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Screening for Major Depressive Disorder Among Children and Adolescents: A Systematic Review for the U.S. Preventive Services Task Force

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Prepared by:
RTI International–University of North Carolina Evidence-based Practice Center
Research Triangle Park, NC

Investigators:
Valerie Forman-Hoffman, PhD, MPH
Emily McClure, MSPH
Joni McKeeman, PhD
Charles T. Wood, MD
Jennifer Cook Middleton, PhD
Asheley C. Skinner, PhD
Eliana M. Perrin, MD, MPH
Meera Viswanathan, PhD

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Structured Abstract

Purpose: To evaluate the evidence on screening and treating children and adolescents for major depressive disorder (MDD) for the U.S. Preventive Services Task Force. This update modified the inclusion criteria used in the 2009 review to focus on screening for MDD (i.e., studies reporting that ≥50% of their sample had MDD); thus, we do not address screening or treatment for minor depression or dysthymia. Little is known about the etiological links between subthreshold depression, dysthymia, and MDD or efficacious treatments for less severe forms of depression in children. Focusing on MDD reduces heterogeneity in patient characteristics and targets children and adolescents experiencing more serious symptoms who are most likely to suffer severe functional impairment and suicidality.

Data Sources: PubMed/MEDLINE, the Cochrane Library, PsycINFO, ClinicalTrials.gov, HSRProj, the World Health Organization International Clinical Trials Registry Platform, and reference lists of published literature (through February 2015). We re-reviewed studies identified in the 2009 report against the revised inclusion and exclusion criteria.

Study Selection: Two investigators independently selected studies reporting on benefits and harms of screening; accuracy of screening tools compared with diagnostic evaluations; and benefits or harms of treatment of MDD compared with placebo, usual care, or waitlist interventions.

Data Extraction: One reviewer extracted data and a second checked accuracy. Two independent reviewers assigned quality ratings using predefined criteria.

Data Synthesis: No trials examine the impact of screening for pediatric MDD in primary care on subsequent improvements in depression and other health-related outcomes. No new screening accuracy studies met our criteria. The limited number of screening accuracy studies from the 2009 review that remain in our synthesis suggest that the Patient Health Questionnaire for Adolescents (PHQ-A) and the Beck Depression Inventory (BDI) can identify adolescents who are at risk of MDD (PHQ-A sensitivity, 73%; PHQ-A specificity, 94%; BDI sensitivity, 84% to 90%; BDI specificity, 81% to 86%). We found no eligible studies on screening accuracy in children. Additionally, we found one new collaborative care study but no other new psychotherapy or combined therapy intervention studies. One new placebo-controlled study, an acute escitalopram trial in adolescents ages 12 to 17 years, met our criteria for treatment efficacy trials. One fluoxetine trial (ages 12 to 17 years), one escitalopram trial (ages 6 to 17 years), one citalopram trial (ages 7 to 17 years), and one cognitive behavior therapy trial (ages 14 to 18 years) from the 2009 review continued to meet our inclusion and exclusion criteria. Evidence from individual selective serotonin reuptake inhibitor (SSRI) trials demonstrated the efficacy of fluoxetine but not citalopram; one escitalopram trial demonstrated efficacy but the other did not. One collaborative care study demonstrated improvement in symptoms, response, and remission but not functional status. We found no evidence of harms attributable to treatment.

Limitations: Our inclusion and exclusion criteria, coupled with our thresholds for quality, resulted in the inclusion of five screening accuracy studies of fewer than 2,900 children and adolescents (none of whom were younger than age 11 years) and six treatment trials that

randomized fewer than 1,500 children and adolescents with MDD conducted over the past three decades. As a result, we cannot make definitive statements regarding associated benefits or harms, particularly for rare outcomes such as suicidality. Small sample sizes, high attrition, and potentially biased ascertainment of the reference standard in screening studies constrain the evidence base. Evidence gaps sharply limit conclusions for screening in children younger than age 11 years, screening and treatment differences by sex or race/ethnicity subgroups, and MDD treatment other than SSRIs.

Conclusion: We found no evidence of a direct link between screening for MDD in children and adolescents in primary care or comparable settings and depression or other health-related outcomes. We found evidence that some screening tools are accurate and some treatments have benefit for MDD among adolescents (but not younger children), with no evidence of associated harms. Although no study found statistically significant harms associated with treatment, lack of precision hampers our ability to rule out effects. Evidence gaps sharply limit conclusions for screening in children younger than age 12 years, screening and treatment differences by sex or race/ethnicity subgroups, and efficacy of MDD treatment other than SSRIs.

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Chapter 1. Introduction

Overview and Objective

The objective of this report is to update the prior U.S. Preventive Services Task Force (USPSTF) recommendations released in 2009 for screening adolescents and children for depression in primary care. The 2009 USPSTF recommendation and conclusions, described below, offer context and rationale for the current update. The remainder of the Introduction includes an overview of the epidemiology of depression in children and adolescents; a discussion of screening, treatment, and current clinical practice in primary care settings; and a description and justification of the changes in scope of this updated review. The Methods section describes the Key Questions (KQs) and analytic framework that guided our review, search strategy, study selection, data abstraction and quality rating, and data analyses. The Results section presents findings organized by KQ. Finally, the Discussion section provides a summary of the results, comment on the applicability and context of the findings, limitations, gaps and future research directions, and conclusions.

Previous USPSTF Recommendation

In 2009, the USPSTF recommended screening adolescents (ages 12 to 18 years) in primary care settings for depression when systems are in place to ensure accurate diagnosis, psychotherapy (cognitive behavioral or interpersonal), and followup (B recommendation). The USPSTF concluded that the evidence was insufficient to assess the balance of benefits and harms of screening children (ages 7 to 11 years) for depression in primary care settings (I statement).

This recommendation for adolescents and I statement for children represented a change from an overall I statement for all age groups in 2002. The 2009 change was predicated on new evidence demonstrating effective treatment for adolescents with depression.

Previous USPSTF Conclusions

Importance

The USPSTF noted that depression among youth is a disabling condition that is associated with serious long-term morbidities and risk of suicide; the panel also noted that the majority of youth with depression are undiagnosed and untreated.

Detection

The USPSTF concluded that adequate evidence exists for screening tests that accurately identify depression in adolescents. The USPSTF found that evidence was inadequate as to whether screening tests accurately identify depression in children.

Benefits of Detection and Early Intervention

The USPSTF confirmed benefits of screening and early intervention for adolescents but not for children. The efficacy of selective serotonin reuptake inhibitors (SSRIs), psychotherapy, and combined therapy (SSRIs and psychotherapy) were demonstrated for adolescents, while only fluoxetine appeared to be efficacious in children—data were too limited on the benefits of psychotherapy and the benefits of psychotherapy combined with SSRIs for children.

Harms of Detection and Early Treatment

The USPSTF found few harms associated with screening but convincing evidence that SSRIs conferred an absolute risk increase of 2 percent for suicidality over placebo-treated children and adolescents. Although SSRI groups did not have statistically significant increased risks of harms versus placebo groups, the USPSTF recommended that treatment of youth with depression with SSRIs should only be considered if judicious clinical monitoring is possible. Furthermore, the USPSTF recommended that specific treatment should be based on individual patients' needs and on mental health treatment guidelines.

Condition Definition

Depression is a mental health condition that may begin during childhood or adolescence. Although occasional feelings of sadness and other symptoms of depression are normal for children and adolescents to experience, children and adolescents with major depressive disorder (MDD) experience one or more major depressive episodes, characterized by heightened periods of low mood and loss of interest or pleasure in their everyday life and with greater intensity for an extended period of time (at least 2 weeks). MDD diagnosis requires five of nine specific symptoms nearly every day (depressed mood, loss of interest or pleasure in most activities, significant appetite or weight changes, changes in sleep, changes in activity, fatigue or loss of energy, guilt/worthlessness, concentration difficulties, and suicidality) that combined cause significant functional impairment across social, occupational, or educational domains. Among some children and adolescents with MDD, these symptoms may present as periods of disruptive mood and irritability rather than as a sad mood and may last for weeks, months, or even years. Dysthymia is another type of depression diagnosis described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV). Dysthymia is also characterized by depressed moods lasting for at least 1 year in children and adolescents, yet it is a more chronic and somewhat less severe form of depression. Associated symptoms and resulting impairment are less than in MDD but may be longer lasting. Other types of minor subsyndromal depression can still negatively affect an individual's functioning but have been studied less than dysthymia and, especially, MDD in children and adolescents.

DSM-5 Definition of MDD

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) was released in May 2013.[1] The criteria for MDD remain largely the same as those in DSM-IV, with the exception of removing the bereavement exclusion criteria. In DSM-5, individuals who

experience depression as a result of grief are not automatically excluded from an MDD diagnosis. The dysthymia diagnosis has been replaced by Persistent Dysthymic Disorder, which now consolidates chronic types of MDD and dysthymic disorder from DSM-IV. Children and adolescents with Persistent Dysthymic Disorder have depressed mood or irritability lasting for at least 1 year (where symptoms are never absent for more than 2 months at a time) accompanied by an additional two symptoms of poor appetite/eating, sleep problems, low energy or fatigue, low self-esteem, poor concentration or difficulty in making decisions, and feelings of hopelessness.

Prevalence

The rates of reported incidence and prevalence of depression in children and adolescents living in the United States vary, as described below. Differences may be attributable to the nature of the sample or how depression is defined and assessed. Diagnosing depression in children can be difficult, particularly for younger children, because limited reading and abilities to verbalize thoughts and behaviors can make it necessary to integrate information from multiple sources (e.g., a parent, a teacher, a child). Prior literature has shown that depression in childhood and adolescence is common and frequent in clinical practice settings.

The most current nationally representative U.S. estimates come from two data sources: 1) the National Comorbidity Survey–Adolescent Supplement (NCS-A), conducted in 2001 to 2004 on a sample of adolescents ages 13 to 18 years, and 2) the 2011 National Survey on Drug Use and Health (NSDUH), an annual survey of children ages 12 to 17 years. The NCS-A examines and reports the prevalence of depression defined as the presence of either MDD or dysthymia in the past 30 days, in the past year, or over a lifetime. The NSDUH assesses and reports the prevalence of a major depressive episode in the past year only. In the NCS-A, the past-30-day, past-year, and lifetime prevalence of depression were 3, 8, and 12 percent, respectively.[2,3] The lifetime prevalence of depression associated with severe impairment, indicative of depression most likely requiring treatment, was 9 percent[3] in the NCS-A. In NSDUH, past-year prevalence of a major depressive episode was estimated as the same as reported in the NCS-A (8%).[4]

Prior studies have noted a progressive increase in the lifetime cases of major depression in the past several decades.[5,6] Affective disorders such as MDD appear to aggregate in families and have younger ages of onset in successive cohorts, a phenomenon seen in other studies of depression.[7] The past several years of NSDUH data, however, have not reflected an increase in major depressive episode prevalence over time.[4]

Little is known about the prevalence of depression in younger children. The most recent nationally representative published estimate comes from the 2005 National Health and Nutrition Examination Survey (NHANES). In this survey, 2 percent of male and 4 percent of female children ages 8 to 15 years had had MDD in the past year.[8] The authors of one review found that an aggregated estimate of 2.8 percent of children younger than age 13 years had depression.[9] In the Oregon Adolescent Depression Project, 5 and 6 percent of children ages 5 to 12.9 years had first and recurrent incidences of MDD,[10] respectively. These estimates are likely higher than those from nationally representative data sources because high schoolers were recruited for

longitudinal followup, with retrospective reports of psychopathology since age 5 years. The prevalence of depression in primary care settings may be up to twice as high as in community samples of children and adolescents.[11] Although well-child visits are recommended for all children and adolescents, the co-occurrence of mental disorders increases the likelihood of seeking treatment.[12] For example, in a sample of young people ages 13 to 18 years attending a primary care clinic, nearly 10 percent had a depressive disorder at consultation.[13] This figure is markedly higher than the recent nationally representative estimate of past-month prevalence of depression in this age group (3%).[14] Rates of depressive disorder among adolescents receiving primary care services are increasing.[15]

Risk and Protective Factors

Prevalence estimates of childhood and adolescent depression vary by demographic characteristics. Girls are more likely to be diagnosed with depression than boys. NCS-A data show that girls are about twice as likely as boys to have lifetime depression (16% vs. 8%, respectively). NSDUH data show that past-year prevalence of a major depressive episode among girls is nearly 3 times as high as that for boys and that sex differences in prevalence rates first emerge during puberty and continue to widen throughout adolescence.[16] In the Oregon Adolescent Depression Project, girls had higher rates of incidence, but not recurrence, of MDD across childhood and adolescence.[10]

The prevalence of depression also increases with age. In the NCS-A, lifetime depression increased from 8.4 percent (among adolescents ages 13 to 14 years), to 12.6 percent (among adolescents ages 15 to 16 years), to 15.4 percent (among adolescents ages 17 to 18 years).[3] In the 2011 NSDUH, past-year major depressive episode prevalence increased from 2.9 percent in 12-year-old children to 11.4 percent in 17-year-old adolescents.[4] In NHANES,[8] past-year MDD without impairment was present in 1.6 percent of children ages 8 to 11 years and in 3.8 percent of those ages 12 to 15 years (with impairment: 1.4% and 3.2%, respectively). Differences in depression prevalence are also found across children and adolescents of varying racial/ethnic groups. These differences may be a result of differing cultural norms affecting the experience, expression, and reporting of depression; socioeconomic differences; acculturation; or combinations of these factors. Hispanic youths tend to have higher rates than their non-Hispanic counterparts.[8] Other studies, such as the NSDUH, have not found the prevalence of depression to vary by race/ethnicity.[4]

A variety of factors contribute to the development of depression, and most people who develop MDD have multiple risk factors.[17] In addition to differences in depression by age, sex, race/ethnicity, and family history of depression, several risk factors may predict increased risk of MDD in childhood and adolescence. In addition to low socioeconomic status,[18,19] having a comorbid mental or physical disorder,[2] negative cognitions, and interpersonal conflicts[20] or suffering negative life events[21] may increase the risk of MDD. However, strong support from family,[19,22] community, peers,[23] teachers,[24] and sports team members may protect a child or adolescent from depression.[12]

Course, Comorbidity, and Sequelae

Depression is a multifactorial condition that tends to affect people differently. Although some risk factors may be enough alone to contribute to the onset of depression, others increase the risk by interacting with one another. For example, some youth exposed to negative life events or chronic stressors do not develop MDD, whereas others with multiple risk factors do.

Age of Onset and Course

The mean age of onset of MDD in childhood and adolescence is approximately 14 to 15 years; onset is earlier in girls than boys. Further, early onset is associated with worse outcomes.[13,25-27] Reports of the average duration of depressive episodes have been variable in samples of children and adolescents, with means ranging from 2 to 17 months[26,28] in childhood and adolescence. Recent data indicate that children ages 5 to 12.9 years have an average duration of 69 weeks, and adolescents ages 13 to 17.9 years have an average duration of 24.4 weeks.[10] At 6-month followup, less than half had recovered. Approximately one third of adolescents with at least one episode of depression will experience another episode in the next 4 years.[29]

Comorbid Mental Health and Substance Use Problems

Children and adolescents with depression are likely to have other comorbid mental health problems.[10,25,30] Approximately two thirds of adolescents with depression have at least one comorbid psychiatric disorder and 10 to 15 percent have two or more comorbidities.[31] In a review,[32] comorbidity with conduct disorder/oppositional defiant disorder ranged from 21 to 83 percent, comorbidity with anxiety disorder ranged from 30 to 75 percent, and comorbidity with attention deficit disorder ranged from 0 to 57.1 percent.[32] MDD and substance use disorders also co-occur at high rates.[7,33,34] Anxiety disorders typically precede depression in children and adolescents, whereas substance use disorders typically follow depression onset by about 4.5 years.[35,36] An additional outcome of concern is that bipolar disorder may initially present with an episode of depression; the diagnosis of bipolar disorder does not become clear until later when manic symptoms appear. In a sample of 1,709 adolescents with bipolar disorder, 61 percent presented with an initial episode of depression.[37]

Although antidepressants can be a helpful treatment for bipolar disorder, they can also have adverse effects, such as inducing mania in those with bipolar disorder.[38] This risk is particularly pronounced in the child and adolescent offspring of parents with bipolar disorder. Prescribers of antidepressants are thus cautioned to closely monitor patients on antidepressants for any signs or symptoms of manic behavior after initiating medication treatment.

Finally, children and adolescents with comorbid diagnoses are likely to have poorer outcomes than those who have MDD alone. Those with comorbid diagnoses are more likely to have severe, longer-lasting, treatment-resistant, or recurrent depressive episodes; suicidal attempts; worse functional impairment; and to use more mental health services.[36,39]

Comorbid Somatic and Chronic Medical Conditions

Children and adolescents with depression frequently present in primary care for somatic complaints and chronic medical conditions. Studies report significant associations between depression and somatic symptoms such as headache and migraine, stomachaches, and musculoskeletal pain[40-42] in adolescent samples. Studies have also shown that children and adolescents with chronic medical conditions such as asthma and diabetes are more likely to have co-occurring depression than those without these chronic illnesses.[43] Overlap between depression and chronic illnesses may be due to shared symptomatology, a side effect of a medication, stress from being ill, or loss of social contact with peers and family members.[44,45] Having depression and a comorbid chronic illness incrementally worsens health compared with depression alone, with any of the chronic diseases alone, and with any combination of chronic diseases without depression.[46]

Suicidality

Childhood depression is associated with increased risk for suicide.[7,16] In 2004, an estimated 9 percent of adolescents ages 12 to 17 years had experienced a lifetime major depressive episode, with more than three quarters of those reporting suicidal thoughts at the time of their worst or most recent episode. This represents 1.8 out of 2.5 million adolescents in the United States.[47] In addition, 10 percent of children ages 5 to 12.9 years and 19 percent of adolescents ages 13 to 17.9 years with MDD attempt suicide.[10] Approximately 5 to 10 percent of adolescents with depression commit suicide within 15 years of their first major depressive episode. In one large meta-analysis that quantified the increased risk of mortality for children, adolescents, and adults with MDD, the standardized mortality ratio was 2,035 (95% CI, 1,827 to 2,259), a suicide risk of more than 20 times that expected.

Implications Into Adulthood

MDD during childhood and adolescence is strongly associated with the development of recurrent depression in adulthood[33,48] and with other mental disorders and, as previously mentioned, with risk of suicidal ideation, suicide attempts, and suicide completion.[33,49] Episodes of recurrent depression may increase in frequency and severity with each episode; patients experiencing recurrent episodes are more likely to become resistant to treatment.[50]

Burden

Depression continues to be a major public health problem. It is the leading cause of disability worldwide,[51] and produces the greatest decrement in health compared to other chronic health conditions,[52] partly because the typical age of onset is earlier for depression than for most other prevalent chronic conditions. Children and adolescents with MDD typically have functional impairment across family, school, social, or work domains. Decreased academic performance and troubled relationships with parents, siblings, and peers are common.[53-55]

The high prevalence of depression, its association with numerous coexisting mental and physical conditions, and consequent impairment in various domains of functioning may lead to lost productivity, decreased quality of life, and strain on an already burdened health care system over the life course.[33] Although the overall economic burden of depression in children and adolescents is largely unknown, health care costs, in general, are higher for children with depressive disorders than for children with other mental health diagnoses (excluding conduct disorder) or children without mental health diagnoses.[56]

In children and adolescents, depression carries the additional burden of negatively affecting developmental trajectory. Changes in a child's behavior attributable to depression can affect peer interactions, academic competence, and family interactions. The onset of depression during childhood and adolescence is associated with significant reductions in "human capital" (i.e., educational and vocational attainment) in affected individuals.[57]

Current Clinical Practice in the United States

Identification of Depression in Primary Care and School Settings

Most children and adolescents (97%) report having a usual place of health care.[58] Although only about 2 to 3 percent present with a primary psychiatric complaint,[59,60] research has shown that depression affects a sizable proportion of adolescents in primary care settings,[61] most of whom present with physical problems. Hallmark symptoms of depression such as sleep and appetite disturbances may present as complaints of tiredness or nonspecific pain, such as stomachaches or headaches. Younger children, in particular, are more likely to experience these somatic complaints, social withdrawal, and irritability, whereas adolescents are more likely to be unable to sleep and have psychomotor agitation.[26,48,62,63]

Because of the ways depression can present, primary care providers play a critical role in identifying depression in children and adolescents, particularly because youth with mental health issues are high users of primary care services.[64] Because they are often the first point of contact for children and their families who are experiencing distress, pediatric care providers can facilitate early identification of mental health issues, begin initial management, and refer children for further assessment and treatment for mental health. Pediatricians, however, tend to be highly specific in assessing emotional and behavioral problems (e.g., 84% of children assessed as nondisturbed did not in fact have a psychiatric disorder in one study) but not very sensitive (e.g., pediatricians identified only 17% of children with behavioral or emotional problems as such).[65]

In addition to primary health care, schools play an important role in identifying and treating depression in children and adolescents. In 2011, 12 percent of adolescents ages 12 to 17 years reported receiving mental health care at school.[4] In one study, 93 percent of school nurses felt that providing mental health care was a critical part of their job, yet less than half reported that they had received any training in mental health.[66] A majority of school nurses surveyed reported that mental health problems of students occupied more than one quarter of their work time.

Proportion and Characteristics of Children and Adolescents With MDD Who Receive Treatment

In nationally representative U.S. studies, less than one half of children and adolescents with MDD receive mental health treatment. In the 2001 to 2004 NCS-A, 39 percent of adolescents ages 13 to 17 years with a past-year MDD or dysthymia diagnosis reported receiving mental health treatment in their lifetime.[67] Those with more severe cases of depression were not more likely to receive treatment. Overall, 36 percent of adolescents with depression reported receiving specialty mental health treatment,[68] and 20 percent reported the use of psychotropic medication. Among adolescents with a mood disorder who received treatment, 59 percent received care in a mental health specialty setting, 40 percent received care in a school setting, 26 percent received care in a general medical setting, 25 percent received care in a human service setting, 17 percent reported use of complementary and alternative medicine (CAM) treatment, and 9 percent received care in a juvenile justice setting.

In the 2011 NSDUH, among U.S. adolescents ages 12 to 17 years with a past-year major depressive episode or a past-year major depressive episode with severe impairment, 38 and 44 percent, respectively, reported receiving depression-specific treatment in the past year.[4] Among adolescents receiving depression treatment, 58.4 percent received care from a counselor, 34 percent from a psychologist, 26 percent from a psychiatrist, 23 percent from a general practitioner or family doctor, 15 percent from an alternative services provider (e.g., religious or spiritual advisor, herbalist, chiropractor, acupuncturist, massage therapist), and 15 percent from a social worker. Similarly, in 2001 to 2004 NHANES data, 44 percent of children ages 8 to 15 years with depression reported receiving treatment.[8]

Several factors are related to whether children and adolescents with depression receive mental health treatment. Sociodemographic correlates include age, sex, race/ethnicity, parent education level, and comorbidity.[8,67,69-71] In addition, females and those with lower parental income, suicidality, severe depression, and specialty mental health treatment are more likely to use psychotropic medications for depression.[68]

Current Screening Practices in Primary Care and School-Based Settings

Studies from the early 2000s found that about half of physicians reported any adolescent screening for depression, and only 17 percent screened all adolescents for depression.[72] Only 3 percent of patients,[72,73] however, had depression screening documented in their medical records.

In 2009, the USPSTF guidelines recommended universal screening for depression in children and adolescents ages 12 to 18 years in primary care settings when resources are available for additional evaluation and care.[74,75] A pilot study showed screening instruments to be well received and accepted by adolescent patients, their parents, and their health care providers.[76] In this study, providers perceived parents and patients as expressing more satisfaction than dissatisfaction with the screening procedures and thought the increased time burden could be handled.[76] After the USPSTF 2009 screening recommendations appeared, several medical

practices and school districts adopted mental health programs that routinely screen for depression, but the larger impact of the recommendation remains unknown.[77-79]

Although a majority of experts from family medicine, pediatrics, nursing, psychology, and child psychiatry endorse routine surveillance for youth at high risk for depression,[80] universal screening is still debated. Some pediatricians report discomfort with making a diagnosis of depression stemming from lack of self-efficacy, training, or experience specific to delivering mental health care.[81] A primary care study in a pediatric population examining physical pain, mental health symptoms, and provider characteristics revealed several factors associated with addressing psychosocial health during primary care visits.[82] The presence of hyperactivity symptoms, mental health complaints, care by a female clinician, and practitioner-reported confidence in mental health treatment correlated with discussions between patients and clinicians about psychosocial health; by contrast, presenting complaints of pain were less likely to prompt psychosocial discussions.

The success of a screening program is predicated on the assumption that it will identify a significant number of children and adolescents with depression who do not already have a diagnosis and engage them in treatment that has been proven to be effective. If clinicians are unable to provide effective depression care themselves or via referral to other health care professionals, the identified child or adolescent is unlikely to benefit from screening. Furthermore, successful screening depends on the willingness of the provider to screen, and some clinicians express concerns about medicalizing emotional distress and question whether psychiatric diagnosis in adolescents is helpful.[83]

Potential risks of screening may include false-positive results leading to unnecessary stigma, inappropriate treatments, and unwarranted use of health care resources.[84,85] In addition, the time involved with screening may lead already busy providers to give depression screening higher priority than other important screening, questions, and discussions within a limited appointment time. Finally, the evidence on the cost-effectiveness of universal depression screening for children is not yet demonstrated.[56] The costs and benefits of screening cannot be easily and validly captured by existing medical record data sources because it is usually coded under a generic risk assessment procedure code (e.g., CPT code 99420: administration and interpretation of health risk assessment instrument) or as part of a well-child visit. Thus, primary research using prospective data need to demonstrate the potential risks and benefits of screening for depression in children and adolescents in primary care settings. The effects of the Patient Protection and Affordable Care Act[86] on screening and treatment rates are still unclear.

Screening Strategies

Screening Tools

Practitioners can use many different screening tools to identify depression in children and adolescents; some have been used in primary care. These instruments need to be reliable, valid, and quick and easy to administer and score in an office setting. **Table 1** describes key elements of these screening tools, including the number of items in each tool, administrative time to

complete the screen, appropriate ages for the screen, and the sensitivity and specificity of the tool.

Several screening tools have been developed specifically for pediatric settings. These include the newly developed Children's Depression Screener (ChilD-S)[87] and the Pediatric Symptom Checklist.[88] In addition, the new Depression Screener for Teenagers (DesTeen), a depression screening instrument designed for pediatric care, focuses on cognitive and emotional symptoms and leaves out items common in somatically ill patients such as loss of appetite, sleep disturbance, and physical complaints in an attempt to tease apart sometimes overlapping depression and somatization symptoms.[89]

Screening positive on an initial screening test does not necessarily indicate the need for treatment. Screening is usually done in two phases: an initial screening is followed by a second phase where skilled clinicians take into account contextual factors surrounding the individual's current situation either through additional probing or via a formal diagnostic interview. Some experts argue that there is the potential to medicalize normal emotions in response to loss or stress among adolescents and suggest that screening instrument questions use language such as "for no good reason" or "way beyond what makes sense in the circumstances" to minimize the number of false positives.[90] In instances where treatment is recommended, treatment can then be initiated either by the screening provider or via referral to another set of treatment providers. In a study that sampled primary care pediatricians, only 17 percent used formal DSM-IV criteria for assigning a diagnosis following a positive result. Once depression was diagnosed, 92 percent of pediatricians reported further assessment of specific symptoms and contributing factors.[73,91] Screening negative, however, does not always preclude referral when clinical judgment or parental concerns suggest otherwise.

Treatment Approaches

Treatment Types

The American Academy of Child and Adolescent Psychiatry[92] (AACAP) recommends conceptualizing the treatment of depressive disorders in three phases: acute, continuation, and maintenance. The goal of treatment during the acute phase is to achieve response and ultimately full symptomatic remission; continuation treatment is required to consolidate the response during the acute phase and to prevent relapse. Some youth will require maintenance treatment to avoid recurrence of depression if they have a more severe, chronic, or recurrent depressive disorder.

AACAP also recommends that each phase of treatment include education of family members and the patient about the cause, symptoms, and treatments of depression and about the risks associated with treatment and with no treatment. Psychoeducation is believed to be especially important for improving treatment adherence. Recommended treatment types may vary by the severity of MDD. For children and adolescents with mild depression, most of whom will not have an MDD diagnosis, supportive treatment that includes active listening, reflection, problem solving, and reviewing coping skills may be adequate. For patients with moderate to severe depression including MDD, psychotherapy (including cognitive behavioral or interpersonal

therapy) or a trial of antidepressants (or both) is indicated.

Pharmacotherapy

Although several antidepressants are approved for treating MDD in adult populations, fluoxetine is the only medication that the U.S. Food and Drug Administration (FDA) has approved for use in treating MDD in children age 8 years or older. In addition, the FDA has approved escitalopram to treat MDD in adolescents ages 12 to 17 years. Other medications may sometimes be prescribed to children on an off-label basis. However, in 2003, the FDA recommended that paroxetine not be used for treating MDD in children and adolescents because of reports of possible suicidal ideation and suicide attempts in children and adolescents taking paroxetine for depression. The following year, in 2004, the FDA issued a public warning about an increased risk of suicidality in children and adolescents treated with antidepressants. The FDA currently requires these medications to carry a boxed warning about the potential danger of suicidality.

Psychotherapy

Cognitive Behavioral Therapy and Interpersonal Therapy

Different types of psychotherapy are used in treating children and adolescents with depression, but cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) have the most evidence supporting their effectiveness.[93] CBT focuses on identifying cognitive distortions that may lead to depressed mood, then using problem solving, behavior activation, and emotion regulation skills to help manage depression. The child works to improve mood by changing unhealthy patterns of thinking and by ultimately working on changing behaviors, often with the assistance of family members.[94]

IPT focuses on improving mood by improving interpersonal functioning and increasing social support. The therapist reviews the patient's patterns in relationships, explores capacity for intimacy, and evaluates current relationships. An interpersonal focus is identified, and treatment focuses on resolving the identified problem area and practicing interpersonal skills in sessions. IPT, originally developed for adults, has been modified for adolescents (IPT-A). This version focuses on increasing adolescents' independence and negotiating support needed from others such as parents; it also includes parental participation.[95]

Other Types of Therapy

Other types of therapy used clinically for treating depression include supportive psychotherapy, family therapy, psychodynamic therapy, behavioral therapy, dialectical behavioral therapy,[96] educational interventions, exercise,[97] mindfulness training, problem-solving therapy, play therapy, and humanistic therapy. Some of these therapies are considered to be CAM treatments. In addition to exercise and mindfulness training, other CAM therapies for depression include massage, relaxation techniques, yoga, dietary supplements/herbal remedies, light therapy, music therapy, and magnetic therapy.

Combination Therapy

Combination therapy is the use of more than one type of treatment, such as two types of medications or one type of pharmacotherapy and one type of psychotherapy.[98-100]

Collaborative Care

Collaborative care interventions operate at the system level of care. Primary care providers and mental health specialists typically work together with the support of a case manager to identify and treat patients in need.

Many of these therapies have not been adequately studied in children and adolescents, and the long-term outcomes of all these interventions remain unknown. In practice, however, the state of Massachusetts has created a statewide system of collaborative care that seeks to connect primary care with child psychiatry: the Massachusetts Child Psychiatry Access Project (MCPAP).[101] MCPAP is a system of regional children's mental health consultation teams designed to help primary care providers meet the needs of children with psychiatric problems. The program, free to all Massachusetts primary care providers who treat children, supports and educates primary care clinicians on how to handle mental health concerns. Primary care providers enrolled in MCPAP reported improvements in their ability to meet the needs of their patients with mental health care needs.[102]

Other Guidelines and Recommendations

Many professional organizations and institutions in the United States recommend screening young people for mental health during the primary care visit (**Appendix A**). The American Academy of Pediatrics (AAP); American Medical Association; and Medicaid's Early and Periodic Screening, Diagnostic, and Treatment Program all recommend routine screening for behavioral and emotional problems. The joint task force of the AAP and AACAP support the emerging use of and payment of primary care physicians for using standardized screening tools for children and adolescents. Several other U.S.-based agencies support the USPSTF 2009 recommendation and further research on children and adolescents' comprehensive access to mental health services.

Comparable international organizations and agencies do not explicitly recommend routine screening for depression in children and adolescents. The Canadian Task Force on Preventative Health Care concludes that there is insufficient evidence to recommend for or against screening for depression among children or adolescents in primary settings. The United Kingdom's National Institute for Health and Clinical Excellence recommends specific psychological therapy for young people with moderate to severe depression. It also recommends that children or young people with moderate to severe depression should not take antidepressant medication except in combination with concurrent psychological therapy, and that antidepressant medication not be offered to children with mild depression.

Rationale for Changes to Scope Since 2009 Review

The USPSTF will use this report to update its 2009 recommendation on screening for child and adolescent depression among average-risk populations recruited from primary care or school-based clinic settings.

This review summarizes the evidence to date for the benefits and harms of screening, the accuracy of feasible screening tests, and the benefits and risks of treating depression using psychotherapy and/or SSRIs among patients ages 7 to 18 years in primary care or school-based clinic settings. The report concludes with a discussion of the implications of the findings and key gaps in this scientific literature.

This updated review contains several changes to its scope, primarily focused on alternative inclusion and exclusion criteria of studies providing supportive evidence. Unlike the prior review, we focus on screening for MDD only (at least 50% of the sample needed to have MDD); we do not address screening or treatment for minor depression or dysthymia. Little is known about the etiological links between subthreshold depression, dysthymia, and MDD in children and adolescents. Focusing on MDD reduces heterogeneity in patient characteristics and targets the children and adolescents experiencing more serious symptoms who are most likely to suffer severe functional impairment and suicidality. In addition, little is known regarding efficacious treatments for subsyndromal or other types of depression like dysthymia or persistent depressive disorder among children or adolescents and at what point along the continuum treatment is warranted. As stated previously, the ultimate goal of screening is to improve health-related outcomes by identifying children and adolescents with depression who are not already identified as such and engaging them in effective treatment. Thus, the paucity of efficacious treatments for dysthymia or subthreshold depression suggests that the net benefit of screening for less severe forms of depression may not outweigh the burden of universal screening. The implications of focusing on MDD and other scope changes are further described below and in the Discussion section.

Chapter 2. Methods

KQs and Analytic Framework

The investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope, KQs, and analytic framework (**Figure 1**) that guided our literature search and review.

KQs

1. Does screening for MDD among children and adolescents in the primary care (or comparable) setting lead to improved health and other related outcomes overall and among subgroups defined by age, sex, or race/ethnicity?
2 Are depression screening instruments for children and adolescents accurate in identifying MDD in primary care settings overall and among subgroups defined by age, sex, or race/ethnicity?
3. Does screening increase the proportion of children and adolescents who are identified with MDD overall and among subgroups defined by age, sex, or race/ethnicity?
4. What are the harms of screening children and adolescents for MDD overall and among subgroups defined by age, sex, or race/ethnicity?
5. Does treatment of MDD among children and adolescents who are identified in primary care improve health and other related outcomes overall and among subgroups defined by age, sex, or race/ethnicity?
6. What are the harms of MDD treatment among children and adolescents overall and among subgroups defined by age, sex, or race/ethnicity?

The USPSTF also requested five contextual questions to help inform the report. We do not show the contextual questions in the Analytic Framework because they were not analyzed using the same rigorous systematic review methodology as the studies that met the report's inclusion criteria. At the title and abstract and full-text article review stages, reviewers categorized the nonincluded studies that related to the specific contextual questions.

Contextual Questions

We addressed risk factors and uptake of USPSTF recommendations via the following contextual questions:

1. What proportion of primary care providers assess, treat, and refer children and adolescents with depression (MDD, dysthymia, and minor depression)? What proportion of providers have access to collaborative systems of care for these patients?
2. What are the most common types of child and adolescent MDD treatment that are initiated in or referred from primary care settings?
3. Is there evidence of valid and reliable risk stratification tools to identify children and adolescents who are at highest risk for MDD?

4. In primary care, school, or comparable settings, are children and adolescents with MDD and comorbid mental health (e.g., attention deficit hyperactivity disorder, anxiety disorders) or chronic physical health conditions (e.g., diabetes, asthma) more likely to be screened, treated, or referred for treatment than children and adolescents with MDD only? Do they receive different treatments than children and adolescents without comorbid conditions?
5. Is there evidence of effectiveness of serotonin–norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors, or CAM treatments among children and adolescents with MDD?

Search Strategies

We searched PubMed/MEDLINE®, the Cochrane Library, and PsycINFO for English-language articles published through February 4, 2015. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, screening tests, interventions, outcomes, and study designs. **Appendix B** describes the complete search strategies. We conducted targeted searches for unpublished literature by searching ClinicalTrials.gov, HSRProj, and the World Health Organization's International Clinical Trials Registry Platform. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.

Study Selection

Newly Identified Studies

We selected studies on the basis of inclusion and exclusion criteria developed for each KQ based on the PICOTS approach for identifying populations, interventions, comparators, outcomes, timing, settings, and study designs[103] (**Appendix B**). **Appendix C** lists excluded studies. We imported all citations identified through searches and other sources into EndNote v.5 (Thomson Reuters, New York, NY). Two investigators independently reviewed titles and abstracts. We dually and independently reviewed the full text of abstracts marked for potential inclusion by either reviewer. Two experienced team members then resolved disagreements.

Population

We included studies that focused on the screening or treatment of children and adolescents between the ages of 0 and 18 years for MDD. Because of the newness of the DSM-5 definition, this review includes studies using MDD diagnosis criteria at the time of their data collection (DSM-III, DSM-III-R, or DSM-IV). We did not include studies of children and adolescents with other types of depression diagnoses; we required a majority (50%) of the sample to have MDD for inclusion. We also included studies that enrolled participants older than age 18 years or with other diagnoses that analyzed results for children or adolescents with MDD separately.

Interventions

For KQs 1 through 4, we searched for studies that examined MDD screening instruments or general mental health screening tools that included depression modules that clinicians could use to identify depressive illness and related outcomes and that were feasible for primary care settings. For KQs 5 and 6, we searched for studies that examined pharmacological, psychotherapeutic, combination, and other interventions (i.e., pure or guided self-help, family support, parental education, and peer support).

Comparators

For KQs 1, 3, and 4, we included studies that compared screened with unscreened groups. For KQ 2 we included studies that compared a screening instrument with a gold standard diagnostic instrument. For KQs 5 and 6, we included studies that compared treatments with placebo, wait-list, usual care, supportive counseling, or sham.

Outcomes and Timing

For KQs 1, 3, and 5, we searched for studies that reported outcomes at 6 weeks or more following screening or treatment. For KQ 2, we searched for studies that compared the diagnostic accuracy of screening tests with an independent gold standard within 2 months.

Settings

For KQs 1 and 3, studies had to be conducted within a primary care setting. For KQs 2 and 4, we included studies conducted in primary care, school, or nonclinic settings. KQs 5 and 6 included primary care and outpatient settings that received referrals from primary care settings. For all KQs, we searched for studies conducted in the United States or in countries with a very high Human Development Index.

Study Designs

For KQs 1, 3, 4, 5, and 6, we included randomized, controlled trials (RCTs); nonrandomized, controlled trials; and systematic reviews published in 2011 or later. For KQs 4 and 6, we included both prospective and retrospective cohort studies with sample sizes of 1,000 or more participants. For KQ 2, we included test/retest studies that stood alone or were used with other study designs.

Studies in the 2009 Review

We applied, dually and independently, the inclusion and exclusion criteria described above to all studies included in the 2009 review.[104] We resolved disagreements by discussion and consensus; if necessary, we sought adjudication of conflicts from other experienced team members.

Data Abstraction and Quality Rating

Newly Identified Studies

We abstracted pertinent information from each included study; details included methods and patient populations, interventions, comparators, outcomes, timing, settings, and study designs. A second investigator checked all data abstractions for completeness and accuracy. For studies of interventions, we also abstracted data on dose and frequency in drug studies. Using predefined criteria developed by the USPSTF and others for additional criteria for diagnostic accuracy studies, two investigators independently assessed the quality of each study as good, fair, or poor (**Appendix D**).[105] Disagreements were resolved by discussion and consensus. Studies with "fatal flaws" were rated as poor quality. For KQ 2, fatal flaws that resulted in poor-quality ratings included use of an inappropriate reference standard, improper administration of the screening test, biased ascertainment of the reference standard, very small sample size, or very narrowly selected spectrum of patients. For KQs 5 and 6, fatal flaws that resulted in poor-quality ratings included initially assembled groups not close to being comparable or maintained throughout the study (including overall attrition of at least 20% or differential attrition of at least 15% between groups), use of unreliable or invalid measurement instruments or unequal application among groups (including not masking outcome assessment), no or little attention given to key confounders, and the lack of intention-to-treat (ITT) analysis (for RCTs).

Studies in the 2009 Report Meeting Inclusion Criteria

One reviewer checked for errors in previously generated abstraction tables and updated them as needed. Two reviewers dually reviewed the quality of all studies included in the 2009 report and resolved disagreement by discussion and consensus.

Data Synthesis and Analysis

In the Results section, we first summarize the newly identified included studies. We then describe the previously identified studies that continue to meet current inclusion and quality criteria. Finally, we present a synthesis of previous and current findings.

The Discussion section summarizes conclusions from the previous review, the 2009 USPSTF recommendation statement, and the implications of the new synthesis for previous conclusions. In addition, we assessed the overall strength of the body of evidence for each KQ using methods developed by the USPSTF, based on the number, quality, and size of studies; consistency of results among studies (similar magnitude and direction of effect); and directness of evidence (evidence links interventions directly to outcome of interest for the review).[105]

Expert Review and Public Comment

A draft report was reviewed by outside content experts, USPSTF members, and AHRQ Medical Officers, and was revised based on comments.

USPSTF Involvement

This review was funded by AHRQ. AHRQ staff and USPSTF members participated in developing the scope of the work and reviewed draft manuscripts, but the authors are solely responsible for the content.

Chapter 3. Results

This chapter provides a comprehensive presentation of the evidence from the 2009 report and our updated searches. Although the KQs in this update are similar to the questions in the 2009 report, our inclusion criteria are more restrictive. In particular, studies require inclusion samples with a majority having a diagnosis of MDD and a setting in countries with a very high Human Development Index; we also exclude paroxetine as a treatment modality. We also reevaluated studies for quality in accordance with current USPSTF criteria.

We first report on the yields from our literature searches. The results presented below first summarize and then describe new studies identified by the updated search that also meet quality criteria. Next, we summarize studies from the 2009 report that continue to meet inclusion and quality criteria (five of the nine studies included in the prior report for KQ 2, four of 17 trials reported in six publications included in the prior report for KQ 5, and three of 17 trials included in the prior report for KQ 6). We follow with a synthesis of the overall (old plus new) evidence, noting results for subgroups when such data are available. **Appendix E** contains full evidence tables for each KQ.

Literature Search

Figure 2 illustrates the yield at each stage of the review process for the update search. We reviewed 10,005 titles and abstracts dually and independently, and identified 367 studies for full-text review. We dually and independently rated the five new included studies reported in six publications (one new screening trial[106] and four treatment trials reported in five publications[107-111]) that met all of our inclusion/exclusion criteria for quality and identified two new studies of good or fair quality, both of which examined the efficacy and harms of MDD treatment for children or adolescents identified in primary care or similar settings.[107,109]

Of these 367 full-text articles, common reasons for exclusion included not meeting review criteria for population (i.e., older than age 18 years, or screening for or treatment of types of depression or psychopathology other than MDD [n=171]), not meeting review criteria for comparator (n=51), not meeting review criteria for publication type (n=35), and not meeting review criteria for outcome (n=29).

In addition to the studies identified through the update search, we included five accuracy studies[112-116] and four trials reported in six publications out of the 37 publications included in the 2009 review.[98,117-121] Thus, we include five accuracy (KQ 2) studies and six trials reported in eight publications (KQ 5) in this review (**Table 2**). Of these, one trial reported on multiple treatment modalities (pharmacotherapy, psychotherapy, and combined treatments).[98,117,118] As a result, the sum of trials reported across all categories of interventions exceeds the total number of trials included.

KQ 1. Effect of Screening for MDD Among Children and Adolescents in the Primary Care Setting on Health and Other Related Outcomes

We did not find any trials that directly assessed the effects of screening (compared with no screening) on health or other related outcomes. The prior review, which included evidence published before May 2007, also found no evidence on this topic.

KQ 2. Accuracy of Depression Screening Instruments for Children and Adolescents Overall and Among Subgroups Defined by Age, Sex, or Race/Ethnicity

Summary of Newly Identified Evidence on Screening

No new studies on the accuracy of screening instruments met both inclusion and quality criteria. One study that did meet our inclusion criteria was rated as poor quality because of the potential for bias in ascertaining the reference standard; a minority of students who had been administered the screening instrument were then interviewed using the reference standard (552 out of the total of 1,392) and no information was available regarding how the sample was selected.[106] We followed up with the authors of the report, but they were unable to recall how the sample was selected for diagnostic interviews.

Study Characteristics of Newly Identified Evidence on Screening

We found no new screening studies that met our inclusion/exclusion and quality criteria published since the 2009 review.

Description of Previously Identified Studies on Screening That Continue to Meet Current Inclusion and Quality Criteria

Of the nine studies (in 12 articles) identified in the previous review, seven studies (in seven articles) continued to meet the inclusion/exclusion criteria for this update prior to quality ratings.[112-116,122, 123] Of the remaining two studies, one presented sensitivity and specificity for any depressive disorder rather than for MDD alone; we excluded it on grounds of not meeting review criteria for population.[124] The other study compared scores on the Beck Depression Inventory (BDI) with those on the Mood Module of the Primary Care Evaluation of Mental Disorders (PRIME-MD).[125] Because PRIME-MD is not a diagnostic instrument, we excluded the study for not meeting review criteria for comparison.

We rated two of the remaining seven studies as poor quality. One study (published in 1988), comparing the BDI with the Childhood Assessment Schedule (CAS) in a school setting in Spain, had a small sample size (N=49) and used a reference standard for children ages 7 to 12 years for

their population of adolescents ages 12 to 18 years.[122] Additionally, the manuscript did not describe how students were selected or state whether the reference standard was independent and blinded. The other poor-quality study had been conducted in 1984, before validated semistructured DSM-III interview protocols suitable for use with adolescents were available.[123] The study compared a "lifetime" diagnosis of depression on the BDI tool with a clinical interview that used a compilation of questions based on the Columbia Clinical Interview. We were unable to find data on the validity and reliability of this instrument for diagnosing MDD in children or adolescents. Additionally, the screening instruments appeared to have been administered in the fall of the school year and the diagnostic interviews in the spring, leading to the investigators' choice of lifetime diagnosis of depression rather than current episode. This outcome is of limited relevance to primary care screening. The 2009 report included eight citations for the five studies that continue to meet eligibility criteria for this update. We excluded three publications; one article did not present information on relevant outcomes[126] and two did not have data from comparison arms.[127,128] For this update, we include five studies of good or fair quality with one publication each[112-116] (**Table 3**).

Detailed Synthesis of Prior Evidence on Screening

Primary Care Settings: Patient Health Questionnaire for Adolescents

One of the five studies drew from primary care samples and evaluated the Patient Health Questionnaire for Adolescents (PHQ-A) (ages 13 to 18 years).[116] The investigators did not report a diagnostic cutoff but did report that sensitivity for a positive test was 73 percent and specificity was 94 percent (**Table 4**). Across all tests, the PHQ-A reported the highest positive predictive value. The study did not report other outcomes or stratify results by age or race/ethnicity.

School Settings: BDI

The remaining studies were conducted in school settings.[112-115] Two evaluated the BDI.[112,113] Ages ranged from 12 to 18 years. For the commonly reported cutoff of 11 in the two included studies, sensitivity ranged from 84 to 90 percent and specificity from 81 to 86 percent. The results cannot be pooled because the information needed to make pooled calculations was not presented. One study demonstrated a higher area under the curve for males than for females.[113] Neither study reported outcomes by race/ethnicity.

School Settings: Center for Epidemiologic Studies-Depression Scale

Two studies evaluated the Center for Epidemiologic Studies-Depression Scale (CES-D) using several different cutoffs.[113,114] Ages ranged from 11 to 15 years in one study;[114] the mean age in the other study was older than 16 years.[113] Sensitivity ranged from 18 to 84 percent and specificity from 38 to 83 percent (**Table 2**). The authors of one study noted little correlation between the results of the instruments and diagnostic interviews. No study reported outcomes by race/ethnicity. We found inconsistent results for sex, with one study finding higher sensitivity and specificity for males and the other for females.[113,114]

School Settings: Clinical Interview Schedule-Revised

One study evaluated a self-administered computerized form of the Clinical Interview Schedule-Revised (CIS-R) questionnaire.[115] The CIS-R assesses multiple mental disorders, including 10 questions on major depression that can be completed in approximately 5 minutes. The mean age of the study sample was 15.7 years; sensitivity was 18 percent and specificity was 97 percent. The study did not report other outcomes or stratify results by age or race/ethnicity.

Summary of Accuracy Results

The PHQ-A and BDI instruments reported the highest sensitivity and specificity. Across all tests and studies, the positive predictive value was low and variable, ranging from 8 to 56 percent. The negative predictive value was 91 percent for CIS-R, higher than 99 percent for both studies of the BDI that used a consistent cutoff of 11, and 99 percent for the CES-D instrument.

Of note, none of the studies meeting criteria for this review tested some of the newer screening instruments developed specifically for children and adolescents. In addition, some studies used instruments originally developed for assessing adult depression because they were conducted before newer, child- or adolescent-specific versions were developed and tested.

KQ 3. Effect of Screening on Proportion of Children and Adolescents Identified With MDD Overall and Among Subgroups Defined by Age, Sex, or Race/Ethnicity

We did not find any studies that addressed whether screening increases the proportion of children or adolescents who are identified with MDD. The prior review also found no evidence on this topic.

KQ 4. Harms of Screening Among Children and Adolescents Identified With MDD Overall and Among Subgroups Defined by Age, Sex, or Race/Ethnicity

We did not find any studies that assessed harms of screening for MDD in children and adolescents. The prior review also found no evidence on this topic.

KQ 5. Effect of Treatment of MDD on Outcomes Among Children and Adolescents Identified With MDD Overall and Among Subgroups Defined by Age, Sex, or Race/Ethnicity

Summary of Newly Identified Evidence on Treatment

We found four new treatment trials (reported in five publications) that fit our inclusion criteria published since the last review, but only two met quality criteria. One trial, presented in two publications, examined the impact of escitalopram on adolescent MDD.[107,108] We rated the publication that examined the extended efficacy, safety, and tolerability of escitalopram relative to placebo[108] as poor quality because of substantial overall attrition (46.7%). Thus, we include only the original trial[107] in our synthesis of KQ 5 evidence. We also found one trial of good quality on collaborative care that we included in this review.[109] We rated a trial that examined the efficacy of Parent–Child Interaction Therapy Emotion Development (PCIT-ED) among preschool children with depression as poor quality because of its large and differential attrition.[111] Likewise, we rated a trial of adjunctive family psychoeducation in adolescents with MDD as poor quality because the study dropped participants from one study site, did not perform ITT analysis, and did not blind outcome assessors.[110]

Study Characteristics of Newly Identified Evidence on Treatment

A study sponsored by Forest Laboratories consisted of an 8-week fair-quality RCT[107] of escitalopram in adolescents ages 12 to 17 years with MDD (randomized n=316) across 40 sites throughout the United States. Inclusion and exclusion criteria created a very narrow patient sample, which compromised generalizability (**Table 5**).

Randomized patients in the escitalopram group received 10 mg/day of escitalopram increased to 20 mg/day after the first 3 or 4 weeks if necessary (and returned to 10 mg/day if the patient experienced any adverse events [AEs]) throughout the 8-week study. Patients in the control group received placebo. The study reported characteristics only of the sample who received at least one dose of medication or placebo. Nearly 17 percent of this sample had been treated with antidepressants previously (61.5% of these treated adolescents were nonresponders), 14.7 percent of the sample had a lifetime secondary psychiatric disorder, and 29.9 percent of the sample had recurrent MDD.

The investigators did not report fidelity and adherence to the treatment regimen or recruitment or intervention settings. Attrition was moderate in both groups. Study characteristics are listed in **Table 6**.

ITT analyses used last observation carried forward (LOCF) methods using analysis of covariance models for continuous outcomes; the investigators adjusted for baseline scores and study site. For response and remission dichotomous outcome variables, they used logistic regression models that included baseline scores and study site as covariates.

One good-quality study in nine pediatric and family medicine clinics in the Group Health system randomized adolescents ages 13 to 17 to collaborative care or enhanced usual care.[109] The majority of the sample was white (69%), female (72%), and had major depression (60%). Depression care managers delivered developmentally sensitive materials, involved both the adolescent and parent in the initial education and engagement session, offered a choice of treatment, and followed up regularly with patients. Patients and their primary care clinicians in the enhanced usual care arm received a letter summarizing test results and encouraging followup and treatment. The investigators monitored fidelity in the intervention arm until the depression care manager was deemed proficient. Of the 101 randomized patients, five in the intervention arm and two in the control arm withdrew. The study used ITT principles but did not specify the approach.

Description of Previously Identified Studies on Treatment That Continue to Meet Current Inclusion and Quality Criteria

Of 17 fair- or good-quality trials (presented in 22 publications) identified in the previous review, nine trials reported in 11 publications met the inclusion/exclusion criteria for this update,[98,117-121,129-133] prior to applying quality criteria. Primary reasons for excluding studies for this review that had been in the prior review were not meeting review criteria for population (MDD for at least 50% of sample not required for inclusion[134-138]), wrong comparator (usual care arm received psychotherapy[136]), not meeting review criteria for intervention (paroxetine[139-141]), not meeting review criteria for outcome (time to response[142]), and not meeting review criteria for geographic setting (one trial presented in two publications was conducted partially in countries with a low Human Development Index[143,144]). Of the nine trials (11 publications) from 2009 meeting new inclusion criteria, four trials (six publications) met updated quality criteria.[98,117-121]

Pharmacotherapy

Five trials reported in seven publications in this updated review assessed pharmacotherapy interventions involving SSRIs. Of these, three trials tested fluoxetine in children and adolescents ages 7 to 17 years[129] and 8 to 17 years[130] and in adolescents ages 12 to 17 years;[98,117,118] one tested citalopram in children and adolescents ages 7 to 17 years;[120] and one tested escitalopram in children and adolescents ages 6 to 17 years.[119] We continue to note the age ranges of each trial for the remainder of the report due to the importance of age group on outcomes. Based on our evaluation of these five trials using updated criteria for quality assessment, we rated two trials as poor. These fluoxetine trials[129,130] had high overall attrition (75% and 28%, respectively) and high differential attrition (21% and 34%, respectively); these two trials rated as poor quality are not synthesized with our newly identified study. Thus, three trials reported in five pharmacotherapy trials from the prior report that met inclusion/exclusion and quality criteria are included in this update.

In all, this report includes the results of four pharmacotherapy trials (one new, three included in the 2009 review) reported in six publications. We used the results of one fluoxetine trial, a previously reported trial presented in three publications conducted among adolescents ages 12 to 17 years.[98,117,118] In addition, we used two trials that studied escitalopram: one previously reported trial conducted in children and adolescents ages 6 to 17 years[119] and one new trial

conducted in adolescents ages 12 to 17 years.[107] The fifth trial reported in the prior review tested citalopram versus placebo in a sample of children and adolescents ages 7 to 17 years.[120]

Psychotherapy

Five psychotherapy trials (seven publications)[98,117,118,121,131-133] in the 2009 review continued to meet our study inclusion prior to applying quality criteria. Studies included two individual IPT trials in adolescents ages 13 to 17 years[131] and 12 to 18 years;[132] three individual CBT trials reported in five publications in adolescents ages 14 to 18 years,[121] 13 to 17 years,[131] and 12 to 17 years;[98,117,118] and one attachment-based family therapy trial in adolescents ages 13 to 17 years.[133] We excluded four psychotherapy trials in the previous review (which tested CBT, group relaxation, individual self-modeling, group self-control, group behavioral problem-solving, and cognitive bibliotherapy [e.g., therapeutic reading] interventions) because inclusion criteria did not require that at least 50 percent of the sample have MDD,[134,135,137,138] and one trial due to wrong comparator.[136] We did not find any additional psychotherapy trials that met our inclusion criteria published since the last review. Of note, no evidence is available from either prior or current studies that tested psychotherapy interventions in children younger than age 12 years.

Based on our evaluation of these five trials using updated criteria for quality assessment, we rated three trials as poor quality.[131-133] For the Rossello et al CBT and IPT trial,[131] our rating was based on baseline differences between groups and no ITT analyses. The Mufson IPT trial had both very high overall attrition and differential attrition (33% and 42%, respectively).[132,121] Finally, the Diamond attachment-based family therapy trial had different followup periods for the wait-list group (6 weeks) and intervention group (12 weeks).[133] For these reasons, we do not summarize information from these three trials in this updated review. We did not identify any new psychotherapy trials that met our inclusion and quality criteria; thus, the two psychotherapy trials we summarize include 1) the March et al trial,[98] with additional outcomes presented in Vitiello et al and Kennard et al,[117,118] in which CBT was compared with placebo and clinical monitoring, and 2) the Clarke trial of group CBT.[121]

Combined Interventions

We did not identify any new studies of combined interventions. The single combined intervention trial presented in three publications in the prior report continued to meet inclusion criteria.[98,117,118] This trial, rated good quality, combined fluoxetine and individual CBT among adolescents with MDD. Thus, the only combined intervention trial described is the March et al[98] trial of combined fluoxetine and CBT versus placebo and the additional two trials reporting on alternative outcomes.[117,118]

Detailed Synthesis of Prior Evidence With New Findings on Treatment

Pharmacotherapy

Fluoxetine

Depression outcomes. The good-quality fluoxetine RCT from the prior report found that the

fluoxetine group was more likely to respond (Clinical Global Impression–Improvement Scale [CGI-I] score of 1 or 2) than the placebo group (60.6% vs. 34.8%; p=0.001; risk ratio, 1.74) at 12 weeks of followup (**Table 7**).[98] The mean depression score as measured by change in either the Children's Depression Rating Scale–Revised (CDRS-R) or Reynolds Adolescent Depression Scale (RADS) score at 12 weeks of followup did not significantly differ between the fluoxetine and placebo groups (least squares mean difference [LSMD], -3.05 [p=0.10] and -1.8 [p=0.34], respectively). The effect size (Hedges g) was 0.68 on the CDRS-R and 0.58 on the CGI-I; the number needed to treat for the dichotomous CGI-I (1 or 2) measure was 4 (95% CI, 3 to 8).

An additional study published using the same data found that 23 percent of the fluoxetine group versus 17 percent of the placebo group had remitted (CDRS-R score ≤28 at 12-week followup; p<0.05).[117]After adjusting for study site, however, this association failed to reach significance (odds ratio [OR], 1.5 [95% CI, 0.74 to 2.88]). When examining the proportion of each group who had remitted using a different definition, however, the fluoxetine group was significantly more likely to no longer meet MDD criteria at followup (OR, 2.4 [95% CI, 1.27 to 4.67]).

Other outcomes. Only one fluoxetine trial reported on other efficacy outcomes in a single publication.[118] The fluoxetine group had greater mean increase in functional status scores as measured by the CGAS (mean change, 12.6) compared with the placebo group (mean change, 10.2; p=0.0381). Changes in global burden of psychiatric problems as measured by the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA) and change in quality of life as measured by the pediatric version of the Short Form of the Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) did not differ between the fluoxetine and placebo groups.

Subgroup differences. The March et al[98] trial did not report efficacy results by subgroups of interest.

Escitalopram

Depression outcomes. A newly identified fair-quality RCT of escitalopram in adolescents found significantly greater CDRS-R depression severity improvement for the escitalopram group than for the placebo group using the LOCF approach (LSMD, -3.356; p=0.022; effect size, 0.27) but not using the observed cases approach (LSMD, -2.787; p=0.07).[107] The escitalopram group also had significantly better CGI-I scores (LSMD, -0.344; p=0.008) and Clinical Global Impression–Severity Scale (CGI-S) change scores (LSMD,-0.37; p=0.007) than the placebo group. For response and remission, the percentage of CGI-I responders was significantly greater for escitalopram- than placebo-treated patients (LOCF; 64.3% vs. 52.9%, respectively; p=0.03; logistic regression). However, when response was defined as a 40 percent or greater improvement from baseline in CDRS-R score, response rates at endpoint were not significantly different between the escitalopram and placebo groups (59.1% vs. 48.4%, respectively, in LOCF logistic regression analysis; p=0.06). Remission rates (CDRS-R score of ≤28 at study endpoint) were 41.6 percent for escitalopram and 35.7 percent for placebo (LOCF; p=0.15; logistic regression).

A fair-quality RCT of escitalopram (n=129) versus placebo (n=132) from the prior report did not

find significant between-group differences in change in depression severity or symptoms as measured by mean CDRS-R scores (LSMD, -1.7; p=0.31), mean CGI-S scores (LSMD, -0.3; p=0.06), or mean CGI-I scores (LSMD, -0.2; p=0.17) at 8 weeks of followup. It also did not find differences in response at 8 weeks as measured by either CGI-I scores (1 or 2; 63% vs. 52%; p=0.14) or CDRS-R scores (≤28; 46% vs. 38%; p=0.32).[119]

Other outcomes. The new escitalopram trial looked for differences in global functioning in adolescents as measured by the CGAS at the end of 8 weeks of treatment;[107] it did not find significant differences between intervention and placebo groups. Likewise, the older Wagner trial did not find significant CGAS change scores at followup between escitalopram and placebo groups.[119]

Subgroup differences. The new escitalopram trial did not examine efficacy outcomes by subgroups of interest.[107] The older escitalopram trial, however, examined changes in CDRS-R, CGI-S, CGI-I, and CGAS scores in the subgroup of adolescents ages 12 to 17 years and the subgroup of children ages 6 to 11 years separately.[119] None of the between-group comparisons among children was significant; among adolescents, however, all changes except CDRS-R scores significantly differed by treatment group (CGI-S LSMD, -0.05 [p=0.02]; CGI-I LSMD, -0.4 [p=0.04]; CGAS LSMD, 5.7 [p=0.005]).

Citalopram

Depression outcomes. The citalopram trial conducted among patients ages 6 to 17 years[120] found no significant differences in response between the drug and placebo groups at followup (CGI-I score of 1 or 2, 47% vs. 45%). Remission (CDRS-R score of ≤28) also did not significantly differ between the citalopram and placebo groups (36% vs. 24%; p=0.08).

Other outcomes. The single citalopram trial did not report on any other outcomes.[120]

Subgroup differences. The single citalopram trial did not report on any efficacy differences by any subgroup, although the investigators had selected participants by separately sampling children ages 7 to 11 years and adolescents ages 12 to 17 years.[120]

Summary of Efficacy Findings

Table 7 and **Figure 3** show the efficacy results for the four SSRI trials (citalopram, escitalopram, and fluoxetine) examining response as the primary outcome.[98,107,119,120] **Figures 4 through 8** display remission outcomes and mean change scores of depression symptom severity, depression symptom improvement, depression severity, and global assessment of functioning, respectively, for studies reporting each of these outcomes.

Psychotherapy

CBT (Monotherapy)

Depression outcomes. The good-quality fluoxetine RCT from the prior report[98] found no

significant differences in response (CGI-I score of 1 or 2 at followup) for the CBT versus the placebo group (43.2% vs. 34.8%; risk ratio, 1.24).[98] The mean depression score as measured by change in either CDRS-R or RADS score at 12-week followup did not significantly differ between the CBT and placebo groups (LSMD, 1.83 [p=0.40] and 4.85 [p=0.21], respectively).

An additional study published using the same data found that no differences in remission between the CBT and placebo groups using criteria of a CDRS-R score of 28 or less (16% vs. 17%, respectively) or a definition of no longer meeting MDD criteria (OR, 1.0 [95% CI, 0.52 to 1.77]).[117]

The fair-quality CBT trial initially randomized adolescents (ages 14 to 18 years) meeting DSM-III-R criteria for MDD or dysthymia to group CBT or group CBT with separate parent sessions versus waitlist control, but combined the two active groups in analysis.[121] The study defined recovery as no longer meeting DSM-III-R criteria for either major depression or dysthymia for the 2 weeks preceding the posttreatment assessment). The study reported an OR of 2.15 for recovery (90% CI, 1.01 to 4.59). At 95%, the CIs span the line of no difference (0.87 to 5.33). The study collected continuous measures of improvement on the Hamilton Depression Rating Scale (HAM-D) and BDI and found no statistically significant differences between the combined intervention arms and the control arm on HAM-D, but a significantly greater difference in BDI scores in the intervention arms (group X time z score for random-effects regression, 2.44; $p<0.05$; change score effect size, 0.54).

Other outcomes. One study did not report significantly different changes in functional status scores as measured by the CGAS, global burden of psychiatric problems as measured by the HoNOSCA, and quality of life as measured by the PQ-LES-Q compared with the placebo group.[118] The second study measured global functioning on the Global Assessment of Functioning (GAF) and emotional and behavioral problems on the Child Behavioral Checklist (CBCL). The study found that children in the combined interventions arms had lower GAF scores than children in the control arms (group X time z score for random-effects regression, 2.70; $p<0.01$; change score effect size, 0.61). The study found no statistically significant differences between the combined intervention arms and the control arm on CBCL measures.[121]

Subgroup differences. The CBT trials [98,117,118,121] did not report any outcome differences by subgroups.

Combined Intervention: Fluoxetine and CBT

Depression outcomes. The single good-quality fluoxetine and CBT intervention RCT from the prior report found that patients in the combined intervention group were significantly more likely to respond (CGI-I score of 1 or 2) than patients in the placebo group (71.0% vs. 34.8%; p=0.001; risk ratio, 2.04).[98] The combined intervention group also had larger decreases in mean depression scores than the placebo group as measured by change in either CDRS-R (LSMD, -7.59; p=0.001) or RADS score at 12-week followup (LSMD, -8.59; p=0.001).

An additional study published using the same data found that the combined fluoxetine and CBT group was significantly more likely than the placebo group to be in remission at 12-week

followup as defined by having a CDRS-R score of 28 or less (37% vs. 17%; OR adjusted for site, 3.0 [95% CI, 1.58 to 5.79]) or by no longer meeting MDD criteria (85.3% vs. 60.4%; OR adjusted for site, 4.1 [95% CI, 2.00 to 8.44]).[117]

Other outcomes. One publication from the single combined fluoxetine and CBT trial presented on other efficacy outcomes.[118] The combined group had significantly better improvement than the placebo group in global functioning (change in CGAS score, 16.6 vs. 7.9; p<0.001), global burden of psychiatric problems (change in HoNOSCA score, -7.2 vs. -5.5; p=0.0393), and quality of life (change in PQ-LES-Q, 12.2 vs. 5.7).

Subgroup differences. The single fluoxetine and CBT combined intervention trial presented in three publications[98,117,118] did not report any outcome differences by subgroups.

Collaborative Care

Depression outcomes. A single collaborative care study found intervention patients had an 8.5-point greater decrease in mean CDRS-R score from baseline than control patients (95% CI, -13.4 to -3.6; p=0.001) at 6 months and a 9.4-point greater decrease from baseline at 12 months (95% CI, -15.0 to -3.8; p=0.001). A test of the interaction between group effects and time was statistically significant at p<0.001. Intervention patients were more likely than control patients to achieve depression response (≥50% reduction in CDRS-R score from baseline) by 12 months (OR, 3.3 [95% CI, 1.4 to 8.2]; p=0.009) but not by 6 months (OR, 3.1 [95% CI, 1.2 to 7.9]; p=0.02). Regarding remission, intervention patients were significantly more likely to achieve depression remission at both 6 months (OR, 5.2 [95% CI, 1.6 to 17.3]; p=0.007) and 12 months (OR, 3.9 [95% CI, 1.5 to 10.6]; p=0.007).

Other outcomes. The single collaborative care study reported on functional status.[109] The intervention arm reported differences in functional status, measured on the Columbia Impairment Scale, between intervention and control patients that were not significant at an a priori p-value threshold of ≤0.01 at 6 months (mean difference, -4.4 [95% CI, -8.4 to -0.5]; p=0.03) or 12 months (mean difference, -4.3 [95% CI, -8.3 to -0.3]; p=0.04).

Subgroup differences. The single collaborative care study[109] did not report any outcome differences by subgroups.

KQ 6. Harms of MDD Treatment for Children and Adolescents Identified With MDD Overall and Among Subgroups Defined by Age, Sex, or Race/Ethnicity

Summary of Newly Identified Evidence on Treatment Harms

Two new studies met inclusion/exclusion criteria for KQ 6 prior to applying quality criteria. One SSRI trial presented in two publications since the last review examined harms associated with an MDD intervention of escitalopram in children or adolescents.[107,108] We rated the publication that

examined the extended safety and tolerability of escitalopram relative to placebo[108] as poor quality because of substantial overall attrition (46.7%). Thus, we include only the original fair-quality trial[107] in our synthesis of KQ 6 evidence, which found no significant differences in AEs, serious adverse events (SAEs), suicidality (which had varying definitions by individual study but generally was defined as suicidal thoughts or behaviors such as plans and attempts), or AEs suggestive of self-harm between the intervention and placebo groups of adolescents ages 12 to 17 years.

One good-quality trial of collaborative care reported the incidence of psychiatric hospitalizations and emergency department (ED) visits[109] and did not find a consistent or significant pattern.

Study Characteristics of Newly Identified Evidence on Treatment Harms

Two new studies were found that addressed harms of MDD treatment, one on pharmacotherapy[107] and one on collaborative care.[109] The study characteristics of these trials are summarized in the corresponding KQ 5 subsection above.

In summary, the new pharmacotherapy study was sponsored by Forest Laboratories and consisted of an 8-week fair-quality RCT[107] of escitalopram in adolescents ages 12 to 17 years with MDD (randomized n=316) across 40 sites throughout the United States. Randomized patients in the escitalopram group (randomized n=158; safety n=157; ITT n=157; completed study n=133 [15.8% attrition]) received 10 mg/day of escitalopram increased to 20 mg/day after the first 3 or 4 weeks if necessary (and returned to 10 mg/day if AEs experienced) throughout the 8-week study. Patients in the control group (randomized n=158; safety n=155; ITT n=154; completed study n=126 [20.3% attrition]) received placebo. Characteristics of the baseline safety sample only were reported: nearly 17 percent of the sample had been treated with antidepressants previously; 61.5 percent of these treated adolescents were nonresponders; 14.7 percent of the sample had a lifetime secondary psychiatric disorder; and 29.9 percent had recurrent MDD. Fidelity and adherence to the treatment regimen was not reported; nor were the recruitment or intervention settings. External validity was assessed as "good"; however, attrition was moderate in both groups. Safety assessments included vital sign measurement; AE reports and severity of event, including self-harm categorized into suicidal attempt, suicidal ideation, self-injurious behavior, accidental overdose, or other; clinical laboratory determinations; monitoring of concomitant medications; clinician rating of severity of suicidal ideation and behavior as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS); and patient rating of suicidal thoughts and cognitions about suicide as measured by the Suicide Ideation Questionnaire-Junior High School (SIQ-JR). The safety analyses generated descriptive statistics. Suicidality was assessed for all patients with a baseline assessment and at least one postbaseline assessment.

The new collaborative care study, described in KQ 5, recorded changes in the number of psychiatric hospitalizations and ED visits with a primary psychiatric diagnosis.[109]

Description of Previously Identified Studies on Treatment Harms That Continue to Meet Current Inclusion and Quality Criteria

Of 17 fair- or good-quality trials reported in 21 publications identified in the previous review for the KQ on treatment efficacy, six trials continue to meet the inclusion/exclusion criteria for KQ 6 of this update,[98,119,120,129,130,132] plus an additional three publications reported on 1) the harms associated with the March et al[98] trial that had four treatment arms (fluoxetine, CBT, fluoxetine and CBT, placebo),[145] and 2) synthesized harms data from the Emslie 1997 and 2002 fluoxetine trials[146] and harms associated with the Emslie 2002 fluoxetine trial.[147] Thus, six trials reported in nine publications included in the prior review met our KQ 6 inclusion criteria prior to applying quality criteria. Three of the 12 excluded trials (reported in 13 publications) did not report harms as outcomes.[121,131,133] As stated in KQ 5, primary reasons for excluding the other trials included in the prior review were not meeting review criteria for population (at least 50% of the sample did not have MDD[134-138]), not meeting review criteria for intervention (paroxetine[139-141]), and not meeting review criteria for geographic setting (one trial presented in two publications was conducted partially in countries with a low Human Development Index[143,144]).

In addition to the six RCTs examining harms that met our inclusion/exclusion criteria, the prior review included eight other meta-analyses or retrospective cohort studies that were excluded from this report. Four meta-analyses were excluded because they did not limit their review to studies with samples where at least 50 percent of the children and adolescents had MDD or did not report outcomes for those with MDD separately.[148-151] Three other meta-analyses[152-154] and one retrospective cohort study[155] were excluded from this report because their synthesized findings included paroxetine as a treatment modality, which was excluded from our review due to increased suicidality in children and adolescents taking paroxetine.

Pharmacotherapy

As stated above in the corresponding KQ 5 section, five of the prior trials reported in eight publications included in this updated review prior to applying quality criteria are pharmacotherapy interventions involving SSRIs; three trials in six publications reported harms associated with fluoxetine in children and adolescents ages 7 to 17 years[129,146,147] and 8 to 17 years[130,146,147] and in adolescents ages 12 to 17 years,[98,145] one examined harms associated with citalopram in children and adolescents ages 7 to 17 years,[120] and one tested harms associated with escitalopram in children and adolescents ages 6 to 17 years.[119]

Upon quality review of these five trials reported in eight publications using updated criteria, we determined that two trials reported in four publications were of poor quality. The two Emslie fluoxetine trials[129,130,146,147] had high overall attrition (75% and 28%) and high differential attrition (21% and 34%). Both of these pharmacotherapy trials also did not report assessor masking for outcome. One additional publication, Emslie 2006,[145] reporting on harms of the Treatment for Adolescents With Depression Study (TADS) trial was also dropped for high attrition. Thus, these two trials reported in four publications and one additional publication reporting on harms of the TADS trial are not synthesized with our newly identified studies

Thus, this report describes the KQ 6 results of four pharmacotherapy trials. One previously

included trial examined harms associated with fluoxetine in adolescents ages 12 to 17 years.[98] Two trials studied escitalopram: one previously reported trial conducted in children and adolescents ages 6 to 17 years[119] and one new trial conducted in adolescents ages 12 to 17 years.[107] Finally, a single trial reported in the prior review examined harms associated with citalopram versus placebo in a sample of children and adolescents ages 7 to 17 years.[120]

Psychotherapy

The two psychotherapy trials that continued to meet inclusion criteria prior to applying quality criteria were both 12-week trials. Studies included an individual IPT trial in adolescents ages 12 to 18 years[132] and one individual CBT trial in adolescents ages 12 to 17 years.[98] We did not find any additional psychotherapy trials that met our inclusion criteria published since the last review. Upon quality review of these two trials using updated criteria, we determined that one trial was of poor quality. The Mufson IPT trial had very high as well as differential attrition (33% and 42%).[132] Thus, this trial was rated as poor quality and is not summarized in this report. We did not identify any new psychotherapy trials that met our inclusion criteria; the only psychotherapy trial summarized is the TADS trial, in which CBT was compared with placebo and clinical monitoring.

Combined Interventions

No new studies of combined interventions were identified. The single combined intervention trial included in the prior report continued to meet inclusion criteria. This trial, which we determined to be of good quality, examined combined fluoxetine and individual CBT among adolescents with MDD. Thus, the only combined intervention trial described is the TADS trial of combined fluoxetine and CBT versus placebo.

Detailed Synthesis of Prior Evidence With New Findings on Treatment Harms

Pharmacotherapy

Fluoxetine

The March 2004[98] good-quality trial found no apparent differences for harm-related AEs or suicide-related SAEs for the fluoxetine versus placebo group (**Table 8**).

Escitalopram

The Emslie[107] fair-quality study examined harms in all participants who received at least one dose of escitalopram or placebo in the double-blind treatment period (8 weeks). The rate of discontinuation due to AEs, SAEs, AEs suggestive of self-harm, suicidality, or laboratory values or tests did not significantly differ between escitalopram and placebo groups, other than a greater decrease in platelet count among the escitalopram group compared to the placebo group.

The Wagner 2006[119] fair-quality study reported two SAEs and one potentially suicide-related

event in the escitalopram group and three SAEs and two potentially suicide-related events in the placebo group.

Citalopram

The Wagner 2004[120] fair-quality study reported no difference in discontinuation (20% vs. 21%) or discontinuation due to AEs (5.9% vs. 5.6%) across citalopram and placebo groups. There were no SAEs, including suicidality, for either citalopram or placebo groups.

Subgroup Differences in Harms

None of the studies included in this review reported harms across different subgroups.

Summary of Harms Findings

Table 8 and **Figure 9** exhibit suicidality outcomes in each of the SSRI trials. **Figure 10** displays the proportion of subjects with SAEs in each of these studies.

Psychotherapy

CBT (Monotherapy)

The March 2004 trial[98] found no apparent differences in harm-related AEs, suicide-related AEs, or psychiatric AEs in CBT versus placebo group patients.

Subgroup Differences in Harms

The single CBT trial included in this review[98] did not report harms across different subgroups.

Combined Interventions: Fluoxetine and CBT

The March 2004 trial[98] found no apparent differences in harm-related AEs, suicide-related AEs, or psychiatric AEs in combined CBT and fluoxetine versus placebo group patients (**Figures 9** and **10**).

Subgroup Differences in Harms

The single fluoxetine and CBT combined intervention trial included in this review[98] did not report harms across different subgroups.

Collaborative Care

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

differences (2% vs. 10%, respectively).[109]

Subgroup Differences

The single collaborative care study[109] did not report any outcome differences by subgroups.

Chapter 4. Discussion

Below, we summarize the findings of the 2009 report[104] about screening for MDD among children and adolescents. We note the 2009 USPSTF recommendations and comment on the implications of this new synthesis for previous USPSTF conclusions. Then we discuss the context for these results, applicability, limitations of the review and the literature, research gaps, and conclusions.

Summary of Review Findings

KQ 1

As in the 2009 report, we found no studies that met our review criteria that specifically addressed our overarching question: whether screening for MDD among children and adolescents in the primary care or comparable setting, followed by interventions for those who test positive, improved health and other related outcomes for such patients.

KQ 2

Prior Review Findings and USPSTF Recommendations on Screening

The 2009 review identified nine screening accuracy studies that used a valid reference standard; they formed the basis of the evidence synthesis on this issue.[112-116,122-125] The USPSTF concluded the following:

1. Two screening instruments, the PHQ-A and the Beck Depression Inventory for Primary Care (BDI-PC), may have had better performance characteristics than other screening tests. However, judging the degree to which differences could be attributed to the quality of the instrument or the characteristics of the population or study was difficult.
2. No instrument had been studied in large numbers of patients from a variety of settings by investigators other than those who developed the questionnaires originally.
3. Studies that involved children demonstrated poorer performance of the screening instruments than studies involving adolescents. Heterogeneity in instruments, samples, and settings hampered assessment of whether results for screening accuracy among adolescents would apply to children.
4. All included studies had limitations, such as high levels of attrition, nonrandom selection, excessive delays between screening and diagnostic interviews, poor reporting of methods, or small samples.

The USPSTF stated in 2009 that adequate evidence supported the conclusion that screening tests accurately identify MDD in adolescents. The USPSTF found inadequate evidence that screening tests accurately identify MDD in children.

Implications of the New Synthesis for Prior Conclusions on Screening

No new studies that met our review criteria examine screening for MDD in primary care or similar settings. Excluding four studies from the prior review (two did not meet inclusion criteria[124,125] and two were rated poor quality[122,123]) does not alter the conclusions of the previous review. In short, the PHQ-A and the BDI screening tools continue to outperform other screening tools, although we did not include the BDI-PC study in our update (because it did not meet inclusion criteria[125]). It is important to note that none of our included studies tested some of the more recent screening instruments that have good psychometric properties, and some of the older studies included in this report use adult versions of screening instruments that have since developed child- or adolescent-specific versions.[89,156] It is also important to note that the positive predictive value of these instruments is relatively low (range, 10% to 56%); thus, 44 to 90 percent of those screening positive for MDD will not, in fact, have a clinical diagnosis of MDD upon further testing. Moreover, the substantial heterogeneity in interventions, populations, and settings and the lack of replication studies makes generalization challenging. Finally, the gap in evidence identified previously, with respect to screening tools for children, persists (**Table 9**).

KQ 3

For this update, we did not identify any studies that tested whether screening increases the proportion of children or adolescents who are identified with MDD overall or among subgroups defined by age, sex, or race/ethnicity. Thus, we are unable to comment on whether screening helps identify children and adolescents with MDD who would not have otherwise been recognized.

KQ 4

As in the 2009 report, we found no studies that examined potential harms of systematic, standardized screening for MDD overall or among subgroups defined by age, sex, or race/ethnicity. One potential harm involves the risk of missing cases of depression during a clinical encounter that had not been identified during the initial screening because the clinician "inappropriately lowered their level of clinical suspicion."[104] The high negative predictive value of the PHQ-A (97%) and the BDI (99%) suggest that few adolescents would have undetected depression. Another potential opportunity cost is allocation of time and resources to screening that could be used elsewhere.[104] The highest positive predictive value is 56 percent, suggesting that in the best-case scenario, nearly half the number of patients who screened positive will not meet criteria for MDD; whether they would meet criteria for dysthymia or minor depression remains unclear.

KQ 5

Prior Review Findings and USPSTF Recommendations on Treatment

In the 2009 review, the USPSTF concluded that good-quality RCTs have tested SSRIs and various psychotherapies among pediatric populations. These trials provided evidence that

efficacious interventions are available, although long-term effects were not known. The USPSTF also noted that:

1. When analysts combined data from trials of all SSRIs for treating depression in youth, patients receiving an SSRI were more likely to show a response to treatment than patients receiving a placebo.
2. Fluoxetine had been studied among children and adolescents ages 7 to 17 years. At the time of the review, this was the only drug approved by the FDA for treating MDD among youth.
3. Available age-stratified meta-analysis results indicated that fluoxetine was efficacious for both children and adolescents.

The USPSTF concluded that readers needed to exercise some caution in interpreting SSRI study results because baseline response rates among placebo-treated patients were very variable across the trials. In addition, some individual SSRIs did not seem to be efficacious. Finally, not all SSRIs had been evaluated in pediatric clinical trials.

The USPSTF found adequate evidence that treatment in adolescents with SSRIs, psychotherapy, and combined therapy (SSRIs and psychotherapy) decreased depressive symptoms. For children, the USPSTF found inadequate evidence to support the benefits of treatment in children. Although SSRIs (e.g., fluoxetine) reduce MDD symptoms in children, the USPSTF concluded that only limited data are available on the benefits of psychotherapy and the benefits of psychotherapy plus SSRIs for children.

Implications of the New Synthesis on Prior Conclusions on Treatment

Fewer studies met inclusion criteria for the current update than for the 2009 report. Our review examines the results of six trials reported in eight publications: four old trials reported in six publications[98,117-121]and one new trial[107] studying a pharmacotherapy intervention, and one new trial[109] that examines a collaborative care intervention. One fair-quality trial studied citalopram,[120] two fair-quality trials studied escitalopram,[107,119] one good-quality trial reported in three publications tested CBT versus placebo and combined fluoxetine and CBT versus placebo,[98,117,118] one fair-quality trial tested group CBT versus waitlist control,[121] and one good-quality trial evaluated collaborative care versus enhanced usual care.[109]

The single citalopram trial in the prior report did not find significant differences in efficacy between treatment groups. Since the publication of the 2009 report, the FDA has approved escitalopram for use in adolescents ages 12 to 17 years who have MDD. One escitalopram trial demonstrated efficacy, although the other study did not. The effect sizes from the escitalopram trials are notably smaller than those for the fluoxetine trial that examined response to treatment.

One good-quality trial found significant associations between fluoxetine and response to treatment[98] (absolute risk difference, 25.7%) and between the combined fluoxetine and CBT intervention and response (absolute risk difference, 36.2%). Thus, evidence from this single trial suggests that fluoxetine may be associated with large effect sizes in the acute phase.

Each of the continuous outcomes reported by the SSRI trials illustrated the robustness of benefits

associated with SSRIs. We found statistically significant decreases in depression severity (CDRS-R) and symptom severity (CGI-S) and increases in depression symptom improvement (CGI-I) and global functioning (CGAS) associated with SSRI use.

Two trials in four publications, conducted in adolescents ages 12 to 18 years, provided information on psychotherapy efficacy or combined therapy[98,117,118,121] and provided inconsistent evidence of difference or no evidence of difference in improvements in depression (change in symptoms, response, remission/recovery) or other outcomes (functioning, child behavior, quality of life).

One study on collaborative care, conducted in adolescents ages 13 to 17 years, found improvements in symptoms, response, and remission but not functional status.[109]

We identified no trials, old or new, that tested psychotherapy or combined interventions in children younger than age 12 years. For that reason, we cannot offer evidence on the efficacy of psychotherapy as a first-line treatment for clinicians who wish to avoid the use of medications in children with MDD.

As noted above, using our inclusion and exclusion criteria and current USPSTF quality ratings, we could include only four good- or fair-quality RCTs. Moreover, we were unable to include previous meta-analyses in our results because the analysts had not required a diagnosis of MDD or that a majority of study participants have MDD, and may have included the SSRI paroxetine as an intervention. (We excluded paroxetine in this update because of its contraindicated use in children and adolescents owing to increased risk of suicidality.)

The four SSRI trials, two CBT trials, combined trial, and collaborative care trial focused on a limited set of outcomes. No trial examined long-term outcomes. Few trials examined the more rigorous definition of remission; that is, the absence of MDD diagnosis at followup.[107,109,120] In addition to response, all studies examined depression severity or symptoms using continuous outcomes, but only two trials looked at other outcomes (e.g., global or social functioning).[107,109,119,157] The impact of interventions on other mental health outcomes and functioning is thus largely unknown.

At the time of this update review, only two medications had FDA approval for treatment of pediatric MDD: fluoxetine in children and adolescents ages 6 to 17 years and escitalopram in adolescents ages 12 to 17 years. Both of these medications appeared to demonstrate efficacy in our included studies, with fluoxetine having a larger effect size than escitalopram, which was only found efficacious in one of the two included escitalopram studies. Of note, however, a recently published multisite study from nine countries found no evidence of efficacy associated with fluoxetine.[158] This study was formally excluded from our review because more than 50 percent of the sample were recruited from a country with a medium or high Human Development Index, which indicated that the findings may not generalize to the United States, a country with a very high Human Development Index. In addition, few included studies examined the more stringent outcome of remission, in which depression symptom severity decreases to a predetermined level indicative of the absence of depression.

We know that efficacy of MDD treatment likely varies by sociodemographic characteristics of patients. To explore this aspect of depression therapy, we searched for studies that examined efficacy in subgroups defined by age, sex, or race/ethnicity, but we uncovered few studies or findings. One subgroup analysis of fluoxetine showed benefits for adolescents but not for children.[119]

KQ 6

Prior Review Findings and USPSTF Recommendations on Treatment Harms

The prior review found 17 trials of harms associated with SSRIs reported in 21 publications and concluded that there does not appear to be an increased risk of suicidal ideation or behaviors with SSRI use. Data from individual studies, however, did not yield statistically significant increases in suicide-related outcomes, either because of lack of effect or lack of power. The prior review also concluded that the evidence was insufficient to determine the role of combined treatment (SSRIs plus psychotherapy) on suicidal ideation or behavior. Finally, the report concluded that no evidence existed on the harms of psychotherapy alone. The USPSTF recommendation stated that good evidence shows that the potential benefits of screening and treatment outweigh any potential harms.

The USPSTF found convincing evidence of harms of SSRIs in adolescents. It found limited evidence regarding the harms of combining SSRIs and psychotherapy. It also found inadequate evidence about the harms of screening and psychotherapy in adolescents, which the USPSTF judged to be probably small. For children, the USPSTF concluded that SSRIs had demonstrated harms (specifically, risk of suicidality); as with adolescents, the USPSTF found limited evidence on the harms of psychotherapy and the harms of combining psychotherapy and SSRIs in children. The USPSTF noted the absence of evidence about the harms of screening children. The USPSTF assessed that the overall evidence regarding the harms of screening and treatment in children is inadequate.

Implications of the New Synthesis on Prior Conclusions on Treatment Harms

Contrary to prior studies that have examined the use of pharmacotherapy for child and adolescent depression in general (rather than just examining MDD as the primary indication), the four trials included in this report of fluoxetine, escitalopram, or citalopram found few apparent associations with harms. Evidence for harms associated with psychotherapy or combined treatments is scarce, coming from a single trial (TADS).[98] Our included studies provide very little evidence regarding harms in children—only two SSRI studies that examined harms were conducted in children and no psychotherapy or combined interventions examined harms in children. The absolute risk difference for suicidality associated with SSRIs in each included study was nearly zero. Our requirement of samples with a majority having a MDD diagnosis, coupled with our exclusion of paroxetine, may explain the limited evidence on harms from SSRIs.

The absolute risk differences for suicidality in the two escitalopram trials were nearly zero. The single citalopram trial reported no instances of suicidality in either the treatment or placebo groups. Although the absolute risk difference for suicidality associated with fluoxetine in a single

trial was 4.7 percent (9/109 in fluoxetine group vs. 4/112 in placebo group), the CI spans the line of no difference (95% CI, -1.5 to 10.9).

The inclusion criteria for the current report precluded synthesis of paroxetine studies. As noted earlier, the FDA recommended in June 2003 that paroxetine not be used in children and adolescents for treating MDD due to increased risk of suicidality. This review does not synthesize results for any SSRIs other than fluoxetine, escitalopram, or citalopram. All appear to have low associated risks of harms. Thus, our analyses cannot address the issue of harms of SSRIs in general. We also note the limited power of included studies, as they cannot rule out absence of harms.

One study on collaborative care found no consistent or significant harms (psychiatric hospitalizations or ED visits).[109]

Applicability of Findings

The included studies have limited applicability to the primary care setting. Studies included in this review generally drew patients from research or academic settings ranging from one to 40 sites. One study was conducted predominantly in clinical settings throughout the community and was described as an effectiveness trial.[98] Another study, on collaborative care, recruited patients from pediatric and family medicine clinics in the Group Health system in Washington state.[109] Thus, few true primary care settings were used as the referral point or the actual intervention setting in our included studies. No school clinics served as treatment sites.

Findings from RCTs may not apply to true clinical practice settings. Stringent inclusion and exclusion criteria required of many of the included trials limit the generalizability of the findings. For example, patients seen in primary care settings often have multiple comorbid conditions, some of which require the use of medications, and often do not have optimal adherence to treatment regimens. Thus, the patients eligible for these trials may not be representative of all patients with MDD seen in primary care, which limits the external validity of our results and conclusions.

Context for Findings

Assessment, Treatment, and Referral of Children and Adolescents for Depression

Even though primary care represents a major point for health service contact and a potential setting for detecting depression and improving adolescent health, primary care providers often lack the tools and communication skills to engage youth and their families in an appropriate course of action for treating or monitoring depression.[160,161] To understand the potential burden from universal screening in primary care settings for pediatricians and specialty mental health providers, we sought to determine the proportion of primary care providers who assess, treat, and refer child and adolescent patients with depression, including MDD, dysthymia, and minor

depression. We found nine national studies and one statewide study that provided statistics on pediatricians' practice behavior in the context of the 2004 FDA boxed warning about the use of antidepressants in pediatric populations.[162-172]

Regarding assessment, the nine national studies did not examine the proportion of pediatricians who assessed depression. Nevertheless, even the small sample of 42 pediatricians in North Carolina highlighted that assessing depression as a diagnosis decreased by 2 percent (from 43% to 41%) after the FDA released the boxed warning.[164] According to one national study, the FDA advisory was associated with significant reductions in aggregate rates of diagnosis of pediatric depression. From 1999 to 2004, diagnosis of pediatric depression increased from 3 to 5 cases per 1,000 children, but after the FDA advisory was issued, the national rate decreased to 1999 levels, a significant deviation from the historical trend.[172]

Regarding treatment, the most recent national study (published in 2012) found that a majority (60%) of U.S. pediatricians do not treat children and adolescents with MDD.[162] Among the 2,000 pediatricians in the sample, 28 percent reported treating children and adolescents, 12 percent indicated they treated only adolescents, and no pediatrician treated children but not adolescents. The first national study to examine pediatrician practice change illustrated that among the 72 percent of pediatricians who were aware of the FDA warning, 80 percent changed their prescribing practices; this included 32 percent who followed their patients more closely and 7 percent who stopped treatment with SSRIs in at least one patient.[163] A Canadian study observed a statistically significant decrease in pediatricians' use of SSRIs after the FDA boxed warning (25% vs. 6%; $p<0.0001$).[163] A North Carolina study also observed a statistically significant decrease (53% vs. 26%; $p<0.01$).[164] Another study examined the difference in trends between prewarning and paroxetine warning periods. Youth paroxetine use significantly increased during the prewarning study period (30% per year; $p<0.001$) before significantly declining during the paroxetine warning study period (-44.2% per year; $p<0.001$).[166]

Regarding referral, the U.S.-based survey of pediatricians found that almost 84 percent refer both children and adolescents to mental health specialists for treatment of MDD.[162] Nearly 8 percent of pediatricians, however, did not refer either children or adolescents to another health care provider for treatment of this disorder.

The national and international warnings about the safety of antidepressants in children and adolescents appear to have influenced local utilization of these medications in young people. According to one national study, there was a significant relationship between the timing of the FDA recommendations and antidepressant utilization in children and adolescents, where antidepressant use decreased over time, particularly use of SSRIs.[170] While the timing of the FDA recommendations was associated with changes in prescribing patterns for children with MDD, the FDA's recommendation regarding increased physician monitoring appears to have been largely ignored.[167,171] Less than 5 percent of all patients met FDA contact recommendations before the advisory, and the rate did not change after the advisory.[167] Another study noted that the lack of evidence of increases in outpatient visits among children with depression may be due to the relatively high cost of office visits, a shortage of providers (particularly child psychiatrists), or the high cost-sharing associated with mental health visits in many health insurance plans.[171]

We did not find any studies on the proportion of providers who have access to collaborative systems of care, such as patient-centered medical homes and accountable care organizations. One effectiveness trial of a quality improvement intervention aimed at increasing access to evidence-based treatments demonstrated that collaborative care models are effective in treating adolescent depression.[173] Another study examined a collaborative care model known as Targeted Child Psychiatric Services, designed for primary care pediatricians and child psychiatrists, that was associated with improved access to pediatric psychiatry services.[174]

Types of Treatment Initiated in or Referred From Primary Care Settings

After the FDA advisories on suicidality associated with the use of paroxetine in patients younger than age 18 years in 2003 and on suicidality associated with all antidepressant use in patients younger than age 18 years in 2004, as noted above, evidence suggests a shift away from prescribing SSRIs and toward other drugs.[163,164,168,169] The decrease in prescribing SSRIs by approximately 22 percent was associated with an increase in suicide rates in children and adolescents by 14 percent between 2003 and 2004, which is the largest year-to-year change in suicide rates in this population since the Centers for Disease Control and Prevention began systematically collecting suicide data in 1979.[175] Evidence also suggests a shift in prescribers from primary care physicians to psychiatrists.[176] These trends may explain the paucity of primary studies on treatment of MDD among children and adolescents in primary care and other comparable settings.

Screening and Treatment for Children and Adolescents With Depression and Coexisting Mental Health Diagnoses

We also sought to determine if children and adolescents with MDD and coexisting mental health diagnoses (e.g., attention deficit hyperactivity disorder, anxiety disorders) or chronic physical health conditions (e.g., diabetes, asthma) were more likely to be screened, treated, or referred for treatment in primary care, school, or comparable settings than children and adolescents with MDD only. We also tried to determine whether patients with such concurrent comorbid conditions received treatments different from those received by children and adolescents without such disorders. We found no such studies focused on these topics, despite widespread knowledge that these populations have an increased risk of MDD.

Risk Stratification

We sought evidence of reliable and valid risk stratification tools that clinicians could use to identify children and adolescents at highest risk for MDD. The ability to stratify children and adolescents reliably by risk would provide great opportunities to allocate interventions appropriately and efficiently. Predicting those at high risk for depression and subsequent sequelae is complicated, however, by the dynamic nature of development. Evidence for valid risk factors that are durable throughout child and adolescent development is limited.

Many investigators have attempted to predict depression with subsets or single questions from

existing screening instruments. Items related to low self-worth within the Short Mood and Feelings Questionnaire (SMFQ) predicted depressive symptoms 12 months later in a group of children ages 10 to 15 years, although the SMFQ was neither designed for prediction nor directly validated with DSM diagnoses.[177] In early adolescence, physical symptoms such as sleep disturbance might improve future prediction of depression as diagnosed by DSM-IV criteria.[178] In 10th- and 11th-grade female adolescents, depressive symptoms, low parental support, poor family and poor school functioning, and bulimic symptoms predicted MDD onset 4 years later.[179] Similarly, others have shown a correlation between high "psychosocial risk" (factors such as low parent education level, parental psychiatric disorders, crowded living, and single parenthood), low self-control temperament, and high scores on the Children's Depression Inventory (CDI) at age 11 years.[180] Overall, tools to predict risk have very poor positive predictive values.

Treatment With Other SSRIs or Psychotherapy That Did Not Meet Study Inclusion and Exclusion Criteria

Finally, we searched our main literature results and additional literature for evidence of efficacy or effectiveness of other types of treatment for pediatric MDD. We specifically searched for the use of SNRIs, norepinephrine-dopamine reuptake inhibitors, or CAM treatments for child or adolescent MDD. Again, we found few trials or data on these therapies with few findings. One study showed that the SNRI venlafaxine has not been proven to be efficacious in children and adolescents.[181] Two newer trials found no evidence of efficacy of the SNRI duloxetine in children and adolescents,[158,182] and one found increased risk of total treatment-emergent AEs and discontinuation due to AEs among children and adolescents treated with 60 mg, but not 30 mg, of duloxetine. With respect to CAM interventions, a small study (N=27) of children and adolescents with depression evaluated 1,000 mg/day of vitamin C versus placebo as an adjunct to fluoxetine 10 or 20 mg/day; vitamin C improved self- and parent-rated severity of depression (CDI and CDRS, respectively) at 3 and 6 months but did not improve the clinician-rated severity score (CGI).[183] Light therapy, omega-3 fatty acids,[184] massage, art and relaxation therapy, distraction techniques, bibliotherapy, and exercise[185,186] have been studied in patients with depression and depressive symptoms; no study of these modalities produced high-quality evidence of benefit.[187]

Limitations

Limitations arise from our stringent criteria and the methodological constraints of published evidence (i.e., publication bias). Most notably, we focus solely on screening for MDD; we do not address screening or treatment for minor depression or dysthymia. Controversy continues to exist regarding whether depressive symptoms exist on a continuous spectrum or whether MDD is a diagnostic entity of distinct clinical significance, particularly among children and adolescents.[188] Although several studies have shown subthreshold depression to be a risk factor for MDD,[189] the temporal sequence and intervening factors are not well understood. Studies conducted in adults that have quantified the risk of developing MDD after having subthreshold depressive symptoms have shown that approximately 8 percent develop diagnostic MDD in the following 3 years.[190] It is inarguably important for primary care providers to have awareness of potential risk factors for

MDD and attempt early intervention, particularly among patients who have already experienced one episode of major depression. However, given the burden of universal screening; the requirement for clear evidence of net benefit for making screening recommendations; and the paucity of evidence on the etiological links between subthreshold depression, dysthymia, and depression, we chose to focus on screening for existing MDD rather than its prevention. An additional change in scope from the last report excluded studies that examined the efficacy or harms associated with paroxetine, which is contraindicated in children, adolescents, and young adults due to heightened suicide risk associated with its use. Because we excluded paroxetine, we did not find clear evidence of harms from SSRIs. Our summary of evidence no longer reflects the historic burden of harms from SSRIs but, in our view, captures more accurately the risk in current practice.

Our narrowed inclusion and exclusion criteria, coupled with our thresholds for quality, result in our including five screening studies of fewer than 3,000 children and adolescents (none of whom are younger than age 11 years) and six treatment trials of fewer than 1,500 children and adolescents with MDD conducted over the past three decades. As a result, we cannot rule out the absence of benefits or harms, particularly for rare outcomes. Guidance suggests that interventions with a relative risk reduction of 20 to 25 percent and a control event rate of 20 percent require a sample size between 2,000 and 4,000. Outcomes such as suicidality occur at much lower rates in the control arm and may require even larger samples to rule out the absence of benefits and harms.[191]

The nature of the population may drive the methodological constraints that we commonly observed, such as small sample size, high attrition, and biased ascertainment of the reference standard in screening studies. Concerns about risks to this vulnerable population may limit enrollment within funded studies (and the number of funded studies). Similarly, these concerns, coupled with the difficulty of following up with children and adolescents directly rather than through adult guardians and the mobility of younger populations, may heighten attrition, particularly for longer-term outcomes. In the context of the dynamic nature of health status among children and adolescents, a time lapse between screening and diagnostic interviews may result in biased ascertainment of the reference standard and explain the poor sensitivity and specificity of screening instruments.

Gaps and Future Research

Several gaps emerged from our review as critical needs for future research. These include:

- Large, good-quality RCTs on the overarching question of the effects of screening on depression and related health outcomes, that evaluate outcomes at intermediate stages, including:
  - Accuracy of screening
  - Whether screening increases the proportion of children and adolescents who are identified with depression
  - Willingness of screened patients to go through additional diagnostic procedures and, if indicated, proportion who are referred and ultimately obtain treatment

    - Harms of screening
    - Benefits and harms of treatment
    - Harms of not treating MDD
- Additional screening studies that include children younger than age 11 years
- Studies of benefits and harms of psychotherapy, nonSSRI medications, CAM, and combination treatments for screen-detected children and adolescents with MDD
- Trials that recruit children and adolescents from school or community health care settings and address practical issues of conducting this research by engaging in cross-site collaborations
- Analyses of differential efficacy by demographic characteristics (e.g., age group, sex, race/ethnicity, socioeconomic status)
- Studies that develop and test risk stratification tools to identify high-risk youth for screening
- Impact of mental health, somatic symptoms, or chronic physical comorbid disorders on screening accuracy, likelihood of screening, and type of MDD treatment selected
- Screening among diverse populations (e.g., different racial/ethnic groups, youth with limited English-speaking abilities)
- Studies that focus on long-term outcomes of screening and subsequent treatment
- Meta-analyses of SSRIs that include only children and adolescents with MDD and do not include paroxetine, which is contraindicated for use in children, adolescents, and young adults, in synthesized findings
- Exploration of where, when, how often, and which children and adolescents are screened for MDD in an attempt to determine best screening practices, including determination of appropriate screening intervals

Conclusions

We found no trials that examine the impact of screening for pediatric MDD in primary care on subsequent improvements in depression and other health-related outcomes. No new studies focused on screening for MDD among children or adolescents met our criteria. The studies from the 2009 review that remain in our synthesis suggest that primary care–feasible screening tools have been reasonably accurate in identifying adolescent MDD, but research on screening for MDD in children younger than age 12 years is in its infancy. Data from individual RCTs demonstrated efficacy of SSRIs, although the citalopram trial and one individual trial of escitalopram did not show significant benefits. No RCT found a significant increase in harms associated with treatment.

In conclusion, we found no evidence of a direct link between screening for MDD in children and adolescents in primary care or comparable settings and depression or other health-related outcomes. We found evidence that some screening tools are accurate and some treatments have benefit for MDD among adolescents (but not younger children), with no evidence of associated harms. Evidence gaps sharply limit conclusions for screening in children younger than age 11 years, screening and treatment differences by sex and race/ethnicity subgroups, and MDD treatment other than SSRIs.

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Figure 1. Screening for Childhood Depression: Analytic Framework

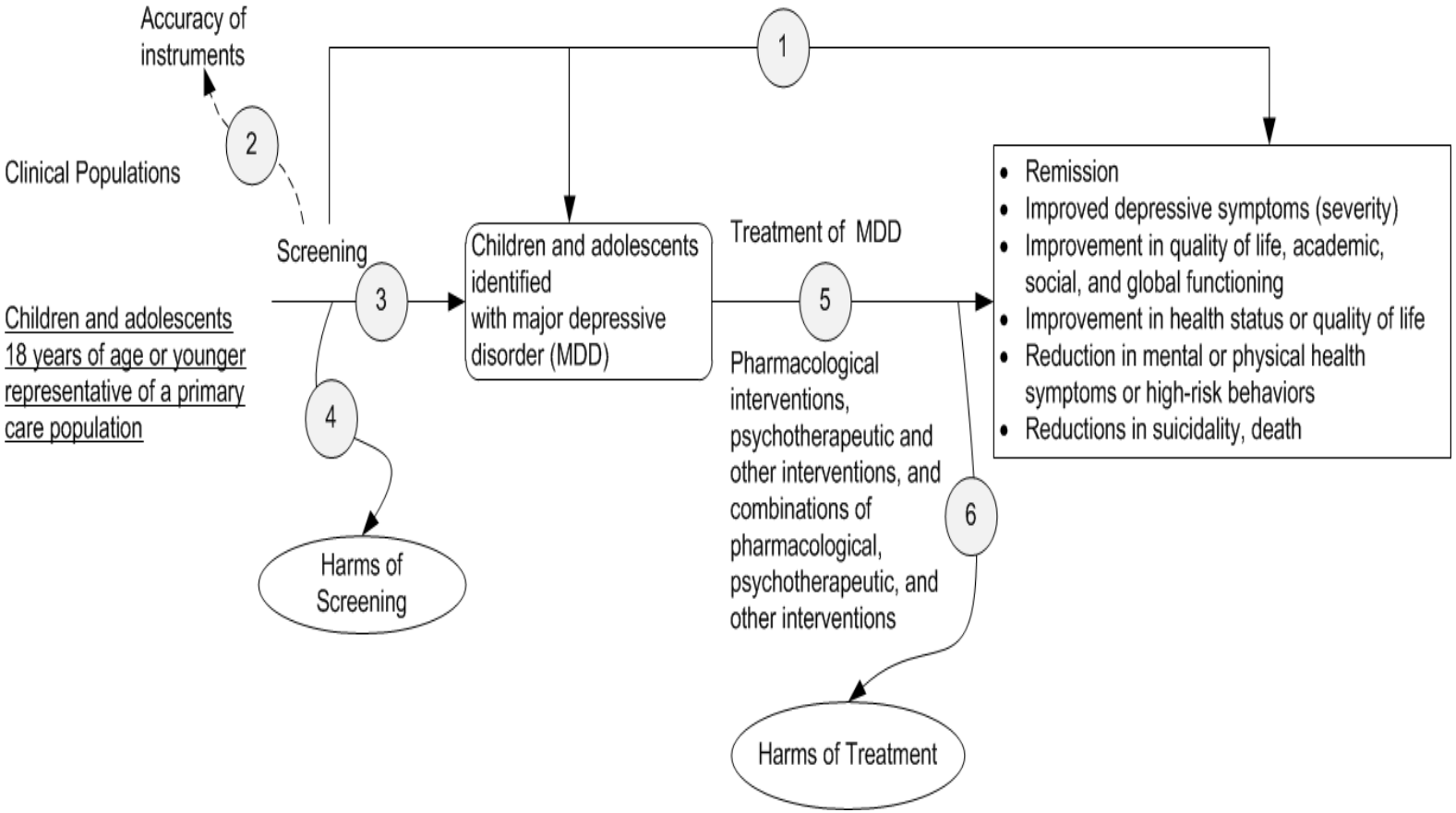


Figure 2. Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) Tree

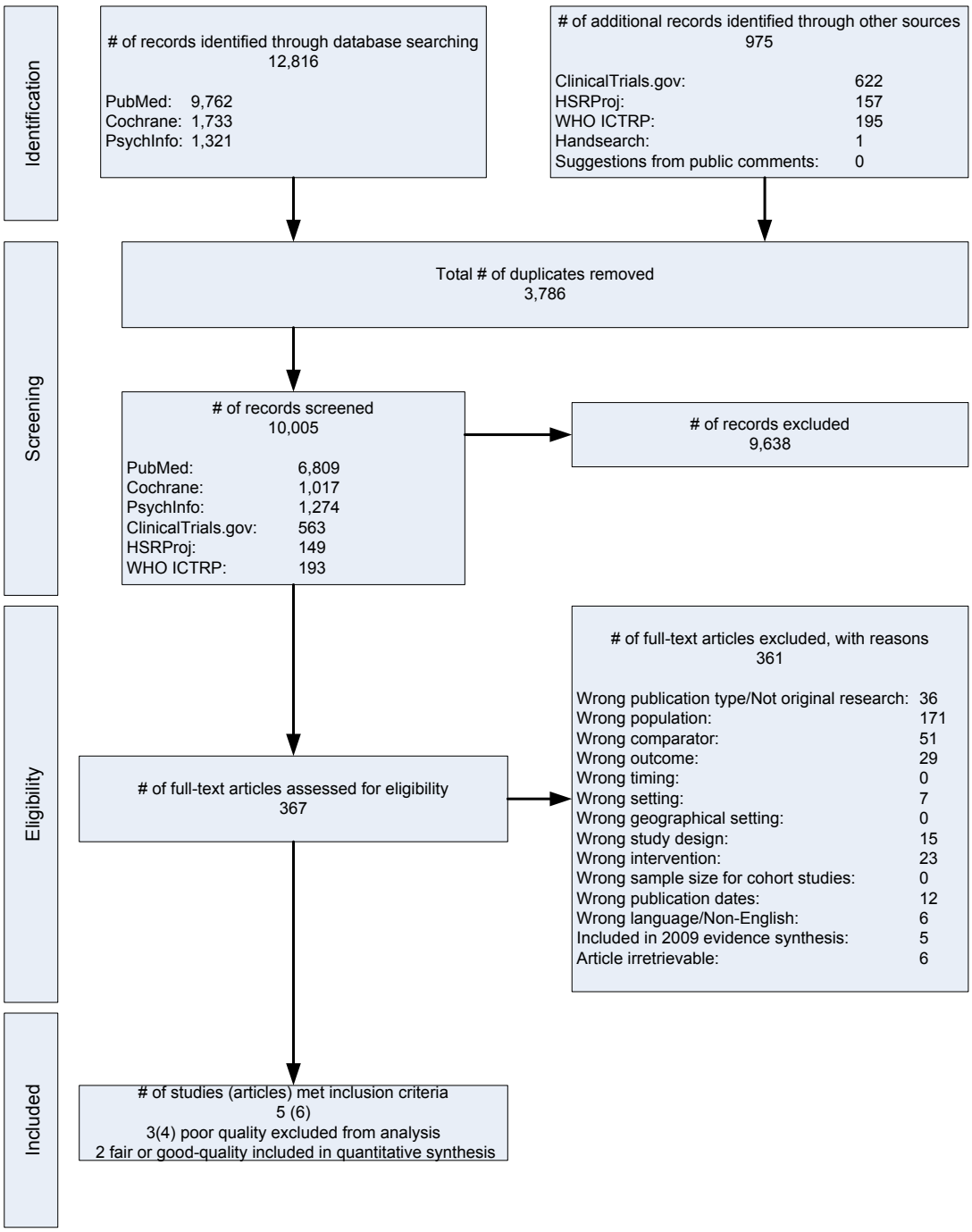
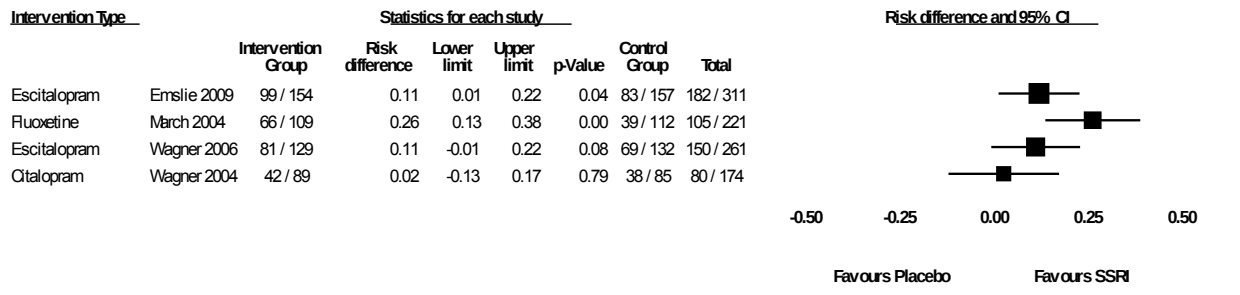
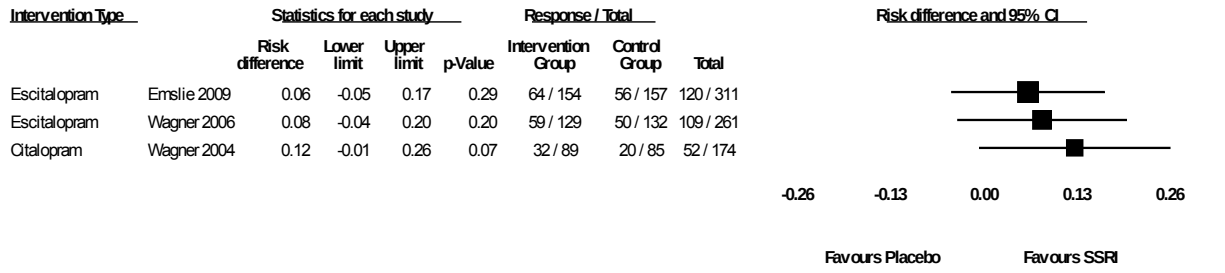


Figure 3. Response in Children and Adolescents Treated With SSRIs for MDD (KQ 5)



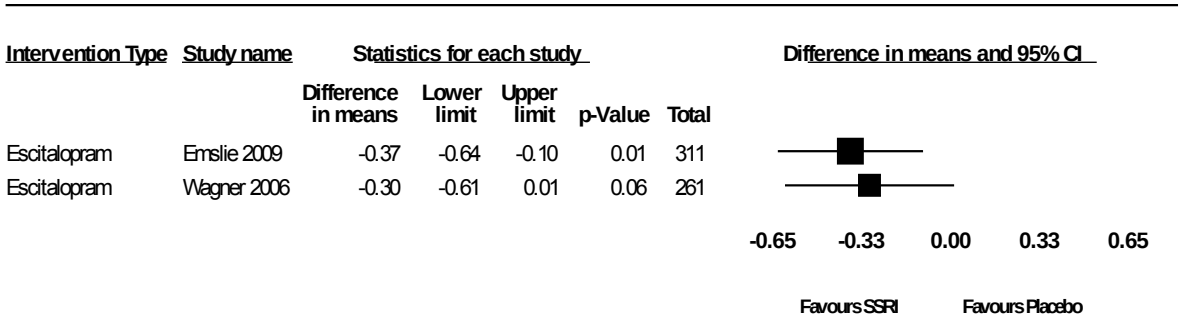
Response: CGI-I of 1 or 2 at follow-up; SSRIs : Selective Reuptake Inhibitors; MDD: Major Depressive Disorder

Figure 4. Remission in Children and Adolescents Treated With SSRIs for MDD (KQ 5)



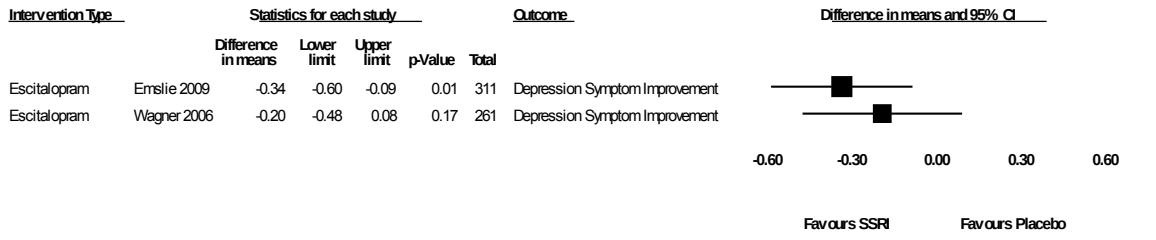
Remission: CDRS-R<=28 at follow-up; SSRIs : Selective Reuptake Inhibitors; MDD: Major Depressive Disorder

Figure 5.Change in Depression Symptom Severity in Children and Adolescents Treated With SSRIs for MDD (KQ 5)



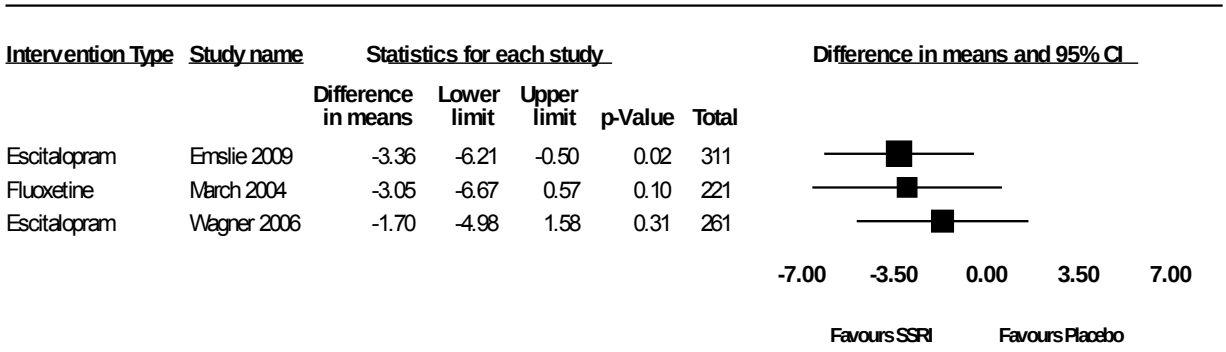
Depression symptom severity: CGI-S change at follow-up; SSRIs : Selective Reuptake Inhibitors; MDD: Major Depressive Disorder

Figure 6. Depression Symptom Improvement in Children and Adolescents Treated With SSRIs for MDD (KQ 5)



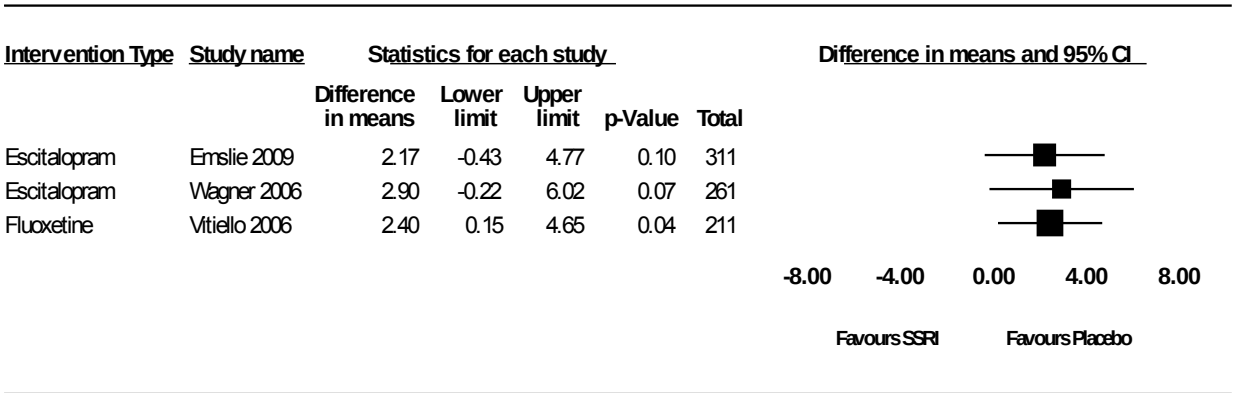
Depression symptom improvement: CGI-I change at follow-up; SSRIs : Selective Reuptake Inhibitors; MDD: Major Depressive Disorder

Figure 7. Change in Depression Severity in Children and Adolescents Treated With SSRIs for MDD (KQ 5)



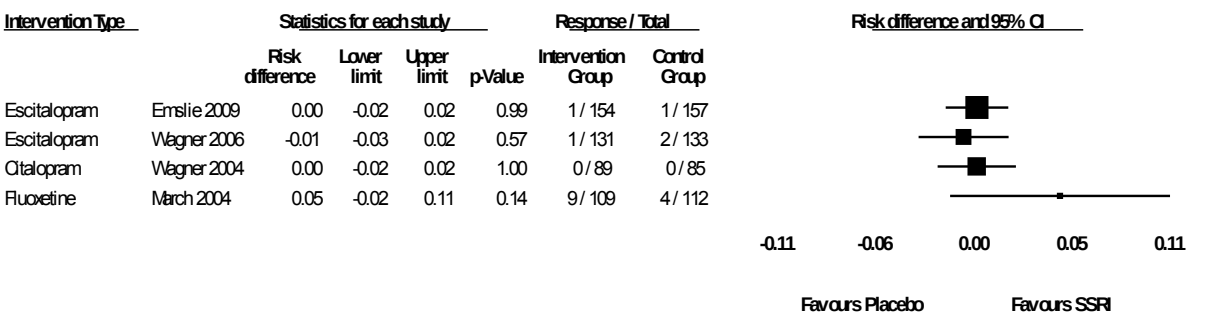
Depression severity: CDRS-R at follow-up; SSRIs : Selective Reuptake Inhibitors; MDD: Major Depressive Disorder

Figure 8. Change in Global Functioning in Children and Adolescents Treated With SSRIs for MDD (KQ 5)



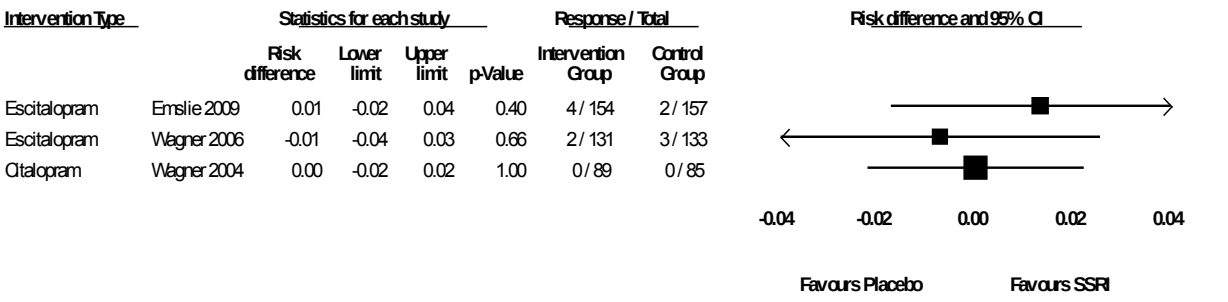
Global Functioning: change in CGAS at follow-up; SSRIs : Selective Reuptake Inhibitors; MDD: Major Depressive Disorder

Figure 9. Suicidality in Children and Adolescents Treated With SSRIs for MDD (KQ 6)



SSRIs : Selective Reuptake Inhibitors; MDD: Major Depressive Disorder

Figure 10. Serious Adverse Events in Children and Adolescents Treated With SSRIs for MDD (KQ 6)



SAEs: Serious Adverse Events; SSRIs : Selective Reuptake Inhibitors; MDD: Major Depressive Disorder

Table 1. Screening Tools for Depression in Children and Adolescents

Screening Tool	Number of Items	Time to Complete	Appropriate Ages	Sensitivity/Specificity
Beck Depression Inventory (BDI)*[192]	21	5-10 minutes	14 years and older	Sensitivity: 84.0% Specificity: 81.0%
Center for Epidemiological Studies Depression Scale (CES-D)*[114,193]	20	5–10 minutes	14 years and older	Sensitivity: 84.0% Specificity: 75.0%
Center for Epidemiological Studies Depression Scale for Children (CES-DC)[194,195]	20	5–10 minutes	12–18 years	Sensitivity: 85.2% Specificity: 75.6%
Children's Depression Inventory-Short Version (CDI:S)[196,197]	10	5 minutes	7–17 years	Sensitivity: 93.3% Specificity: 70.7%
Children's Depression Screener (ChiID-S)[87]	22	5–10 minutes	9–12 years	Sensitivity: 91.0% Specificity: 89.0%
Depression Screener for Teenagers (DesTeen)[89]	13	5 minutes	13–16 years	Sensitivity: 90.0% Specificity: 80.0%
Mood and Feelings Questionnaire[198]	13	5 minutes	8–18 years	Sensitivity: 78.0% Specificity: 78.0%
Patient Health Questionnaire-Adolescent Version (PHQ-2)[89]	2	5 minutes	12–18 years	Sensitivity: 89.5% Specificity: 77.5%
Patient Health Questionnaire-Adolescent Version (PHQ-A)[199]	9	2–10 minutes	12–18 years	Sensitivity: 89.5% Specificity: 77.5%
Pediatric Symptom Checklist briefer parent and youth forms (PSC-17)[200]	17	5–10 minutes	11–18 years	Sensitivity: 85.0% Specificity: 88.0%
Pediatric Symptom Checklist Original (PSC)[88]	35	5–10 minutes	6–18 years	Sensitivity: 95.0% Specificity: 68.0%
Pediatric Symptom Checklist Youth Self-Report (PSC-Y)[156]	35	5–10 minutes	11–18 years	Sensitivity: 94.0% Specificity: 88.0%
Reynolds Adolescent Depression Scale-Second Edition (RADS-2)[201]	30	5–10 minutes	11–18 years	Sensitivity: 84.0% Specificity: 92.0%
Reynolds Child Depression Scale (RCDS)[202]	30	5–10 minutes	7–13 years	Sensitivity: 73.0% Specificity: 97.0%

* Newer versions have replaced these instruments that currently are more frequently used in child and adolescent samples.

Table 2. Comparison of Studies Meeting Inclusion and Quality Criteria in Previous and Present USPSTF Reviews

Key Question	Study	USPSTF Review	
		2009	Current
KQ 1. Improved Health From Screening	None		
KQ 2. Accuracy of Screen Instruments	Barrera 1988[122]	X	
	Canals 1995[126]	X	
	Canals 1997[127]	X	
	Canals 2001[112]	X	X
	Garrison 1991[114]	X	X
	Garrison 1990[128]	X	
	Goodman 2003[124]	X	
	Johnson 2002[116]	X	X
	Patton 1999[115]	X	X
	Roberts 1991[113]	X	X
	Whitaker 1990[123]	X	
	Winter 1999[125]	X	
KQ 3. Clinical Utility of Screening	None		
KQ 4. Harms of Screening	None		
KQ 5. Benefits of Treatment	Ackerson 1998[137]	X	
	Berard 2006[140]	X	
	Clarke 1999[121]	X	X
	Diamond 2002[133]	X	
	Emslie 1997[129]	X	
	Emslie 2002[130]	X	
	Emslie 2009[107]		X
	Kahn 1990[138]	X	
	Kennard 2006[117]	X	X
	Keller 2001[139]	X	
	Kratochvil 2006[142]	X	
	Lewinsohn 1990[134]	X	
	March 2004[98]	X	X
	Mufson 1999[132]	X	
	Mufson 2004[136]	X	
	Richardson 2014[109]		X
	Rosello 1999[131]	X	
	Stark 1987[135]	X	
	Vitiello 2006[118]	X	X
	Wagner 2004[120]	X	X
	Wagner 2006[119]	X	X
KQ 6. Harms of Treatment	Bridge 2007[152]	X	
	Emslie 1997[129]	X	
	Emslie 2002[130]	X	
	Emslie 2006[145]	X	
	Emslie 2009[107]		X
	Hammad 2006[148]	X	
	Kaizar 2006[153]	X	
	March 2004[98]	X	X
	Martin 2004[151]	X	
	Mayes 2007[146]	X	
	Mufson 1999[132]	X	
	Nilsson 2004[147]	X	
	Olfson 2006[150]	X	
	Richardson 2014[109]		X
	Sondergard 2006[149]	X	
	Valuck 2004[155]	X	
	Wagner 2004[120]	X	X
	Wagner 2006[119]	X	X
	Wallace 2006[154]	X	

Table 3. Study Characteristics of Included Screening Studies

Study Reference Quality	Screening Tool	Selection Method
Johnson et al, 2002[116] Fair	PHQ-A	13- to 18-year-old English-speaking youth with at least 9 years of education, from primary care and school nurses' offices in California, Ohio, New Jersey, and New York. 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)
Canals et al, 2001[112] Fair	BDI BDI	All age-eligible children per municipal census in urban Spain recruited and completed assessments through schools. Original sample: Boys aged 11 and girls aged 10 Current sample: All of original sample who could be found and consented (304/579)
Roberts et al, 1991[113] Fair	BDI CES-D	Random sample of nine high schools in five communities (stratified by school) in west-central Oregon; rural oversampled to get equal proportion urban/rural
Garrison et al, 1991[114] Fair	CES-D CES-D	Students in or transferring to designated schools for middle or high school in southeastern metropolitan school district; United States
Patton et al, 1999[115] Fair	CIS-R	45 schools in Victoria, Australia selected with probability proportional to number of year nine students in each of three types of schools. Two classes randomly selected from each school. All CIS-R-positive youth and random sample of CIS-R-negative students selected for diagnostic interview

BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies–Depression Scale; CIS-R, Clinical Interview Schedule–Revised; PHQ-A, Patient Health Questionnaire for Adolescents.

Table 4. Childhood Depression Screening Test Accuracy

Author, Year USPSTF Quality	N	Instrument	Age Range or Mean Age, Years	Sensitivity	Specificity	Prevalence	Positive Predictive Value	Negative Predictive Value	Area Under the Curve (95% CI)
Johnson et al, 2002[116] Fair	403[a]	PHQ-A positive	13–18	73%	94%	Assumed current: 9.4%[b] (38/403)	56%	97%	NR
Canals et al, 2001[112] Fair	290	BDI ≥11 BDI ≥16	17–18	90% 90%	86% 96%	Current: 3.4% (SE, 1.4; SCAN, appears to be weighted for selection)[127]	20% 47%	99.5% 99.6%	NR
Roberts et al, 1991[113] Fair	1,704	BDI ≥11 CES-D ≥24	Mean age: 16.6	84% 84%	81% 75%	Weighted data NR	10% 8%	99.5% 99%	Male: 0.93 (0.84–1.02)[c] Female: 0.83 (0.75–0.91)[c] Male: 0.87 (0.75–0.99)[c] Female: 0.83 (0.75–0.91)[c]
Garrison et al, 1991[114] Fair	332	CES-D ≥22 CES-D ≥12	11–15 11–15	18% (male) 83% (female) 85% (male) 84% (female)	83% (male) 77% (female) 49% (male) 38% (female)	Weighted data NR	9% 25% 13% 11%	NR NR NR NR	Male: 0.61 Female: 0.77
Patton, 1999[115] Fair	158	CIS-R positive	Mean age: 15.7	18%	97%	Current: 6.2% (95% CI, 0.3 to 11.8); past 6 months: 12.1% (95% CI, 5.0 to 19.3); (CIDI, estimate weighted for selection)	49%	91%	NR

[a] 403 patients completed screening and diagnostic interviews, but 162 patients were excluded due to the time lag between screening and interview.
[b] The clinical validation interview included items from the Structured Clinical Interview for DSM-III-R, the PRIME-MD Clinical Evaluation Guide, and the DSM-IV Global Assessment of Functioning.
[c] CI calculated from reported standard errors.

BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies–Depression Scale; CI, confidence interval; CIDI, Comprehensive International Diagnostic Interview; CIS-R, Clinical Interview Schedule–Revised; EPDS, Edinburgh Postnatal Depression Scale; NR, not reported; PHQ-A, Patient Health Questionnaire for Adolescents; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SE, standard error; USPSTF, U.S. Preventive Services Task Force.

Table 5. Inclusion and Exclusion Criteria of MDD Treatment Trials in Children and Adolescents (KQ 5)

Author, Year Quality Rating	Intervention	Inclusion/Exclusion Criteria
March, 2004[98] Kennard 2006[117] Vitiello 2006[118] Good	IG1: fluoxetine CG: placebo	Exclusion: Aged <12 or >17 years, unable to receive care as outpatient, didn't meet DSM-IV criteria for MDD at consent or baseline, CDRS-R score <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.
Wagner, 2006[119] Fair	IG: escitalopram CG: placebo	Inclusion: Outpatients aged 6–17 years; primary diagnosis of MDD for at least 4 weeks with a CDRS-R score ≥40. Diagnosis established at initial screening visit though use of K-SADS-PL and semistructured diagnostic interview to assess MDD. Patients with normal results at screening from physical examination, laboratory tests, and ECG were included. Exclusion: Primary psychiatric diagnosis other than MDD, any psychotic features, any personality disorder, or met DSM-IV criteria for ADHD, PTSD, bipolar disorder, mental retardation, conduct disorder, or oppositional defiant disorder. A history of anorexia nervosa, bulimia, or substance abuse, including alcohol, within the past year. In females, pregnancy, lactation, and not using adequate contraception. Initiation of psychotherapy or behavioral therapy during the study or 3 months before the screening visit were not enrolled. Severe suicidal ideation requiring inpatient treatment; previous treatment with and failure of antidepressant or anxiolytic medication (within 2 weeks of baseline, 4 weeks for fluoxetine), antipsychotic or stimulant (6 months before screening); concomitant treatment with certain prescriptions or over-the-counter medications, including any psychotropic drug; or concurrent psychotherapy were excluded.
Emslie et al, 2009[107] Fair	IG: escitalopram CG: placebo	Inclusion: Outpatients aged 12–17 years, met diagnostic criteria for MDD; score ≥45 on the CDRS-R at screening and baseline, patient and parental consent; parent's attendance at study visits. K-SADS-PL, CGI-S score ≥4, Kaurman Brief Intelligence Test score ≥80; normal physical examination, laboratory tests, and ECG at screening. Negative serum b-human chorionic gonadotropin pregnancy test (females with childbearing potential), caregiver capable of providing information about patient's condition. Family support to guarantee adequate safety monitoring.
Clarke et al, 1999[121] Fair	IG1: child CBT IG2: child CBT with separate parent sessions CG: waitlist control	Inclusion: 1) Aged 14–18 years and 2) current DSM-III-R diagnosis of major psychiatric disorder or dysthymia Exclusion: 1) Current mania/hypomania, panic disorder, generalized anxiety disorder, conduct disorder, psychoactive substance abuse/dependence, lifetime organic brain syndrome, mental retardation, or schizophrenia; 2) receiving other treatment for depression and unwilling to discontinue; or 3) needed immediate, acute treatment.
Wagner, 2004[120] Fair	IG: citalopram CG: placebo	Inclusion: Outpatients aged 7–17 years; primary diagnosis of MDD for at least 4 weeks, with a CDRS-R score ≥40. Diagnosis established at initial screening visit though use of K-SADS-PL and semistructured diagnostic interview to assess MDD. Patients with normal results at screening from physical examination, laboratory tests, and ECG were included. Exclusion: Primary psychiatric diagnosis other than MDD, any psychotic features, any personality disorder, or met DSM-IV criteria for ADHD, PTSD, bipolar disorder, mental retardation, conduct disorder, or oppositional defiant disorder. History of anorexia nervosa, bulimia, or substance abuse, including alcohol, within the past year. In females, pregnancy, and not using adequate contraception. Initiation of psychotherapy or behavioral therapy during the study or 3 months before the screening visit were not enrolled. Severe suicidal ideation requiring inpatient treatment; previous treatment with and failure of antidepressant or anxiolytic medication, antipsychotic or stimulant; concomitant treatment with certain prescriptions or over-the-counter medications, including any psychotropic drug; or concurrent psychotherapy were excluded.

Table 5. Inclusion and Exclusion Criteria of MDD Treatment Trials in Children and Adolescents (KQ 5)

Author, Year Quality Rating	Intervention	Inclusion/Exclusion Criteria
Richardson, 2014[109]		Inclusion: Adolescent participants (ages 13–17 years), screening PHQ-9 score of ≥10, met criteria for major depression on the K-SADS-PL[203] or had a second positive PHQ-9 with a CDRS-R[204] score of ≥42. Exclusion: Non-English speaking, suicidal plan or recent attempt, bipolar, drug/alcohol misuse (CRAFFT18 score ≥5), seeing a psychiatrist, and developmental delay.

AD, antidepressant medication; ADHD, attention deficit hyperactivity disorder; CBT, cognitive behavioral therapy; CDRS-R, Children's Depression Rating Scale–Revised; CG, control group; CGI-I, Clinical Global Impression–Improvement Scale; CI, confidence interval; DSM-IV, *Diagnostic and Statistical Manual*, Fourth Edition; ECG, electrocardiography; IG, intervention group; K-SADS-PL, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version; MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire; PTSD, posttraumatic stress disorder; SSRI, selective serotonin reuptake inhibitor.

Table 6. Characteristics of RCTs of MDD Treatment in Children and Adolescents (KQ 5)

Author, Year Quality Rating	Intervention	Age Range, Years	N Patients Randomized	Length of Intervention, Weeks
Pharmacotherapy (n=4 trials reported in 6 publications; 1 new since 2009)				
March et al 2004[98] Kennard 2006[117] Vitiello 2006[118] Good	IG1: fluoxetine CG: placebo	12–17	221	12
Wagner 2006[119] Fair	IG: escitalopram CG: placebo	6–17	268	8
Emslie et al, 2009[107a] Fair	IG: escitalopram CG: placebo	12–17	316	8
Wagner 2004[120] Fair	IG: citalopram CG: placebo	7–17	178	8
Psychotherapy (n=2 trial reported in 4 publications)				
Clarke et al, 1999[121] Fair	IG1: child CBT IG2: child CBT with separate parent sessions CG: waitlist control	14–18	123	8
March et al, 2004[98] Kennard 2006[117] Vitiello 2006[118] Good	IG2: individual CBT CG: placebo + clinical monitoring	12–17	223	12
Combined Psychotherapy and Pharmacotherapy (n=1 trial reported in 3 publications)				
March et al, 2004[98] Kennard 2006[117] Vitiello 2006[118] Good	IG3: individual CBT + fluoxetine CG: placebo + clinical monitoring	12–17	219	12
Collaborative Care (n=1 trial reported in 1 publication)				
Richardson 2014[109a] Good	IG: collaborative care CG: enhanced usual care	13–17	101	52

[a] New evidence.
[b] With worsening of depressive symptoms for at least 2 weeks, or a clinician determination that there was significant clinical deterioration suggesting that full relapse would be likely without altering treatment, even if the CDRS-R score was ≤40.

CBT, cognitive behavioral therapy; CDRS-R, Children's Depression Rating Scale–Revised; CG, control group; IG, intervention group.

Table 7. Summary of Efficacy Outcomes in RCTs of SSRIs for the Treatment of MDD in Children and Adolescents

Pharmacotherapy and Study	Response Rate		Response (CGI-I = 1 or 2) Risk Difference % (95% CI)	Depression Severity (Change in CDRS-R) Mean Change (95% CI)	Depression Symptom Improvement (Change in CGI-I) Mean Change (95% CI)	Depression Symptom Severity (Change in CDI-S) Mean Change (95% CI)	Global Functioning (Change in CGAS) Mean Change (95% CI)
	Treatment Group	Placebo Group					
March et al, 2004[98,117,118] (fluoxetine)	60.6%	34.8%	25.7 (13.0 to 38.5)	-3.1 (-6.7 to 0.6)	NR	NR	2.4 (0.2 to 4.7)
Wagner 2004[120] (citalopram)	47.2%	44.7%	2.4 (-12.8 to 16.8)	NR	NR	NR	NR
Wagner 2006[119] (escitalopram)	63%	52%	10.5 (-1.4 to 22.4)	-1.7 (-5.0 to 1.6)	-0.2 (-0.5 to 0.1)	-0.3 (-0.6 to 0.01)	2.9 (-0.2 to 6.0)
Emslie et al, 2009[107] (escitalopram)	64.3%	52.9%	11.4 (0.5 to 22.3)	-3.4 (-6.2 to -0.5)	-0.3 (-0.6 to -0.1)	-0.4 (-0.6 to -0.1)	2.2 (-0.4 to 4.8)

CDI-S, Children's Depression Inventory–Short Version; CDRS-R, Children's Depression Rating Scale–Revised; CGAS, Children's Global Assessment Scale; CGI-I, Clinical Global Impression–Improvement Scale; CI, confidence interval; NR, not reported.

Table 8. Summary of Suicide-Related Adverse Events Among Children and Adolescents Treated With Antidepressants (KQ 6)

Drug (Number of Studies)	Suicide Events/Total N (%)		Risk Difference % (95% CI)
	Treatment	Placebo	
Fluoxetine (n=1)	9/109 (8.3)	4/112 (3.6)	4.7 (-1.5 to 10.9)
Escitalopram (n=1)	1/154 (0.6)	1/157 (0.6)	0 (-1.8 to 1.8)
Escitalopram (n=1)	1/131 (0.8)	2/133 (1.5)	-0.7 (-3.3 to 1.8)
Citalopram (n=1)	0/89 (0)	0/85 (0)	0 (-2.2 to 2.2)

CI, confidence interval; KQ, key question; N, number.

Table 9. Summary of Evidence for Benefits and Harms of Screening for and Treatment of MDD in Children and Adolescents

Key Question	Intervention	Trials, *k* Observations, *n*	Major Limitations	Consistency	Applicability	Quality Ratings	Summary of Findings
Key Question 1 (effect of screening on health and other outcomes)	NA	k=0	NA	NA	NA	NA	No studies assessed the overarching Key Question
Key Question 2 (accuracy of screening)	Primary care-based (PHQ-A)	k=1, n=403	Single study, published in 2002, from primary care and school clinic-based sample; only 61% of the sample answering the screener had diagnostic interviews	NA	Adolescents only (13–18)	1: Fair	Lower sensitivity (73%) than specificity (94%), positive predictive value is 56%, negative predictive value is 97%
	School-based (BDI, CES-D, CIS-R)	k=4, n=2,474	Some studies had low response rates; 2 studies did not describe the time lapse between the screener and diagnostic interview; if lengthy, it could explain poor sensitivity	Inconsistent	No study evaluated children younger than 11	4: Fair	Among instruments, BDI has the highest sensitivity and specificity; other instruments have lower sensitivity and specificity than PHQ-A or BDI but have substantial heterogeneity in populations, instruments, and cutoffs
Key Question 3 (proportion with MDD identified with screening)	NA	k=0	NA	NA	NA	NA	No studies assessed proportion with MDD identified with screening
Key Question 4 (harms of screening)	NA	k=0	NA	NA	NA	NA	No studies assessed harms of screening
Key Question 5 (benefits of treatment)	SSRIs	k=4, n=983	Limited number of studies; only escitalopram had more than 1 trial; few outcomes studied; only 1 study examined subgroup differences in efficacy	Inconsistent	Inclusion/exclusion criteria very rigorous in most trials, may not be applicable to primary care; no studies recruited patients from primary care or school clinic settings	1: Good 3: Fair	The fluoxetine study found a statistically significant benefit of the intervention of response in adolescents; 1 of 2 escitalopram trials found statistically significant benefits for relapse; the citalopram trial did not find significant differences in outcomes between groups
	Psychotherapy	k=2, n=346	2 interventions evaluated; no trials included children younger than 12; no subgroup differences in efficacy examined; few	Inconsistent	1 effectiveness study on adolescents with MDD conducted at 13 academic and community clinics	1: Good 1: Fair	Neither trial showed improvement on remission or recovery. Inconsistent effects on symptoms, response, and functioning. No effect on

Table 9. Summary of Evidence for Benefits and Harms of Screening for and Treatment of MDD in Children and Adolescents

Key Question	Intervention	Trials, *k* Observations, *n*	Major Limitations	Consistency	Applicability	Quality Ratings	Summary of Findings
			outcomes examined		throughout the United States; 1 effectiveness study on adolescents in 2 research clinic sites		depression severity, global burden of psychiatric problems, child behavioral or emotional issues, or quality of life (single trial each).
	Combined	k=1, n=219	Only 1 intervention evaluated; no trials included children younger than 12; no subgroup differences in efficacy examined; few outcomes examined	Unknown consistency (single study)	1 effectiveness study in adolescents with MDD conducted at 13 academic and community clinics throughout the United States	1: Good	The single combined fluoxetine and CBT trial showed benefit for response, depression symptoms, and depression severity in the treatment group vs. placebo
	Collaborative care	k=1, n=101	Only 1 intervention evaluated; no trials included children younger than 12; potential for contamination because of individual rather than clinic-based assignment	Unknown consistency (single study)	1 effectiveness study in adolescents, majority with MDD (60%) from pediatric and family medicine clinics in the Group Health system in the United States, mostly white (69%) and female (72%)	1: Good	The single trial of collaborative care showed benefit for symptom reduction and remission at 6 and 12 months; improvement in clinically significant response at 12 months but not 6 months; and no benefit in functioning at either time point
Key Question 6 (harms of treatment)	SSRIs	k=4, n=983	Limited number of studies; only escitalopram had more than 1 trial; analyses not powered to find statistically significant differences between groups; no trials assessed subgroup differences	Consistent	Inclusion/exclusion criteria very rigorous in most trials, may not be applicable to primary care; no studies recruited patients from primary care or school clinic settings	1: Good 3: Fair	Analyses not powered to detect significant differences between groups but no individual SSRIs appear to be associated with increased risks, with fluoxetine having the highest absolute risk differences between intervention and placebo groups for suicidality
	Psychotherapy	k=1, n=223	Only 1 intervention evaluated; no trials included children younger than 12; no subgroup differences in harms examined	Unknown consistency (single study)	1 effectiveness study in adolescents with MDD conducted at 13 academic and community clinics throughout the United States	1: Good	Analyses not powered to detect significant differences between groups; single trial of CBT appeared to show only negligible differences in harms for intervention group vs. placebo
	Combined	k=1, n=219	Only 1 intervention evaluated; no trials included children younger than 12; no subgroup	Unknown consistency (single study)	1 effectiveness study in adolescents with MDD conducted at 13 academic and	1: Good	Analyses not powered to detect significant differences between groups; single trial of fluoxetine and CBT appeared to show

Table 9. Summary of Evidence for Benefits and Harms of Screening for and Treatment of MDD in Children and Adolescents

Key Question	Intervention	Trials, *k* Observations, *n*	Major Limitations	Consistency	Applicability	Quality Ratings	Summary of Findings
			differences in harms examined		community clinics throughout the United States		only negligible differences in harms for intervention group vs. placebo
	Collaborative care	k=1, n=101	Only 1 intervention evaluated; no trials included children younger than 12; no subgroup differences in harms examined	Unknown consistency (single study)	1 effectiveness study in adolescents, majority with MDD (60%) from pediatric and family medicine clinics in the Group Health system in the United States, mostly white (69%) and female (72%)	1: Good	Analyses not powered to detect significant differences between groups; more intervention patients experienced a psychiatric hospitalization (3 [6%] vs. 2 [4%]); more control patients experienced an ED visit with a primary psychiatric diagnosis (1 [2%] vs. 5 [10%])

BDI, Beck Depression Inventory; CBT, cognitive behavioral therapy; CES-D, Center for Epidemiological Studies–Depression Scale; CIS-R, Clinical Interview Schedule–Revised; EPDS, Edinburgh Postnatal Depression Scale; MDD, major depressive disorder; n, number; NA, not applicable; PHQ-A, Patient Health Questionnaire for Adolescents; SSRI, selective serotonin reuptake inhibitor.

Appendix A. Non-USPSTF Guidelines and Recommendations on Screening in Children and Adolescents

Organization	Recommendation
United States	
American Academy of Pediatrics (AAP), Bright Futures[1]	Recommends screening annually for emotional and behavioral problems for children and adolescent patients.
American Medical Association (AMA), Guidelines for Adolescent Preventive Services[2]	Recommends that primary care physicians use a systematic strategy for screening and health guidance, which is designed to identify whether an adolescent engages in or is at risk of depression and/or suicide.
Medicaid's Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program[3]	Recommends screening services to detect physical and mental conditions at periodic, age-appropriate intervals and if risk is identified, followup with diagnostic and treatment coverage.
American Academy of Pediatrics (AAP)/ American Academy of Child and Adolescent Psychiatry (AACAP) Joint Task Force[4]	Supports the emerging use of standardized screening tools for children and adolescents by paying for the mental health screen at routine medical visits and for the administration, scoring, and interpretation of standardized mental-health assessment instruments.
American Academy of Family Physicians[5]	Recommends screening of adolescents (12 to 18 years of age) for MDD when systems are accessible to ensure accurate diagnosis, treatment (psychotherapy), and followup.
Institute of Medicine and National Research Council, "Preventing Mental, Emotional, and Behavioral Disorders Among Young People: Progress and Possibilities"[6]	Recommends that the Federal government expand early identification and prevention of mental, emotional, and behavioral disorders in young people through a national research plan to measure trends in utilization of services and implement evidence-based screening and prevention.
Society for Adolescent Medicine and Medicine[7]	Supports adolescents' access to a comprehensive range of mental health services; importance of early identification; and appropriate, timely treatment of antidepressant medications with close monitoring for unusual changes in behavior.
Guidelines for Adolescent Depression in Primary Care (GLAD-PC)[8]	Supports primary care providers to identify (via screening tools and followup clinical interviews) and coordinate depression care for their adolescent population.
National Alliance on Mental Illness[9]	Recommends that primary care providers and child-serving agencies adopt evidence-based practices of screening and early recognition tools to identify and diagnose mental illness as early as possible.
International	
Canadian Task Force on Preventive Health Care[10]	Insufficient evidence to recommend for or against screening for depression among children or adolescents in primary care settings
National Institute for Health and Clinical Excellence (NICE)–United Kingdom[11]	Recommends specific psychological therapy (CBT and IPT for at least 3-month duration) for young people with moderate to severe depression and antidepressant medication only for moderate to severe cases and when offered with concurrent psychological therapy.

CBT, cognitive behavioral therapy; IPT, interpersonal therapy; MDD, major depressive disorder; USPSTF, U.S. Preventive Services Task Force.

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2. Elster AB, Kuznets NJ, eds. Guidelines for Adolescent Preventive Services. Baltimore: Williams and Wilkins; 1994.
3. U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health. EPSDT Program Background. www.mchb.hrsa.gov/epsdt/overview.html. Accessed February 15, 2013.
4. American Academy of Child and Adolescent Psychiatry, Committee on Health Care Access and Economics Task Force on Mental Health. Improving mental health services in primary care: reducing administrative and financial barriers to access and collaboration. Pediatrics. 2009 Apr;123(4):1248-51. PMID: 19336386.

Appendix A. Non-USPSTF Guidelines and Recommendations on Screening in Children and Adolescents

5. American Academy of Family Physicians. Recommendations for Depression Screening, Children and Adolescents. 2009 www.aafp.org/online/en/home/clinical/exam/depression.html. Accessed February 15, 2013.
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7. Kapphahn CJ, Morreale MC, Rickert VI, et al. Financing mental health services for adolescents: a position paper of the Society for Adolescent Medicine. Journal of Adolescent Health. 2006 Sep;39(3):456-8. PMID: 16919815.
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10. MacMillan HL, Patterson CJ, Wathen CN. Screening for depression in primary care: updated recommendations from the Canadian Task Force on Preventive Health Care. London, Ontario: Canadian Task Force on Preventive Health Care; 2004.
11. National Institute for Health and Clinical Excellence. Depression in children and young people: identification and management in primary, community, and secondary care. 2005 www.nice.org.uk/nicemedia/live/10970/29856/29856.pdf. Accessed February 14, 2013

Search Strategy

4/1/13 PubMed Systematic Reviews and Meta-Analyses

Search	Query	Items found
#1	Search ("Depression" OR "Depressive Disorder" OR "Postpartum Depression" OR "Major Depressive Disorder" OR "Dysthymic Disorder" OR "dysthymia" □ OR "S Disorder")	283359
#2	Search "Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depression, Postpartum"[Mesh] OR "Depressive Disorder, Major"[Mesh] OR "Dysthymic Disorder"[Mesh] OR "Seasonal Affective Disorder"[Mesh]	142442
#3	Search ((#1 OR #2))	283359
#4	Search ((#1 OR #2)) Filters: Publication date from 2005/11/01	97513
#5	Search ((#1 OR #2)) Filters: Publication date from 2005/11/01; English	90387
#6	Search ((#1 OR #2)) Filters: Publication date from 2005/11/01; English; Child: birth-18 years	18857
#7	Search (#6 AND systematic[SB])	630
#8	Search (depression[TIAB] OR depressed[TIAB] OR depressive[TIAB])	274236
#9	Search (child[TIAB] OR children[TIAB] OR adolescen*[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB])	924661
#10	Search ((#8 AND #9))	22932
#11	Search ((#10 AND (publisher[SB] OR in process[SB])))	486
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#13	Search (#11 AND (meta-analysis[TIAB] OR medline[TIAB] OR systematic*[TIAB] OR search*[TIAB]))	18
#14	Search (#12 OR #13)	20
#15	Search (#12 OR #13) Filters: Publication date from 2005/11/01	10
#16	Search (#12 OR #13) Filters: Publication date from 2005/11/01; English	10
#17	Search (#7 OR #16)	640
#18	Search ((#17) AND ("retraction" □[All Fields] OR "[el Fields]" OR "Published Erratum"[pt] OR "Duplicate Publication"[pt]))	0
#19	Search ((#17) AND ("retraction" □[A OR "Published Erratum"[pt] OR "Duplicate Publication"[pt])) Schema: all	0
#20	Search (((Mass Screening[MeSH] OR screen[TIAB] OR screening[TIAB] OR screened[TIAB] OR screens[TIAB] OR "case finding"[TIAB] OR casefinding[TIAB] OR "depression inventory" □[TIAB "depression scales" □[TIAB] scales" □[T "mood and feelings questionnaire" □[T reynold*[TIAB] OR kutcher*[TIAB] OR "depression scale for children" □[TIAB] C depression inventory" □[TIAB] C Epidemiologic Studies Depression Scale" □[TIAB] C Depression Scales" □[TIAB])))	482377
#21	Search (((Antidepressive Agents, Second-Generation[MeSH] OR Serotonin Uptake Inhibitors[MeSH] OR Antidepressive Agents[MeSH] OR antidepressant*[TIAB] OR antidepressives[TIAB] OR (antidepressive agent*[TIAB]) OR (antidepressive drug*[TIAB]) OR (selective serotonin reuptake inhibitor*[TIAB]) OR ssri[TIAB] OR ssris[TIAB] OR Fluoxetine[MeSH] OR fluoxetine[TIAB] OR Prozac[TIAB] OR Fluvoxamine[MeSH] OR fluvoxamine[TIAB] OR luvox[TIAB] OR Paroxetine[MeSH] OR paroxetine[TIAB] OR paxil[TIAB] OR Sertraline[MeSH] OR sertraline[TIAB] OR Zoloft[TIAB] OR Citalopram[MeSH] OR citalopram[TIAB] OR celexa[TIAB] OR escitalopram[TIAB] OR Lexapro[TIAB])))	79849
#22	Search (Psychotherapy[MeSH] OR Psychotherapy, Brief[MeSH] OR Psychotherapy, Group[MeSH] OR psychotherapy*[TIAB] OR Cognitive Therapy[MeSH] OR (cognitive[TIAB] AND (therap*[TIAB] OR treatment*[TIAB] OR intervention*[TIAB])) OR Behavior Therapy[MeSH] OR (behavior*[TIAB] AND (therap*[TIAB] or treatment*[TIAB] or intervention*[TIAB])) OR (interpersonal therap*[TIAB]) OR (interpersonal intervention*[TIAB]) OR Self-Help Groups[MeSH] OR (self help[TIAB]) OR Family Therapy[MeSH] OR (family support[TIAB]) OR (parent*[TIAB] AND education[TIAB]) OR Parents/education[MeSH] OR Counseling[MeSH] OR Directive Counseling[MeSH] OR counsel*[TIAB] OR Problem Solving[MeSH] OR (problem solving[TIAB]))	423044

Appendix B. Search Strategy and Detailed Methods

Search	Query	Items found
#23	Search (#17 AND (#20 OR #21 OR #22))	363
#24	Search (("serotonin norepinephrine reuptake inhibitors"[All Fields] OR snri*[All Fields] OR "norepinephrine reuptake inhibitors"[all fields] OR venlafaxine[Supplementary Concept] OR venlafaxine[All Fields] OR duloxetine[Supplementary Concept] OR duloxetine[All Fields] OR Bupropion[MeSH] OR Bupropion[All Fields]))	7765
#25	Search ((#1 OR #2)) Filters: English	249079
#26	Search ((#1 OR #2)) Filters: English; Child: birth-18 years	43699
#27	Search ((#26 AND systematic[SB]))	963
#28	Search (#12 OR #13) Filters: English	18
#29	Search (#27 OR #28)	981
#30	Search (#29 AND #24)	23
#31	Search (#23 OR #30)	370

1/9/14 PubMed Systematic Reviews and Meta-Analyses

Search	Query	Items found
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#4	Search ((#1 OR #2)) Filters: Publication date from 2012/04/01	29804
#5	Search ((#1 OR #2)) Filters: Publication date from 2012/04/01; English	28472
#6	Search ((#1 OR #2)) Filters: Publication date from 2012/04/01; English; Child: birth-18 years	3780
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#11	Search ((#10 AND (publisher[SB] OR in process[SB])))	993
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#14	Search (#12 OR #13)	52
#15	Search (#12 OR #13) Filters: Publication date from 2012/04/01	36
#16	Search (#12 OR #13) Filters: Publication date from 2012/04/01; English	36
#17	Search (#7 OR #16)	188
#18	Search ((#17) AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt]))	0
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#20	Search (((Mass Screening[MeSH] OR screen[TIAB] OR screening[TIAB] OR screened[TIAB] OR screens[TIAB] OR "case finding"[TIAB] OR casefinding[TIAB] OR "depression inventory"[TIAB] OR "depression inventories"[TIAB] OR "depression scale"[TIAB] OR "depression scales"[TIAB] OR "depression rating scale"[TIAB] OR "depression rating scales"[TIAB] OR "self report rating scale"[TIAB] OR "self report rating scales"[TIAB] OR "mood and feelings questionnaire"[TIAB] OR "mood and feelings questionnaires"[TIAB] OR reynold*[TIAB] OR kutcher*[TIAB] OR "depression scale for children"[TIAB] OR "beck depression inventory"[TIAB] OR "beck depression inventories"[TIAB] OR "Center for Epidemiologic Studies Depression Scale"[TIAB] OR "Center for Epidemiologic Studies Depression Scales"[TIAB]))	512518
#21	Search (((Antidepressive Agents, Second-Generation[MeSH] OR Serotonin Uptake Inhibitors[MeSH] OR Antidepressive Agents[MeSH] OR antidepressant*[TIAB] OR antidepressives[TIAB] OR (antidepressive agent*[TIAB]) OR (antidepressive drug*[TIAB]) OR	82780

Appendix B. Search Strategy and Detailed Methods

Search	Query	Items found
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#24	Search (#17 AND (#20 OR #21 OR #22 OR #23))	91

4/10/14 PubMed Systematic Reviews and Meta-Analyses

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Appendix B. Search Strategy and Detailed Methods

Search	Query	Items found
	depression inventory"[TIAB] OR "beck depression inventories"[TIAB] OR "Center for Epidemiologic Studies Depression Scale"[TIAB] OR "Center for Epidemiologic Studies Depression Scales"[TIAB]))	
#21	Search (((Antidepressive Agents, Second-Generation[MeSH] OR Serotonin Uptake Inhibitors[MeSH] OR Antidepressive Agents[MeSH] OR antidepressant*[TIAB] OR antidepressives[TIAB] OR (antidepressive agent*[TIAB]) OR (antidepressive drug*[TIAB]) OR (selective serotonin reuptake inhibitor*[TIAB]) OR ssri[TIAB] OR ssris[TIAB] OR Fluoxetine[MeSH] OR fluoxetine[TIAB] OR Prozac[TIAB] OR Fluvoxamine[MeSH] OR fluvoxamine[TIAB] OR luvox[TIAB] OR Paroxetine[MeSH] OR paroxetine[TIAB] OR paxil[TIAB] OR Sertraline[MeSH] OR sertraline[TIAB] OR Zoloft[TIAB] OR Citalopram[MeSH] OR citalopram[TIAB] OR celexa[TIAB] OR escitalopram[TIAB] OR Lexapro[TIAB]))	83888
#22	Search (Psychotherapy[MeSH] OR Psychotherapy, Brief[MeSH] OR Psychotherapy, Group[MeSH] OR psychotherapy*[TIAB] OR Cognitive Therapy[MeSH] OR (cognitive[TIAB] AND (therap*[TIAB] OR treatment*[TIAB] OR intervention*[TIAB])) OR Behavior Therapy[MeSH] OR (behavior*[TIAB] AND (therap*[TIAB] or treatment*[TIAB] or intervention*[TIAB])) OR (interpersonal therap*[TIAB]) OR (interpersonal intervention*[TIAB]) OR Self-Help Groups[MeSH] OR (self help[TIAB]) OR Family Therapy[MeSH] OR (family support[TIAB]) OR (parent*[TIAB] AND education[TIAB]) OR Parents/education[MeSH] OR Counseling[MeSH] OR Directive Counseling[MeSH] OR counsel*[TIAB] OR Problem Solving[MeSH] OR (problem solving[TIAB]))	453098
#23	Search (("serotonin norepinephrine reuptake inhibitors"[All Fields] OR snri*[All Fields] OR "norepinephrine reuptake inhibitors"[all fields] OR venlafaxine[Supplementary Concept] OR venlafaxine[All Fields] OR duloxetine[Supplementary Concept] OR duloxetine[All Fields] OR Bupropion[MeSH] OR Bupropion[All Fields]))	8425
#24	Search (#17 AND (#20 OR #21 OR #22 OR #23))	96
#25	Search ((#17 AND (#20 OR #21 OR #22 OR #23))) Filters: Publication date from 2013/01/01	61

10/14/14 PubMed Systematic Review and Meta-analysis

Search	PubMed Query	Items found
#1	Search ("Depression" OR "Depressive Disorder" OR "Postpartum Depression" OR "Major Depressive Disorder" OR "Dysthymic Disorder" OR "dysthymia" OR Disorder")	311030
#2	Search ("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depression, Postpartum"[Mesh] OR "Depressive Disorder, Major"[Mesh] OR "Dysthymic Disorder"[Mesh] OR "Seasonal Affective Disorder"[Mesh])	152455
#3	Search (#1 or #2)	311030
#4	Search (#1 or #2) Filters: Publication date from 2013/01/13	31303
#5	Search (#1 or #2) Filters: Publication date from 2013/01/13; English	30121
#6	Search (#1 or #2) Filters: Publication date from 2013/01/13; English; Child: birth-18 years	3612
#7	Search (#6 AND systematic[SB])	142
#8	Search (depression[TIAB] OR depressed[TIAB] OR depressive[TIAB])	303074
#9	Search (child[TIAB] OR children[TIAB] OR adolescen*[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB])	1013337
#10	Search (#8 AND #9)	26498
#11	Search (#10 AND (publisher[SB] OR in process[SB])	1094
#12	Search (#11 AND systematic[SB])	42
#13	Search (#11 AND (meta-analysis[TIAB] OR medline[TIAB] OR systematic*[TIAB] OR search*[TIAB]))	52
#14	Search (#12 OR #13)	56
#15	Search (#12 OR #13) Filters: Publication date from 2013/01/13	38
#16	Search (#12 OR #13) Filters: Publication date from 2013/01/13; English	36
#17	Search (#7 OR #16)	178
#18	Search ((#17) AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt]))	0
#19	Search (((#17) AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt])) Schema: all)	0

Appendix B. Search Strategy and Detailed Methods

Search	PubMed Query	Items found
#20	Search (Mass Screening[MeSH] OR screen[TIAB] OR screening[TIAB] OR screened[TIAB] OR screens[TIAB] OR "case finding"[TIAB] OR casefinding[TIAB] OR "depression inventory"[TIAB] OR "depression inventories"[TIAB] OR "depression scale"[TIAB] OR "depression scales"[TIAB] OR "depression rating scale"[TIAB] OR "depression rating scales"[TIAB] OR "self report rating scale"[TIAB] OR "self report rating scales"[TIAB] OR "mood and feelings questionnaire"[TIAB] OR "mood and feelings questionnaires"[TIAB] OR reynold*[TIAB] OR kutcher*[TIAB] OR "depression scale for children"[TIAB] OR "beck depression inventory"[TIAB] OR "beck depression inventories"[TIAB] OR "Center for Epidemiologic Studies Depression Scale"[TIAB] OR "Center for Epidemiologic Studies Depression Scales"[TIAB])	545042
#21	Search (Antidepressive Agents, Second-Generation[MeSH] OR Serotonin Uptake Inhibitors[MeSH] OR Antidepressive Agents[MeSH] OR antidepressant*[TIAB] OR antidepressives[TIAB] OR (antidepressive agent*[TIAB]) OR (antidepressive drug*[TIAB]) OR (selective serotonin reuptake inhibitor*[TIAB]) OR ssri[TIAB] OR ssris[TIAB] OR Fluoxetine[MeSH] OR fluoxetine[TIAB] OR Prozac[TIAB] OR Fluvoxamine[MeSH] OR fluvoxamine[TIAB] OR luvox[TIAB] OR Paroxetine[MeSH] OR paroxetine[TIAB] OR paxil[TIAB] OR Sertraline[MeSH] OR sertraline[TIAB] OR Zoloft[TIAB] OR Citalopram[MeSH] OR citalopram[TIAB] OR celexa[TIAB] OR escitalopram[TIAB] OR Lexapro[TIAB])	86219
#22	Search (Psychotherapy[MeSH] OR Psychotherapy, Brief[MeSH] OR Psychotherapy, Group[MeSH] OR psychotherapy*[TIAB] OR Cognitive Therapy[MeSH] OR (cognitive[TIAB] AND (therap*[TIAB] OR treatment*[TIAB] OR intervention*[TIAB])) OR Behavior Therapy[MeSH] OR (behavior*[TIAB] AND (therap*[TIAB] or treatment*[TIAB] or intervention*[TIAB])) OR (interpersonal therap*[TIAB]) OR (interpersonal intervention*[TIAB]) OR Self-Help Groups[MeSH] OR (self help[TIAB]) OR Family Therapy[MeSH] OR (family support[TIAB]) OR (parent*[TIAB] AND education[TIAB]) OR Parents/education[MeSH] OR Counseling[MeSH] OR Directive Counseling[MeSH] OR counsel*[TIAB] OR Problem Solving[MeSH] OR (problem solving[TIAB])	470068
#23	Search ("serotonin norepinephrine reuptake inhibitors"[All Fields] OR snri*[All Fields] OR "norepinephrine reuptake inhibitors"[all fields] OR venlafaxine[Supplementary Concept] OR venlafaxine[All Fields] OR duloxetine[Supplementary Concept] OR duloxetine[All Fields] OR Bupropion[MeSH] OR Bupropion[All Fields])	8775
#24	Search (#17 AND (#20 OR #21 OR #22 OR #23))	**92**

2/4/15 PubMed Systematic Review and Meta-analysis

Search	Query	Items found
#1	Search (("Depression" OR "Depressive Disorder" OR "Postpartum Depression" OR "Major Depressive Disorder" OR "Dysthymic Disorder" OR "dysthymia" OR "Seasonal Affective Disorder"))	316759
#2	Search (("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depression, Postpartum"[Mesh] OR "Depressive Disorder, Major"[Mesh] OR "Dysthymic Disorder"[Mesh] OR "Seasonal Affective Disorder"[Mesh]))	155405
#3	Search (#1 or #2)	316759
#4	Search (#1 or #2) Filters: Publication date from 2014/10/01	7644
#5	Search (#1 or #2) Filters: Publication date from 2014/10/01; English	7479
#6	Search (#1 or #2) Filters: Publication date from 2014/10/01; English; Child: birth-18 years	97
#7	Search ((#6 AND systematic[SB]))	5
#8	Search ((depression[TIAB] OR depressed[TIAB] OR depressive[TIAB]))	308874
#9	Search ((child[TIAB] OR children[TIAB] OR adolescen*[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB]))	1030322
#10	Search (#8 AND #9)	27165
#11	Search ((#10 AND (publisher[SB] OR in process[SB]))	1095
#12	Search ((#11 AND systematic[SB]))	37
#13	Search ((#11 AND (meta-analysis[TIAB] OR medline[TIAB] OR systematic*[TIAB] OR search*[TIAB])))	53
#14	Search (#12 or #13)	57
#15	Search (#12 or #13) Filters: Publication date from 2014/10/01	29
#16	Search (#12 or #13) Filters: Publication date from 2014/10/01; English	28

Appendix B. Search Strategy and Detailed Methods

Search	Query	Items found
#17	Search (#7 or #16)	33
#18	Search (((#17) AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt])))	0
#19	Search ((((#17) AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt])) Schema: all))	0
#20	Search ((Mass Screening[MeSH] OR screen[TIAB] OR screening[TIAB] OR screened[TIAB] OR screens[TIAB] OR "case finding"[TIAB] OR casefinding[TIAB] OR "depression inventory"[TIAB] OR "depression inventories"[TIAB] OR "depression scale"[TIAB] OR "depression scales"[TIAB] OR "depression rating scale"[TIAB] OR "depression rating scales"[TIAB] OR "self report rating scale"[TIAB] OR "self report rating scales"[TIAB] OR "mood and feelings questionnaire"[TIAB] OR "mood and feelings questionnaires"[TIAB] OR reynold*[TIAB] OR kutcher*[TIAB] OR "depression scale for children"[TIAB] OR "beck depression inventory"[TIAB] OR "beck depression inventories"[TIAB] OR "Center for Epidemiologic Studies Depression Scale"[TIAB] OR "Center for Epidemiologic Studies Depression Scales"[TIAB]))	557499
#21	Search ((Antidepressive Agents, Second-Generation[MeSH] OR Serotonin Uptake Inhibitors[MeSH] OR Antidepressive Agents[MeSH] OR antidepressant*[TIAB] OR antidepressives[TIAB] OR (antidepressive agent*[TIAB]) OR (antidepressive drug*[TIAB]) OR (selective serotonin reuptake inhibitor*[TIAB]) OR ssri[TIAB] OR ssris[TIAB] OR Fluoxetine[MeSH] OR fluoxetine[TIAB] OR Prozac[TIAB] OR Fluvoxamine[MeSH] OR fluvoxamine[TIAB] OR luvox[TIAB] OR Paroxetine[MeSH] OR paroxetine[TIAB] OR paxil[TIAB] OR Sertraline[MeSH] OR sertraline[TIAB] OR Zoloft[TIAB] OR Citalopram[MeSH] OR citalopram[TIAB] OR celexa[TIAB] OR escitalopram[TIAB] OR Lexapro[TIAB]))	87539
#22	Search ((Psychotherapy[MeSH] OR Psychotherapy, Brief[MeSH] OR Psychotherapy, Group[MeSH] OR psychotherapy*[TIAB] OR Cognitive Therapy[MeSH] OR (cognitive[TIAB] AND (therap*[TIAB] OR treatment*[TIAB] OR intervention*[TIAB])) OR Behavior Therapy[MeSH] OR (behavior*[TIAB] AND (therap*[TIAB] or treatment*[TIAB] or intervention*[TIAB])) OR (interpersonal therap*[TIAB]) OR (interpersonal intervention*[TIAB]) OR Self-Help Groups[MeSH] OR (self help[TIAB]) OR Family Therapy[MeSH] OR (family support[TIAB]) OR (parent*[TIAB] AND education[TIAB]) OR Parents/education[MeSH] OR Counseling[MeSH] OR Directive Counseling[MeSH] OR counsel*[TIAB] OR Problem Solving[MeSH] OR (problem solving[TIAB]))	479761
#23	Search (("serotonin norepinephrine reuptake inhibitors"[All Fields] OR snri*[All Fields] OR "norepinephrine reuptake inhibitors"[all fields] OR venlafaxine[Supplementary Concept] OR venlafaxine[All Fields] OR duloxetine[Supplementary Concept] OR duloxetine[All Fields] OR Bupropion[MeSH] OR Bupropion[All Fields]))	8988
#24	Search ((#17 AND (#20 OR #21 OR #22 OR #23)))	14

4/1/13 PubMed KQ1-4

Search	Query	Items found
1	Search (("Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR "Depression"[MeSH] OR depress*[TIAB]))	331041
2	Search ((Mass Screening[MeSH] OR screen[TIAB] OR screening[TIAB] OR screened[TIAB] OR screens[TIAB] OR "case finding"[TIAB] OR casefinding[TIAB] OR "depression inventory" □[TIA "depression scales" at[TIAB] OR " scales" □["mood and feelings questionnaire" □ reynold*[TIAB] OR kutcher*[TIAB] OR "depression scale for children" [TIAB] OR "beck depression inventory" □[TIAB] Epidemiologic Studies Depression Scale" □[TIAB] Depression Scales" □[TIAB]))	482377
3	Search ((#1 AND #2))	33723
4	Search ((#1 AND #2)) Filters: Preschool Child: 2-5 years	527
5	Search ((#1 AND #2)) Filters: Preschool Child: 2-5 years; Child: 6-12 years	2180
6	Search ((#1 AND #2)) Filters: Preschool Child: 2-5 years; Child: 6-12 years; Adolescent: 13-18 years	7593

Appendix B. Search Strategy and Detailed Methods

Search	Query	Items found
7	Search ((Children*[TIAB] OR childhood[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB] OR pediatric*[TIAB] OR paediatric*[TIAB] OR adolescen*[TIAB] OR boys[TIAB] OR girls[TIAB] OR youth[TIAB] OR youths[TIAB] OR child[TIAB]))	1137683
8	Search (#3 AND #7)	4229
9	Search (#6 OR #8)	8696
10	Search (#6 OR #8) Filters: English	8152
11	Search (#6 OR #8) Filters: Humans; English	7829
12	Search (#6 OR #8) Filters: Publication date from 2006/11/01; Humans; English	3896
13	Search (#12 AND ("retraction" [All Fields] OR "Retracted Publication" [pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt]))	17
14	Search (#6 OR #8) Filters: Case Reports	97
15	Search (#6 OR #8) Filters: Case Reports; Editorial	108
16	Search (#6 OR #8) Filters: Case Reports; Editorial; Letter	121
17	Search (#6 OR #8) Filters: Case Reports; Editorial; Letter; News	124
18	Search (#12 NOT #17)	3855

1/9/14 PubMed KQ 1-4

Search	Query	Items found
1	Search (("Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR "Depression"[MeSH] OR depress*[TIAB]))	345809
2	Search ((Mass Screening[MeSH] OR screen[TIAB] OR screening[TIAB] OR screened[TIAB] OR screens[TIAB] OR "case finding"[TIAB] OR casefinding[TIAB] OR "depression inventory"[TIAB] OR "depression inventories"[TIAB] OR "depression scale"[TIAB] OR "depression scales"[TIAB] OR "depression rating scale"[TIAB] OR "depression rating scales"[TIAB] OR "self report rating scale"[TIAB] OR "self report rating scales"[TIAB] OR "mood and feelings questionnaire"[TIAB] OR "mood and feelings questionnaires"[TIAB] OR reynold*[TIAB] OR kutcher*[TIAB] OR "depression scale for children"[TIAB] OR "beck depression inventory"[TIAB] OR "beck depression inventories"[TIAB] OR "Center for Epidemiologic Studies Depression Scale"[TIAB] OR "Center for Epidemiologic Studies Depression Scales"[TIAB]))	512803
3	Search ((#1 AND #2))	36631
4	Search ((#1 AND #2)) Filters: Preschool Child: 2-5 years	544
5	Search ((#1 AND #2)) Filters: Preschool Child: 2-5 years; Child: 6-12 years	2256
6	Search ((#1 AND #2)) Filters: Preschool Child: 2-5 years; Child: 6-12 years; Adolescent: 13-18 years	7865
7	Search ((Children*[TIAB] OR childhood[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB] OR pediatric*[TIAB] OR paediatric*[TIAB] OR adolescen*[TIAB] OR boys[TIAB] OR girls[TIAB] OR youth[TIAB] OR youths[TIAB] OR child[TIAB]))	1191518
8	Search (#3 AND #7)	4645
9	Search (#6 OR #8)	9275
10	Search (#6 OR #8) Filters: English	8701
11	Search (#6 OR #8) Filters: Humans; English	8115
12	Search (#6 OR #8) Filters: Publication date from 2012/04/01; Humans; English	951
13	Search (#12 AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt]))	6
14	Search (#6 OR #8) Filters: Case Reports	98
15	Search (#6 OR #8) Filters: Case Reports; Editorial	109
16	Search (#6 OR #8) Filters: Case Reports; Editorial; Letter	123
17	Search (#6 OR #8) Filters: Case Reports; Editorial; Letter; News	127
18	Search (#12 NOT #17)	941

Appendix B. Search Strategy and Detailed Methods

4/10/14 PubMed KQ 1-4

Search	Query	Items found
1	Search (("Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR "Depression"[MeSH] OR depress*[TIAB]))	351089
2	Search ((Mass Screening[MeSH] OR screen[TIAB] OR screening[TIAB] OR screened[TIAB] OR screens[TIAB] OR "case finding"[TIAB] OR casefinding[TIAB] OR "depression inventory"[TIAB] OR "depression inventories"[TIAB] OR "depression scale"[TIAB] OR "depression scales"[TIAB] OR "depression rating scale"[TIAB] OR "depression rating scales"[TIAB] OR "self report rating scale"[TIAB] OR "self report rating scales"[TIAB] OR "mood and feelings questionnaire"[TIAB] OR "mood and feelings questionnaires"[TIAB] OR reynold*[TIAB] OR kutcher*[TIAB] OR "depression scale for children"[TIAB] OR "beck depression inventory"[TIAB] OR "beck depression inventories"[TIAB] OR "Center for Epidemiologic Studies Depression Scale"[TIAB] OR "Center for Epidemiologic Studies Depression Scales"[TIAB]))	523516
3	Search ((#1 AND #2))	37597
4	Search ((#1 AND #2)) Filters: Preschool Child: 2-5 years	560
5	Search ((#1 AND #2)) Filters: Preschool Child: 2-5 years; Child: 6-12 years	2308
6	Search ((#1 AND #2)) Filters: Preschool Child: 2-5 years; Child: 6-12 years; Adolescent: 13-18 years	8035
7	Search ((Children*[TIAB] OR childhood[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB] OR pediatric*[TIAB] OR paediatric*[TIAB] OR adolescen*[TIAB] OR boys[TIAB] OR girls[TIAB] OR youth[TIAB] OR youths[TIAB] OR child[TIAB]))	1210445
8	Search (#3 AND #7)	4779
9	Search (#6 OR #8)	9503
10	Search (#6 OR #8) Filters: English	8922
11	Search (#6 OR #8) Filters: Humans; English	8297
12	Search (#6 OR #8) Filters: Publication date from 2012/04/01; Humans; English	1132
13	Search (#12 AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt]))	6
14	Search (#6 OR #8) Filters: Case Reports	98
15	Search (#6 OR #8) Filters: Case Reports; Editorial	109
16	Search (#6 OR #8) Filters: Case Reports; Editorial; Letter	123
17	Search (#6 OR #8) Filters: Case Reports; Editorial; Letter; News	127
18	Search (#12 NOT #17)	1122
#19	Search ((#12 NOT #17)) Filters: Publication date from 2013/01/01	583

10/14/14 PubMed KQ 1-4

Search	PubMed Query	Items found
#1	Search ((("Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR "Depression"[MeSH] OR depress*[TIAB])))	362065
#2	Search (((Mass Screening[MeSH] OR screen[TIAB] OR screening[TIAB] OR screened[TIAB] OR screens[TIAB] OR "case finding"[TIAB] OR casefinding[TIAB] OR "depression inventory"[TIAB] OR "depression inventories"[TIAB] OR "depression scale"[TIAB] OR "depression scales"[TIAB] OR "depression rating scale"[TIAB] OR "depression rating scales"[TIAB] OR "self report rating scale"[TIAB] OR "self report rating scales"[TIAB] OR "mood and feelings questionnaire"[TIAB] OR "mood and feelings questionnaires"[TIAB] OR reynold*[TIAB] OR kutcher*[TIAB] OR "depression scale for children"[TIAB] OR "beck depression inventory"[TIAB] OR "beck depression inventories"[TIAB] OR "Center for Epidemiologic Studies Depression Scale"[TIAB] OR "Center for Epidemiologic Studies Depression Scales"[TIAB])))	545042
#3	Search (#1 and #2)	39657
#4	Search (#1 and #2) Filters: Preschool Child: 2-5 years	596
#5	Search (#1 and #2) Filters: Preschool Child: 2-5 years; Child: 6-12 years	2422
#6	Search (#1 and #2) Filters: Preschool Child: 2-5 years; Child: 6-12 years; Adolescent: 13-18 years	8429
#7	Search (((Children*[TIAB] OR childhood[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB] OR pediatric*[TIAB] OR paediatric*[TIAB] OR adolescen*[TIAB] OR	1247789

	boys[TIAB] OR girls[TIAB] OR youth[TIAB] OR youths[TIAB] OR child[TIAB]))	
#8	Search (#3 AND #7)	5054
#9	Search (#6 OR #8)	10012
#10	Search (#6 OR #8) Filters: English	9404
#11	Search (#6 OR #8) Filters: Humans; English	8708
#12	Search (#6 OR #8) Filters: Publication date from 2013/01/13; Humans; English	906
#13	Search ((#12 AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt]))	1
#14	Search (#6 OR #8) Filters: Case Reports	100
#15	Search (#6 OR #8) Filters: Case Reports; Editorial	112
#16	Search (#6 OR #8) Filters: Case Reports; Editorial; Letter	126
#17	Search (#6 OR #8) Filters: Case Reports; Editorial; Letter; News	130
#18	Search (#12 NOT #17)	**900**

2/2/15 PubMed KQ 1-4

Search	Query	Items found
#1	Search ((((("Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR "Depression"[MeSH] OR depress*[TIAB]))))	368353
#2	Search ((((Mass Screening[MeSH] OR screen[TIAB] OR screening[TIAB] OR screened[TIAB] OR screens[TIAB] OR "case finding"[TIAB] OR casefinding[TIAB] OR "depression inventory"[TIAB] OR "depression inventories"[TIAB] OR "depression scale"[TIAB] OR "depression scales"[TIAB] OR "depression rating scale"[TIAB] OR "depression rating scales"[TIAB] OR "self report rating scale"[TIAB] OR "self report rating scales"[TIAB] OR "mood and feelings questionnaire"[TIAB] OR "mood and feelings questionnaires"[TIAB] OR reynold*[TIAB] OR kutcher*[TIAB] OR "depression scale for children"[TIAB] OR "beck depression inventory"[TIAB] OR "beck depression inventories"[TIAB] OR "Center for Epidemiologic Studies Depression Scale"[TIAB] OR "Center for Epidemiologic Studies Depression Scales"[TIAB]))))	557499
#3	Search ((#1 and #2))	40878
#4	Search ((#1 and #2)) Filters: Preschool Child: 2-5 years	613
#5	Search ((#1 and #2)) Filters: Preschool Child: 2-5 years; Child: 6-12 years	2491
#6	Search ((#1 and #2)) Filters: Preschool Child: 2-5 years; Child: 6-12 years; Adolescent: 13-18 years	8687
#7	Search ((((Children*[TIAB] OR childhood[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB] OR pediatric*[TIAB] OR paediatric*[TIAB] OR adolescen*[TIAB] OR boys[TIAB] OR girls[TIAB] OR youth[TIAB] OR youths[TIAB] OR child[TIAB]))))	1268997
#8	Search ((#3 AND #7))	5194
#9	Search (#6 or #8)	10295
#10	Search (#6 or #8) Filters: English	9675
#11	Search (#6 or #8) Filters: Humans; English	8980
#12	Search (#6 or #8) Filters: Publication date from 2014/10/01; Humans; English	22
#13	Search (((#12 AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt]))))	0
#14	Search (#6 or #8) Filters: Case Reports	102
#15	Search (#6 or #8) Filters: Case Reports; Editorial	114
#16	Search (#6 or #8) Filters: Case Reports; Editorial; Letter	128
#17	Search (#6 or #8) Filters: Case Reports; Editorial; Letter; News	132
#18	Search ((#12 NOT #17))	22

4/1/13 PubMed KQ5

Search	Query	Items found
1	Search ((Depressive Disorder[MeSH] OR Depressive Disorder, Major[MeSH] OR Depression[MeSH] OR depress*[TIAB] OR depression[TIAB] OR depressive[TIAB] OR depressed[TIAB]))	331041

Appendix B. Search Strategy and Detailed Methods

Search	Query	Items found
2	Search (Antidepressive Agents, Second-Generation[MeSH] OR Serotonin Uptake Inhibitors[MeSH] OR Antidepressive Agents[MeSH] OR antidepressant*[TIAB] OR antidepressives[TIAB] OR (""antidepressive agent"[TIAB] OR ""ant agents"[TI (""selective serotonin reuptake inhibitor"[TIAB] OR ""s inhibitors"[TIAB] OR ""selective serotonin reuptake inhibitors"[TIAB] OR fluoxetine[MeSH] OR fluoxetine[TIAB] OR Prozac[TIAB] OR Fluvoxamine[MeSH] OR fluvoxamine[TIAB] OR luvox[TIAB] OR Paroxetine[MeSH] OR paroxetine[TIAB] OR paxil[TIAB] OR Sertraline[MeSH] OR sertraline[TIAB] OR Zoloft[TIAB] OR Citalopram[MeSH] OR citalopram[TIAB] OR celexa[TIAB] OR escitalopram[TIAB] OR Lexapro[TIAB])	79849
3	Search ((Psychotherapy[MeSH] OR Psychotherapy, Brief[MeSH] OR Psychotherapy, Group[MeSH] OR psychotherapy*[TIAB] OR Cognitive Therapy[MeSH] OR (cognitive[TIAB] AND (therap*[TIAB] OR treatment*[TIAB] OR intervention*[TIAB])) OR ""Behavior Therapy"[MeSH] O intervention*[TIAB])) OR (interpersonal[TIAB] AND therap*[TIAB]) OR (interpersonal[TIAB] AND intervention*[TIAB]) OR ""Self-Help Groups"[MeS Therapy[MeSH] OR (""family support"[TI Parents/education[MeSH] OR Counseling[MeSH] OR ""Directive Counseling"[MeS counsel*[TIAB] OR ""Problem Solving"[MeSH] OR ("	424720
4	Search ((#1 AND #2) OR (#1 AND #3))	69802
5	Search ((#1 AND #2) OR (#1 AND #3)) Filters: Preschool Child: 2-5 years	1111
6	Search ((#1 AND #2) OR (#1 AND #3)) Filters: Preschool Child: 2-5 years; Child: 6-12 years	4622
7	Search ((#1 AND #2) OR (#1 AND #3)) Filters: Preschool Child: 2-5 years; Child: 6-12 years; Adolescent: 13-18 years	11897
8	Search ((Children*[TIAB] OR childhood[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB] OR pediatric*[TIAB] OR paediatric*[TIAB] OR adolescen*[TIAB] OR boys[TIAB] OR girls[TIAB] OR youth[TIAB] OR youths[TIAB] OR child[TIAB]))	1137683
9	Search (#4 AND #8)	7314
10	Search (#7 OR #9)	13652
11	Search (#7 OR #9) Filters: Clinical Trial	3048
12	Search (#7 OR #9) Filters: Clinical Trial; Controlled Clinical Trial	3048
13	Search (#7 OR #9) Filters: Clinical Trial; Controlled Clinical Trial; Randomized Controlled Trial	3048
14	Search (((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]))	538548
15	Search (#10 AND #14)	2641
16	Search (#13 OR #15)	3286
17	Search (#13 OR #15) Filters: English	3147
18	Search (#13 OR #15) Filters: Publication date from 2006/11/01; English	1428
19	Search (("serotonin norepinephrine reuptake inhibitors"[All Fields] OR snri*[All Fields] OR "norepinephrine reuptake inhibitors"[all fields] OR venlafaxine[Supplementary Concept] OR venlafaxine[All Fields] OR duloxetine[Supplementary Concept] OR duloxetine[All Fields] OR Bupropion[MeSH] OR Bupropion[All Fields]))	7765
20	Search (#1 AND #19)	3322
21	Search (#1 AND #19) Filters: Preschool Child: 2-5 years	10
22	Search (#1 AND #19) Filters: Preschool Child: 2-5 years; Child: 6-12 years	79
23	Search (#1 AND #19) Filters: Preschool Child: 2-5 years; Child: 6-12 years; Adolescent: 13-18 years	387
24	Search (#20 AND #8)	145
25	Search (#23 OR #24)	432
26	Search (#23 OR #24) Filters: English	413
27	Search (#18 OR #26)	1735
28	Search (#27 AND (""retraction"[Publication Type] OR ""Retracted Publication"[All Fields] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt])))	10
29	Search (#18 OR #26) Filters: Case Reports	31
30	Search (#18 OR #26) Filters: Case Reports; Editorial	34

Appendix B. Search Strategy and Detailed Methods

Search	Query	Items found
31	Search (#18 OR #26) Filters: Case Reports; Editorial; Letter	40
32	Search (#18 OR #26) Filters: Case Reports; Editorial; Letter; News	40
33	Search (#27 NOT #32)	1695

1/9/14 PubMed KQ5

Search	Query	Items found
1	Search ((Depressive Disorder[MeSH] OR Depressive Disorder, Major[MeSH] OR Depression[MeSH] OR depress*[TIAB] OR depression[TIAB] OR depressive[TIAB] OR depressed[TIAB]))	345690
2	Search (Antidepressive Agents, Second-Generation[MeSH] OR Serotonin Uptake Inhibitors[MeSH] OR Antidepressive Agents[MeSH] OR antidepressant*[TIAB] OR antidepressives[TIAB] OR ("antidepressive agent"[TIAB] OR "antidepressive agents"[TIAB]) OR ("antidepressive drug"[TIAB] OR "antidepressive drugs"[TIAB]) OR ("selective serotonin reuptake inhibitor"[TIAB] OR "selective serotonin reuptake inhibitors"[TIAB]) OR ssri[TIAB] OR ssris[TIAB] OR Fluoxetine[MeSH] OR fluoxetine[TIAB] OR Prozac[TIAB] OR Fluvoxamine[MeSH] OR fluvoxamine[TIAB] OR luvox[TIAB] OR Paroxetine[MeSH] OR paroxetine[TIAB] OR paxil[TIAB] OR Sertraline[MeSH] OR sertraline[TIAB] OR Zoloft[TIAB] OR Citalopram[MeSH] OR citalopram[TIAB] OR celexa[TIAB] OR escitalopram[TIAB] OR Lexapro[TIAB])	82780
3	Search (("serotonin norepinephrine reuptake inhibitors"[All Fields] OR snri*[All Fields] OR "norepinephrine reuptake inhibitors"[all fields] OR venlafaxine[Supplementary Concept] OR venlafaxine[All Fields] OR duloxetine[Supplementary Concept] OR duloxetine[All Fields] OR Bupropion[MeSH] OR Bupropion[All Fields]))	8271
4	Search ((Psychotherapy[MeSH] OR Psychotherapy, Brief[MeSH] OR Psychotherapy, Group[MeSH] OR psychotherapy*[TIAB] OR Cognitive Therapy[MeSH] OR (cognitive[TIAB] AND (therap*[TIAB] OR treatment*[TIAB] OR intervention*[TIAB])) OR "Behavior Therapy"[MeSH] OR (behavior*[TIAB] AND (therap*[TIAB] OR treatment*[TIAB] OR intervention*[TIAB])) OR (interpersonal[TIAB] AND therap*[TIAB]) OR (interpersonal[TIAB] AND intervention*[TIAB]) OR "Self-Help Groups"[MeSH] OR ("self help"[TIAB]) OR Family Therapy[MeSH] OR ("family support"[TIAB]) OR (parent*[TIAB] AND education[TIAB]) OR Parents/education[MeSH] OR Counseling[MeSH] OR "Directive Counseling"[MeSH] OR counsel*[TIAB] OR "Problem Solving"[MeSH] OR ("problem solving"[TIAB])))	446537
5	Search ((#1 AND (#2 OR #3 OR #4)))	73782
6	Search ((#1 AND (#2 OR #3 OR #4))) Filters: Preschool Child: 2-5 years	1135
7	Search ((#1 AND (#2 OR #3 OR #4))) Filters: Preschool Child: 2-5 years; Child: 6-12 years	4732
8	Search ((#1 AND (#2 OR #3 OR #4))) Filters: Preschool Child: 2-5 years; Child: 6-12 years; Adolescent: 13-18 years	12221
9	Search ((Children*[TIAB] OR childhood[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB] OR pediatric*[TIAB] OR paediatric*[TIAB] OR adolescen*[TIAB] OR boys[TIAB] OR girls[TIAB] OR youth[TIAB] OR youths[TIAB] OR child[TIAB]))	1190906
10	Search (#5 AND #9)	7835
11	Search (#8 OR #10)	14340
12	Search (#8 OR #10) Filters: Clinical Trial	3142
13	Search (#8 OR #10) Filters: Clinical Trial; Controlled Clinical Trial	3142
14	Search (#8 OR #10) Filters: Clinical Trial; Controlled Clinical Trial; Randomized Controlled Trial	3142
15	Search (((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]))	555543
16	Search (#11 AND #15)	2760
17	Search (#14 OR #16)	3427
18	Search (#14 OR #16) Filters: English	3285
19	Search (#14 OR #16) Filters: Publication date from 2012/04/01; English	376
20	Search (#19 AND (("retraction"[All Fields] OR "Retracted Publication"[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt])))	3
21	Search (#19) Filters: Case Reports	0

Appendix B. Search Strategy and Detailed Methods

Search	Query	Items found
22	Search (#19) Filters: Case Reports; Editorial	0
23	Search (#19) Filters: Case Reports; Editorial; Letter	0
24	Search (#19) Filters: Case Reports; Editorial; Letter; News	0
25	Search (#19 NOT #24)	376

4/10/14 PubMed KQ5

Search	Query	Items found
1	Search ((Depressive Disorder[MeSH] OR Depressive Disorder, Major[MeSH] OR Depression[MeSH] OR depress*[TIAB] OR depression[TIAB] OR depressive[TIAB] OR depressed[TIAB]))	351089
2	Search (Antidepressive Agents, Second-Generation[MeSH] OR Serotonin Uptake Inhibitors[MeSH] OR Antidepressive Agents[MeSH] OR antidepressant*[TIAB] OR antidepressives[TIAB] OR (“antidepressive agent”[TIAB] OR “antidepressive agents”[TIAB]) OR (“antidepressive drug”[TIAB] OR “antidepressive drugs”[TIAB]) OR (“selective serotonin reuptake inhibitor”[TIAB] OR “selective serotonin reuptake inhibitors”[TIAB]) OR ssri[TIAB] OR ssris[TIAB] OR Fluoxetine[MeSH] OR fluoxetine[TIAB] OR Prozac[TIAB] OR Fluvoxamine[MeSH] OR fluvoxamine[TIAB] OR luvox[TIAB] OR Paroxetine[MeSH] OR paroxetine[TIAB] OR paxil[TIAB] OR Sertraline[MeSH] OR sertraline[TIAB] OR Zoloft[TIAB] OR Citalopram[MeSH] OR citalopram[TIAB] OR celexa[TIAB] OR escitalopram[TIAB] OR Lexapro[TIAB])	83888
3	Search (("serotonin norepinephrine reuptake inhibitors"[All Fields] OR snri*[All Fields] OR "norepinephrine reuptake inhibitors"[all fields] OR venlafaxine[Supplementary Concept] OR venlafaxine[All Fields] OR duloxetine[Supplementary Concept] OR duloxetine[All Fields] OR Bupropion[MeSH] OR Bupropion[All Fields]))	8425
4	Search ((Psychotherapy[MeSH] OR Psychotherapy, Brief[MeSH] OR Psychotherapy, Group[MeSH] OR psychotherapy*[TIAB] OR Cognitive Therapy[MeSH] OR (cognitive[TIAB] AND (therap*[TIAB] OR treatment*[TIAB] OR intervention*[TIAB])) OR “Behavior Therapy”[MeSH] OR (behavior*[TIAB] AND (therap*[TIAB] OR treatment*[TIAB] OR intervention*[TIAB])) OR (interpersonal[TIAB] AND therap*[TIAB]) OR (interpersonal[TIAB] AND intervention*[TIAB]) OR “Self-Help Groups”[MeSH] OR (“self help”[TIAB]) OR Family Therapy[MeSH] OR (“family support”[TIAB]) OR (parent*[TIAB] AND education[TIAB]) OR Parents/education[MeSH] OR Counseling[MeSH] OR “Directive Counseling”[MeSH] OR counsel*[TIAB] OR “Problem Solving”[MeSH] OR (“problem solving”[TIAB])))	455003
5	Search ((#1 AND (#2 OR #3 OR #4)))	75240
6	Search ((#1 AND (#2 OR #3 OR #4))) Filters: Preschool Child: 2-5 years	1157
7	Search ((#1 AND (#2 OR #3 OR #4))) Filters: Preschool Child: 2-5 years; Child: 6-12 years	4799
8	Search ((#1 AND (#2 OR #3 OR #4))) Filters: Preschool Child: 2-5 years; Child: 6-12 years; Adolescent: 13-18 years	12440
9	Search ((Children*[TIAB] OR childhood[TIAB] OR teen[TIAB] OR teens[TIAB] OR teenage*[TIAB] OR pediatric*[TIAB] OR paediatric*[TIAB] OR adolescen*[TIAB] OR boys[TIAB] OR girls[TIAB] OR youth[TIAB] OR youths[TIAB] OR child[TIAB]))	1210445
10	Search (#5 AND #9)	8032
11	Search (#8 OR #10)	14651
12	Search (#8 OR #10) Filters: Clinical Trial	3210
13	Search (#8 OR #10) Filters: Clinical Trial; Controlled Clinical Trial	3210
14	Search (#8 OR #10) Filters: Clinical Trial; Controlled Clinical Trial; Randomized Controlled Trial	3210
15	Search (((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]))	563838
16	Search (#11 AND #15)	2831
17	Search (#14 OR #16)	3510
18	Search (#14 OR #16) Filters: English	3365
19	Search (#14 OR #16) Filters: Publication date from 2012/04/01; English	456
20	Search (#19 AND ((“retraction”[All Fields] OR “Retracted Publication”[pt] OR Comment[pt] OR "Published Erratum"[pt] OR "Duplicate Publication"[pt])))	3

Appendix B. Search Strategy and Detailed Methods

Search	Query	Items found
21	Search (#19) Filters: Case Reports	0
22	Search (#19) Filters: Case Reports; Editorial	0
23	Search (#19) Filters: Case Reports; Editorial; Letter	0
24	Search (#19) Filters: Case Reports; Editorial; Letter; News	0
25	Search (#19 NOT #24)	456
26	Search (#19) Filters: Publication date from 2013/01/01	255

1/13/14 PsycInfo KQ6

ID	Search	Hits
S47	TI (depress* OR depression OR depressive OR depressed) OR AB (depress* OR depression OR depressive OR depressed)	210,349
S2	SU depression	116,686
S3	SU Depressive Disorder	8,125
S5	SU major depressive disorder	3,064
S48	S2 OR S3 OR S5 OR S47	116,686
S16	SU second generation antidepressants	20
S17	SU serotonin uptake inhibitors	84
S18	SU antidepressants	16,987
S19	SU Fluoxetine	3,559
S20	SU Fluvoxamine	936
S21	SU Paroxetine	1,680
S22	SU Sertraline	1,289
S23	SU Citalopram	1,183
S24	TI (antidepressant* OR antidepressives OR antidepressive agent* OR antidepressive drug* OR selective serotonin reuptake inhibitor* OR ssri OR ssris OR fluoxetine OR Prozac OR fluvoxamine OR luvox OR paroxetine OR paxil OR sertraline OR Zoloft OR citalopram OR celexa OR escitalopram OR Lexapro) OR AB (antidepressant* OR antidepressives OR antidepressive agent* OR antidepressive drug* OR selective serotonin reuptake inhibitor* OR ssri OR ssris OR fluoxetine OR Prozac OR fluvoxamine OR luvox OR paroxetine OR paxil OR sertraline OR Zoloft OR citalopram OR celexa OR escitalopram OR Lexapro)	38,487
S25	SU Bupropion	915
S26	serotonin norepinephrine reuptake inhibitors OR snri* OR "norepinephrine reuptake inhibitors" OR venlafaxine OR duloxetine OR Bupropion	4,397
S27	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26	41,957
S28	SU Psychotherapy	89,020
S29	SU Psychotherapy, brief	4,885
S30	SU Psychotherapy, Group	18,079
S31	SU cognitive therapy	22,624
S32	SU behavior therapy	26,187
S33	SU Self-Help Groups	858
S34	SU Family Therapy	18,962
S35	SU counseling	55,343
S36	SU Directive Counseling	70
S37	SU Problem Solving	26,539
S38	TI (psychotherapy* OR (cognitive AND (therap* OR treatment* OR intervention*)) OR (behavior* AND (therap* OR treatment* OR intervention*)) OR interpersonal therap* OR interpersonal intervention* OR self help OR family support OR parent* education OR counsel* OR problem solving) OR AB (psychotherapy* OR (cognitive AND (therap* OR treatment* OR intervention*)) OR (behavior* AND (therap* OR treatment* OR intervention*)) OR interpersonal therap* OR interpersonal intervention* OR self help OR family support OR parent* education OR counsel* OR problem solving)	388,998
S39	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38	447,920

Appendix B. Search Strategy and Detailed Methods

ID	Search	Hits
S53	S27 AND S48	20,036
S54	S39 AND S48	20,398
S55	S53 OR S54	36,707
S9	TX child OR children OR adolescen* OR teen OR teens OR teenage*	814,963
S56	S55 AND S9	5,828
S57	SU Adverse Drug Reaction Reporting Systems	0
S58	SU Drug Toxicity	78
S59	SU Drug Hypersensitivity	10
S60	SU Death	31,580
S61	SU Suicide	27,627
S62	SU Attempted Suicide	7,838
S63	SU Self-Injurious Behavior	2,331
S64	SU Adverse effects	1,140
S65	SU Chemically induced	26
S66	SU Drug effects	22,036
S67	SU Mortality	10,955
S68	SU Poisoning	1,581
S69	SU Toxicity	2,846
S70	TI (Harm* OR death OR suicide OR suicidal* OR mania OR manic episode* OR self damage* OR self injur* OR self inflict* OR death* OR adverse effect* OR adverse event* OR adverse reaction* OR overdos*) OR AB (Harm* OR death OR suicide OR suicidal* OR mania OR manic episode* OR self damage* OR self injur* OR self inflict* OR death* OR adverse effect* OR adverse event* OR adverse reaction* OR overdos*) OR KW overdos*	166,608
S71	S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70	196,561
S72	S56 AND S71	1,283
S73	SU second generation antidepressants AND SU (adverse effects OR poisoning OR toxicity)	0
S74	SU serotonin uptake inhibitors AND SU (adverse effects OR poisoning OR toxicity)	0
S75	SU Fluoxetine AND SU (adverse effects OR poisoning OR toxicity)	38
S76	SU Fluvoxamine AND SU (adverse effects OR poisoning OR toxicity)	12
S77	SU Paroxetine AND SU (adverse effects OR poisoning OR toxicity)	21
S78	SU Sertraline AND SU (adverse effects OR poisoning OR toxicity)	18
S79	SU Citalopram AND SU (adverse effects OR poisoning OR toxicity)	16
S80	SU Bupropion AND SU (adverse effects OR poisoning OR toxicity)	10
S81	S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80	106
S82	S81 AND S9	11
S83	S72 OR S82	1,292
S84	S72 OR S82; Limiters - Published Date from: 20120501-	112
S85	S72 OR S82; Limiters - Published Date from: 20120501-; Document Type: Journal Article	94
S90	S72 OR S82; Limiters - Published Date from: 20130101-; Document Type: Journal Article	62

10/16/14 PsycInfo KQ6

#	Query	Limiters/Expanders	Last Run Via	Results
S62	S61	Limiters - Published Date: 20140401-; Document Type: Journal Article Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	39
S61	S50 OR S60	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,750
S60	S33 AND S59	Search modes -	Interface - EBSCOhost Research	11

Appendix B. Search Strategy and Detailed Methods

#	Query	Limiters/Expanders	Last Run Via	Results
		Boolean/Phrase	Databases Search Screen - Advanced Search Database - PsycINFO	
S59	S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	109
S58	SU Bupropion AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	10
S57	SU Citalopram AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	16
S56	SU Sertraline AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	18
S55	SU Paroxetine AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	22
S54	SU Fluvoxamine AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	12
S53	SU Fluoxetine AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	40
S52	SU serotonin uptake inhibitors AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	0
S51	SU second generation antidepressants AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	0
S50	S34 AND S49	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,743
S49	S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	205,099
S48	TI (Harm* OR death OR suicide OR suicidal* OR mania OR manic episode* OR self damage* OR self injur* OR self inflict* OR death* OR adverse effect* OR adverse event* OR adverse reaction* OR overdos*) OR AB (Harm* OR death OR suicide OR suicidal* OR	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	174,056

Appendix B. Search Strategy and Detailed Methods

#	Query	Limiters/Expanders	Last Run Via	Results
	mania OR manic episode* OR self damage* OR self injur* OR self inflict* OR death* OR adverse effect* OR adverse event* OR adverse reaction* OR overdos*)) OR KW overdos*			
S47	SU Toxicity	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,960
S46	SU Poisoning	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,617
S45	SU Mortality	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	11,636
S44	SU Drug effects	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	22,780
S43	SU Chemically induced	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	26
S42	SU Adverse effects	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,223
S41	SU Self-Injurious Behavior	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,544
S40	SU Attempted Suicide	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	8,086
S39	SU Suicide	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	28,719
S38	SU Death	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	32,946
S37	SU Drug Hypersensitivity	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	10
S36	SU Drug Toxicity	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	82
S35	SU Adverse Drug Reaction Reporting	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases	0

Appendix B. Search Strategy and Detailed Methods

#	Query	Limiters/Expanders	Last Run Via	Results
	Systems		Search Screen - Advanced Search Database - PsycINFO	
S34	S32 AND S33	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	12,432
S33	TX child OR children OR adolescen* OR teen OR teens OR teenage*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	841,528
S32	S30 OR S31	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	63,900
S31	S5 AND S29	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	42,311
S30	S5 AND S17	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	26,997
S29	S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	462,660
S28	TI (psychotherapy* OR (cognitive AND (therap* OR treatment* OR intervention*)) OR (behavior* AND (therap* OR treatment* OR intervention*)) OR interpersonal therap* OR interpersonal intervention* OR self help OR family support OR parent* education OR counsel* OR problem solving) OR AB ((psychotherapy* OR (cognitive AND (therap* OR treatment* OR intervention*)) OR (behavior* AND (therap* OR treatment* OR intervention*)) OR interpersonal therap* OR interpersonal intervention* OR self help OR family support OR parent* education OR counsel* OR problem solving))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	402,762
S27	SU Problem Solving	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	27,171
S26	SU Directive Counseling	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases	70

Appendix B. Search Strategy and Detailed Methods

#	Query	Limiters/Expanders	Last Run Via	Results
			Search Screen - Advanced Search Database - PsycINFO	
S25	SU counseling	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	56,470
S24	SU Family Therapy	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	19,281
S23	SU Self-Help Groups	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	867
S22	SU behavior therapy	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	27,431
S21	SU cognitive therapy	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	23,869
S20	SU Psychotherapy, Group	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	18,293
S19	SU Psychotherapy, brief	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	4,965
S18	SU Psychotherapy	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	90,926
S17	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	43,188
S16	serotonin norepinephrine reuptake inhibitors OR snri* OR "norepinephrine reuptake inhibitors" OR venlafaxine OR duloxetine OR Bupropion	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	4,582
S15	SU Bupropion	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	937
S14	TI (antidepressant* OR antidepressives OR antidepressive agent* OR antidepressive drug* OR selective serotonin reuptake inhibitor* OR ssri OR ssris OR fluoxetine OR Prozac OR fluvoxamine OR luvox OR paroxetine OR paxil OR sertraline OR Zoloft OR citalopram OR	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	39,617

Appendix B. Search Strategy and Detailed Methods

#	Query	Limiters/Expanders	Last Run Via	Results
	celexa OR escitalopram OR Lexapro) OR AB (antidepressant* OR antidepressives OR antidepressive agent* OR antidepressive drug* OR selective serotonin reuptake inhibitor* OR ssri OR ssris OR fluoxetine OR Prozac OR fluvoxamine OR luvox OR paroxetine OR paxil OR sertraline OR Zoloft OR citalopram OR celexa OR escitalopram OR Lexapro)			
S13	SU Citalopram	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,205
S12	SU Sertraline	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,317
S11	SU Paroxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,698
S10	SU Fluvoxamine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	941
S9	SU Fluoxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	3,613
S8	SU antidepressants	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	17,519
S7	SU serotonin uptake inhibitors	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	85
S6	SU second generation antidepressants	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	21
S5	S1 OR S2 OR S3 OR S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	223,975
S4	SU major depressive disorder	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	5,568
S3	SU Depressive Disorder	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	8,670

Appendix B. Search Strategy and Detailed Methods

#	Query	Limiters/Expanders	Last Run Via	Results
S2	SU depression	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	121,695
S1	TI depress* OR depression OR depressive OR depressed) OR AB (depress* OR depression OR depressive OR depressed	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	218,453

2/5/15 PsycInfo KQ6

#	Query	Limiters/Expanders	Last Run Via	Results
S62	S61	Limiters - Published Date: 20141001-20150231; Document Type: Journal Article Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	32
S61	S50 OR S60	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,521
S60	S33 AND S59	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	8
S59	S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	112
S58	SU Bupropion AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	11
S57	SU Citalopram AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	17
S56	SU Sertraline AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	19
S55	SU Paroxetine AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	22
S54	SU Fluvoxamine AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	12
S53	SU Fluoxetine AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	40
S52	SU serotonin uptake inhibitors AND SU (adverse effects OR	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	0

Appendix B. Search Strategy and Detailed Methods

#	Query	Limiters/Expanders	Last Run Via	Results
	poisoning OR toxicity)		Database - PsycINFO	
S51	SU second generation antidepressants AND SU (adverse effects OR poisoning OR toxicity)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	0
S50	S34 AND S49	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,516
S49	S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	209,895
S48	TI (Harm* OR death OR suicide OR suicidal* OR mania OR manic episode* OR self damage* OR self injur* OR self inflict* OR death* OR adverse effect* OR adverse event* OR adverse reaction* OR overdos*) OR AB (Harm* OR death OR suicide OR suicidal* OR mania OR manic episode* OR self damage* OR self injur* OR self inflict* OR death* OR adverse effect* OR adverse event* OR adverse reaction* OR overdos*)) OR KW overdos*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	178,142
S47	SU Toxicity	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	3,020
S46	SU Poisoning	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,637
S45	SU Mortality	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	11,911
S44	SU Drug effects	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	23,328
S43	SU Chemically induced	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	27
S42	SU Adverse effects	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,267
S41	SU Self-Injurious	Search modes -	Interface - EBSCOhost Research	2,708

Appendix B. Search Strategy and Detailed Methods

#	Query	Limiters/Expanders	Last Run Via	Results
	Behavior	Boolean/Phrase	Databases Search Screen - Advanced Search Database - PsycINFO	
S40	SU Attempted Suicide	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	8,210
S39	SU Suicide	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	29,258
S38	SU Death	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	33,574
S37	SU Drug Hypersensitivity	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	10
S36	SU Drug Toxicity	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	83
S35	SU Adverse Drug Reaction Reporting Systems	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	0
S34	S32 AND S33	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	11,479
S33	TX child OR children OR adolescen* OR teen OR teens OR teenage*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	726,957
S32	S30 OR S31	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	65,801
S31	S5 AND S29	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	43,733
S30	S5 AND S17	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	27,648
S29	S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	471,440
S28	TI (psychotherapy* OR (cognitive AND (therap* OR treatment* OR intervention*)) OR (behavior* AND (therap* OR treatment* OR intervention*)) OR interpersonal therap* OR	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	410,868

#	Query	Limiters/Expanders	Last Run Via	Results
	interpersonal intervention* OR self help OR family support OR parent* education OR counsel* OR problem solving) OR AB ((psychotherapy* OR (cognitive AND (therap* OR treatment* OR intervention*)) OR (behavior* AND (therap* OR treatment* OR intervention*)) OR interpersonal therap* OR interpersonal intervention* OR self help OR family support OR parent* education OR counsel* OR problem solving))			
S27	SU Problem Solving	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	27,531
S26	SU Directive Counseling	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	71
S25	SU counseling	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	57,058
S24	SU Family Therapy	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	19,493
S23	SU Self-Help Groups	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	872
S22	SU behavior therapy	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	28,113
S21	SU cognitive therapy	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	24,467
S20	SU Psychotherapy, Group	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	18,460
S19	SU Psychotherapy, brief	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	5,005
S18	SU Psychotherapy	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	92,053

Appendix B. Search Strategy and Detailed Methods

#	Query	Limiters/Expanders	Last Run Via	Results
S17	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	43,941
S16	serotonin norepinephrine reuptake inhibitors OR snri* OR "norepinephrine reuptake inhibitors" OR venlafaxine OR duloxetine OR Bupropion	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	4,686
S15	SU Bupropion	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	947
S14	TI (antidepressant* OR antidepressives OR antidepressive agent* OR antidepressive drug* OR selective serotonin reuptake inhibitor* OR ssri OR ssris OR fluoxetine OR Prozac OR fluvoxamine OR luvox OR paroxetine OR paxil OR sertraline OR Zoloft OR citalopram OR celexa OR escitalopram OR Lexapro) OR AB (antidepressant* OR antidepressives OR antidepressive agent* OR antidepressive drug* OR selective serotonin reuptake inhibitor* OR ssri OR ssris OR fluoxetine OR Prozac OR fluvoxamine OR luvox OR paroxetine OR paxil OR sertraline OR Zoloft OR citalopram OR celexa OR escitalopram OR Lexapro)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	40,301
S13	SU Citalopram	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,223
S12	SU Sertraline	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,330
S11	SU Paroxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,709
S10	SU Fluvoxamine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	946
S9	SU Fluoxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases	3,650

Appendix B. Search Strategy and Detailed Methods

#	Query	Limiters/Expanders	Last Run Via	Results
			Search Screen - Advanced Search Database - PsycINFO	
S8	SU antidepressants	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	17,848
S7	SU serotonin uptake inhibitors	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	86
S6	SU second generation antidepressants	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	22
S5	S1 OR S2 OR S3 OR S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	230,176
S4	SU major depressive disorder	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	5,752
S3	SU Depressive Disorder	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	8,901
S2	SU depression	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	124,526
S1	TI depress* OR depression OR depressive OR depressed) OR AB (depress* OR depression OR depressive OR depressed	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	230,176

Grey Literature Searches

9/3/2013 ClinicalTrials.Gov

Search	Query	Items found
1	(depression OR depressive disorder OR dysthym*)[DISEASE]	3214
2	"Child" [AGE-GROUP]	33276
3	(screen* OR case find* OR inventor* OR scale OR questionnaire)[TREATMENT]	4719
4	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (screen* OR case find* OR inventor* OR scale OR questionnaire) [TREATMENT] AND "Child" [AGE-GROUP]	36
5	(Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion) [TREATMENT]	2514
6	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion) [TREATMENT] AND "Child" [AGE-GROUP]	83

7	(Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT]	10841
8	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (Psychotherapy OR ((cognitive OR behavior OR interpersonal) AND (therapy OR treatment OR intervention)) OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT] AND "Child" [AGE-GROUP]	227
9	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT] AND "Child" [AGE-GROUP]	309

1/13/2014 ClinicalTrials.Gov

Search	Query	Items found
1	(depression OR depressive disorder OR dysthym*)[DISEASE]	3362
2	"Child" [AGE-GROUP]	34641
3	(screen* OR case find* OR inventor* OR scale OR questionnaire)[TREATMENT]	5056
4	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (screen* OR case find* OR inventor* OR scale OR questionnaire) [TREATMENT] AND "Child" [AGE-GROUP]	38
5	(Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion) [TREATMENT]	2583
6	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion) [TREATMENT] AND "Child" [AGE-GROUP]	87
7	(Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT]	11555
8	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (Psychotherapy OR ((cognitive OR behavior OR interpersonal) AND (therapy OR treatment OR intervention)) OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT] AND "Child" [AGE-GROUP]	239
9	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT] AND "Child" [AGE-GROUP]	325
10	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR	159

Appendix B. Search Strategy and Detailed Methods

Search	Query	Items found
	Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT] AND "Child" [AGE-GROUP] AND ("09/03/2012" : MAX) [LAST-RELEASE-DATE]	

4/10/2014 ClinicalTrials.Gov

Search	Query	Items found
1	(depression OR depressive disorder OR dysthym*)[DISEASE]	3472
2	"Child" [AGE-GROUP]	35709
3	(screen* OR case find* OR inventor* OR scale OR questionnaire)[TREATMENT]	5336
4	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (screen* OR case find* OR inventor* OR scale OR questionnaire) [TREATMENT] AND "Child" [AGE-GROUP]	40
5	(Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion) [TREATMENT]	2644
6	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion) [TREATMENT] AND "Child" [AGE-GROUP]	89
7	(Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT]	12090
8	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (Psychotherapy OR ((cognitive OR behavior OR interpersonal) AND (therapy OR treatment OR intervention)) OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT] AND "Child" [AGE-GROUP]	249
9	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT] AND "Child" [AGE-GROUP]	337
10	(depression OR depressive disorder OR dysthym*) [DISEASE] AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT] AND "Child" [AGE-GROUP] AND ("01/01/2014" : MAX) [LAST-RELEASE-DATE]	55

Appendix B. Search Strategy and Detailed Methods

10/28/14 ClinicalTrials.gov

"Child" [AGE-GROUP] AND (depression OR depressive disorder OR dysthym*) [DISEASE] AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT] AND ("04/10/2014" : "10/28/2014") [LAST-RELEASE-DATE]

2/5/15 ClinicalTrials.gov

"Child" [AGE-GROUP] AND (depression OR depressive disorder OR dysthym*) [DISEASE] AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) [TREATMENT] AND ("10/28/2014" : "02/05/2015") [LAST-RELEASE-DATE]

9/3/2013 HSRProj

Search	Query	Items found
1	(depression OR depressive disorder OR dysthym*)	897
2	(child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	2337
3	(screen* OR case find* OR inventor* OR scale OR questionnaire)	1284
4	(depression OR depressive disorder OR dysthym*) AND (screen* OR case find* OR inventor* OR scale OR questionnaire) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	37
5	(Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion)	136
6	(depression OR depressive disorder OR dysthym*) AND (Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	10
7	(Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving)	3436
8	(depression OR depressive disorder OR dysthym*) AND (Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	129
9	(depression OR depressive disorder OR dysthym*) AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving)	137

Search	Query	Items found
	AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	

1/13/14 HSRProj

Search	Query	Items found
1	(depression OR depressive disorder OR dysthym*)	893
2	(child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	2265
3	(screen* OR case find* OR inventor* OR scale OR questionnaire)	1250
4	(depression OR depressive disorder OR dysthym*) AND (screen* OR case find* OR inventor* OR scale OR questionnaire) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	36
5	(Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion)	126
6	(depression OR depressive disorder OR dysthym*) AND (Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	10
7	(Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving)	3379
8	(depression OR depressive disorder OR dysthym*) AND (Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	126
9	(depression OR depressive disorder OR dysthym*) AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	136
10	((depression OR depressive disorder OR dysthym*) AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)) Advanced Search on : Project status = Ongoing & Completed(Default) : Initial Year Range = 2012 - Year	20

Appendix B. Search Strategy and Detailed Methods

4/10/14 HSRProj

Search	Query	Items found
1	(depression OR depressive disorder OR dysthym*)	917
2	(child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	2303
3	(screen* OR case find* OR inventor* OR scale OR questionnaire)	1297
4	(depression OR depressive disorder OR dysthym*) AND (screen* OR case find* OR inventor* OR scale OR questionnaire) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	36
5	(Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion)	126
6	(depression OR depressive disorder OR dysthym*) AND (Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	10
7	(Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving)	3479
8	(depression OR depressive disorder OR dysthym*) AND (Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	127
9	(depression OR depressive disorder OR dysthym*) AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)	137
10	((depression OR depressive disorder OR dysthym*) AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)) Advanced Search on : Project status = Ongoing & Completed(Default) : Initial Year Range = 2014 - Year	0

Appendix B. Search Strategy and Detailed Methods

10/28/14 HSRProj

10	(depression OR depressive disorder OR dysthym*) AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth) Advanced Search on : Project status = Ongoing & Completed(Default) : Initial Year Range = 2014 - Year

2/5/15 HSRProj

(depression OR depressive disorder OR dysthym*) AND (screen* OR case find* OR inventor* OR scale OR questionnaire OR Antidepressive Agents* OR Serotonin Uptake Inhibitor* OR antidepressant* OR antidepressive* OR selective serotonin reuptake inhibitor* OR ssri* OR Fluoxetine OR Prozac OR Fluvoxamine OR luvox OR Paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR snri* OR nri* OR venlafaxine OR duloxetine OR Bupropion OR Psychotherapy OR cognitive therapy OR behavior therapy OR interpersonal therapy OR cognitive treatment OR behavior treatment OR interpersonal treatment OR cognitive intervention OR behavior intervention OR interpersonal intervention OR self-help OR family therapy OR family support OR parent education OR counsel* OR problem solving) AND (child* OR teen* OR pediatric OR paediatric OR adolescen* OR boys OR girls OR youth)
Advanced Search on : Project status = Ongoing & Completed(Default) : Initial Year Range = 2014 - Year

9/3/2013 WHO ICTRP

Search	Query	Items found
1	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Search for clinical trials in children Recruitment Status: ALL	13503
2	Condition: depression OR depressive disorder OR dysthymi Search for clinical trials in children Recruitment Status: ALL	6631
3	Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL	3766
4	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Condition: depression OR depressive disorder OR dysthymi Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL	666
5	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Condition: depression OR depressive disorder OR dysthymi Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL Minus ClinicalTrials.Gov	181

1/13/14 WHO ICTRP

Search	Query	Items found
1	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Search for clinical trials in children Recruitment Status: ALL	14158
2	Condition: depression OR depressive disorder OR dysthymi	555

	Search for clinical trials in children Recruitment Status: ALL	
3	Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL	3927
4	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Condition: depression OR depressive disorder OR dysthymi Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL	172
5	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Condition: depression OR depressive disorder OR dysthymi Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL Date of registration: From 03/09/2012	27
6	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Condition: depression OR depressive disorder OR dysthymi Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL Date of registration: From 03/09/2012 Minus ClinicalTrials.Gov	11

4/10/14 WHO ICTRP

Search	Query	Items found
1	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Search for clinical trials in children Recruitment Status: ALL	4113
2	Condition: depression OR depressive disorder OR dysthymi Search for clinical trials in children Recruitment Status: ALL	468
3	Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL	850
4	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Condition: depression OR depressive disorder OR dysthymi Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL	174
5	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Condition: depression OR depressive disorder OR dysthymi Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL Date of registration: From 01/01/2014	2
6	Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth Condition: depression OR depressive disorder OR dysthymi Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel Search for clinical trials in children Recruitment Status: ALL	1

Date of registration: From 01/01/2014
Minus ClinicalTrials.Gov

10/28/14 WHO ICTRP
Search:
Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth
Condition: depression OR depressive disorder OR dysthymi
Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel
Search for clinical trials in children
Recruitment Status: ALL
Date of registration: From 01/01/2014
Minus ClinicalTrials.Gov (1)

2/5/15 WHO ICTRP
Advanced Search:
Title: child OR teen OR pediatric OR paediatric OR adolescen OR boys OR girls OR youth
Condition: depression OR depressive disorder OR dysthymi*
Intervention: screen OR case find OR antidepressant OR antidepressive OR cognitive OR behavior OR interpersonal OR counsel
Search for clinical trials in children
Recruitment Status: ALL
Date of registration: From 10/28/2014 – 02/05/2015

Appendix B Table 1. Inclusion/Exclusion Criteria

	Inclusion	Exclusion
Populations	**KQs 1–4:** Children and adolescents age 18 years or younger who are representative of a population seen in a primary care setting **KQs 5, 6:** Children and adolescents age 18 years or younger who are representative of a population seen in a primary care or similar setting identified with MDD	• Populations in which the majority of the sample is not age 18 years or younger, such as adults older than age 18 years • Mixed populations of adults and children without a separate analysis of pediatric outcomes (age 18 years or younger) • Population in which the sample is not representative of a population in a primary care setting, such as one sampled entirely from a specialty care population or from a population in which >50% of the sample has a medical condition (e.g., cancer) or other psychiatric disorder (e.g., eating disorder) • Screening for or treatment of minor depression, dysthymia, or other diagnoses without a separate analysis of MDD
Interventions: Screening	• Screening instruments that are feasible for primary care or comparable settings; that is, instruments that take ≤15 minutes to complete if delivered prior to clinician and patient face-to-face contact (e.g., in the waiting or examination room, before clinician entrance), ≤5 minutes or five questions if used during the face-to-face visit, and feasible to score in primary care settings • More general mental health screening tools, if they have a depression module or are being used to identify depressive illness and related outcomes	• Screening instruments that are not feasible for primary care or comparable settings; that is, instruments that take >15 minutes to complete if delivered prior to clinician and patient face-to-face contact (e.g., in the waiting or examination room, before clinician entrance), >5 minutes or five questions if used during the face-to-face visit, or not feasible to score in primary care settings • More general mental health screening tools, if they do not have a depression module and are not being used to identify depressive illness
Interventions: Treatment	**Pharmacological interventions:** • Selective serotonin reuptake inhibitors: fluoxetine, fluvoxamine, sertraline, citalopram, and escitalopram **Psychotherapy interventions:** • Cognitive-behavioral therapy • Interpersonal psychotherapy **Other interventions:** • Pure or guided self-help • Family support • Parental education • Peer support • Collaborative care interventions • Other interventions not specifically listed in the exclusion criteria **Combined interventions:** • Combinations of pharmacological, psychological, behavioral, or other interventions	**Pharmacological interventions:** • Tricyclic antidepressants • Monoamine oxidase inhibitors • Paroxetine • SNRIs, NDRIs, other types of off-label pharmacological interventions **Other therapy:** • CAM • Electroconvulsive therapy • Other interventions that are not primary care feasible or referable
Comparisons	**KQs 1, 3, 4:** • Screened vs. unscreened **KQ 2:** • Screening instrument vs. gold standard diagnostic instrument **KQ 5:** • Medications vs. placebo • Nonpharmacological vs. wait-list control, usual care, or supportive counseling	**KQs 1, 3–6:** • Single-group design with no comparator • Active comparator of screening instrument (KQs 1–4) or treatment (KQs 5, 6)

Appendix B Table 1. Inclusion/Exclusion Criteria

	Inclusion	Exclusion
	• Intervention vs. sham **KQ 6:** • Medications vs. placebo • Intervention vs. wait-list control • Intervention vs. usual care • Intervention vs. sham	
Outcomes	**KQ 1:** Primary outcomes of interest: • Remission from MDD • Depressive symptoms (severity) Additional outcomes of interest: • Health status, quality of life • Academic, psychosocial, and global functioning • High-risk behaviors (e.g., delinquency, unplanned pregnancy, substance use) • Mental or physical health symptoms • Suicidality or death **KQ 2:** • Sensitivity • Specificity • Positive predictive value • Receiver operator curve characteristics (area under the curve) **KQ 3:** • MDD diagnosis **KQ 4:** • False-positive results leading to unnecessary treatment • Stigma • Opportunity costs • Resources (staff needed to perform screening and training for staff on the use of screening instruments) **KQ 5:** Primary outcomes of interest • Remission from MDD • Depressive symptoms or severity • Recurrence of MDD Additional outcomes of interest • Health status, quality of life • Academic, psychosocial, and global functioning • High-risk behaviors (e.g., delinquency, unplanned pregnancy, substance use) • Mental or physical health symptoms **KQ 6:** Suicidality or death • Death from suicide or other causes • Other serious psychiatric events (such as hospitalization, suicidal ideation, and suicide attempts) • Triggering symptoms of mania • Discontinuation of medication due to adverse events • Side effects of medications	**KQs 1, 3, 4–6:** All other outcomes not listed in inclusion criteria

Appendix B Table 1. Inclusion/Exclusion Criteria

	Inclusion	Exclusion
Timing	**KQs 1, 3, 5:** Outcomes reported at 6-week followup or later **KQ 2:** Diagnostic accuracy compared with an independent standard, assessed at ≤2 months after the screening test	**KQs 1, 3, 5:** Outcomes reported earlier than 6 weeks following screening or treatment **KQ 2:** Diagnostic accuracy compared with an independent standard, assessed at >2 months after the screening test
Settings	**KQs 1, 3:** • Primary care settings • United States and other countries with a very high Human Development Index **KQs 2, 4:** • Primary care-, school-, or nonclinic-based settings (e.g., church or after school) • United States and other countries with a very high Human Development Index **KQs 5, 6:** • Primary care • Outpatient settings that receive referrals from primary care settings • United States and other countries with a very high Human Development Index	**KQs 1, 3:** • Settings not comparable with a primary care setting (e.g., mental health specialty settings) • Inpatients or those in residential or drug treatment programs; conducted with incarcerated populations • Countries with a Human Development Index of low to high **KQs 2, 4:** • Settings not comparable with a primary care-, school-, or nonclinic-based setting (e.g., mental health specialty settings) • Inpatients or those in residential treatment or drug treatment programs; conducted with incarcerated populations • Countries with a Human Development Index of low to high **KQs 5, 6:** • Inpatients or those in residential or drug treatment programs; conducted with incarcerated populations • Countries with a Human Development Index of low to high
Study Designs	**KQs 1, 3, 4–6:** • Randomized, controlled trials • Controlled clinical trials • Systematic reviews published since 2011 **Criteria specific to KQ 2:** • Test/retest studies (test compared with gold standard) that are stand alone or incorporated within other study designs **Criteria specific to KQ 4:** • Prospective cohort studies with sample size ≥1,000 • Retrospective cohort studies with sample size ≥1,000 **Criteria specific to KQ 6:** • Prospective cohort studies with a sample size ≥1,000 • Retrospective cohort studies with a sample size ≥1,000	**KQs 1, 3, 4–6:** • Letters to the editor without primary • Reviews published since 2011 **Criteria specific to KQs 1, 3:** • Perspective or retrospective cohort studies **Criteria specific to KQ 2:** • Does not report sensitivity and specificity compared with an independently assessed criterion standard for MDD **Criteria specific to KQ 4:** • Prospective cohort studies with a sample size <1,000 • Retrospective cohort studies with a sample size <1,000 **Criteria specific to KQ 6:** • Prospective cohort studies with a sample size <1,000 • Retrospective cohort studies with a sample size <1,000
Language	English	Non-English
Date of Publication	Any date subsequent to the latest date searched in the prior review	Any date included in the prior review

Appendix C. Excluded Studies

X 1 Wrong publication type (Editorials, Letters, Opinions, or Commentaries to the editor with no primary data, Nonsystematic Review articles)
X 2 Wrong population (Majority of sample not 0 – 18 years of age or study did not report that at least 50 percent of the sample had MDD)
X 3 Wrong or no comparator (Single group design with no comparator; Active comparator of screening instrument or treatment [e.g., head-to-head trial])
X 4 Wrong or no outcome (See Include/Exclude criteria for exceptions)
X 5 Wrong timing (Outcomes reported < 6 weeks following screening or treatment; diagnostic accuracy compared with independent standard assessed >2 months after screening
X 6 Wrong setting (Settings not comparable with a primary care of school-based setting; In-patients or those in residential treatment or drug treatment program; incarcerated populations)
X 7 Wrong geographical setting (Countries with human development index of low to high)
X 8 Wrong Study Design (Case reports, case series)
X 9 Wrong or no intervention (As defined for screenings and pharmaceutical interventions in Include/Exclude criteria)
X 10 Study size (for cohort studies, only) <1,000 subjects
X 11 Wrong publication date (for SR and MA only) published before 2011
X 12 Wrong language
X 13 Included in the 2009 Report
X 14 Full text unavailable for review

1. Suicidal ideas with paroxetine or venlafaxine. Prescrire Int. 2004 Feb;13(69):21. PMID: 15055220. Exclusion Code: X 1
2. Depression in children and young people: identification and management in primary, community and secondary care (Structured abstract). Database of Abstracts of Reviews of Effects: British Psychological Society; 2005. p. 233. Exclusion Code: X 11
3. Fluoxetine: new indication. Depression in children: too many uncertainties. Prescrire Int. 2008 Oct;17(97):186-7. PMID: 19534039. Exclusion Code: X 1
4. An update on depression in children and adolescents. J Clin Psychiatry. 2008 Nov;69(11):1818-28. PMID: 19200430. Exclusion Code: X 1
5. Extended-release fluvoxamine (Luvox CR). Med Lett Drugs Ther. 2008 Jun 30;50(1289):50-1. PMID: 18583947. Exclusion Code: X 2
6. School-based safety interventions. Identifying children and teens at risk for depression or violence. Harv Ment Health Lett. 2008 Sep;25(3):1-3. PMID: 18839479. Exclusion Code: X 1
7. Second-step treatments for adolescent depression. The TORDIA study suggests options when initial drug treatment fails. Harv Ment Health Lett. 2010 Oct;27(4):6. PMID: 21032849. Exclusion Code: X 1
8. A Study in the Treatment of Children and Adolescents With Major Depressive Disorder. 2012. Exclusion Code: X 2
9. Aebi M, Metzke CW, Steinhausen HC. Prediction of major affective disorders in adolescents by self-report measures. J Affect Disord. 2009 May;115(1-2):140-9. PMID: 18947881. Exclusion Code: X 3
10. Akerblad AC, Bengtsson F, Knorring L, et al. Response, remission and relapse in relation to adherence in primary care treatment of depression: a 2-year outcome study. Int Clin Psychopharmacol; 2006. p. 117-24. Exclusion Code: X 2
11. Alegria M, Ludman E, Kafali EN, et al. Effectiveness of the Engagement and Counseling for Latinos (ECLA) intervention in low-income Latinos. Med Care. 2014 Nov;52(11):989-97. PMID: 25310525. Exclusion Code: X 2
12. Allgaier AK, Pietsch K, Frühe B, et al. Screening for depression in adolescents: Validity of the patient health questionnaire in pediatric care. Depress Anxiety. 2012;29(10):906-13. PMID: 2012-26844-010. PMID: 22753313. First Author & Affiliation: Allgaier, Antje-Kathrin. Exclusion Code: X 6
13. Allgaier A-K, Krick K, Opitz A, et al. Improving early detection of childhood depression in mental health care: The Children's Depression Screener (ChilD-S). Psychiatry Res. 2014;217(3):248-52. PMID: 2014-24132-003. Exclusion Code: X 6

14. Allgaier A-K, Pietsch K, Frühe B, et al. Depression in pediatric care: Is the WHO-Five Well-Being Index a valid screening instrument for children and adolescents? Gen Hosp Psychiatry. 2012;34(3):234-41. PMID: 2012-12199-003. PMID: 22325631. First Author & Affiliation: Allgaier, Antje-Kathrin. Exclusion Code: X 3
15. Anderson HD, Pace WD, Libby AM, et al. Rates of 5 common antidepressant side effects among new adult and adolescent cases of depression: a retrospective US claims study. Clin Ther. 2012 Jan;34(1):113-23. PMID: 22177545. Exclusion Code: X 3
16. Anderson R, Ukoumunne OC, Sayal K, et al. Cost-effectiveness of classroom-based cognitive behaviour therapy in reducing symptoms of depression in adolescents: a trial-based analysis. J Child Psychol Psychiatry. 2014 May 12PMID: 24813670. Exclusion Code: X 2
17. Anderson SE, Murray DM, Johnson CC, et al. Obesity and depressed mood associations differ by race/ethnicity in adolescent girls. Int J Pediatr Obes. 2010 Apr 6PMID: 20367561. Exclusion Code: X 8
18. Aragones E, Pinol JL, Labad A. Depression and physical comorbidity in primary care. J Psychosom Res. 2007 Aug;63(2):107-11. PMID: 17662745. Exclusion Code: X 2
19. Araneda RM, Solar FC, González PR, et al. Propiedades psicométricas del Inventario de Depresión de Beck-II en adolescentes Chilenos. Terapia Psicologica. 2008;26(1):59-69. PMID: 2008-12716-005. First Author & Affiliation: Araneda, Roberto Melipillán. Exclusion Code: X 12
20. Arita JH, Lin J, Pinho RS, et al. Adolescents with chronic migraine commonly exhibit depressive symptoms. Acta Neurol Belg. 2013 Mar;113(1):61-5. PMID: 23055110. Exclusion Code: X 2
21. Armenta BE, Sittner Hartshorn KJ, Whitbeck LB, et al. A longitudinal examination of the measurement properties and predictive utility of the Center for Epidemiologic Studies Depression Scale among North American Indigenous adolescents. Psychol Assess. 2014;26(4):1347-55. PMID: 2014-35683-001. Exclusion Code: X 4
22. Arnberg A, Ost LG. CBT for Children with Depressive Symptoms: A Meta-Analysis. Cogn Behav Ther. 2014 Sep 24:1-14. PMID: 25248459. Exclusion Code: X 2
23. Arnberg FK, Linton SJ, Hultcrantz M, et al. Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. PLoS One. 2014;9(5):e98118. PMID: 24844847. Exclusion Code: X 2
24. Asarnow JR, Berk M, Hughes JL, et al. The SAFETY Program: A Treatment-Development Trial of a Cognitive-Behavioral Family Treatment for Adolescent Suicide Attempters. J Clin Child Adolesc Psychol. 2014 Sep 25:1-10. PMID: 25255931. Exclusion Code: X 2
25. Asarnow JR, Jaycox LH, Tang L, et al. Long-term benefits of short-term quality improvement interventions for depressed youths in primary care. Am J Psychiatry; 2009. p. 1002-10. Exclusion Code: X 2
26. Atkinson SD, Prakash A, Zhang Q, et al. A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorder. J Child Adolesc Psychopharmacol; 2014. p. 180-9. Exclusion Code: X 6
27. Baksheev GN, Robinson J, Cosgrave EM, et al. Validity of the 12-item General Health Questionnaire (GHQ-12) in detecting depressive and anxiety disorders among high school students. Psychiatry Res. 2011 May 15;187(1-2):291-6. PMID: 21067813. Exclusion Code: X 3
28. Balasubramaniam M, Telles S, Doraiswamy PM. Yoga on our minds: a systematic review of yoga for neuropsychiatric disorders. Front Psychiatry. 2012;3:117. PMID: 23355825. Exclusion Code: X 2
29. Balazs J, Miklosi M, Kereszteny A, et al. Adolescent subthreshold-depression and anxiety: psychopathology, functional impairment and increased suicide risk. J Child Psychol Psychiatry. 2013 Jan 18PMID: 23330982. Exclusion Code: X 8
30. Bansal V, Goyal S, Srivastava K. Study of prevalence of depression in adolescent students of a public school. Ind Psychiatry J. 2009 Jan;18(1):43-6. PMID: 21234162. Exclusion Code: X 3
31. Bearsley-Smith C, Browne MO, Sellick K, et al. Does interpersonal psychotherapy improve clinical care for adolescents with depression attending a rural child and adolescent mental health service? Study protocol for a cluster randomised feasibility trial. BMC Psychiatry; 2007. p. 53. Exclusion Code: X 4

32. Berard R, Fong R, Carpenter DJ, et al. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. J Child Adolesc Psychopharmacol; 2006. p. 59-75. Exclusion Code: X 9
33. Bhalerao S. Exclusion Code: X 14
34. Blazquez A, Mas S, Plana MT, et al. Plasma fluoxetine concentrations and clinical improvement in an adolescent sample diagnosed with major depressive disorder, obsessive-compulsive disorder, or generalized anxiety disorder. J Clin Psychopharmacol. 2014 Jun;34(3):318-26. PMID: 24743718. Exclusion Code: X 3
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Appendix D Table 1. Quality Ratings of Screening Accuracy for MDD in Children and Adolescents (KQ 2) (Part 1)

First Author, Year	Screening Test adequately described?	Were selection criteria clearly described?	Is the reference standard likely to correctly classify MDD?	Is the time period between the screening test and the comparator short enough?	Do start of follow-up and start of intervention coincide?
Barrera et al, 1998[1]	Yes	No	No	Yes	Yes
Canals et al, 2001[2]	Yes	Yes	Yes	Yes	Yes
Cuijpers et al, 2008[3]	Yes	Yes	Yes	Yes	Yes
Garrison et al, 1991[4]	Yes	Yes	Yes	NR	Yes
Johnson et al, 2002[5]	Yes	Yes	Yes	If gap >18 days, dropped	Yes
Patton et al, 1999[6]	Yes	Yes	Yes	Unclear	Yes
Roberts et al, 1991[7]	Yes	Yes	Yes	Yes	Yes
Winter et al, 1999[8]	Yes	Yes	Unclear	Yes	Yes
Whitaker et al, 1990[9]	No	Yes	Unclear	Unclear	Yes

KQ, Key Question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 2. Quality Ratings of Screening Accuracy for MDD in Children and Adolescents (KQ 2) (Part 2)

First Author, Year	Did the whole or a random selection of the sample receive screening test?	Did patients receive the same reference regardless of test results?	Was the reference standard independent of the test?	Quality Rating	Comments
Barrera et al, 1998[1]	Yes	Yes	NR	Poor	No description of selection of students; small sample size (N=49); unclear whether reference standard was independent and blinded; reference standard reliability and validity not proven for adolescents; author acknowledges that they used the CAS instead of the more-appropriate K-SADS because they had to use interviewers who were not clinically experienced.
Canals et al, 2001[2]	No (290/304)	Yes	Unclear	Fair	Sample not representative of a school-based sample; more than half dropped out over time; mean age 18 and these are the remaining 304 of an original sample of 579 10 and 11 year olds who participated in a study many years ago; means children were stable, didn't move around a lot, and were still in school; 14 dropped out between screener and PRIME-MD assessment
Cuijpers et al, 2008[3]	No	Yes	Yes	Poor	Two different samples (one obtained through schools and the other through the Internet). Patients were stratified according to screening test results and then selected based on this stratification to receive the diagnostic interview (MINI)
Garrison et al, 1991[4]	No	Yes	Yes	Fair	Time period between screening and interview not reported; Sample included all persons with high screening scores and a random sample of the remainder
Johnson et al., 2002[5]	Yes	Yes	Yes	Fair	Sample came from two sources (each consisting of many primary care and school nurse offices); Only 162 of 403 completed interviews from the second sample were used in analyses b/c the length of time between test and interview was more than 16 days
Patton et al, 1999[6]	Yes: All CIS-R+ subjects were invited to second phase interview. For each CIS-R+ subject, two CIS-R) subjects were selected at random for interview from the same school.	Yes	Yes	Fair	Time lapse could explain the poor sensitivity

Appendix D Table 2. Quality Ratings of Screening Accuracy for MDD in Children and Adolescents (KQ 2) (Part 2)

First Author, Year	Did the whole or a random selection of the sample receive screening test?	Did patients receive the same reference regardless of test results?	Was the reference standard independent of the test?	Quality Rating	Comments
Roberts et al, 1991[7]	Yes (but response rate was only 61%)	Yes	Unclear	Fair	Response rates were low (39%)
Winter et al, 1999[8]	Yes	Yes	Yes	Poor	PRIME-MD is another screening tool, not a diagnostic instrument. The authors acknowledge that, in addition, the PRIME-MD had not even been validated on the adolescent population prior to this study (nor had reliability in adolescent sample been done).
Whitaker et al, 1990[9]	No (Stratified random sample was based on screening scores)	No--there was no diagnostic interview that had been validated in 1984	Yes	Poor	Risk of inappropriate and biased ascertainment of reference standard, time between screener and interview not specified.

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.
Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.
Poor: Has fatal flaw such as: Uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow selected spectrum of patients.

CAS, Child Assessment Schedule; CIS-R, Clinical Interview Schedule-Revised; K-SADS, Kiddie-Schedule for Affective Disorders and Schizophrenia; KQ, Key Question; MDD, major depressive disorder; MINI, Mini-International Neuropsychiatric Interview; NR, not reported, PRIME-MD, Primary Care Evaluation of Mental Disorders.

Appendix D Table 3. Quality Ratings of Included RCTs Examining the Benefits of SSRIs in Treating MDD in Children and Adolescents (KQ 5) (Part 1)

First Author, Year	Was eligibility criteria described clearly?	Was inclusion/exclusion criteria measured using valid/reliable measures, implemented across all study participants?	Was symptom status determined using valid/ reliable methods?	Was randomization adequate?	Was allocation concealment adequate?	Did strategy for recruiting differ across study groups?
Emslie et al, 1997[10]	Yes	Yes	Yes	Yes	Yes	No
Emslie et al, 2002[11]	Yes	Yes	Yes	Yes	NR	NR
Emslie et al, 2009[12]	Yes	Yes	Yes	NR	NR	No
Findling et al, 2013[13]	Yes	Yes	Yes	NR	NR	No
Kennard et al, 2006[14]	No (references March 2004 publication)	NR	Yes	NR	NR	NR
March et al, 2004[15]	Yes	Yes	Yes	Yes	NR	No
Vitiello et al, 2006[16]	No (references March 2004 publication)	NR	Yes	NR	NR	NR
Wagner et al, 2004[17]	Yes	Yes	Yes	NR	NR	No
Wagner et al, 2006[18]	Yes	Yes	Yes	Yes	NR	NR

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 4. Quality Ratings of Included RCTs Examining the Benefits of SSRIs in Treating MDD in Children and Adolescents (KQ 5) (Part 2)

First Author, Year	Did start of follow-up and start of intervention coincide?	Were baseline characteristics similar between groups? If not, did the analysis control for differences?	Were outcome assessors blinded?	Was intervention fidelity adequate?	Did variation from the study protocol compromise conclusions?
Emslie et al, 1997[10]	Yes	Yes	Unclear (double blind in title)	NR	No
Emslie et al, 2002[11]	Yes	Yes	Yes	NR	No
Emslie et al, 2009[12]	Yes	Significance not reported	Yes	NR	No
Findling et al, 2013[13]	Yes	Significance not reported	Yes	NR	No
Kennard et al, 2006[14]	Yes	NR	Double blind for placebo and fluoxetine groups; single blind (evaluators) for CBT and combined groups	NR	No
March et al, 2004[15]	Yes	Yes	Yes	NR	No
Vitiello et al, 2006[16]	Yes	NR	Double blind for placebo and fluoxetine groups; single blind (evaluators) for CBT and combined groups	NR	No
Wagner et al, 2004[17]	Yes, other than 1 week placebo lead-in period	yes	Unclear (double Blind in title)	NR	No
Wagner et al, 2006[18]	Yes, other than 1 week lead-in placebo	Yes	Blinded at least for harms, double-blinded otherwise	NR	No

KQ, key question; MDD, major depressive disorder; NA, not applicable; NR, not reported.

Appendix D Table 5. Quality Ratings of Included RCTs Examining the Benefits of SSRIs in Treating MDD in Children and Adolescents (KQ 5) (Part 3)

First Author, Year	Overall attrition	Did high attrition raise concern for bias?	Was analysis conducted on ITT basis?	Did the study have cross-overs or contamination raising concern for bias?	Were outcomes pre-specified/defined and adequately described?	Were outcome measures valid/ reliable?
Emslie et al, 1997[10]	75%	Yes	Yes	NR	Yes	Yes
Emslie et al, 2002[11]	28%	Yes	Yes	NR	Yes	Yes
Emslie et al, 2009[12]	17%	No	Yes	No	Yes	Yes
Findling et al, 2013[13]	46.7%	Yes - Overall No - Differential	Yes	No	Yes	Yes
Kennard et al, 2006[14]	13.70%	No (differential attrition NR, based on March 2004 publication)	Yes	NR	Yes	Yes
March et al, 2004[15]	18%	No	Yes	No	Yes	Yes
Vitiello et al, 2006[16]	13.7% (Based on March 2004 publication)	NR (Based on March 2004 publication)	Yes	NR	Yes	Yes
Wagner et al, 2004[17]	21%	Yes	Yes	NR	Yes	Yes
Wagner et al, 2006[18]	18%	No	Yes	NR	Yes	Yes

ITT, intent to treat; KQ, key question; MDD, major depressive disorder; NR = not reported.

Appendix D Table 6. Quality Ratings of Included RCTs Examining the Benefits of SSRIs in Treating MDD in Children and Adolescents (KQ 5) (Part 4)

First Author, Year	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Emslie et al, 1997[10]	Yes	Yes (not LOCF)	Yes	Poor	Attrition and differential attrition
Emslie et al, 2002[11]	Yes	NR	Yes	Poor	Attrition and differential attrition
Emslie et al, 2009[12]	Yes	Yes	Yes	Fair	Differences appear to be minimal between groups at baseline but p values not presented; randomization and allocation not reported
Findling et al, 2013[13]	Yes	Yes	Yes	Poor	Substantial overall attrition; differences appear to be minimal between groups at baseline but p values not presented; randomization and allocation not reported
Kennard et al, 2006[14]	Yes	Yes	Yes	Good	Rating good even though they did not report everything b/c we know the March 2004 study is of good quality.
March et al, 2004[15]	Yes	Yes	Yes	Good	Allocation concealment method and fidelity to CBT protocol both not reported but all other ratings indicated high quality
Vitiello et al, 2006[16]	Yes	Yes	Yes	Good	Rating good even though they did not report everything b/c we know the March 2004 study is of good quality.
Wagner et al, 2004[17]	Yes	NR	Yes	Fair	Overall 21% attrition; Patient and assessor blinding not specified
Wagner et al, 2006[18]	Yes	Yes	Yes; study site not adjusted for	Fair	Outcome assessment not reported as masked

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

CBT, cognitive behavioral therapy; G, group; ITT, intent to treat; KQ, key question; LOCF, last observation carried forward; MDD, major depressive disorder; NR, not reported.

Appendix D Table 7. Quality Ratings of Included RCTs Examining the Benefits of Psychotherapy in Treating MDD in Children and Adolescents (KQ 5) (Part 1)

First Author, Year	Was eligibility criteria described clearly?	Was inclusion/exclusion criteria measured using valid/reliable measures, implemented across all study participants?	Was symptom status determined using valid/ reliable methods?	Was randomization adequate?	Was allocation concealment adequate?	Did strategy for recruiting differ across study groups?
Clarke et al, 1999[19]	Yes	Yes	Yes	NR	NR	No
Diamond et al, 2002[20]	No (reported that "20% met other exclusion criteria" after screening, but this other exclusion criteria is never reported)	Yes	Yes	NR	NR	No
Kennard et al, 2006[14]	No (references March 2004 publication)	NR	Yes	NR	NR	NR
Luby et al, 2012[21]	Yes	Yes	Yes	Yes	Unclear	No
March et al, 2004[15]	Yes	Yes	Yes	Yes	NR	No
Mufson et al, 1999[22]	Yes	Yes	Yes	Yes	NR	No
Rossello et al, 1999[23]	Yes	Yes	Yes	NR	NR	No
Sanford et al, 2006[24]	Yes	Yes	Yes	Yes	Yes	No
Vitiello et al, 2006[16]	No (references March 2004 publication)	NR	Yes	NR	NR	NR

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 8. Quality Ratings of Included RCTs Examining the Benefits of Psychotherapy in Treating MDD in Children and Adolescents (KQ 5) (Part 2)

First Author, Year	Did start of follow-up and start of intervention coincide?	Were baseline characteristics similar between groups? If not, did the analysis control for differences?	Were outcome assessors blinded?	Was intervention fidelity adequate?	Did variation from the study protocol compromise conclusions?
Clarke et al, 1999[19]	Yes	NR	Yes	NR	NR
Diamond et al, 2002[20]	Yes	Yes	Yes	NR	No
Kennard et al, 2006[14]	Yes	NR	Double blind for placebo and fluoxetine groups; single blind (evaluators) for CBT and combined groups	NR	No
Luby et al, 2012[21]	Yes	Yes	Yes	Yes	No
March et al, 2004[15]	Yes	Yes	Yes	NR	No
Mufson et al, 1999[22]	Yes	Yes	Yes	Yes	No
Rossello et al, 1999[23]	Yes	NR	NR	Yes	No
Sanford et al, 2006[24]	Yes	Yes	Yes	Yes	Yes
Vitiello et al, 2006[16]	Yes	NR	Double blind for placebo and fluoxetine groups; single blind (evaluators) for CBT and combined groups	NR	No

CBT, cognitive behavioral therapy; KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 9. Quality Ratings of Included RCTs Examining the Benefits of Psychotherapy in Treating MDD in Children and Adolescents (KQ 5) (Part 3)

First Author, Year	Overall attrition	Did high attrition raise concern for bias?	Was analysis conducted on ITT basis?	Did the study have cross-overs or contamination raising concern for bias?	Were outcomes pre-specified/defined and adequately described?	Were outcome measures valid/ reliable?
Clarke et al, 1999[19]	22%	Yes	Yes	NR	Yes	Yes
Diamond et al, 2002[20]	3%	No	No	No	Yes	No (BDI<9 used as the response to treatment at 6 weeks does not have clinical significance and has not been validated as 'response" or "remission" or "recovery"
Kennard et al, 2006[14]	13.70%	No (differential attrition NR, based on March 2004 publication)	Yes	NR	Yes	Yes
Luby et al, 2012[21]	46.30%	Yes- Overall Yes - Differential	Yes	No	Yes	Yes
March et al, 2004[15]	18%	No	Yes	No	Yes	Yes
Mufson et al, 1999[22]	33%	Yes	Yes	No	Yes	Yes
Rossello et al, 1999[23]	17.8%	No	No	No	Yes	Yes
Sanford et al, 2006[24]	Unclear, 1 of 2 recruiting sites dropped because of poor adherence	Unclear	No	Unclear	Yes	Yes
Vitiello et al, 2006[16]	13.7% (Based on March 2004 publication	NR (No based on March 2004 publication)	Yes	NR	Yes	Yes

BDI, Beck Depression Inventory; ITT, intent to treat; KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 10. Quality Ratings of Included RCTs Examining the Benefits of Psychotherapy in Treating MDD in Children and Adolescents (KQ 5) (Part 4)

First Author, Year	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Clarke et al, 1999[19]	Yes	Yes	Yes	Fair	Randomization and allocation concealment not reported. High attrition for an acute-phase trial, but ITT analysis done. Differential rate of attrition across sites with unknown implication
Diamond et al, 2002[20]	No (only 6 week comparisons can be made)	NR	Yes	Poor	Differential follow up periods between groups (6 weeks for WL, 12 weeks for treatment). Focus on 6 week follow-up only uses BDI>9 as outcome
Kennard et al, 2006[14]	Yes	Yes	Yes	Good	Rating good even though they didn't report everything b/c we know the March study is of good quality.
Luby et al, 2012[21]	Yes	Yes	Yes	Poor	Large and differential attrition leaving 53.7% of the sample for followup outcome measurement; ITT analysis retains all randomized patients with a baseline measurement, but is still limited to 45/54 patients (79.6%)
March et al, 2004[15]	Yes	Yes	Yes	Good	Allocation concealment method and fidelity to CBT protocol not reported; All other ratings indicated high quality
Mufson et al, 1999[22]	Yes	Yes	Yes	Poor	High overall and differential attrition; LOCF analysis of mostly control patients is likely to underestimate their natural improvement over the course of time and therefore result in type 1 error.
Rossello et al, 1999[23]	Yes	No	No	Poor	No ITT analyses conducted; randomization method not reported; blinding of assessors not reported; no group differences reported at baseline other than for outcomes so don't know how groups may have differed on sociodemographic characteristics, etc., and analyses were not adjusted.
Sanford et al, 2006[24]	Yes	No	Yes	Poor	High risk of bias from having dropped an entire recruitment site and not having accounted for the numbers lost in the analysis. Outcome assessment not blinded.
Vitiello et al, 2006[16]	Yes	Yes	Yes	Good	Rating good even though they didn't report everything b/c we know the March study is of good quality.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

KQ, key question; MDD, major depressive disorder; NR, not reported; WL, waitlist.

Appendix D Table 11. Quality Ratings of Included RCTs Examining the Benefits of Collaborative Care in Treating MDD in Children and Adolescents (KQ 5) (Part 1)

First Author, Year	Was eligibility criteria described clearly?	Was inclusion/exclusion criteria measured using valid/reliable measures, implemented across all study participants?	Was symptom status determined using valid/ reliable methods?	Was randomization adequate?	Was allocation concealment adequate?	Did strategy for recruiting differ across study groups?
Richardson et al, 2014[25]	Yes	Yes	Yes	Yes	NA	No

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 12. Quality Ratings of Included RCTs Examining the Benefits of Collaborative Care in Treating MDD in Children and Adolescents (KQ 5) (Part 2)

First Author, Year	Did start of follow-up and start of intervention coincide?	Were baseline characteristics similar between groups? If not, did the analysis control for differences?	Were outcome assessors blinded?	Was intervention fidelity adequate?	Did variation from the study protocol compromise conclusions?
Richardson et al, 2014[25]	Yes	Yes	Yes	NR	No

CBT, cognitive behavioral therapy; KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 13. Quality Ratings of Included RCTs Examining the Benefits of Collaborative Care in Treating MDD in Children and Adolescents (KQ 5) (Part 3)

First Author, Year	Overall attrition	Did high attrition raise concern for bias?	Was analysis conducted on ITT basis?	Did the study have cross-overs or contamination raising concern for bias?	Were outcomes pre-specified/defined and adequately described?	Were outcome measures valid/ reliable?
Richardson et al, 2014[25]	7%	No	Yes	No	Yes	Yes

BDI, Beck Depression Inventory; ITT, intent to treat; KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 14. Quality Ratings of Included RCTs Examining the Benefits of Collaborative Care in Treating MDD in Children and Adolescents (KQ 5) (Part 4)

First Author, Year	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Richardson et al, 2014[25]	Yes	Yes	Yes	Good	Just under 80% attrition at 6 month f/u and less than that at 12 month f/u?

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

KQ, key question; MDD, major depressive disorder; NR, not reported; WL, waitlist.

Appendix D Table 15. Quality Ratings of Included RCTs Examining the Benefits of SSRIs in Combination With Psychotherapy in Treating MDD in Children and Adolescents (KQ 5) (Part 1)

First Author, Year	Was eligibility criteria described clearly?	Was inclusion/exclusion criteria measured using valid/reliable measures, implemented across all study participants?	Was symptom status determined using valid/ reliable methods?	Was randomization adequate?	Was allocation concealment adequate?	Did strategy for recruiting differ across study groups?
Kennard et al, 2006[14]	No (References March 2004 publication)	NR	Yes	NR	NR	NR
March et al, 2004[15]	Yes	Yes	Yes	Yes	NR	No
Vitiello et al, 2006[16]	No (References March 2004 publication)	NR	Yes	NR	NR	NR

KQ, key question; MDD, major depressive disorder.

Appendix D Table 16. Quality Ratings of Included RCTs Examining the Benefits of SSRIs in Combination With Psychotherapy in Treating MDD in Children and Adolescents (KQ 5) (Part 2)

First Author, Year	Did start of follow-up and start of intervention coincide?	Were baseline characteristics similar between groups? If not, did the analysis control for differences?	Were outcome assessors blinded?	Was intervention fidelity adequate?	Did variation from the study protocol compromise conclusions?
Kennard et al, 2006[14]	Yes	NR	Double blind for placebo and fluoxetine groups; single blind (evaluators) for CBT and combined groups	NR	No
March et al, 2004[15]	Yes	Yes	Yes	NR	No
Vitiello et al, 2006[16]	Yes	NR	Double blind for placebo and fluoxetine groups; single blind (evaluators) for CBT and combined groups	NR	No

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 17. Quality Ratings of Included RCTs Examining the Benefits of SSRIs in Combination With Psychotherapy in Treating MDD in Children and Adolescents (KQ 5) (Part 3)

First Author, Year	Overall attrition	Did high attrition raise concern for bias?	Was analysis conducted on ITT basis?	Did the study have cross-overs or contamination raising concern for bias?	Were outcomes pre-specified/defined and adequately described?	Were outcome measures valid/ reliable?
Kennard et al, 2006[14]	13.70%	No (differential attrition NR, based on March 2004)	Yes	NR	Yes	Yes
March et al, 2004[15]	18%	No	Yes	No	Yes	Yes
Vitiello et al, 2006[16]	13.7% (Based on March 2004)	NR (No based on March 2004)	Yes	NR	Yes	Yes

ITT, intent to treat; KQ, key question; MDD, major depressive disorder.

Appendix D Table 18. Quality Ratings of Included RCTs Examining the Benefits of SSRIs in Combination With Psychotherapy in Treating MDD in Children and Adolescents (KQ 5) (Part 4)

First Author, Year	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Kennard et al, 2006[14]	Yes	Yes	Yes	Good	Rating good even though they didn't report everything b/c we know the March study is of good quality.
March et al, 2004[15]	Yes	Yes	Yes	Good	Allocation concealment method and fidelity to CBT protocol not reported; All other ratings indicated high quality
Vitiello et al, 2006[16]	Yes	Yes	Yes	Good	Rating good even though they didn't report everything b/c we know the March study is of good quality.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

CBT, cognitive behavioral therapy; KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 19. Quality Ratings of Included RCTs Examining the Harms of SSRIs in Treating MDD in Children and Adolescents (KQ 6) (Part 1)

First Author, Year	Was eligibility criteria described clearly?	Was inclusion/exclusion criteria measured using valid/reliable measures, implemented across all study participants?	Was symptom status determined using valid/ reliable methods?	Was randomization adequate?	Was allocation concealment adequate?	Did strategy for recruiting differ across study groups?
Emslie et al, 1997[10]	Yes	Yes	Yes	Yes	Yes	No
Emslie et al, 2002[11]	Yes	Yes	Yes	Yes	NR	NR
Emslie et al, 2006[26]	Yes	Yes	Yes	Yes	NR	No
Emslie et al, 2009[12]	Yes	Yes	Yes	NR	NR	No
March et al, 2004[15]	Yes	Yes	Yes	Yes	NR	No
Mayes et al,2007[27]	Not in this pub but yes, in prior pubs	Not in this pub but yes, in prior pubs	Yes	NR	NR	No
Nilsson et al, 2004[28]	No (Reported in Emslie 2002)	NR	Yes	NR	NR	NR
Wagner et al, 2004[17]	Yes	Yes	Yes	NR	NR	No
Wagner et al, 2006[18]	Yes	Yes	Yes	Yes	NR	NR

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 20. Quality Ratings of Included RCTs Examining the Harms of SSRIs in Treating MDD in Children and Adolescents (KQ 6) (Part 2)

First Author, Year	Did start of follow-up and start of intervention coincide?	Were baseline characteristics similar between groups? If not, did the analysis control for differences?	Were outcome assessors blinded?	Was intervention fidelity adequate?	Did variation from the study protocol compromise conclusions?
Emslie et al, 1997[10]	Yes other than 2 week evaluation period and 1 week placebo lead-in	Yes	Unclear, although "Double Blind" is in title	NR	No
Emslie et al, 2002[11]	Yes other than 2 week evaluation period and 1 week placebo lead-in	Yes	yes	NR	No
Emslie et al, 2006[26]	Yes	NR	NR	NR	No
Emslie et al, 2009[12]	Yes	Significance not reported	Yes	NR	No
March et al, 2004[15]	Yes	Yes	Yes	NR	No
Mayes et al, 2007[27]	Yes	NR	NR	NR	NR
Nilsson et al, 2004[28]	Yes	NR	Yes	NR	NR
Wagner et al, 2004[17]	Yes, other than 1 week placebo lead-in period	Yes	Unclear, although "Double Blind" is in title	NR	No
Wagner et al, 2006[18]	Yes other than 1 week lead-in placebo	Yes	Blinded at least for harms, double-blinded otherwise	NR	No

KQ, key question; MDD, major depressive disorder; NA, not applicable; NR, not reported.

Appendix D Table 21. Quality Ratings of Included RCTs Examining the Harms of SSRIs in Treating MDD in Children and Adolescents (KQ 6) (Part 3)

First Author, Year	Overall attrition	Did high attrition raise concern for bias?	Was analysis conducted on ITT basis?	Did the study have cross-overs or contamination raising concern for bias?	Were outcomes pre-specified/defined and adequately described?	Were outcome measures valid/ reliable?
Emslie et al, 1997[10]	75%	Yes	Yes	NR	Yes	Yes
Emslie et al, 2002[11]	28%	Yes	Yes	NR	Yes	Yes
Emslie et al, 2006[26]	N/A--attrition not assessed (all observations taken)	No	No	No	Yes	Yes
Emslie et al, 2009[12]	17%	No	Yes	No	Yes	Yes
March et al, 2004[15]	18%	No	Yes	No	Yes	Yes
Mayes et al, 2007[27]	NR	NR	No	NR	Yes	Yes
Nilsson et al, 2004[28]	56.20%	No (55% vs. 57.2%)	Yes	NR	Yes	Yes
Wagner et al, 2004[17]	21%	Yes	Yes	NR	Yes	Yes
Wagner et al, 2006[18]	18%	No	Yes	NR	Yes	Yes

ITT, intent to treat; KQ, key question; MDD, major depressive disorder; NA, not applicable; NR, not reported.

Appendix D Table 22. Quality Ratings of Included RCTs Examining the Harms of SSRIs in Treating MDD in Children and Adolescents (KQ 6) (Part 4)

First Author, Year	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Emslie et al, 1997[10]	Yes	Yes (not LOCF)	Yes	Poor	Attrition and differential attrition
Emslie et al, 2002[11]	Yes	NR	Yes	Poor	Attrition and differential attrition
Emslie et al, 2006[26]	Yes	No	No	Poor	ITT not used; also, this is more concerning for the other intervention groups, but "clinicians and study participants were not blind to treatment in the COMB and CBT arms, which undoubtedly affected not only efficacy, but also safety outcomes"
Emslie et al, 2009[12]	Yes	Yes	Yes	Fair	Differences appear to be minimal between groups at baseline but p values not presented; randomization and allocation not reported
March et al, 2004[15]	Yes	Yes	Yes	Good	Allocation concealment method and fidelity not reported; other ratings indicated high quality
Mayes et al, 2007[27]	Yes	No	Yes	Poor	"However, because subjects who did not return for at least one post-randomization visit were excluded, this is not a “pure” intent-to-treat analysis."
Nilsson et al, 2004[28]	Yes	Yes	Yes	Poor	High attrition
Wagner et al, 2004[17]	Yes	NR	Yes	Fair	Overall 21% attrition; blinding not specified
Wagner et al, 2006[18]	Yes	Yes	Yes (although study site not adjusted for)	Fair	Outcome assessment not reported as masked.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

CBT, cognitive behavioral therapy; COMB, combination; G, group; ITT, intent to treat; KQ, key question; LOCF, last observation carried forward; MDD, major depressive disorder; NR, not reported; pub, publication.

Appendix D Table 23. Quality Ratings of Included RCTs Examining the Harms of Psychotherapy in Treating MDD in Children and Adolescents (KQ 6) (Part 1)

First Author, Year	Was eligibility criteria described clearly?	Was inclusion/exclusion criteria measured using valid/reliable measures, implemented across all study participants?	Was symptom status determined using valid/ reliable methods?	Was randomization adequate?	Was allocation concealment adequate?	Did strategy for recruiting differ across study groups?
Emslie et al, 2006[26]	Yes	Yes	Yes	Yes	NR	No
March et al, 2004[15]	Yes	Yes	Yes	Yes	NR	No
Mufson et al, 1999[22]	Yes	Yes	Yes	Yes	NR	No

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 24. Quality Ratings of Included RCTs Examining the Harms of Psychotherapy in Treating MDD in Children and Adolescents (KQ 6) (Part 2)

First Author, Year	Did start of follow-up and start of intervention coincide?	Were baseline characteristics similar between groups? If not, did the analysis control for differences?	Were outcome assessors blinded?	Was intervention fidelity adequate?	Did variation from the study protocol compromise conclusions?
Emslie et al, 2006[26]	Yes	NR	NR	NR	No
March et al, 2004[15]	Yes	Yes	Yes	NR	No
Mufson et al, 1999[22]	Yes	Yes	Yes	Yes	No

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 25. Quality Ratings of Included RCTs Examining the Harms of Psychotherapy in Treating MDD in Children and Adolescents (KQ 6) (Part 3)

First Author, Year	Overall attrition	Did high attrition raise concern for bias?	Was analysis conducted on ITT basis?	Did the study have cross-overs or contamination raising concern for bias?	Were outcomes pre-specified/defined and adequately described?	Were outcome measures valid/ reliable?
Emslie et al, 2006[26]	N/A--attrition not assessed (all observations were taken)	No	No	No	Yes	Yes
March et al, 2004[15]	18%	No	Yes	No	Yes	Yes
Mufson et al, 1999[22]	33%	Yes	Yes	No	Yes	Yes

ITT, intent to treat; KQ, key question; MDD, major depressive disorder; NA, not applicable.

Appendix D Table 26. Quality Ratings of Included RCTs Examining the Harms of Psychotherapy in Treating MDD in Children and Adolescents (KQ 6) (Part 4)

First Author, Year	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Emslie et al, 2006[26]	Yes	No	No	Poor	ITT not used; "clinicians and study participants were not blind to treatment in the COMB and CBT arms, which undoubtedly affected not only efficacy, but also safety outcomes"
March et al, 2004[15]	Yes	Yes	Yes	Good	Allocation concealment method and fidelity to CBT protocol not reported; all other ratings indicated high quality
Mufson et al, 1999[22]	Yes	Yes	Yes	Poor	High attrition and differential attrition; LOCF analysis of mostly control patients likely to underestimate their natural improvement over the course of time and therefore result in type 1 error.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

CBT, cognitive behavioral therapy; COMB, combination; ITT, intent to treat; KQ, key question; LOCF, last observation carried forward; MDD, major depressive disorder; N/A, not applicable; NR, not reported.

Appendix D Table 27. Quality Ratings of Included RCTs Examining the Harms of Collaborative Care in Treating MDD in Children and Adolescents (KQ 6) (Part 1)

First Author, Year	Was eligibility criteria described clearly?	Was inclusion/exclusion criteria measured using valid/reliable measures, implemented across all study participants?	Was symptom status determined using valid/ reliable methods?	Was randomization adequate?	Was allocation concealment adequate?	Did strategy for recruiting differ across study groups?
Richardson et al, 2014[25]	Yes	Yes	Yes	Yes	NA	No

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 28. Quality Ratings of Included RCTs Examining the Harms of Collaborative Care in Treating MDD in Children and Adolescents (KQ 6) (Part 2)

First Author, Year	Did start of follow-up and start of intervention coincide?	Were baseline characteristics similar between groups? If not, did the analysis control for differences?	Were outcome assessors blinded?	Was intervention fidelity adequate?	Did variation from the study protocol compromise conclusions?
Richardson et al, 2014[25]	Yes	Yes	Yes	NR	No

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 29. Quality Ratings of Included RCTs Examining the Harms of Collaborative Care in Treating MDD in Children and Adolescents (KQ 6) (Part 3)

First Author, Year	Overall attrition	Did high attrition raise concern for bias?	Was analysis conducted on ITT basis?	Did the study have cross-overs or contamination raising concern for bias?	Were outcomes pre-specified/defined and adequately described?	Were outcome measures valid/ reliable?
Richardson et al, 2014[25]	7%	No	Yes	No	Yes	Yes

ITT, intent to treat; KQ, key question; MDD, major depressive disorder; NA, not applicable.

Appendix D Table 30. Quality Ratings of Included RCTs Examining the Harms of Collaborative Care in Treating MDD in Children and Adolescents (KQ 6) (Part 4)

First Author, Year	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Richardson et al, 2014[25]	Yes	Yes	Yes	Good	Just under 80% attrition at 6 month f/u and less than that at 12 month f/u?

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

CBT, cognitive behavioral therapy; COMB, combination; ITT, intent to treat; KQ, key question; LOCF, last observation carried forward; MDD, major depressive disorder; N/A, not applicable; NR, not reported.

Appendix D Table 31. Quality Ratings of Included RCTs Examining the Harms of SSRIs in Combination With Psychotherapy in Treating MDD in Children and Adolescents (KQ 6) (Part 1)

First Author, Year	Was eligibility criteria described clearly?	Was inclusion/exclusion criteria measured using valid/reliable measures, implemented across all study participants?	Was symptom status determined using valid/ reliable methods?	Was randomization adequate?	Was allocation concealment adequate?	Did strategy for recruiting differ across study groups?
March et al, 2004[15]	Yes	Yes	Yes	Yes	NR	No
Emslie et al, 2006[26]	Yes	Yes	Yes	Yes	NR	No

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 32. Quality Ratings of Included RCTs Examining the Harms of SSRIs in Combination With Psychotherapy in Treating MDD in Children and Adolescents (KQ 6) (Part 2)

First Author, Year	Did start of follow-up and start of intervention coincide?	Were baseline characteristics similar between groups? If not, did the analysis control for differences?	Were outcome assessors blinded?	Was intervention fidelity adequate?	Did variation from the study protocol compromise conclusions?
March et al, 2004[15]	Yes	Yes	Yes	NR	No
Emslie et al, 2006[26]	Yes	NR	NR	NR	No

KQ, key question; MDD, major depressive disorder; NR, not reported.

Appendix D Table 33. Quality Ratings of Included RCTs Examining the Harms of SSRIs in Combination With Psychotherapy in Treating MDD in Children and Adolescents (KQ 6) (Part 3)

First Author, Year	Overall attrition	Did high attrition raise concern for bias?	Was analysis conducted on ITT basis?	Did the study have cross-overs or contamination raising concern for bias?	Were outcomes pre-specified/defined and adequately described?	Were outcome measures valid/ reliable?
March et al, 2004[15]	18%	No	Yes	No	Yes	Yes
Emslie et al, 2006[26]	NA--attrition not assessed (all observations were taken)	No	No	No	Yes	Yes

ITT, intent to treat; KQ, key question; MDD, major depressive disorder; N/A, not applicable.

Appendix D Table 34. Quality Ratings of Included RCTs Examining the Harms of SSRIs in Combination With Psychotherapy in Treating MDD in Children and Adolescents (KQ 6) (Part 4)

First Author, Year	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
March et al, 2004[15]	Yes	Yes	Yes	Good	Allocation concealment method and fidelity to CBT protocol both not reported but all other ratings indicated high quality
Emslie et al, 2006[26]	Yes	No	No	Poor	ITT not used; "clinicians and study participants were not blind to treatment in the COMB and CBT arms, which undoubtedly affected not only efficacy, but also safety outcomes"

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.
Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

CBT, cognitive behavioral therapy; COMB, combination; ITT, intent to treat; KQ, key question; MDD, major depressive disorder.

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Appendix E Table 1. Evidence Table for Screening Accuracy for MDD in Children and Adolescents (KQ 2)

First Author, Year Funder	Setting	Prevalence of Depression	Number of Patients (CONSORT-Type Numbers) Exclusions (# and Reason)	Patient Characteristics	Primary Screening Test Characteristics	Reference/Gold Standard
Canals et al, 2001[1] Canals et al, 1997[2] Canals et al, 1995[3] Funder: Fondo de Investigación Sanitaria (FIS 94/0866), Ministerio de Sanidad y Consumo	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)
Garrison et al, 1991[4] Garrison et al, 1990[5] Funder: NIMH	Location: Middle and high schools in southeastern metropolitan school district; United States 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
Johnson et al, 2002[6] Funder: Aaron Diamond Foundation, Hibbard E. Williams	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	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	Mean age: 15.9 (SD 1.2) Female: 63.3% Ethnicity: 77.2% White 4.2% African American 12.4% Hispanic	Test: PHQ-A Screening cutoff: NR - used "diagnostic algorithm"	Diagnostic interview with mental health professional

Appendix E Table 1. Evidence Table for Screening Accuracy for MDD in Children and Adolescents (KQ 2)

First Author, Year Funder	Setting	Prevalence of Depression	Number of Patients (CONSORT-Type Numbers) Exclusions (# and Reason)	Patient Characteristics	Primary Screening Test Characteristics	Reference/Gold Standard
Research Fund, University of California, Davis School of Medicine, Pfizer US Pharma-ceuticals	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)		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)	SES: NR Risk factors: NR		
Patton et al, 1999[7] Funder: Victorian Health Promotion Foundation and the Australian Rotary Health Research Fund.	Location: Schools in Victoria, Australia; students of government, catholic, and independent schools Target population: 45 schools selected with probability proportional to number of year 9 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

Appendix E Table 1. Evidence Table for Screening Accuracy for MDD in Children and Adolescents (KQ 2)

First Author, Year Funder	Setting	Prevalence of Depression	Number of Patients (CONSORT-Type Numbers) Exclusions (# and Reason)	Patient Characteristics	Primary Screening Test Characteristics	Reference/Gold Standard
Roberts et al, 1991[8] Funder: NIMH	Study Design: Test/Retest Location: High schools in west-central Oregon, United States 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 8.1% Nonwhite 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 E Table 1. Evidence Table for Screening Accuracy for MDD in Children and Adolescents (KQ 2)

First Author, Year	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Other Performance Characteristics	USPSTF Quality Score	Applicability
Canals et al, 2001[1] Canals et al, 1997[2] Canals et al, 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 8 years after original sample more likely to be female, parents have higher levels of education and SES, but probably not problematic enough to disqualify.
Garrison et al, 1991[4] Garrison et al, 1990[5]	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
Johnson et al, 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

Appendix E Table 1. Evidence Table for Screening Accuracy for MDD in Children and Adolescents (KQ 2)

First Author, Year	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Other Performance Characteristics	USPSTF Quality Score	Applicability
Patton et al, 1999[7]	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
Roberts et al, 1991[8]	Overall BDI: 83.7 CESD: 83.7 (Current MDD) Serial Screens Females BDI: 63.60 CESD: 63.60 Males BDI: 61.50 CESD: 84.60 Parallel Screens Females BDI: 87.90 CESD: 90.90 Males BDI: 92.30 CESD: 92.30	Overall BDI: 80.9 CESD: 75.2 (Current MDD) Serial Screens Females BDI: 87.40 CESD: 90.80 Males BDI: 96.00 CESD: 92.70 Parallel Screens Females BDI: 72.30 CESD: 70.70 Males BDI: 86.00 CESD: 73.70	Overall BDI: 10.2 CESD: 8.0 (Current MDD) Serial Screens Females BDI: 17.10 CESD: 21.90 Males BDI: 22.20 CESD: 17.70 Parallel Screens Females BDI: 11.50 CESD: 11.20 Males BDI: 10.90 CESD: 6.10	Overall BDI: 99.5 CESD: 99.4 (Current MDD) Serial Screens Females BDI: 98.30 CESD: 98.40 Males BDI: 99.30 CESD: 99.70 Parallel Screens Females BDI: 99.30 CESD: 99.50 Males BDI: 99.80 CESD: 99.80	Overall: NR Males BDI:.93 CESD:.87 Females BDI:.83 CESD: .83	Fair	Fair. Only 61% of recruited youth participated

AUC, area under the curve; BDI, Beck Depression Inventory; calc, calculated; CAS, Child Assessment Schedule; CESD, Center for Epidemiologic Studies Depression Scale; CESD-C, Center for Epidemiologic Studies Depression Scale for Children; CI, confidence interval; CIDI, Composite International Diagnostic Interview; CIS-R, Clinical Interview Schedule-Revised; KQ, key question; K-SADS, Kiddie-Schedule for Affective Disorders and Schizophrenia; MDD, major depressive disorder; NIMH, National Institutes of Health; NR, not reported; PHQ-A, Patient Health Questionnaire for Adolescents; SD, standard deviation; SES, socio-economic status.

Appendix E Table 2. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year USPSTF Quality Funder	Setting	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention Characteristics	Outcomes	Other Treatments (e.g. Antidepressants; Measured, Not Reported, etc.)
Emslie et al., 2009[9] Fair Funder: Forest Laboratories	Study design: RCT Location: 40 sites in the US Selection method: recruitment method not reported	Inclusion: Outpatients 12 -17 years, met diagnostic criteria for MDD; score ≥45 on the CDRS-R at screening and baseline, patient and parental consent; parent's attendance at study visits. Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children--Present and Lifetime, CGI-S score >=4, Kaurman Brief Intelligence Test score >=80; normal physical examination, lab tests and ECG at screening. Negative serum b-human chorionic gonadotropin pregnancy test (females with childbearing potential), caregiver capable of providing information about patient's condition. Family support to guarantee adequate safety monitoring.	Mean Age: 14.6 Female: 58.97 Ethnicity: White: 75.64% Nonwhite: 24.36% Previous and/or ongoing secondary psychiatric disorders: 14.74% Top 3 secondary psychiatric disorders: (1) ADD/ADHD, (2) Enuresis, (3) generalized anxiety disorder Recurrent MDD: 28.85	IG (n = 126): Escitalopram (Flexible dose 10 mg/day to 20 mg/day), 8 weeks CG (n=133): Placebo, 8 weeks	Depression Outcomes: CDRS-R score, CGI-I score, CGAS Measurement method: Clinician rated measures were assessed by a blinded assessor at baseline, weeks 2, 4, 6, and 8 Definition of response: CGI-I <2, ≥40% reduction in CDRS-R score Definition of Remission: CDRS score ≤28 Other outcomes: Adverse events; MCSSRS; suicide behavior, suicide ideation	16.67% Treated with antidepressants previously 61.54% Nonresponders of those previously treated
March et al, 2004[10] Kennard et al, 2006[11] Vitiello et al, 2006[12] Fluoxetine vs. Placebo Good	Study design: RCT Location: US; 13 academic and community clinics Selection method: Recruited from	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,	Mean Age: 14.6 (1.5) Female: 54.4% Ethnicity White: 73.8% Black: 12.5 Hispanic: 8.9%	IG (n=109): Six 20-30 minute medication visits over 12 weeks. Flexible dosing schedule depending on CGI-S score and ascertainment of clinically significant adverse events.	Depression outcomes: CDRS-R score; CGI-I score; RADS; Suicidal Ideation Questionnaire-Junior High School Version, remission, loss of MDD diagnosis;	Excluded concurrent treatment with psychotropic medication or psychotherapy outside study

Appendix E Table 2. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year USPSTF Quality Funder	Setting	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention Characteristics	Outcomes	Other Treatments (e.g. Antidepressants; Measured, Not Reported, etc.)
Funder: NIMH	clinics, advertisements, primary care and mental health clinicians; schools and juvenile justice facilities	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.	Psychiatric comorbidities Any psychiatric comorbidity: 52.06% Anxiety: 27.40% Disruptive behavior: 23.46% OCD: 2.73% ADHD: 13.67%	Dose started at 10 mg/day and adjusted to 20 mg/day in week 1 and, if necessary, up to 40 mg/day in week 8. 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	CDRS-R ≤28 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: CGAS, PQ-LES-Q, HoNOSCA, Adverse Events, suicide-related AEs, psychiatric-related AEs, non-psychiatric-related AEs	
Wagner et al, 2004[13] Fair Funder: Forest Pharmaceuticals	Study Design: RCT Location: US, 21 hospital, academic, and research centers Selection method: Provided assent and parents	Inclusion: Outpatients 7–17 years; primary diagnosis of MDD for at least 4 weeks, with a CDRS-R score ≥40. Diagnosis established at initial screening visit though use of K-SADS-PL and semi-structured diagnostic interview to assess MDD. Patients with normal results at screening from physical examination, laboratory tests, and electrocardiography were included. Exclusion: Primary psychiatric diagnosis other than MDD, any	Age: 12.12 Female: 53.45% Ethnicity White: 77.01% Nonwhite: 22.99% Psychiatric comorbidities Dysthymia: 3.45% Enuresis: 4.01%	IG (n=89): Citalopram (Flexible dose 20 to 40 mg/day), 8 weeks CG (n=85): Placebo	Depression Outcomes: CDRS, CGI Measurement method: Double blind at weeks 1, 2, 4, 6, and 8 weeks Definition of response or remission:	Excluded concurrent treatment with psychotropic medication or psychotherapy outside study Previously treated with antidepressants: 19.02 History of nonresponse: 15.49

Appendix E Table 2. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year USPSTF Quality Funder	Setting	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention Characteristics	Outcomes	Other Treatments (e.g. Antidepressants; Measured, Not Reported, etc.)
	provided consent. Patients' legal guardian was required to accompany the patient to each study visit.	psychotic features, any personality disorder, or met DSM-IV criteria for ADHD, PTSD, bipolar disorder, mental retardation, conduct disorder, or oppositional defiant disorder. History of anorexia nervosa, bulimia, or substance abuse, including alcohol, within the past year. In females, pregnancy, and not using adequate contraception. Initiation of psychotherapy or behavioral therapy during the study or 3 months before the screening visit were not enrolled. Severe suicidal ideation requiring inpatient treatment; previous treatment with and failure of antidepressant or anxiolytic medication, antipsychotic or stimulant; concomitant treatment with certain prescriptions or over-the-counter medications, including any psychotropic drug; or concurrent psychotherapy were excluded.	Previous ADHD: 2.87% Current ADHD: 0%		Response defined as CDRS ≤28 Other outcomes: Adverse events	
Wagner et al, 2006[14] Fair Funder: Abbott Laboratories, AstraZeneca, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson, Organon, Pfizer, and NIMH	Study design: RCT Location: US, 25 sites Selection method: Provided assent and parents provided consent. Patients' legal guardian was also required to accompany the patient to each study visit.	Inclusion: Outpatients 6–17 years; primary diagnosis of MDD for at least 4 weeks, with a CDRS-R score ≥40. Diagnosis established at initial screening visit though use of K-SADS-PL and semi-structured diagnostic interview to assess MDD. Patients with normal results at screening from physical examination, laboratory tests, and electrocardiography were included. Exclusion: Primary psychiatric diagnosis other than MDD, any psychotic features, any personality disorder, or met DSM-IV criteria for ADHD, post-traumatic stress disorder, bipolar disorder, mental retardation, conduct disorder, or oppositional defiant disorder. A history of anorexia nervosa,	Mean Age: 12.3 (SD, 3.0) Female: 51.9% Ethnicity: Caucasian:71.2% African American: 13.6% Asian: 1.1% Other: 14.0% Psychiatric comorbidities: Comorbid anxiety disorders: 6.1%	IG (n=131): Escitalopram fixed dose (10 mg/day for first 4 weeks) Flexible dose (10 to 20 mg/day based on clinical response and tolerability) CG (n=133): Placebo	Depression outcomes: CDRS-R, CGI-I, CGI-S, CGAS Measurement method: Double blind at weeks 1, 2, 4, 6, and 8 weeks Definition of response or remission: Response defined as CDRS ≤28 and CGI-I ≤2	Excluded concurrent treatment with psychotropic medication or psychotherapy outside study

Appendix E Table 2. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year USPSTF Quality Funder	Setting	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention Characteristics	Outcomes	Other Treatments (e.g. Antidepressants; Measured, Not Reported, etc.)
		bulimia, or substance abuse, including alcohol, within the past year. In females, pregnancy, lactation, and not using adequate contraception. Initiation of psychotherapy or behavioral therapy during the study or 3 months before the screening visit were not enrolled. Severe suicidal ideation requiring inpatient treatment; previous treatment with and failure of antidepressant or anxiolytic medication (within 2 weeks of baseline, 4 weeks for fluoxetine), antipsychotic or stimulant (6 months before screening); concomitant treatment with certain prescriptions or over-the-counter medications, including any psychotropic drug; or concurrent psychotherapy were excluded.			Other outcomes: Adverse events	

Appendix E Table 2. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year	Attrition	Response (Dichotomous Measure)	Response (Continuous Measure)	Other Outcomes	Other Outcomes Adverse Events	Subgroup Analyses Conducted
Emslie et al, 2009[9]	17%	CDRS-R ≤28 IG: 41.6 (64) CG: 35.7 (56) p = 0.15 CGI ≤2 IG: 64.3% (99) CG: 52.9% (83) p = 0.03	CDRS-R Change (ITT, LOCF) LSM (SEM) IG: -22.1 (1.22) CG: -18.8 (1.27) LSMD (95% CI) -3.356 (-6.226 to -0.486)	Suicidal tendency IG: 1 CG: 1 Hospitalizations IG: 4 CG: 1 MCSSRS (worsening suicidal behavior) IG: 2 CG: 3 MCSSRS (increase in suicidal ideation) IG: 12 CG: 12 SIQ-JR (Mean change) IG: -4.6 (12.0) CG: -2.9 (10.2) Any suicidal behavior and/or ideation IG: 13 (10.2%) CG: 12 (9.2%) Serious (>5%) Inflicted injury IG: 2 CG: 0 Irritability IG: 1 CG: 0 Aggravated depression IG: 0 CG: 1	Discontinuation due to adverse events IG: 4 CG: 1 Patients reporting adverse events IG: 121 (78.1%) CG: 118 (75.2%) Serious adverse events IG: 4 CG: 2 Death from suicide or other causes IG: 0 CG: 0 Difference(s) between Groups: d=0 Weight Gain IG: 1.2 CG: 1.2 Most frequent (%) Inflicted injury IG: 9.0 CG:13.4 Pharyngitis IG: 8.4 CG: 9.6 Fatigue IG: 7.7 CG: 8.3	None

Appendix E Table 2. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year	Attrition	Response (Dichotomous Measure)	Response (Continuous Measure)	Other Outcomes	Other Outcomes Adverse Events	Subgroup Analyses Conducted
Emslie et al, 2009[9] (cont'd)				Most frequent (%) Headache IG: 25.2 CG: 25.5 Menstrual cramps IG:10.9 CG: 15.2 Insomnia IG: 10.3 CG: 6.4 Nausea IG: 10.3 CG: 8.3 Abdominal pain IG: 9.0 CG: 7.0	Influenza-like symptoms IG:7.1 CG:3.2 Rhintis IG:7.1 CG:8.9 Vomiting IG:6.5 CG:5.7 Diarrhea IG:5.2 CG:3.2 Upper respiratory tract infection IG:5.2 CG:7.6 Most frequent (%) Appetite decrease IG:2.6 CG: 3.8 Urinary tract infection IG: 2.6 CG: 0.6 Coughing IG:1.3 CG: 4.5	

Appendix E Table 2. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year	Attrition	Response (Dichotomous Measure)	Response (Continuous Measure)	Other Outcomes	Other Outcomes Adverse Events	Subgroup Analyses Conducted
March et al, 2004[10] Kennard et al, 2006[11] Vitiello et al, 2006[12] Fluoxetine vs. Placebo	Attrition: 18% overall 14% Flu+ CBT 17% Flu 22% CBT 21% CG	CGI ≤2 IG: 60.6% (95% CI, 51 to 70) CG: 34.8% (95% CI, 26 to 44) p=0.001 CGAS >60 at 12 wks IG: 50.5% CG: 35.7% p=0.23 CDRS-R ≤28 at 12 wks IG: 23% CG: 17% p>0.05 OR, 1.5 (95% CI, 0.74 to 2.88) Loss of MDD Diagnosis at 12 wks IG: 78.6 % CG: 60.4% OR, 2.4 (95% CI, 1.27 to 4.67)	CDRS-R pre, wk6, wk12 IG: 58.9 (4.0), 39.8 (7.4), 36.3 (8.1) CG: 61.2 (4.3), 44.9 (7.3), 41.8 (8.0) p=0.10 RADS pre, wk6, wk12 IG: 77.0 (9.6), 63.4 (12.4), 60.6 (13.1) CG: 81.3 (9.2), 69.4 (10.9), 66.7 (11.4) p=0.34 CGAS mean change at 12 weeks IG: 12.6 CG: 10.2 p=0.0381	HoNOSCA Mean change at 12 wks IG: -5.7 CG: -5.5 p=0.5861 PQ-LES-Q Mean change at 12 wks IG: 6.3 CG: 5.7 p=0.7215	Suicidal Ideation Questionnaire pre, wk6, wk12 IG: 21.8 (15.7), 16.2 (12.4), 14.4 (11.1) CG: 24.2 (16.5), 16.9 (11.7), 15.0 (11.1) p=0.36 Harm- and suicide-related adverse events: CBT vs. Placebo Harm-related: IG: 13 (11.93%) CG: 6 (5.36%) OR, 2.39 (95% CI, 0.87 to 6.54) Suicide-related: IG: 9 (8.26%) CG: 4(3.57%) OR, 2.43 (95% CI, 0.73 to 8.14) Psychiatric adverse events: IG: 23 (21%) CG: 11 (9.8%)	None
Wagner et al, 2004[13]	Overall: 19%	CDRS-R ≤28 IG: 36% CG: 24% p<0.05 CGI ≤2 IG: 47% CG: 45%	CDRS-R score IG vs. CG, p<0.05 (presented in graphic) CDRS-R effect size week 8 = 2.9 (LOCF)	None	Discontinuation due to AE IG: 5.6% CG: 5.9% No SAE observed No suicide	None

Appendix E Table 2. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year	Attrition	Response (Dichotomous Measure)	Response (Continuous Measure)	Other Outcomes	Other Outcomes Adverse Events	Subgroup Analyses Conducted
			CGI severity change IG: -1.3 CG: -1.0 p not reported LOCF		Occurred with a frequency >5% Rhinitis IG: 13.5% CG: 5.9% Nausea IG: 13.5% CG: 3.5% Abdominal pain IG: 11.2% CG: 7.1% Influenza-like symptoms IG: 6.7% CG: 0.0% Fatigue IG: 5.6% CG: 1.2% Diarrhea IG: 5.6% CG: 1.2% Back pain IG: 5.6% CG: 3.5%	
Wagner et al, 2006[14]	Overall: 19%	CGI-I ≤2 IG: 63% CG: 52% p=0.14 CDRS-R ≤28 IG: 46% CG: 38% p=0.32	CDRS-R change (LOCF) IG: -21.9 CG: -20.2 p=0.31 CGI-S change (LOCF) IG: -1.6 CG: -1.3 p=0.057	CGI-I mean week 8 IG: 2.3 CG: 2.5 p=0.169 CGAS change (LOCF) IG: 15.6 CG: 12.7 p=0.065	Adverse events Overall IG: 68.7% (90) CG: 67.7% (90) p=0.90 Serious adverse events IG: 37.4% of events CG: 32% of events	Post hoc analyses adjusting for age group in 12 to 17 sample for CGI-S, CGI-I, and CGAS changes using LOCF N=77/80 CDRS-R change IG: -20.1 CG: -17.5 p=0.23

Appendix E Table 2. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year	Attrition	Response (Dichotomous Measure)	Response (Continuous Measure)	Other Outcomes	Other Outcomes Adverse Events	Subgroup Analyses Conducted
					Suicide-related events IG: 1 CG: 2	CGI-S change IG: -1.5 CG: -1.0 p=0.02
					Headache IG: 22.9% CG: 21.8%	CGI-I change IG: 2.4 CG: 2.8 p=0.04
					Abdominal pain IG: 10.7% CG: 5.3%	CGAS change IG: 15.7 CG: 10.0 p=0.005
					Nausea IG: 7.6% CG: 4.5%	Changes for kids ages 6-11 were not significant
					Accidental injury IG: 6.9% CG: 7.5%	N=52/52 CDRS change IG: -24.0 CG: -23.5 p=0.87
					Rhinitis IG: 6.1% CG: 6.0	CGI-S change IG: -1.7 CG: -1.7 p=0.64
					Pharyngitis IG: 5.3% CG: 6.0%	CGI-I change IG: 2.2 CG: 2.1 p=0.78
					Upper respiratory tract infection IG: 5.3% CG: 6.0%	CGAS change IG: 15.0 CG: 16.8 p=0.49
					Vomiting IG: 5.3% CG: 3.8%	

ADD, attention deficit disorder; ADHD, attention deficit/hyperactivity disorder; AE, adverse event; CBT, cognitive-behavioral therapy; CDR-S-R, Children's Depression Rating Scale-Revised; CG, control group; CGAS, Children's Global Assessment Scale; CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; CI, confidence interval; Flu, fluoxetine; HoNOSCA, Health of the Nation Outcome Scales for Children and Adolescents; IG, intervention group; ITT, intent to treat; KQ, key question; K-SADS, Kiddie-Schedule for Affective Disorders and Schizophrenia; LOCF, last observation carried

Appendix E Table 2. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Treating MDD in Children and Adolescents (KQs 5 and 6)

forward; LSM, least square mean; LSMD, least squares mean difference; MDD, major depressive disorder; MCSSRS, Modified Columbia Suicide Severity Rating Scale; n, sample size; NIMH, National Institutes of Health; NA, not applicable; NR, not reported; OCD, obsessive compulsive disorder; OR, odds ratio; PQ-LES-Q, Pediatric Quality of Life Questionaire; PTSD, posttraumatic stress disorder; RADS, Reynolds Adolescent Depression Scale; RCT, randomized control trial; SAE, serious adverse events; SD, standard deviation; SIQ-JR, Suicide Ideation Questionnaire-Junior High School version; SSRI, selective serotonin reuptake inhibitor; US, United States; wk, week.

Appendix E Table 3. Evidence Table of RCTs Examining the Benefits and Harms of Psychotherapy in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year USPSTF Quality Funder	Setting	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention Characteristics	Outcomes	Other Treatments (e.g. Antidepressants; Measured, Not Reported, etc.)
Clarke et al, 1999[15] Fair NIMH	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 or 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); 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	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	Excluded if receiving other treatment for depression and unwilling to discontinue
March et al, 2004[10] Kennard et al, 2006[11] Vitiello et al, 2006[12] Good Funder: NIMH	Study design: RCT Location: US; 13 academic and community clinics Selection method: Recruited from clinics,	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),	Mean Age: 14.6 (1.5) Female: 54.4% Ethnicity White: 73.8% Black: 12.5% Hispanic: 8.9% Psychiatric comorbidities	IG (n=111): Individual CBT; 15, 50- to 60-minute sessions over 12 weeks; includes 2 parent-only sessions and 1 to 3 combined parent-adolescent sessions depending on need CG (n=112): Placebo pill; adjusted starting dose 10 to 40 mg/d, with clinical	Depression outcomes: CDRS-R score; dichotomized CGI-I score; RADS; Suicidal Ideation Questionnaire-Junior High School Version, remission, loss of MDD diagnosis and CDRS-R ≤28 Measurement method: Clinician-rated measures	Excluded concurrent treatment with psychotropic medication or psychotherapy outside study

Appendix E Table 3. Evidence Table of RCTs Examining the Benefits and Harms of Psychotherapy in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year USPSTF Quality Funder	Setting	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention Characteristics	Outcomes	Other Treatments (e.g. Antidepressants; Measured, Not Reported, etc.)
	advertisements, primary care and mental health clinicians; schools and juvenile justice facilities	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.	Any psychiatric comorbidity: 52.06% Anxiety: 27.40% Disruptive behavior: 23.46% OCD: 2.73% ADHD: 13.67%	management (6 physician visits lasting 20 to 30 minutes to monitor clinica status and medication effects and offer general encouragement about the effectiveness of pharmacotherapy)	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: CGAS, PQ-LES-Q, HoNOSCA, Adverse Events, suicide-related AEs, psychiatric-related AEs, non-psychiatric-related AEs 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 (harm-related AEs, suicide-related AEs, psychiatric-related AEs, non-psychiatric-related AEs	

Appendix E Table 3. Evidence Table of RCTs Examining the Benefits and Harms of Psychotherapy in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year USPSTF Quality Funder	Setting	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention Characteristics	Outcomes	Other Treatments (e.g. Antidepressants; Measured, Not Reported, etc.)
Richardson et al, 2014[16] Good Funder: NIH	Study design: RCT Location: US, 9 pediatric and family care clinics in Washington State Selection method: Recruited from pediatric and family care clinics in Washington State	Inclusion: Outpatients 13-17 years old, met MDD criteria on the Kiddie-Structured Interview for Affective Disorders and Schizophrenia or had a second positive PHQ-9 with a CDRS-R score of ≥ 42. Exclusion: Non-English speaking, suicidal plan or recent attempt, bipolar, drug/alcohol misuse (CRAFFT score ≥5), seeing a psychiatrist, and developmental delay. Adolescents taking antidepressants or receiving psychotherapy who were still symptomatic were eligible to participate.	Mean Age: 15.1 Female: 72% Ethnicity White: 69% Nonwhite: 31% Psychiatric comorbidities Brief Screen for Child Anxiety and Related Emotional Disorders (SCARED) ≥3: 72%	IG (n=50): ROAD, adapted collaborative care intervention based on the IMPACT Team Care model. Included developmentally sensitive materials and structured involvement of adolescent and parent in the initial education and engagement session, the choice of treatment, and follow-up contacts. Delivered by master's level clinicians, 12 months. CG (n=51): Usual Care, 12 months	Depression Outcomes: CDRS-R, PHQ-9 Measurement method: Blinded research assistants at 6 and 12 months Definition of response or remission: Response defined as ≥50% reduction in CDRS-R, Remission defined as <5 on PHQ-9 Other outcomes: Functional Status, CIS; Quality of Care, Adverse events	Undergoing active treatment at start of study: 17% Treated for depression/anxiety in prior 6 months: 39% Antidepressants used in 6 months prior to baseline: 25% Counseling for depression/anxiety in prior 6 months: 38%

Appendix E Table 3. Evidence Table of RCTs Examining the Benefits and Harms of Psychotherapy in Treating MDD in Children and Adolescents (KQs 5 and 6)

Study Reference USPSTF Quality	Attrition	Response (Dichotomous Measure)	Response (Continuous Measure)	Other Outcomes	Other Outcomes Adverse Events	Subgroup Analyses conducted
Clarke et al, 1999[15] Fair NIMH	22% overall 18% CBT 24% CBT + parent 25% WL	**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 to 4.59) Trend for treated males to have better outcomes than treated females (81.0% vs. 60.4%, p=0.096)	**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	Not reported	None
March et al, 2004[10] Kennard et al, 2006[11] Vitiello et al, 2006[12]	Overall: 18%	CGI ≤2 IG: 43.2% (95% CI, 34 to 52) CG: 34.8% (95% CI, 26 to 44) p=0.20 CGAS >60 at 12 wks IG: 45.0% CG: 35.7% p=0.139 CDRS-R ≤28 at 12 wks IG: 16% CG: 17% p >0.05 OR, 0.9 (95% CI, 0.44 to 1.88) Loss of MDD Diagnosis at 12	CDRS-R pre, wk6, 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, wk6, 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 CGAS mean change at 12 wks IG: 10.0 CG: 10.2 p=0.3805	HoNOSCA mean change at 12 wks IG: -4.6 CG: -5.5 p=0.3344 PQ-LES-Q mean change at 12 wks IG: 4.2 CG: 5.2 p=0.4630	Suicidal Ideation Questionnaire pre, wk6, 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: IG: 5 (4.5%) CG: 6 (5.4%) OR, 0.83 (95% CI, 0.25 to 2.81) Suicide-related: IG: 5 (4.5%)	None

Appendix E Table 3. Evidence Table of RCTs Examining the Benefits and Harms of Psychotherapy in Treating MDD in Children and Adolescents (KQs 5 and 6)

Study Reference USPSTF Quality	Attrition	Response (Dichotomous Measure)	Response (Continuous Measure)	Other Outcomes	Other Outcomes Adverse Events	Subgroup Analyses conducted
		wks IG: 61.1% CG: 60.4% OR, 1.0 (95% CI, 0.52 to 1.77)			CG: 4 (3.6%) OR, 1.27 (95% CI, 0.33 to 4.87) Psychiatric adverse events IG: 1 (panic attack) CG: 11 (9 patients)	
Richardson et al, 2014[16]	Overall: 6.9%	≥50 reduction CDRS-R IG: 67.6% (95% CI, 52.2% to 83.0%) CG: 38.6% (95% CI, 23.7% to 53.5%) Remission at 12 months IG: 50.4% (95% CI, 34.7% to 66.1%) CG: 20.7% (95% CI, 8.2% to 33.2%) IG more likely to achieve remission at 6 months (OR, 5.2 [95% CI, 1.6 to 17.3]; p=0 .007) and 12 months (OR, 3.9 [95% CI, 1.5 to 10.6]; p=0.007)	CDRS-R Score IG Baseline: 48.3 (95% CI, 45.5% to 51.0%) IG 12 months: 27.5 (95% CI, 23.8% to 31.1%) CG Baseline: 46.0 (95% CI, 43.1% to 48.9%) CG 12 months: 34.6 (95% CI, 30.6% to 38.6%) 8.5 greater decrease in IG mean CDRS-R from baseline than control (95% CI, -13.4% to -3.6%, p=0.001) at 6 months 9.4 greater decrease in IG mean CDRS-R from baseline than control (95% CI, -15% to -3.8%, p=0.001) at 12 months	CIS (Functional Status) Between group mean difference at 6 months: -4.4 (95% CI, -8.4% to -0.5%, p=0.03) Between group mean difference at 12 months: -4.3 (95% CI, -8.3% to -0.3%; p=0.04)	Adverse events Psychiatric hospitalization (# of patients) IG: 3 CG: 2 Emergency department visits (# of patients) IG: 1 CG: 5	None

ADD, attention deficit disorder; ADHD, attention deficit/hyperactivity disorder; AE, adverse event; CBT, cognitive-behavioral therapy; CDRS-R, Children's Depression Rating Scale-Revised; CG, control group; CGI-I, Clinical Global Impressions-Improvement; CI, confidence interval; CIS, Columbia Impairment Scale; HoNOSCA, Health of the Nation Outcome Scales for Children and Adolescents; IG, intervention group; KQ, key question; MDD, major depressive disorder; n, sample size; NIH, National Institutes of Health; NIMH, National Institute of Mental Health; OCD, obsessive compulsive disorder; PHQ-9, Patient Health Questionnaire 9-item; PQ-LES-Q, Pediatric Quality of Life Questionnaire; RADS, Reynolds Adolescent Depression Scale; RCT, randomized control trial; SD, standard deviation; SIQ-JR, Suicide Ideation Questionnaire-Junior High School version; SSRI, selective serotonin reuptake inhibitor; US, United States; wk, week.

Appendix E Table 4. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Combination With Psychotherapy in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year USPSTF Quality Funder	Setting	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention Characteristics	Outcomes	Other Treatments
March et al, 2004[10] Kennard et al, 2006[11] Vitiello et al, 2006[12] Combined Fluoxetine+CBT vs. Placebo Good Funder: NIMH	Study design: RCT (n = 109 in combined fluoxetine+CBT group; 112 in placebo control group) Location: US; 13 academic and community clinics Selection method: Recruited from clinics, advertisements, 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.	Mean Age: 14.6 (1.5) Female: 54.4% Ethnicity White: 73.8% Black: 12.5 Hispanic: 8.9% Psychiatric comorbidities Any psychiatric comorbidity: 52.06% Anxiety: 27.40% Disruptive behavior: 23.46% OCD: 2.73% ADHD: 13.67%	IG (n=109): all components from both fluoxetine and CBT group. CBT functionally independent of medication management; protocols for administering medication and CBT functionally independent for all medication increases other than those depending on presence o partial response; when partial response was present, the pharmacotherapist consulted CBT therapist re: AE profile when considering whether to adjust dose of fluoxetine. CG (n=112): Placebo pill; adjusted starting dose 10 to 40 mg/d, with clinical management (6 physician visits lasting 20-30 minutes to monitor clinica 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, remission, loss of MDD diagnosis 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: CGAS, PQ-LES-Q, HoNOSCA, Adverse Events, suicide-related AEs, psychiatric-related AEs, non-psychiatric-related AEs	Excluded concurrent treatment with psychotropic medication or psychotherapy outside study

Appendix E Table 4. Evidence Table of RCTs Examining the Benefits and Harms of SSRIs in Combination With Psychotherapy in Treating MDD in Children and Adolescents (KQs 5 and 6)

First Author, Year USPSTF Quality	Attrition	Response (Dichotomous Measure)	Response (Continuous Measure)	Other Outcomes	Other Outcomes Adverse Events	Subgroup Analyses Conducted
March et al, 2004[10] Kennard et al, 2006[11] Vitiello et al, 2006[12] Combined Fluoxetine+ CBT vs. Placebo	Overall: 18%	CGI ≤2 IG: 71% (95% CI, 62 to 80) CG: 34.8% (95% CI, 26 to 44) p=0.001 CGAS >60 at 12 wks IG: 64.5% CG: 35.7% p=0.0001 CDRS-R ≤28 at 12 wks IG: 37% CG: 17% P=0.0009 OR, 3.0 (95% CI, 1.58 to 5.79) Loss of MDD Diagnosis at 12 wks IG: 85.3% CG: 60.4% OR, 4.1 (95% CI, 2.00 to 8.44)	CDRS-R pre, wk6, wk12 IG: 60.8 (4.9), 38.1 (7.8), 33.8 (8.2) CG: 61.2 (4.3), 44.9 (7.3), 41.8 (8.0) p=0.001 RADS pre, wk6, wk12 IG: 80.1 (9.2), 60.9 (11.6), 57.0 (12.2) CG: 81.3 (9.2), 69.4 (10.9), 66.7 (11.4) p=0.001 CGAS mean change at 12 wks IG; 16.6 CG: 10.2 p<0.0001	HoNOSCA Mean change at 12 wks IG: -7.2 CG: -5.5 (5.71) P=0.0393 PQ-LES-Q Mean change at 12 wks IG: 12.2 CG: 5.7 P=0.001	Suicidal Ideation Questionnaire pre, wk6, wk12 IG: 27.3 (18.5), 14.3 (12.6), 11.8 (11.7) CG: 24.2 (16.5), 16.9 (11.7), 15.0 (11.1) p=0.02 Harm- and suicide-related adverse events: CBT vs. Placebo Harm-related: IG: 9 (8.4%) CG: 6 (5.4%) OR, 1.62 (95% CI, 0.56 to 4.72) Suicide-related: IG: 6 (5.6%) CG: 4 (3.6) OR, 1.60 (95% CI, 0.44 to 5.85) Psychiatric adverse events: IG: 16 (12 patients) CG: 11 (9 patients)	None

ADD, attention deficit disorder; ADHD, attention deficit/hyperactivity disorder; AE, adverse event; CBT, cognitive-behavioral therapy; CDR-S-R, Children's Depression Rating Scale-Revised; CG, control group; CGI-I, Clinical Global Impressions-Improvement; HoNOSCA, Health of the Nation Outcome Scales for Children and Adolescents; IG, intervention group; KQ, key question; MDD, major depressive disorder; n, sample size; NIMH, National Institutes of Health; OCD, obsessive compulsive disorder; PQ-LES-Q, Pediatric Quality of Life Questionnaire; RADS, Reynolds Adolescent Depression Scale; RCT, randomized control trial; SD, standard deviation; SIQ-JR, Suicide Ideation Questionnaire-Junior High School version; SSRI, selective serotonin reuptake inhibitor; US, United States; wk, week.

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Appendix F. Ongoing Trials

Principal Investigators	Location	Population	Approximate Size	Investigations	Outcomes	Status as of 2015
Greg N Clarke, PhD	US	12-18 with diagnosis of MDD	240	CBT vs. TAU	Recovery of response from the index episode of major depression Improvements in continuous depression symptomatology Depression response Rates of new, recurrent episodes of MDD Improvement in psychosocial function Clinical improvements Reduction in depression-related dysfunction	Study completed: January 2014. Publication in progress.
Mathijs Lucassen, PhD	New Zealand	7-14 with a diagnosis of anxiety, depression, trauma-related symptoms or disruptive behaviour	400	MATCH-ADTC vs. UC	Child Health Utlitity (CHU9D) Development and Well-Being Assessment (DAWBA) Strengths and Difficulties Questionaire (SDQ) Top Problems Assessment (TPA)	Recruiting participants until October 2015. Estimated study completion date not provided.
Barry Wright, MD	United Kingdom	12-18 with low mood/depression	48	CBT vs. Behavioral Self-help websites	Short Beck Depression Inventory Mood and Feelings Questionnaire Spence Children's Anxiety Scale Health status (EQ-5D-Y and HUI2)	Estimated study completion date: May 2016.

CBT, cognitive-behavioral therapy; MATCH-ADTC, Modular Approach to Therapy for Children; MDD, major depressive disorder; TAU, treatment as usual; UC, usual care; US, United States; vs., versus.