Effective Health Care

Evidence-based Treatments for Women with Depression

Results of Topic Selection Process

AHRQ will not proceed with the development of a new evidence review on the nomination *Evidence-based Treatments for Women with Depression*. The questions in the nomination, with the exception of harms, were found to be addressed primarily by number of current and in process evidence reviews. We identified a 2014 AHRQ review, two Cochrane reviews (2013, 2014), and one in-process review examining the benefits and harms associated with interventions for depression in pregnant/postpartum women. We identified a 2015 VA evidence map and a 2014 Individual Patient Data meta-analysis examining sex differences associated with interventions for depression. We identified four reviews published since 2012 and an in-process Cochrane review examining costs associated with treatments for depression. Research examining harms specifically in non-pregnant/postpartum women may be too limited at this time.

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Nomination

Topic Number: 0516 " **Received On:** 12/31/2012

Topic Name: Evidence-based Treatments for Women with Depression

Nominator: A physician

Nomination Summary: The nominator is interested in identifying the effectiveness, harms, and costs associated with interventions for treating depression in adult women. The nominator notes that depression can affect a patient's motivation to seek and comply with care, and that it is prevalent among patients with substance abuse and severe and/or chronic pain. Treating depression effectively may serve as a strategy to increase engagement in other aspects of care. The nominator hopes that an AHRQ systematic review will identify knowledge gaps and inform research priorities for treating depression among adult women.

Key Questions from Nomination: "For women with depression, what are the various evidence-based treatments (e.g. medication, exercise, meditation, psychotherapy) and what are their relative costs including consideration for time to recover and to decrease further episodes?"

Revised Key Questions: We have revised the key questions to better address the nominator's interest in evidence based treatments by removing reference to specific interventions. In addition, to better address the nominator's concern about relative times to recovery, we specified interest in both short and long term outcomes. Finally, to address the nominator's concern regarding relative cost, we have added the examination of harms in addition to costs.

Key Question 1. In adult women, what is the short and long-term effectiveness of evidence-based treatments for depression?

a. In pregnant and postpartum women?
b. In all other female populations?

Key Question 2. What are the harms associated with evidence-based treatments used to treat depression in adult women?

a. In pregnant and postpartum women?
b. In all other female populations?

Key Question 3. What are the costs associated with evidence-based treatments used to treat depression in adults?

Policy and/or Clinical Context from the Nomination: "Depression may be the primary diagnosis that interferes in a patient's motivation to seek and comply with health care treatment, making it the gateway target to significantly increase access to care."

Effective Health Care

Evidence-based Treatments for Women with Depression

Topic #: 0516

Nomination Date: December 31, 2012

Topic Brief Date: February 2016

Authors:
Stephanie Veazie
Karli Kondo
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Rose Relevo

Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings from the Topic Brief:

- Key Question 1a.
  - A new evidence review on the benefits related to the short- and long-term effectiveness of evidence-based treatments for depression in pregnant and postpartum women *would likely be duplicative*. We identified four existing reviews and four PROSPERO protocols relevant to the topic.
- Key Question 1b.
  - A new evidence review on the benefits related to the short- and long-term effectiveness of evidence-based treatments for depression in non-pregnant/postpartum women *would likely be duplicative*.
- Key Question 2a.
  - A new evidence review on the harms related to the short- and long-term effectiveness of evidence-based treatments for depression in pregnant and postpartum women *would likely be duplicative*. We identified three systematic reviews and four PROSPERO protocols relevant to the topic.
- Key Question 2b.
  - A new evidence review on the harms related to the short and long-term effectiveness of evidence-based treatments for depression in non-pregnant/postpartum women *would not be duplicative*. One evidence map was relevant to the topic. The evidence map identified only one systematic review (the archived AHRQ review), which included two RCTs comparing sexual dysfunction in men and women receiving paroxetine, and does not address the range of harms known to be relevant in general populations.
  - We reviewed one of the 200 randomly selected articles related to the topic, for an expected total of 28 studies.
- Key Question 3.

- A new evidence review examining costs associated with treatments for depression *would likely be duplicative*. We identified three evidence reviews, one technology assessment, and two protocols relevant to the topic.

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NOTE: The purpose of the topic selection process for the Agency for Healthcare Research and Quality's (AHRQ) Effective Healthcare Program (EHC) is the prioritization of nominations for systematic reviews and other AHRQ EHC reports. This topic brief is not, nor is it intended as a systematic review of the topic.

Introduction

Depression is a common mood disorder that is the single greatest cause of disability worldwide,[1] with approximately 9.5% of the U.S. adult population experiencing a depressive illness.[2] In women, approximately 11% of non-pregnant women of reproductive age experience major depressive disorder (MDD),[3] with 8-19% of women experiencing postpartum depression.[3,4] Major depressive disorder is defined as the presence of at least five of the following symptoms for two weeks or more: depressed or sad mood, feeling tired or fatigued, gaining or losing weight, psychomotor agitation or retardation, diminished interest in activities, inappropriate guilt, difficulty concentrating, and recurring thoughts of death.[5] Other forms of depression include persistent depressive disorder (depressive symptoms lasts for at least 2 years), and postpartum depression.

There are a wide range of pharmacological treatments for depression, including first-generation antidepressants (tricyclic antidepressants, or TCAs)[6] and second-generation antidepressants (SGA).[7] Non-pharmacological treatments for depression include complementary and alternative medicine therapies (e.g. acupuncture, omega-3 fatty acids, S-adenosyl-L-methionine, and St. John's wort) and depression-focused psychotherapies.[7] While research exists guiding the use of pharmacological and non-pharmacological interventions in general populations, less is known about how these interventions may differentially result in benefits and harms to women.[6]

The key questions for this nomination are as follows:

Key Question 1. In adult women, what is the short and long-term effectiveness of evidence-based treatments for depression?

a. In pregnant and postpartum women?
b. In all other female populations?

Key Question 2. What are the harms associated with evidence-based treatments used to treat depression in adult women?

a. In pregnant and postpartum women?
b. In all other female populations?

Key Question 3. What are the costs associated with evidence-based treatments used to treat depression in adults?

Methods

To assess topic nomination #0516, *Evidence-based Treatments for Women with Depression* for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of our assessment determining the need for further evaluation. Details related to our assessment are provided in Appendix A.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new research* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.

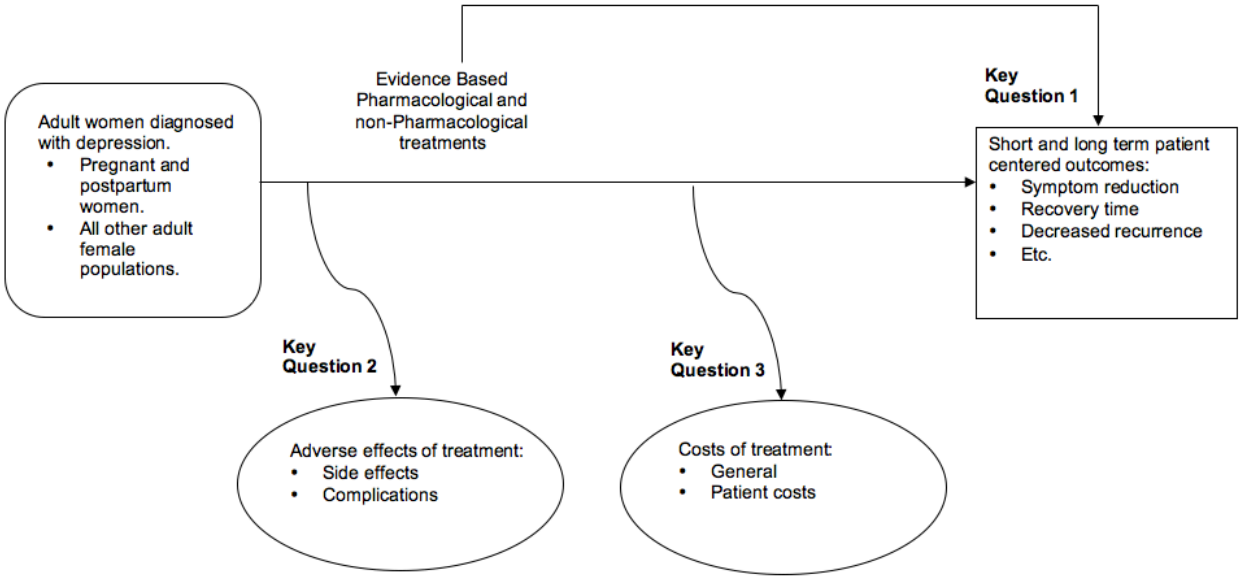
5. " Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. " Determine the *potential value* of a new systematic review or other AHRQ product.

To define the inclusion criteria for the key questions, we specify the population, interventions, comparators, outcomes, and timing (PICOT) of interest. PICOT are outlined in Table 1. In addition, our approach was guided by an analytic framework (see Figure 1).

Table 1. PICOT by key question

	KQ 1: In adult women, what is the short and long-term effectiveness of evidence-based treatments for depression? a. In pregnant and postpartum women? b. In all other female populations?	KQ 2: What are the harms associated with evidence-based treatments used to treat depression in adult women? a. In pregnant and postpartum women? b. In all other female populations?	KQ 3: What are the costs associated with evidence-based treatments used to treat depression in adult women?
Population	Adult (18 years or older) women with depression or men and with results reported for women.	Adult (18 years or older) women with depression or men and with results reported for women.	All adults
Intervention	Evidence-based treatments for depression in women.	Evidence-based treatments for depression in women.	Evidence-based treatments for depression in women.
Comparators	Placebo, control, other active interventions, treatment as usual, wait-list	Placebo, control, other active interventions, treatment as usual, wait-list	Placebo, control, other active interventions, treatment as usual, wait-list
Outcomes	Symptom reduction, recovery time, decreased recurrence, etc.	Harms	Costs
Timing	Short-term and long-term	Short-term and long-term	Short-term and long-term

Figure 1 Analytic Framework



Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of a New Evidence Review/Duplication

To assess duplication, we conducted a search for existing or in-progress high quality systematic reviews. We searched the following organizations/websites: Agency for Healthcare Research and Quality (AHRQ), Veterans Administration (VA), Cochrane Systematic Reviews and Protocols, PubMed/MEDLINE, Health Technology Assessment (HTA), and PROSPERO.

Impact of New Evidence

We reviewed whether a new evidence review could potentially impact the standard of care or resolve practice variation (see Appendix A).

Available Primary Research for an Evidence Review

Literature search. To assess the volume of literature and the size of a potential systematic review, a research librarian created search strategy designed to address the key questions in the nomination (see Appendix C). We conducted a literature search of PubMed/MEDLINE covering February 2011 to February 2016. Using established PubMed/MEDLINE filters, we categorized studies as randomized controlled trials,[7] systematic reviews,[8] and other. For searches identifying greater than 200 unique titles, we randomly selected a total of 200 articles to review and calculated the percent included and the expected total included for the total yield and each of the three independent categories.

Study Selection. We developed criteria for population, interventions, comparators, outcomes, and timing (PICOT) as criteria for inclusion/exclusion (see Table 1). One investigator reviewed the titles and abstracts.

Value

We evaluated whether the proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change and whether the review has the potential to influence practice (see Appendix A).

Compilation of Findings

We constructed a table outlining the selection guidelines and criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

Evidence-based Treatments for Women with Depression is an appropriate and important topic. Depression is the second leading causes of disability in the world,[6] with women more likely to be diagnosed than men.[9] Approximately 11% of non-pregnant women of reproductive age experience major depressive disorder (MDD),[3] with 8-19% of women experiencing postpartum depression.[3,4] In the U.S., the estimated economic burden associated with depressive disorders is greater than $80 billion a year, with more than 30% attributable to direct medical expenses.[6] Depression can negatively impact quality of life (QoL), productivity, and is a risk factor for suicide. Depression is treated with a wide range of pharmacological and non-pharmacological interventions, with varying degrees of effectiveness and potential harms to patients. Of concern are both the under-treatment of patients using non-pharmacological methods, and the over-treatment of patients using antidepressants.[6] Given the lack of extensive research examining the benefits and harms of interventions for depression in women specifically, a clear understanding of the effectiveness, harms, and costs would be of interest to clinicians, patients, and payers. See Appendix A for details.

Desirability of New Review/Duplication

Our search for duplication resulted in nine evidence reviews,[6,10-17] one health technology assessment (HTA),[18] seven protocols,[19-25] two archived AHRQ reviews,[26,27] one evidence map,[28] and one evidence brief[29] related to the key questions in the nomination.

Key Question 1

In adult women, what is the short and long-term effectiveness of evidence-based treatments for depression?

Six evidence reviews,[6,11-13,15,16] four protocols,[20,21,23,25] two archived AHRQ reviews,[26,27] one evidence map,[28] and one evidence brief[29] were identified that cover the scope of Key Question 1.

Key Question 1a. In pregnant and postpartum women?

A new evidence review examining treatments for pregnant or postpartum women with depression would be duplicative. We identified four evidence reviews[12,13,15,16] and four PROSPERO protocols[20,21,23,25] covering the scope of the key question (Table 2).

Two reviews examined antidepressants.[15,16] A 2014 AHRQ systematic review evaluated second generation antidepressants (SGA) for pregnant and postpartum women. Outcomes examined included maternal depression symptoms, functional capacity, breastfeeding, mother-infant dyad interactions, and infant and child development.[15] The second, a 2014 Cochrane meta-analysis,[16] examined antidepressants (e.g., sertraline, fluoxetine, paroxetine, and nortriptyline) for a wide range of outcomes, including postnatal depression included treatment remission and response, as well as change in depressive symptoms, symptom severity, global mental health, maternal functioning, quality of life (QoL), obsessions and compulsions, and social adjustment.

Two additional 2013 Cochrane reviews address the topic.[12,13] One examined alternative treatments[12] (i.e., acupuncture, maternal massage, bright light therapy and omega-3 oils) for the treatment of antenatal depression on maternal clinical depression, depressive symptomology, treatment response, depression remission, and anxiety.[12] The second examined psychosocial (e.g., classes/groups, home visits, lay-based telephone support, early postpartum follow-up) and psychological interventions (e.g., debriefing, cognitive behavioral therapy [CBT], and

interpersonal psychotherapy) for postpartum depression on maternal (e.g., depressive symptoms, anxiety, stress) and infant outcomes (e.g. infant/child development).[13] We identified no studies examining outcomes related to engagement in other aspects of care.

Finally, we identified four protocols.[20,21,23,25] Interventions include interventions for the treatment of depression in pregnant and postpartum women generally,[20,23] as well as mindfulness[25] and antidepressants[21] specifically.

Table 2. Key Question 1a. In adult pregnant and postpartum women, what is the short and long-term effectiveness of evidence-based treatments for depression?: Evidence reviews

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
McDonagh, et al., 2014[15] AHRQ	Antidepressant Treatment of Depression During Pregnancy and the Postpartum Period	CDSR, CCRCT, CINAHL, MEDLINE and OLDMEDLINE, PsycINFO, and Scopus from inception to July 2013. Grey literature was searched. 130 studies (124 observational and 6 RCTs) were included in the review overall, with 6 RCTs and 15 observational studies providing direct evidence.	This review examined treatment with second generation antidepressants (SGAs). Comparators were placebo, no active treatment or usual care, other antidepressants, and other nonpharmacological treatments. Outcomes included depressive symptomology, anxiety, functional capacity, pregnancy weight gain, breastfeeding, and infant/child outcomes.	"Evidence about the comparative benefits and harms of pharmacological treatment of depression in pregnant and postpartum women was largely inadequate to allow well-informed decisions about treatment."
Molyneaux et al., 2014[16] Cochrane	Antidepressant treatment for postnatal depression	CCDANCTR (July 11, 2014), The Cochrane Pregnancy and Childbirth Group's Specialized Register, ClinicalTrials.gov, WHO, reference lists, and personal communication with a number of pharmaceutical companies and, identified topic experts, and the International Marcé Society. Searches extended to July 2014. Six randomized controlled parallel groups design studies were included.	Study specific antidepressants included sertraline, fluoxetine, paroxetine, and nortriptyline. One included study allowed for a choice of antidepressant, with an SSRI being the first line of treatment. One study examined sertraline + BDP. Comparators included placebo, treatment as usual, listening visits, placebo + counseling, and another antidepressant. Outcomes included treatment remission and response, as well as change in depressive symptoms, symptom severity, global mental health,	"Pooled estimates for response and remission found that SSRIs were significantly more effective than placebo for women with postnatal depression. However the quality of evidence contributing to this comparison was assessed as very low owing to the small sample size for this comparison (146 participants from three studies), the risk of bias in included studies and the inclusion of one study where all participants in both study arms additionally received psychological therapy.

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
			maternal functioning, QoL, obsessions and compulsions, and social adjustment.	There was insufficient evidence to conclude whether, and for whom, antidepressant or psychological/psychosocial treatments are more effective."
Dennis et al., 2013[12] Cochrane	Interventions (other than pharmacological, psychosocial or psychological) for treating antenatal depression	Cochrane Pregnancy and Childbirth Group's Trials Register (Jan 2013). Secondary references were checked, and experts were consulted. Six RCTs were included in review.	Interventions included: acupuncture, maternal massage, bright light therapy and omega-3 oils. Comparators were usual antenatal treatment and placebo. Outcomes included treatment response, remission, and depressive symptomology.	"The evidence is inconclusive to allow us to make any recommendations for depression-specific acupuncture, maternal massage, bright light therapy, and omega-3 fatty acids for the treatment of antenatal depression."
Dennis et al., 2013[13] Cochrane	Psychosocial and psychological interventions for preventing postpartum depression	Cochrane, MEDLINE and EMBASE, trials found in the Cochrane Pregnancy and Childbirth Group Registry through December 2013. Included 28 trials.	Psychosocial interventions included classes/groups professional- and lay-base, home visits, lay-based telephone support, early postpartum follow-up (e.g., routine postpartum care initiated earlier than standard practice), and continuity/models of care. Psychological interventions included debriefing, CBT, and interpersonal psychotherapy In the majority of studies, the control group was reported to have received usual antenatal/postnatal care. Maternal outcomes included postpartum depression, maternal mortality at 24 weeks, anxiety, stress, parental stress, perceived social support, maternal-infant attachment, and	From full text: "Professionally-based home visits such as intensive nursing home visits and flexible postpartum care provided by midwives, postpartum lay (peer)-based telephone support, and interpersonal psychotherapy appear to show promise in the prevention of postpartum depression. Interventions that are individually-based and initiated postnatally may be beneficial. Finally, interventions targeting 'at-risk' mothers may be more beneficial and feasible than those including a general maternal population." There was no strong evidence to recommend other interventions examined.

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
			maternal dissatisfaction. Infant outcomes included infant immunization, infant development, and child abuse.	
Levin et al.[25] PROSPERO protocol (expected completion May 2016)	To what extent do mindfulness-based interventions reduce depression and anxiety and stress among pregnant and postpartum women?	Authors will search "major databases" from 1983 to 8/30/2015 and will include RCTs and observational studies. Pregnant and postpartum women 18+.	The review will focus on mindfulness interventions that teach formal mindful meditation with the expectation of formal practice on a regular basis. Comparison to non-mindfulness interventions. Outcomes measures will be formally validated depression scales.	NA
Saccone et al.[21] PROSPERO protocol (expected completion Nov 2014)	Depression drug treatment during pregnancy and neonatal outcomes: a pooled meta-analysis of randomized trials	Authors will search MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, ScienceDirect.com, MEDSCAPE and the Cochrane from database inception to October 2014. RCTs only, pregnant women.	This meta-analysis will examine the benefits and harms to both mother and infant related to the use of antidepressants (SSRI, serotonin norepinephrine reuptake inhibitor (SNRI), selective SNRI, tricyclic antidepressant (TCA) and norepinephrine reuptake inhibitors trazodone and nefazodone).	NA
Morrell et al.[20] PROSPERO protocol (expected completion Jan 2014)	An evidence synthesis to evaluate the clinical effectiveness and cost-effectiveness of interventions to prevent postnatal depression	Authors will search PsycINFO, CDSR, DARE, NHS HTA, MEDLINE, EMBASE, CINAHL, Science Citation Index, Premedline, PROSPERO, NHS EED, CCRCT, MIDIRS, ASSIA, Social Care Online, Social Science Citation Index). Searches will be restricted to English language literature and	This systematic review and meta-analysis will examine the benefits, harms, and costs of antenatal and postnatal interventions.	NA

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
		to RCTs, systematic reviews or economic evaluations but with no restriction by publication date.		
Wallace et al.[23] PROSPERO protocol (expected completion December 2015)	Screening, assessment and management of postpartum depression	Authors will search CINAHL, MEDLINE, MEDLINE In Process, CENTRAL, EMBASE, and PsycINFO for SR/MAs and studies examining interventions for pregnant postpartum depression (infants < 12 months).	This systematic review will examine effective management interventions for women experiencing depression during pregnancy and postpartum up to one year after childbirth.	NA

*Summaries from full text are noted when applicable. Abbreviations: AHRQ= Agency for Healthcare Research and Quality; ASSIA= Applied Social Science Index and Abstracts; BDP= Brief Dynamic Psychotherapy; CBT= Cognitive Behavioral Therapy; CCDANCTR= Cochrane Collaboration Depression, Anxiety, and Neurosis Controlled Trials Register; CCRCT= Cochrane Central Register of Controlled Trials; CDSR=Cochrane Database of Systematic Reviews; CINAHL=Cumulative Index to Nursing and Allied Health Literature; DARE= Database of Abstracts of Reviews of Effects; MIDIRS=Midwives Information and Resource Service; NHS EED= National Health Services Economic Evaluation Database; NHS HTA= National Health Services Health Technology Assessment; QoL= Quality of Life; RCT= Randomized Controlled Trial; SGA= Second Generation Antidepressant; SNRI= Serotonin-Norepinephrine Reuptake Inhibitor; SR/MA= Systematic Review/Meta-Analysis; SSRI= Selective Serotonin Reuptake Inhibitor; TCA= Tricyclic Antidepressant; WHO= World Health Organization

Key Question 1b. In all other female populations?

A new evidence review examining treatments for depression in general female populations or examined gender differences would be duplicative. We identified two reviews,[6,11] two archived AHRQ reviews,[26,27] one evidence map,[28] and one evidence brief[29] covering the scope of the key question (Table 3).

A 2015 AHRQ[6] review compared pharmacological to nonpharmacological interventions for adults with major depressive disorder. One included trial examining women only compared SGA to CBT for symptom reduction. No other included studies examined women only, and no subgroup analysis by gender was performed.

We also identified a VA ESP (Veterans Administration Evidence-based Synthesis Program) evidence brief examining repetitive transcranial magnetic stimulation for treatment resistant depression (2 included randomized controlled trials [RCTs] examined gender differences on treatment response),[29] and an individual patient data (IPD) meta-analysis of 14 RCTs examining gender as a moderator between CBT or CBT plus psychopharmacological treatments and a reduction of depressive symptomology.[11]

A completed, but not yet released VA ESP evidence map of systematic reviews examined gender effects in depression and other conditions. Of 86 identified systematic reviews that examined interventions for depression, 14 reported effects by gender. The map provides a

qualitative summary of conclusions from the 14 systematic reviews by intervention. Populations included persistent depressive disorder, and a broad range of depressive disorders, and major depressive disorder. Interventions included psychotherapy, antidepressants (selective serotonin reuptake inhibitors [SSRIs], sertraline, paroxetine, desvenlafaxitine, venlafaxtine), combined antidepressants with psychotherapy, quality improvement, and self-help. Outcomes reported as depressive symptoms, and treatment effects.[28] We identified no studies examining outcomes related to engagement in other aspects of care.

Finally, two archived AHRQ reviews[26,27] of antidepressants for depression include an examination of differential effects by gender on depressive symptomology and treatment response. Archived reports are more than three years old and the findings may not be current.

Table 3. Key Question 1b. In adult (other than prenatal and postpartum) women, what is the short and long-term effectiveness of evidence-based treatments for depression?: Evidence reviews

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
Gartlehner, 2015[6] AHRQ	Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder	MEDLINE, EMBASE, Cochrane Library, AMED, PsycINFO, and CINAHL from Jan 1990 to Jan 2015. The review included 44 RCTs. One trial was among women only.	One trial among women compared SGA to CBT. Primary outcome was depressive symptomology.	Women vs. Men (from full report): "SGAs and CBT showed similar reduction in depressive symptoms in a trial that included only minority women."
Duan-Porter, 2015[28] VA ESP Not yet public	Mapping the Evidence: Sex effects in high-impact conditions for women veterans -- depression, diabetes and chronic pain	PubMed, Cochrane and manual searches (Jan 2009 to Oct 2014). Of the 86 systematic reviews related to interventions for depressive disorders, 14 reviews reported sex effects.	Populations included persistent depressive disorder, and a broad range of depressive disorders, and major depressive disorder. Interventions included psychotherapy, antidepressants (SSRIs, sertraline, paroxetine, desvenlafaxitine, venlafaxtine), combined antidepressants with psychotherapy, quality improvement, and self-help. Outcomes reported as depressive symptoms, and treatment effects.	Possible differences by sex for SSRIs in older adults, duloxetine, and CBT. No differences by sex for combined antidepressants and psychotherapy.
Peterson, 2014[29] VA ESP	Factors that Optimize Therapy with Repetitive Transcranial	MEDLINE, PsycINFO, and Cochrane from inception to April 2014. 63 articles were	Bilateral rTMS was compared to right low-frequency dorsolateral	"Sex was not significantly associated with response in two multicenter head-to-

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
	Magnetic Stimulation for Treatment-Resistant Depressions	included in analysis, including multicenter trials, systematic reviews, an AHRQ comparative effectiveness review and a health technology assessment. Two RCTs analyzed treatment response by sex.	prefrontal cortex (RLF-DLPFC) rTMS. Primary outcome was treatment response.	head trials of bilateral versus RLF-DLPFC rTMS treatment (N= 219 and N=130, respectively). We did not identify any analyses of response or remission rates by sex among studies of LHF-DLPFC rTMS."
Cuijpers, 2014[11]	Gender as predictor and moderator of outcome in cognitive behavior therapy and pharmacotherapy for adult depression: an "individual patient data" meta-analysis	Pubmed, PsycINFO, EMBASE, and Cochrane, and primary studies from published meta-analyses of psychological treatment for depression. 14 RCTs included.	CBT was compared to pharmacotherapy, and CBT and pharmacotherapy was compared to pill placebo. Primary outcome was a reduction of depressive symptoms.	"Gender was neither a nonspecific predictor (indicating whether gender is related to improvement, regardless of comparison or control groups), nor a specific predictor (predicting outcome of CBT and pharmacotherapy compared to pill placebo). The average differences between men and women within three conditions (CBT, pharmacotherapy, and pill placebo) were less than one point on the HAM-D-17."
AHRQ Archived				
Santaguida, 2012[27] AHRQ Archived	Treatment for Depression After Unsatisfactory Response to SSRIs	MEDLINE, CCRCT, PsycINFO, CDSR, EMBASE, CINAHL, and AMED from 1980 to April 2011. Grey literature was also searched. Forty-four studies (41 among adults) were included in the review, including randomized trials, quasi-randomized trials and observational studies. Three studies among adults analyzed outcomes by gender.	Interventions/ comparators included second-generation antidepressants and augmenters. Primary outcome was treatment response.	Men vs. Women (from full report): "Three studies evaluated gender and showed no statistical difference on treatment response."
Gartlehner, 2011[26]	Comparative benefits and	PubMed, EMBASE, Cochrane, PsycINFO,	Two RCTs compared SGAs	Men vs. Women (from full report): The 2 RCTs

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
AHRQ Archived	harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis.	and International Pharmaceutical Abstracts (1980 to Jan 2011). The review included 248 good or fair quality studies (104 head-to-head randomized controlled trials (RCTs), 84 placebo-controlled RCTs, 46 meta-analyses or systematic reviews, observational studies, and studies of other design).Two RCTs examined differential effects for men and women.	(Paroxetine vs Sertraline and Paroxetine vs Bupropion) in terms of efficacy by sex. Primary outcome was depressive symptomology.	did not find any differences in efficacy between SGAs by sex.

*Summaries from full text are noted when applicable. Abbreviations: AHRQ= Agency for Healthcare Research Quality; AMED= Allied and Complementary Medicine Database; CBT= Cognitive Behavioral Therapy; CDSR= Cochrane Database of Systematic Reviews; CINAHL= Cumulative Index to Nursing and Allied Health Literature; ESP= Evidence-based Synthesis Program; HAM-D-17= Hamilton Depression Scale; RCT= Randomized Controlled Trial; RLF-DLPFC= Right Low-Frequency Dorsolateral Prefrontal Cortex; rTMS= Repetitive Transcranial Magnetic Stimulation; SGA= Second Generation Antidepressants; SSRI= Selective Serotonin Reuptake Inhibitor

Key Question 2

In adult women, what are the harms associated with evidence-based treatments for depression?

Three evidence reviews,[12,15,16] four PROSPERO protocols,[19-21,24] one archived AHRQ review,[26] and one evidence map[28] addressed key question 2.

Key Question 2a. In pregnant and postpartum women?

A new evidence review examining harms associated with treatments for depression in pregnant and postpartum women would be duplicative. We identified three systematic reviews[12,15,16] and four PROSPERO protocols[19-21,24] covering the scope of the key question (Table 4).

A 2014 AHRQ[15] review examined harms related to antidepressants in pregnant and postpartum women. The review examined both maternal harms (i.e., danger to self or infant, pregnancy weight gain), and a wide range of infant/child harms (i.e., all-cause mortality, congenital anomalies, cardiac malformations, pulmonary hypertension, respiratory distress, neonatal convulsions, preterm birth, growth for gestational age, language development, developmental milestones, motor and speech delays, behavioral outcomes, autism spectrum disorders, education and learning, illness, Attention Deficit Hyperactivity Disorder [ADHD], and internalizing and externalizing behaviors). In addition, we examined a 2014 Cochrane review of antidepressants in postpartum women.[16] Examined harms were decreased appetite, dizziness, headache, somnolence and drowsiness, nausea, diarrhea, hypomanic switch, and overall number of side effects.

In a 2013 Cochrane review[12] examining alternative treatments for antenatal depression, harms (e.g., nausea, headache, eye strain, nausea, dizziness, and agitation) were reported in four RCTs, examining acupuncture, bright light therapy and omega-3 oils.

We also identified four protocols[19-21,24] examining harms associated with treatments for depression in prenatal or postpartum women. Interventions include antidepressants during pregnancy,[21] non-pharmacological interventions,[19] and interventions to treat depression in infertility.[24] Examined harms include maternal[20,21] and infant outcomes.[19-21,24]

Table 4. Key Question 2a: In adult pregnant and postpartum women, what are the harms associated with evidence-based treatments for depression?: Evidence reviews

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
McDonagh, 2014[15] AHRQ	Antidepressant Treatment of Depression During Pregnancy and the Postpartum Period	CDSR, CCRCT, CINAHL, MEDLINE and OLDMEDLINE, PsycINFO, and Scopus from inception to July 2013. Grey literature was also searched. 130 studies (124 observational and 6 RCTs) were included in the review overall, with 6 RCTs and 15 observational studies providing direct evidence.	This review examined treatment with second generation antidepressants (SGAs). Comparators were placebo, no active treatment or usual care, other antidepressants, and other nonpharmacological treatments. Examined maternal harms were danger to self or infant, pregnancy weight gain. Infant/child harms included all-cause mortality, congenital anomalies, cardiac malformations, pulmonary hypertension, respiratory distress, neonatal convulsions, preterm birth, growth for gestational age, language development, developmental milestones, motor and speech delays, behavioral outcomes, autism spectrum disorders, education and learning, illness, ADHD, and internalizing and	From full report: "We found no direct evidence on maternal harms of pharmacologic treatments for depression during pregnancy, primarily because for this population there is only observational evidence and the harms outcomes for this report, for example, rates of specific adverse effects (e.g., suicidal ideation, hepatoxicity, and loss of libido) are not reported… there is limited direct evidence about serious infant harms, with suggestion of increased risk of respiratory distress associated with exposure to SSRIs. This evidence is insufficient to draw conclusions for major malformations due to the limitations of the few small studies found. Low strength evidence suggests that there is no increased risk of neonatal convulsions, but a statistically significant increase in risk of neonatal respiratory distress with use of SSRIs."

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
			externalizing behaviors.	
Molyneaux et al., 2014[16] Cochrane	Antidepressant treatment for postnatal depression	CCDANCTR (July 11, 2014), The Cochrane Pregnancy and Childbirth Group's Specialized Register, ClinicalTrials.gov, WHO, reference lists, and personal communication with a number of pharmaceutical companies and, identified topic experts, and the International Marcé Society. Searches extended to July 2014. Six randomized controlled parallel groups design studies were included.	Study specific antidepressants included sertraline, fluoxetine, paroxetine, and nortriptyline. One included study allowed for a choice of antidepressant, with an SSRI being the first line of treatment. One study examined sertraline + BDP. Comparators included placebo, treatment as usual, listening visits, placebo + counseling, and another antidepressant. Examined harms included decreased appetite, dizziness, headache, somnolence and drowsiness, nausea, diarrhea, hypomanic switch, and overall number of side effects.	From full report: "Side effects were reported by a substantial proportion of women and were mainly characteristic of the type of antidepressant used with nausea, diarrhea and headaches reported with SSRIs and constipation with nortriptyline. It was often difficult to interpret the severity of side effects and several studies were limited in their assessment and reporting of side effects and adverse events."
Dennis, 2013[12] Cochrane	Interventions (other than pharmacological, psychosocial or psychological) for treating antenatal depression	Cochrane Pregnancy and Childbirth Group's Trials Register (Jan 2013). Six RCTs were included in review, four of which reported on harms.	Four studies examined side effects (e.g., nausea, headache, eye strain, nausea, dizziness, and agitation) associated with acupuncture, bright light therapy and omega-3 oils.	Women only: "Women in the placebo group were just as likely to report a side effect as those in the omega-3 group (RR 1.12, 95% CI 0.56 to 2.27)."
Saccone et al.[21] PROSPERO protocol (expected completion Nov 2014)	Depression drug treatment during pregnancy and neonatal outcomes: a pooled meta-analysis of randomized	Authors will search MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, ScienceDirect.com,	This meta-analysis will examine the benefits and harms to both mother and infant related to the use of antidepressants (SSRI, serotonin norepinephrine reuptake inhibitor	NA

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
	trials	MEDSCAPE and the Cochrane from database inception to October 2014. RCTs only, pregnant women.	(SNRI), selective SNRI, tricyclic antidepressant (TCA) and norepinephrine reuptake inhibitors trazodone and nefazodone).	
Morrell et al.[20] PROSPERO protocol (expected completion Jan 2014)	An evidence synthesis to evaluate the clinical effectiveness and cost-effectiveness of interventions to prevent postnatal depression	Authors will search PsycINFO, CDSR, DARE, NHS HTA, MEDLINE, EMBASE, CINAHL, Science Citation Index, Premedline, PROSPERO, NHS EED, CCRCT, MIDIRS, ASSIA, Social Care Online, Social Science Citation Index). Searches will be restricted to English language literature and to RCTs, systematic reviews or economic evaluations but with no restriction by publication date.	This systematic review and meta-analysis will examine the benefits, harms, and costs of antenatal and postnatal interventions.	NA
Jarde et al.[19] PROSPERO protocol (expected completion July 2015)	Pregnancy outcomes in women with depression treated non-pharmacologically	Authors will search MEDLINE, EMBASE, PsycINFO, CENTRAL, and Web of Science from 2010 to the present. Randomized and quasi-randomized controlled trials and observational studies (cohort studies, case-control studies and cross-sectional studies) examining with a comparison group will be included.	This systematic review will examine outcomes associated with non-pharmacological interventions. Identified outcomes are preterm birth, small for gestational age, large for gestational age, low birth weight, NICU admission, gestational age at birth, and birth weight.	NA
Akioyamen et al.[24] PROSPERO protocol (expected completion date April	Maternal treatment for depression in infertility: effects on conception, birth and neonatal	Authors will search MEDLINE, EMBASE, CINAHL, the Cochrane Library, PsycINFO, ProQuest Dissertation & Theses, and PubMed from	This systematic review will examine the relationship between concurrent maternal treatment for depression and infertility and outcomes related to	NA

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
2015)	health	database inception to the present for SR/MAs, trials, and observational studies examining concurrent infertility and depression treatment.	birth and long-term maternal and child health (as measured through assessments of mental health and markers of growth and metabolism).	

*Summaries from full text are noted when applicable. Abbreviations: ADHD= Attention Deficit Hyperactivity Disorder; AHRQ= Agency for Healthcare Research and Quality; ASSIA= Applied Social Science Index of Abstracts; BDP= Brief Dynamic Psychotherapy; CCDANCTR= Cochrane Collaboration Depression Anxiety, and Neurosis Controlled Trials Register; CCRCT= Cochrane Central Register of Controlled Trials; CDSR= Cochrane Database of Systematic Reviews; CINAHL= Cumulative Index to Nursing and Allied Health Literature; DARE= Database of Abstracts of Reviews of Effects; MIDIRS= Midwives Information and Resource Service; NHS EED= National Health Service Economic Evaluation Database; NHS HTA= National Health Service Health Technology Assessment; NICU= Neonatal Intensive Care Unit; RCT= Randomized Controlled Trial; SGA= Second Generation Antidepressants; SNRI= Serotonin-Norepinephrine Reuptake Inhibitor; SR/MA= Systematic Review/Meta-Analysis; SSRI= Selective Serotonin Reuptake Inhibitor; TCA= Tricyclic Antidepressant; WHO= World Health Organization

Key Question 2b. In all other female populations?

A new evidence review examining harms associated with treatments for depression in general female populations or examining gender differences would not be duplicative. We identified only one evidence map[28] and one archived AHRQ review[26] covering the scope of the key question (Table 5).

A completed, but not-yet-released VA ESP evidence map of systematic reviews examined gender effects in depression and other conditions.[28] Of 86 identified systematic reviews that examined interventions for depression, 14 reported effects by gender. The map provides a qualitative summary of conclusions from the 14 systematic reviews by intervention. Only one of the included reviews, an archived AHRQ review,[26] reported harms (i.e., two RCTs comparing sexual dysfunction in men and women receiving paroxetine).

Table 5. Key Question 2b. In adult (other than prenatal and postpartum) women, what are the harms associated with evidence-based interventions used to treat depression in adult women?: Evidence reviews

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
Duan-Porter, 2015[28] VA ESP	Mapping the Evidence: Sex effects in high-impact conditions for women veterans -- depression, diabetes and	PubMed, Cochrane and manual searches (Jan 2009 to Oct 2014). Of the 86 systematic reviews related to interventions for depressive disorders, *14 reported sex effects.*	One included review (Gartleherner, 2011 – see below) reported sexual dysfunction.	Men vs. Women: Possible differences in adverse events (sexual dysfunction) by sex for paroxetine. No differences in adverse events overall by sex for

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
	chronic pain			antidepressants.
AHRQ Archived				
Gartlehner et al., 2011[26] AHRQ Archived	Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis.	PubMed, EMBASE, Cochrane, PsycINFO, and International Pharmaceutical Abstracts (1980 to Jan 2011). The review included 248 good or fair quality studies (104 head-to-head randomized controlled trials [RCTs], 84 placebo-controlled RCTs, 46 meta-analyses or systematic reviews, observational studies, and studies of other design).Two RCTs examined differential harms for men and women.	Two RCTs compared SGAs (Paroxetine vs Sertraline and Paroxetine vs Bupropion) in terms of harms by sex. Examined sexual dysfunction.	Men vs. Women (full report): "Evidence from one RCT comparing paroxetine with sertraline and one RCT comparing paroxetine with bupropion SR suggests differences in sexual side effects between men and women. The strength of evidence is low."

*Summaries from full text are noted when applicable. Abbreviations: AHRQ= Agency for Healthcare Research and Quality; RCT= Randomized Controlled Trial; SGA= Second Generation Antidepressants; VA ESP= Veteran's Affairs Evidence-based Synthesis Program

Key Question 3

What are the costs associated with evidence-based treatments used to treat depression in adults?

A new review examining the costs associated with treatments for depression would be duplicative. We identified three evidence reviews,[10,14,17] one technology assessment,[18] and two protocols[20,22] covering the scope of the key question (Table 6). Reviews examined costs associated with CBT,[10] antidepressants,[17,18] and collaborative care.[14] The in-process reviews will compare the cost effectiveness of antidepressants to SAM-e,[22] and cost-effectiveness of interventions to prevent postnatal depression.[20]

Table 6. Key Question 3. What are the costs associated with evidence-based treatments used to treat depression in adults?: Evidence reviews

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
Brettschneider et al., 2015[10]	Cost-utility analyses of cognitive-behavioural therapy of depression: a systematic review.	The authors searched Medline, EMBASE, PsycINFO and NHS EED to identify CUA of CBT for MDD. 22 studies were included (full text not available).	Cost data were inflated to the year 2011 and converted into USD using purchasing power parities (USD PPP) to ensure comparability of the data. Outcomes were cost utility ratios/QALY.	"We found consistent evidence that individualized CBT is cost-effective from the perspective of a third-party payer for short-term treatment and for relapse prevention of MDD in the adult population."
Jeeva et al., 2013[14]	Is treatment of depression cost-effective in people with diabetes? A systematic review of the economic evidence.	Authors searched MEDLINE, EMBASE, PsycINFO, CINAHL, and NHS EED from January 2000 to May 2012 for studies examining patients with diabetes and comorbid MDD. Four studies were included.	Interventions were collaborative care, and included a care planning process of stepped depression management tailored to individual needs, care manager, psychological therapy and/or antidepressant therapy. Three of the four included studies examined cost-utility, with one study examining cost-effectiveness. Three of four studies present a payer perspective, with the fourth presenting a societal viewpoint. Costs are adjusted to a single price year (USD 2011), using a medical care services index. Outcomes included net cost, net savings, net value of depression free days, and QALY.	"The review highlighted the paucity of evidence in this area. The four studies indicated the potential of interventions to reduce depression and be cost-effective compared with usual care. Two studies reported costs per QALY gained of USD 267 to USD 4,317, whilst two studies reported the intervention dominated usual care, with net savings of USD 440 to USD 612 and net gains in patient free days or QALYs."
Pan et al., 2012[17]	Cost-effectiveness comparisons between antidepressant treatments in depression: evidence from database analyses and prospective studies.	Authors searched MEDLINE, EMBASE, PsycINFO from 1999-September 2010 for studies comparing antidepressant treatments or to placebo. 40 papers were included: 28 retrospective	A relatively large number of industry-sponsored evaluations of escitalopram were identified and these found escitalopram to be potentially cost-effective in depression treatment. Evidence of cost-effectiveness differences between other individual SSRIs	Evidence regarding the cost-effectiveness of different antidepressants in depression continues to accumulate. Beyond the efficacy or tolerability data found for newer antidepressants in controlled trials, further research from

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
		database analyses and 12 prospective studies (six conventional RCTs, five pragmatic RCTs and one naturalistic observational study).	was not unequivocally established. Inconsistent findings further emerged concerning the cost-effectiveness of SSRIs versus TCAs between retrospective database analyses and prospective studies.	real-world settings is needed to examine the relative cost-effectiveness of different antidepressant agents.
Edwards et al., 2013[18] HTA	Lithium or an atypical Antidepressant drug in the management of treatment resistant depression: a systematic review and economic evaluation.	The authors searched Cochrane, EMBASE, MEDLINE, PsycINFO and NHS EED. All databases were searched from inception to August 2011. Additional data were obtained from manufacturers. Four studies were included.	One study evaluated augmentation of antidepressant therapy (aripiprazole); the three remaining studies evaluated antidepressant monotherapy compared with either each other or TMS. Two studies were from the payer perspective, one from a societal viewpoint and one from a payer perspective, with the impact of the societal perspective examined with a sensitivity analysis. Outcomes included incremental cost per remission, incremental cost per QALY, and percentage of primary and secondary care patients achieving remission and associated costs.	"Cost-effectiveness analyses suggest that augmentation with lithium is less expensive and more effective than augmentation with AAP. However, the uncertainty in the clinical estimates of discontinuation and treatment response is reflected in the model results. A RCT comparing the two augmentation strategies, reporting relevant outcomes, including QoL, is needed."
Galizia et al., 2014[22] Cochrane Protocol	S-adenosyl methionine (SAM-e) for depression in adults.	The authors will search MEDLINE, EMBASE, and PsycINFO, CENTRAL, as well as international trials registers through the WHO-ICTRP, ClinicalTrials.gov, drug companies.	SAM-e will be compared to placebo or antidepressants. The following economic outcomes were identified: mean total direct medical cost per patient, including medication costs, consultant fees and inpatient treatment costs; direct resources use associated with complications of treatment; time to onset	NA

Reference	Title	Resources Searched and Inclusion Criteria	Summary (interventions, comparators, outcomes, etc.)	Conclusions Reported in the Abstract*
			of antidepressant effect measured as change in depression score (days); time to return to work (days); incremental cost per disability-adjusted life year (DALY)	
Morrell et al.[20] PROSPERO protocol (expected completion Jan 2014)	An evidence synthesis to evaluate the clinical effectiveness and cost-effectiveness of interventions to prevent postnatal depression	Authors will search PsycINFO, CDSR, DARE, NHS HTA, MEDLINE, EMBASE, CINAHL, Science Citation Index, Premedline, PROSPERO, NHS EED, CCRCT, MIDIRS, ASSIA, Social Care Online, Social Science Citation Index). Searches will be restricted to English language literature and to RCTs, systematic reviews or economic evaluations but with no restriction by publication date.	This systematic review and meta-analysis will examine the benefits, harms, and costs of antenatal and postnatal interventions.	NA

*Summaries from full text are noted when applicable. Abbreviations: AAP= Atypical Antidepressants; ASSIA= Applied Social Science Index and Abstracts; CBT= Cognitive Behavioral Therapy; CCRCT= Cochrane Central Register of Controlled Trials; CDSR= Cochrane Database of Systematic Reviews; CINAHL= Cumulative Index to Nursing and Allied Health Literature; CUA= Cost Utility Analysis; DARE= Database of Abstracts of Reviews of Effects; DALY= Disability-Adjusted Life Year; MIDIRS= Midwives Information and Resource Service; MMD= Major Depressive Disorder; NHS EED= National Health Service Economic Evaluation Database; NHS HTA= National Health Services Health Technology Assessment; QALY= Quality-Adjusted Life Year; QoL= Quality of Life; RCT= Randomized Controlled Trial; SAM-e= S-adenosyl Methionine; SSRI= Selective Serotonin Reuptake Inhibitor; TCA= Tricyclic Antidepressant; TMS = Transcranial Magnetic Stimulation; USD= United States Dollar; USD PPP= United States Dollar Purchasing Power Parities; WHO ICTRP= World Health Organization International Clinical Trials Registry Platform

Impact of New Review

We reviewed whether a new evidence review could potentially impact the standard of care or resolve practice variation for the treatment of women with depression. Current care, especially the prescription of selective serotonin reuptake inhibitors (SSRIs) the mainstay of depression treatment, is frequently guided in practice by the side effects of individual medications. Older SR have indicated sex related differences in the incidence of side effects, indicating that a new

review focused on sex-related differences of the harms of depression treatment could improve care for women.

Primary Research

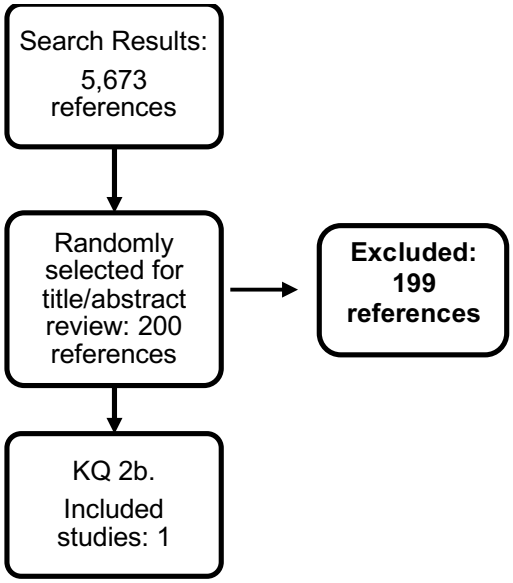
We conducted a search for original research for key question 2b, harms associated with evidence based treatments for depression in non-pregnant/postpartum women. We identified current or in-process systematic reviews covering the scope for all other key questions in the nomination.

Literature Search

The literature search identified 5,673 unique titles (see Appendix C for links to the search results). We randomly selected 200 titles and abstracts to review to evaluate the feasibility of conducting a new evidence review. Upon abstract review, we identified one study relevant to one or more of the key questions in the nomination. Based on an inclusion percentage of 0.5%, our expected total number of studies is 28 (see Appendix D for more detail).

Figure 2 shows the citation yield from electronic database searches, numbers of exclusions, and the final yield of included studies.

Figure 2. Literature Search Results



Key Question 2b.
In non-pregnant/postpartum adult women, what are the harms associated with evidence-based treatments for depression?

We identified one study related to harms in non-pregnant/postpartum women. A 12-week, open-label part-randomized multi-center trial of 630 men and women (395 women) diagnosed with MDD compared changes in body weight associated with nortriptyline and escitalopram (participants with contraindications to one of the study drugs were non-randomly assigned to the

other drug). Results indicated that a significant proportion of participants taking nortriptyline experienced weight gain. No significant weight gain was associated with escitalopram, and the difference between the groups was significant when controlling for baseline body mass index (BMI), and remained significant after restricting the analysis to randomized participants. There was no difference in weight gain by gender (Table 7).

Table 7. Key Question 2b. In non-pregnant/postpartum adult women, what are the harms associated with evidence-based treatments for depression?: Literature search

Reference	Title	# Patients/ Population; Intervention and Comparator	Summary of Findings from Abstract	Conclusions Reported in the Abstract*
Uher et al., 2011[31]	Changes in body weight during pharmacological treatment of depression	630 men and women with MDD Compared weight changes associated with nortriptyline (n = 246) and escitalopram (n = 384).	Weight increased significantly more during treatment with nortriptyline compared to escitalopram. The weight gain commenced during the first 6 weeks of nortriptyline treatment, reached on average 1.2 kg at 12 weeks (0.44-point BMI increase), and continued throughout the 6-month follow-up period. Participants who were underweight at baseline gained most weight. Participants who were obese at baseline did not gain more weight during treatment. Weight gain occurred irrespective of whether weight loss was a symptom of current depressive episode and was identified as an undesired effect of the antidepressant by most participants who gained weight. There was little weight change during treatment with escitalopram, with an average increase of 0.14 kg (0.05-point BMI increase) over 12 weeks of treatment. [Findings did not differ by gender.]	"Treatment with the tricyclic antidepressant nortriptyline was associated with moderate weight gain, which cannot be explained as a reversal of symptomatic weight loss and is usually perceived as an undesired adverse effect. While treatment with nortriptyline may be recommended in underweight subjects with typical neuro-vegetative symptoms, escitalopram is a suitable alternative for subjects at risk of weight gain."

*Summaries from full text are noted when applicable. Abbreviations: BMI= Body Mass Index; MDD= Major Depressive Disorder

Value

A new systematic review examining depression treatments for women has limited value. Despite limited evidence examining harms specific to non-pregnant/postpartum women, there are numerous existing evidence reviews that address both the benefits and harms of interventions for depression in the general population and for pregnant and postpartum women, which are currently used to guide clinical practice There is currently no identified organizational stakeholder.

Summary of Findings and Conclusion

The SRC conclusions based on the results of our assessment of this topic nomination are as follows:

- Key Question 1a.
    - A new evidence review on the benefits related to the short- and long-term effectiveness of evidence-based treatments for depression in pregnant and postpartum women *would likely be duplicative*. We identified four existing reviews[12,13,15,16] and four PROSPERO protocols[20,21,23,25] relevant to the topic.
- Key Question 1b.
    - A new evidence review on the benefits related to the short- and long-term effectiveness of evidence-based treatments for depression in non-pregnant/postpartum women *would likely be duplicative*. We identified two existing reviews,[6,11] one evidence map,[28] and one evidence brief[29] relevant to the topic.
- Key Question 2a.
    - A new evidence review on the harms related to the short- and long-term effectiveness of evidence-based treatments for depression in pregnant and postpartum women *would likely be duplicative*. We identified three systematic reviews[12,15,16] and four PROSPERO protocols[19-21,24] relevant to the topic.
- Key Question 2b.
    - A new evidence review on the harms related to the short and long-term effectiveness of evidence-based treatments for depression in non-pregnant/postpartum women *would not be duplicative*. One evidence map was relevant to the topic. The evidence map identified only one systematic review (the archived AHRQ review), which included two RCTs comparing sexual dysfunction in men and women receiving paroxetine, and does not address the range of harms known to be relevant in general populations.
    - We reviewed one of the 200 randomly selected articles related to the topic, for an expected total of 28 studies.
- Key Question 3.
    - A new evidence review examining costs associated with treatments for depression *would likely be duplicative*. We identified three evidence reviews,[10,14,17] one technology assessment,[18] and two protocols[20,22] relevant to the topic.

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Appendices

Appendix A: Selection Criteria Summary

Appendix B: Search for Existing Guidance

Appendix C: Original Nomination Form

Appendix D: Search for Existing Evidence Results

Appendix E: Original Nomination

Appendix A: Selection Criteria Summary

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents a health care drug and intervention available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	No, this is not a nomination for a comparative effectiveness review, but a review examining overall effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Approximately 11% of non-pregnant women of reproductive age experience major depressive disorder (MDD),[1] with 8-19% of women experiencing postpartum depression.[1,2]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Depression impacts quality of life,[3] productivity,[4] and is a risk factor for suicide.[5]
2c. Represents important uncertainty for decision makers	The topic may represent important uncertainty for decision makers given the wide range of treatment options and variability in effectiveness of treatment.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of treatments for depression.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	In the U.S., the estimated economic burden associated with depressive disorders is greater than $80 billion a year, with more than 30 percent attributable to direct medical expenses.[6] Patients with depression account for approximately 8 million ambulatory care visits each year.[7] Each year, depression accounts for 200 million lost workdays and costs employers between $17 and $44 billion.[4]
3. Desirability of New Research/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	Treatment for depression is already covered by available high-quality systematic reviews and evidence maps: • An AHRQ evidence report/technology assessment on pharmacological treatments for pregnant and postpartum women with depression.[8] • A Cochrane review on antidepressant treatment for postnatal depression.[9]

	• A Cochrane review on interventions other than psychopharmacological, psychological, and psychosocial interventions, for treating antenatal depression.[10] • A protocol for a meta-analysis of RCTs examining depression drug treatment during pregnancy and neonatal outcomes. • A VA evidence map of sex and gender differences in treatments for depression.[11] • An IPD meta-analysis of the role of gender in moderating the effectiveness of cognitive behavioral therapy and treatment with antidepressants.[12] • A cost-utility analyses of cognitive-behavioral therapy of depression.[13] • A review examining the cost effectiveness of depression treatment for patients with diabetes.[14] • A review comparing the cost-effectiveness of antidepressant treatments.[15] • A technology assessment comparing lithium to Antidepressants for treatment resistant depression.[16] • A Cochrane protocol for a review which will examine the benefits and costs of S-adenosyl methionine (SAM-e) for depression in adults.[17]
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	While the standards of care for treatment for depression in general are not unclear, current guidelines applicable to non-pregnant/postpartum women address risks associated with possible decreases contraceptive effectiveness,[18] with only one known guideline specific to the treatment for depression in women.[19] A 2009 review examined sex specific differences in side effects for psychotropic drugs. Findings indicated that women experienced significantly more nausea and dizziness than men associated with sertraline and imipramine, and that in a study of clomipramine, citalopram, paroxetine or moclobemide,[20] women experienced more tremor. While this review may be dated, it does illustrate the potential for increased risks for women associated with treatments for depression. A better understanding of the potential harms for non-pregnant/postpartum women is needed to inform and guide clinical practice.

4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	No, current practice does not vary from established clinical guidelines.
5. Feasibility	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	Key Question 2b. We identified only one study from our randomly selected 200 titles related to harms for women, for an expected total of 28 studies.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	It is uncertain whether a new review would be of value. Currently, only one known guideline (1999) outlines treatment for depression in non-pregnant/postpartum women.[19] While a new evidence review examining harms in women specifically may provide guidance for clinical care, we are unable to assess whether the findings of a review would be used to guide practice.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	No, there is no identified partner.

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Appendix B: Search for Existing Guidance

Listed below are the sources searched and results of our search for existing guidance. A research librarian conducted the search and selected potentially relevant evidence based on the key question in the nomination and the associated PICOTS. An investigator reviewed each of the links to evidence below for inclusion. The links below do not represent the evidence selected for inclusion (see main topic brief).

Source	Evidence
AHRQ and Other Federal Products	
Evidence-based Treatments for Women with Depression	
AHRQ: Evidence reports and technology assessments, USPSTF recommendations, and related DEcIDE projects, and Horizon Scan ▪ EPC Program Reports and In-Process Topics: http://www.ahrq.gov/research/findings/evidence-based-reports ▪ Archived EPC Program Reports: http://archive.ahrq.gov/clinic/epcarch.htm ▪ EHC Program Reports: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/ ▪ Technology Assessments: http://www.ahrq.gov/clinic/techix.htm ▪ USPSTF Reports: http://www.uspreventiveservicestaskforce.org/uspstopics.htm ▪ USPSTF In-Process Topics: http://www.uspreventiveservicestaskforce.org/Page/Name/topics-in-progress ▪ DEcIDE Projects: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-	Antidepressant Treatment of Depression During Pregnancy and the Postpartum Period http://www.ncbi.nlm.nih.gov/books/NBK233904/ Treatment for Depression After Unsatisfactory Response to SSRIs Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current. http://www.ncbi.nlm.nih.gov/books/NBK97406/ Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current. http://www.ncbi.nlm.nih.gov/books/NBK83442/ Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults Current: This report was assessed in August 2012 and conclusions were considered current. http://www.ncbi.nlm.nih.gov/books/NBK65315/ Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression http://www.ncbi.nlm.nih.gov/books/NBK43023/ Full Title: Treatment of Depression—Newer Pharmacotherapies This information is for reference purposes only. It was current when produced and may now be outdated. Archive material is no longer maintained, and some links may not work http://archive.ahrq.gov/clinic/tp/deprtp.htm Addressing Knowledge Gaps in the Treatment of Depression http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-

guides-reviews-and-reports/ ▪ AHRQ Horizon Scanning (click on status update reports): http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=881 ▪ AHRQ-funded projects that may be conducting systematic reviews (1. Under TEXT SEARCH, enter in key text terms, select projects and publications; 2.Under PROJECT DETAILS and then under "Agency/Institute/Center," select Agency for Healthcare Research and Quality and check the boxes for "Admin" and "Funding"; 3) Scroll to the end and click on SUBMIT QUERY http://projectreporter.nih.gov/reporter.cfm	reports/?pageaction=displayproduct&productid=293 Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2152 Comparative Effectiveness of Interventions for Depression in the Community https://projectreporter.nih.gov/project_info_description.cfm?aid=8900247 Effectiveness of Treating Prenatal Depression to Reduce Postpartum Depression https://projectreporter.nih.gov/project_info_description.cfm?aid=8901862
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program ▪ HSR&D ESP Reports and In-Progress Topics: http://www.hsrd.research.va.gov/publications/esp/ ▪ PBM Recommendations: http://www.pbm.va.gov/PBM/clinicalguidance/clinicalrecommendations.asp ▪ PBM Drug Class Reviews: http://www.pbm.va.gov/PBM/clinicalguidance/drugclassreviews.asp	Determining the Efficacy of Psychotherapy for Treatment Resistant Depression http://www.hsrd.research.va.gov/publications/esp/resistdep.cfm Determining Key Features of Effective Depression Interventions http://www.hsrd.research.va.gov/publications/esp/depinter.cfm Determining the Responsiveness of Depression Questionnaires and Optimal Treatment Duration for Antidepressant Medications http://www.hsrd.research.va.gov/publications/esp/depression.cfm Brief Psychotherapy for Depression in Primary Care: A Systematic Review of the Evidence http://www.hsrd.research.va.gov/publications/esp/brief-psychotherapy.cfm Evidence Brief: Factors that Optimize Therapy with Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depressions http://www.hsrd.research.va.gov/publications/esp/rtms.cfm

Other PBM products may be reviewed if deemed necessary; however, these are generally not reviewed for most topics unless the nomination is closely linked to the VA population and VA policies: http://www.pbm.va.gov/ClinicalGuidance.aspx	Mapping the Evidence: Sex Effects in High-impact Conditions for Women Veterans -- Depression, Diabetes, and Chronic Pain www.hsrd.research.va.gov/publications/esp/womenshealthevidence.cfm The Pharmacologic Management of Major Depression in the Primary Care Setting http://www.pbm.va.gov/clinicalguidance/vanatioanalclinicalpracticeguidelines/DepressionPharmacologicManagement.pdf
Cochrane and Other Systematic Reviews	
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/	Antidepressant treatment for postnatal depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002018.pub2/abstract Interventions (other than pharmacological, psychosocial or psychological) for treating antenatal depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006795.pub3/abstract Alternating current cranial electrotherapy stimulation (CES) for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010521.pub2/abstract Dance movement therapy for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009895.pub2/abstract Reiki for depression and anxiety http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006833.pub2/abstract 'Third wave' cognitive and behavioural therapies versus treatment as usual for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008705.pub2/abstract Alprazolam for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007139.pub2/abstract Music therapy for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004517.pub2/abstract Fluoxetine versus other types of pharmacotherapy for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004185.pub3/abstract Behavioural therapies versus other psychological therapies for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008696.pub2/abstract

	Paroxetine versus other anti-depressive agents for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006531.pub2/abstract Citalopram versus other anti-depressive agents for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006534.pub2/abstract Duloxetine versus other anti-depressive agents for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006533.pub2/abstract Mirtazapine versus other antidepressive agents for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006528.pub2/abstract Agomelatine versus other antidepressive agents for major depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008851.pub2/abstract Exercise for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004366.pub6/abstract Omega-3 fatty acids for depression in adults http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004692.pub4/abstract Cognitive behavioural therapies versus other psychological therapies for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008698/abstract Interventions to improve return to work in depressed people http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006237.pub3/abstract Vortioxetine for depression in adults http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011520/abstract Antidepressants for depression during pregnancy http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010710/abstract Bupropion versus other antidepressive agents for depression http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011036/abstract Psychological therapies for treatment-resistant depression in adults http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010558/abstract Pharmacological interventions for treatment-resistant depression in adults

	http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010557/abstract
PubMed Health	Depression The Treatment and Management of Depression in Adults (Updated Edition) http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0016605/
Systematic Reviews and Meta-analyses (PubMed/MEDLINE)	PubMed searched on January 19, 2016 "Depressive Disorder/therapy"[Mesh] AND (systematic[sb] AND "2011/01/21"[PDat] : "2016/01/19"[PDat] AND "female"[MeSH Terms]) N=211 http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49474027/public/ see file Depression SR.txt can be imported into EndNote using PubMed filter
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/ (Search HTA tab results)	A randomised controlled trial of computerised cognitive behaviour therapy for the treatment of depression in primary care: the Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy (REEACT) trial http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0004/158512/FullReport-hta191010.pdf http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32010000387&UserID=0 Repetitive transcranial magnetic stimulation for treatment resistant depression https://obrieniph.ucalgary.ca/system/files/rtms-for-treatment-resistant-depression-aug-6-2014.pdf http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32015000510&UserID=0 The long-term efficacy of psychotherapy, alone or in combination with antidepressants, in the treatment of adult major depression. http://kce.fgov.be/sites/default/files/page_documents/KCE_230_Depression_Report.pdf http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32014001117&UserID=0 Transcranial direct current stimulation for depression The report may be purchased from: http://www.hayesinc.com/hayes/crd/?crd=16339 http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32014000475&UserID=0 Transcranial magnetic stimulation for the treatment of adults with PTSD, GAD, or depression: a review of clinical effectiveness and guidelines http://www.cadth.ca/sites/default/files/pdf/htis/nov-2014/RC0599%20Transcranial%20Magnetic%20Stimulation%20for%20PTSD%20draft%20Final.pdf http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32015000829&UserID=0 Transcranial magnetic stimulation for treatment-resistant depression The report may be purchased from: http://www.hayesinc.com/hayes/crd/?crd=7409 http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32014000476&UserID=0

	Transcranial Magnetic Stimulation (TMS) to enhance pharmacotherapy for depression The report may be purchased from: http://www.hayesinc.com/hayes/crd/?crd=16420 Transcranial Magnetic Stimulation (TMS) to enhance pharmacotherapy for depression Deep brain stimulation for treatment-resistant depression: a preliminary evidence review http://www.hqontario.ca/Portals/0/Documents/eds/per/dbs-depression-1308-en.pdf http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32014000075&UserID=0 Lithium or an atypical Antidepressant drug in the management of treatment resistant depression: a systematic review and economic evaluation http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32011001128&UserID=0 Monarch™ External Trigeminal Nerve Stimulation (eTNS™) System for depression http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32013000557&UserID=0 Transcendental meditation for posttraumatic stress disorder, depression, and anxiety: a review of clinical effectiveness http://www.cadth.ca/media/pdf/htis/sep-2013/RC0481%20Transcendental%20Meditation%20for%20PTSD%20Final_no%20abs.pdf http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32014000092&UserID=0 Transcranial magnetic stimulation for depression http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=32011000436&UserID=0
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/	To what extent do mindfulness-based interventions reduce depression and anxiety and stress among pregnant and postpartum women? http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016032652 Bright light therapy for nonseasonal depression: meta-analysis of clinical trials http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015032297 Lurasidone for bipolar depression http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015026665 Incidence and risk of depression in menopausal women with vasomotor symptoms: a systematic review and meta-analysis of longitudinal cohort studies http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015025913 Switching of antidepressants in patients with treatment refractory depression http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015024870

	The utility of probiotics in alleviating depression and anxiety symptoms: a systematic review http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015024791 Acupuncture therapy for depression: a systematic review and meta-analysis http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015023712 Light therapy as an intervention for non-seasonal depression: a systematic review http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015017887 Quetiapine for adults with bipolar depression http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015014038 Depression drug treatment during pregnancy and neonatal outcomes: a pooled meta-analysis of randomized trials http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014014665 A systematic review of web-based interventions to prevent depression http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014014804 Using exercise to fight depression in older adults - a systematic review and meta-analysis http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014014103 Comparison of cognitive behavioral therapy and SSRIs for depression on quality of life http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014009831

Appendix C. Search Strategy

Harms of treatment for depression feasibility search		
Depression (all types)		(((("Depression"[Mesh]) OR "Depressive Disorder"[Mesh]*)) OR (((depression[Title/Abstract] OR depression[Title/Abstract] OR dysthymic[Title/Abstract] OR dysphoric[Title/Abstract] OR "seasonal affective"[Title/Abstract])))
AND		
Treatment	Pharmacologic Treatment	((((((((((((((((((“Bupropion”[Mesh] OR “Bupropion”[tiab] OR 34911-55-2[rn]))))) OR (((“Citalopram”[Mesh] OR “Citalopram”[tiab] OR 59729-33-8[rn]))))) OR (((“Escitalopram”[tiab] OR 128196-01-0[rn]))))) OR (((“O-desmethylvenlafaxine” [Supplementary Concept] OR Desvenlafaxine[tiab] OR 93413-62-8[rn]))))) OR (((“Fluoxetine”[Mesh] OR “Fluoxetine”[tiab] OR 54910-89-3[rn]))))) OR (((“Fluvoxamine”[Mesh] OR “Fluvoxamine”[tiab] OR 54739-18-3[rn]))))) OR ((((“milnacipran”[Supplementary Concept] OR “Levomilnacipran”[tiab] OR 96847-54-0[rn])))))) OR (((“mirtazapine”[Supplementary Concept] OR “mirtazapine”[tiab] OR 85650-52-8[rn]))))) OR ((Search (“nefazodone”[Supplementary Concept] OR “nefazodone”[tiab] OR 82752-99-6[rn]))))) OR (((“Paroxetine”[Mesh] OR “Paroxetine”[tiab] OR 61869-08-7[rn]))))) OR (((“Sertraline”[Mesh] OR “Sertraline”[tiab] OR 79617-96-2[rn]))))) OR (((“Trazodone”[Mesh] OR “Trazodone”[tiab] OR 19794-93-5[rn]))))) OR (((“venlafaxine”[Supplementary Concept] OR “venlafaxine”[tiab] OR 93413-69-5[rn]))))) OR (((“vilazodone”[Supplementary Concept] OR “vilazodone”[tiab] OR 163521-12-8[rn]))))) OR (((“vortioxetine”[Supplementary Concept] OR “vortioxetine”[tiab] OR 508233-74-7[rn]))))) OR (((“Antidepressive Agents, Second-Generation”[Mesh] OR “Antidepressive Agents, Second-Generation”[Pharmacological Action])))) OR (((“duloxetine” [Supplementary Concept] OR duloxetine[tiab]))))
	OR	
	Non-pharmacologic treatment	((((((((((“Psychotherapy”[Mesh] OR psychotherap*[tiab]))))) OR (((Acceptance and Commitment Therap*[tiab] OR Cognitive Therap*[tiab] OR Cognitive behavioral Therap*[tiab] OR interpersonal therap*[tiab] OR psychodynamic therap*[tiab] OR behavioral therap*[tiab])))) OR ((Search “Hypericum”[Mesh] OR “Hypericum“[tiab] OR “St. Johns Wort”[tiab] OR “Saint Johns Wort”[tiab] OR “St. John’s Wort”[tiab] OR “Saint John’s Wort”[tiab] OR LI160[tiab] OR LI160[tiab] OR WS5572[tiab] OR WS5573[tiab] OR LoHyp-57[tiab])))) OR ((“s adenosyl l methionine”[tiab] OR “s adenosylmethionine”[tiab] OR “S-Adenosylmethionine”[Mesh])))) OR ((Search “Fatty Acids, Omega-3”[Mesh] OR (omega 3[tiab] AND fatty acid*[tiab]) OR fish oil[tiab] OR flax seed[tiab] OR borage seed[tiab] OR Borago[tiab] OR evening primrose[tiab] OR Oenothera[tiab] OR eicosapentaenoic acid[tiab] OR PUFA[tiab])))) OR ((“Acupuncture”[Mesh] OR “Acupuncture Therapy”[Mesh] OR Acupuncture[tiab] OR Electroacupuncture[tiab])))) OR ((“Yoga”[Mesh] OR yoga[tiab])))) OR ((“Meditation”[Mesh] OR meditation[tiab] OR mindfulness[tiab])))) OR ((((“Exercise“[Mesh] OR physical activit*[tiab] OR “physical exercise”[tiab]))))

Human Limit		NOT (((“Animals”[Mesh] NOT “Humans”[Mesh])))
Adult Limit		NOT (((“Infant”[Mesh] OR “Child”[Mesh] OR “Adolescent”[Mesh]) NOT “Adult”[Mesh])))
Limit to last 5 years		Filters activated: published in the last 5 years
N=11504		
Harms	General	(("adverse effects" [Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ((harm[Title/Abstract] OR harms[Title/Abstract] OR adverse[Title/Abstract] OR "side effects"[Title/Abstract] OR reaction[Title/Abstract]))
	OR	
	Specific	(((nausea[Title/Abstract] OR weight[Title/Abstract] OR sexual[Title/Abstract] OR fatigue[Title/Abstract] OR insomnia[Title/Abstract] OR "dry mouth"[Title/Abstract] OR vision[Title/Abstract] OR constipation[Title/Abstract] OR dizziness[Title/Abstract] OR agitation[Title/Abstract] OR irritability[Title/Abstract] OR anxiety[Title/Abstract])))
N=5673		

With specific limits to Harms
Systematic Review **N=636**
http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49638261/public/
Depression Harm SR.txt
Randomized Controlled Trials **N= 3052**
http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49638301/public/
Depression Harm RCT.txt
All other **N=1985**
http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49638317/public/
Depression Harms Other.txt

Appendix D: Search for Existing Evidence Results

Table 1. Search for Existing Evidence Results: Key Question 2b

Nomination: Women with Depression

	Search Yield	Included/ Reviewed	Percent Included	Expected Total Included Studies
MEDLINE All Results	5673	1/200	0.5%	28
MEDLINE Clinical trials[1]	3052	1/130	8%	25
MEDLINE Evidence Reviews[2]	636	0/10	0%	0
MEDLINE Other Studies	1985	0/60	0%	0

Note. If results eligible for review was > 200, we review a random sample of 200, and calculate the expected number of total studies.

[1] We use the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE.http://handbook.cochrane.org/chapter_6/box_6_4_b_cochrane_hsss_2008_sensprec_pubmed.htm

[2] We use The Systematic Reviews Subset in PubMed http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html

Appendix E: Original Nomination

Topic Suggestion Description

Date submitted: December 31, 2012

Briefly describe a specific question, or set of related questions, about a health care test or treatment that this program should consider.

For individuals with depression what are the various evidence based treatments and what is their relative costs including consideration for time to recover and decrease further episodes?

Importance

Describe why this topic is important.

Depression may be the primary diagnosis that interferes in a patients motivation to seek and comply with health care treatment, making it the gateway target to significantly increase access to care. It is almost universal in dual eligible recipients/substance abuse or severe and chronic illnesses.

Potential Impact

How will an answer to your research question be used or help inform decisions for you or your group?

No answer provided.

Technical Experts and Stakeholders

Are there health care-focused, disease-focused, or patient-focused organizations or technical experts that you see as being relevant to this issue? Who do you think we should contact as we consider your nomination? This information will not influence the progress of your suggestion through the selection process, but it may be helpful to those considering your suggestion for further development?

No answer provided.

Nominator Information

Other Information About You: (optional)

Please choose a description that best describes your role or perspective: (you may select more than one category if appropriate)

Physician $

May we contact you if we have questions about your nomination?

No $