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Screening for Depression in Adult Patients in Primary Care Settings: A Systematic Evidence Review

Elizabeth A. O'Connor, PhD; Evelyn P. Whitlock, MD, MPH; Tracy L. Beil, MS; and Bradley N. Gaynes, MD, MPH

Background: In primary care settings, prevalence estimates of major depressive disorder range from 5% to 13% in all adults, with lower estimates in those older than 55 years (6% to 9%). In 2002, the U.S. Preventive Services Task Force (USPSTF) recommended screening adults for depression in clinical practices that have systems to ensure accurate diagnosis, effective treatment, and follow-up.

Purpose: To conduct a targeted, updated systematic review for the U.S. Preventive Services Task Force about the benefits and harms of screening adult patients for depression in a primary care setting, the benefits of depression treatment in older adults, and the harms of depression treatment with antidepressant medications.

Data Sources: MEDLINE, the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, PsycINFO (1998 to 2007), expert suggestions, and bibliographies of recent systematic reviews.

Study Selection: Fair- to good-quality randomized clinical trials or controlled clinical trials; systematic reviews; meta-analyses; and large observational studies of serious adverse events and early discontinuation due to adverse effects. All studies were published in English.

Data Extraction: Two investigators abstracted, critically appraised, and synthesized 33 articles that met inclusion criteria.

Data Synthesis: Nine fair- or good-quality trials indicate that primary care depression screening and care management programs with staff assistance, such as case management or mental health specialist involvement, can increase depression response and remission. Benefit was not evident in screening programs without staff assistance in depression care. Seven regulatory reviews or meta-analyses and 3 large cohort studies indicate no increased risk for completed suicide deaths with antidepressant treatment. Risk for suicidal behaviors was increased in young adults (aged 18 to 29 years) who received antidepressants, particularly those who received paroxetine, but was reduced in older adults.

Limitation: Examination of harms was limited to serious adverse events, and existing systematic reviews were primarily used. Additional studies published from 2007 to 2008 extend this review.

Conclusion: Depression screening programs without substantial staff-assisted depression care supports are unlikely to improve depression outcomes. Close monitoring of all adult patients who initiate antidepressant treatment, particularly those younger than 30 years, is important both for safety and to ensure optimal treatment.

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For author affiliations, see end of text.

Major depressive disorder (MDD) is common, with an estimated lifetime prevalence of 13.2%. In primary care settings, prevalence estimates of MDD range from 5% to 13% in all adults (1, 2), with lower estimates in those older than 55 years (6% to 9%) (3, 4). Primary care practitioners manage approximately one third to one half of nonelderly adults (5, 6) and almost two thirds of older adults (7) who received treatment for MDD. The severity of depressive symptoms in patients who receive treatment in primary care is equivalent to that of patients treated in psychiatric settings (8). For example, approximately 43% of such primary care patients report some degree of suicidal ideation within the previous week (8, 9).

In 2002, the U.S. Preventive Services Task Force (USPSTF) recommended screening adults for depression in clinical practices that have systems to ensure accurate diagnosis, effective treatment, and follow-up. Subsequent reviewers have concluded that screening does not improve health outcomes (10), but care management systems for depressed patients improve depression remission rates (11). Commentators on these divergent reviews have been divided (12, 13).

We conducted this systematic review to aid the USPSTF in updating its 2002 recommendation for adult depression screening in primary care. We sought to 1) identify evidence published since the previous review on the benefits of screening for depression in primary care and integrate it with the previously identified evidence and 2) review the evidence in several areas in which evidence was insufficient at the time of the previous review or not was examined by the previous review (14). This includes the benefits of depression treatment in older adults, the harms of depression screening, and the harms of depression treatment with antidepressant medications.

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Methods

Scope of the Review

We developed an analytic framework (**Appendix Figure 1**, available at www.annals.org) and 5 key questions that focused on the evidence that the USPSTF required to update its recommendation by using the USPSTF's methods (15).

1. Is there direct evidence that screening for depression among adults and elderly patients in primary care reduces morbidity and/or mortality?

1a. What is the effect of clinician feedback of screening test results (with or without additional care management support) on depression response and remission in screening-detected depressed patients receiving usual care?

2. What are the adverse effects of screening for depressive disorders in adults and elderly patients in primary care?

3. Is antidepressant and/or psychotherapy treatment of elderly depressed patients effective in improving health outcomes?

4. What are the adverse effects of antidepressant treatment (particularly selective serotonin reuptake inhibitors [SSRIs] and other second-generation drugs) for depression in adults and elderly patients?

This article discusses methods and results for key questions 1, 1a, and 4. Detailed methods and results for the remaining key questions are in the full report (16).

Data Sources and Searches

We used the Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, MEDLINE, and PsycINFO to search for relevant systematic reviews, meta-analyses, and primary studies published in English from January 1998 to December 2007. The full report provides the search strategies (16).

Study Selection

Two investigators reviewed 4088 abstracts published in English and 412 full-text articles (**Appendix Figure 2**, available at www.annals.org) against key question–specific inclusion and exclusion criteria (**Appendix Table 1**, available at www.annals.org). Articles for key questions 1 and 1a were limited to randomized and controlled clinical trials that were conducted in primary care or similar settings. Key question 1 trials compared outcomes in screened and unscreened patients. Trials for key question 1a were required to have used the screening results for care decisions for intervention recipients and not for the control participants. Outcomes for these 2 questions were focused on depression response and remission.

We focused our review of harms of treatment (key question 4) on already-synthesized evidence, supplemented by large observational studies. Methods for incorporating systematic reviews and meta-analyses are detailed elsewhere (**Appendix Table 2**, available at www.annals.org). We examined serious adverse effects associated with antidepressant treatment, including suicide-related events (completed suicide, serious self-harm or attempted suicide, suicidal ideation, or suicidal behavior [usually defined to include suicide attempts, preparatory acts, or nonfatal serious self-harm]), and serious psychiatric events, including hospitalization. For older adults, we also considered evidence of serious medical events (for example, upper gastrointestinal bleeding) that were associated with SSRI and other second-generation antidepressant use. We examined rates of early discontinuation as a proxy for less serious adverse effects, particularly discontinuation due to adverse effects as a measure of tolerability. We focused on second-generation antidepressants (SSRIs in particular) because of their preponderance of use in the United States (17, 18).

Updated Searching and Study Examination

Because of the delay between completion of the systematic review and publication, we repeated our search strategy through February 2009. We reviewed 800 abstracts against inclusion and exclusion criteria, and 21 seemed to meet criteria for this systematic review. After examining results of each of these new studies (as described in the abstracts), we determined that they would be unlikely to change our conclusions. **Appendix Table 3** (available at www.annals.org) lists these studies.

Data Extraction and Quality Assessment

Two investigators rated articles for quality by using design-specific quality criteria on the basis of the USPSTF methods (15). The National Institute for Health and Clinical Excellence (19) criteria (for all study designs) and the Oxman criteria (20) (for systematic reviews) supplemented these methods. One investigator abstracted data from included studies into evidence tables and another verified it. The full review shows complete quality criteria (16).

Regulatory reviews provided unique challenges and could not be evaluated by using typical quality criteria. For example, their search approach was different because they can mandate that manufacturers supply requested data. Because of the large number of trials (often in the hundreds) and proprietary information involved, however, they did not provide detailed information about individual trials.

Data Synthesis and Analysis

Data synthesis was primarily qualitative because of clinical heterogeneity. For cohort studies included for key question 4, we calculated absolute event rates and CIs for suicide-related events on the basis of reported data if this information was not provided. The 95% CIs were calculated on the basis of a Poisson distribution by using the GENMOD procedure (SAS software, version 8.2, SAS Institute, Cary, North Carolina) with the RISK option. Similarly, for the meta-analyses of antidepressant trials included for key question 4, we calculated missing CIs by using the FREQ procedure.

Role of Funding Source

The Agency for Healthcare Research and Quality funded this work, provided project oversight, and assisted in external review of the draft report but had no role in the design, conduct, or reporting of the review. The authors worked with 4 USPSTF members at key points throughout the review process to develop the analytic framework and key questions and resolve issues about scope and approach. The draft systematic review was reviewed by 6 experts and was revised on the basis of their feedback.

RESULTS

Key Question 1

Is there direct evidence that screening for depression among adults and elderly patients in primary care reduces morbidity and/or mortality?

One fair-quality randomized, controlled trial (RCT) of primary care patients reported mixed results when screened participants were compared with an unscreened usual care group (21) (**Table**). Concerns about the follow-up sample, however, limit our confidence in the results. At 3-month follow-up, the proportion of people who met criteria for depression, according to the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised,* was similar in the screened (37%) and usual care groups (46%) ($P = 0.19$), although power to detect a population-level effect was inadequate ($n = 218$). After the investigators controlled for baseline severity of depression (which differed between the screened and usual care groups in the full randomized sample), the mean reduction in symptom counts derived from the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised*, was similar for the 2 groups (1.6 in screened patients vs. 1.5 in unscreened patients; $P = 0.21$). However, among the subset of patients who were depressed at baseline, screened patients were more likely than unscreened patients to be in complete remission at follow-up (≤1 symptom of depression in 48% of those screened vs. 27% of those not screened; $P < 0.05$). Only patients from 1 of the 2 study sites were included in the follow-up sample. At this site, only those with a diagnosis of depression at baseline and a random sample of the remaining participants (oversampling those with depressive symptoms at baseline), were reassessed at 3 months, thus limiting the study power to detect group differences and potentially introducing bias. Data were not presented on the baseline similarity between the follow-up sample and the original sample or between the intervention and control groups for the follow-up sample, which would have given some assurance that bias was minimized. This study was also at risk for intervention contamination because providers saw patients in both study conditions.

Key Question 1a

What is the effect of clinician feedback of screening test results (with or without additional care management support) on depression response and remission in screening-detected depressed patients receiving usual care?

Two good-quality (22, 23) and 6 fair-quality (24–29) RCTs reported the effect of depression screening results feedback on health outcomes in screened populations (**Table**) and generally found that programs involving staff support in depression care can reduce depressive symptoms beyond usual care (**Table** and **Appendix Table 4**, available at www.annals.org). Four of these studies involved general adult populations ($n = 1908$) (22, 23, 26, 27), and 4 focused on older adults ($n = 1443$) (24, 25, 28, 29).

General Adult Populations

In general adult populations, 4 trials (22, 23, 26, 27) screened a total of 38 843 primary care patients to detect 1908 depressed adult patients. Bergus and colleagues (26) conducted a small, fair-quality RCT in a rural setting that provided no depression care support beyond simple feedback of screening results and was not effective in reducing symptoms of depression. This trial did not report blinding of outcomes assessment and was underpowered to detect anything other than a very large effect. Another small, fair-quality RCT reported improved depressive symptoms but had a highly selected participant sample because investigators only enrolled screened adults with newly detected depression who were not seeking treatment of depression (27). In this trial, clinicians received a detailed depression treatment protocol during the visit that included a recommended follow-up schedule and educational materials for the patient. Providers also received logistical support from other staff for scheduling follow-up visits and facilitating referrals. Both of these trials had very small samples and were vulnerable to contamination because providers saw both intervention and control participants.

Two good-quality trials with considerably higher-intensity interventions involving depression care by other staff were effective in improving depression outcomes (22, 23), particularly for adults with newly detected depression. These trials included such elements as intensive clinician and office support staff training, support staff or specialty mental health provider participation in ongoing depression care, and several follow-up contacts. The more intensive of these trials (23) found that 40% of participants in either of the 2 treatment groups were still positive for depression on the Composite International Diagnostic Interview 2-item screen compared with 50% of usual care participants ($P = 0.001$). The effect was maintained at 12 months. At 5-year follow-up, program benefits were sustained for 1 of the 2 treatment groups, in which positive Composite International Diagnostic Interview screening scores were 36% among intervention participants and 44% among usual care participants ($P = 0.05$) (30). These results provide good evidence for the effectiveness of their program. It is

Table. **Summary of Results for KQ1 and KQ1a: Studies Examining Health Outcomes of Screening Results Feedback Among Screening-Identified Depressed Patients in Primary Care**

Study, Year (Reference)	Setting	Approach to Intervention Beyond Screening Results Feedback	Sample Characteristics
General adult population			
Williams et al, 1999 (21)	Multisite, Veterans Affairs, community health clinic	None (KQ1: included unscreened control group)	863 participants; 71% women; calculated age, 58 y; proportion treated, not reported
Bergus et al, 2005 (26)	Rural	None	59 participants; 67% women (calculated); calculated age, 41 y; 38% received medication for depression or anxiety
Jarjoura et al, 2004 (27)	Urban, indigent	Improve quality of provider's care; logistic support for provider; other staff provide some depression care	61 participants; 69% women (calculated); calculated age, 45 y; 0% currently treated
Wells et al, 2000 (23) and 2004 (30); Sherbourne et al, 2001 (31)	Multisite, urban, rural	Improve quality of provider's care; logistic support for provider; other staff provide some depression care	1356 participants; 71% women; age 44 y; proportion treated, not reported
Rost et al, 2001 (22) and 2000 (32); cases in which depression was identified by the provider as part of usual care before the study	Multisite, urban, rural	Improve quality of provider's care; logistic support for provider; other staff provide some depression care	243 participants; 84% women‡; age 43 y‡; 100% recently treated
Rost et al, 2001 (22), 2000 (32), and 2002 (33); cases in which depression was newly identified by screening related to the study	Multisite, urban, rural	Improve quality of provider's care; logistic support for provider; other staff provide some depression care	189 participants; 84% women‡; age 43 y‡; 0% recently treated
Older adult population			
Bosmans et al, 2006 (28)	Urban, the Netherlands	Improve quality of provider's care	145 participants; 60% women; calculated age, 65 y; 0% currently treated; 83% history of depression
Whooley et al, 2000 (24)	Urban	Improve quality of provider's care; other staff provide some depression care (minimally implemented)	331 participants; 61% women; calculated age, 76 y; 20% received antidepressants for ≥12 mo
Callahan et al, 1994 (25)	Urban	Improve quality of provider's care; logistic support for PCP	175 participants; 76% women; age 65 y; 11.4% received antidepressants
Rubenstein et al, 2007 (29)	Urban, Veterans Affairs	Logistical support for PCP; other staff provide some depression care	792 participants (206 screened positive for depression); 3.2% women; age 74 y; proportion treated, not reported

CES-D = Center for Epidemiological Studies depression scale; CIDI = Composite International Diagnostic Interview, full interview; CIDI-2 = Composite International Diagnostic Interview, 2-item depression screen; DIS = diagnostic interview schedule for *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised;* GDS = Geriatric Depression Scale; HDRS = Hamilton Depression Rating Scale; IV1= psychotherapy, IV2 = medication support; IV = intervention; KQ = key question; MADRS = Montgomery–Asberg Depression Rating Scale; MDD = major depressive disorder; PCP = primary care provider; PHQ-9 = Patient Health Questionnaire-9 item; PRIME-MD = Primary Care Evaluation of Mental Disorders, Mood Module screening items; UC = usual care; Z-BDI = Beck Depression Inventory, standardized on control group change.
* $P < 0.05$.
† $P < 0.01$.
‡ These statistics refer to the entire study sample.
§ Results for the 2 intervention groups were reported combined at 6- and 12-mo follow-up. They were reported separately at 24- and 57-mo follow-up.
¶ Reported that groups did not differ at 6 or 9 mo, but did not provide exact scores.
** Results only for subgroup that screened positive for depression.

impossible to determine, however, what role the screening component played in the success of their program. Furthermore, although this intervention was proven feasible for primary care settings, it involved substantial institutional commitment and may not reflect the care that would be found currently in most settings.

Older Adult Populations

In screening focused on older adults, 4 fairly large-scale trials (24, 25, 28, 29) screened 12 432 primary care patients to identify 1443 depressed older adults to test the effect of screening feedback with some care supports on remission and symptom reduction. Only 1 of 4 interventions in these trials improved depression beyond usual care (29). This trial attempted to identify patients with any of 5 high-risk conditions, 1 of which was depression. It involved the assistance of a case manager, who conducted an in-depth assessment and then referred the patient to primary or specialty care or to a multidisciplinary geriatric assessment team for further assessment. The case manager also provided patient education and follow-up. After 1 year, there was a 1-point difference in im-

Table—Continued

Length of Follow-up	Patients Depressed at Follow-up			Scale Score Decrease from Baseline		
	IV Group, %	UC Group, %	Measure	IV Group, %	UC Group, %	Measure
3 mo (all patients)	37	46	MDD per DIS	1.6	1.5	Number of MDD symptoms per DIS
3 mo (those depressed at baseline)	52*	73*	≥2 MDD symptoms per DIS			
10 wk	46	63	PHQ ≥6	5.8	5.8	PHQ-9
6 mo	48	62	PHQ ≥6	5.7	5.0	
6 mo	–	–	–	7.6*	0*	Z-BDI
12 mo	–	–	–	6.5*	0*	
6 mo	40†§	50†	CIDI-2	–	–	–
12 mo	42†§	51†	CIDI-2	–	–	–
57 mo	38 (IV1)*	44*	CIDI-2	–	–	–
	36 (IV2)	44	CIDI-2			
24 mo	39 (IV1)	34	CIDI	–	–	–
	31 (IV2)	34	CIDI			
6 mo	–	–	–	14.5	11.0	CES-D
6 mo	–	–	–	21.7*	13.5*	CES-D
24 mo	26*	59*	CES-D ≥15	–	–	–
12 mo	57	52	PRIME-MD	7.8	7.2	MADRS
24 mo	42	50	GDS ≥6	1.8	2.2	GDS
6 mo	87	88	HDRS ≥16	–¶	–	CES-D
9 mo	–	–	–	–	–	CES-D
12 mo**	–	–	–	3.7*	2.7*	GDS

provement between the groups on the 30-point Geriatric Depression Scale ($P = 0.05$), which may not reflect a clinically important difference. Although the trial was of good quality overall, this specific comparison was not a randomized comparison because it included only participants who had a positive screening result for depression. Data on baseline comparability in this subset were not provided. Also, because the sample was limited to patients who scored in a "high-risk" range for multiple conditions, the generalizability of this trial to the general primary care population of older adults may be limited. The remaining 3 trials in older adults, which found no treatment effects, had either fairly high attrition (24, 25) or differential attrition throughout the recruitment process (28).

Key Question 2

What are the adverse effects of screening for depressive disorders in adults and elderly patients in primary care?

No evidence was found that addressed harms of screening.

Key Question 3

Is antidepressant and/or psychotherapy treatment of elderly depressed patients effective in improving health outcomes?

We found evidence that pharmacologic and psychotherapeutic approaches are effective in older adults. Details can be found in the full report (16).

Key Question 4

What are the adverse effects of antidepressant treatment (particularly SSRIs and other second-generation drugs) for depression in adults and elderly patients?

We found 7 regulatory reviews or published meta-analyses reported in 10 articles (34–43) that each reviewed an average of 326 (range, 57 to 702) short-term RCTs of antidepressant treatment versus placebo in adults with MDD or other psychiatric conditions. Overall, these meta-analyses suggested no increase in suicide but did suggest age-related effects on suicide-related and other outcomes (**Appendix Table 5**, available at www.annals.org). Most

patients (88% to 95%) tolerated these medications, although adverse side effects and overall discontinuation rates were higher in older adults (44–51). Large population-based observational studies suggest that upper gastrointestinal bleeding is a concern for older adults, particularly when antidepressants are combined with nonsteroidal anti-inflammatory drugs (NSAIDs).

Completed Suicide

None of the 7 meta-analyses supplied clear evidence that use of second-generation antidepressants (or SSRIs in particular) increased odds of completed suicide in adults of any age compared with placebo. However, power to detect these rare events was limited, given very few suicides (7 to 43 total suicides among all patients per review). In most meta-analyses, pooled rates of suicide ranged from 3.8 to 8.8 per 10 000 adults who received antidepressants compared with 2.3 to 9.3 per 10 000 patients who received placebo. The 2 meta-analyses that represented outliers were probably because of methodological differences in meta-analysis design (16). A report by the U.S. Food and Drug Administration estimated many fewer suicides than other reviews and used a hierarchical outcome assignment method administered by trial sponsors, which may have underascertained suicides (34, 35). The much higher estimates of suicide rates in patients who received antidepressants and placebo in another review (37) could reflect the greater disease severity among studied patients. In addition, there were several quality concerns about this review, which include unclear event classification schema and lack of quality appraisal.

To complement short-term data from trials, we examined 3 fair- or good-quality large observational studies that reported suicide with antidepressant treatment in a total of 383 796 patients in a large HMO in the United States and in general practices in the United Kingdom (52–54) (**Appendix Table 6**, available at www.annals.org). Among the 2 highest-quality studies, crude suicide rates were 4.7 and 4.8 per 10 000 persons after 6 to 8 months of receiving treatment primarily with second-generation antidepressants, with slightly higher rates reported among those younger than 30 years. These studies also indicated higher risk for suicide among men compared with women. Although these observational studies do not provide comparative information for persons who were not receiving antidepressants, they give credence to the estimate of approximately 4 per 10 000 suicide cases among patients who received antidepressants, which was found most consistently in the meta-analyses of short-term trial data.

Suicidal Behaviors

Suicidal behaviors were defined differently across studies but usually included suicide attempts, preparatory acts, or serious self-harm. Results from 5 meta-analyses that reported 9 separate pooled estimates showed no statistically significant differences in the odds of suicidal behaviors in adults who received treatment with antidepressants compared with placebo, with several exceptions. In 1 fair-quality systematic review, odds of suicidal behaviors were increased in adults of all ages who were treated with SSRIs for any indication (odds ratio [OR], 2.70 [CI, 1.22 to 6.97]) (42); this report was limited to published studies only and did not have clear adverse event ascertainment for most patients. In a review of regulatory data of placebo-controlled trials by the U.S. Food and Drug Administration, odds of suicidal behavior were approximately doubled in adults younger than 25 years who received second-generation antidepressants for all psychiatric disorders (OR, 2.31 [CI, 1.02 to 5.64]) (34). In contrast, the odds of suicidal behaviors were unchanged among middle-aged adults and were greatly reduced in older adults receiving second-generation antidepressants (OR, 0.06 [CI, 0.01 to 0.58]) (35).

The highest odds of nonfatal suicidal behavior were reported in adults of all ages who received treatment for MDD with paroxetine compared with placebo (OR, 6.70 [CI, 1.1 to 149.4]). The increased risk is assumed to be primarily in young adults because most events (8 of 11) occurred in those aged 18 to 29 years. This good-quality review conducted by the manufacturer used independent, adverse event assignment by experts.

Two good-quality observational studies suggested that, in contrast to a higher risk for suicide in men, there were no sex-based differences in risks for self-harm, but there were age-related differences (53, 54). Suicide attempts were greater in younger persons (31.4 per 10 000 person-years in those younger than 18 years vs. 7.8 per 10 000 person-years for those 18 years or older) (54) and rates of self-harm were higher in those aged 19 to 30 years (214.7 per 10 000 person-years) than those older than 30 years (88.3 per 10 000 person-years) (53). For all ages, the highest risk for suicidal behaviors occurred during the month before treatment initiation and the first month of treatment (54). Rates of suicidal behaviors in real-world practice situations were similar to trial rates for 1 study (54) but were substantially higher in the other (53); this higher rate could reflect real differences or may represent study differences in definitions (and perhaps ascertainment).

Suicidal Ideation

Three meta-analyses used a combined end point of suicidal ideation or behavior (34, 38, 41). They found no differences between patients who received treatment with antidepressants or placebo, except for a reduction in older adults who received treatment with second-generation antidepressants for all psychiatric conditions (OR, 0.39 [CI, 0.18 to 0.78]) (34).

Serious Psychiatric Events

We found no existing systematic reviews that addressed serious psychiatric events, such as psychiatric hospitalization or precipitation of mania. Observational data did not provide reliable estimates of the effect of antidepressant use on these outcomes.

Tolerability

We found 8 systematic reviews (44–51) and 2 large cohort or uncontrolled treatment trials (55, 56) that reported overall discontinuation rates or discontinuation because of adverse effects. Rates of early treatment discontinuation ranged from 16% to 29% in meta-analyses of antidepressant trials in primary care patients with depression, with a best estimate of 20% to 23% in "real-world" trials of primary care. Early discontinuation could be due to lack of effect, adverse effects, or other unknown reasons and therefore does not clearly reflect tolerability. Rates of early discontinuation due to adverse effects were lower (5% to 12%) and are a direct reflection of tolerability. Patients 55 years or older had higher discontinuation rates overall (27% to 36%) and because of adverse effects (17% to 22%). With longer follow-up, adverse event discontinuation rates increased, particularly in those who switched or augmented medications because of lack of efficacy or intolerable side effects.

Older Adults

As reported earlier, older adults were at lower risk for suicide-related harms during antidepressant treatment. For serious medical events in older adults, we found a fair-quality systematic review of 6 large observational studies from Denmark, Canada, the United Kingdom, and Holland that examined bleeding risk with SSRIs (57). Among 26 005 Danish patients 16 years or older (almost half of whom were 60 years or older), risk for hospitalization for upper gastrointestinal bleeding was increased compared with nonrecipients during intervals of current SSRI use only, with an excess risk of 3.1 per 1000 treatment-years. In 317 824 Canadian patients 65 years or older who received antidepressants, risk for hospitalization for upper gastrointestinal bleeding increased greatly with age, from 4.1 hospitalizations per 1000 person-years of SSRI treatment in those aged 65 to 70 years to 12.3 hospitalizations per 1000 person-years in octogenarians. Excess hospitalizations for upper gastrointestinal bleeding were increased 5-fold (33.2 per 1000 treatment-years) in persons with previous upper gastrointestinal bleeding. In some studies (58–60), but not all (61), odds of upper gastrointestinal bleeding among SSRI recipients were further increased at least 2- to 3-fold when SSRI recipients were also receiving NSAIDs, with less risk associated with concurrent use of aspirin or other anticoagulant medications.

Discussion

Summary of Findings

We found that primary care depression screening programs were likely to be effective when other staff provided part of the depression care, such as assessment and monitoring in coordination with the primary care provider's treatment or when extra efforts were made to enroll patients in specialty mental health treatment. This conclusion is based on 4 newly published trials and 5 trials that were included in the previous review. We found no data that identified harms of depression screening. Harms of screening were not discussed in the previous report. We also found that depression treatment in older adults was effective, which complements the previous review's finding that depression treatment is effective in general adult populations. Details of these data can be found in the full report of this review (16).

Finally, we examined harms of second-generation antidepressant use in adults, which were not addressed in the previous review. We found that young adults (aged 18 to 29 years) seem to have an increased risk for suicidal behavior (but not suicide deaths), particularly early in the course of treatment. We found no apparent increase or decrease in risk for suicidal behavioral or deaths in middle-aged populations as a result of second-generation antidepressant use. These conclusions are not definitive, however, because suicide deaths were very rare (and therefore power to detect an increased risk was limited) and data on suicidal behavior were not unanimous. Older adults seem to have lower risk for suicidal behavior, although the risk for upper gastrointestinal bleeding is increased and is a particular concern when combined with NSAIDs.

Comparisons With Other Reviews of Depression Screening

In comparison with the 2002 systematic review (62), a 2005 Cochrane review (10), which excluded all studies that included "complex quality improvement/care management" strategies, concluded that screening programs were not effective in improving health outcomes. Our findings both confirm and extend these 2 previous reviews. Consistent with both the USPSTF and Cochrane reviews, the limited evidence we found on screening and feedback without further care supports suggests that this approach is unlikely to have an effect. Our findings show that depression care support programs that include screening can improve depression symptoms and remission in adult populations.

Why Screening Programs Alone May Not Be Effective

It is puzzling, at first glance, why screening and feedback of results alone would not clearly improve depression outcomes, because it is fairly well-established that they do increase recognition of depression (62). Critics of widespread depression screening suggest that the differences between clinically and screen-detected cases could partially explain this discrepancy (63, 64). Patients whose depression is undetected in primary care tend to be less impaired and have milder levels of depression than those who are identified without screening (65–68). These patients may not need active treatment or may not respond as well to medication (69).

The greatest barrier to long-term relief from depression is probably insufficient treatment, rather than inade-

quate identification. In real-world primary care settings, up to 40% to 67% of patients discontinue their antidepressant medication within 3 months, and few receive adequate follow-up (70–72). Thus, efforts to increase appropriate treatment and improve adherence to treatment are likely to provide the greatest effect. Given the burden on the primary care clinician, it is not surprising that the greatest gains are seen in programs in which other staff provides some of the depression care. Considerable research in recent years has focused on treatment approaches that do just this, such as disease management and collaborative care, which are generally effective (11, 73–76) and cost-effective (77). There are probably several mechanisms by which these interventions produce benefits; such mechanisms include enhanced treatment adherence through closer monitoring of treatment tolerability and response, treatment adjustments, and psychosocial support.

Age-Related Risks Associated With Second-Generation Antidepressant Use

Two meta-analyses suggested an increased risk for suicidal behavior in younger adults, particularly those with MDD or those receiving paroxetine (34, 41), whereas another demonstrates a protective effect of antidepressant treatment of older adults (35). Other studies outside the scope of this review generally confirm a beneficial effect of antidepressants on suicides in older adults (78, 79). However, the increased risk for upper gastrointestinal bleeding in older adults is a concern. Concurrent use of NSAIDs, and to a lesser extent low-dose aspirin and other anticoagulants, seemed to further increase bleeding risks. A recently published meta-analysis estimated increased odds of upper gastrointestinal hemorrhage with SSRI use (OR, 2.36 [CI, 1.44 to 3.85]), particularly when NSAIDs were used concurrently (OR, 6.33 [CI, 3.40 to 11.8]) (80). In people aged 50 years or older without other risk factors, but with both SSRI and NSAID use, the number needed to treat to harm was 106. Among postmarketing reports for adults primarily older than 60 years, median time to bleeding was after 25 weeks of SSRI treatment. These findings may have implications for all adults but particularly for vulnerable older adults or those with a history of gastrointestinal bleeding, given the prevalence of use of analgesic medications (over-the-counter as well as prescription) for therapeutic and preventive reasons.

Limitations of the Review and the Literature

This review took a targeted approach that focused on critical key questions and evidence gaps at the time of the last review and limited the evidence reviews for some questions. We limited the evidence for harms of antidepressant treatment to systematic reviews, supplemented by large prospective observational studies to address deficiencies in short-term RCTs. Although this approach was pragmatic (and our consideration of the literature suggested to us that it was generally adequate), it would not have captured rare or emerging serious medical events that were not already well studied or systematically reviewed. Detailed considerations of potential side effect differences were beyond the scope of this report but are considered elsewhere (47, 81). Furthermore, studies that probably met the review criteria but would not fundamentally change the review findings were published between the completion of our review and publication of this article. **Appendix Table 3** (available at www.annals.org) lists these studies, but they were not formally incorporated into this article.

Furthermore, the available evidence base in antidepressant treatments has limitations. Much of the evidence for serious suicide-related harms derives from short-term RCTs conducted for drug development and regulatory approval. This evidence may not be generalizable to primary care because of recruitment of motivated patients, exclusion of patients with the most severe depression or suicidal patients, high withdrawal rates (81), and sponsorship by the drug industry (which has been shown to be more likely to demonstrate positive effects than independent studies) (82). Also, high placebo effects are documented and may be due to several factors, including the trend toward less severely depressed patients in more recent clinical trials and the ameliorating effect on depression stemming from the support of being in a trial (83).

Conclusion

Good evidence supports the health benefits of programs that combine depression screening and feedback with the support of additional staff to provide some depression care in adults who visit primary care. However, available evidence does not support screening and feedback of results to the clinician in the absence of additional staff that provides some depression care support. The most comprehensive programs included clinician training and treatment protocols provided at the point of care, patient educational materials, office staff training and participation in providing post-visit follow-up, and available mental health referral. Closer monitoring may also be important for reducing uncommon, but potentially serious, adverse events.

Concerns about rare, but very serious, suicide-related antidepressant treatment harms have prompted repeated meta-analyses. The most current evidence on completed suicide does not demonstrate an effect of second-generation antidepressants compared with placebo. However, several meta-analyses suggest a true short-term increase in suicidal behavior in young adults (aged 18 to 29 years) who receive antidepressants, particularly those with MDD and those receiving paroxetine. Thus, careful monitoring during early treatment, particularly in younger adults, seems prudent.

From Kaiser Permanente Center for Health Research, Portland, Oregon, and University of North Carolina, Chapel Hill, North Carolina.

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Request for Single Reprints: Elizabeth A. O'Connor, PhD, Kaiser Permanente Center for Health Research, 3800 North Interstate Avenue, Portland, OR 97227; e-mail, Elizabeth.OConnor@kpchr.org.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. O'Connor and Whitlock and Ms. Beil: Kaiser Permanente Center for Health Research, 3800 North Interstate Avenue, Portland, OR 97227.
Dr. Bradley: University of North Carolina, Department of Psychiatry, CB 7160, Chapel Hill, NC 27599.

Author Contributions: Conception and design: E.A. O'Connor, E.P. Whitlock, T.L. Beil, B.N. Gaynes.
Analysis and interpretation of the data: E.A. O'Connor, E.P. Whitlock, B.N. Gaynes.
Drafting of the article: E.A. O'Connor, E.P. Whitlock.
Critical revision of the article for important intellectual content: E.P. Whitlock, B.N. Gaynes.
Final approval of the article: E.P. Whitlock, B.N. Gaynes.
Provision of study materials or patients: T.L. Beil.
Statistical expertise: E.A. O'Connor.
Obtaining of funding: E.P. Whitlock.
Administrative, technical, or logistic support: T.L. Beil.
Collection and assembly of data: E.A. O'Connor, T.L. Beil, B.N. Gaynes.

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102. **Marks DM, Park MH, Ham BJ, Han C, Patkar AA, Masand PS, et al.** Paroxetine: safety and tolerability issues. Expert Opin Drug Saf. 2008;7:783-94. [PMID: 18983224]
103. **Möller HJ, Baldwin DS, Goodwin G, Kasper S, Okasha A, Stein DJ, et al; WPA Section on Pharmacopsychiatry.** Do SSRIs or antidepressants in general increase suicidality? WPA Section on Pharmacopsychiatry: consensus statement. Eur Arch Psychiatry Clin Neurosci. 2008;258 Suppl 3:3-23. [PMID: 18668279]
104. **Papakostas GI, Nelson JC, Kasper S, Möller HJ.** A meta-analysis of clinical trials comparing reboxetine, a norepinephrine reuptake inhibitor, with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. Eur Neuropsychopharmacol. 2008;18:122-7. [PMID: 17719752]
105. **Rahme E, Dasgupta K, Turecki G, Nedjar H, Galbaud du Fort G.** Risks of suicide and poisoning among elderly patients prescribed selective serotonin reuptake inhibitors: a retrospective cohort study. J Clin Psychiatry. 2008;69:349-57. [PMID: 18278986]

Appendix Table 1. Inclusion and Exclusion Criteria for KQs Discussed*

KQ1 and KQ1a: Screening trials

Inclusion criteria

1. Screening: study of depression screening
2. Requires 1 of the following outcomes: depressive symptoms, quality-of-life ratings, assessments of functioning, depressive illness diagnosis, suicidality (attempts or ideation), change in health status (e.g., death, improvement in comorbid disorders, and reduction in physical symptoms)

Exclusion criteria

1. Focus on inpatient, residential treatment, psychiatric, or community settings
2. Focus on interventions that are not primary care feasible or referable (e.g., electroconvulsive therapy)
3. Does not meet quality criteria, including follow-up <6 wk
4. Focus on children or adolescents
5. None of the outcomes listed above
6. Focus on pregnancy-related screening
7. Examination of genetic modifiers
8. Does not meet any inclusion criterion
9. Not a general primary care population
10. Not English language or nondeveloped country
11. Noncomparative study or excluded design
12. Comparative effectiveness study
13. Missing both depression-specific screen and depression-specific outcome
14. Screen not used in clinical care

KQ4: Harms of depression treatment with antidepressants

Inclusion criteria

1. Systematic review; regulatory review; large cohort, or large, prospective observational study addressing adverse events associated with depression treatment or screening
2. For studies of suicidality
   a. Minimum of 10 000 participants for cohort or observational study
   b. Minimum follow-up of 6 months
3. For studies of nonsuicidality harms
   a. Minimum of 1000 participants for cohort or observational studies
   b. Minimum follow-up of 3 months
   c. May include comparative effectiveness without control group if absolute rates of harms in an understudied population are provided

Exclusion criteria

1. Focus on inpatient, residential treatment, psychiatric, or community settings
2. Focus on interventions that are not primary care feasible or referable (e.g., electroconvulsive therapy)
3. Does not meet quality criteria
4. Focus on children or adolescents
5. None of the adverse effects of interest to our review above
6. Focus on pregnancy-related screening
7. Updated or covered by another more recent meta-analysis or systematic review
8. Does not meet any inclusion criterion
9. Not a general primary care population
10. Not English language or nondeveloped country
11. Not a study design specified above
12. Comparative effectiveness study

KQ = key question.
* See full report for other KQ criteria (16).

Appendix Table 2. Use of Existing Systematic Reviews

Consistent with recently articulated methods (84), we initially conducted a comprehensive search of systematic reviews by using MEDLINE, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, Health Technology Assessments, and PsycINFO from 1998 to August 2006. We identified reviews that were relevant to 1 or more KQ on the basis of populations, interventions, and outcomes in the scope of the current review and then assessed the quality of those that were identified as relevant. Strategies for using systematic reviews were different for KQ1, KQ1a, and KQ4.

KQ1 and KQ1a: Effectiveness of depression screening

One recent good-quality review (10) examined questions similar to those addressed in our review but had more restrictive inclusion and exclusion criteria. Therefore, we proceeded with our systematic review of primary evidence by using the bibliography of this review and all others with potential relevance to KQ1 and KQ1a to identify primary evidence.

KQ4: Harms of depression treatment with antidepressants

We identified relevant systematic reviews and included them as evidence for KQ4, given the large number of regulatory studies used. We included all fair- or good-quality systematic reviews that reported on suicidality (completed suicide, suicidal behavior, or suicidal ideation), tolerability (operationalized as rates of overall discontinuation and discontinuation due to adverse effects), or risk for gastrointestinal bleeding in our report. We reported specific analyses of most relevance where possible. For example, if a systematic review ran separate meta-analyses of all antidepressant recipients and the subgroup of antidepressant recipients who received them for depression, we reported the latter analysis.

KQ = key question.

Appendix Table 3. Studies Found in Bridge Search With Possible Inclusion or Exclusion Criteria*

Study, Year (Reference)	Brief Summary or Analysis†
KQ1	
No studies were found.	NA
KQ1a	
Schreuders et al, 2007 (85)	Primary care patients were screened. Those with ≥3 primary care visits in the previous 6 mo who screened high on a general mental health instrument (not depression-specific) were recruited. Results show that additional problem-solving treatments by nurse specialists did not improve mental health outcomes. The depressed sample could not be identified at baseline to determine effect for these persons.
van Marwijk et al, 2008 (86)	Primary care practices screened patients, providers conducted consultation, and antidepressant treatment was proposed. A small effect was found at 6-mo follow-up but disappeared at 12-mo follow-up. This was consistent with other results that no long-term effect was sustained without additional care supports for providers.
Wang et al, 2007 (87)	Depression outreach and care management program in a worksite setting was effective. This was consistent with other results that showed that care management involving ongoing monitoring and communication with providers was effective. The generalizability of results to primary care was questionable.
KQ2	
No studies were found.	NA
KQ3	
Nelson et al, 2008 (88)	Meta-analysis of second-generation antidepressants in older adults concluded that second-generation antidepressants were more effective than placebo in older depressed adults.
Pinquart et al, 2007 (89)	Meta-analysis of psychotherapy and other behavioral interventions for depression in older adults concluded that cognitive behavioral therapy and reminiscence therapy are effective.
Sneed et al, 2008 (90)	Meta-analysis of clinical trials that compared antidepressants with placebo or an active comparator in older adults. The response rates were higher in the active comparator trials compared with the placebo trials. This was not relevant to our report because our focus was on establishing efficacy rather than comparative efficacy or effectiveness.
Wilson et al, 2008 (91)	Reviewed psychotherapy for depression in older adults and included far fewer studies than the reviews used in the full report (16). Cognitive behavioral therapy was more effective than wait-list controls (5 trials) and active controls for outcomes measured by 1 instrument but not another (3 trials total).
KQ4	
Aursnes and Gjertsen, 2008 (92)	Reviewed regulatory data and compared results with published SPC. Five of 19 adverse effects were found in data but not mentioned in SPC. The abstract did not mention any serious adverse events.
Barbui et al, 2009 (93)	Systematic review of observational studies that reported suicide attempts of those receiving SSRIs vs. those who did not. Use of SSRIs may be associated with reduced risk for suicide in adults with depression but may increase suicidality in adolescents.
Beasley et al, 2007 (94)	Assessed suicidality emergence reported in the largest available double-blind, placebo-controlled fluoxetine trials in adults with major depression. Fluoxetine led to greater benefit rather than risk for suicidality.
Cipriani et al, 2007 (95)	Review of reviews of acute-phase treatment with antidepressants. Some evidence supports that SSRIs may increase suicidal thoughts, but not actual suicide. Uncertainty remains, and balance between risks and benefits should be considered for each individual patient.
Cooper-Kazaz and Lerer, 2008 (96)	Examined the thyroid hormone triiodothyronine as a supplement to antidepressant treatment. Triiodothyronine was well tolerated in most studies and adverse effects were not an impediment to its use, but more research is needed for definitive conclusions.
de Abajo and García-Rodríguez 2008 (97)	Used a large general practice database to examine upper gastrointestinal effects of second-generation antidepressants. Antidepressants with relevant blockade action on the serotonin reuptake mechanism increase risk for upper gastrointestinal bleeding, particularly in association with nonsteroidal anti-inflammatory drugs. Use of acid-suppressing agents limits increased risk.
Deshauer et al, 2008 (98)	Meta-analysis of placebo-controlled SSRI trials ≥6 mo. Evidence supports the current recommendation of continued treatment for 6–8 mo after initial recovery, but no data were found for treatment that lasted >1 y. Withdrawal was reported as proxy for tolerability. No mention of serious adverse effects was found in the abstract.
Hansen et al, 2008 (99)	Meta-analysis for use of second-generation antidepressants for relapse prevention. Withdrawal due to adverse effects (7% receiving active treatment and 5% receiving placebo, which is in the range of those reported in this report) was reported. No mention of serious adverse effects was found in the abstract.
Katzman et al, 2007 (100)	Meta-analysis comparing paroxetine with placebo and other active agents. A consistently better effect occurred with paroxetine than placebo. Inconsistent results were found when placebo was compared with other active agents. The abstract had minimal mention of tolerability and no mention of serious adverse effects.
Marcinko, 2007 (101)	Estimates of risk–benefit ratio. No description of data sources or suggestion that new data were presented in this publication.
Marks et al, 2008 (102)	Review of paroxetine. This study did not seem to be a systematic review.
Möller et al, 2008 (103)	Review of publications (RCTs and observational designs) related to antidepressants and suicide, suicidality, suicidal behavior, and aggression. Antidepressants, including SSRIs, carry a small risk for inducing suicidal thoughts and attempts in patients younger than 25 years but must be balanced against well-known beneficial effects.
Papakostas et al, 2008 (104)	Review compared reboxetine with SSRIs and found tolerability better for SSRIs, although some mild adverse effects were more common in SSRI recipients. Efficacy seems to be similar. No mention of serious adverse effects was found in the abstract.
Rahme et al, 2008 (105)	Used a large Canadian health care database to compare risk for suicide death and poisoning during periods of antidepressant treatment vs. periods without treatment in older patients. No differences were found in suicide rates between SSRI use vs. nonuse. Higher rates among those who received both SSRIs and other antidepressants may be due to severity of an underlying disorder. Poisoning is higher during SSRI use vs. nonuse for some agents.

KQ = key question; NA = not applicable; RCT = randomized, controlled trial; SPC = Summary of Product Characteristics; SSRI = selective serotonin reuptake inhibitor.
* From January 2008 to February 2009.
† Based on abstract review or brief examination of publication.

Appendix Table 4. **Summary of Depression Care Support Elements Provided in Programs of Depression Screening With Feedback of Results to Providers**

Category of Depression Care	Depression Care Component	Studies in the General Adult Population				Studies in Older Adults			
		Bergus et al, 2005 (26)	Jarjoura et al, 2004 (27)*	Wells et al, 2000 (23) and 2004 (30); Sherbourne et al, 2001 (31)*	Rost et al, 2001 (22), 2000 (32), and 2002 (33)†	Bosmans et al, 2006 (28)	Whooley et al, 2000 (24)	Callahan et al, 1994 (25)	Rubenstein et al, 2007 (29)*
Screening	Screening results given to provider for review	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Improve quality of PCP care	Provider prompted or trained in further assessment	–	Yes	–	Yes	Yes	Yes	–	–
	Provider given generic treatment protocol and depression management training	–	Yes	Yes	Yes	Yes	Yes	Yes	–
	Provider given patient-specific treatment recommendations	–	–	–	–	–	–	Yes	–
Logistical support to PCP	Support or study staff provided proactive logistical help, *e.g.*, with follow-up appointments and referrals	–	Yes	Yes	Yes	–	–	Yes	Yes
Other staff provide some or most of depression care	Psychoeducational classes	–	–	–	–	–	Yes‡	–	–
	Support or study staff provided monitoring and/or case management	–	–	Yes	Yes	–	–	–	Yes
	Routine referral to behavioral counseling	–	Yes	–	–	–	–	–	–
	Study, mental health, or other specialty staff provided depression care or medication management	–	Partial	Yes	–	–	–	–	Partial
Other	Financial commitment by provider's institution	–	–	Yes	–	–	–	–	–

PCP = primary care provider.
* Statistically significant group differences.
† Group differences were significant only for the subgroup or participants with newly identified depression.
‡ This program offered a group psychoeducational class that only 12% of the intervention participants attended.

Appendix Table 5. Summary of Rate of Suicide and Related Behavior or Ideation From Systematic Reviews

Study, Year (Reference); Search Dates	Treatment	Completed Suicide		
		Events/ Persons, *n/n*	Rate per 10 000 Persons	Odds Ratio (95% CI)
Levenson and Holland, 2006 (34), and Stone and Jones, 2006 (35); through September 2006				
MDD only (162 RCTs)	2nd-gen AD Placebo	4/22 379 1/14 873	1.79 0.67	2.66* (0.26–130.9)
All psychiatric indications (295 RCTs)	2nd-gen AD Placebo	5/39 799 2/27 309	1.3 0.73	1.72* (0.28–18.01)
All psychiatric indications for patients aged 18–24 y (272 RCTs)	2nd-gen AD Placebo	–	–	–
All psychiatric indications for patients aged 25–30 y (295 RCTs)	2nd-gen AD Placebo	–	–	–
All psychiatric indications for patients aged 31–64 y (295 RCTs)	2nd-gen AD Placebo	–	–	–
All psychiatric indications for patients aged ≥65 y (233 RCTs)	2nd-gen AD Placebo	–	–	–
Hammad et al, 2006 (36); through 2000				
MDD only (207 RCTs)	SSRIs only SSRI/other Placebo	6/14 675 15/25 604 2/8868	4.1 5.9 2.3	SSRI vs. placebo, 1.81* (0.32–18.37); SSRI + other vs. placebo, 2.60* (0.60–23.4)
Khan et al, 2003 (37); January 1985 to January 2000				
Indications not stated (total RCTs not reported)	SSRIs Placebo	38/26 109 5/4895	14.6 10.2	1.43* (0.56–4.64)
Indications not stated (number of RCTs not reported)	SSRIs Active controls	38/26 109 34/17 273	14.6 19.7	0.74* (0.45–1.21)
Gunnell et al, 2005 (38), Saperia et al, 2006 (39), and CSM, 2004 (40); through 2003				
All indications (439 RCTs)	SSRIs Placebo	9/23 804 7/17 022	3.8 4.1	0.85 (0.20–3.40)
GlaxoSmithKline, 2006 (41); through December 2004				
MDD cases (19 RCTs)	Paroxetine Placebo	–	–	–
MDD cases for patients aged 18–30 y (number of RCTs not reported)	Paroxetine Placebo	–	–	–
Fergusson et al, 2005 (42); 1967 to June 2003				
All indications (411 RCTs)	SSRIs Placebo	4/10 557 3/7 856	3.8 4.0	0.95 (0.24–3.78)
Storosum et al, 2001 (43); 1983 to 1997				
Probable MDD cases (77 short-term RCTs)	SSRIs Placebo	7/7944 4/4302	8.8 9.3	0.95* (0.24–4.42)

2nd-gen AD = second-generation antidepressant; CSM = Committee on Safety of Medicines; MDD = major depressive disorder; RCT = randomized, controlled trial; SSRI = selective serotonin reuptake inhibitor.
* Calculated.
† $P < 0.05$.
‡ Patients aged 25–64 y. Cited in reference 35.
§ Nonfatal self-harm; also includes fluoxetine-related suicides for reference 38.
¶ Ideation only.

Appendix Table 5—**Continued**

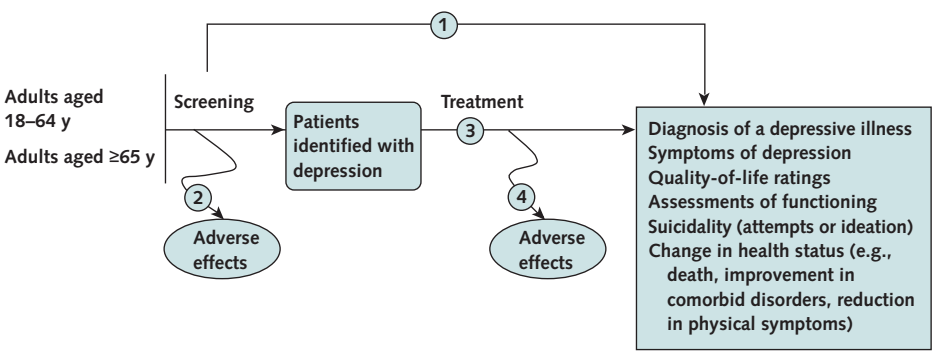
Suicidal Behaviors			Suicidal Behavior or Ideation		
Events/ Persons, *n/n*	Rate per 10 000 Persons	Odds Ratio (95% CI)	Events/ Persons, *n/n*	Rate per 10 000 Persons	Odds Ratio (95% CI)
–	–	–	163/22 309 123/14 728	73.1 83.5	0.86 (0.67–1.10)
79/39 729 49/27 164	19.9 18.0	1.11 (0.77–1.61)	248/39 729 196/27 164	62.4 72.2	0.84 (0.69–1.02)
23/3810 8/2604	60.4 30.7	2.31 (1.02–5.64)†	47/3810 21/2604	123.4 80.6	1.55 (0.91–2.70)
–	–	1.03 (0.68–1.58)‡	41/5558 27/3772	73.8 71.6	0.79 (0.64–0.98)‡
–	–	1.03 (0.68–1.58)‡	147/27 086 124/18 354	54.3 67.6	0.79 (0.64–0.98)‡
–	–	0.06 (0.01–0.58)†	12/3227 24/2397	37.1 100.1	0.39 (0.18–0.78)†
–	–	–	–	–	–
–	–	–	–	–	–
128§/30 814 75§/21 689	41.5 34.6	1.21 (0.87–1.83)	97¶/26 882 80¶/18 822	36.1 42.5	0.80 (0.49–1.30)
11/3455 1/1978	31.8 5.1	6.7 (1.10–149.4)†	31/3455 11/1978	89.7 55.6	1.3 (0.7–2.8)
8/612 0/339	130.7 0	Cannot calculate	–	–	–
23/10 557 6/7856	21.8 7.6	2.70 (1.22–6.97)†	–	–	–
29/7944 17/4302	36.5 39.5	0.92* (0.49–1.79)	–	–	–

Appendix Table 6. Summary of Rate of Suicide and Related Behavior Reported in Cohort Studies*

Study, Year (Reference); Subgroup	Treatment	Completed Suicide		Suicidal Behaviors	
		Events/Persons, *n/n*	Rate per 10 000 Persons (95% CI)	Events/Persons, *n/n*	Rate per 10 000 Persons (95% CI)
Simon et al, 2006 (54); MDD only in prepaid group practice	2nd-generation antidepressant and TCAs	31/65 103	4.8 (3.3–6.8)†	76/65 103	11.7 (9.3–14.6)†
Martinez et al, 2005 (53); patients aged <90 y with new antidepressant prescription	Any antidepressant (primarily 1st-generation)	69/146 095	4.7 (3.7–6.0)†	1968/146 095‡	134.7 (128.9–140.8)†
Martinez et al, 2005 (53); patients aged 19–30 y with new antidepressant prescription	Any antidepressant (primarily 1st-generation)	19/34 792	5.5 (3.5–8.6)†	747/34 792	214.7 (199.8–230.7)†
Jick et al, 1995 (52); pharmaceutical event monitoring data for all indications	Any antidepressant (primarily 1st-generation)	143/172 598	8.3 (7.0–9.8)†	–	–

MDD = major depressive disorder; TCA = tricyclic antidepressant.
* Includes 95% CI around event rate if no comparison.
† Calculated.
‡ Nonfatal harms.

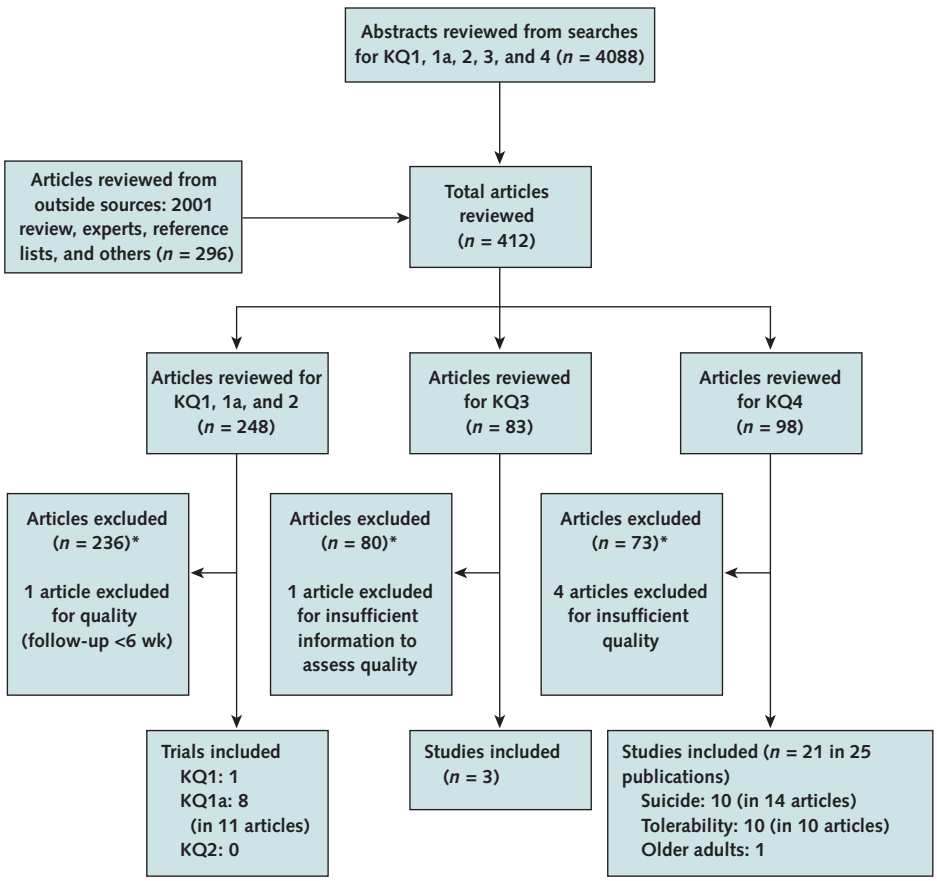
Appendix Figure 1. Analytic framework and key questions.



1. Is there direct evidence that screening for depression among adults and elderly patients in primary care reduces morbidity and/or mortality?
   a. What is the effect of clinician feedback of screening test results (with or without additional care management support) on depression response and remission in screening-detected depressed patients receiving usual care?
2. What are the adverse effects of screening for depressive disorders in adults and elderly patients in primary care?
3. Is antidepressant and/or psychotherapy treatment of elderly depressed patients effective in improving health outcomes?
4. What are the adverse effects of antidepressant treatment (particularly SSRIs and other second-generation drugs) for depression in adults and elderly patients?

SSRI = selective serotonin reuptake inhibitor.

Appendix Figure 2. **Search results and article flow, by key question.**



KQ = key question.
* Numbers differ slightly from the full report (16) because only articles relevant to the more limited body of literature discussed in this publication are included in this figure.