

# Screening for Child and Adolescent Depression in Primary Care Settings: A Systematic Evidence Review for the US Preventive Services Task Force

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## ABSTRACT

**CONTEXT.** Depression among youth is a disabling condition that is associated with serious long-term morbidities and suicide.

**OBJECTIVE.** To assess the health effects of routine primary care screening for major depressive disorder among children and adolescents aged 7 to 18 years.

**METHODS.** Medline, the Cochrane Central Registry of Controlled Trials, PsycInfo, the Cochrane Database of Systematic Reviews, recent systematic reviews, experts, and bibliographies from selected studies were the data sources. The studies selected were fair- and good-quality (on the basis of US Preventive Services Task Force criteria) controlled trials of screening and treatment (selective serotonin reuptake inhibitor and/or psychotherapy), diagnostic accuracy studies, and large observational studies that reported adverse events. Two reviewers quality-graded each article. One reviewer abstracted relevant information into standardized evidence tables, and a second reviewer checked key elements.

**RESULTS.** We found no data describing health outcomes among screened and unscreened populations. Although the literature on diagnostic screening test accuracy is small and methodologically limited, it indicates that several screening instruments have performed fairly well among adolescents. The literature on treatment efficacy of selective serotonin reuptake inhibitors and/or psychotherapy is also small but includes good-quality randomized, controlled trials. Available data indicate that selective serotonin reuptake inhibitors, psychotherapy, and combined treatment are effective in increasing response rates and reducing depressive symptoms. Not all specific selective serotonin reuptake inhibitors, however, seem to be efficacious. Selective serotonin reuptake inhibitor treatment was associated with a small absolute increase in risk of suicidality (ie, suicidal ideation, preparatory acts, or attempts). No suicide deaths occurred in any of the trials.

**CONCLUSIONS.** Limited available data suggest that primary care-feasible screening tools may accurately identify depressed adolescents and treatment can improve depression outcomes. Treating depressed youth with selective serotonin reuptake inhibitors may be associated with a small increased risk of suicidality and should only be considered if judicious clinical monitoring is possible. *Pediatrics* 2009;123:e716–e735

**M**AJOR depressive disorder (MDD) is a debilitating condition that has been increasingly recognized among youth, particularly adolescents. The prevalence of current or recent depression among children is 3% and among adolescents is 6%.<sup>1</sup> The lifetime prevalence of MDD among adolescents may be as high as 20%.<sup>2–4</sup> Adolescent-onset MDD is associated with an increased risk of death by suicide, suicide attempts, and recurrence of major depression by young adulthood.<sup>5–7</sup> MDD is also associated with early pregnancy, decreased school performance, and impaired work, social, and family functioning during young adulthood.<sup>6–8</sup> Despite the significant public health burden of MDD, studies have indicated that the majority of depressed youth do not receive any type of treatment.<sup>9–11</sup>

Mass screening in primary care could help clinicians identify missed cases and increase the proportion of depressed children and adolescents who initiate appropriate treatment. It could also help clinicians to identify cases earlier in the course of disease. Depression-screening tools have been developed that are feasible for use in primary care settings.<sup>12</sup> Current, reliable data describing screening practices for pediatric depression, however, are not available. In

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### Key Words

depression, primary care, screening, treatment, children, adolescents

### Abbreviations

MDD—major depressive disorder  
 SSRI—selective serotonin reuptake inhibitor  
 FDA—Food and Drug Administration  
 USPSTF—US Preventive Services Task Force  
 KQ—key question  
 DARE—Database of Abstracts of Reviews of Effects  
 CDSR—Cochrane Database of Systematic Reviews  
 AHRQ—Agency for Healthcare Research and Quality  
 PHQ-A—Patient Health Questionnaire for Adolescents  
 BDI-PC—Beck Depression Inventory-Primary Care Version  
 SDQ—Strengths and Difficulties Questionnaire  
 RCT—randomized, controlled trial  
 CI—confidence interval  
 RD—risk difference  
 SRE—suicide-related adverse event  
 RR—relative risk  
 TADS—Treatment for Adolescents With Depression Study  
 CBT—cognitive behavioral therapy  
 IPT-A—interpersonal psychotherapy for adolescents  
 CCRCT—Cochrane Collaboration Registry of Clinical Trials

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1 study from the past decade, providers in community health centers reported screening 64% of patients but documented screening for only 3%.<sup>13</sup> Providers in a health maintenance organization estimated screening an average of 46% of their patients.<sup>14</sup> These data, however, may overestimate how often primary care clinicians actually screen for depression among pediatric populations. Data based on direct observation or provider and/or patient report after specific clinical encounters would be more reliable.

For mass screening to be effective, it would be necessary for delivered treatments to be effective in improving patients' depression and alleviating suffering more quickly than no treatment. Trials demonstrating the efficacy of drug treatments and time-limited psychotherapies among pediatric populations were first published during the 1990s.<sup>15</sup> Presently, fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is the only pharmacologic agent that the US Food and Drug Administration (FDA) has approved for the treatment of pediatric MDD. In 2004, however, the FDA released a black-box warning about suicidality and antidepressant use in pediatric patients. There have been numerous subsequent publications discussing this issue, including the publication of the findings from the FDA meta-analyses evaluating risk of suicidality among 4582 pediatric patients treated with antidepressants.<sup>16</sup>

Among depressed youth identified in primary care, the majority seem to start treatment.<sup>17–19</sup> During 1998, for example, 69.7% of youth with visits in primary care for newly identified episodes of depression were either seen by a mental health specialist or received 1 or more dispensings of psychotropic medication in a health maintenance organization during the subsequent 30 to 90 days.<sup>17</sup> Similarly, data from the National Ambulatory Medical Care Survey (NAMCS) and the outpatient component of the National Hospital Ambulatory Medical Care Survey (NHAMCS) showed that of adolescent primary care visits in which depression was reported, antidepressants were prescribed 52% of the time, and 68% of the visits included psychotherapy or counseling.<sup>18</sup>

In 2002, the US Preventive Services Task Force (USPSTF) concluded that there was insufficient evidence to recommend for or against routine screening of children or adolescents for depression (I recommendation).<sup>20</sup> At the time of that review, no controlled trials of screening among child or adolescent populations were available.<sup>15</sup> Likewise, relatively few studies of diagnostic accuracy, particularly in primary care settings or among children, were available. Furthermore, only 2 trials of SSRIs among pediatric patients with MDD had been published. Our objective was to systematically assess the evidence on screening for MDD among average-risk child and adolescent primary care populations to assist the USPSTF in updating its 2002 recommendation. We have summarized the evidence for the benefits and harms of screening, the accuracy of primary care–feasible screening tests, and the benefits and risks of treating depression by using psychotherapy and/or SSRIs among patients aged 7 to 18 years. The Oregon Evidence-Based Practice Center conducted the review, and the full evidence report is

available at [www.preventiveservices.ahrq.gov](http://www.preventiveservices.ahrq.gov). This article summarizes the report's findings.

## METHODS

We developed an analytic framework (Fig 1) and 5 key questions (KQs), by using USPSTF methods<sup>21</sup>, to guide our literature search. For all KQs, we searched for systematic reviews, meta-analyses, and evidence-based guidelines on depression screening, treatment, or associated harms in children and adolescents in the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews (CDSR), Medline, and PsycINFO from 1998 to May 2006. We also conducted a series of literature searches through May 2007 for each KQ (detailed in Appendix 1) and reviewed the search results for applicability to all KQs. Articles were also obtained from outside experts and through reviewing bibliographies of other relevant articles and systematic reviews. In addition to these searches for published trials, we searched pharmaceutical company and federal agency trial registries for unpublished trials of SSRIs. All searches were limited to articles in English. Inclusion and exclusion criteria specific to each question are detailed in Appendices 2 and 3.

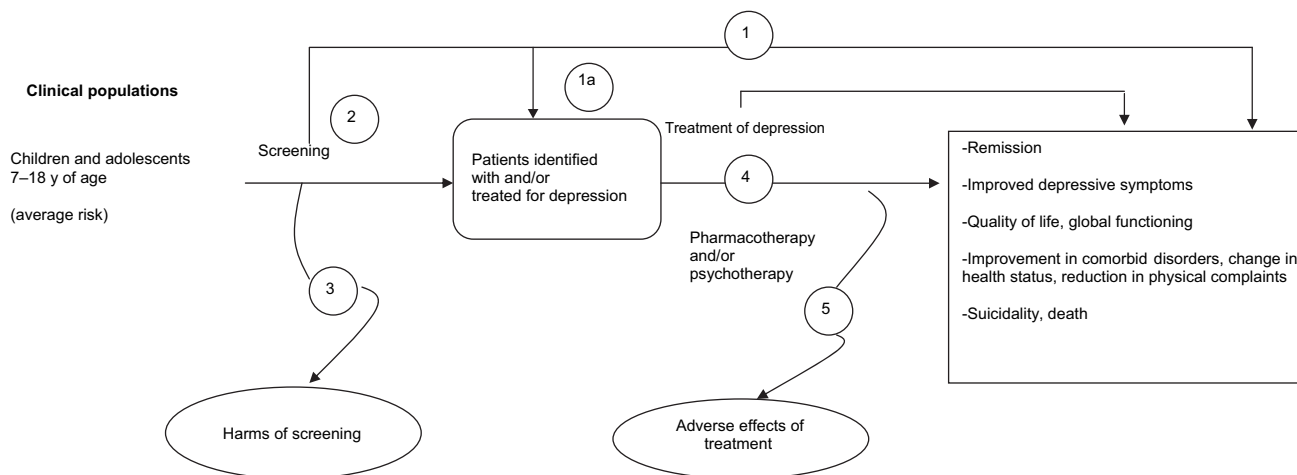
Two investigators independently reviewed all abstracts for KQs 4 and 5. The initial search for KQs 1 through 3 produced a very high yield (3418 abstracts). Therefore, we used a modified approach to reviewing these abstracts as described in Appendix 2. Two investigators evaluated abstracts against a set of inclusion/exclusion criteria, including independent review using design-specific quality criteria based on the USPSTF methods, supplemented by National Institute for Health and Clinical Excellence<sup>22</sup> criteria for quality of systematic reviews (Appendix 4). Two investigators critically appraised all studies excluded for quality reasons. Data from included studies were abstracted into evidence tables by 1 investigator and checked by another investigator. Details of our quantitative synthesis approach and rationale are described in detail in Appendix 2. We identified numerous recent systematic evidence reviews relevant to our KQs.<sup>16,23–40</sup> Our approach to incorporating these reviews is described in Appendix 2.

We worked with 4 USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and KQs and to resolve issues around scope and approach. Research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. AHRQ staff provided oversight for the project, including reviewing the draft report and assisting in the external review of the draft evidence synthesis.

## RESULTS

### KQ1: Does Screening for Depression Among Children and Adolescents in the Primary Care Setting Improve Health Outcomes?

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



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

1. Does screening for depression among children and adolescents in the primary care setting improve health outcomes?
- 1a. Does screening increase the proportion of patients identified with and/or treated for depression?
2. Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?
3. What are the harms of screening?
4. Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?
5. What are the adverse effects of treatment?

FIGURE 1  
Analytic framework.

#### KQ1a: Does Screening Increase the Proportion of Patients Identified With and/or Treated for Depression?

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

#### KQ2: Are Depression-Screening Instruments for Children and Adolescents Accurate in Identifying Depression in Primary Care or School-Based Clinics?

The overall body of evidence describing the accuracy of depression-screening instruments for children and adolescents is limited both in quantity and quality. Available evidence applies mostly to adolescents. We identified 9 relevant fair-quality studies<sup>4,41-51</sup> that reported the accuracy of 6 different depression-screening instruments (Table 1). Two of the studies were conducted in primary care or school-based health clinics, 1 study was conducted in a community sample, and 6 were conducted in school population samples (not through school health clinics). Most studies restricted study samples to adolescents aged 12 years or older.

The performance characteristics of screening tests were quite varied across the studies. Sensitivity ranged from 18% to 100%, and specificity ranged from 38% to 97%. This wide variation may be a result of the large number of instruments that was tested and the great amount of heterogeneity across the populations included. The multiple differences between trials (including lack of replicating results for most of the tools studied) make generalizations difficult. Another important

limitation is that all studies had methodologic flaws, including nonrandom selection, excessive delays between screening and diagnostic interviews, high levels of attrition, poor reporting of methods or attrition, small samples, or using a less-than-ideal reference standard. No single study stood out as being of good quality.

Sensitivity in the 2 primary care studies<sup>41,42</sup> ranged from 73% for the Patient Health Questionnaire for Adolescents (PHQ-A) to 91% for the Beck Depression Inventory-Primary Care Version (BDI-PC). Specificity ranged from 91% (BDI-PC) to 94% (PHQ-A). The prevalence of MDD among the 2 study samples was 9% to 11%, yielding positive predictive values of 56% for both tests and negative predictive values of 97% to 99% in these 2 primary care samples. Because both studies examined only adolescents, no information was found that is directly applicable to screening younger children presenting to primary care.

Studies that involved younger children tended to have poorer performance.<sup>43,49,50</sup> The single study that involved a community sample reported sensitivities ranging from 33% to 63% for the Strengths and Difficulties Questionnaire (SDQ), examining various combinations of child, parent, and teacher report with 2 different age ranges. The 33% sensitivity in the SDQ for child-only report in those aged 11 to 15 years improved to 63% when both parent and child reports were used. Sensitivity for those aged 5 to 10 years (parent report only) was 53%.

**TABLE 1 Depression Screening Instrument Accuracy Summary for Current MDD (KQ2)**

Study	No. Completing Screen and Diagnostic Interview	Instrument	Age, Range or Mean, y	Sensitivity, %	Specificity, %	PPV, %	NPV, %	USPSTF Study Quality <sup>a</sup>
Primary care samples								
Johnson et al <sup>41</sup> (2002)	241 <sup>c</sup>	PHQ-A-positive	13–18	73	94	56	97	Fair
Winter et al <sup>42</sup> (1999) <sup>b</sup>	100	BDI-PC ≥ 4	12–17	91	91	55.6	98.8	Fair
Community samples								
Goodman et al <sup>43</sup> (2003)	7984	SDQ-positive	5–10	54 (p)	NR	NR	NR	Fair
			11–15	33 (c)	NR	NR	NR	
			11–15	44 (p)	NR	NR	NR	
			11–15	63 (c and p)	NR	NR	NR	
School samples								
Canals et al <sup>44–46</sup> (2001, 1997, and 1995)	290	BDI ≥ 11	17–18	90	86	20	99.5	Fair
		BDI ≥ 16		90	96	47	99.6	
Barrera and Garrison-Jones <sup>47</sup> (1988) <sup>b</sup>	49	BDI ≥ 11	12–17	100	77	NR	NR	Fair
		BDI ≥ 16		100	93	NR	NR	
Whitaker et al <sup>4</sup> (1990) <sup>b</sup>	356	BDI ≥ 16	14–17	77	65	NR	NR	Fair
Roberts et al <sup>48</sup> (1991) <sup>b</sup>	1704	BDI ≥ 11	16.6	84	81	10	99.5	Fair
		CES-D ≥ 24		84	75	8	99	
Garrison et al <sup>49,50</sup> (1991 and 1990) <sup>b</sup>	332	CES-D ≥ 22	11–15	18 (male)	83 (male)	9	NR	Fair
				83 (female)	77 (female)	25	NR	
		CES-D ≥ 12	11–15	85 (male)	49 (male)	13	NR	
				84 (female)	38 (female)	11	NR	
Patton et al <sup>51</sup> (1999)	170	CIS-R-positive	15.7	18	97	49	91	Fair

p indicates parent; c, child; NR, not reported; CES-DC, Center for Epidemiological Studies-Depression Scale for Children; CES-D, Center for Epidemiological Studies-Depression Scale; CIS-R, Revised Clinical Interview Schedule.

<sup>a</sup> USPSTF quality criteria are described in Appendix 4.

<sup>b</sup> Included in the 2002 USPSTF report.<sup>20</sup>

<sup>c</sup> Four-hundred three patients completed screen and diagnostic interviews, but 162 patients were excluded because of a time lag between screen and interview.

### KQ3: What Are the Harms of Screening?

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

### KQ4: Does Treatment of Depression (SSRIs and/or Psychotherapy) Among Screen-Detected Children and Adolescents Identified in Primary Care or Comparable Populations Improve Health Outcomes?

We identified 18 fair- or good-quality randomized, controlled trials (RCTs) that reported health outcomes among children or adolescents with MDD treated with SSRIs,<sup>52–65</sup> psychotherapy,<sup>55–58,66–74</sup> or both an SSRI and psychotherapy<sup>55–58</sup> (Table 2). These trials evaluated the short-term efficacy of 5 different SSRIs against placebo-control conditions, 10 different group or individually delivered psychotherapies compared with control conditions, and combined therapy (cognitive behavioral psychotherapy and an SSRI). Two of these trials were conducted in community or school-based clinical settings (both good-quality RCTs),<sup>55,72</sup> and the remainder were conducted in academic research centers or in schools. The majority (6 of 9) of SSRI trials included children as young as 8 years old in their study samples. In contrast, the majority of trials that tested psychotherapy interventions included only adolescents aged 12 to 14 years and older. Only 2 psychotherapy trials included 9- or 10-year-olds, and no completed trials included children aged 7 or 8 years.

Nine of the SSRI or psychotherapy trials were rated as good quality according to USPSTF criteria, and 9 were of

fair quality. Good-quality trials typically used a multi-gated screening procedure, including a clinical assessment, to identify depressed participants, measured outcomes through blinded clinical assessments (and often also self-reported depression symptoms), and analyzed intention-to-treat populations, most often by using LOCF (last-observation-carried-forward) data to replace missing values. Depression outcomes were reported after 8 to 12 weeks of SSRI treatment or 4 to 16 weeks of psychotherapy. No controlled data were available for longer-term outcomes. The definition of treatment response differed among trials.

Across the 9 SSRI trials, response rates among treatment and placebo groups varied considerably. Of the patients in treatment groups, 36% to 69% met response criteria at postintervention follow-up, compared with 24% to 59% of patients in placebo-control groups. We calculated that the pooled absolute risk difference (RD) in the response rate between treatment and intervention groups was 12% (95% confidence interval [CI]: 7–16; random-effects analysis) for the 9 SSRI trials, indicating higher response rates among those treated with SSRIs (Fig 2). When considering individual SSRIs, fluoxetine and citalopram both yielded statistically significant higher response rates. Data from meta-analyses of efficacy among children and adolescents analyzed separately in a recent systematic review by Bridge et al<sup>26</sup> in 2007 suggested that overall, SSRIs were less effective among children. When restricting the analysis to only fluoxetine trials, however, results were similar for both

**TABLE 2 Characteristics of RCTs of Depression Treatment in Children and Adolescents (KQ4)**

Reference	Intervention	Age Range, y	No. of Patients Randomly Assigned	Length of Intervention, wk	Response Criteria	Response Rate		Risk Difference, % (95% CI) or P	USPSTF Quality <sup>a</sup>
						Treatment Group	Control Group		
<b>SSRIs</b>									
Emslie et al <sup>52,54</sup> (1997)	IG: fluoxetine; CG: placebo	7–17	96	8	CG-I ≤ 2	27/48 (56%)	16/48 (33%)	23 (4 to 42)	Fair
Emslie et al <sup>53,54</sup> (2002)	IG: fluoxetine; CG: placebo	8–17	219	9	≥30% decrease in CDRS-R	71/109 (65%)	54/101 (54%)	12 (–2 to 25)	Fair
TADS <sup>55–58</sup> (2004)	IG1: fluoxetine; CG: placebo	12–17	221	12	CG-I ≤ 2	66/109 (61%)	39/112 (35%)	26 (13 to 39)	Good
Keller et al <sup>59</sup> (2001)	IG: paroxetine; CG: placebo	12–18	180 <sup>b</sup>	8	HAM-D ≤ 8 or ≥50% reduction from baseline	60/90 (67%)	48/87 (55%)	12 (–3 to 26)	Good
Berard et al <sup>60</sup> (2006)	IG: paroxetine; CG: placebo	13–18	286	12	≥50% decrease in MADRS	107/177 (61%)	53/91 (58%)	2 (–10 to 15)	Good
Emslie et al <sup>61</sup> (2006)	IG: paroxetine; CG: placebo	7–17	206	8	CG-I ≤ 2	49/101 (49%)	46/100 (46%)	3 (–11 to 16)	Good
Wagner et al <sup>62,63</sup> (2003) <sup>c</sup>	IG: sertraline; CG: placebo	6–17	376	10	≥40% decrease in adjusted CDRS-R	127/185 (69%)	105/179 (59%)		Good
Wagner et al <sup>64</sup> (2004)	IG: citalopram; CG: placebo	7–17	178	8	CDRS-R score ≤ 28	32/89 (36%)	20/85 (24%)	12 (–1 to 26)	Fair
Wagner et al <sup>65</sup> (2006)	IG: escitalopram; CG: placebo	6–17	268	8	CG-I ≤ 2	81/129 (63%)	69/132 (52%)	11 (–1 to 22)	Good
<b>Psychotherapy Interventions</b>									
Clarke <sup>66</sup> (1999)	IG1: group CBT; IG2: group CBT + parent; CG: waitlist	14–18	123	8	No longer meeting DSM-III-R criteria for 2 wk based on LIFE clinical interview	IG1: 24/37 (64.9%); IG2: 22/32 (68.8%)	13/27 (48.1%)	<.05 (IG1 and IG2 combined vs CG)	Good
Kahn and Kehle <sup>67</sup> (1990)	IG1: group CBT; IG2: group relaxation; IG3: individual self-modeling; CG: waitlist	10–14	68	6–8	Moved from dysfunctional to functional BID score	IG1: 13/17 (76%); IG2: 11/17 (65%); IG3: 10/17 (59%)	3/17 (18%)	NR	Fair
Lewinsohn <sup>68</sup> (1990)	IG1: group CBT; IG2: group CBT + parent; CG: waitlist	14–18	69	7	No longer meeting DSM-III-R criteria based on K-SADS-E	IG1: 42.9%; IG2: 47.6%	5.3%	<.01 (IG1 and IG2 combined vs CG)	Fair
Stark et al <sup>69</sup> (1987)	IG1: group self-control; IG2: group behavioral problem solving; CG: waitlist	9–12	29	5	CDI < 13	IG1: 7/9 (78%); IG2: 6/10 (60%)	1/9 (11%)	NR	Fair
Rosello <sup>70</sup> (1999)	IG1: individual IPT; IG2: individual CBT; CG: waitlist	13–17	71	12	CDI ≤ 17	IG1: 82%; IG2: 59%	NR	NR	Fair
Mufson <sup>71</sup> (1999)	IG1: individual IPT-A; CG: clinical monitoring	12–18	48	12	HRSD < 6 CGI-S	75%; 20/21 (95.5%)	46%; 7/11 (61.5%)	.04; <.001	Fair
Mufson et al <sup>72</sup> (2004)	IG1: individual IPT-A; CG: treatment as usual	12–18	64	16	HAMD ≤ 6	17/34 (50%)	10/29 (34%)	NR	Good
Diamond et al <sup>73</sup> (2002)	IG1: attachment-based family therapy; CG: waitlist	13–17	32	12	No longer meeting criteria for MDD on K-SADS-P	13/16 (81%)	7/15 (47%)	.04	Good
Ackerson <sup>74</sup> (1998)	IG1: cognitive bibliotherapy; CG: waitlist	14–18	30	4	NR	NR	NR	NA	Fair
TADS <sup>55–58</sup> (2004)	IG2: individual CBT; CG: placebo + clinical monitoring	12–17	223	12	CGI improvement score of 1 or 2	43.2% (95% CI: 34–52)	34.8% (95% CI: 26–44)	.20	Good
<b>Psychotherapy and SSRI</b>									
TADS <sup>55–58</sup> (2004)	IG3: individual CBT + fluoxetine; CG: placebo + clinical monitoring	12–17	209	12	CGI improvement score of 1 or 2	71% (95% CI: 62–80)	34.8% (95% CI: 26–44)		Good

IG indicates intervention group; CG, control group; CGI-I, Clinical Global Impression-Improvement Scale; CDRS-R, Children's Depression Rating Scale-Revised; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*; LIFE, Longitudinal Interval Follow-up Evaluation; BID, Bellevue Index of Depression; K-SADS-E, Kiddie-Schedule for Affective Disorders and Schizophrenia-Epidemiological edition; HRSD, Hamilton Rating Scale for Depression; CGI-S, Clinical Global Impression-Severity of Illness; NR, not reported; K-SADS-P, Kiddie-Schedule for Affective Disorders and Schizophrenia-Present Version.

<sup>a</sup> USPSTF quality criteria are described in Appendix 4.

<sup>b</sup> An additional 95 patients were randomly assigned to imipramine treatment.

<sup>c</sup> Two separate RCTs were pooled by study authors and reported in 1 publication.

Review : KQ4 SSRIs  
 Comparison: 01 SSRI vs placebo  
 Outcome: 01 Response rate

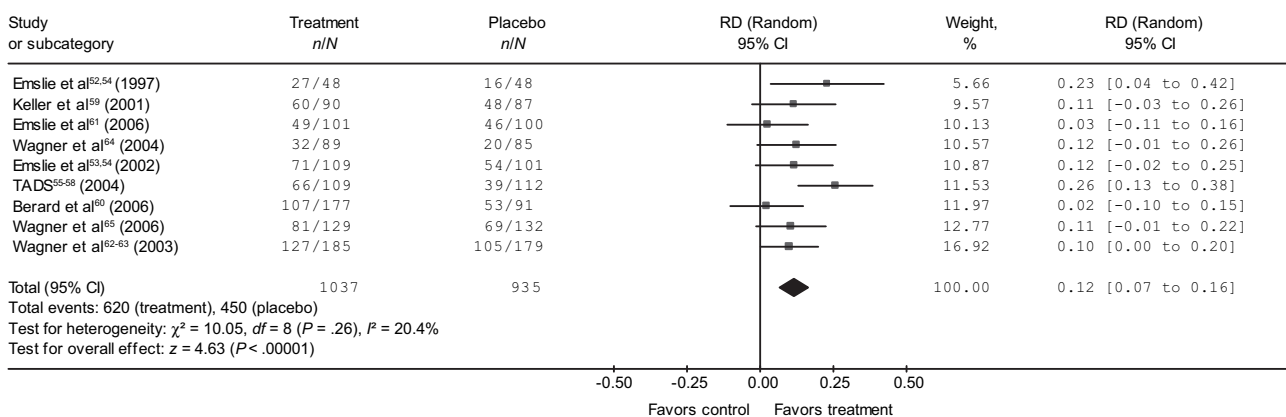


FIGURE 2  
 Response to SSRIs to treat MDD in RCTs including children and adolescents (KQ4).

children (RD: 21% [95% CI: 4–37]) and adolescents (RD: 20% [95% CI: 7–33]). These results were statistically significant for both groups.

Nine of the 10 psychotherapy trials found that treated patients had higher short-term response rates or a greater reduction in depression symptoms after interventions compared with a variety of control conditions. Two studies included children aged 9 or 10 years, and both reported that mean clinician-rated depression scores improved more among treated patients than control group patients. No trials included children aged 7 or 8 years.

One trial tested the effect of psychotherapy plus an SSRI (fluoxetine) compared with a placebo-control condition.<sup>55–58</sup> Among adolescents treated with the combination therapy, 71% (95% CI: 62–80) achieved response criteria compared with 34.8% (95% CI: 26–44) of placebo-control patients. This trial did not include any patients younger than 12 years.

#### KQ5: What Are the Adverse Effects of Treatment?

Data describing the adverse effects of SSRIs were available from the 9 RCTs included for KQ4, for which we calculated pooled absolute RDs for suicide-related adverse events (SREs) using data for a subset of trials included in the Bridge et al review.<sup>26</sup> SREs include suicidal ideation (ie, passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior), suicide attempts, or preparatory actions toward imminent suicidal behavior (eg, a person tries to hang himself or herself but is prevented from doing so by a family member). Data were also available from 4 other meta-analyses that calculated the pooled relative risk (RR) or RD of SREs on the basis of outcomes assessed by using blinded suicidology experts<sup>16,26,27</sup> or included other serious adverse events in addition to SREs.<sup>40</sup> In addition, data from large retrospective cohort or case-control studies provided observational data describing risk of suicidality, suicide death, and manic conver-

sion.<sup>75–78</sup> Previous systematic reviews and meta-analyses did not exclude trials on the basis of quality criteria, and some did not report any quality-rating procedure or results. In contrast, we were able to review published results from all currently completed trials and analyze them in detail by using our typical USPSTF quality-rating criteria. We excluded 2 SSRI trials because of poor methodologic quality.<sup>79,80</sup> Authors of previous reviews have also used varying inclusion and exclusion criteria (eg, MDD trials only, SSRIs only) and have used both fixed-effects and random-effects approaches to meta-analyses, as well as Bayesian methods of meta-analyses. The random-effects and Bayesian approaches assume additional sources of trial-related variation across studies and typically produce RR estimates that are smaller in magnitude and wider in CI. The FDA researchers used fixed-effects methods, validated by results of heterogeneity tests, to calculate the more conservative estimate. Meta-analyses also differed in terms of calculating RR or RD. The FDA analysis focused on RR and, therefore, could not include data from 4 trials (non-SSRI MDD trials) that did not include serious adverse-event outcomes in either group.

Most conservative estimates from the FDA analysis indicate that treating any pediatric population with antidepressants for any indication doubles the RR of a SRE (RR: 1.95 [95% CI: 1.28–2.98]).<sup>16</sup> The absolute RD between intervention and control populations in that report was 1% (95% CI: 1–2). Published meta-analyses did not report the pooled RD among SSRI trials for treating pediatric MDD, considering data from all currently available completed trials (including a recently published trial of escitalopram<sup>65</sup>). We calculated the pooled RD of those trials that were of at least fair or good quality and found an absolute RD of 1% (95% CI: 0–2; Fig 3). In total, even the most conservative estimates indicate that the risk of suicidality may increase absolutely by 1% or 2%. No suicide deaths occurred in any of the trials.

Review : KQ5 SSRIs  
 Comparison: 01 SSRI vs placebo  
 Outcome: 06 Suicidal ideation or behavior rate

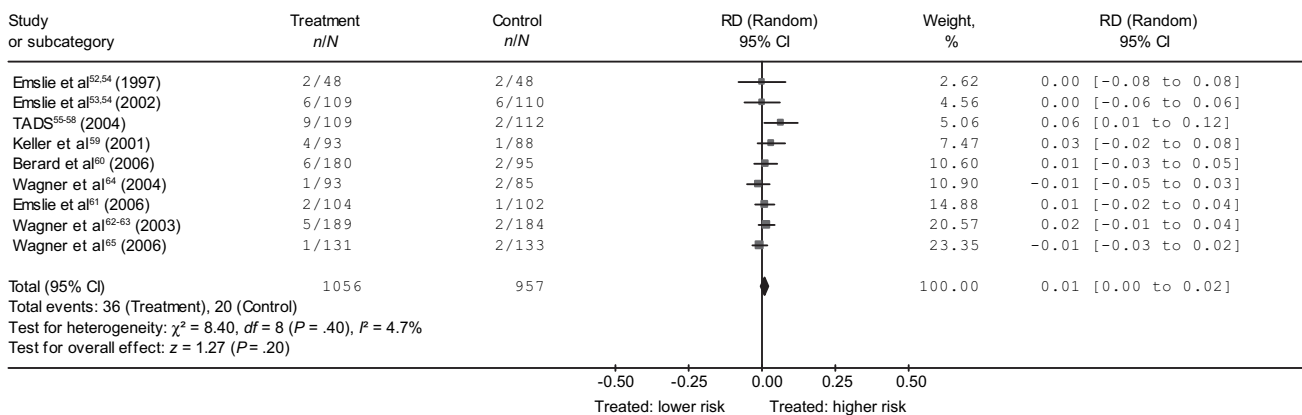


FIGURE 3  
 Suicidal ideation or behavior risk in children or adolescents treated with SSRIs for MDD (KQ5).

Data from observational studies have provided conflicting results regarding the relationship between antidepressant use and suicide attempts and death.<sup>75–77</sup> An important limitation of observational studies is the inability to control for confounding by the indication. One additional cohort study found that antidepressant use was associated with an increased risk of conversion from a unipolar depressive disorder to a bipolar disorder.<sup>78</sup>

The Treatment for Adolescents With Depression Study (TADS) was the only trial that reported adverse effects of combined SSRI and psychotherapy treatment.<sup>55,56</sup> The SRE rate among the cognitive behavioral therapy (CBT) plus fluoxetine group was 6% compared with 4% in the placebo-control group. Results were not statistically different, but the study was not designed to have power to detect a difference of this magnitude.

Results for all KQs are summarized in Table 3.

## DISCUSSION

We found no studies that directly examined the health outcomes of screening children and adolescents for depression. Therefore, we cannot say whether the use of systematic screening improves identification, treatment, and outcomes of depression over standard identification methods. Although some screening instruments seem to have better performance characteristics than others, it is difficult to say the degree to which differences are caused by the quality of the instrument or the characteristics of the population or study. None of the instruments have been studied in large numbers of patients from a variety of settings, including studies by investigators other than those who developed the questionnaires. Of primary importance to this review, 2 primary care studies reported sensitivities of 73% and 91% and specificities of 91% and 94% in instruments developed for primary care (the PHQ-A and BDI-PC). Both of these studies examined only adolescents, so no information was found that is directly applicable to younger children.

More data were reported in other settings using a variety of instruments, some including younger children (although most were at least 10 years old). In these studies, sensitivities ranged from 18% to 100% and specificities ranged from 38% to 97% and differed depending on what instrument, cutoff score, and informant source was used. Data describing the accuracy of using depression-screening instruments in younger children remain very limited. Only 1 study included children younger than 10 and reported generally poor sensitivity and did not report specificity. We found no studies that examined potential harms of systematic, standardized screening for depression in any setting. Theoretical harms are similar to those that have been discussed for suicide-screening programs.<sup>81</sup> Until systematic depression screening is tested in a controlled manner, however, actual harms to patients or costs to health care systems, relative to undetected and untreated depression, cannot be measured.

The quantity of efficacy data from RCTs of interventions to treat pediatric MDD is also quite limited, particularly when compared with the large body of evidence supporting efficacy among adults. Despite this limitation in quantity, however, good-quality RCTs have been conducted to test SSRIs and psychotherapies among pediatric populations and provide evidence that efficacious interventions are available, although long-term effects are not known. Meta-analyses have consistently found that fluoxetine is efficacious for treating pediatric populations. Fluoxetine has been studied among both children and adolescents aged 7 to 17 years and is the only drug that is approved by the FDA for treating MDD among youth. Available age-stratified meta-analysis results indicate that fluoxetine is efficacious for both children and adolescents. The absolute RD is ~20% for both age groups, which would mean that ~5 children or adolescents with MDD would need to be treated with fluoxetine for 1 to benefit. When combining data from trials of all SSRIs for treating MDD in youth, we found that patients treated with an SSRI were more likely to show a response to treatment than patients treated with

**TABLE 3 Summary of Evidence Quality According to KQ**

KQ	No. of Studies	Design	Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
1	None	—	—	—	—	—	—
1a	None	—	—	—	—	—	—
2	9	Screening accuracy studies using a valid reference standard	Younger ages poorly represented, majority of studies in school settings, few instruments examined in >1 study	Fair	Fair; 2 studies conducted in primary care settings, 1 in community setting, 6 in school settings	Fair	Two instruments demonstrated good sensitivity and specificity in primary care settings in adolescents; only 1 study (in a community setting) included children <10 y of age, and the majority included adolescents ≥12 y; the large number of instruments and heterogeneity in samples and settings makes generalization across studies difficult and may explain the wide range of performance characteristics reported (sensitivity ranged from 18% to 100% and specificity ranged from 38% to 97%)
3	None	—	—	—	—	—	—
4	9 SSRIs	RCTs	No long-term outcomes; trials excluded patients with many comorbid disorders	Fair	Fair; primarily conducted in research or specialty settings	Good (3 fair, 6 good)	SSRI users had higher response rates than those taking placebo medication, with an absolute RD between treatment and control groups of 12% (95% CI: 7–16); fluoxetine and citalopram both yielded statistically significant higher response rates; data from meta-analyses of efficacy among children and adolescents analyzed separately suggested that SSRIs were less effective among children
	Psychotherapy						
10	10	RCTs	No data for ages 7–8; limited data for ages 9–10; short-term outcomes only	Good	Fair; only 2 trials in community clinics	Fair (6 fair, 4 good)	Most of the psychotherapy trials found that treated patients had higher response rates or remission rates or a greater reduction in depression symptoms after interventions compared with a variety of different types of control conditions
	SSRI and psychotherapy combined						
1	1	RCT	Single study	NA	Good	Fair (1 good-quality RCT)	Combined fluoxetine and individual CBT group showed a response rate of 71% vs 35% in those taking placebo and receiving weekly clinical monitoring
5	17 SSRIs	RCTs, meta-analyses, cohort studies, case-control study	Inadequate power to assess suicidality	Fair	Fair	Fair	Even the most conservative estimates indicate that the risk of suicidality may increase absolutely by 1% or 2%
	Psychotherapy						
	None	—	—	—	—	—	—



placebo pills. These pooled results, however, must be interpreted with caution. Baseline response rates among placebo-treated patients were quite variable across the trials, and some individual SSRIs do not seem to be efficacious. Furthermore, not all SSRIs have been evaluated in pediatric clinical trials. One good-quality trial conducted in community clinics also evaluated combined therapy with fluoxetine plus individual CBT and found that nearly 3 of 4 patients responded to combined therapy, in contrast with only 1 in 3 who responded in the placebo group.<sup>55</sup> These results indicate that 2 to 3 adolescents would need to be treated with combined CBT plus fluoxetine therapy for 1 adolescent to benefit from the therapy. Results of psychotherapy trials indicate that a variety of psychotherapy types are efficacious among adolescents, including group CBT and interpersonal psychotherapy (IPT-A).

The most conservative estimates from the final results of the FDA analyses indicate that treating youth with antidepressants leads to a 2% absolute increase in risk of experiencing either suicidal ideation or behavior.<sup>16</sup> No suicide deaths occurred during these trials. When data are pooled for individual drugs, they have not yielded statistically significant increases in suicide-related outcomes. That lack of statistically significant effects, however, may be a result of lack of power. For fluoxetine, 6% (17 of 287) of treated patients and 4% (11 of 289) of placebo-control patients experienced either suicidal ideation or behavior during a trial, yielding an absolute RD of 2%. This result, however, was not statistically significant.

On the basis of the estimate of increased absolute risk of 2%, for 1 patient to develop suicidality attributable to antidepressant therapy, ~50 patients would need to be treated. Authors of several meta-analyses have argued that additional sources of heterogeneity must be incorporated to more accurately assess the true risk of either efficacy or harms. The FDA analyses used fixed-effects models to calculate RDs and risk ratios. In contrast, Bridge et al used a random-effects model that incorporated additional sources of within and between meta-analysis trial heterogeneity. They found that the absolute RD was 1% and that the number needed to harm was 112. In either case, available data indicate that a patient is more likely to benefit from treatment than to develop suicidality. Nevertheless, suicidality is an extremely serious condition and could translate, theoretically, into an increased risk of suicide death (current trial data are insufficient to address this issue). As a result, the overall balance of risk and benefit of treatment with antidepressants is not yet clear.

Data are also currently insufficient to determine the role of combined treatment (SSRI plus psychotherapy) on SREs. The TADS was the only RCT included in this review that evaluated combined therapy.<sup>55</sup> SREs were less common among patients treated with combined therapy (fluoxetine and CBT; 5.6%), compared with fluoxetine alone (8.3%) but more common than among patients in the placebo-control group (3.6%). These differences, however, were not statistically significant. The trial was not powered sufficiently to detect differences of

these magnitudes. Therefore, it is uncertain whether combined therapy would lead to a slight increase in suicidality compared with placebo if more data from larger numbers of patients were available. The additional TADS safety results reported by Emslie et al<sup>56</sup> in 2006 indicate that the suicidality results vary depending on how it is measured. Two recent comparative efficacy trials compared combined therapy with SSRI treatment alone, and neither found statistically significant differences between groups for suicidality measures.<sup>82,83</sup> The decision to treat an individual pediatric patient with an antidepressant should be based on the clinical situation and guidelines from mental health specialists. Thus, careful consideration must be given to how closely a patient will be able to be monitored, either through the clinical setting or at home, after initiating a therapy. Harms of psychotherapy have not been systematically reported in trials in the past. Recently, Bridge et al<sup>84</sup> highlighted the importance of assessing suicidality at baseline and during follow-up assessments in trials of psychotherapy.

This review focuses on MDD and does not address evidence to support screening or treatment for dysthymia, minor depression, or other psychiatric disorders in children and adolescents. Research addressing MDD in children and adolescents is less comprehensive than that for adults. Unlike the adult literature, no research has directly evaluated the benefits of screening for depression in children and adolescents in primary care. There is also a more limited volume of research on screening instruments, on pharmacologic or psychotherapeutic treatments, and on community treatment patterns in children and adolescents, compared with research in depressed adults. Research is particularly limited on screening instruments and treatments appropriate for children aged 10 years and younger.

There are many important areas that have not yet been studied. Future research in this area should include:

- large-scale RCTs (or well-controlled clinical trials) of primary care or health care system depression-screening programs documenting health outcomes, including harms, and rates of diagnosis and treatment initiation to guide clinicians in depression-screening programs for children and adolescents;
- descriptive epidemiologic studies describing the prevalence of MDD (diagnosed and undiagnosed, treated and untreated) in children and adolescents in primary health care settings according to age, gender, and race/ethnicity;
- trials comparing depression treatment adherence and outcomes (including benefits achieved and harms avoided or increased) from depression collaborative care management approaches compared with usual clinical care;
- analyses of predictors of treatment that may be relevant to the implementation and sustainability of interventions in primary care, such as patient treatment

preference or level of provider training needed for delivering effective interventions;

- comparative effectiveness of pharmacologic and non-pharmacologic treatments for MDD in children and adolescents, particularly those at high risk for suicidality or nonadherence to pharmacotherapy; and
- observational outcomes studies of risks for longer-term outcomes, including mania precipitation, with use of antidepressants, particularly SSRIs.

## CONCLUSIONS

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

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

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**APPENDIX 1 Search Strategies**

Systematic reviews and meta-analyses

Databases: DARE, the CDSR, Medline, PsycINFO, 1998–2006

1. Search “depression” or “depressive disorder” or “depression, postpartum” or “depressive disorder, major” or “dysthymic disorder” or “seasonal affective disorder”; limits, all child: 0–18 years, English, publication date from 1998–2006
2. Search 1 and systematic.sb
3. Search depression.ti.ab. or depressed.ti.ab. or depressive.ti.ab
4. Search child.ti.ab or children.ti.ab. or adolescen\*.ti.ab. or teen.ti.ab. or teens.ti.ab. or teenage\*.ti.ab.
5. Search 3 and 4
6. Search 5 and (publisher.sb. or in process.sb.)
7. Search 6 and systematic.sb.
8. Search 6 and (meta-analysis.ti.ab. or medline.ti.ab. or systematic\*.ti.ab. or search\*.ti.ab.)
9. Search 7 or 8
10. Search 7 or 8 limits: English, Publication date from 1998–2006
11. Search 2 or 10

Screening outcomes, screening accuracy, and screening adverse effects (KQs 1–3)

Databases: Medline, PsycINFO, Cochrane Central Register of Controlled Trials 1998–2006

1. Depressive disorder/
2. Depressive disorder, major/
3. Depression/
4. depress\$.ti.ab.
5. 1 or 2 or 3 or 4
6. Mass screening/
7. screen\$.ti.ab.
8. case finding.ti.ab.
9. casefinding.ti.ab.
10. child\$ depression inventory\$.ti.ab.
11. child\$ depression scale\$.ti.ab.
12. child\$ depression rating scale\$.ti.ab.
13. child\$ self-report rating scale\$.ti.ab.
14. “mood and feelings questionnaire\$.ti.ab.
15. reynold\$ child\$ depression.ti.ab.
16. reynold\$ adolesc\$ depression.ti.ab.
17. kutcher\$ adolesc\$.ti.ab.
18. “depression scale for children\$.ti.ab.
19. Beck Depression Inventory\$.ti.ab.
20. Center for Epidemiologic Studies Depression Scale\$.ti.ab.
21. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 5 and 21
23. Limit 22 to (“child [6 to 12 years]” or “adolescent [13 to 18 years]”)
24. children\$.ti.ab.
25. childhood.ti.ab.
26. teen.ti.ab.
27. teens.ti.ab.
28. teenage\$.ti.ab.
29. pediatric\$.ti.ab.
30. paediatric\$.ti.ab.
31. adolescen\$.ti.ab.
32. boys.ti.ab.
33. girls.ti.ab.
34. youth.ti.ab.
35. youths.ti.ab.
36. child.ti.ab.
37. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 22 and 37
39. 23 or 38
40. Limit 39 to English language
41. Limit 40 to year = “1998–2006”

**APPENDIX 1 Continued**

Treatment efficacy (KQ4)

Databases: Medline, PsycINFO, Cochrane Central Register of Controlled Trials SSRIs: 2004–2006; psychotherapy: 1998–2006

1. Depressive disorder/
2. Depressive disorder, major/
3. Depression/
4. depress\$.ti. or (depression or depressive or depressed).ab.
5. 1 or 2 or 3 or 4
6. Antidepressive agents, second-generation/
7. Serotonin uptake inhibitors/
8. Antidepressive agents/
9. antidepressant\$.ti.ab.
10. antidepressives.ti.ab.
11. antidepressive agent\$.ti.ab.
12. antidepressive drug\$.ti.ab.
13. selective serotonin reuptake inhibitor\$.ti.ab.
14. ssri.ti.ab.
15. ssris.ti.ab.
16. Fluoxetine/
17. fluoxetine.ti.ab.
18. prozac.ti.ab.
19. Fluvoxamine/
20. fluvoxamine.ti.ab.
21. luvox.ti.ab.
22. Paroxetine/
23. paroxetine.ti.ab.
24. paxil.ti.ab.
25. Sertraline/
26. sertraline.ti.ab.
27. zoloft.ti.ab.
28. Citalopram/
29. citalopram.ti.ab.
30. celexa.ti.ab.
31. escitalopram.ti.ab.
32. lexapro.ti.ab.
33. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. Psychotherapy/
35. Psychotherapy, brief/
36. Psychotherapy, group/
37. psychotherap\$.ti.ab.
38. Cognitive therapy/
39. (cognitive adj (therap\$ or treatment\$ or intervention\$)).ti.ab.
40. Behavior therapy/
41. (behavio\$ adj (therap\$ or treatment\$ or intervention\$)).ti.ab.
42. interpersonal therap\$.ti.ab.
43. interpersonal intervention\$.ti.ab.
44. Self-help groups/
45. self help.ti.ab.
46. Family therapy/
47. family support.ti.ab.
48. parent\$ education.ti.ab.
49. Parents/ed [education]
50. Counseling/
51. Directive counseling/
52. counsel\$.ti.ab.
53. Problem solving/
54. problem solving.ti.ab.
55. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56. 5 and 33
57. Limit 56 to year = “2004–2006”
58. 5 and 55
59. Limit 58 to year = “1998–2006”

**APPENDIX 1 Continued**

- 60. 57 or 59
- 61. Limit 60 to ("child [6 to 12 years]" or "adolescent [13 to 18 years]")
- 62. children\$.ti,ab.
- 63. child.ti,ab.
- 64. childhood.ti,ab.
- 65. teen.ti,ab.
- 66. teens.ti,ab.
- 67. teenage\$.ti,ab.
- 68. pediatric\$.ti,ab.
- 69. paediatric\$.ti,ab.
- 70. adolescen\$.ti,ab.
- 71. boys.ti,ab.
- 72. girls.ti,ab.
- 73. youth.ti,ab.
- 74. youths.ti,ab.
- 75. 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
- 76. 60 and 75
- 77. 61 or 76
- 78. Limit 77 to (clinical trial or controlled clinical trial or randomized, controlled trial)
- 79. Clinical trials/or controlled clinical trials/or randomized, controlled trials/
- 80. Double-blind method/or random allocation/or single-blind method/
- 81. random\$.ti,ab.
- 82. 79 or 80 or 81
- 83. 77 and 82
- 84. 78 or 83
- 85. Limit 84 to English language
- 86. Limit 85 to news
- 87. 85 not 86

## Treatment adverse effects (KQ5)

Databases: Medline, PsycINFO, Cochrane Central Register of Controlled Trials  
SSRIs: 2004–2006; Psychotherapy: 1990–2006

- 1. Depressive disorder/
- 2. Depressive disorder, major/
- 3. Depression/
- 4. depress\$.ti. or (depression or depressive or depressed).ab.
- 5. 1 or 2 or 3 or 4
- 6. Antidepressive agents, second-generation/
- 7. Serotonin uptake inhibitors/
- 8. Antidepressive agents/
- 9. antidepressant\$.ti,ab.
- 10. antidepressives.ti,ab.
- 11. antidepressive agent\$.ti,ab.
- 12. antidepressive drug\$.ti,ab.
- 13. selective serotonin reuptake inhibitor\$.ti,ab.
- 14. ssri.ti,ab.
- 15. ssris.ti,ab.
- 16. Fluoxetine/
- 17. fluoxetine.ti,ab.
- 18. prozac.ti,ab.
- 19. Fluvoxamine/
- 20. fluvoxamine.ti,ab.
- 21. luvox.ti,ab.
- 22. Paroxetine/
- 23. paroxetine.ti,ab.
- 24. paxil.ti,ab.
- 25. Sertraline/
- 26. sertraline.ti,ab.
- 27. zoloft.ti,ab.
- 28. Citalopram/
- 29. citalopram.ti,ab.
- 30. celexa.ti,ab.
- 31. escitalopram.ti,ab.
- 32. lexapro.ti,ab.

**APPENDIX 1 Continued**

- 33. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
- 34. 1 or 3 or 4
- 35. 33 and 34
- 36. Limit 35 to year = "2004–2006"
- 37. Psychotherapy/
- 38. Psychotherapy, brief/
- 39. Psychotherapy, group/
- 40. psychotherap\$.ti,ab.
- 41. Cognitive therapy/
- 42. (cognitive adj (therap\$ or treatment\$ or intervention\$)).ti,ab.
- 43. Behavior Therapy/
- 44. (behavio\$ adj (therap\$ or treatment\$ or intervention\$)).ti,ab.
- 45. interpersonal therap\$.ti,ab.
- 46. interpersonal intervention\$.ti,ab.
- 47. Self-help groups/
- 48. self help.ti,ab.
- 49. Family therapy/
- 50. family support.ti,ab.
- 51. parent\$ education.ti,ab.
- 52. Parents/ed [education]
- 53. Counseling/
- 54. Directive counseling/
- 55. counsel\$.ti,ab.
- 56. Problem solving/
- 57. problem solving.ti,ab.
- 58. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
- 59. 5 and 58
- 60. Limit 59 to year = "1990–2006"
- 61. 36 or 60
- 62. Limit 61 to ("child (6 to 12 years)" or "adolescent (13 to 18 years)")
- 63. children\$.ti,ab.
- 64. child.ti,ab.
- 65. childhood.ti,ab.
- 66. teen.ti,ab.
- 67. teens.ti,ab.
- 68. teenage\$.ti,ab.
- 69. pediatric\$.ti,ab.
- 70. paediatric\$.ti,ab.
- 71. adolescen\$.ti,ab.
- 72. boys.ti,ab.
- 73. girls.ti,ab.
- 74. youth.ti,ab.
- 75. youths.ti,ab.
- 76. 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75
- 77. 61 and 76
- 78. 62 or 77
- 79. harm\$.ti,ab.
- 80. (adverse effects or chemically induced or drug effects or mortality or poisoning or toxicity).fs.
- 81. adverse effect\$.ti,ab.
- 82. adverse event\$.ti,ab.
- 83. adverse reaction\$.ti,ab.
- 84. Adverse drug reaction reporting systems/
- 85. Drug toxicity/
- 86. Drug hypersensitivity/
- 87. Death/
- 88. death.ti,ab.
- 89. death\$.ti,ab.
- 90. Suicide/
- 91. Suicide, attempted/
- 92. suicide.ti,ab.
- 93. suicidal\$.ti,ab.

## APPENDIX 1 Continued

94. mania.ti,ab.
95. manic episode\$.ti,ab.
96. overdos\$.ti,ab,mh.
97. self damag\$.ti,ab.
98. self injur\$.ti,ab.
99. self injurious behavior/
100. self inflict\$.ti,ab.
101. 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100
102. 78 and 101
103. Antidepressive agents, second-generation/ae, po, to [adverse effects, poisoning, toxicity]
104. Serotonin uptake inhibitors/ae, po, to [adverse effects, poisoning, toxicity]
105. Fluoxetine/ae, po, to [adverse effects, poisoning, toxicity]
106. Fluvoxamine/ae, po, to [adverse effects, poisoning, toxicity]
107. Paroxetine/ae, po, to [adverse effects, poisoning, toxicity]
108. Sertraline/ae, po, to [adverse effects, poisoning, toxicity]
109. Citalopram/ae, po, to [adverse effects, poisoning, toxicity]
110. 103 or 104 or 105 or 106 or 107 or 108 or 109
111. Limit 110 to year = "2004–2006"
112. Limit 111 to ("child [6 to 12 years]" or "adolescent [13 to 18 years])"
113. 111 and 76
114. 112 or 113
115. 102 or 114
116. Limit 115 to English language
117. Limit 116 to humans
118. Limit 116 to animals
119. 118 not 117
120. 116 not 119
121. Limit 120 to news
122. 120 not 121

## APPENDIX 2 Detailed Methods

### Literature Search Strategy

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

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

For KQ4, the preliminary search yielded 1 systematic review<sup>38</sup> and 1 meta-analysis<sup>40</sup> of SSRI treatment efficacy and adverse effects in children and adolescents that covered the years through 2004. We used these reviews as source documents and bridged their searches for SSRI treatment and harms. Therefore, for KQ4, we searched for RCTs/controlled clinical trials of psychotherapy and SSRI treatment in children and adolescents in Medline, PsycINFO, and the CCRCT in 2 separate searches covering 1998 through May 2007 for psychotherapy and 2004 through May 2007 for SSRIs.

For KQ5, we searched for adverse effects of SSRIs and psychotherapeutic treatment, without restrictions on study designs, in 2 separate searches

## APPENDIX 2 Continued

covering 1990 through May 2007 for psychotherapy and 2004 through May 2007 for SSRIs. Our search period for adverse effects of psychotherapy began in 1990, because harms of treatment were not addressed in the previous USPSTF report.

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

### Inclusion and Exclusion Criteria

We developed the following set of inclusion/exclusion criteria that were applied to the KQs. Additional exclusion criteria are specified in Appendix 3.

### Populations

This review addresses children and adolescents aged 7 to 18 years of age in the United States and other similarly developed Westernized populations (defined as being at a human development index of  $>0.90$ ). Currently available screening tools are reported to be appropriate for children aged 7 years and older.<sup>12</sup> Furthermore, the prevalence of depression among children younger than 6 years is estimated to be less than 1%; thus, the predictive value of a positive test is likely to be low.

### Populations With Risk Factors

We addressed the prevalence of depression among populations with risk factors through a contextual question and also captured studies that evaluated screening and treatment among populations with risk factors. We examined studies conducted among populations with the following clinically relevant risk factors recommended by experts who reviewed the work plan for this review: children of depressed parents, previous personal history of a major depressive episode, chronic medical conditions with high prevalence among primary care populations (eg, asthma), substance abuse, and acute negative life events. After reviewing the evidence for depression screening and treatment in populations with risk factors, the USPSTF decided that the review should not address screening and treatment in high-risk populations separately because of the lack of relevant studies. In our discussion of this review, however, we did consider this evidence in relation to our findings' applicability to these high-risk populations. We did not examine primary epidemiologic studies that identified risk factors for childhood depression. We excluded studies that focused on patients with bipolar disorder or with psychotic disorders, including psychotic depression, as well as patients with severe medical conditions (eg, cancer) that may have interfered with the performance of screening tools or treatment or were not generally represented in primary care populations. We also excluded studies that focused on identifying parental depression, including postpartum maternal depression.

### Diseases

This report includes studies that focused on MDD or depression not otherwise specified, as defined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. We also included studies that used a predetermined cutoff on a screening test to define major depression. We did not address screening or treatment of dysthymia or minor depression or prevention of depression. We did not address screening specifically for suicide prevention, which has been addressed by a separate USPSTF recommendation.<sup>12</sup>

**Settings**

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

**Screening Interventions**

This review includes only studies of screening instruments that are feasible for primary care settings. Specifically, a screening tool should take no longer than 15 minutes to complete if delivered before clinician and patient face-to-face contact (eg, in the waiting room or in the examination room before clinician entrance) and no longer than 5 minutes or 5 questions if used during the face-to-face visit. More general mental health screening tools were included if they had a depression module or were being used to identify depressive illness and related outcomes.

**Treatment Interventions**

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

**Outcomes**

We included the following outcomes if they were reported at 6 weeks' follow-up time or later. The primary health outcomes of interest were remission from depression, improved depressive symptoms, and recurrence of depression. Additional outcomes of interest included quality of life, global functioning, psychosocial functioning, educational achievement, unplanned pregnancy, substance abuse, improvement in comorbid disorders, change in health status, and reduction in physical complaints. For harms, we focused on death, other serious psychiatric events (such as hospitalization, suicidal ideation, and suicide attempts), triggering symptoms of mania, and discontinuation of medication resulting from adverse events.

**Study Designs**

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

For KQ 2, addressing the accuracy of screening, we included studies of diagnostic accuracy that reported sensitivity and specificity compared with an independently assessed criterion standard for MDD or depression not

otherwise specified within 2 months of the screening test. For KQs 3 and 5, evaluating the harms of screening and treatment, we used evidence from RCTs preferentially, then well-designed non-RCTs and high-quality observational studies with sample sizes of at least 1000.

**Quality**

We excluded studies that met criteria for "poor" quality in the USPSTF design-specific criteria (Appendix 4).

**Language**

We excluded non-English-language abstracts and articles.

**Article Review and Data Abstraction**

We reviewed a total of 4979 abstracts and 444 complete articles for all KQs (Appendix 5). Although we conducted 3 searches to cover depression screening, depression treatment efficacy, and depression treatment harms, we reviewed all abstracts for potential inclusion for any of the KQs. Two investigators independently reviewed all abstracts for KQs 4 and 5. The search for KQs 1 through 3 produced a very high yield (3418 abstracts). Therefore, we used a modified approach to reviewing these abstracts. One investigator reviewed all the abstracts for KQs 1 through 3. A second investigator independently reviewed all abstracts from the CCRCT search, the 500 most recently published abstracts from both Medline and PsycINFO, and every fifth abstract in the remaining set for Medline and PsycINFO, representing an additional random subset of 20% that were dually reviewed. Therefore, 1562 (46%) of the 3418 screening abstracts were dually reviewed for inclusion or exclusion. There were a total of 22 (1.4%) discrepancies between the 2 reviewers for the 1562 dual-reviewed abstracts. None of these 22 abstracts were included in the final review; therefore, we feel confident that no relevant articles were missed by having a second investigator dual review only a subset of the abstracts.

Two investigators independently reviewed articles against inclusion/exclusion criteria specific for each KQ and marked articles for exclusion as soon as an exclusion criterion was met. Included studies that met all criteria were then independently rated for quality by 2 investigators by using the USPSTF's study design-specific criteria supplemented by National Institute for Health and Clinical Excellence criteria for quality assessment<sup>22</sup> (Appendix 4). The Methods Work Group of the USPSTF has defined a 3-category rating of "good," "fair," and "poor" on the basis of these criteria. In general, a good study meets all criteria well. A fair study does not meet, or it is not clear that it meets, at least 1 criterion, but has no known important limitation that could invalidate its results. A poor study has important limitations. Articles were rated as good, fair, or poor by each rater, and disagreements were settled by consensus. Studies that received a poor final quality rating were excluded from the review. Listings of excluded articles for each KQ, along with the reason for exclusion, are in the full evidence report which is available at [www.preventiveservices.ahrq.gov](http://www.preventiveservices.ahrq.gov) (Appendix C, Tables C1, C3, C4, C6, and C9). All exclusion criteria are listed in Appendix 3.

We identified numerous recent systematic evidence reviews that examined the efficacy of SSRIs for treating MDD in youth and included both published and unpublished results.<sup>26,31,38–40</sup> We included results from the most recently published good-quality systematic evidence review of antidepressant efficacy by Bridge et al.<sup>26</sup> Numerous systematic evidence reviews and meta-analyses evaluating the efficacy of psychotherapy for treating depression in youth have also been published recently. These reviews only partially overlapped with our inclusion and exclusion criteria and could not directly answer the scope of our KQs. Therefore, we used the 5 most recently published systematic evidence reviews as supplemental sources for identifying trials relevant for this report.<sup>23,25,31,86,87</sup> Numerous recent systematic evidence reviews and regulatory agency reports have also synthesized available data from RCTs to estimate whether excess risk of suicide-related events (SRE) occurs among depressed children or adolescents treated with SSRIs or atypical antidepressants.<sup>16,26–40</sup> For this report, we included the most recently published reviews that used suicide-related outcome SRE data that were blindly classified by suicidology experts at Columbia University (requested by the FDA Division of Neuropharmacological Drug Products).<sup>16,26,27</sup> (Only 1 of these reports incorporated a recently published trial of escitalopram.<sup>26</sup>)



## APPENDIX 2 Continued

There are 4 systematic reviews/meta-analyses and 31 studies (reported in 39 articles) included in this review. We found no studies for KQs 1, 1a, and 3. For KQ2, we found 9 studies reported in 12 articles, 5 of which were included in the previous USPSTF report. KQ4 includes 1 systematic review and 18 trials reported in 22 articles, 3 of which were included in the previous USPSTF report, and KQ5 includes 4 meta-analyses and 13 trials reported in 17 articles, none of which were included in the previous USPSTF report because harms were not addressed. One primary reviewer abstracted relevant information such as study setting, population, screening method, and outcomes into standardized evidence tables for each included article. A second reviewer checked the abstracted data for accuracy and completeness. These tables are in Appendix C, Tables C2, C5, C7 and C8, of the full evidence report (available at [www.preventiveservices.ahrq.gov](http://www.preventiveservices.ahrq.gov)).

### Data Synthesis

We found no data for KQs 1, 1a, and 3. Data synthesis for KQ2 was qualitative, because heterogeneity in the instruments, samples, and settings studied did not allow for quantitative syntheses. For psychotherapy trials included in KQs 4 and 5, we did not conduct meta-analyses because of the heterogeneity of the interventions. Instead, we qualitatively summarized our findings in the results text and summary tables. For evidence on the efficacy and adverse effects of SSRIs (KQ4 and 5), binary outcome data for response rate and SREs were pooled across the trials that met our inclusion and exclusion criteria. We used a recent good-quality systematic review (Bridge et al<sup>26</sup>) as a source of outcome data for response rate and SRE. Bridge et al used SRE data that were based on the blinded review of outcomes by suicidology experts from Columbia University (the same data used in analyses by the FDA). For newer trials, the authors used methodology similar to that in the Columbia University review. We quality-rated all individual trials and compared all data for response outcomes against outcomes reported in published versions of individual trials. This review revealed no discrepancies. We could not analyze the data for SRE, because the FDA provided these outcomes to Bridge et al. Heterogeneity tests were performed on outcome results. Authors of previous meta-analyses of these data argued that fixed-effect models are not appropriate for this body of literature.<sup>26,27</sup> Commentators on these previous meta-analyses, however, have argued that using this approach is appropriate for adverse-event outcomes because the trials are already biased toward finding null effects resulting from lack of systematic measurement of adverse events, underreporting outcomes, and measurement error.

We agree with the assessment by Bridge et al that these trials are likely to have heterogeneity across studies not accounted for by observed covariates. We used a random-effects model (method of DerSimonian and Laird<sup>88</sup>) to calculate the pooled RD. Random-effects approaches generally yield lower risk estimates and wider CIs (yielding more-conservative estimates of efficacy and less-conservative estimates of adverse events). To incorporate more conservative estimates of adverse events into the review, we included results from meta-analyses using fixed-effects models. We conducted sensitivity analyses recalculating pooled RDs by using a fixed-effects model to understand how this difference in approach would affect results. We focused on the RD, instead of RR, because the data are more directly applicable to comparing risks and benefits (ie, calculating and comparing numbers needed to treat or harm). All meta-analyses were conducted by using RevMan 4.2 software (Cochrane Collaboration. Available at [www.cc-ims.net/RevMan](http://www.cc-ims.net/RevMan)).

### External Review Process

The USPSTF appointed 3 liaisons to guide the scope and reporting of this review. The work plan for the review was sent to 5 experts on childhood mental health, whom we asked to comment on the general proposed approach, scope of the review, and adequacy of the identified questions. In addition, 5 outside experts provided feedback on a draft version of this evidence synthesis.

## APPENDIX 2 Continued

### USPSTF Involvement

This research was funded by the AHRQ under a contract to support the work of the USPSTF. The authors worked with 3 USPSTF liaisons at key points throughout the review process to develop and refine the scope, analytic framework, and KQs; to resolve issues around the review process; and to finalize the evidence synthesis. The AHRQ had no role in study selection, quality assessment, or synthesis, although AHRQ staff provided project oversight, reviewed the draft evidence synthesis, and distributed the initial evidence report for external review of content by outside experts, including representatives of professional societies and federal agencies. The final published systematic evidence review was revised on the basis of comments from these external reviewers.

## APPENDIX 3 Exclusion Criteria for KQs

Exclusion criteria applied to all KQs

- Population
    - Focuses on adults (>18 y old) or children aged 0–6 or does not report pediatric outcomes separately
    - Focuses on patients with severe medical illnesses (eg, cancer), bipolar disorder, or psychotic disorder
    - Focuses on identifying or treating maternal depression (eg, during pregnancy or after delivery)
    - Focuses on identifying or treating parental depression
    - Conducted in population that is not comparable to primary care (eg, high-risk conditions not prevalent in primary care populations)
    - Focuses on patients with minor depression or dysthymia or does not present MDD outcomes separately
    - Conducted exclusively in high-risk populations
    - Conducted in non-Westernized population
  - Setting
    - Not conducted in primary care, school-based clinics, or other setting with primary care-comparable population (ie, church or after-school program)
    - Conducted with inpatients or those in residential treatment or drug treatment programs
    - Conducted with incarcerated populations
  - Design
    - Editorials
    - Letters
    - Noncomparative studies
    - Nonsystematic reviews
    - Opinions
    - Comparative effectiveness studies
    - Abstracts
  - Quality
    - Does not meet quality criteria
    - No relevant outcomes
    - Precedes search period
    - Article covered by an included systematic review
    - Systematic review used as source document only
    - Non-English
- Additional exclusion criteria specific to each KQ
- KQ1: Does screening for depression among children and adolescents in the primary care setting improve health outcomes?
    - Relevance
      - Does not focus on screening and treatment of depression
      - Reports on test that is not relevant to or feasible in primary care setting
      - Focuses on screening for suicide risk
    - Setting
      - Conducted in outpatient mental health clinic
    - Quality
      - Only short-term health outcomes <6 wk are reported
  - KQ2: Are depression screening instruments for children and adolescents accurate in identifying depression in primary care or school-based clinics?
    - Relevance
      - Does not focus on depression screening
      - Does not use a credible reference standard or reports on test that is not relevant to or feasible in primary care setting
      - Focuses on screening for suicide risk
    - Setting
      - Conducted in outpatient mental health clinic

**APPENDIX 3 Continued**

Design  
Does not report sensitivity and specificity compared with an independently assessed criterion standard for MDD or depression not otherwise specified within 2 mo of the screening test

KQ3: What are the harms of screening?

Relevance  
Does not focus on harms of depression screening  
Focuses on screening for suicide risk

Setting  
Conducted in outpatient mental health clinic

KQ4: Does the treatment of depression (SSRIs and/or psychotherapy) among screen-detected children and adolescents identified in primary care or comparable populations improve health outcomes?

Relevance  
Does not focus on depression treatment  
Focuses on efficacy of tricyclic antidepressants, atypical antidepressants, MAOIs, electroconvulsive therapy, or other medications/procedures that are not primary care–feasible or referable  
Focuses on treatment comparison, matching, or fine-tuning  
Examination of nondemographic modifiers (eg, genetics, personality characteristics)  
Focuses on prevention of depression (either universal or among populations with risk factors)  
Focuses on health systems approach to depression treatment such as collaborative care interventions

**APPENDIX 3 Continued**

Setting  
Intervention not primary care–feasible or widely available for primary care referral

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

Quality  
Only short-term health outcomes <6 wk are reported

KQ5: What are the adverse effects of treatment?

Relevance  
Does not focus on harms of depression treatment  
Focuses on harms of tricyclic antidepressants, atypical antidepressants, MAOIs, electroconvulsive therapy, or other medications/procedures that are not primary care–feasible or referable  
Focuses on treatment comparison, matching, or fine-tuning  
Examination of nondemographic modifiers (eg, genetics, personality characteristics)  
Focuses on harms of prevention of depression (either universal or among populations with risk factors)

Setting  
Focuses on harms of intervention that is not primary care–feasible or widely available for primary care referral

Design  
High-quality observational study with a sample size of <1000

**APPENDIX 4 Quality Rating Criteria**

Design	USPSTF Quality Rating Criteria <sup>a</sup>	National Institute for Health and Clinical Excellence Methodology Checklists <sup>b</sup>
Systematic reviews and meta-analyses	Comprehensiveness of sources considered/search strategy used	The study addresses an appropriate and clearly focused question
	Standard appraisal of included studies Validity of conclusions	A description of the methodology used is included The literature search is sufficiently rigorous to identify all the relevant studies
	Recency and relevance are especially important for systematic reviews	Study quality is assessed and taken into account There are enough similarities between the studies selected to make combining them reasonable
Case-control studies	Accurate ascertainment of cases	The study addresses an appropriate and clearly focused question
	Nonbiased selection of cases/controls with exclusion criteria applied equally to both Response rate	The cases and controls are taken from comparable populations The same exclusion criteria are used for both cases and controls
	Diagnostic testing procedures applied equally to each group	What percentage of each group (cases and controls) participated in the study?
	Measurement of exposure accurate and applied equally to each group	Comparison is made between participants and nonparticipants to establish their similarities or differences
	Appropriate attention to potential confounding variables	Cases are clearly defined and differentiated from controls Is it clearly established that controls are noncases? Measures have been taken to prevent knowledge of primary exposure influencing case ascertainment Exposure status is measured in a standard, valid, and reliable way The main potential confounders are identified and taken into account in the design and analysis Have CIs been provided?

Design	USPSTF Quality Rating Criteria <sup>a</sup>	National Institute for Health and Clinical Excellence Methodology Checklists <sup>b</sup>
Cohort studies	<p>Initial assembly of comparable groups uses consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts</p> <p>Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)</p> <p>Important differential loss to follow-up or overall high loss to follow-up</p> <p>Measurements: equal, reliable, and valid (includes masking of outcome assessment)</p> <p>Clear definition of the interventions</p> <p>All important outcomes considered</p>	<p>All relevant outcomes are measured in a standard, valid, and reliable way</p> <p>What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</p> <p>All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis)</p> <p>When the study is carried out at &gt;1 site, results are comparable for all sites</p> <p>The study addresses an appropriate and clearly focused question</p> <p>The 2 groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation</p> <p>The study indicates how many of the people asked to take part did so, in each of the groups being studied</p> <p>The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis</p> <p>What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?</p> <p>Comparison is made between full participants and those lost to follow-up, according to exposure status</p> <p>The outcomes are clearly defined</p> <p>The assessment of outcome is made blind to exposure status</p> <p>When blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome</p> <p>The measure of assessment of exposure is reliable</p> <p>Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable</p> <p>Exposure level or prognostic factor is assessed more than once</p> <p>The main potential confounders are identified and taken into account in the design and analysis</p> <p>Have CIs been provided?</p> <p>The nature of the test being studied is clearly specified</p> <p>The test is compared with an appropriate gold standard</p> <p>When no gold standard exists, a validated reference standard is used as a comparator</p> <p>Patients for testing are selected either as a consecutive series or randomly from a clearly defined study population</p> <p>The test and gold standard are measured independently (blind) of each other</p> <p>The test and gold standard are applied as close together in time as possible</p> <p>Results are reported for all patients who are entered into the study</p>
Diagnostic accuracy studies	<p>Screening test relevant, available for primary care, adequately described</p> <p>Study uses a credible reference standard, performed regardless of test results</p> <p>Reference standard interpreted independently of screening test</p> <p>Handles indeterminate result in a reasonable manner</p> <p>Spectrum of patients included in study</p> <p>Sample size</p> <p>Administration of reliable screening test</p>	<p>The nature of the test being studied is clearly specified</p> <p>The test is compared with an appropriate gold standard</p> <p>When no gold standard exists, a validated reference standard is used as a comparator</p> <p>Patients for testing are selected either as a consecutive series or randomly from a clearly defined study population</p> <p>The test and gold standard are measured independently (blind) of each other</p> <p>The test and gold standard are applied as close together in time as possible</p> <p>Results are reported for all patients who are entered into the study</p>

**APPENDIX 4 Continued**

Design	USPSTF Quality Rating Criteria <sup>a</sup>	National Institute for Health and Clinical Excellence Methodology Checklists <sup>b</sup>
RCTs	<p>Initial assembly of comparable groups uses adequate randomization, including first concealment and whether potential confounders were distributed equally among groups</p> <p>Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)</p> <p>Important differential loss to follow-up or overall high loss to follow-up</p> <p>Measurements: equal, reliable, and valid (includes masking of outcome assessment)</p> <p>Clear definition of the interventions</p> <p>All important outcomes considered</p>	<p>The study addresses an appropriate and clearly focused question</p> <p>The assignment of subjects to treatment groups is randomized</p> <p>An adequate concealment method is used</p> <p>Subjects and investigators are kept "blind" about treatment allocation</p> <p>The treatment and control groups are similar at the start of the trial</p> <p>The only difference between groups is the treatment under investigation</p> <p>A prediagnosis is made and reported</p>
Hierarchy of research design <sup>a</sup>	<p>I Properly conducted randomized controlled trial (RCT)</p> <p>II-1: Well designed controlled trial without randomization</p> <p>II-2: Well-designed cohort or case-control analytic study</p> <p>II-3: Multiple time series with or without the intervention; dramatic results from uncontrolled experiments</p> <p>III: Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees</p>	

<sup>a</sup> See reference 21.

<sup>b</sup> See reference 22.

**APPENDIX 5 Search Results and Article Flow**

