

Evidence-based Practice Center Systematic Review Protocol

Project Title: Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder

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(Amendments Details—see Section VII)

I. Background and Objectives for the Systematic Review

Clinical and Methodological Issues

Context. Depressive disorders can be serious, disabling illnesses. Major depressive disorder (MDD),¹ defined as the presence of depressed mood or loss of interest or pleasure, along with at least four additional MDD diagnosis criteria or symptoms for a duration of at least 2 weeks, is the most prevalent and disabling, affecting more than 16 percent of U.S. adults (lifetime).² The burden of depressive illnesses, in both human and financial terms, is enormous. MDD, in particular, exerts a negative impact on physical health. It reduces participation in preventive activities³ as well as adherence to medical treatment,⁴ and it increases the likelihood of chronic conditions such as obesity, smoking, sedentary lifestyles, diabetes, and cancer.^{5,6} MDD may be associated with a general increase in chronic disease. Mortality rates attributable to MDD and other depressive illnesses are high; approximately 4 percent of adults with a mood disorder commit suicide, and about two-thirds of suicides are preceded by depression.⁷

In 2000, the U.S. economic burden associated with depressive disorders was estimated to be \$83.1 billion, a number that has likely increased during the past 10 years. More than 30 percent of these costs are attributable to direct medical expenses.⁷

In any given year, nearly 7 percent of the U.S. adult population (approximately 17.5 million people in 2014) experiences an episode of MDD that warrants treatment.² Approximately half of these patients seek help. Most patients receiving care obtain treatment in primary care settings,⁸ where second-generation antidepressants (SGAs) are the most commonly prescribed.⁹ Patients who initially present to a psychiatric clinic are, in general, similar to those who seek treatment in primary care settings.^{10,11} For patients who do receive care, only 20 percent receive a minimal degree of adequate treatment, based on available evidence-based guidelines as receiving either pharmacotherapy (at least 2 months of an appropriate medication for MDD plus more than four visits to any type of physician) or psychotherapy (at least eight visits with any health care professional lasting an average of at least 30 minutes).¹² Relative to these guidelines,^{13,14} the risk of *undertreatment* for patients with MDD can be substantial.

For those receiving treatment, *overtreatment* with antidepressant medications poses another potential risk. Several recent studies have highlighted differences in response to pharmacotherapy based on baseline depression severity, suggesting a risk of excessive use of these treatment interventions for patients with mild disease (defined by the DSM-

V as disease in which “[f]ew, if any, of the symptoms in excess of those required to make the diagnosis are present, the intensity of symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning.”¹ Eligibility criteria for most clinical trials require severely or very severely depressed patients (with the number of symptoms substantially in excess of what is required for diagnosis, intervention is seriously distressing, and symptoms markedly interfere with social and occupational functioning),¹ raising questions about the generalizability of their results to populations with milder degrees of MDD (as might be more commonly found in some primary care settings).¹⁵⁻¹⁷ Several meta-analyses have reported that as baseline depressive symptoms increase, response to pharmacotherapy improves. One meta-analysis of patient-level data from six randomized controlled trials (RCTs) of antidepressants reported that response to two types of antidepressants (imipramine or paroxetine) begins to outpace placebo response only when baseline Hamilton Depression scores exceed 25.¹⁵ In other words, patients with mild MDD who are identified and treated may be at risk of antidepressant overtreatment. Therefore, considering the role of depression severity in MDD on treatment outcomes can be crucial in guiding treatment selection.

In addition to depression severity, the number of antidepressant failures can also influence the likelihood of clinical benefit.

Outcomes following an initial, evidence-based treatment with antidepressants in primary care settings are equivalent to those in tertiary care psychiatric clinics. In each of these types of settings, approximately 30 percent of patients will experience symptom remission; about 70 percent will have an inadequate treatment response.^{18,19} Providing this latter group (i.e., the remaining 70 percent) with a second treatment attempt produces similar rates of improvement;²⁰ such interventions can include switching antidepressants or augmenting with a second medication. These data suggest that outcomes achieved in psychiatric clinics for both an initial treatment attempt and a second attempt are applicable to primary care settings. However, remission decreases to 15 percent for patients who have not yet recovered following two adequate antidepressant trials. This pattern suggests that patients experiencing treatment failure following two adequate trials of antidepressants would benefit from referral to a psychiatric clinic where clinicians can try more complicated treatment regimens.²¹ Accordingly, this Systematic Review (SR) will focus on the initial two treatment attempts for depressive illness.

Impetus for Review. Primary care physicians provide the largest number of antidepressant prescriptions and account for most of the near doubling in the use of antidepressants over the past decade.²² Accordingly, much of this treatment may be for patients with mild MDD, suggesting a risk of overtreatment for this group. At the same time, primary care physicians appreciate that other potentially effective interventions are available. A systematic review that outlines the benefits and harms of treatment options for major depressive disorder can inform clinical decision making by providers and patients. This review will focus on two key issues facing primary care physicians:

1. As an initial treatment choice, how effective are SGAs compared with nonpharmacologic interventions?

2. For patients whose depression did not achieve remission following initial treatment with an SGA, what is the comparative effectiveness of alternative pharmacologic and nonpharmacologic options? These options include adding a pharmacologic or nonpharmacologic treatment to the initial medication choice (which we refer to as augmentation) or switching to a different SGA or to a nonpharmacologic treatment.

Interventions for MDD. Pharmacotherapy remains the primary intervention for MDD patients in primary care. Nonetheless, primary care patients and clinicians may prefer other options (or at least want to be able to consider them). These include psychotherapeutic interventions, complementary and alternative medicine (CAM) options, or exercise. As noted above, clinicians want comparative effectiveness data to help guide treatment selection across these various choices.²³ We review below the treatment options relevant to this comparative effectiveness review. Given the likelihood of greater benefit of pharmacotherapy for more severely depressed patients, an important clinical issue is the role of psychotherapy, CAM interventions, or exercise as potential monotherapy for patients with mild MDD; a related issue concerns their roles as potential adjuncts to antidepressants for patients with more severe MDD.

Pharmacotherapy for MDD. Pharmacotherapy (e.g., SGAs) dominates the medical management of depressive disorders. This SR will focus on SGAs, which we define as including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, bupropion, mirtazapine, nefazodone, and trazodone. Focusing solely on SGAs more accurately represents the pharmaceutical therapies that primary care clinicians prescribe most often.^{9,24} Furthermore, because SGAs are most frequently used as first-line therapy, we will focus only on comparisons that include SGAs in at least one arm of any given comparative study.

Available evidence for MDD does not warrant choosing one SGA over another based on either greater efficacy or greater effectiveness.²⁴ Only about 60 percent of patients treated with SGAs respond to treatment (meaning specifically that their depressive severity decreases by at least half); approximately 30 percent achieve remission during the first-line treatment.²⁵

More than 60 percent of patients experience at least one adverse effect during treatment. Although most adverse effects are minor, such as constipation, diarrhea, and dizziness, they frequently lead to discontinuation of treatment.²⁶

As documented above, 70 percent of MDD patients do not achieve remission following initial pharmacological treatment, and available data indicate that no one antidepressant performs better than any other. Accordingly, various other interventions—such as medication combinations, psychotherapy, or CAM treatments—are important options for patients and clinicians. In addition, lifestyle changes, for example, increased exercise, have been recommended as adjunctive treatments for MDD.^{27,28} Finally, strategies to augment antidepressant medications for those failing an initial treatment attempt may provide better treatment response than single medications alone.²⁹

Psychotherapy for MDD. The American Psychological Association recently concluded that the general effects of the major psychotherapies that have been studied are significant and large.^{30,31} Some effects of psychotherapy tend to last longer and to be less

subject to relapse requiring additional treatment than outcomes following pharmacological interventions;³² however, the effect of depressive severity on these results is not clear. The psychological interventions used to treat depressed patients include acceptance and commitment therapy, cognitive therapy, cognitive behavioral therapy, interpersonal therapy, psychodynamic therapies, and other talk therapies.

In general, these interventions potentially help people identify how past and present factors may contribute to their depression and teach them how to deal effectively with them. Certain psychological interventions can help individuals identify negative or distorted thought patterns that contribute to feelings of hopelessness and helplessness that accompany depression. These interventions can also help people acquire skills to relieve suffering and prevent later bouts of depression; among them are developing or strengthening social networks, creating new ways to cope with challenges, and following self-care plans that include positive lifestyle changes. To date, however, little is known about the comparative efficacy and effectiveness or harms of psychological interventions to treat depression.

CAM for MDD. CAM interventions are a growing area of both treatment and research. They are most often used in conjunction with conventional treatments (complementary medicine) rather than as alternatives to conventional therapies (alternative medicine). Numerous clinical trials and reviews of CAM therapies for depression exist, including a number of Cochrane reviews.³³⁻³⁶ In addition to SRs, the American Psychiatric Association Task Force and the Canadian Network for Mood and Anxiety Treatments have issued practice guidelines that incorporate the adjunctive use of several CAM interventions.^{37,38} Although the evidence base from high-quality RCTs is limited, sufficient evidence exists to support St. John's wort for mild to moderate MDD.^{39,40} The evidence base is not as robust for the use of yoga, acupuncture, meditation, S-adenosyl-L-methionine, and omega-3 fatty acids.^{35,41-45}

Adverse events are uncommon for most CAM treatments, but concern exists for potential drug interactions between some dietary supplements and other medications. Importantly, more than half of patients with depression are estimated to use some form of CAM therapy, and the majority of patients do not spontaneously disclose CAM use to their care providers.⁴⁶

The comparative effectiveness (either benefits or harms) of CAM and other therapies is not known. As noted for other interventions, the role of depressive severity on these outcomes remains unclear as well.

Exercise for MDD. The use of exercise as either a primary treatment or an augmentation strategy for depression has a growing literature and evidence base. The most comprehensive Cochrane review⁴⁷ identified 32 trials involving 1,858 participants with diagnosed MDD; the authors found a moderate clinical benefit of exercise versus no treatment or control. Although small in number, some studies compare exercise with cognitive therapy, medications, and alternative therapies; most find no clear difference between benefits.

This literature continues to evolve. SRs suggest small but clinically meaningful benefits (in the elderly a reduction of approximately 20 percent in depressive severity).⁴⁸ In addition, recently published clinical trial data indicate comparable benefit for exercise

and depression in patients with cardiovascular disease, with additional improvements in cardiovascular biomarkers, suggesting benefit for both clinical outcomes and quality of life.⁴⁹

Nevertheless, the comparative effectiveness of exercise as either a primary treatment for MDD or an augmentation therapy is unknown. This evidence base continues to evolve with several clinical trials under way addressing MDD and exercise (<http://ccdan.cochrane.org/specialised-register>; <http://clinicaltrials.gov/>), suggesting a need for a review of this area.

Exercise covers a broad range of activities performed over varying durations of time, done singly, in classes, or in informal groups. This SR will focus on the benefits and harms of formal exercise activities that enroll people with an explicit diagnosis of MDD because these interventions are the ones most likely to be studied in trials.

II. The Key Questions

Following the posting of the Key Questions (KQs) for public comment (February 3 to 24, 2014), we modified the questions in several ways. We removed all references to subsyndromal depression from all four KQs, because this disease category should be addressed in a separate review. Second, we simplified KQ 1a to focus on comparisons of SGAs and nonpharmacologic therapies; the PICOTS (given below, plus Table 1 for comparators) will clarify the options (single or combinations of interventions). Third, we modified the wording in KQs 2a and 3a to remove any negative connotations to the patient being treated (e.g., from patients who had failed an initial attempt to patients who did not achieve remission following an initial adequate trial with an SGA). Public reviewers stated that distinguishing between the levels of depression severity in our analysis was important. In response to that advice, we modified KQs 1b, 2b, and 3b to include moderate MDD, and we removed the severity subgroup from KQ 4.

Key Questions

KQ 1a: In adult patients with MDD who are undergoing an initial treatment attempt, what is the effectiveness of second-generation antidepressants (SGAs) monotherapy compared with the effectiveness of either nonpharmacological monotherapy or combination therapy (involving nonpharmacological treatments with or without an SGA)?

KQ 1b: Does treatment effectiveness vary by MDD severity?

KQ 2a: In adult patients with MDD who did not achieve remission following an initial adequate trial with an SGA, what is the effectiveness of switching to a different SGA compared with the effectiveness of nonpharmacological monotherapy or combination therapy (involving nonpharmacologic treatments with or without SGA or augmenting an SGA with another medication)?

KQ 2b: Does treatment effectiveness vary by MDD severity?

KQ 3a: In adult patients with MDD, what are the comparative risks of harms between SGAs and nonpharmacological therapies

- for those undergoing an initial treatment attempt or

- for those who did not achieve remission following an initial adequate trial with an SGA?

KQ 3b: Do the risks of treatment harms vary by MDD severity?

KQ 4: Do the benefits and risks of harms of these treatment options differ by subgroups of patients with MDD defined by common accompanying psychiatric symptoms (coexisting anxiety, insomnia, low energy or somatization) or demographic characteristics (age, sex, or race or ethnicity)?

Population(s)

For this evidence review, we will include adult (18 years or older) outpatients of all races and ethnicities with MDD during either an initial treatment attempt (KQ 1) or a second treatment attempt in patients who did not achieve remission following an initial adequate trial with an SGA (KQ 2).

Subgroups of interest are based on

- common accompanying psychiatric symptoms (anxiety, insomnia, low energy, somatization),
- age,
- sex, and
- race or ethnicity.

We will not include patients with perinatal depression, seasonal affective disorder, psychotic depression, or treatment-resistant depression (i.e., more than one treatment failure).

Interventions

We are interested in two major categories of interventions: (1) nonpharmacological interventions as monotherapies, in combination with one another, or in combination with SGAs (as noted for KQ 1 below) and (2) pharmacological interventions (SGAs in combination with each other or with other pharmaceutical agents, as noted for KQ 2 below).

- For KQ 1 (initial treatment attempt):
 - Common depression-focused psychotherapies
 - Acceptance and commitment therapy
 - Cognitive and behavioral approaches
 - Interpersonal therapy
 - Psychodynamic and attachment-based approaches
 - CAM
 - Acupuncture
 - Meditation (e.g., mindfulness-based stress reduction)
 - Omega-3 fatty acids
 - S-adenosyl-L-methionine (S-AMe)
 - St. John's wort (Hypericum)
 - Yoga

- Exercise
- Combinations of eligible interventions with one another
- Combinations of eligible interventions with SGAs
- For KQ 2 (in addition to the treatments listed for KQ 1):
 - Combinations of SGAs with SGAs
 - Bupropion
 - Citalopram
 - Escitalopram
 - Desvenlafaxine
 - Duloxetine
 - Fluoxetine
 - Fluvoxamine
 - Levomilnacipran
 - Mirtazapine
 - Nefazodone
 - Paroxetine
 - Sertraline
 - Trazodone
 - Venlafaxine
 - Vilazodone
 - Vortioxetine
 - Combinations of SGAs with other pharmacotherapies
 - Atypical antipsychotics (aripiprazole, asenapine maleate, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone)
 - Psychostimulants (amphetamine-dextroamphetamine, armodafinil, dexamfetamine, dextroamphetamine, lisdexamfetamine, methylphenidate, modafinil)
 - Buspirone
 - Levothyroxine (T4)
 - Lithium
 - Pindolol
 - Triiodo-thyronine (T3)

Comparators

We are interested in direct comparisons of eligible interventions with SGAs as single interventions. We will exclude studies that do not include SGA monotherapies in at least one arm of the study. Table 1 lists possible head-to-head comparisons of eligible interventions with SGAs.

Table 1: Possible comparisons of nonpharmacological treatments with SGAs

For all populations of interest (i.e., KQ 1, KQ 2, KQ 3, and KQ 4)
SGAs vs. psychotherapies
SGAs vs. CAM
SGAs vs. exercise
SGAs vs. SGA + psychotherapies
SGAs vs. SGA + CAM
SGAs vs. SGA + exercise
SGAs vs. combinations of eligible interventions
In addition for populations who did not achieve remission following an initial adequate trial with an SGA (i.e., KQ 2, KQ 3, and KQ 4):
SGAs vs. SGA + SGA
SGAs vs. SGA + other pharmacotherapies

CAM = complementary and alternative medicine; SGA = second-generation antidepressant.

Outcomes

- Efficacy: response, remission, speed of response, speed of remission, relapse, quality of life, functional capacity, reduction of suicidality, hospitalization
- Adverse events (safety and tolerability): overall adverse events, withdrawals because of adverse events, serious adverse events, specific adverse events (including hyponatremia, seizures, suicidality, hepatotoxicity, weight gain, gastrointestinal symptoms, sexual side effects), withdrawals because of specific adverse events, or drug interactions (pharmacologic and alternative treatments)

Timing

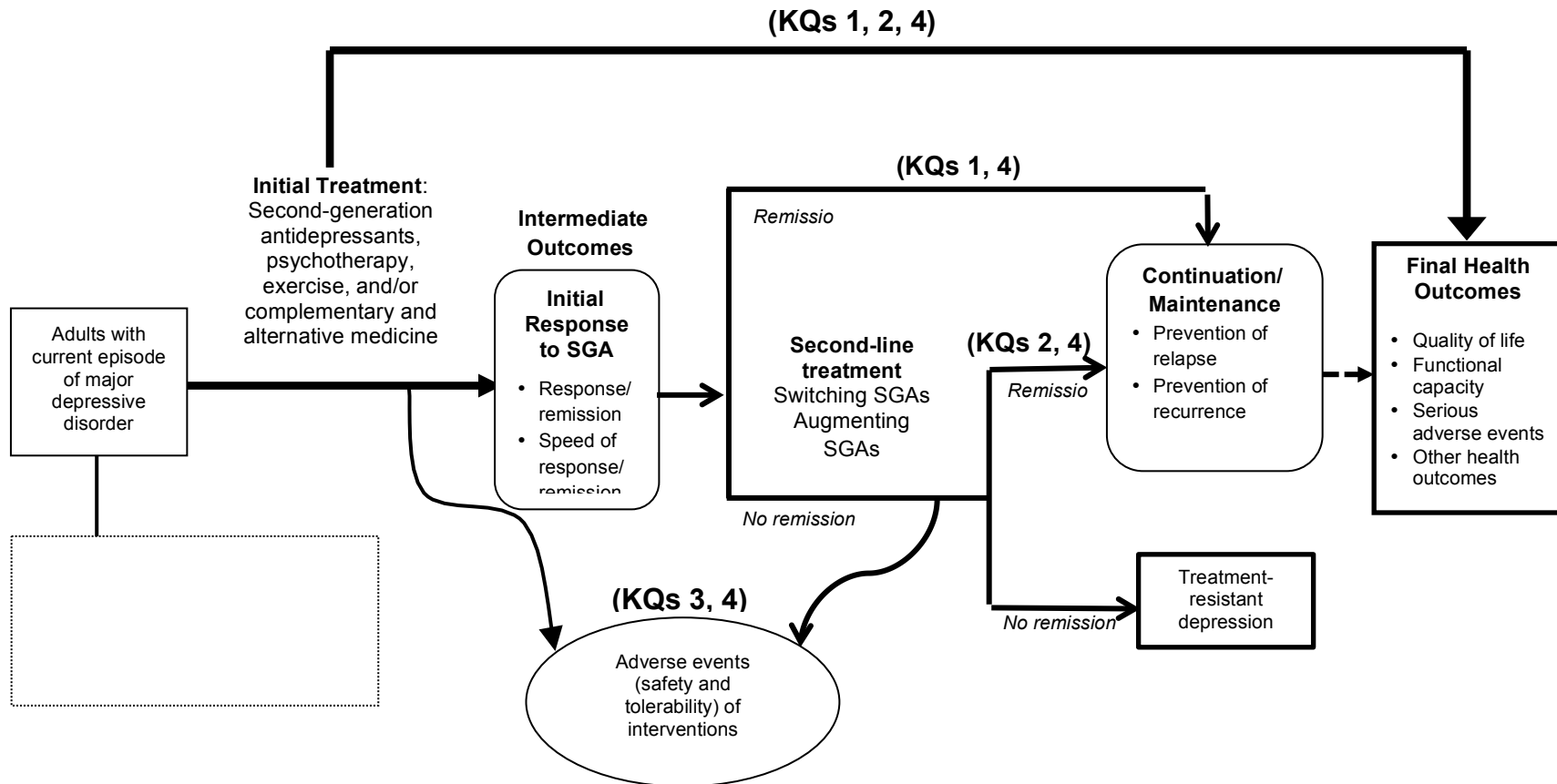
We will have no limitations on study duration or length of followup.

Setting

Primary, secondary, and tertiary care outpatient settings

III. Analytic Framework

Figure 1. Analytic Framework for Treatment of Major Depressive Disorder



KQ = Key Question; SGA = second-generation antidepressant

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review: We specified our inclusion and exclusion criteria based on the population, intervention, comparators, outcomes, timing, and settings (PICOTS) identified through the topic refinement exercise (Table 2). Our exclusion of most non–English-language studies is based on limitations of time and resources, but we will attempt to include all articles published in English, German, and Italian because these are languages the Evidence-based Practice Center (EPC) staff can work with easily. We will exclude study designs without control groups to ensure that our pool of included studies can inform the causal link between the intervention and outcomes.

Table 2. Inclusion/exclusion criteria

Category	Criteria	
	Inclusion	Exclusion
Population	Adult (18 years or older) outpatients of all races and ethnicities with MDD during either an initial treatment attempt or a second treatment attempt in patients who did not remit following an initial adequate trial with an SGA	<ul style="list-style-type: none"> • Children under age 18 • Patients with perinatal depression, seasonal affective disorder, psychotic depression, or treatment-resistant depression (i.e., more than one treatment failure)
Geography	No limit	No limit
Date of search	Searches will go back until 1990; searches will be updated after the draft report goes out for peer review	
Settings	<ul style="list-style-type: none"> • Primary, secondary, and tertiary care outpatient settings 	<ul style="list-style-type: none"> • Inpatient settings
Interventions	<ul style="list-style-type: none"> • As defined in the PICOTS criteria 	<ul style="list-style-type: none"> • First-generation antidepressants • Any other interventions not defined in the PICOTS criteria
Control interventions	<ul style="list-style-type: none"> • As defined in the PICOTS criteria 	
Outcomes	<ul style="list-style-type: none"> • As defined in the PICOTS criteria 	<ul style="list-style-type: none"> • Studies that do not include at least one of the outcomes listed under the inclusion criteria
Timing of intervention	<ul style="list-style-type: none"> • No limitations 	
Publication language	<ul style="list-style-type: none"> • English, German, Italian 	<ul style="list-style-type: none"> • All other languages
Study design	<ul style="list-style-type: none"> • Original research • Eligible study designs include: <ul style="list-style-type: none"> ○ For efficacy/effectiveness <ul style="list-style-type: none"> - RCTs - SRs with meta-analyses ○ In addition for harms <ul style="list-style-type: none"> - Nonrandomized controlled trials - Prospective controlled cohort studies - Retrospective controlled cohort studies - Case-control studies - Nonrandomized studies must have a minimum sample size of 500 participants 	<ul style="list-style-type: none"> • Case series • Case reports • Nonsystematic reviews • SRs without meta-analyses • Studies without a control group • Nonrandomized studies with fewer than 500 participants
Publication type	Any publication reporting primary data	Publications not reporting primary data

MDD = major depressive disorder; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; RCT = randomized controlled trial; SGA=second-generation antidepressant; SR = Systematic Review.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions: We will systematically search, review, and analyze the scientific evidence for each KQ. We will take the following steps to perform the literature search. To identify articles relevant to each KQ, we will begin with a focused MEDLINE® search for eligible interventions using a combination of medical subject headings (MeSH®) and title and abstract keywords, limiting the search to English-, German-, and Italian-language and human-only studies. We will also search the Cochrane Library, the International Pharmaceutical Abstracts database, EMBASE, AMED (Allied and Complementary Medicine Database), PsycINFO, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) using analogous search terms. These searches will include RCTs for benefits (effectiveness) and be expanded to nonrandomized studies to assess harms. We selected these databases based on preliminary searches and consultation with content experts. The search period will go back to January 1990. We will conduct quality checks to ensure that the searches identify known studies. If we do not identify the known studies, we will revise and rerun our searches.

In addition, we will search the “gray literature” for unpublished studies relevant to this review following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* for these steps

(<http://www.effectivehealthcare.ahrq.gov/ehc/products/60/318/CER-Methods-Guide-140109.pdf>).⁵⁰ We will include studies that meet all the inclusion criteria and contain enough methodological information to enable us to assess risk of bias. Potential sources of gray literature include ClinicalTrials.gov, the World Health Organization’s International Clinical Trials Registry Platform, and others. The Scientific Resource Center of the Agency for Healthcare Research and Quality (AHRQ) will manage the process of submitting requests for scientific information packets, which contain information about drugs and CAM interventions.

In addition, in an attempt to avoid retrieval bias, we will manually search the reference lists of landmark studies and background articles on this topic to look for any relevant citations that our electronic searches might have missed.

We will conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. We will investigate any literature that the peer reviewers or the public suggest and, if appropriate, will incorporate additional studies into the final review. The appropriateness of those studies will be determined using the methods described above.

We will include pooled estimates of effect or other relevant results from SRs with meta-analyses that meet our inclusion/exclusion criteria for population, comparisons and outcomes. We will evaluate the quality of included SRs using the AMSTAR tool.⁵¹ Should identified SRs use inclusion/exclusion criteria that differ from ours or SRs without meta-analyses, we will review their reference lists to ensure that we include all relevant studies.

Data Abstraction and Data Management: Two trained research team members will independently review all titles and abstracts identified through searches for eligibility against our inclusion/exclusion criteria. Studies marked for possible inclusion by either

reviewer will undergo a full-text review. For studies without adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in an EndNote® bibliographic database (Thomson Reuters, New York, NY).

We will retrieve and review the full text of all titles included during the title/abstract review phase. Two trained team members will independently review each full-text article for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third member of the review team. All results will be tracked in an EndNote database. We will record the reason that each excluded full-text publication did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet our inclusion criteria, we will abstract important information into evidence tables. We will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers will extract the relevant data from each included article into the evidence tables. A second member of the team will review all data abstractions for completeness and accuracy. We will abstract the following data from included articles: study design, eligibility criteria, intervention, additional medications allowed, methods of outcome assessment, population characteristics (such as age, sex, race or ethnicity, or mean disease duration), sample size, loss to followup, withdrawals because of adverse events, results, and adverse events reported. We will record intention-to-treat (ITT) results if available.

Assessment of Methodological Risk of Bias of Individual Studies: To assess the risk of bias (internal validity) of studies, we will use predefined criteria based on guidance provided by AHRQ.⁵² We will use the Cochrane risk of bias tool for RCTs,⁵³ and the RTI tool for observational studies.⁵⁴ In general terms, results of a study with low risk of bias are considered to be valid. Medium risk of bias implies some confidence that the results represent true treatment effect. The study is susceptible to some bias, but the problems are not sufficient to invalidate the results (i.e., no flaw is likely to cause major bias). A study with medium risk of bias is susceptible to some bias but probably not sufficient enough to invalidate its results. A study with high risk of bias has significant methodological flaws (e.g., stemming from serious errors in design or analysis) that may invalidate its results. We will consider the risk of bias for each relevant outcome of a study.

Two independent reviewers will assess the risk of bias for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team. We will rate studies that meet all criteria as having “low risk of bias.” “Medium risk of bias” ratings will be given to studies that presumably fulfill all quality criteria but do not report their methods sufficiently to answer all of our questions. We will give a “high risk of bias” rating to studies that have a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories.

Data Synthesis: If we find three or more similar studies for a comparison of interest, we will consider quantitative analysis (i.e., meta-analysis) of the data from those studies. We will also consider conducting mixed treatment comparisons meta-analysis using Bayesian methods to compare the pharmacologic interventions with each other if we identify a sufficient number of studies with a common comparator (e.g., placebo). For all analyses, we will use random-effects models to estimate pooled or comparative effects.

To determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.⁵⁵ We will do this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences. If we conduct quantitative syntheses (i.e., meta-analysis), we will assess statistical heterogeneity in effects between studies by calculating the χ^2 -statistic and the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity). The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., p-value from the chi-squared test or a confidence interval for I^2). If we include any meta-analyses with considerable statistical heterogeneity in this report, we will provide an explanation for doing so, considering the magnitude and direction of effects. We will also examine potential sources of heterogeneity using sensitivity analysis or analysis of subgroups. We plan to stratify analyses and/or perform subgroup analyses when possible and appropriate to examine clinical heterogeneity.

For any quantitative analyses, we will conduct sensitivity analyses including high risk-of-bias studies. Planned stratifications or categories for subgroup analyses include the subgroups listed in the analytic framework and geographic location of studies. When quantitative analyses are not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we will synthesize the data qualitatively.

For SRs meeting all of the inclusion criteria, we will abstract study design and methods, number of studies and number of patients included in meta-analyses, characteristics of included studies, populations, and interventions, results, and adverse events, if reported. As appropriate, we may update the results of these reviews quantitatively or qualitatively and assess the Strength of Evidence as described below.

We will follow EPC guidance to assess publication bias.⁵⁶

Grading the Strength of Evidence for Individual Comparisons and Outcomes: We will grade the strength of evidence based on the guidance established for the EPC Program.⁵⁷ Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: risk of bias (includes study design and aggregate quality), consistency, directness, precision of the evidence, and reporting bias. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect). We will ask for input from the Technical Expert Panel (TEP) to determine minimally important differences, which we will use to grade precision.

Grades reflect the strength of the body of evidence to answer KQs on the comparative effectiveness, efficacy, and harms of the interventions included in this review. Two

trained reviewers will assess each domain for each key outcome, and differences will be resolved by consensus. One of the two reviewers will always be a senior researcher with experience in grading the strength of evidence. We will grade the strength of evidence for the outcomes deemed to be of greatest importance to decisionmakers and those commonly reported in the literature by carefully considering the ratings of each domain.

Assessing Applicability We will assess applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.⁵⁸ We will use the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age of enrolled populations, sex of enrolled populations (e.g., fewer men may be enrolled in some studies), and race or ethnicity of enrolled populations.

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
October 28, 2014	II. The Key Questions	KQ 2a: In adult patients with MDD who did not achieve remission following an initial adequate trial with an SGA, what is the effectiveness of switching to a different SGA compared with the effectiveness of nonpharmacological monotherapy or combination therapy (involving nonpharmacologic treatments with or without SGA or augmenting an SGA with another medication)?	KQ2a: In adult patients with MDD who did not achieve remission following an initial adequate trial with one SGA, what is the comparative effectiveness of second line therapies*? * Any comparison that involves an eligible intervention (whether as a monotherapy or a combination therapy) and compares an intervention to one involving an SGA is eligible.	The wording of Key Question 2a in the original protocol was too limiting, which resulted in relevant comparisons being excluded. In response, we modified the criteria to comprehensively capture strategy comparisons relevant to the key question.

		KQ 3a: In adult patients with MDD, what are the comparative risks of harms between SGAs and nonpharmacological therapies	KQ3a: In adult patients with MDD, what are the comparative risks of these treatment options	The wording of the question needed to be revised because the treatment comparisons are more than just SGAs and nonpharmacological therapies, they include all of the treatment comparisons of KQ1 and KQ2, thus the change to “of these treatment options”
July 23, 2014	II. The Key Questions - Interventions	For KQ1 (initial treatment attempt): Common depression-focused psychotherapies – Acceptance and commitment therapy – Cognitive and behavioral approaches – Interpersonal therapy – Psychodynamic and attachment-based approaches	For KQ1 (initial treatment attempt): Common depression-focused psychotherapies* * Cochrane Depression and Anxiety and Neurosis Group typology of psychological therapies (https://ccdan.cochrane.org/sites/ccdan.cochrane.org/files/uploads/CCDAN%20topics%20list_psychological%20therapies%20for%20website.pdf)	After reviewing psychotherapy studies and the difficulties faced in classifying the interventions into our original protocol categories, we determined that it was best to apply the more comprehensive typology of psychological therapies developed by the Cochrane Depression, Anxiety and Neurosis Group (CCDAN)

October 28, 2014	II. The Key Questions - Comparators	Table 1: First Section Header: For all populations of interest (i.e., KQ1, KQ2, KQ3, and KQ4) Second Section Comparator Rows: SGAs vs. SGA + SGA SGAs vs. SGA + other pharmacotherapies	Table 1: First Section Header: For all populations of interest (i.e., KQ1, KQ3, and KQ4) Second Section header In addition for populations who did not achieve remission following an initial adequate trial with an SGA (i.e., KQ2, KQ3, and KQ4): <ul style="list-style-type: none"> • SGA switch^a vs. SGA switch^a • SGA switch^a vs. nonpharmacologic • SGA switch^a vs. SGA augmentation^b • SGA augmentation^b vs. SGA augmentation^b • SGA augmentation^b vs. nonpharmacologic ^a Switching to another SGA ^b Augmenting with a second SGA, for an additional non-SGA medication, or a nonpharmacologic treatment	When we revised KQ2a, we broadened the management strategies that could be compared.
July 1, 2014	IV. Methods	Table 2. Inclusion/exclusion criteria: Study design Exclusions:	Add: <ul style="list-style-type: none"> • Post hoc analyses and pooled studies • Secondary analyses 	These designs had been omitted in the original protocol and we have added them here for transparency
July 1, 2014	IV. Methods	Table 2. Inclusion/exclusion criteria: Population Exclusions: treatment-resistant depression (i.e., more than one treatment failure)	Revise i.e., to “two or more treatment failures”	Rewording the definition of treatment failure to make it clearer for readers of the report

VIII. Review of Key Questions

For all EPC reviews, the EPC reviewed and refined KQs as needed with input from Key Informants and the TEP to ensure that the questions are specific and explicit about what information is being reviewed. In addition, the KQs were posted for public comment and put into final form by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the KQs for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for SRs or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report; they will not have reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end users, individuals are invited to serve as Key Informants, and those who present with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multidisciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes and identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant SR. Therefore, study questions, design issues, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They will not have reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts; those who present with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer Reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. In preparing the final draft of the report, the EPC considers all peer review comments on the preliminary draft of the report. Peer Reviewers do not participate in writing or editing the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical Briefs, be published 3 months after the publication of the Evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total more than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHS A290201200008i from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.