the shortened Mood and Feelings Questionnaire in a community sample of children and adolescents: a preliminary research note. *Psychiatry Research* 1998;81(2):259-68.	Does not meet criteria for study design
Timbremont B, Braet C, Dreessen L. Assessing depression in youth: relation between the Children's Depression Inventory and a structured interview. *Journal of Clinical Child & Adolescent Psychology* 2004;33(1):149-57.	Conducted exclusively in high-risk populations
Truman J, Robinson K, Evans AL et al. The Strengths and Difficulties Questionnaire: a pilot study of a new computer version of the self-report scale. *Eur Child Adolesc Psychiatry.* 2003;12:9-14.	Screening test results do not use a credible reference standard or test is not relevant to or feasible in primary care setting
Valla JP, Bergeron L, Berube H, Gaudet N, St-Georges M. A structured pictorial questionnaire to assess DSM-III-R-based diagnoses in children (6-11 years): development, validity, and reliability. *J Abnorm Child Psychol.* 1994;22:403-423.	Does not report outcomes listed in inclusion criteria
Valla JP, Bergeron L, Smolla N. The Dominic-R: a pictorial interview for 6- to 11-year-old children. *Journal of the American Academy of Child & Adolescent Psychiatry* 2000;39(1):85-93.	Does not focus on depression screening or treatment or harms of either

Appendix C Table C3. Studies Excluded from the Review for Key Question 2

Key Question 2: Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?	
Reference	**Reason for exclusion***
Volpe, Robert J. and DuPaul, George J. Handbook of psychoeducational assessment: Ability, achievement, and behavior in children. 357-387. 2001.	Does not focus on depression screening or treatment or harms of either
Weeks SK, Andreson MA, Harmon LS, Michaels TK. Getting inside depression and suicide ideation. One comprehensive screening approach targets patients 4 years and older. *Holistic Nursing Practice.* 2005;5-9.	Does not meet criteria for study design
White D, Leach C, Sims R, Atkinson M, Cottrell D. Validation of the Hospital Anxiety and Depression Scale for use with adolescents.[see comment]. *British Journal of Psychiatry* 1999;175:452 -4.	Conducted exclusively in high-risk populations
Wilcox H, Field T, Prodromidis M, Scafidi F. Correlations between the BDI and CES-D in a sample of adolescent mothers. *Adolescence* 1998;33(131):565-74.	Focus on identifying maternal depression
Wilhelm, Key, Kotze, Beth, Waterhouse, Merilyn, Hadzi-Pavlovic, Dusan, and Parker, Gordon. Screening for Depression in the Medically Ill: A Comparison of Self-Report Measures, Clinician Judgment, and DSM-IV Diagnoses. *Psychosomatics: Journal of Consultation Liaison Psychiatry* 20004;45(6), 461-469.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Yates P, Kramer T, Garralda E. Depressive symptoms amongst adolescent primary care attenders. Levels and associations. *Soc Psychiatry Psychiatr Epidemiol.* 2004;39:588-594.	Does not meet criteria for study design
Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. *J Psychiatr Res.* 2004;38:577-582.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Zuckerbrot RA, Jensen PS. Improving recognition of adolescent depression in primary care. *Archives of Pediatrics & Adolescent Medicine* 2006;160(7):694-704.	Used as a source document only

Appendix C Table C4. Studies Excluded from the Review for Key Question 3

Key Question 3: What are the harms of screening?	
Reference	**Reason for exclusion***
Christensen H, Griffiths KM, Korten A. Web-based cognitive behavior therapy: analysis of site usage and changes in depression and anxiety scores. *J Med Internet Res.* 2002;4:e3.	Does not focus on depression screening or treatment or harms of either
Geddes J, Butler R. Depressive disorders. *Clin Evid.* 2002;951-973.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Gould MS, Marrocco FA, Kleinman M et al. Evaluating iatrogenic risk of youth suicide screening programs: a randomized controlled trial. *JAMA* 2005;293(13):1635-43.	Does not focus on depression screening or treatment or harms of either
Hazell P. Depression in children and adolescents. *Evid Based Ment Health.* 2003;6:103-104.	Does not meet criteria for study design
Klein DN, Dougherty LR, Olino TM. Toward guidelines for evidence-based assessment of depression in children and adolescents. *J Clin Child Adolesc Psychol.* 2005;34:412-432.	Does not meet criteria for study design
Moor S, Ann M, Hester M et al. Improving the recognition of depression in adolescence: Can we teach the teachers? *J Adolesc.* 2007; 30(1):81-95.	Does not focus on depression screening or treatment or harms of either
Pignone, M. P., Gaynes, B. N., Rushton, J. L., Mulrow, C. D., Orleans, C. T., Whitener, B. L., Mills, C., and Lohr, K. N. Screening for Depression. i-D-83. 2002. Rockville, MD, Agency for Healthcare Research and Quality.	Used as source document only
Winter LB, Steer RA, Jones-Hicks L, Beck AT. Screening for major depression disorders in adolescent medical outpatients with the Beck Depression Inventory for Primary Care. *J Adolesc Health.* 1999;24:389-394.	Does not focus on depression screening or treatment or harms of either
Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. *J Psychiatr Res.* 2004;38:577-582.	Does not meet setting criteria

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Setting	Inclusion and exclusion criteria	Patient characteristics	Baseline depression score (IG/CG) Average duration of illness (months)	Intervention characteristics	Outcomes	Response (dichotomous measure)
Clarke, 1999[1] Good quality MDD or dysthymia	**Study design:** RCT (n = 123) **Location:** US, recruited at 2 sites, setting where intervention was delivered is not described **Selection method:** Recruited at 2 sites via announcements to health professionals and school counselors, television and newspaper stories, and advertisements	**Inclusion:** age 14 to 18 years, current DSM-III-R diagnosis of MDD or dysthymia **Exclusion:** 1) exhibited current mania/hypomania, panic disorder, generalized anxiety disorder, conduct disorder, psychoactive substance abuse/dependence, lifetime organic brain syndrome, mental retardation, or schizophrenia; 2) currently receiving other treatment for depression (and were unwilling to discontinue); 3) needed immediate, acute treatment	**Age:** 16.2 years (SD = 1.3) **Female:** 71% **Ethnicity:** NR **Psychiatric comorbidities:** 23.6% current anxiety disorder, 23.6% history of nonaffective disorder **Other:** 4.2% not in school, 43.8% lived in 2-parent families, 27.7% had 1 or 2 parents with graduate or postgraduate education	**Baseline:** BDI CBT: 26.5 (9.4) CBT + parent: 26.4 (8.7) Waitlist: 24.2 (10.8) HAM-D CBT: 13.0 (5.3) CBT + parent: 15.1 (6.0) Waitlist: 14.5 (5.9) **Duration of illness:** NR 87.5% had MDD, 46.9% recurrent affective disorder, n=73 had "pure" MDD, 12 had "pure" dysthymia, 11 had comorbid MDD/dysthymia	**IG1 (n=45)**: Group CBT (Adolescent Coping With Depression Course) for adolescents only; No family involvement; mixed-gender groups of 10 adolescents; 16, 2-hour sessions over 8 weeks; delivered by advanced graduate psychology or social work students or masters- or doctoral-level clinicians, plus 40 hrs of specialized training and weekly supervision meetings **IG2 (n=42)**: Group CBT same as IG1 plus 8 weekly 2-hour parent sessions (6 separate, 2 held jointly with adolescent group) over 8 weeks **CG (n=36)**: Waitlist	**Depression outcomes:** Longitudinal Interval Follow-up Evaluation (LIFE) - (requires symptom-free for 8 weeks for recovery criteria); HAM-D;GAF; BDI; CBCL **Measurement method:** Blinded interviewers **Definition of response or remission:** Recovery - no longer meeting DSM-III-R criteria for either major depression or dysthymia for 2 weeks preceding the post-treatment assessment	**Recovery rates:** IG1: 24/37 (64.9%) IG2: 22/32 (68.8%) CG: 13/27 (48.1%) (IG1 + IG2 vs CG: $p < 0.05$; Cohen's h = 0.38 (small to medium effect); OR 2.15 (95% CI 1.01, 4.59)) Trend for treated males to have better outcomes than treated females (81.0% vs 60.4%, $p = 0.096$)

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Response (continuous measure)	Other outcomes Adverse events	Funding source	Attrition	Other treatments (e.g. antidepressants; measured, not allowed, reported, etc.)	Comments	Other positive outcomes reported
Clarke, 1999[1] Good quality MDD or dysthymia	**HAM-D** pre post IG1: 13.0 (5.3) 4.6 (4.8) IG2: 15.1(6.0) 6.7 (7.1) CG: 14.5 (5.9) 7.7 (7.0) Group x time - IG1 & 2 combined vs. CG: p = ns **Self-reported measures:** BDI **Parent-reported measures:** CBCL Depression, CBCL internalizing, CBCL externalizing	**GAF** pre post IG1: 60.4 (6.8) 71.0 (11.7) IG2: 54.4 (8.2) 69.9 (14.9) CG: 58.3 (7.2) 64.5 (11.8) Group x time - IG1 & 2 combined vs. CG: p < 0.05	NIMH	**Attrition:** 22% overall 18% CBT 24% CBT + parent 25% WL	Excluded if receiving other treatment for depression and unwilling to discontinue	Participants in the two treatment groups who recovered were randomized to three different relapse prevention conditions	CBCL (parent)

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Setting	Inclusion and exclusion criteria	Patient characteristics	Baseline depression score (IG/CG) Average duration of illness (months)	Intervention characteristics	Outcomes	Response (dichotomous measure)
Kahn, 1990[2] Fair quality Depression	**Study design:** RCT (n=68) **Location:** US **Selection method:** 1 middle school	**Inclusion:** RADS ≥ 72, CDI ≥ 15 **Exclusion:** Receiving antidepressants or another treatment for depression	**Age:** 10-14 years **Female**: 51% **Ethnicity:** NR **Psychiatric comorbidities:** NR	**Baseline:** BID Group CBT: 44.65 (15.56) Relaxation: 38.06 (15.26) Self-modeling: 52.82 (18.45) Waitlist: 42.82 (13.60) **Duration of illness:** NR	**IG1 (n=17):** Group CBT; no family involvement; 12, 50-minute sessions over 6- to 8-week period **IG2 (n=17):** Group relaxation; no family involvement; 12, 50-minute sessions over 6- to 8-week period **IG3 (n=17):** Individual self-modeling; no family involvement; 12 sessions over 6-to 8-week period **CG (n=17):** Waitlist	**Depression outcomes:** RADS, CDI, BID (Bellevue Index of Depression, structured interview) **Measurement method:** Questionnaires and interview at screening, re-evaluation (not reported here), post-treatment, 1-month post-treatment **Definition of response or remission**: RADS and CDI scores for response, remission not assessed **Other outcomes**: In dysfunctional range based on RADS, CDI, BID, cutoff used NR	(none)

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Response (continuous measure)	Other outcomes Adverse events	Funding source	Attrition	Other treatments (e.g. antidepressants; measured, not allowed, reported, etc.)	Comments	Other positive outcomes reported
Kahn, 1990[2] Fair quality Depression	**RADS** pre post 1-mo IG1: 87.0 (9.0) 53.4 (14.7) 54.2 (16.8) IG2: 83.4 (8.0) 61.8 (14.9) 61.6 (17.3) IG3: 81.7 (10.7) 62.1 (12.0) 64.2 (15.9) CG: 85.4 (11.0) 80.1 (13.4) 74.7 (16.6) F(3,64)=7.87, p<0.001 (pre-post tx*time effect) **CDI** pre post 1-mo IG1: 31.1 (9.6) 7.3 (typo) 9.1 (9.9) IG2: 26.9 (10.8) 12.9 (10.7) 13.9 (13.4) IG3: 27.2 (7.8) 13.6 (7.4) 14.6 (9.2) CG: 28.1 (9.8) 26.9 (15.4) 22.5 (15.5) F(3,64)=6.86, p<0.001 (pre-post tx*time effect) **BID** pre post IG1: 44.7 (15.6) 15.7 (10.0) IG2: 38.1 (15.3) 19.2 (20.4) IG3: 52.8 (18.5) 17.6 (14.7) CG: 42.8 (13.6) 29.7 (16.7) F(3,64)=6.51, p<0.001 (pre-post tx*time effect)	Change from dysfunctional to functional range **Pre-treatment to post-treatment** RADS IG1: 15/17 (88%) IG2: 11/17 (65%) IG3: 12/17 (70%) CG: 2/17 (12%) CDI IG1: 15/17 (88%) IG2: 13/17 (76%) IG3: 10/17 (59%) CG: 2/17 (12%) BID IG1: 13/17 (76%) IG2: 11/17 (65%) IG3: 10/17 (59%) CG: 3/17 (18%) **Pre-treatment to 1-mo followup** RADS IG1: 15/17 (88%) IG2: 11/17 (65%) IG3: 8/17 (50%) CG: 3/16 (19%) CDI IG1: 13/17 (76%) IG2: 11/17 (65%) IG3: 7/17 (44%) CG: 3/16 (19%)	NR	**Attrition:** 0%	Excluded if receiving outpatient psychological/ psychiatric services		Piers Harris Children's Self-Concept Scale

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Setting	Inclusion and exclusion criteria	Patient characteristics	Baseline depression score (IG/CG) Average duration of illness (months)	Intervention characteristics	Outcomes	Response (dichotomous measure)
Lewinsohn, 1990[3] Fair quality MDD, minor or intermittent depression	**Study design:** RCT (n=69) **Location:** US **Selection method:** Recruited via letters and announcements to health professionals, school counselors, and the media	**Inclusion:** DSM-III diagnosis of MDD or RDS diagnosis of current episode of minor or intermittent depressive disorder; age 14-18, grades 9-12 **Exclusion:** DSM-III or RDC diagnosis of current episode or bipolar disorder with mania, bipolar disorder with hypomania, panic disorder, generalized anxiety disorder, alcoholism, conduct disorder or drug use disorder, major depressive/psychotic subtype, organic brain syndrome or mental retardation, history of schizophrenia, need for immediate treatment and/or actively suicidal and/or need for hospitalization	**Age:** 14-18 years **Female:** 61% **Ethnicity:** NR **Psychiatric comorbidities:** NR, but excluded bipolar, panic disorder, GAD, CD, substance abuse 49% MDD; 7% RDC diagnosis of minor depression; 44% RDC diagnosis of intermittent depression 40% history of suicide attempt; 30% had previous psychological or psychiatric treatment	**Baseline:** BDI Group CBT: 21.67 (11.34) Group CBT + parent: 21.26 (11.35) Waitlist: 23.84 (11.43) CES-D Group CBT: 13.29 (5.21) Group CBT + parent: 12.84 (6.65) Waitlist: 14.89 (4.30) **Duration of illness:** NR	**IG1 (n=21):** Group CBT; no family involvement; 14, 2-hour sessions, twice a week for 7 weeks **IG2 (n=19):** Group CBT plus separate parent sessions; 14, 2-hour sessions, twice a week for 7 weeks for the child; the parent received 7, 2-hour sessions meeting once per week; parents seen separately **CG (n=19):** Waitlist	**Depression outcomes:** CES-D, BDI, CBCL-Depression **Measurement method:** Interview at intake, post-treatment, 1, 6, 12, and 24 months post-treatment **Definition of response or remission:** CES-D, BDI, and CBCL scores for response, remission per K-SADS interview for major, minor, or intermittent depression	**Post-treatment depressive diagnosis:** IG1: 57.1% IG2: 52.4% CG: 94.7% Chi-sq=9.41, p<0.01

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Response (continuous measure)	Other outcomes Adverse events	Funding source	Attrition	Other treatments (e.g. antidepressants; measured, not allowed, reported, etc.)	Comments	Other positive outcomes reported
Lewinsohn, 1990[3] Fair quality MDD, minor or intermittent depression	**CES-D** Pre Post IG1: 13.3 (5.2) 7.2 (4.9) IG2: 12.8 (6.7) 5.7 (4.8) CG: 14.9 (4.3) 12.9 (4.7) F(1,38)=4.85, p<0.001 Followup (ns): IG1 IG2 1-mo 6.8 (5.3) 5.5 (4.0) 6-mo 6.3 (4.5) 5.4 (3.8) 12-mo 6.5 (5.7) 6.1 (3.7) 24-mo 7.1 (6.8) 5.6 (3.9) **BDI** Pre Post IG1: 21.7 (11.3) 10.0 (11.9) IG2: 21.3 (11.4) 6.5 (8.5) CG: 23.8 (11.4) 20.5 (10.3) F(1,38)=4.27, p<0.001 Followup (ns): IG1 IG2 1-mo 10.0 (11.2) 6.7 (7.9) 6-mo 8.2 (12.5) 6.5 (11.7) 12-mo 6.0 (7.1) 4.4 (4.5) 24-mo 8.4 (12.5) 5.5 (6.4) **CBCL-D** Pre Post IG1: 13.7 (4.0) 9.0 (5.4) IG2: 13.1 (4.9) 3.5 (2.7) CG: 12.8 (5.5) 8.3 (4.2) F(1,38)=4.08, p<0.001 Followup (p<0.01): IG1 IG2 1-mo 6.2 (6.0) 3.3 (2.7) 6-mo 7.5 (6.1) 6.5 (4.4) 12-mo 5.2 (3.7) 6.2 (4.3) 24-mo 6.3 (7.4) 5.9 (5.2)	(none)	NIMH	**Attrition:** 14% overall 13% Group CBT 10% Group CBT + Parent 21% Waitlist	All participants had to discontinue whatever treatment they might have been in	Higher attrition in waitlist group	Issues Checklist (child and parent), Child Behavior Checklist (parent)

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Setting	Inclusion and exclusion criteria	Patient characteristics	Baseline depression score (IG/CG) Average duration of illness (months)	Intervention characteristics	Outcomes	Response (dichotomous measure)
Stark, 1987[4] Fair quality Moderate to severe depression	**Study design:** RCT (n=29) **Location:** US **Selection method:** 1 elementary school	**Inclusion:** CDI > 16 at first assessment and CDI ≥ 13 at second assessment **Exclusion:** NR	**Age:** 9-12 years **Female:** 43% **Ethnicity:** NR **Psychiatric comorbidities:** NR	**Baseline:** CDRS-R Group S-C: 37.22 (8.36) Group BPS: 33.50 (10.27) Waitlist: 30.33 (6.28) CDI Group S-C: 21.60 (5.48) Group BPS: 22.40 (8.47) Waitlist: 20.11 (9.88) **Duration of illness**: NR	**IG1 (n=9):** Group Self-Control Therapy; no family involvement; 12, 45- to 50-minute sessions during a 5-week period **IG2 (n=10):** Group Behavioral Problem-Solving Therapy; no family involvement; 12, 45- to 50-minute sessions during a 5-week period **CG (n=9):** Waitlist	**Depression outcomes:** CDI, CDRS-R, CDS, CBCL-Depression **Measurement method:** Blind assessment by interview and self-report questionnaire packet at intake, pre-treatment, post-treatment, 8-week post-treatment **Definition of response or remission:** CDI, CDRS, CDS, and CBCL scores for response, CDI<13 for remission	**Recovery rates based on CDI post-treatment:** IG1: 7/9 (78%) IG2: 6/10 (60%) CG: 1/9 (11%) **8 weeks post-treatment:** IG1: 88% IG2: 67% CG: NR

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Response (continuous measure)	Other outcomes Adverse events	Funding source	Attrition	Other treatments (e.g. antidepressants; measured, not allowed, reported, etc.)	Comments	Other positive outcomes reported
Stark, 1987[4] Fair quality Moderate to severe depression	**CDI** Screen Pre-tx Post-tx 8-week IG1: 22.4 (5.7) 21.6 (5.5) 8.0 (6.7) 5.4 (5.0) IG2: 25.0 (4.8) 22.4 (8.5) 9.0 (8.3) 7.3 (7.2) CG: 22.6 (6.0) 20.1 (9.9) 18.6 (9.9) (none) post-treatment ANCOVA F(2,27)=6.37, p=0.01 8-week ANCOVA F(1,18)=0.48, ns **CDS** Pre-tx Post-tx 8-week IG1: 72.4 (10.3) 50.1 (8.7) 46.5 (8.3) IG2: 71.1 (10.4) 55.1 (12.2) 50.0 (13.2) CG: 67.6 (17.8) 61.1 (16.7) (none) post-treatment ANCOVA F(2,27)=2.91, p=0.07 8-week ANCOVA F(1,18)=0.42, ns **CDRS-R** Pre-tx Post-tx 8-week IG1: 37.2 (8.4) 22.9 (4.4) 20.7 (3.5) IG2: 33.5 (10.3) 24.2 (6.0) 24.3 (4.7) CG: 30.3 (6.3) 28.2 (6.2) (none) post-treatment ANCOVA F(2,27)=2.41, p=.11 8-week ANCOVA F(1,18)=6.36, p=0.02 **CBCL-Dep** Pre-tx Post-tx 8-week IG1: 69.4 (6.8) 66.9 (9.7) 66.2 (4.3) IG2: 72.3 (10.0) 63.4 (10.0) 60.4 (9.3) CG: 64.0 (11.3) 67.6 (11.2) (none) post-treatment ANCOVA F(2,21)=0.50, ns 8-week ANCOVA F(1,12)=1.44, ns	(none)	NR	**Attrition:** 3% overall (The 1 subject who withdrew was in one of the two intervention groups)	NR, but 2 of the waitlist subjects referred to school psychologist by their teachers for behavior related to depression and met with him on a weekly basis		CSEI (self-esteem), RCMAS (anxiety), Treatment-generated expectancies and credibility, CBCL (parent)

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Setting	Inclusion and exclusion criteria	Patient characteristics	Baseline depression score (IG/CG) Average duration of illness (months)	Intervention characteristics	Outcomes	Response (dichotomous measure)
Rosello, 1999[5] - indiv. CBT Fair quality MDD or dysthymia	**Study design:** RCT (n=71) **Location:** Puerto Rico **Selection method:** Referred to clinic by local schools	**Exclusion:** Serious suicide risk, psychotic features, bipolar disorders, alcoholism, conduct disorder, drug use disorder, organic brain disease, hyperaggression, need for acute care, receiving other treatment for depression	**Age:** 13-17 years **Female:** 54% **Ethnicity:** 100% Latino **Psychiatric comorbidities:** NR, but excluded bipolar, CD, substance abuse	**Baseline:** CDI IPT: 21.21 (7.53) CBT: 20.12 (6.95) Waitlist: 20.13 (5.99) **Duration of illness:** NR	**IG1 (n=19):** Individual IPT; no family involvement; 12, 1-hour weekly sessions **IG2 (n=21):** Individual CBT; no family involvement; 12, 1-hour weekly sessions **CG (n=18):** Waitlist	**Depression outcomes:** CDI **Measurement method:** Assessment by interview at intake, post-treatment, 3-month followup **Definition of response or remission**: CDI score for response, none for remission **Other outcomes**: Effect size based on CDI, % severely depressed per CDI >=19	(none)
Mufson, 1999[6] Fair quality MDD	**Study design:** RCT (n = 48) **Location:** US **Selection method:** Recruited from two specialty mental health clinics; most patients were self-referred or referred by parents or mental health professionals in school-based mental health clinics	**Inclusion:** MDD by DSM-III-R and HRSD ≥ 15 **Exclusion:** HRSD <15, suicidal, were receiving other treatment for MDD, chronic medical illness, psychosis, bipolar I or II, conduct disorder, substance abuse disorder, current eating disorder, OCD	**Age:** 12-18 years **Female:** 73% **Ethnicity:** 71% Hispanic **Psychiatric comorbidities:** Dysthymic disorder: 29% IPT, 13% CG Any anxiety disorder: 88% IPT, 88% CG	**Baseline:** BDI IPT: 18.8 (8.5) Clinical monitoring: 22.8 (10.6) HRSD IPT: 19.2 (7.5) Clinical monitoring: 18.7 (8.6) **Duration of illness:** NR	**IG (n=24):** Individual IPT; no family involvement; weekly sessions for 12 weeks, with weekly additional telephone contact in first 4 weeks **CG (n=24):** Clinical monitoring; monthly, 30-minute sessions to discuss symptoms and functioning (no advice giving or skills training)	**Depression outcomes:** HRSD, BDI, CGI-S **Measurement method:** Assessed by blinded clinician at weeks 0, 2, 4, 6, 8, 10, and 12 **Definition of response or remission:** Recovery defined as HRSD < 6 or BDI ≤ 9; CGI-S if "very much, much, or minimally improved" **Other outcomes:** Suicidality assessed by K-SADS-E depression section and suicide section	**Recovery rate based on HRSD:** IG: 75% CG: 46% p = 0.04 **Recovery based on CGI-S:** Recovered: IG 20/21 (95.5%) CG: 7/11 (61.5%) p <0.001

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Response (continuous measure)	Other outcomes Adverse events	Funding source	Attrition	Other treatments (e.g. antidepressants; measured, not allowed, reported, etc.)	Comments	Other positive outcomes reported
Rosello, 1999[5] - indiv. CBT Fair quality MDD or dysthymia	**CDI** pre post 3-month IG1: 21.2 (7.5) 10.8 (6.5) 13.8 (9.5) IG2: 20.1 (7.0) 13.3 (7.6) 8.9 (6.8) CG: 20.1 (6.0) 15.8 (6.8) (none) pre-post change differences, IG1 vs CG, F (1,33)=11.62, p<0.002 pre-post change differences, IG2 vs CG, F (1,37)=2.58, p<0.015	Effect size for IG1: 0.73 Effect size for IG2: 0.43 Severely depressed at post-tx: IG1: 11% IG2: 24% CG: 34%	NIMH and University of Puerto Rico	**Attrition:** 18% overall IPT 17% CBT 16% Waitlist 22%	Excluded if currently receiving psychotropic medication or psychotherapy		Piers-Harris Children's Self-Concept Scale, Social Adjustment Scale for Children and Adolescents, Family Emotional Involvement and Criticism Scale, CBCL
Mufson, 1999[6] Fair quality MDD	**HRSD** pre post IG: 19.2 (7.5) 6.3 (7.7) CG: 18.7 (8.6) 11.8 (8.9) p =0.02 **BDI** pre post IG: 18.8 (8.5) 5.9 (8.1) CG: 22.8 (10.6) 12.9 (12.6) p = 0.05 **CGI-S (week 12)** IG: 2.4 (1.6) CG: 4.2 (1.1) p < 0.001 (Note: there were no significant differences at baseline)	C-GAS: no differences between groups at week 12 **Adverse events (reasons for patient removal from study):** CG: 4 patients removed for suicidality, 4 for noncompliance, 1 for school refusal, 1 for psychotic features IG: 2 for suicidality No significant differences between groups on any measure of suicide plan or attempt at week 12 on the K-SADS	NIMH	**Attrition:** 33% overall 12% IG 54% CG	Excluded patients in another treatment for the same condition	Highly differential attrition	CGAS (global functioning), SAS-SR (social functioning), Social Problem-Solving Inventory

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Setting	Inclusion and exclusion criteria	Patient characteristics	Baseline depression score (IG/CG) Average duration of illness (months)	Intervention characteristics	Outcomes	Response (dichotomous measure)
Mufson, 2004[7] Good quality MDD, dysthymia, adjustment disorder with depressed mood, or depression NOS	**Study design:** RCT (n = 64); randomized at clinician and student levels **Location:** US; Urban impoverished areas of NYC **Selection method:** Five school-based health clinics (3 middle schools, 2 high schools) Patients who were referred to school mental health clinics were screened for eligibility	**Inclusion:** Referred to school health clinic for mental health intake; HAM-D ≥ 10 and C-GAS score ≤ 65 at intake and again at study baseline; DSM-IV diagnosis of MDD, dysthymia, adjustment disorder with depressed mood, or depressive disorder NOS **Exclusion:** Actively suicidal or mentally retarded; life-threatening medical illness; current diagnosis of substance abuse disorder, psychosis, or schizophrenia; currently in treatment for depression or currently taking antidepressant medication English-speaking patients accepted at all schools; monolingual Spanish-speaking patients accepted at 2 schools	**Age:** 12-18 years, mean 15.1 (1.9) **Female**: 84% **Ethnicity:** 71% Hispanic **Psychiatric comorbidities:** (possible/ probable per baseline clinical interview) Anxiety disorder: 20 (32%) ODD: 5 (8%) Substance use: 10 (16%) ADHD: 4 (6%) **Other:** % living in single parent home 79.3% IG, 75.0% CG; public assistance: 34.4% IG, 37.9% CG; years of parental education mother 10.54 (3.5) IG, 11.34(3.6) CG; father 11.22 (3.2) IG, 11.24 (3.7) CG	**Baseline:** BDI IG 20.8 (8.7) CG 21.8 (8.5) HAM-D IG 18.9 (5.9) CG 18.3 (5.0) **Duration of illness:** NR MDD 52.9% IG, 48.3% CG DD 14.7% IG, 20.7% CG Double depression 5.9% IG, 6.9% CG Depressive disorder NOS 11.8% IG, 10.3% CG Adjustment disorder 14.8% IG, 13.8% CG Previous mental health treatment: 26.5% IG, 31.0% CG Previous treatment for mood/anxiety/ depression 17.7% IG, 13.79% CG	**IG (n=34):** Individual Interpersonal Therapy for Adolescents (IPT-A); no family involvement; 8 consecutive, 35-minute weekly sessions followed by 4 sessions scheduled at any frequency during next 8 weeks (16 weeks in total); delivered by school clinicians (social workers and doctoral-level clinical psychologists) trained in IPT-A by manual, 2 half days didactic training, weekly supervision **CG (n=29):** Treatment as usual; whatever psychological treatment they would have received in the school-based clinic if the study has not been in place; most received individual psychotherapy, 8 received family therapy, and 5 participated in group therapy	**Depression outcomes:** Hamilton Depression Rating Scale, Beck Depression Inventory, Children's Global Assessment Scale, Clinical Global Impressions Scale **Measurement method:** Assessments performed by psychologist or social worker masked to treatment condition and not shared with treating clinicians; baseline, weeks 4,8,12, 16, or early termination from protocol **Definition of response or remission:** Recovery criteria HAMD ≤ 6 or BDI ≤ 9	**Recovery rates based on HAM-D:** IG: 17/34 (50%) CG: 10/29 (34%) **Recovery rate based on BDI:** IG: 25/34 (74%) CG: 15/29 (52%) p = 0.048

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Response (continuous measure)	Other outcomes Adverse events	Funding source	Attrition	Other treatments (e.g. antidepressants; measured, not allowed, reported, etc.)	Comments	Other positive outcomes reported
Mufson, 2004[7] Good quality MDD, dysthymia, adjustment disorder with depressed mood, or depression NOS	**HAM-D** pre post (week 12) IG 18.9 (5.9) 8.7 (8.0) CG: 18.3 (5.0) 12.8 (8.4) p = 0.04; ES 0.50 Differences between groups emerged at week 8 with 4.1 point difference (p=0.003); Random regression analysis to estimate slope indicated IG recovered at a significantly faster rate than the CG **BDI** pre post (wk 12) IG: 20.8 (8.7) 8.4 (11.0) CG: 21.8 (8.5) 12.3 (9.7) p = ns; ES = 0.37 Differences between groups emerged at week 8 with 5.42 point difference (p=0.001)	**General Functioning:** **CGAS** pre post (wk 12) IG: 52.6 (5.3) 66.7 (13.0) CG: 52.7 (6.3) 59.5 (13.5) p = 0.04; ES 0.54 **CGI-S** pre post (wk 12) IG: 3.9 (0.8) 2.4 (1.3) CG 3.8 (0.7) 3.0 (1.4) p=0.03; ES 0.48 **Adverse events:** 1 adolescent in IG referred to ED for suicidality and hospitalized one week; 1 adolescent in CG referred to ED, hospitalized overnight, and withdrawn from study	SAMHSA and NIMH	**Attrition:** 11% overall 13% IG 10% CG	Excluded if currently in treatment for depression, but remained in study if needed to receive antidepressants during study	IPT-A group had more females (91% vs 76%) and higher proportion with current SI or past suicide attempt, although differences are not statistically significant	SAS-SR (social functioning)

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Setting	Inclusion and exclusion criteria	Patient characteristics	Baseline depression score (IG/CG) Average duration of illness (months)	Intervention characteristics	Outcomes	Response (dichotomous measure)
Diamond, 2002[8] Good quality MDD	**Study design:** RCT (n = 32) **Location:** US **Selection method:** Referred by schools or parents	**Inclusion:** DSM-III-R primary diagnosis of MDD, age 13 - 17 years, primary caretaker willing to participate **Exclusion:** Initial BDI < 16, report other problems as primary, receiving antidepressant medication or psychotherapy, > 13 days of substance use in previous 90 days, needed higher level care, having psychotic features, plus other exclusion criteria not described	**Age:** 14.9 (SD = 1.5) **Female**: 78% female **Ethnicity:** 69% African American, 31% White **Psychiatric comorbidities:** NR, and only substance abuse excluded; parents report 47% above clinical cutoff for delinquency and 30% for aggressiveness, 42% parental depression, 47% parental anxiety, 37% parental hostility **Other:** 80% from single parent families; 69% < $30,000 annual income, 34% < 20,000 annual income; 47% heard random gunshots in 6 months prior; 31% had family members using drugs or alcohol, 19% had unwanted sexual experiences	**Baseline:** BDI IG: 23.8 (7.4) CG: 28.0 (7.1) HAM-D IG: 20.1 (5.6) CG: 17.1 (7.0) **Duration of illness:** NR	**IG (n=16):** Attachment-based Family Therapy; (treatment can include all family and extrafamilial members (e.g., teachers), but the therapist flexibly determines the composition of each session based on the evolving treatment plan; 12 weekly, 60- to 90-minute sessions, plus weekly calls as needed; delivered by doctoral- and masters-level therapists, most experienced in family therapy, received training (amount unspecified) and weekly supervision **CG (n=16):** 6-week waitlist; received weekly 15-minute calls restricted to monitoring for potential clinical deterioration with BDI	**Depression outcomes:** HAM-D, BDI **Measurement method:** Blinded interviewers; assessments by trained masters- or doctoral-level diagnosticians; diagnoses determined in weekly consensus meeting with senior diagnostician **Definition of response or remission:** Clinical significance determined by percentage of adolescents with BDI scores in a non-clinical range (≤ 9)	**No longer meet criteria for MDD at post-treatment/post waitlist:** IG: 13/16 (81%) CG: 7/15 (47%) p = 0.04 **Clinical significant reduction in symptoms post intervention/post-waitlist:** IG: 62% CG: 19% p = 0.01 **6-week outcomes: Clinically significant reduction in symptoms** IG: 56% CG: 19% p = 0.03

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Response (continuous measure)	Other outcomes Adverse events	Funding source	Attrition	Other treatments (e.g. antidepressants; measured, not allowed, reported, etc.)	Comments	Other positive outcomes reported
Diamond, 2002[8] Good quality MDD	**HAM-D** pre 6wk post-int IG: 20.1 (5.6) - 10.3 (8.7) CG: 17.1 (7.0) 15.3 (6.7) N/A condition-by-time comparison of IG at post-intervention vs. CG at 6 wks (post-wait list period): p = 0.005; effect size = 1.21 **BDI** pre 6wk post-int IG: 23.8 (7.4) 11.1 (8.8) 10.4 (9.8) CG: 28.0 (7.1) 18.5 (11.1) N/A condition-by-time comparison of IG at post-intervention vs. CG at 6 wks (post-wait list period): ns	**Additional condition-by-time comparisons of IG at post-intervention vs. CG at 6 wks/post waitlist:** Reduction in anxiety symptoms (STAIC) p=0.007; ES 1.24 **Child-reported level of family conflict (SRFF-Conflict subscale)** p=0.03; ES =1.21 **Suicidal ideation** p=0.09; ES = 0.52 **Reduction in hopelessness** p=0.08; ES 0.78	NARSD, American Suicide Foundation, NIMH	**Attrition:** 0%	Excluded if receiving antidepressants or psychotherapy	Low SES population, majority are African American; data on comorbid conditions not available because had to keep assessment short to engage population Screened patients with BDI twice, one week apart, before inviting for full evaluation, KSADS-P interview	Self-Report of Family Functioning, Inventory of Parent and Peer Attachment, Beck Hopelessness Scale, STAIC (anxiety), Suicidal Ideation Questionnaire, Youth Self-Report

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Setting	Inclusion and exclusion criteria	Patient characteristics	Baseline depression score (IG/CG) Average duration of illness (months)	Intervention characteristics	Outcomes	Response (dichotomous measure)
Ackerson, 1998[9] Fair quality Mild and moderate depressive symptomatology	**Study design:** RCT (n=30) **Location:** US **Selection method:** Recruited through mental health and social services agencies, schools, hospitals, and media announcements	**Exclusions:** CDI score <10, HDRS score <10, not living at home with a parent willing to participate in the assessment phases of the study, reading level <6th grade equivalence, psychotic or suicide symptoms, participation in psychotherapy	**Age**: 14-18 years **Female:** 64% **Ethnicity:** 36% Nonwhite **Psychiatric comorbidities**: NR, and none excluded	**Baseline:** CDI Bibliotherapy: 19.2 (7.1) Waitlist: 16.8 (4.5) HRSD Bibliotherapy: 19.9 (5.5) Waitlist: 21.0 (5.0)	**Cognitive bibliotherapy (n=12):** No family involvement; 4 weeks to read Feeling Good book and complete exercises in workbook; weekly telephone calls to collect number of pages read and number of exercises completed in workbook (no counseling provided during calls) **CG (n=10):** Waitlist; telephoned weekly during waiting period, but content of calls NR	**Depression outcomes:** HRSD, CDI, CBCL-depression scale **Measurement method:** Interview, blinding of interviewers NR; assessments for treatment group: baseline, post-treatment, 1-month post-tx.; assessments for waitlist group: baseline, 1 mo later (before tx initiation), post-treatment **Definition of response or remission:** None **Other outcomes:** Clinical significance of change, per HRSD <10, CDI <10, CBCL-D T-score <60 + change on standardized version of each measure of 1.96 or more	(none)

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Response (continuous measure)	Other outcomes Adverse events	Funding source	Attrition	Other treatments (e.g. antidepressants; measured, not allowed, reported, etc.)	Comments	Other positive outcomes reported
Ackerson, 1998[9] Fair quality Mild and moderate depressive symptomatology	**HRSD** Time 1 Time 2 Time 3 IG: 19.9 (5.5) 8.8 (5.3) 6.8 (4.9) CG: 21.0 (5.0) 20.5 (3.4) 9.2 (2.4) F (1,20)=37.78, p<0.05 **CDI** Time 1 Time 2 Time 3 IG: 19.2 (7.1) 9.4 (6.7) 6.8 (5.0) CG: 16.8 (4.5) 15.8 (5.2) 7.7 (3.5) F(1,20)=24.40, p<0.05 **CBCL-D** Time 1 Time 2 Time 3 IG: 71.9 (9.5) 64.8 (10.1) 60.8 (6.7) CG: 70.9 (9.1) 69.5 (11.1) 61.7 (7.5) F(1,20)=4.98, p<0.05	**Clinically significant change (among completers):** 59% per HDRS 64% per CDI 14% per CBCL-D **Adverse Events:** NR	NR	**Attrition:** 27% overall 20% IG 33% CG	Excluded if participating in psychotherapy, and no participants were receiving antidepressants, although 1 received methylphenidate for ADD		CBCL (parent), Automatic Thoughts Questionnaire, Dysfunctional Attitudes Questionnaire

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Setting	Inclusion and exclusion criteria	Patient characteristics	Baseline depression score (IG/CG) Average duration of illness (months)	Intervention characteristics	Outcomes	Response (dichotomous measure)
TADS, 2004[10-15] - CBT only Good quality MDD	**Study design:** RCT (n = 223 in CBT and placebo control groups) **Location:** US; 13 academic and community clinics **Selection method:** Recruited from clinics, advertise-ments, primary care and mental health clinicians; schools and juvenile justice facilities	**Exclusion:** Aged <12 or >17 years, unable to receive care as outpatient, didn't meet DSM-IV criteria for MDD at consent/baseline, CDRS-R <45 at baseline, IQ <80, prior treatment with AD, depressive mood had to have been present in at least 2 of 3 contexts (home, school, among peers), current or past diagnosis of bipolar disorder, severe conduct disorder, current substance abuse or dependence, pervasive developmental disorder(s), 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, and/or pregnancy or refusal to use birth control No patients were asked or required to discontinue other forms of psychiatric treatment to enter the study; excluded for dangerousness to self or others if they had been hospitalized for dangerousness within 3 months of consent or were deemed by a cross-site panel to be high risk because of a suicide attempt requiring medical attention within 6 months, clear intent or an active plan to commit suicide, or suicidal ideation with a disorganized family unable to guarantee safety monitoring	**Age:** 12-17 years **Female:** 54% **Ethnicity**: 26% Nonwhite **Psychiatric comorbidities:** Any psychiatric comorbidity: 58% CBT, 51% Placebo Anxiety: 32% CBT, 25% Placebo Disruptive behavior: 24% CBT, 25% Placebo OCD: 2% CBT, 4% Placebo ADHD: 13% CBT, 17% Placebo	**Baseline:** CDRS-R CBT 59.6 (9.2) Placebo 61.1 (10.5) **Average duration of illness (median, weeks):** CBT: 52.0 Placebo: 35.5	**IG (n=111):** Individual CBT; 15, 50- to 60-minute sessions over 12 weeks; includes 2 parent-only sessions and 1-3 combined parent-adolescent sessions depending on need **CG (n=112):** Placebo pill; adjusted starting dose 10 mg/d to 40 mg/d, with clinical management (6 physician visits lasting 20-30 minutes to monitor clinical status and medication effects and offer general encouragement about the effectiveness of pharmacotherapy	**Depression outcomes:** CDRS-R score, dichotomized CGI-I score; RADS: Suicidal Ideation Questionnaire-Junior High School Version **Measurement method:** Clinician-rated measures were assessed by a blinded assessor at baseline, week 6, week 12 **Definition of response or remission:** Response defined as CGI-I score 1 or 2 **Other outcomes:** Integrated procedures for adverse event monitoring	**Response rate:** IG: 43.2% (95% CI 34, 52) CG: 34.8% (95% CI 26, 44) p = 0.20

Appendix C Table C5. Evidence Table of Randomized Controlled Trials for Efficacy and Adverse Effects of Psychotherapy in Treating Depression in Children and Adolescents

Study reference USPSTF quality Target depressive disorder	Response (continuous measure)	Other outcomes Adverse events	Attrition	Funding source	Other treatments (e.g. antidepressants; measured, not allowed, reported, etc.)	Comments	Other positive outcomes reported
TADS, 2004[10] - CBT only Good quality MDD	**CDRS** pre wk 6 wk12 IG: 59.6 (4.5) 44.6 (8.3) 42.1 (9.2) CG: 61.2 (4.3) 44.9 (7.3) 41.8 (8.0) p=0.40 **RADS** pre wk 6 wk12 IG: 78.7 (10.6) 69.1 (13.6) 68.0 (14.2) CG: 81.3 (9.2) 69.4 (10.9) 66.7 (11.4) p=0.21	**Suicidal Ideation Questionnaire** pre wk 6 wk12 IG: 21.9 (16.3) 13.2 (11.3) 11.4 (10.4) CG: 24.2 (16.5) 16.9 (11.7) 15.0 (11.1) p=0.76 **Harm- and suicide-related adverse events:** CBT vs. Placebo Harm-related: OR 0.83 (95% CI 0.25, 2.81) Suicide-related: OR 1.27 (0.33, 4.87) **Psychiatric adverse events:** (Table 4) 1 panic attack occurred in the CBT group compared to 11 events in the placebo group	**Attrition:** 18% overall 14% Flu+ CBT 17% Flu 22% CBT 21% CG	NIMH	Excluded concurrent treatment with psychotropic medication or psychotherapy outside study		CGI

USPSTF-United States Preventive Services Task Force; IG-intervention group; CG-control group; MDD-major depressive disorder; RCT-randomized controlled trial; US-United States; DSM-III-R-Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised; NR-not reported, BDI-Beck Depression Inventory; HAM-D-Hamilton Rating Scale for Depression; CBT-cognitive-behavioral therapy; GAF-Global Assessment of Function; OR-odds ratio; CI-confidence interval; vs-versus; CBCL-Child Behavior Checklist; RADS-Reynolds Adolescent Depression Scale; BID-Bellevue Index of Depression; tx-treatment; HRSD-Hamilton Rating Scale for Depression; OCD-obsessive-compulsive disorder; IPT-interpersonal therapy; CGI-S-Clinical Global Assessment-Severity of Illness scale; K-SADS- Kiddie-Schedule for Affective Disorders and Schizophrenia; SAS-SR-Social Adjustment Scale-Self-Report; NIMH-National Institute of Mental Health; IPT-A-interpersonal therapy for adolescents; ES-effect size; SAMHSA-Substance Abuse and Mental Health Services Administration; K-SADS-P- Kiddie-Schedule for Affective Disorders and Schizophrenia-Present Version; NARSD- National Alliance for Research on Schizophrenia and Depression; SES-socioeconomic status

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15. Vitiello B, Rohde P, Silva S et al. Functioning and quality of life in the Treatment for Adolescents with Depression Study (TADS). *SO: Journal of the American Academy of Child and Adolescent Psychiatry.* 2006;45:1419-1426.

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Ambrosini PJ, Wagner KD, Biederman J et al. Multicenter open-label sertraline study in adolescent outpatients with major depression. *Journal of the American Academy of Child & Adolescent Psychiatry* 1999;38(5):566-72.	Does not meet criteria for study design
Ames D. Depression and the elderly. In: Dawson A, Tylee A, eds. *Depression: Social and economic timebomb: strategies for quality care: proceedings of an international meeting*. xv ed. London: BMJ; 2001:49-54.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Antidepressants for children and adolescents: an update. *Harv Ment Health Lett.* 2006;22:4-5.	Does not meet criteria for study design
Antidepressants for young people. *Can Fam Physician.* 2004;50:1648.	Does not meet criteria for study design
Apter, Alan, Kronenberg, Sefi, and Brent, David. Turning darkness into light: A new landmark study on the treatment of adolescent depression. Comments on the TADS study. *European Child & Adolescent Psychiatry* 2005;14(3), 113-116.	Does not meet criteria for study design
Asarnow JR, Jaycox LH, Duan N et al. Effectiveness of a quality improvement intervention for adolescent depression in primary care clinics: a randomized controlled trial. *JAMA.* 2005;293:311-319.	Relevance (QI or collaborative care intervention)
Asarnow, Joan Rosenbaum, Scott, Cynthia V., and Mintz, Jim. A combined cognitive-behavioral family education intervention for depression in children: A treatment development study. *Cognitive Therapy and Research* 2002;26(2), 221-229.	Does not meet quality criteria: lack of usable data, important aspects of study design not reported (e.g., adherence, attrition), no comparison of groups at baseline
Barbe, Remy P., Bridge, Jeffrey A., Birmaher, Boris, Kolko, David J., and Brent, David A. Lifetime History of Sexual Abuse, Clinical Presentation, and Outcome in a Clinical Trial for Adolescent Depression. (References). *Journal of Clinical Psychiatry* 2004;65(1), 77-83.	Conducted exclusively in high-risk populations
Barnhart WJ, Makela EH, Latocha MJ. SSRI-induced apathy syndrome: a clinical review. *Journal of Psychiatric Practice.* 2004;10:196-199.	Does not meet criteria for study design
Barrera, Maur, Chung, Joanna Y. Y., Greenberg, Mark, and Fleming, Carly. Preliminary investigation of a group intervention for siblings of pediatric cancer patients. *Children's Health Care* 2002;31(2), 131-142.	Conducted exclusively in high-risk populations
Baumgartner JL, Emslie GJ, Crismon ML. Citalopram in children and adolescents with depression or anxiety. *Annals of Pharmacotherapy* 2002;36(11):1692 -7.	Does not meet criteria for study design
Bezchlibnyk-Butler K, Aleksic I, Kennedy SH. Citalopram--a review of pharmacological and clinical effects. *J Psychiatry Neurosci.* 2000;25:241-254.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Birmaher B, Brent D. Should we use antidepressants for the treatment of major depressive disorder in children and adolescents? *Revista Brasileira de Psiquiatria.* 2005;27:89-90.	Does not meet criteria for study design
Birmaher B. Clinical outcome after short-term psychotherapy for adolescents with major depressive disorder. *Arch Gen Psychiatry.* 2000;29-36.	Focus on treatment comparison, matching, or fine-tuning
Blockman M. Selective serotonin reuptake inhibitors in children with major depression. *S Afr Med J.* 2006;Suid-Afrikaanse:476-477.	Does not meet criteria for study design

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Bower P, Garralda E, Kramer T, Harrington R, Sibbald B. The treatment of child and adolescent mental health problems in primary care: a systematic review. *Fam Pract.* 2001;18(4):373-382.	Does not focus on depression screening or treatment or harms of either
Bower P, Rowland N, Mellor Clark J, Heywood P, Godfrey C, Hardy R. Effectiveness and cost effectiveness of counselling in primary care. *Cochrane Database of Systematic Reviews.* 2006.	Does not focus on depression screening or treatment or harms of either
Boylan K, Romero S, Birmaher B. Psychopharmacologic treatment of pediatric major depressive disorder. *Psychopharmacology (Berl).* 2007; 191(1):27-38.	Does not meet criteria for study design
Braconnier A, Le CR, Cohen D. Paroxetine versus clomipramine in adolescents with severe major depression: a double-blind, randomized, multicenter trial. *J Am Acad Child Adolesc Psychiatry.* 2003;42:22-29.	Focus on treatment comparison, matching, or fine-tuning
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;54:877-885.	Focus on treatment comparison, matching, or fine-tuning (comparative efficacy trial)
Bridge JA, Salary CB, Birmaher B, Asare AG, Brent DA. The risks and benefits of antidepressant treatment for youth depression. *Annals of Medicine* 2005;37(6):404-12.	Does not meet criteria for study design
Brown C. Factors associated with symptomatic improvement and recovery from major depression in primary care patients. *General Hospital Psychiatry.* 2000;242-250.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Burns BJ, Hoagwood K, Mrazek PJ. Effective treatment for mental disorders in children and adolescents. *Clin Child Fam Psychol Rev.* 1999;2:199-254.	Does not meet criteria for study design
Burton E, Stice E, Bearman SK, Rohde P. Experimental test of the affect-regulation theory of bulimic symptoms and substance use: a randomized trial. *International Journal of Eating Disorders.* 2007;40:27-36.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Butler, L. Miezitis S. Friedman R. & Cole E. The effect of two school-based intervention programs on depressive symptoms in preadolescents. *American Educational Research Journal* 1980;17:111-119.	Does not meet criteria for study design
Byford S H. Cost-effectiveness analysis of a home based social work intervention for children and adolescents who have deliberately poisoned themselves. *The British journal of psychiatry : the journal of mental science.* 1999; 174:56-62.	Does not focus on depression screening or treatment or harms of either
Carpenter, D. J., Lipschitz, A., Fong, R., Krulewicz, S., Wilkinson, C., and Davies, J. Is it appropriate to combine data from children and adolescents in pediatric MDD clinical trials? Poster presented at: New Clinical Drug Evaluation Unit annual meeting. 6-8-2005. Boca Raton, FL.	Does not meet criteria for study design
Carty, Jill A. An examination of the relative effectiveness of three cognitive behavioral group treatments for depression in an Australian treatment-resistant population. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2001;62(1-B), 539.	Does not meet setting criteria
Cecchini TB. An interpersonal and cognitive-behavioral approach to childhood depression: A school-based primary prevention study. *Dissertation Abstracts International: Section B: The Sciences and Engineering.* 1998;58:6803.	Focus on prevention of depression (either universal or among populations with risk factors)
Chabrol H. CBT versus supportive therapy for depression. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2005;44:841-843.	Does not meet criteria for study design

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Cheung AH, Emslie GJ, Mayes TL. Review of the efficacy and safety of antidepressants in youth depression. *Journal of Child Psychology and Psychiatry.* 2005;46:-754.	Used as source document only
Cheung AH, Emslie GJ, Mayes TL. The use of antidepressants to treat depression in children and adolescents. *CMAJ.* 2006;174:193-200.	Does not meet criteria for study design
Christensen H, Griffiths KM, Korten A. Web-based cognitive behavior therapy: analysis of site usage and changes in depression and anxiety scores. *J Med Internet Res.* 2002;4:e3.	Does not focus on depression screening or treatment or harms of either
Cipriani A, Brambilla P, Furukawa T et al. Fluoxetine versus other types of pharmacotherapy for depression. *Cochrane Database of Systematic Reviews.* 2006.	Focus on treatment comparison, matching, or fine-tuning
Clarke G, Debar L, Lynch F et al. A randomized effectiveness trial of brief cognitive-behavioral therapy for depressed adolescents receiving antidepressant medication. *Journal of the American Academy of Child & Adolescent Psychiatry* 2005;44(9):888-98.	Relevance (QI or collaborative care intervention)
Clarke G, Hawkins W, Murphy M, Sheeber L, Lewinsohn P, Seeley J. Targeted Prevention of Unipolor Depressive Disorder in an At-Risk Sample of High School Adolescents: A Randomized Trial of a Group Cognitive Intervention. *American Academy of Child and Adolescent Psychiatric.* 1995;34:312-321.	Focus on prevention of depression (either universal or among populations with risk factors)
Clarke G. Cognitive-behavioral treatment and prevention of adolescent depression. *2001 Annual Meeting of the American Psychiatric Association.* 2001;2001-2010.	Does not meet criteria for study design
Clarke GN, Hornbrook M, Lynch F et al. A randomized trial of a group cognitive intervention for preventing depression in adolescent offspring of depressed parents. *Arch Gen Psychiatry.* 2001;58:1127-1134.	Focus on prevention of depression (either universal or among populations with risk factors)
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;41:305-313.	Conducted exclusively in high-risk populations
Cohen D. Should the use of selective serotonin reuptake inhibitors in child and adolescent depression be banned?. *Psychotherapy & Psychosomatics.* 2007;76:5-14.	Does not meet criteria for study design
Cohen JA. Treating traumatized children: current status and future directions. *Journal of Trauma & Dissociation.* 2005;6:109-121.	Does not focus on depression screening or treatment or harms of either
Committee on Safety of Medicines. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. ii-185. 2004.	Used as source document only
Committee on Safety of Medicines. Selective serotonin reuptake inhibitors (SSRIs) - overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents: Summary of clinical trials. MHRA . 2005. 2-9-2007.	Used as source document only
Compton SN, Burns BJ, Egger HL, Robertson E. Review of the evidence base for treatment of childhood psychopathology: internalizing disorders. *J Consult Clin Psychol.* 2002;70(6):1240-1266.	Precedes search period
Compton SN, March JS, Brent D, Albano AM, Weersing R, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. *J Am Acad Child Adolesc Psychiatry.* 2004;43:930-959.	Used as source document only
Cornelius JR, Clark DB, Bukstein OG, Birmaher B, Salloum IM, Brown SA. Acute phase and five-year follow-up study of fluoxetine in adolescents with major depression and a comorbid substance use disorder: a review. *Addict Behav.* 2005;30:1824-1833.	Conducted exclusively in high-risk populations

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Cornelius, Jack R., Clark, Duncan B., Bukstein, Oscar G., Kelly, Thomas M., Salloum, Ihsan M., and Wood, D. Scott. Fluoxetine in adolescents with comorbid major depression and an alcohol use disorder: A 3-year follow-up study. *Addictive Behaviors* 2005;30(4), 807-814.	Conducted exclusively in high-risk populations
Council of Scientific Affairs (A-05). Safety and Efficacy of Selective Serotonin Reuptake Inhibitors (SSRIs) in Children and Adolescents. 10. 2006.	Does not meet criteria for study design
Courtney DB. Selective serotonin reuptake inhibitor and venlafaxine use in children and adolescents with major depressive disorder: a systematic review of published randomized controlled trials. *Can J Psychiatry.* 2004;49:557-563.	Used as source document only
Creed F. Does psychological treatment help only those patients with severe irritable bowel syndrome who also have a concurrent psychiatric disorder? *The Australian and New Zealand journal of psychiatry.* 2005;807-815.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Crisp, Heather L., Gudmundsen, Gretchen R., and Shirk, Stephen R. Transporting Evidence-Based Therapy for Adolescent Depression to the School Setting. *Education & Treatment of Children* 2006;29(2), 287-309.	Does not meet criteria for study design
Cuijpers P, van Straten A, Smit F. Preventing the incidence of new cases of mental disorders: a meta-analytic review. *J Nerv Ment Dis.* 2005;193:119-125.	Does not focus on depression screening or treatment or harms of either
Cuijpers P, van Straten A, Smits N, Smit F. Screening and early psychological intervention for depression in schools : Systematic review and meta-analysis. *Eur Child Adolesc Psychiatry.* 2006;15(5):300-7.	Used as source document only
Cuijpers P, Van SA, Warmerdam L. Problem solving therapies for depression: a meta-analysis. *European Psychiatry: the Journal of the Association of European Psychiatrists.* 2007;22:9-15.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Curry JF, Wells KC. Striving for Effectiveness in the Treatment of Adolescent Depression: Cognitive Behavior Therapy for Multisite Community Intervention. *Cognitive and Behavioral Practice.* 2005;12:-185.	Does not meet criteria for study design
Curtis, SE. Cognitive-behavioural treatment of adolescent depression. Unpublished doctoral dissertation . 1992. Logan, Utah State University.	Does not meet quality criteria: high potential for bias due to author-conducted interventions and outcome testing
Dana, Edward Carleton. A cognitive-behavioral intervention for conduct-disordered and concurrently conduct-disorded and depressed children. Dissertation Abstracts International Section A: Humanities and Social Sciences 59(1-A), 0322. 1998.	Conducted exclusively in high-risk populations
den Boer PCAM, Wiersma D, Russo S, van den Bosch RJ. Paraprofessionals for anxiety and depressive disorders. *Cochrane Database of Systematic Reviews.* 2006.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
De Cuyper S, Timbremont B, Braet C, De B, V, Wullaert T. Treating depressive symptoms in schoolchildren: a pilot study. *European Child & Adolescent Psychiatry* 2004;13(2):105-14.	Focus on patients with minor depression or dysthymia or doesn't present MDD outcomes separately

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
de Jonghe F. Combining psychotherapy and antidepressants in the treatment of depression. *Journal of Affective Disorders.* 2001;217-229.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Deas D. A double-blind, placebo-controlled trial of sertraline in depressed adolescent alcoholics: A pilot study. *Human psychopharmacology.* 2000;461-469.	Conducted exclusively in high-risk populations
den Boer PCAM, Wiersma D, Russo S, van den Bosch RJ. Paraprofessionals for anxiety and depressive disorders. *Cochrane Database of Systematic Reviews.* 2006.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Denton WH, Walsh SR, Daniel SS. Evidence-based practice in family therapy: adolescent depression as an example. *J Marital Fam Ther.* 2002;28:39-45.	Does not meet criteria for study design
Diamond G, Josephson A. Family-based treatment research: a 10-year update. *J Am Acad Child Adolesc Psychiatry.* 2005;44:872-887.	Does not meet criteria for study design
Doggrell SA. Fluoxetine--do the benefits outweigh the risks in adolescent major depression?. *Expert Opinion on Pharmacotherapy.* 2005;6:147-150.	Does not meet criteria for study design
Donaldson D. Treatment for adolescents following a suicide attempt: results of a pilot trial. *J Am Acad Child Adolesc Psychiatry.* 2005;113-120.	Does not focus on depression screening or treatment or harms of either
Duff AJ. Psychological interventions in cystic fibrosis and asthma. *Paediatric Respiratory Reviews* 2001;2(4):350-7.	Does not focus on depression screening or treatment or harms of either
Eggert LL, Thompson EA, Herting JR, Nicholas LJ. Reducing suicide potential among high-risk youth: tests of a school-based prevention program. *Suicide Life Threat Behav.* 1995;25:276-296.	Focus on screening for suicide risk
Emslie GJ, Heiligenstein JH, Hoog SL et al. Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2004;43(11):1397-405.	Focus on prevention of depression (either universal or among populations with risk factors)
Emslie GJ, Hughes CW, Crismon ML et al. A feasibility study of the childhood depression medication algorithm: the Texas Children's Medication Algorithm Project (CMAP). *Journal of the American Academy of Child & Adolescent Psychiatry* 2004;43(5):519-27.	Does not focus on depression screening or treatment or harms of either
Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Carmody T, Mayes TL. Fluoxetine in child and adolescent depression: acute and maintenance treatment. *Depress Anxiety.* 1998;7:32-39.	Does not meet criteria for study design
Emslie GJ, Ryan ND, Wagner KD. Major depressive disorder in children and adolescents: clinical trial design and antidepressant efficacy. *J Clin Psychiatry.* 2005;66 Suppl 7:14-20.	Does not meet criteria for study design
Ettelson, Rebecca Gail. The treatment of adolescent depression. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2003;64(4-B), 1899.	Focus on patients with minor depression or dysthymia or doesn't present MDD outcomes separately
Fawcett J, Barkin RL. A meta-analysis of eight randomized, double-blind, controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety. *J Clin Psychiatry.* 1998;59:123-127.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately

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Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Fischer, SA. Development and evaluation of group cognitive-behavioral therapy for depressed and suicidal adolescents in juvenile detention. Unpublished doctoral dissertation . 1995. Tuscaloosa, University of Alabama.	Does not meet setting criteria
Fletcher, Janine, Lovell, Karina, Bower, Peter, Campbell, Malcolm, and Dickens, Chris. Process and Outcome of a Non-Guided Self-Help Manual for Anxiety and Depression in Primary Care: A Pilot Study. *Behavioural and Cognitive Psychotherap*y 2005;33(3), 319-331.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Gaynor, Scott T. Complementing cbt with learning through in vivo experience (live): An open clinic trial with depressed adolescents. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2001;61(7-B), 3842.	Does not meet criteria for study design
Geddes J, Butler R. Depressive disorders. *Clin Evid.* 2002;951-973.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Glass RM. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *The Journal of pediatrics.* 2005; 146(1):145.	Does not meet criteria for study design
Glod CA LA. Bupropion Versus Citalopram Versus Placebo in Adolescents With Major Depression. *157th Annual Meeting of the American Psychiatric Association.* 2004;2004-2006.	Does not meet criteria for study design
Goodyer I, Dubicka B, Wilkinson P et al. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial. *BMJ.* 2007; 335(7611):142	Focus on treatment comparison, matching, or fine-tuning
Green , H., McGinnity, A., Meltzer, H., Ford, T., and Goodman, R. Mental health of children and young people in Great Britain, 2004. 1-284. 2005. Hampshire, Palgrave Macmillan.	Does not focus on depression screening or treatment or harms of either
Green J. Depressing research. *Lancet.* 2004;363:2088.	Does not meet criteria for study design
Hammerness PG, Vivas FM, Geller DA. Selective serotonin reuptake inhibitors in pediatric psychopharmacology: a review of the evidence. *J Pediatr.* 2006;148:158-165.	Does not meet criteria for study design
Hamrin V, Pachler MC. Depression in children and adolescents: the latest evidence-based psychopharmacological treatments. *J Psychosoc Nurs Ment Health Serv.* 2004;42:10-15.	Does not meet criteria for study design
Hansen RA, Gartlehner G, Lohr KN, Gaynes BN, Carey TS. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. *Ann Intern Med.* 2005;143(6):415-426.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Harrington R, Whittaker J, Shoebridge P, Campbell F. Systematic review of efficacy of cognitive behaviour therapies in childhood and adolescent depressive disorder. *BMJ.* 1998;316:1559-1563.	Used as source document only
Harrington R, Wood A, Verduyn C. Clinically depressed adolescents. *Graham, Philip Jeremy (Ed).* 1998;NY, US.	Focus on treatment comparison, matching, or fine-tuning
Harrington R. Randomized trial of a home-based family intervention for children who have deliberately poisoned themselves. *J Am Acad Child Adolesc Psychiatry.* 1998;512-518.	Population not comparable to primary care

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Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Harrington R. Deliberate self-poisoning in adolescence: why does a brief family intervention work in some cases and not others? *Journal of Adolescence.* 2000;13-20.	Population not comparable to primary care
Hayes, Claire and Morgan, Mark. Evaluation of a Psychoeducational Program to Help Adolescents Cope. *Journal of Youth and Adolescence* 2005;34(2), 111-121.	Does not focus on depression screening or treatment or harms of either
Hazell P, O'Connell D, Heathcote D, Robertson J, Henry D. Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. *BMJ.* 1995;310:897-901.	Focus on efficacy of Tricyclic anti-depressants, atypical anti-depressants, MAOI inhibitors, or other medications/procedures that are not primary care feasible or referable
Hazell P. Depression in Children and Adolescents. *Clinical Evidence.* 2002;307-313.	Does not meet criteria for study design
Hazell P. Depression in children and adolescents. *Evid Based Ment Health.* 2003;6:103-104.	Does not meet criteria for study design
Hegmann T. The case of the missing evidence: antidepressant use in children. *JAAPA.* 2004;17:15-16.	Does not meet criteria for study design
Helping depressed children. *Nature.* 2004;431:111.	Does not meet criteria for study design
Hickman, KA. Effects of social skills training on depressed children attending a behavioral day treatment program. Unpublished doctoral dissertation . 1994. Hempstead, New York, Hofstra University.	Population not comparable to primary care
Hodgkinson, B., Evans, D., O'Donnell, A., and Walsh, K. Comparing the effectiveness of individual therapy and group therapy in the treatment of depression: systematic review. Adelaide, S. Australia, Australia: Joanna Briggs Institute for Evidence Based Nursing and Midwifery . 1999.	Precedes search period
Hollon, Steven D., Garber, Judy, and Shelton, Richard C. Treatment of Depression in Adolescents With Cognitive Behavior Therapy and Medications: A Commentary on the TADS Project. *Cognitive and Behavioral Practice* 2005;12(2), 149-155.	Does not meet criteria for study design
Hughes CW, Emslie GJ, Crismon ML et al. Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. *J Am Acad Child Adolesc Psychiatry.* 2007;2007:667-686.	Does not meet criteria for study design
Hyun MS, Chung HI, Lee YJ. The effect of cognitive-behavioral group therapy on the self-esteem, depression, and self-efficacy of runaway adolescents in a shelter in South Korea. *Applied nursing research : ANR.* 2005;160-166.	Does not meet population criteria
James A. The use of Selective Serotonin Re-uptake Inhibitors (SSRIs) in the treatment of depressive disorders in children and adolescents. *Epidemiol Psichiatr Soc.* 2005;14:63-67.	Does not meet criteria for study design
Jane-Llopis E, Hosman C, Jenkins R, Anderson P. Predictors of efficacy in depression prevention programmes. Meta-analysis. *Br J Psychiatry.* 2003;183:384-397.	Focus on prevention of depression (either universal or among populations with risk factors)
Jaycox LH, Reivich KJ, Gillham J, Seligman ME. Prevention of depressive symptoms in school children. *Behav Res Ther.* 1994;32:801-816.	Focus on prevention of depression (either universal or among populations with risk factors)

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Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Jensen PS. After TADS, can we measure up, catch up, and ante up? *Journal of the American Academy of Child & Adolescent Psychiatry.* 2006;45:1456-1460.	Does not meet criteria for study design
Jensen, Peter S. NIMH's TADS: More Than Just a Tad of Progress? *Cognitive and Behavioral Practice* 2005;12(2), 156-158.	Does not meet criteria for study design
Jorm AF, Allen NB, O'Donnell CP, Parslow RA, Purcell R, Morgan AJ. Effectiveness of complementary and self-help treatments for depression in children and adolescents. *Med J Aust.* 2006;185:368-372.	Does not meet criteria for study design
Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin A L. Efficacy and safety of antidepressants for children and adolescents. *BMJ.* 2004;328:879-883.	Does not meet criteria for study design
Kahn, RHC. The effect of a group support intervention program on depression, social adjustment and self-esteem. Unpublished doctoral dissertation . 1989. Washington, DC, Catholic University of America.	Focus on patients with minor depression or dysthymia or doesn't present MDD outcomes separately
Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J. A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety. *Health Technol Assess.* 2002;6:1-89.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Kaufman, Noah K., Rohde, Paul, Seeley, John R., Clarke, Gregory N., and Stice, Eric. Potential Mediators of Cognitive-Behavioral Therapy for Adolescents With Comorbid Major Depression and Conduct Disorder. *Journal of Consulting and Clinical Psychology* 2005;73(1), 38-46.	Conducted exclusively in high-risk populations
Kazdin AE, Bass D, Ayers WA, Rodgers A. Empirical and clinical focus of child and adolescent psychotherapy research. *J Consult Clin Psychol.* 1990;58:729-740.	Does not meet criteria for study design
Kennard, Betsy D., Ginsburg, Golda S., Feeny, Norah C., Sweeney, Michael, and Zagurski, Robin. Implementation Challenges to TADS Cognitive-Behavioral Therapy. *Cognitive and Behavioral Practice* 2005;12(2), 230-239.	Does not focus on depression screening or treatment or harms of either
Kerfoot, Michael, Harrington, Richard, Harrington, Val, Rogers, Julia, and Verduyn, Chrissie. A step too far? Randomized trial of cognitive-behaviour therapy delivered by social workers to depressed adolescents. *European Child & Adolescent Psychiatry* 2004;13(2), 92-99.	Focus on patients with minor depression or dysthymia or doesn't present MDD outcomes separately
King CA, Kirschenbaum DS. An experimental evaluation of a school-based program for children at risk: Wisconsin Early Intervention. *J Community Psychol.* 1990;18:-177.	Does not focus on depression screening or treatment or harms of either
Klein DN, Dougherty LR, Olino TM. Toward guidelines for evidence-based assessment of depression in children and adolescents. *J Clin Child Adolesc Psychol.* 2005;34:412-432.	Does not meet criteria for study design
Kolko DJ, Brent DA. Cognitive and family therapies for adolescent depression: treatment specificity, mediation, and moderation. *J Consult Clin Psychol.* 2000;603-614.	Focus on treatment comparison, matching, or fine-tuning
Kowalenko, Nick, Rapee, Ronald M., Simmons, Julie, Wignall, Ann, Hoge, Rebecca, Whitefield, Kathy, Starling, Julia, Stonehouse, Roger, and Baillie, Andrew J. Short-term effectiveness of a school-based early intervention program for adolescent depression. *Clinical Child Psychology and Psychiatry* 2005;10, 493-507.	Does not meet quality criteria: important aspects of study design not reported (e.g., adherence, fidelity), assignment not random at one school

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Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Kratochvil, Christopher J., Simons, Anne, Vitiello, Benedetto, Walkup, John, Emslie, Graham, Rosenberg, David, and March, John S. A Multisite Psychotherapy and Medication Trial for Depressed Adolescents: Background and Benefits. *Cognitive and Behavioral Practice* 2005;12(2), 159-165.	Does not meet criteria for study design
Lamb JM, Puskar KR, Sereika SM, Corcoran M. School-based intervention to promote coping in rural teens. *MCN Am J Matern Child Nurs.* 1998;23:187-194.	Focus on prevention of depression (either universal or among populations with risk factors)
Lerner M. Treatment of Suicide Ideators: A Problem Solving Approach. *Behavior Therapy.* 1990;21:403-411.	Focus on screening for suicide risk
Lewinsohn PM, Clarke GN. Psychosocial treatments for adolescent depression. *Clin Psychol Rev.* 1999;19:329-342.	Does not meet criteria for study design
Liddle B, Spence SH. Cognitive-behaviour therapy with depressed primary school children: A cautionary note. *Behavioural Psychotherapy.* 1990;18:85-102.	Does not meet quality criteria: important aspects of study design not reported (e.g., adherence, attrition, fidelity, handling of missing data)
Lima MS, Hotopf M. Pharmacotherapy for dysthymia. *Cochrane Database of Systematic Reviews.* 2006.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Lima MS, Moncrieff J, Soares BGO. Drugs versus placebo for dysthymia. *Cochrane Database of Systematic Reviews.* 2006.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Lip GYH, Lane DA, Millane TA. Psychological interventions for depression in adolescent and adult congenital heart disease. *Cochrane Database of Systematic Reviews.* 2006.	Focus on patients with severe medical illnesses (e.g., cancer)
Listug-Lunde, Lori B. A cognitive-behavioral treatment for depression in Native American middle-school students. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2005;66(2-B), 1176.	Does not meet quality criteria: outcome assessment not blinded, 70% of control group received treatment
Lynch FL, Hornbrook M, Clarke GN et al. Cost-effectiveness of an intervention to prevent depression in at-risk teens. *Arch Gen Psychiatry.* 2005;62:1241-1248.	Focus on prevention of depression (either universal or among populations with risk factors)
MacGillivray S, Arroll B, Hatcher S et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *BMJ.* 2003;326:1014-1017.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Mandoki MW, Tapia MR, Tapia MA, Sumner GS, Parker JL. Venlafaxine in the treatment of children and adolescents with major depression. *Psychopharmacol Bull.* 1997;33:149-154.	Focus on efficacy of Tricyclic anti-depressants, atypical anti-depressants, MAOI inhibitors, or other medications/procedures that are not primary care feasible or referable

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Mann JJ, Emslie G, Baldessarini RJ et al. ACNP Task Force report on SSRIs and suicidal behavior in youth. *Neuropsychopharmacology.* 2006;31:473-492.	Used as source document only
March JS, Klee BJ, Kremer CM. Treatment benefit and the risk of suicidality in multicenter, randomized, controlled trials of sertraline in children and adolescents. *J Child Adolesc Psychopharmacol.* 2006;16:91-102.	Used as source document only
March JS. Authors of TADS study reply to letter raising concerns. *Br Med J.* 2005; 330(7493):730-1.	Does not meet criteria for study design
March JS. Treatment for adolescents with depression study (Tads). *158th Annual Meeting of the American Psychiatric Association.* 2005;2005-2026.	Does not meet criteria for study design
March, John S. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial: Reply. *JAMA: Journal of the American Medical Association* 2004;292(21), 2578-2579.	Does not meet criteria for study design
Marks IM. The maturing of therapy. Some brief psychotherapies help anxiety/depressive disorders but mechanisms of action are unclear. *British Journal of Psychiatry.* 2002;180:200-204.	Does not meet criteria for study design
McClellan JM, Werry JS. Evidence-based treatments in child and adolescent psychiatry: an inventory. *J Am Acad Child Adolesc Psychiatry.* 2003;42:1388-1400.	Does not report outcomes listed in inclusion criteria
Medicines and Healthcare Products Regulatory Agency. Selective Serotonin reuptake inhibitors (SSRIs): overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents - summary of clinical trials. 1-190. 2003.	Used as source document only
Melvin GA, Tonge BJ, King NJ, Heyne D, Gordon MS, Klimkeit E. A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2006;45:1151-1161.	Focus on treatment comparison, matching, or fine-tuning
Merry S, McDowell H, Hetrick S, Bir J, Muller N. Psychological and/or educational interventions for the prevention of depression in children and adolescents. *Cochrane Database Syst Rev.* 2004;CD003380.	Focus on prevention of depression (either universal or among populations with risk factors)
Merry S, McDowell H, Wild CJ, Bir J, Cunliffe R. A randomized placebo-controlled trial of a school-based depression prevention program. *Journal of the American Academy of Child & Adolescent Psychiatry* 2004;43(5):538-47.	Focus on prevention of depression (either universal or among populations with risk factors)
Michael KD, Crowley SL. How effective are treatments for child and adolescent depression? A meta-analytic review. *Clin Psychol Rev.* 2002;22:247-269.	Precedes search period
Michael KD, Huelsman TJ, Crowley SL. Interventions for Child and Adolescent Depression: Do Professional Therapists Produce Better Results? *Journal of Child and Family Studies.* 2005;14:11855,4-1185570.	Precedes search period
Moak DH. Sertraline and cognitive behavioral therapy for depressed alcoholics: results of a placebo-controlled trial. *Journal of Clinical Psychopharmacology.* 2003;553-562.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Moldenhauer Z, Melnyk BM. Use of antidepressants in the treatment of child and adolescent depression: are they effective? *Pediatr Nurs.* 1999;25:643-646.	Precedes search period

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Moldenhauer, Zendi. Adolescent depression: A primary care pilot intervention study. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2004;65(2-B), 656.	Does not meet quality criteria: outcome assessment not blinded, high level of attention received by control group, differences between accepters and decliners
Moor S, Ann M, Hester M et al. Improving the recognition of depression in adolescence: Can we teach the teachers? *J Adolesc.* 2007; 30(1):81-95.	Does not focus on depression screening or treatment or harms of either
Moore M, Carr A. Depression and grief. *Carr, Alan (Ed).* 2000;364.	Conducted exclusively in high-risk populations
Moreno C, Arango C, Parellada M, Shaffer D, Bird H. Antidepressants in child and adolescent depression: where are the bugs? *Acta Psychiatr Scand.* 2007;115:184-195.	Does not meet criteria for study design
Moscovitch A. A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. *Psychopharmacology (Berl).* 2004;390-397.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Mufson L, Moreau D, Weissman MM, Wickramaratne P, Martin J, Samoilov A. Modification of interpersonal psychotherapy with depressed adolescents (IPT-A): phase I and II studies. *J Am Acad Child Adolesc Psychiatry.* 1994;1994:695-705.	Does not meet criteria for study design
Mufson, L. and Dorta, K. P. Interpersonal psychotherapy for depressed adolescents: Theory, practice, and research. 2000.	Does not meet criteria for study design
Mufson, Laura and Moreau, Donna. Interpersonal psychotherapy for adolescent depression. 35-66. 1998. Washington, DC, American Psychiatric Association.	Does not focus on depression screening or treatment or harms of either
Mulrow CD, Williams JW, Jr., Trivedi M et al. Treatment of depression--newer pharmacotherapies. *Psychopharmacol Bull.* 1998;34:409-795.	Precedes search period
National Institute for Clinical Excellence. Depression in Children and Young People: Identification and management in primary, community and secondary care. 1-233. 2005. Northhamptonshire, The British Psychological Society.	Used as a source document only
Nelms BC. Childhood depression: Be on the alert. *Journal of Pediatric Health Care* 2003;17(4):161-2.	Does not meet criteria for study design
Newcorn JH. Selective serotonin reuptake inhibitor treatment of major depressive disorder in children and adolescents.(comment). *Current Psychiatry Reports.* 2004;6:85-87.	Does not meet criteria for study design
O'Kearney, Richard, Gibson, Mal, Christensen, Helen, and Griffiths, Kathy M. Effects of a cognitive-behavioural internet program on depression, vulnerability to depression and stigma in adolescent males: A school-based controlled trial. *Cognitive Behaviour Therapy* 2006;35(1), 43-54.	Focus on prevention of depression (either universal or among populations with risk factors)
Oldham J. The risk/benefit ratio of psychiatric treatment. *Journal of Psychiatric Practice.* 2005;11:137.	Does not meet criteria for study design
Olfson M, Marcus SC, Shaffer D. Antidepressant drug therapy and suicide in severely depressed children and adults: A case-control study. *Arch Gen Psychiatry.* 2006;63:865-872.	Does not report outcomes listed in inclusion criteria

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Papanikolaou K, Richardson C, Pehlivanidis A, Papadopoulou-Daifoti Z. Efficacy of antidepressants in child and adolescent depression: a meta-analytic study. *J Neural Transm.* 2006;113:399-415.	Used as source document only
Patterson GR, DeGarmo D, Forgatch MS. Systematic changes in families following prevention trials. *J Abnorm Child Psychol.* 2004;32:621-633.	Does not focus on depression screening or treatment or harms of either
Pattison, Sue and Harris, Belinda. Counselling children and young people: A review of the evidence for its effectiveness. Counselling & Psychotherapy Research 2006; 6(4), 233-237.	Used as source document only
Pignone, M. P., Gaynes, B. N., Rushton, J. L., Mulrow, C. D., Orleans, C. T., Whitener, B. L., Mills, C., and Lohr, K. N. Screening for Depression. i-D-83. 2002. Rockville, MD, Agency for Healthcare Research and Quality.	Used as source document only
Pine DS, Cohen JA. Trauma in children and adolescents: risk and treatment of psychiatric sequelae. (Review) (80 refs). *Biological Psychiatry.* 2002;51:519-531.	Does not meet criteria for study design
Pruitt, Irene T. P. Family Treatment Approaches for Depression in Adolescent Males. American Journal of Family Therapy 2007;35(1), 69-81.	Does not meet criteria for study design
Puskar K. Effect of the Teaching Kids to Cope (TKC) program on outcomes of depression and coping among rural adolescents. *Journal of child and adolescent psychiatric nursing : official publication of the Association of Child and Adolescent Psychiatric Nurses, Inc.* 2003;71-80.	Does not meet quality criteria: no clear description of intervention and control groups, important aspects of study design not reported (e.g., patient characteristics)
Quintana H, Butterbaugh GJ, Purnell W, Layman AK. Fluoxetine monotherapy in attention-deficit/hyperactivity disorder and comorbid non-bipolar mood disorders in children and adolescents. *Child Psychiatry & Human Development.* 2007;37:241-253.	Conducted exclusively in high-risk populations
Rapaport MH. Prevalence, recognition, and treatment of comorbid depression and anxiety. *J Clin Psychiatry.* 2001;62:Suppl-10.	Does not meet criteria for study design
Rawson HE, Tabb LC. Effects of therapeutic intervention on childhood depression. *Child & Adolescent Social Work Journal.* 1993;10:39-52.	Population not comparable to primary care
Reed MK. Social skills training to reduce depression in adolescents. *Adolescence.* 1994;29:293-302.	Does not meet quality criteria: outcome assessment not blinded, lack of usable data, important aspects of study design not reported (e.g., method of assessment for MDD)
Reger G, Wong-McDonald A, Liberman RP. Psychiatric rehabilitation in a community mental health center. *Psychiatr Serv.* 2003;54:1457-1459.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Reinecke MA, Ryan NE, DuBois DL. Cognitive-behavioral therapy of depression and depressive symptoms during adolescence: a review and meta-analysis. *J Am Acad Child Adolesc Psychiatry.* 1998;37:26-34.	Used as source document only

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Reynolds WM, Coats KI. A comparison of cognitive-behavioral therapy and relaxation training for the treatment of depression in adolescents. *J Consult Clin Psychol.* 1986;54:653-660.	Does not meet quality criteria: outcome assessment not blinded, differential attrition, both interventions conducted by same therapist
Richards A. PHASE: a randomised, controlled trial of supervised self-help cognitive behavioural therapy in primary care. *The British journal of general practice : the journal of the Royal College of General Practitioners.* 2003;764-770.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Riggs, Paula D. and Davies, Robert D. A clinical approach to integrating treatment for adolescent depression and substance abuse. *Journal of the American Academy of Child & Adolescent Psychiatry* 2002;41(10), 1253-1255.	Conducted exclusively in high-risk populations
Rihmer Z, Akiskal H. Do antidepressants t(h)reat(en) depressives? Toward a clinically judicious formulation of the antidepressant-suicidality FDA advisory in light of declining national suicide statistics from many countries. *Journal of Affective Disorders.* 2006;94:3-13.	Does not meet criteria for study design
Rishel CW, Greeno CG, Marcus SC et al. Impact of maternal mental health status on child mental health treatment outcome. *Community Mental Health Journal* 2006;42(1):1-12.	Conducted exclusively in high-risk populations
Rohde P, Clarke GN, Mace DE, Jorgensen JS, Seeley JR. An efficacy/effectiveness study of cognitive-behavioral treatment for adolescents with comorbid major depression and conduct disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 2004;43(6):660 -8.	Conducted exclusively in high-risk populations
Rohde P. Impact of comorbidity on a cognitive-behavioral group treatment for adolescent depression. *J Am Acad Child Adolesc Psychiatry.* 2001;795-802.	Conducted exclusively in high-risk populations
Rollman BL, Hanusa BH, Gilbert T, Lowe HJ, Kapoor WN, Schulberg HC. The electronic medical record. A randomized trial of its impact on primary care physicians' initial management of major depression (corrected). *Arch Intern Med.* 2001;161:189-197.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Ryan ND. Medication treatment for depression in children and adolescents. *Cns Spectrums* 2003;8(4):283-7.	Does not meet criteria for study design
Ryan ND. Treatment of depression in children and adolescents. *Lancet.* 2005;366:933-940.	Does not meet criteria for study design
Rynn M, Wagner KD, Donnelly C et al. Long-term sertraline treatment of children and adolescents with major depressive disorder. *Journal of Child & Adolescent Psychopharmacology* 2006;16(1-2):103-16.	Does not meet criteria for study design
Safer DJ. Should selective serotonin reuptake inhibitors be prescribed for children with major depressive and anxiety disorders? *Pediatrics.* 2006;118:1248-1251.	Does not meet criteria for study design
Salerian AJ. Use of selective serotonin reuptake inhibitors in childhood depression. *Lancet.* 2004;364:660-661.	Does not meet criteria for study design
Salkovskis P, Rimes K, Stephenson D, Sacks G, Scott J. A randomized controlled trial of the use of self-help materials in addition to standard general practice treatment of depression compared to standard treatment alone. *Psychological Medicine* 2006;36(3):325-33.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Sanford, Mark, Boyle, Michael, McCleary, Lynn, Miller, Jennifer, Steele, Margaret, Duku, Eric, and Offord, David. A pilot study of adjunctive family psychoeducation in adolescent major depression: Feasibility and treatment effect. *Journal of the American Academy of Child & Adolescent Psychiatry* 2006;45(4), 386-395.	Focus on treatment comparison, matching, or fine-tuning
Sanford, Mark, Byrne, Carolyn, Williams, Susan, Atley, Sandy, Ridley, Ted, Miller, Jennifer, and Allin, Heather. A Pilot Study of a Parent-Education Group for Families Affected by Depression. *Canadian Journal of Psychiatry* 2003;48(2), 78-86.	Conducted exclusively in high-risk populations
Santor DA, Kusumakar V. Open trial of interpersonal therapy in adolescents with moderate to severe major depression: effectiveness of novice IPT therapists. *Journal of the American Academy of Child & Adolescent Psychiatry* 2001;40(2):236-40.	Does not meet criteria for study design
Scahill L, Hamrin V, Pachler ME. The use of selective serotonin reuptake inhibitors in children and adolescents with major depression. *Journal of Child & Adolescent Psychiatric Nursing.* 2005;18:86-89.	Does not meet criteria for study design
Scahill L. Selective serotonin reuptake inhibitors in children and adolescents with major depression. *Revista Brasileira de Psiquiatria.* 2005;27:91-92.	Does not meet criteria for study design
Schmitz JM AP. Fluoxetine treatment of cocaine-dependent patients with major depressive disorder. *Drug Alcohol Depend.* 2001;207-214.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Scott, Cynthia V. Evaluation of cognitive-behavioral group therapy in treating depressive symptoms in prepubertal children: A pilot study. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 1999;60(6-B), 2960.	Does not meet quality criteria: outcome assessment not blinded, important aspects of study design not reported (e.g., attrition, number of subjects within groups)
Sharp SC, Hellings JA. Efficacy and safety of selective serotonin reuptake inhibitors in the treatment of depression in children and adolescents: practitioner review. *Clinical Drug Investigation.* 2006;26:247-255.	Used as source document only
Sheffield J. A universally administered primary prevention programme for depression reduces symptoms in German adolescents with low self-efficacy. *Evid Based Ment Health.* 2006;9:51.	Focus on prevention of depression (either universal or among populations with risk factors)
Simeon JG, Dinicola VF, Ferguson HB, Copping W. Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. *Prog Neuropsychopharmacol Biol Psychiatry.* 1990;14:791-795.	Does not meet quality criteria: important aspects of study design not reported (e.g., attrition, blinding of outcome assessment), lack of usable data
Soffer AG. School-based social skills training to reduce children's depressive symptomatology. *Dissertation Abstracts International* 2003;63(12-A):4224 .	Focus on prevention of depression (either universal or among populations with risk factors)
Solhkhah R, Wilens TE, Daly J, Prince JB, Van Patten SL, Biederman J. Bupropion SR for the treatment of substance-abusing outpatient adolescents with attention-deficit/hyperactivity disorder and mood disorders. *Journal of Child & Adolescent Psychopharmacology* 2005;15(5):777-86.	Conducted exclusively in high-risk populations
Stark KD. *Childhood depression: School-based intervention.* New York: Guilford Press; 1990.	Focus on treatment comparison, matching, or fine-tuning

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Stein BD, Jaycox LH, Kataoka SH et al. A mental health intervention for schoolchildren exposed to violence: a randomized controlled trial.(see comment). *JAMA* 2003;290(5):603-11.	Conducted exclusively in high-risk populations
Stein MD, Zitner LE, Jensen PS. Adherence to treatment of depression in active injection drug users: the minerva study. *J Subst Abuse Treat.* 2004;87-93.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Stein RE, Zitner LE, Jensen PS. Interventions for adolescent depression in primary care. *Pediatrics.* 2006;118:669-682.	Used as source document only
Steiner M, Hirschberg AL, Bergeron R, Holland F, Gee MD, Van EE. Luteal phase dosing with paroxetine controlled release (CR) in the treatment of premenstrual dysphoric disorder. *American Journal of Obstetrics & Gynecology.* 2005;193:352-360.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Sweeney, Michael, Robins, Michele, Ruberu, Maryse, and Jones, Jennifer. African-American and Latino Families in TADS: Recruitment and Treatment Considerations. *Cognitive and Behavioral Practice* 2005;12(2), 221-229.	Does not meet criteria for study design
Szigethy, Eva, Carpenter, Johanna, Baum, Emily, Kenney, Elyse, Baptista-Neto, Lourival, Beardslee, William R., and DeMaso, David Ray. Case study: Longitudinal treatment of adolescents with depression and inflammatory bowel disease. *Journal of the American Academy of Child & Adolescent Psychiatry* 2006;45(4), 396-400.	Does not meet criteria for study design
Talbot, Nancy L., Conwell, Yeates, O'Hara, Michael W., Stuart, Scott, Ward, Erin A., Gamble, Stephanie A., Watts, Arthur, and Tu, Xin. Interpersonal psychotherapy for depressed women with sexual abuse histories: A pilot study in a community mental health center. *Journal of Nervous and Mental Disease* 2005;193(12), 847-850.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Thaper, Anita. Texas Medication Algorithm Project Overview. Texas . 2006.	Excluded for study relevance
Tucker P, Beebe KL, Burgin C et al. Paroxetine treatment of depression with posttraumatic stress disorder: effects on autonomic reactivity and cortisol secretion. *Journal of Clinical Psychopharmacology.* 2004;24:131-140.	Does not meet population criteria
Valuck RJ, Libby AM, Sills MR, Giese AA, Allen RR. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. *CNS Drugs.* 2004;18:1119-1132.	Does not report outcomes listed in inclusion criteria
Vergouwen AC BA. A cluster randomized trial comparing two interventions to improve treatment of major depression in primary care. *Psychol Med.* 2005;25-33.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Vitiello B. Selective serotonin reuptake inhibitors (SSRIs) in children and adolescents. *Journal of Child & Adolescent Psychopharmacology.* 2006;16:7-9.	Does not meet criteria for study design
von Knorring, Anne Liis, Olsson, Gunilla Ingrid, Thomsen, Per Hove, Lemming, Ole Michael, and Hulten, Agnes. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *Journal of Clinical Psychopharmacology* 2006;26(3), 311-315.	Does not meet quality criteria: control group conditions not clearly described, eligibility criteria changed midway through study, important aspects of study design not reported (blinding of outcome assessment)

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Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Vostanis P, Feehan C, Grattan E, Bickerton WL. A randomised controlled out-patient trial of cognitive-behavioural treatment for children and adolescents with depression: 9-month follow-up. *J Affect Disord.* 1996;40:105-116.	Focus on treatment comparison, matching, or fine-tuning
Vostanis P, Feehan C, Grattan E, Bickerton WL. Treatment for children and adolescents with depression: Lessons from a controlled trial. *Clinical Child Psychology and Psychiatry.* 1996;1:199-212.	Focus on treatment comparison, matching, or fine-tuning
Walker EA, Katon WJ, Russo. Predictors of outcome in a primary care depression trial. *Journal of general internal medicine : official journal of the Society for Research and Education in Primary Care Internal Medicine.* 2000;859-867.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Wallace AE, Neily J, Weeks WB, Friedman MJ. A cumulative meta-analysis of selective serotonin reuptake inhibitors in pediatric depression: Did unpublished studies influence the efficacy/safety debate? (References). *Journal of Child and Adolescent Psychopharmacology.* 2006;16:-58.	Used as source document only
Weersing, V. Robin, Iyengar, Satish, Kolko, David J., Birmaher, Boris, and Brent, David A. Effectiveness of Cognitive-Behavioral Therapy for Adolescent Depression: A Benchmarking Investigation. Behavior Therapy 2006;37(1), 36-48.	Does not meet criteria for study design
Weersing VR, Weisz JR. Community clinic treatment of depressed youth: benchmarking usual care against CBT clinical trials. *Journal of Consulting & Clinical Psychology.* 2002;70:299-310.	Does not meet criteria for study design
Weissman MM. Recent non-medication trials of interpersonal psychotherapy for depression. *International Journal of Neuropsychopharmacology.* 2007;10:117-122.	Does not meet criteria for study design
Weisz JR, Thurber CA, Sweeney L, Proffitt VD, LeGagnoux GL. Brief treatment of mild-to-moderate child depression using primary and secondary control enhancement training. *J Consult Clin Psychol.* 1997;65:703-707.	Does not meet quality criteria: no clear description of control group, important aspects of study design not reported (e.g., attrition)
Weisz JR, Doss AJ, Hawley KM. Youth psychotherapy outcome research: a review and critique of the evidence base. *Annu Rev Psychol.* 2005;56:337-363.	Does not report outcomes listed in inclusion criteria
Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull.* 2006;132:132-149.	Used as source document only
Weisz JR, Weiss B, Alicke MD, Klotz ML. Effectiveness of psychotherapy with children and adolescents: a meta-analysis for clinicians. *J Consult Clin Psychol.* 1987;55:542-549.	Does not focus on depression screening or treatment or harms of either
Wells, Karen C. and Albano, Anne Marie. Parent Involvement in CBT Treatment of Adolescent Depression: Experiences in the Treatment for Adolescents With Depression Study (TADS). *Cognitive and Behavioral Practice* 2005;12(2), 209-220.	Does not report outcomes listed in inclusion criteria
Wernicke JF. Safety and side effect profile of fluoxetine. *Expert Opinion on Drug Safety.* 2004;3:495-504.	Does not meet criteria for study design
Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet.* 2004;363:1341-1345.	Used as source document only
Wignall, Ann. Evaluation of a Group CBT Early Intervention Program for Adolescents With Comorbid Depression and Behaviour Problems. Australian Journal of Guidance & Counselling 16[1], 119-132. 2006.	Conducted exclusively in high-risk populations
Wohlfarth, Tamar, Lekkerkerker, Frits, and van Zwieten, Barbara. Use of selective serotonin reuptake inhibitors in childhood depression. *Lancet* 2004;364(9435), 659-660.	Does not meet criteria for study design

Appendix C Table C6. Studies Excluded from the Review for Key Question 4

Key Question 4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?	
Reference	**Reason for exclusion***
Wong IC, Besag FM, Santosh PJ, Murray ML. Use of selective serotonin reuptake inhibitors in children and adolescents. *Drug Saf.* 2004;27:991-1000.	Does not meet criteria for study design
Wood A, Harrington R, Moore A. Controlled trial of a brief cognitive-behavioural intervention in adolescent patients with depressive disorders. *J Child Psychol Psychiatry.* 1996;37:737-746.	Focus on treatment comparison, matching, or fine-tuning
Wright JH, Wright AS, Albano AM, Basco MR, Goldsmith LJ, Raffield T, Otto MW. Computer-assisted cognitive therapy for depression: maintaining efficacy while reducing therapist time. *The American journal of psychiatry.* 2005;1158-1164.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Young JF, Mufson L, Davies M. Impact of comorbid anxiety in an effectiveness study of interpersonal psychotherapy for depressed adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2006;45:904-912.	Conducted exclusively in high-risk populations
Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. *J Psychiatr Res.* 2004;38:577-582.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Zito JM, Safer DJ. Antidepressant treatment in children and adolescents: bridging the gap between efficacy and effectiveness. *Curr Psychiatry Rep.* 2001;3:115-125.	Does not meet criteria for study design

Appendix C Table C7. Evidence Table of Case-Control Studies for Adverse Effects of Selective Serotonin Reuptake Inhibitors in Treating Depression in Children and Adolescents: Key Question 5

Study ID USPSTF quality rating	Setting	Number of participants Exclusions (# and reason)	Proportion participating	Patient characteristics	SSRI(s) studied
Olfson, 2006[1] Good	**Target population:** Medicaid beneficiaries with inpatient stay for depression; 6- to 18-year-old cases with any attempt (controls same because of matching) **Selection method:** Medicaid data files to find patients with inpatient stay for depression, limited to people with ≥1 medication during 2-year observation period Matched 1 case to 1-5 controls by age, sex, race, state, date of discharge, presence of claims for substance abuse disorder, recent suicide attempt, or use of antipsychotic, stimulant, anxiolytic, or mood-stabilizing medication in prior 60 days Used National Death Index records to identify completed suicide	**Suicide attempts:** 784 cases 3,635 control **Completed suicide:** 94 cases 435 controls **Exclusions:** Patients with ≥1 inpatient or ≥2 outpatient claims for pregnancy, bipolar, schizophrenia, other psychoses, mental retardation, dementia/delirium, ineligible for Medicaid benefits in 60 days prior to event or >15 days inpatient in 60 days prior	100% cases 100% controls	**Mean Age:** 15.4 (SD 1.8) **Female:** 74.5% **Ethnicity:** 73.9% non-Hispanic White **Other:** Substance abuse history: 10.3% Antipsychotic use: 13.7% Mood stabilizer use: 12.9% Anxiolytic/hypnotic use: 7.2% Stimulant use: 3.8%	Fluoxetine, Paroxetine, Sertraline, Citalopram, Fluvoxamine Other agents: TCAs, Venlafaxine, Mirtazapine, Bupropion, Trazodone, Nefazodone

Appendix C Table C7. Evidence Table of Case-Control Studies for Adverse Effects of Selective Serotonin Reuptake Inhibitors in Treating Depression in Children and Adolescents: Key Question 5

Study ID USPSTF quality rating	Comparison	Followup	Outcome measures	Effect size	Applicability	Comments
Olfson, 2006[1] Good	Any antidepressants vs. no antidepressants Any SSRI vs. no antidepressant All individual agents vs. no antidepressant	Up to 2 years, length of followup differs depending on when discharge was within a 2-year window	Suicide attempt or completed suicide in a 2-year window	**Suicide attempts, any antidepressant:** 1.52 (1.12, 2.07); risk of attempt increased with sertraline, venlafaxine, or TCA (no OR reported) **Completed suicide, any antidepressant:** 15.62 (1.65, ∞) Completed suicide, SSRI: 11.26 (0.97, ∞) **Proportion of patients on SSRI:** Completed suicide: 37.5% No suicide: 7.7% p = 0.005	Fair	Applicability to primary care limited due to severity of population studies; also, they minimized confounding by severity by studying a sample high-severity sample, but still have issue of confounding within that range

SSRI-Selective Serotonin Reuptake Inhibitor; SD-standard deviation; TCA-tricyclic antidepressant; vs-versus

References

1. Olfson M, Marcus SC, Shaffer D. Antidepressant drug therapy and suicide in severely depressed children and adults: A case-control study. *Arch Gen Psychiatry.* 2006;63:865-872.

Appendix C Table C8. Evidence Table of Cohort Studies for Adverse Effects of Selective Serotonin Reuptake Inhibitors in Treating Depression in Children and Adolescents: Key Question 5

Study ID USPSTF quality rating	Setting	Number of patients	Patient characteristics	SSRI(s) studied
Valuck, 2004[1] Good	**Target population:** 12- to 18-year-olds who received either a diagnosis of MDD or an antidepressant med (or both) 1/1998 - 3/2003; limited to population with no diagnosis/medication in 12 months prior to index visit or dispensing **Selection method:** Used medical claims database that included paid claims from 74 managed care plans and 58 million covered lives	24,119	**Age:** 12-18 (56.8% are 16-18) **Female:** 63.0% **Other:** 8.0% Medicaid 51.4% from Midwest	TCAs, SSRIs+ Venlafaxine, other Specific agents not specified
Sondergard, 2006[2] Fair	**Target population:** Cohort: 10- to 17-year-olds who purchased an antidepressant between 1/1/1995 - 12/31/1999 Controls: 10- to 17-year-olds, excluding those who died or emigrated during observation period	Cohort: 2,311 Control: 50,000	**Other:** 57.4% of cohort had psychiatric hospital contact 1.1% of controls had psychiatric hospital contact	Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine
Martin, 2004[3] Fair-good	**Target population:** 5- to 29-year-olds with a primary diagnosis of depressive or anxiety disorder who had pharmacy claims data available for study period 1/1/1997 - 12/31/2001	87,920 total 49,381 aged 5-19 years	**Age:** 72% are 15-29 **Female:** 60% **Other:** 18.8% severe depression diagnosis 53.6% mild depression diagnosis 27.6% anxiety diagnosis 0.2% inpatient mental health stay	SSRI, TCA, other antidepressants, agents not specified

Appendix C Table C8. Evidence Table of Cohort Studies for Adverse Effects of Selective Serotonin Reuptake Inhibitors in Treating Depression in Children and Adolescents: Key Question 5

Study ID USPSTF quality rating	Comparison	Followup	Outcome measures	Results	Comments
Valuck, 2004[1] Good	Antidepressant treatment (any of 3 categories or multiple categories) vs. no antidepressant	6 months - 6 years, 3 months Average length 1.36 yrs (SD 9.1 months)	Suicide attempt per ICD code	Hazard ratio (95% CL) from Cox prop. Hazards model, including propensity scores to control for confounding of med with severity, plus other covariates: **SSRI vs. no antidepressant:** 1.59 (0.89, 2.82) **TCA vs. no antidepressant:** too little data to estimate **Other vs. no antidepressant:** 1.03 (0.43, 2.44) **Multiple vs. no antidepressant:** 1.43 (0.70, 2.89)	
Sondergard, 2006[2] Fair	Those with antidepressant purchase vs. similar-aged youth without antidepressant purchase	Up to 5 years	Death registry record with cause of death as intentional self-harm	**Treated with SSRI vs. no SSRI, adjusting for psychiatric care:** OR 4.47 (95% CI 0.95, 20.96)	Comparing youth exposed to antidepressants with general pool of youth, controlling for duration of psychiatric contact; did not account for presence of depressive disorders, much less severity of depression

Appendix C Table C8. Evidence Table of Cohort Studies for Adverse Effects of Selective Serotonin Reuptake Inhibitors in Treating Depression in Children and Adolescents: Key Question 5

Study ID USPSTF quality rating	Comparison	Follow up	Outcome measures	Results	Comments
Martin, 2004[3] Fair-good	Youth with antidepressant claim vs. youth without antidepressant claim	Up to 5 years	Presence of 2 or more claims with bipolar diagnosis after depression or anxiety diagnosis established	**Rate of conversion to bipolar**: 5- to 29-year-olds: 7.7% per year among antidepressant-exposed 2.5% per year among non-exposed Rate ratio 3.1 (95% CI 3.0, 3.2) 5- to 14-year-olds: 8.0% per year antidepressant-exposed 2.7% per year non-exposed Rate ratio 2.9 (95% CI 2.8, 3.1) 15- to 29-year-olds: 7.7% per year antidepressant-exposed 5.6% per year non-exposed Rate ratio 1.4 (95% CI 1.3, 1.5)	Not clear if those with any bipolar diagnosis prior to depression or anxiety diagnosis established were allowed in the sample

SSRI-Selective Serotonin Reuptake Inhibitor; UK-United Kingdom; TCA-tricyclic antidepressant; CI-confidence interval; vs.-versus; MDD-Major Depressive Disorder; SD-standard deviation

References

1. Valuck RJ, Libby AM, Sills MR, Giese AA, Allen RR. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. *CNS Drugs.* 2004;18:1119-1132.

2. Sondergard L, Kvist K, Andersen PK, Kessing LV. Do antidepressants precipitate youth suicide?: a nationwide pharmacoepidemiological study. *Eur Child Adolesc Psychiatry.* 2006;15:232-240.

3. Martin A, Young C, Leckman JF, Mukonoweshuro C, Rosenheck R, Leslie D. Age effects on antidepressant-induced manic conversion. *Archives of pediatrics & adolescent medicine.* 2004;158:773-780.

Appendix C Table C9. Studies Excluded from the Review for Key Question 5

Key Question 5: What are the adverse effects of treatment?	
Reference	**Reason for exclusion***
Andrade C, Bhakta SG, Singh NM. Controversy revisited: selective serotonin reuptake inhibitors in paediatric depression. *World Journal of Biological Psychiatry.* 2006;7:251-260.	Does not meet criteria for study design
Antidepressants for children and adolescents: an update. *Harv Ment Health Lett.* 2006;22:4-5.	Does not meet criteria for study design
Apter A, Lipschitz A, Fong R et al. Evaluation of suicidal thoughts and behaviors in children and adolescents taking paroxetine. *J Child Adolesc Psychopharmacol.* 2006;16:77-90.	Used as a source document only
Aursnes I, Tvete IF, Gaasemyr J, Natvig B. Suicide attempts in clinical trials with paroxetine randomised against placebo. *BMC Medicine.* 2005;3:14.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Bauer MS, Wisniewski SR, Kogan JN, Marangell LB, Thase ME, Sachs G. Brief report: paroxetine in younger and adult individuals at high risk for suicide. *Psychopharmacol Bull.* 2006;39:31-37.	Does not focus on depression screening or treatment or harms of either
Beasley CM, Jr., Koke SC, Nilsson ME, Gonzales JS. Adverse events and treatment discontinuations in clinical trials of fluoxetine in major depressive disorder: an updated meta-analysis. *Clin Ther.* 2000;22:1319-1330.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Berkowitz RI, Fabricatore AN. Obesity, psychiatric status, and psychiatric medications. *Psychiatr Clin North Am.* 2005;28:39-54.	Does not report outcomes listed in inclusion criteria
Birmaher B, Brent D. Should we use antidepressants for the treatment of major depressive disorder in children and adolescents? *Revista Brasileira de Psiquiatria.* 2005;27:89-90.	Does not meet criteria for study design
Blockman M. Selective serotonin reuptake inhibitors in children with major depression. *S Afr Med J.* 2006; 96(6):476-7.	Does not meet criteria for study design
Blumer D, Montouris G, Davies K. The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. *Epilepsy & Behavior.* 2004;5:826-840.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Boylan K, Romero S, Birmaher B. Psychopharmacologic treatment of pediatric major depressive disorder. *Psychopharmacology (Berl).* 2007; 191(1):27-38.	Does not meet criteria for study design
Bridge JA, Barbe RP, Birmaher B, Kolko DJ, Brent DA. Emergent suicidality in a clinical psychotherapy trial for adolescent depression. *American Journal of Psychiatry* 2005;162(11):2173-5.	Does not meet criteria for study design
Bridge JA, Salary CB, Birmaher B, Asare AG, Brent DA. The risks and benefits of antidepressant treatment for youth depression. *Annals of Medicine* 2005;37(6):404-12.	Does not meet criteria for study design
Byford S H. Cost-effectiveness analysis of a home based social work intervention for children and adolescents who have deliberately poisoned themselves. *The British journal of psychiatry : the journal of mental science.* 1999;Vol-62.	Conducted in population that is not comparable to primary care (e.g., high risk conditions not prevalent in primary care populations)
Caballero J, Nahata MC. Selective serotonin-reuptake inhibitors and suicidal ideation and behavior in children. *Am J Health Syst Pharm.* 2005;62:864-867.	Does not meet criteria for study design
Carpenter, D. J., Lipschitz, A., Fong, R., Krulewicz, S., Wilkinson, C., and Davies, J. Is it appropriate to combine data from children and adolescents in pediatric MDD clinical trials? Poster presented at: New Clinical Drug Evaluation Unit annual meeting. 6-8-2005. Boca Raton, FL.	Does not meet criteria for study design

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Key Question 5: What are the adverse effects of treatment?	
Reference	**Reason for exclusion***
Center for Drug Evaluation and Research. Statistical Review: Fluoxetine (Prozac). Application Number: 18-936/SE5-064. 1-37. 2001.	Used as a source document only
Chavira DA, Stein MB. Combined psychoeducation and treatment with selective serotonin reuptake inhibitors for youth with generalized social anxiety disorder. Journal of Child & Adolescent Psychopharmacology. 2002;12:47-54.	Does not focus on depression screening or treatment or harms of either
Cheung AH, Emslie GJ, Mayes TL. Review of the efficacy and safety of antidepressants in youth depression. *Journal of Child Psychology and Psychiatry.* 2005;46:-754.	Used as a source document only
Christensen H, Griffiths KM, Korten A. Web-based cognitive behavior therapy: analysis of site usage and changes in depression and anxiety scores. *J Med Internet Res.* 2002;4:e3.	Does not focus on depression screening or treatment or harms of either
Cohen D. Should the use of selective serotonin reuptake inhibitors in child and adolescent depression be banned?. *Psychotherapy & Psychosomatics.* 2007;76:5-14.	Does not meet criteria for study design
Committee on Safety of Medicines. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. ii-185. 2004.	Used as a source document only
Committee on Safety of Medicines. Selective serotonin reuptake inhibitors (SSRIs) - overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents: Summary of clinical trials. MHRA . 2005. 2-9-2007.	Used as a source document only
Council of Scientific Affairs (A-05). Safety and Efficacy of Selective Serotonin Reuptake Inhibitors (SSRIs) in Children and Adolescents. 10. 2006.	Does not meet criteria for study design
Culpepper L, Davidson JR, Dietrich AJ, Goodman WK, Kroenke K, Schwenk TL. Suicidality as a possible side effect of antidepressant treatment. *J Clin Psychiatry.* 2004;65:742-749.	Does not meet criteria for study design
Diller L. Antidepressants and children's depression. *Am J Psychiatry.* 2005;162:1226-1227.	Does not meet criteria for study design
Doggrell SA. Fluoxetine--do the benefits outweigh the risks in adolescent major depression?. *Expert Opinion on Pharmacotherapy.* 2005;6:147-150.	Does not meet criteria for study design
Donnelly CL. Pharmacologic treatment approaches for children and adolescents with posttraumatic stress disorder. *Child & Adolescent Psychiatric Clinics of North America.* 2003;12:251-269.	Does not focus on depression screening or treatment or harms of either
Dubicka B, Hadley S, Roberts C. Suicidal behaviour in youths with depression treated with new-generation antidepressants: Meta-analysis. *Br J Psychiatry.* 2006;189:393-398.	Used as a source document only
Faedda GL, Baldessarini RJ, Glovinsky IP, Austin NB. Treatment-emergent mania in pediatric bipolar disorder: a retrospective case review. *Journal of Affective Disorders.* 2004;82:149-158.	Does not focus on depression screening or treatment or harms of either
Fairbanks JM, Gorman JM. Fluvoxamine. 2004:283-90.	Does not focus on depression screening or treatment or harms of either
Fazel, Seena, Grann, Martin, and Goodwin, Guy M. Suicide trends in discharged patients with mood disorders: Associations with selective serotonin uptake inhibitors and comorbid substance misuse. *International Clinical Psychopharmacology* 2006;21(2), 111-115.	Does not meet criteria for study design
Fichter MM, Kruger R, Rief W, Holland R, Dohne J. Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating-specific psychopathology. *Journal of Clinical Psychopharmacology.* 1996;16:9-18.	Does not focus on depression screening or treatment or harms of either

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Key Question 5: What are the adverse effects of treatment?	
Reference	**Reason for exclusion***
Findling, Robert L., Nucci, Gianluca, Piergies, Antoni A., Gomeni, Roberto, Bartolic, Edward I., Fong, Regan, Carpenter, David J., Leeder, J. Steven, Gaedigk, Andrea, and Danoff, Theodore M. Multiple Dose Pharmacokinetics of Paroxetine in Children and Adolescents with Major Depressive Disorder or Obsessive-Compulsive Disorder. *Neuropsychopharmacology* 2006;31(6), 1274-1285.	Does not meet criteria for study design
Flores-Suarez LF, Vega-Memije ME, Chanussot-Deprez C. Cutaneous vasculitis during selective serotonin reuptake inhibitor therapy. *Am J Med.* 2006;119:e1-e3.	Does not meet criteria for study design
Fluvoxamine: new indication. No progress in obsessive-compulsive disorder. *Prescrire Int.* 2004;13:163-165.	Does not focus on depression screening or treatment or harms of either
Garland EJ, Baerg EA. Amotivational syndrome associated with selective serotonin reuptake inhibitors in children and adolescents. *J Child Adolesc Psychopharmacol.* 2001;11:181-186.	Does not meet criteria for study design
Geddes J, Butler R. Depressive disorders. *Clin Evid.* 2002;951-973.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Geller DA, Wagner KD, Emslie G et al. Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2004;43:1387-1396.	Does not focus on depression screening or treatment or harms of either
Gherpelli, Jose Luiz Dias and Esposito, Sandro Blasi. A prospective randomized double blind placebo controlled crossover study of fluoxetine efficacy in the prophylaxis of chronic daily headache in children and adolescents. *Arquivos de Neuro-Psiquiatria* 2005;63(3-A), 559-563.	Does not focus on depression screening or treatment or harms of either
Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and rate of suicide. *Arch Gen Psychiatry.* 2005;62:165-172.	Does not meet criteria for study design
Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent suicide. *Am J Psychiatry.* 2006;163:1898-1904.	Does not meet criteria for study design
Gillette, Daniel W. Desipramine and ibuprofen. Journal of the American Academy of *Child & Adolescent Psychiatry* 1998;37(11), 1129.	Does not meet criteria for study design
Go FS MEB. Manic behaviors associated with fluoxetine in three 12- to 18-year-olds with obsessive-compulsive disorder. *Journal of Child and Adolescent Psychopharmacology.* 1998;73-80.	Does not focus on depression screening or treatment or harms of either
Goldney RD. Suicide and antidepressants: what is the evidence? *Australian & New Zealand Journal of Psychiatry.* 2006;40:381-385.	Does not meet criteria for study design
Goodman, Wayne K., Murphy, Tanya K., and Lazoritz, Martin. Risk of Suicidality During Antidepressant Treatment of Children and Adolescents. *Primary Psychiatry* 2006;13(1), 43-50.	Does not meet criteria for study design
Goodman, Wayne K., Murphy, Tanya K., and Storch, Eric A. Risk of adverse behavioral effects with pediatric use of antidepressants. Psychopharmacology 2007;191(1), 87-96.	Does not meet criteria for study design
Guaiana, Giuseppe, Andretta, Margherita, Corbari, Letizia, Mirandola, Mersia, Sorio, Adriano, D'Avanzo, Barbara, and Barbui, Corrado. Antidepressant Drug Consumption and Public Health Indicators in Italy, 1955 to 2000. *Journal of Clinical Psychiatry* 2005;66(6), 750-755.	Does not meet criteria for study design

Appendix C Table C9. Studies Excluded from the Review for Key Question 5

Key Question 5: What are the adverse effects of treatment?	
Reference	**Reason for exclusion***
Gunnell, David and Ashby, Deborah. Antidepressants and suicide: What is the balance of benefit and harm. *BMJ: British Medical Journal* 2004;329(7456), 34-38.	Does not meet criteria for study design
Gunnell, David and Ashby, Deborah. Rising prescription rate does not mean rising rate of new users: Reply. *BMJ: British Medical Journal* 2004;329(7463), 461-462.	Does not meet criteria for study design
Gunther T, Holtkamp K, Jolles J, Herpertz-Dahlmann B, Konrad K. The influence of sertraline on attention and verbal memory in children and adolescents with anxiety disorders. *Journal of Child & Adolescent Psychopharmacology.* 2005;15:608-618.	Does not focus on depression screening or treatment or harms of either
Hadley SJ, Greenberg J, Hollander E. Diagnosis and treatment of body dysmorphic disorder in adolescents. *Current Psychiatry Reports.* 2002;4:108-113.	Does not meet criteria for study design
Hall WD. How have the SSRI antidepressants affected suicide risk? *Lancet.* 2006;367:1959-1962.	Does not meet criteria for study design
Harrington R. Randomized trial of a home-based family intervention for children who have deliberately poisoned themselves. *J Am Acad Child Adolesc Psychiatry.* 1998;512-518.	Does not report outcomes listed in inclusion criteria
Hazell P. Depression in children and adolescents. *Evid Based Ment Health.* 2003;6:103-104.	Does not meet criteria for study design
Helgason T, Tomasson H, Zoega T. Antidepressants and public health in Iceland. Time series analysis of national data. *British Journal of Psychiatry.* 2004;184:157-162.	Does not meet criteria for study design
Helping depressed children. *Nature.* 2004;431:111.	Does not meet criteria for study design
Hollander, Eric, Swanson, Erika, Anagnostou, Evdokia, Phillips, Ann, Chaplin, William, and Wasserman, Stacey. Liquid fluoxetine versus placebo for repetitive behaviors in childhood autism. *Progress in Neurotherapeutics and Neuropsychopharmacology* 2006;(1):105-113.	Does not focus on depression screening or treatment or harms of either
Irons, Jane. Fluvoxamine in the treatment of anxiety disorders. *Neuropsychiatric Disease And Treatment* 2005;1(4), 289-299.	Does not focus on depression screening or treatment or harms of either
Isacsson G, Holmgren P, Ahlner J. Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. *Acta Psychiatrica Scandinavica* 2005;111(4):286-90.	Does not meet criteria for study design
James A. The use of Selective Serotonin Re-uptake Inhibitors (SSRIs) in the treatment of depressive disorders in children and adolescents. *Epidemiol Psichiatr Soc.* 2005;14:63-67.	Does not meet criteria for study design
Jellinek MS. Making safety data available. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2004;43:1189.	Does not meet criteria for study design
Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA.* 2004;292:338-343.	Focus on treatment comparison, matching, or fine-tuning
Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin A L. Efficacy and safety of antidepressants for children and adolescents. *BMJ.* 2004;328:879-883.	Does not meet criteria for study design
Kamijima K, Murasaki M, Asai M et al. Paroxetine in the treatment of obsessive-compulsive disorder: randomized, double-blind, placebo-controlled study in Japanese patients. *Psychiatry & Clinical Neurosciences.* 2004;58:427-433.	Does not focus on depression screening or treatment or harms of either
Kaplan A, Hollander E. A review of pharmacologic treatments for obsessive-compulsive disorder. *Psychiatr Serv.* 2003;54:1111-1118.	Does not focus on depression screening or treatment or harms of either

Appendix C Table C9. Studies Excluded from the Review for Key Question 5

Key Question 5: What are the adverse effects of treatment?	
Reference	**Reason for exclusion***
Klein DN, Dougherty LR, Olino TM. Toward guidelines for evidence-based assessment of depression in children and adolescents. *J Clin Child Adolesc Psychol.* 2005;34:412-432.	Does not meet criteria for study design
Kolevzon A, Mathewson KA, Hollander E. Selective serotonin reuptake inhibitors in autism: a review of efficacy and tolerability. *J Clin Psychiatry.* 2006;67:407-414.	Does not focus on depression screening or treatment or harms of either
Kondro W, Sibbald B. Drug company experts advised staff to withhold data about SSRI use in children. *CMAJ Canadian Medical Association Journal.* 2004;170:783.	Does not meet criteria for study design
Kramer G. Broadening the perspective: treating the whole patient. *Epilepsia.* 2003;44:Suppl-22.	Does not meet criteria for study design
Kratochvil, Christopher J., Simons, Anne, Vitiello, Benedetto, Walkup, John, Emslie, Graham, Rosenberg, David, and March, John S. A Multisite Psychotherapy and Medication Trial for Depressed Adolescents: Background and Benefits. *Cognitive and Behavioral Practice* 2005;12(2), 159-165.	Does not meet criteria for study design
Krulewicz S, Carpenter DJ, Fong R et al. Analysis of electrocardiographic data following use of paroxetine in pediatric depression and obsessive-compulsive disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 2006;45(4):422-30.	Does not report outcomes listed in inclusion criteria
Leon AC, Marzuk PM, Tardiff K, Bucciarelli A, Markham PT, Galea S. Antidepressants and youth suicide in New York City, 1999-2002. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2006;45:1054-1058.	Does not meet criteria for study design
Leon, Andrew C., Marzuk, Peter M., Tardiff, Kenneth, and Teres, Jedediah J. Paroxetine, Other Antidepressants, and Youth Suicide in New York City: 1993 Through 1998. *Journal of Clinical Psychiatry* 2004;65(7), 915-918.	Does not meet criteria for study design
Lim CJ, Leckman JF, Young C, Martin A. Antidepressant-induced manic conversion: a developmentally informed synthesis of the literature. *Int Rev Neurobiol.* 2005;65:25-52.	Does not meet criteria for study design
Ludwig J, Marcotte DE. Anti-depressants, suicide, and drug regulation. *Journal of Policy Analysis & Management.* 2005;24:249-272.	Does not meet criteria for study design
MacGillivray S, Arroll B, Hatcher S et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *BMJ.* 2003;326:1014-1017.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Mancini C, Van AM, Bennett M, Patterson B, Watson C. Emerging treatments for child and adolescent social phobia: a review. *Journal of Child & Adolescent Psychopharmacology.* 2005;15:589-607.	Does not focus on depression screening or treatment or harms of either
Mancini J, Thirion X, Masut A et al. Anxiolytics, hypnotics, and antidepressants dispensed to adolescents in a French region in 2002. *Pharmacoepidemiol Drug Saf.* 2006;15:494-503.	Does not focus on depression screening or treatment or harms of either
Mann JJ, Emslie G, Baldessarini RJ et al. ACNP Task Force report on SSRIs and suicidal behavior in youth. *Neuropsychopharmacology.* 2006;31:473-492.	Used as a source document only
March JS, Biederman J, Wolkow R et al. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA.* 1998;280:1752-1756.	Does not focus on depression screening or treatment or harms of either
March JS, Klee BJ, Kremer CM. Treatment benefit and the risk of suicidality in multicenter, randomized, controlled trials of sertraline in children and adolescents. *J Child Adolesc Psychopharmacol.* 2006;16:91-102.	Used as a source document only

Appendix C Table C9. Studies Excluded from the Review for Key Question 5

Key Question 5: What are the adverse effects of treatment?	
Reference	**Reason for exclusion***
Marquet RL, Bartelds AI, Kerkhof AJ, Schellevis FG, van der ZJ. The epidemiology of suicide and attempted suicide in Dutch General Practice 1983-2003. *BMC Family Practice.* 2005;6:45.	Does not focus on depression screening or treatment or harms of either
Martin RM, May M, Gunnell D. Did intense adverse media publicity impact on prescribing of paroxetine and the notification of suspected adverse drug reactions? Analysis of routine databases, 2001-2004. *Br J Clin Pharmacol.* 2006;61:224-228.	Does not focus on depression screening or treatment or harms of either
Martinez C, Rietbrock S, Wise L et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. *BMJ.* 2005;330:389.	Focus on treatment comparison, matching, or fine-tuning
Masi G. Pharmacotherapy of pervasive developmental disorders in children and adolescents. *CNS drugs.* 2004;18:1031-1052.	Does not focus on depression screening or treatment or harms of either
McElroy SL, Kotwal R, Kaneria R, Keck PE, Jr. Antidepressants and suicidal behavior in bipolar disorder. *Bipolar Disorders.* 2006;8:t-617.	Does not focus on depression screening or treatment or harms of either
McKeown RE, Cuffe SP, Schulz RM. US suicide rates by age group, 1970-2002: an examination of recent trends. *American Journal of Public Health.* 2006;96:1744-1751.	Does not meet criteria for study design
McQuillan CT, Rodriguez J. Adolescent suicide: a review of the literature. *Bol Asoc Med P R.* 2000;92:30-38.	Does not meet criteria for study design
Medicines and Healthcare Products Regulatory Agency. Selective Serotonin reuptake inhibitors (SSRIs): overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents - summary of clinical trials. 1-190. 2003.	Used as a source document only
Moor S, Ann M, Hester M et al. Improving the recognition of depression in adolescence: Can we teach the teachers? *J Adolesc.* 2007; 30(1):81-95.	Does not focus on depression screening or treatment or harms of either
Mosholder AD, Willy M. Suicidal adverse events in pediatric randomized, controlled clinical trials of antidepressant drugs are associated with active drug treatment: A meta-analysis. (References). *Journal of Child and Adolescent Psychopharmacology.* 2006;16:-32.	Used as a source document only
Mosholder, Andrew D. and Pamer, Carol A. Postmarketing surveillance of suicidal adverse events with pediatric use of antidepressants. *Journal of Child and Adolescent Psychopharmacology* 2006;16(1-2), 33-36.	Does not meet criteria for study design
Murphy, Tanya K., Storch, Eric A., and Strawser, Melissa S. Selective Serotonin Reuptake Inhibitor-Induced Behavioral Activation in the PANDAS Subtype. *Primary Psychiatry* 2006;13(8), 87-89.	Does not focus on depression screening or treatment or harms of either
Najjar F, Price LH. Citalopram and dystonia. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2004;43:8-9.	Does not meet criteria for study design
Nakahira H, Tomotake M, Ohmori T. Fluvoxamine induced complex partial seizure in the treatment of bulimia nervosa. *General Hospital Psychiatry.* 2005;27:148-150.	Does not focus on depression screening or treatment or harms of either
Nardi DA, Barrett S. Potential effects of antidepressant agents on the growth and development of children and adolescents. *Journal of Psychosocial Nursing & Mental Health Services* 2005;43(1):22-35.	Does not meet criteria for study design
Oldham J. The risk/benefit ratio of psychiatric treatment. *Journal of Psychiatric Practice.* 2005;11:137.	Does not meet criteria for study design

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Key Question 5: What are the adverse effects of treatment?	
Reference	**Reason for exclusion***
National Institute for Clinical Excellence. Depression in Children and Young People: Identification and management in primary, community and secondary care. 1-233. 2005. Northhamptonshire, The British Psychological Society.	Used as a source document only
Palermo MT, Curatolo P. Pharmacologic treatment of autism. *J Child Neurol.* 2004;19:155-164.	Does not focus on depression screening or treatment or harms of either
Papanikolaou K, Richardson C, Pehlivanidis A, Papadopoulou-Daifoti Z. Efficacy of antidepressants in child and adolescent depression: a meta-analytic study. *J Neural Transm.* 2006;113:399-415.	Used as a source document only
Perlis RH, Beasley CM, Wines JD et al. Treatment-associated suicidal ideation and adverse effects in an open, multicenter trial of fluoxetine for major depressive episodes. *SO: Psychotherapy and psychosomatics.* 2007;76:40-46.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Pignone, M. P., Gaynes, B. N., Rushton, J. L., Mulrow, C. D., Orleans, C. T., Whitener, B. L., Mills, C., and Lohr, K. N. Screening for Depression. i-D-83. 2002. Rockville, MD, Agency for Healthcare Research and Quality.	Used as a source document only
Plioplys S. Depression in children and adolescents with epilepsy. *Epilepsy & Behavior.* 2003;4:Suppl-45.	Does not meet criteria for study design
Pravin D, Srinath S, Girimaji S, Seshadri SP. Citalopram and mania. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2004;43:791.	Does not meet criteria for study design
Pretorius E. Corticosteroids, depression and the role of serotonin. *Rev Neurosci.* 2004;15:109-116.	Does not report outcomes listed in inclusion criteria
Ramasubbu R. Cerebrovascular effects of selective serotonin reuptake inhibitors: a systematic review. *J Clin Psychiatry.* 2004;65:1642-1653.	Does not meet criteria for study design
Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. *Clinical Pharmacology & Therapeutics.* 2004;75:234-241.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Regan J, Hamer G, Wright A, White C. SSRI and suicide in adolescents. *Tenn Med.* 2004;97:121-122.	Does not meet criteria for study design
Reseland S, Bray I, Gunnell D. Relationship between antidepressant sales and secular trends in suicide rates in the Nordic countries. *British Journal of Psychiatry.* 2006;188:354-358.	Does not meet criteria for study design
Rihmer Z, Akiskal H. Do antidepressants t(h)reat(en) depressives? Toward a clinically judicious formulation of the antidepressant-suicidality FDA advisory in light of declining national suicide statistics from many countries. *Journal of Affective Disorders.* 2006;94:3-13.	Does not meet criteria for study design
Ryan ND. Treatment of depression in children and adolescents. *Lancet.* 2005;366:933-940.	Does not meet criteria for study design
Rynn M, Wagner KD, Donnelly C et al. Long-term sertraline treatment of children and adolescents with major depressive disorder. *Journal of Child & Adolescent Psychopharmacology* 2006; 6(1-2):103-16.	Does not meet criteria for study design
Safer DJ. Should selective serotonin reuptake inhibitors be prescribed for children with major depressive and anxiety disorders? *Pediatrics.* 2006;118:1248-1251.	Does not meet criteria for study design
Safer, Daniel J. and Zito, Julie Magno. Treatment-emergent adverse events from selective serotonin reuptake inhibitors by age group: Children versus adolescents. *Journal of Child and Adolescent Psychopharmacology* 2006;16(1-2), 159-169.	Used as a source document only

Appendix C Table C9. Studies Excluded from the Review for Key Question 5

Key Question 5: What are the adverse effects of treatment?	
Reference	**Reason for exclusion***
Salerian AJ. Use of selective serotonin reuptake inhibitors in childhood depression. *Lancet.* 2004;364:660-661.	Does not meet criteria for study design
Scahill L, Hamrin V, Pachler ME. The use of selective serotonin reuptake inhibitors in children and adolescents with major depression. *Journal of Child & Adolescent Psychiatric Nursing.* 2005;18:86-89.	Does not meet criteria for study design
Scharko AM, Reiner WG. Ssri-induced sexual dysfunction in adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2004;43:1067-1068.	Does not report outcomes listed in inclusion criteria
Scharko AM. Selective serotonin reuptake inhibitor-induced sexual dysfunction in adolescents: a review. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2004;43:1071-1079.	Does not report outcomes listed in inclusion criteria
Seidel L, Walkup JT. Selective serotonin reuptake inhibitor use in the treatment of the pediatric non-obsessive-compulsive disorder anxiety disorders. *Journal of Child & Adolescent Psychopharmacology.* 2006;16:171-179.	Does not focus on depression screening or treatment or harms of either
Sharp SC, Hellings JA. Efficacy and safety of selective serotonin reuptake inhibitors in the treatment of depression in children and adolescents: practitioner review. *Clinical Drug Investigation.* 2006;26:247-255.	Used as a source document only
Shen Y and Center for Drug Evaluation and Research. Statistical reviews: application No. 18-936/SE5-064. 1-39. 2003.	Article covered by an included systematic evidence review
Shirazi E, aghband-Rad J. An open trial of citalopram in children and adolescents with depression. *Journal of Child & Adolescent Psychopharmacology.* 2005;15:233-239.	Does not meet criteria for study design
Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. *Am J Psychiatry.* 2006;163:41-47.	Does not meet criteria for study design
Sondergard L, Kvist K, Lopez AG, Andersen PK, Kessing LV. Temporal changes in suicide rates for persons treated and not treated with antidepressants in Denmark during 1995-1999. *Acta Psychiatr Scand.* 2006;114:168-176.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Stein DJ, Ipser JC, Balkom AJ. Pharmacotherapy for social phobia. *Cochrane Database of Systematic Reviews.* 2004;CD001206.	Does not focus on depression screening or treatment or harms of either
Stein DJ, Kasper S, Andersen EW, Nil R, Lader M. Escitalopram in the treatment of social anxiety disorder: analysis of efficacy for different clinical subgroups and symptom dimensions. *Depression & Anxiety.* 2004;20:175-181.	Does not focus on depression screening or treatment or harms of either
Stein DJ, Zungu-Dirwayi N, van Der Linden GJ, Seedat S. Pharmacotherapy for posttraumatic stress disorder. *Cochrane Database of Systematic Reviews.* 2000;CD002795.	Does not focus on depression screening or treatment or harms of either
Suicidal ideas with paroxetine or venlafaxine. *Prescrire Int.* 2004;13:21.	Does not meet criteria for study design
Szigethy, Eva, Whitton, Sarah W., Levy-Warren, Anna, DeMaso, David Ray, Weisz, John, and Beardslee, William R. Cognitive-Behavioral Therapy for Depression in Adolescents With Inflammatory Bowel Disease: A Pilot Study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2004;43(12), 1469-1477.	Does not meet criteria for study design
Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. *Arch Gen Psychiatry.* 2006;63:1358-1367.	Conducted in population that is not comparable to primary care (e.g., high risk conditions not prevalent in primary care populations)

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Key Question 5: What are the adverse effects of treatment?	
Reference	**Reason for exclusion***
Tucker P, Beebe KL, Burgin C et al. Paroxetine treatment of depression with posttraumatic stress disorder: effects on autonomic reactivity and cortisol secretion. *Journal of Clinical Psychopharmacology.* 2004;24:131-140.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. *Osteoporos Int.* 2006;17:807-816.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Vieweg WV, Pandurangi AK, Anum EA, Lanier JO, Fierro MF, Fernandez A. Toxicology Findings in Child and Adolescent Suicides in Virginia: 1987-2003. *Prim Care Companion J Clin Psychiatry.* 2006;8:142-146.	Does not meet criteria for study design
Vitiello B. Selective serotonin reuptake inhibitors (SSRIs) in children and adolescents. *Journal of Child & Adolescent Psychopharmacology.* 2006;16:7-9.	Does not meet criteria for study design
von Knorring, Anne Liis, Olsson, Gunilla Ingrid, Thomsen, Per Hove, Lemming, Ole Michael, and Hulten, Agnes. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *Journal of Clinical Psychopharmacology* 2006;26(3), 311-315.	Does not meet quality criteria: control group conditions not clearly described, eligibility criteria changed midway through study, important aspects of study design not reported (blinding of outcome assessment)
Wadsworth EJ, Moss SC, Simpson SA, Smith AP. Psychotropic medication use and accidents, injuries and cognitive failures. *Human psychopharmacology.* 2005;20:391-400.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Wagner KD, Berard R, Stein MB et al. A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. *Arch Gen Psychiatry.* 2004;61:1153-1162.	Does not focus on depression screening or treatment or harms of either
Walkup JT LMRMP. Searching for moderators and mediators of pharmacological treatment effects in children and adolescents with anxiety disorders. *J Am Acad Child Adolesc Psychiatry.* 2003;13-21.	Does not focus on depression screening or treatment or harms of either
Warning: selective serotonin reuptake inhibitors in children and adolescents. *S Afr Med J.* 2005; 95(9):660.	Does not meet criteria for study design
Waxmonsky J. Assessment and treatment of attention deficit hyperactivity disorder in children with comorbid psychiatric illness. *Curr Opin Pediatr.* 2003;15:476-482.	Conducted exclusively in high-risk populations
Weiss, Jeffrey J. and Gorman, Jack M. Antidepressant Adherence and Suicide Risk in Depressed Youth. *American Journal of Psychiatry* 2005;162(9), 1756-1757.	Does not meet criteria for study design
Weisz JR, Doss AJ, Hawley KM. Youth psychotherapy outcome research: a review and critique of the evidence base. *Annu Rev Psychol.* 2005;56:337-363.	Does not report outcomes listed in inclusion criteria
Wernicke JF. Safety and side effect profile of fluoxetine. *Expert Opinion on Drug Safety.* 2004;3:495-504.	Does not meet criteria for study design
Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet.* 2004;363:1341-1345.	Used as a source document only
Wilens TE, Biederman J, Kwon A et al. A systematic chart review of the nature of psychiatric adverse events in children and adolescents treated with selective serotonin reuptake inhibitors. *J Child Adolesc Psychopharmacol.* 2003;13:143-152.	Does not meet criteria for study design

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Key Question 5: What are the adverse effects of treatment?	
Reference	**Reason for exclusion***
Winters NC. Are antidepressants safe for adolescents?. *Postgrad Med.* 2005;118:33-34.	Does not meet criteria for study design
Wohlfarth T, Storosum J. Later results don't confirm antidepressant suicide link. *Nature.* 2005;437:1232.	Does not meet criteria for study design
Wohlfarth TD, van Zwieten BJ, Lekkerkerker FJ et al. Antidepressants use in children and adolescents and the risk of suicide. *Eur Neuropsychopharmacol.* 2006;16:79-83.	Used as a source document only
Wohlfarth, Tamar, Lekkerkerker, Frits, and van Zwieten, Barbara. Use of selective serotonin reuptake inhibitors in childhood depression. *Lancet* 2004;364(9435), 659-660.	Does not meet criteria for study design
Wong IC, Besag FM, Santosh PJ, Murray ML. Use of selective serotonin reuptake inhibitors in children and adolescents. *Drug Saf.* 2004;27:991-1000.	Does not meet criteria for study design
Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. *J Psychiatr Res.* 2004;38:577-582.	Focus on adults (>18 years old) or children ages 0-6 or doesn't report pediatric outcomes separately
Zlotnik, Gideon. Letter to the editor. *Nordic Journal of Psychiatry* 2004;58(2), 175.	Does not meet criteria for study design

Appendix D. Ongoing and Pending Trials

Principal investigators	Location	Population	Approximate size	Investigations	Outcomes	Status as of 2007
KQ1: Screening outcomes						
Audrey Burnam, PhD Lisa Jaycox, PhD	US	13- to 17-year-olds receiving care at a participating primary care physician office; half with major depression diagnosis, half with no detectable mental disorder	800	1) Impact of depression on adolescent and family functioning, 2) Effect of diagnosis feedback vs. educational brochure on care received, and 3) Barriers and facilitators to receiving appropriate care	1) Baseline and followup assessments 2) Receipt of care and satisfaction 3) Descriptive analysis	In progress
KQ2: Screening efficacy						
Lise Bergeron, PhD	Canada	6- to 11-year-olds from both general and clinical populations	600	Dominic Interactive	Reliability and validity	Submitted for publication
Kelly J. Kelleher, MD, MPH	US	Children aged 11 and older	5,900	Trial of Automated Risk Appraisal for Adolescents (TARAA) vs. usual care	Care comparison	Completion expected August 2008
KQ3: Screening harms						
KQ4: Treatment efficacy, SSRIs						
Forest Laboratories	US	12- to 17-year-olds with diagnosis of MDD	Not available	Escitalopram vs. placebo	CDRS-R, CGI-I, CGAS	Recruitment completed
KQ4: Treatment efficacy, psychotherapy						
Laura Mufson, PhD	New York	Females 12 to 18 years old with diagnosis of MDD, Dysthymic Disorder, Depressive Disorder NOS, or Adjustment Disorder with depressed mood in school-based health clinics	125	Group IPT vs. TAU	Depressive symptoms (HRSD and CES-D), overall impairment (C-GAS), social functioning (SAS-SR)	In progress
Kevin Stark, PhD	Austin	Females 9 to 13 years old with diagnosis of depressive disorder, including MDD, dysthymia, depression NOS, and MDD in partial remission	Currently 128, with screening of one cohort remaining	School-based CBT, CBT with parent training component, minimal contact control condition	Depressive symptoms (CDI, BDI-Y, K-SADS, CBCL), GAS, cognition, family functioning, educational functioning	Results expected in 2008

Appendix D. Ongoing and Pending Trials

Principal investigators	Location	Population	Approximate size	Investigations	Outcomes	Status as of 2007
Robin Weersing, PhD	Pennsylvania	8- to 17-year-olds	60	Eight sessions of CBT vs. community referral	Symptoms of depression and anxiety; ratings of global improvement	Data collection complete, expect to submit for publication end of 2007
KQ5: Treatment harms						
Enid M. Hunkeler, MA	California	Children and adolescents who were members of the Kaiser Permanente Medical Care Program from 1995 through 2003	800,000	Antidepressant medications and suicidal behavior	Completed suicides and suicide attempts	Manuscript in progress
Onur N. Karayal, MD, MPH John S. March, MD, MPH	US and Canada	7- to 17-year-olds enrolled in the Child and Adolescent Psychiatry Trials Network with a diagnosis of an anxiety disorder, depressive disorder, eating disorder or obsessive-compulsive disorder and who were prescribed an SSRI or SNRI	2,420	Risks and benefits of treatment with an SSRI or SNRI	DPS-IV and PAERS	Completion expected February 2010
Kelly J. Kelleher, MD, MPH	US	Youth, adults, and older adults	Not available	Relationships among antidepressant use, suicide, and suicidality	Bayesian hierarchical models	Completion expected June 2011

MDD-Major Depressive Disorder; NOS-not otherwise specified; HRSD-Hamilton Rating Scale for Depression; CES-D-Center for Epidemiological Studies-Depression Scale; C-GAS-Global Assessment Scale for Children; SAS-SR-Social Adjustment Scale-Self-Report; IPT-Interpersonal Psychotherapy; SSRI-selective serotonin reuptake inhibitor; CBT-Cognitive-Behavioral Therapy; CDRS-R-Children's Depression Rating Scale-Revised; Kiddie-SADS-Kiddie Schedule for Affective Disorders and Schizophrenia; NOS-not otherwise specified; SNRI-serotonin-norepinephrine reuptake inhibitor; DPS-IV-DISC Predictive Scales; PAERS-Pediatric Adverse Event Rating Scale