



VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF MAJOR DEPRESSIVE DISORDER

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Version 3.0 – 2016

Prepared by:

**The Management of Major Depressive Disorder
Working Group**

With support from:

**The Office of Quality, Safety and Value, VA, Washington, DC
&
Office of Evidence Based Practice, U.S. Army Medical Command**

Version 3.0 – 2016

Based on evidence reviewed through January 2015

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I. Introduction

The Department of Veterans Affairs (VA) and the Department of Defense (DoD) Evidence-Based Practice Working Group (EBPWG) were established and first chartered in 2004, with a mission to advise the “...Health Executive Council on the use of clinical and epidemiological evidence to improve the health of the population across the Veterans Health Administration (VHA) and Military Health System,” by facilitating the development of clinical practice guidelines (CPG) for the VA and DoD populations.^[2] This CPG is intended to provide primary care clinicians with a framework by which to evaluate, treat, and manage the individual needs and preferences of patients with major depressive disorder (MDD), thereby leading to improved clinical outcomes.

In 2009, the VA and DoD published a CPG for the Management of Major Depressive Disorder (2009 MDD CPG), which was based on evidence reviewed through 2007. Since the release of that guideline, a growing body of research has expanded the general knowledge and understanding of MDD and its management. Recognition of the complex nature of this condition has led to the adoption of new strategies to manage and treat patients with MDD, including new developments related to pharmacotherapy and other treatment options.

Consequently, a recommendation to update the 2009 MDD CPG was implemented in 2014. The updated CPG includes objective, evidence-based information on the management of MDD. It also brought diagnostic criteria for MDD in congruence with the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). It is intended to assist healthcare providers in all aspects of patient care including, but not limited to, diagnosis, treatment, and follow-up. The system-wide goal of evidence-based guidelines is to improve the patient’s health and wellbeing by guiding health providers who are taking care of patients with MDD along the management pathways that are supported by evidence. The expected outcomes of successful implementation of this guideline are to improve how providers:

- Assess the patient’s condition and determine the best treatment method
- Optimize the use of therapy to improve symptoms and functioning, treatment of the condition’s acute phase, prevent relapse, and improve both health and quality of life outcomes
- Minimize preventable complications and morbidity
- Emphasize the use of patient-centered care

II. Background

A. Major Depressive Disorder

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure in regular activities, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Major depressive disorder is the most prevalent and disabling form of depression. In addition to the immediate symptoms of depression, MDD results in poor quality of life overall, decreased productivity, and can increase mortality from suicide. Social difficulties including stigma, loss of employment, and marital conflict as a result of depression can also occur. Anxiety,

posttraumatic stress disorder (PTSD), and substance misuse are common co-occurring conditions that may worsen the existing depression and complicate treatment.

Depression is considered to be a largely biological illness but can result from a combination of genetic, biological, environmental, and psychological factors. Trauma, loss of a loved one, a difficult relationship, or any stressful situation may trigger depression, but depression can also occur without an obvious trigger.

B. Depression in the General Population

According to the National Alliance on Mental Illness, an estimated 16 million American adults—almost 7% of the population—had at least one major depressive episode in the past year. Women are 70% more likely than men to experience depression, and young adults aged 18–25 are 60% more likely to have depression than people aged 50 or older.^[3] Depressive disorders often start at a young age; they reduce people’s functioning and often recur.^[4] According to the World Health Organization (WHO), MDD (identified as unipolar depressive disorders by WHO) ranked first worldwide among the leading causes of disability (i.e., aggregate years lived with disability [YLD]).^[5]

The incremental economic burden of individuals with MDD was \$210.5 billion in 2010, in both direct and indirect costs, compared to \$173.2 billion in 2005, an increase of 21.5% over this period.^[6] Additionally, co-occurring conditions accounted for a larger percentage of the economic burden of MDD than the MDD itself.

Although depression can be a devastating illness, it often responds to treatment. There are a variety of treatment options available for people with depression including drugs and psychotherapy. Depression is frequently underdiagnosed, however; among people with severe depressive symptoms, for example, only about one-third (35%) had seen a mental health professional for treatment in the past year.^[7]

C. Depression in the VA/DoD Populations

Military personnel are prone to depression, at least partially as a result of exposure to traumatic experiences, including witnessing combat and separation from family during deployment or military trainings.^[8,9] For example, based on data collected in 2011 from a de-identified cross-sectional survey of active duty soldiers, The Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) described the 30-day prevalence of MDD as 4.8% compared to less than 1%—five times higher— among a civilian comparison group.^[10] A meta-analysis of 25 epidemiological studies estimated the prevalence of recent major depression based on the DSM-IV criteria at rates of 12.0% among currently deployed U.S. military personnel, 13.1% among previously deployed, and 5.7% among those never deployed.^[11] However, the 25 studies from which these estimates are drawn described a wide range of prevalences depending on the screening or diagnostic instrument, population, and time period used. Being female, enlisted, 17-25 years old, unmarried, and having had less than a college education were risk factors for depression.^[11] In an analysis among current and former U.S. military personnel who were included in the Millennium Cohort Study and observed from July 1, 2001 to December 31, 2008, the risk of suicide increased in men and in those who were depressed.^[12]

In fiscal year 2015, among Veterans served by the Veterans Health Administration (VHA), the documented prevalence of any depression (including depression not otherwise specified) was 19.8% while the documented prevalence of MDD only was 6.5%.^[13]

III. Scope of the Guideline

This CPG is designed to assist providers in managing patients with MDD. The patient population of interest for this CPG includes adults who are eligible for care in the VHA and DoD healthcare delivery system. It includes Veterans as well as deployed and non-deployed active duty Service Members. It also includes care provided by DoD and VA staff as well as care obtained by the DoD and VA from community partners. This CPG does not provide recommendations for the management of MDD in children or adolescents, or for the management of co-occurring disorders. The CPG also does not consider the management of unspecified depressive disorder, or complicated bereavement or the range of other depressive disorders identified in DSM-5: disruptive mood dysregulation disorder, persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder or unspecified depressive disorder (depression not otherwise specified). The principals in this document should be strongly considered when treating these other depressive disorders and in particular, unspecified depressive disorders.

A. Target Population

This guideline applies to adults with MDD being treated in any VA/DoD clinical setting. This includes those newly diagnosed, those receiving ongoing treatment and those with chronic depression.

B. Audiences

The guideline is relevant to all healthcare professionals who treat patients for MDD. This version of the guideline was specifically tailored to be of greatest value to the primary care provider and general mental healthcare provider; thus it includes recommendations on how and when to refer to specialty mental healthcare.

C. Outcomes of Interest

- Improvement in quality of life and social and occupational functioning
- Improvement of symptoms
- Retention (keeping patients engaged in treatment)
- Improvement in co-occurring conditions
- Reduced mortality
- Prevention of recurrence or relapse

D. Goals of the Guideline

- Offer best practice advice on the care of adults who have a diagnosis of MDD
- Recommend optimal assessment and diagnosis for MDD
- Recommend best practices for treatment interventions (pharmacotherapy, psychotherapies, and somatic therapies) in patients with MDD
- Address indications for consultation and referral to specialty care

IV. About this Clinical Practice Guideline

This guideline represents a significant step toward improving the treatment and management of patients with MDD in the VA and DoD populations. However, as with other CPGs, challenges remain, including the need to develop effective strategies for guideline implementation and to evaluate the effect of guideline adherence on clinical outcomes.

This CPG is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advances and patterns evolve. This CPG is based on evidence reviewed through January 2015, and is intended to provide a general guide to best practices. The guideline can assist providers, but the use of a CPG must always be considered as a general recommendation, within the context of a provider's clinical judgment, for the care of an individual patient.

A. Methods

The current document is an update to the 2009 MDD CPG. The methodology used in developing the 2016 CPG follows the Guideline for Guidelines,^[2] an internal document of the VA and DoD EBPWG. The Guideline for Guidelines can be downloaded from <http://www.healthquality.va.gov/policy/index.asp>. This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and DoD, known as the Work Group, and ultimately, the development and submission of an updated MDD CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations, and writing and publishing a guideline document to be used by providers within the VA/DoD healthcare system. Specifically, the Champions and the Work Group for this guideline were responsible for identifying the key questions of greatest clinical relevance, importance, and interest for the management of patients with MDD. The Champions and the Work Group also provided direction on inclusion and exclusion criteria for the evidence review and assessed the level of quality of the evidence. In addition, the Champions assisted in:

- Identifying appropriate disciplines of individuals to be included as part of the Work Group
- Directing and coordinating the Work Group
- Participating throughout the guideline development and review processes

The VA Office of Quality, Safety and Value, in collaboration with the Office of Evidence-Based Practice, U.S. Army Medical Command, the proponent for CPGs for the DoD, identified two clinical leaders, David Oslin, MD from VA and Major Lucretia Vaughan, MD from DoD, as Champions for the 2016 MDD CPG. It should be noted that three other VA Champions were identified prior to the selection of Dr. Oslin, but due to a perceived conflict of interest as well as competing time commitments, they were unable to remain in their role. Dr. Oslin was appointed as the VA Champion in May 2015 right before the face-to-face meeting was held.

The Lewin Team (Team), including The Lewin Group, Duty First Consulting, ECRI Institute, and Sigma Health Consulting, LLC, was contracted by the VA and DoD to support the development of this CPG and

to conduct the evidence review. The Team held the first conference call in November 2014, with participation from the contracting officer's representative (COR), leaders from the VA Office of Quality, Safety and Value and the DoD Office of Evidence-Based Practice, the DoD Champion and the initial VA Champion. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review about the management of MDD. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of MDD from which Work Group members were recruited. The specialties and clinical areas of interest included: psychiatry, psychology, nursing, pharmacy, social work, family medicine, internal medicine, emergency medicine, and mental and behavioral healthcare. The guideline development process for the 2016 MDD CPG update consisted of the following steps:

1. Formulating evidence questions (key questions)
2. Conducting the systematic review
3. Convening a face-to-face meeting with the CPG Champions and Work Group members
4. Reviewing former recommendations not included in the systematic review and without an updated literature review
5. Drafting and submitting a final MDD CPG to the VA/DoD EBPWG

[Appendix A](#) provides a detailed description of each of these tasks.

a. Reconciling 2009 CPG Recommendations

Evidence-based CPGs should be current, which typically requires revisions of previous recommendations based on new evidence or as scheduled according to time-based expirations.^[14] For example, the United States Preventive Services Task Force (USPSTF) has a process for periodically refining or otherwise updating its recommendations pertaining to preventive services.^[15] Further, the inclusion criteria for the National Guideline Clearinghouse specify that a guideline must have been developed, reviewed, or revised within the past five years.

The MDD CPG Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the key questions. In addition to those new and updated recommendations, the CPG Work Group considered the current applicability and relevance of the remaining recommendations that were made in the previous 2009 MDD CPG. While these remaining 2009 recommendations were reviewed by the group, the literature supporting these recommendations was not reviewed as part of a systematic literature search. Therefore, the determination of carrying forward or modifying these prior recommendations was based on expert opinion as well as on the evidence review from the previous version of the guideline. In order to be fully transparent, [Appendix F](#) displays all the recommendations from the 2009 MDD CPG and the information regarding how 2009 recommendations were incorporated into the 2016 MDD CPG, including the recommendation category and the 2016 recommendation to which it corresponds, if applicable.

A set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE, UK).^[16,17] These categories, along with their corresponding definitions,

were used to account for the various ways in which recommendations could have been updated. In brief, the categories took into account whether or not the evidence that related to a recommendation was reviewed, the degree to which the recommendation was modified, and the degree to which a recommendation is relevant in the current patient care environment and within the scope of the CPG. Additional information regarding these categories and their definitions can be found in [Appendix A](#). The categories for the recommendations included in the 2016 version of the guideline are noted in the [Recommendations](#). The categories for the recommendations from the 2009 MDD CPG are noted in [Appendix F](#).

The CPG Work Group recognized the need to accommodate the transition in evidence rating systems from the 2009 MDD CPG to the current CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system) the CPG Work Group converted the USPSTF strengths of evidence accompanying the carryover recommendations from the 2009 guideline to the GRADE system. As such, the CPG Work Group considered the strength of the evidence cited for each recommendation in the 2009 MDD CPG as well as both the harms and benefits of each intervention, the patients' values and preferences, and other implications, where possible and relevant. The CPG Work Group referred to the available evidence as summarized in the body of the 2009 MDD CPG and did not re-assess the evidence systematically for those recommendations that did not correspond to the current key questions. In some instances, peer-reviewed literature published since the 2009 MDD CPG was selectively considered along with the evidence base used for that CPG. When such newer literature was considered when converting the strength of the recommendation from the USPSTF to GRADE system, it is noted and cited in the discussion that follows the corresponding recommendation, as well as in [Appendix E](#).

The CPG Work Group recognizes that, while there are sometimes practical reasons for incorporating findings from a previous systematic review, previous recommendations,[\[18\]](#) or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive systematic review and, therefore, may introduce bias. Another example of a difference between the previous guideline and the current one is that the prior guideline process included a consideration of patients' values and preferences less consistently or systematically, so older recommendations may be less patient-centered.

b. Peer Review Process

The CPG was developed through an iterative process in which the Work Group produced multiple drafts of the CPG. The process for developing the initial draft is described in more detail in [Drafting and Submitting the Final Clinical Practice Guideline](#).

Once a near-final draft of the guideline was agreed upon by the Champions and Work Group members, the draft was sent out for peer review and comment. The draft was posted on a wiki website for a period of 14 business days. The peer reviewers comprised individuals working within the VA and DoD health systems as well as experts from relevant outside organizations designated by the Work Group members. It is important to note that while external reviewers have organizational affiliations, they do not necessarily review the CPG on behalf of their organization. Individuals at the following organizations were contacted to review the guideline:

- American Psychiatric Association (Society of Uniformed Services Psychiatrists)
- University of Washington Advancing Integrated Mental Health Solutions (AIMS) Center
- University of Indiana
- Vanderbilt University
- University of Pennsylvania

The VA and DoD Leadership reached out to both the internal and external peer reviewers to solicit their feedback on the CPG. Reviewers were provided a hyperlink to the wiki website where the draft CPG was posted. For transparency, all reviewer feedback, along with the name of the reviewer, was posted in tabular form on the wiki site. All feedback from the peer reviewers was discussed and considered by the Work Group. Modifications made throughout the CPG development process were made in accordance with the evidence.

B. Conflict of Interest

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest (COI) in the past 12 months. Verbal affirmations of no COI were also used as necessary during meetings throughout the guideline development process. The project team was also subject to random web-based surveillance (e.g., ProPublica).

If a project team member reported a COI (actual or potential), then it was reported to the Office of Evidence Based Practice. It was also discussed with the MDD CPG Work Group in tandem with their review of the evidence and development of recommendations. The Office of Evidence Based Practice and the MDD CPG Work Group determined whether or not action, such as restricting participation and/or voting on sections related to the conflict or removal from the Work Group, was necessary. If it was deemed necessary, action was taken by the co-chairs and Office of Evidence Based Practice to mitigate the COI, based on the level and extent of involvement.

Due to COI concerns, two VA co-chairs were replaced early on in the CPG development process. In order to mitigate the risk of bias while maximizing the contributions of those with expertise in a specific area of MDD treatment, co-chairs asked Work Group members to disclose relevant relationships during related guideline development discussions. After discussion among the Champions, Work Group, and VA/DoD Leadership, it was decided that members with potential COIs could contribute to the discussions related to their particular areas of expertise as well as the overarching guideline document in order to ensure differing viewpoints and experiences were adequately represented.

C. Highlighted Features of this CPG

The 2016 edition of the VA/DoD Guideline for the Management of MDD is the second update to the original CPG. It provides best practice recommendations for the care of populations with MDD with any level of severity with or without co-occurring conditions. A particular strength of this CPG is the multidisciplinary stakeholder involvement from its inception, ensuring representation from a broad spectrum of clinicians engaged in treatment and management of patients with MDD.

The literature review of interventional studies encompassed studies published between 2007 and January 2015, and targeted 10 key questions focusing on the ways the delivery of healthcare could be optimized for patients with MDD.

The framework for recommendations used in this CPG considered factors beyond the strength of the evidence, including balancing desired outcomes with potential harms of treatment, equity of resource availability, and the potential for variation in patient values. A straightforward algorithm accompanies the guideline to facilitate the CPG's translation into effective practice.

D. Patient-centered Care

Guideline recommendations are intended to be patient-centered. Regardless of setting or availability of professional expertise, any patient in the healthcare system should be provided with the interventions that are recommended in this guideline as appropriate to the patient's specific condition and circumstances.

Treatment and care should take into account a patient's needs and preferences. Thus, good communication between healthcare professionals and the patient is essential. Information shared between providers and patients should likewise be supported by evidence and tailored to the patient's needs. The information that patients are given about their healthcare should be culturally appropriate and available to people who do not speak or read English or who have limited literacy skills. It should also be accessible to people with additional needs such as physical or learning disabilities.

Care of Veterans and Service Members in transition between facilities, services, or from the DoD healthcare system to the VA healthcare system should be based on a plan for this transition and be managed according to best practice guidance. Healthcare teams should work collaboratively to provide assessment and services to patients within this transitioning population. Management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Another element in being patient-centered is balancing patient preferences within the setting that allows the provider to maximize the resources available to care for the patient. There are two areas in which this is addressed specifically in this guideline. First, in complex patients with comorbid conditions, suicidal ideation, or a history of recurrent episodes, optimal care is likely to require the skills and resources only available in a specialty mental health program ([Recommendation 5](#)). It is important to help patients understand the rationale for this recommendation. Similarly, for patients with milder forms of MDD, treatment within primary care settings with the resources of collaborative care can be as effective in managing the illness as referring to a specialty clinic. Those resources and settings are described in detail in [Recommendation 6](#).

E. Knowledge Gaps and Future Directions

In preparing the CPG, the workgroup identified areas that should be addressed as priorities in future research.

Questions arose for which evidence was lacking, thus calling for more health services research and, specifically, a greater number and range of comparative effectiveness trials. For example, there is surprisingly little research on the management of complex cases of MDD despite its frequent

appearance in routine practice. Specifically, it would be helpful to know how and when to combine psychotherapy and medications as initial therapy and whether there are particular combinations that are more effective than others for both complex and uncomplicated patients. There also needs to be a better understanding of the value and use of measurement-based care, including the place of pharmacogenetics in the treatment of MDD. Additional research is required in the use of genetic testing to aid in the selection of the most appropriate medication for a specific patient. Currently, there is insufficient evidence to support the routine use of genetic testing for the selection of one antidepressant over another. Trials that address how often to deploy assessment instruments (function, symptom, global) and determine the impact of assessment on outcomes are needed. Good quality research studies on the benefits, harms, and burdens of couples therapy compared with individual therapy for MDD is also limited. Additional studies with larger sample sizes and greater heterogeneity among study subjects should be research priorities for understanding this treatment intervention given the link between relationship distress and depression as well as the potential for benefit.

The digital age has arrived in mental health as both the DoD and VA have adapted procedures (including assessment, pharmacotherapy and psychotherapy) for care delivery via telehealth (e.g., videoconferencing, telephone care). Yet we know little about how best to augment clinical care and improve outcomes using technology, including smartphones, social media, or computerized therapies. The current evidence review did not systematically evaluate the literature on the use of telehealth modalities for treating major depression; therefore there is not a specific recommendation regarding its implementation overall, only as part of collaborative care models in [Recommendation 6](#), for which there is evidentiary support. We did, however, consider recent studies indicating that telehealth approaches are acceptable to patients and may not be significantly less effective than traditional approaches.^[19,20] Given the need to improve access to adequate mental healthcare for servicemen and women and their families, and the potential for telehealth to improve access, we strongly recommend that the next revision of the guideline formally review the literature on telehealth modalities and incorporate this information into the guideline. While they are unlikely to replace clinicians, how these technologies will be used by patients and providers continues to evolve.

There are large gaps in knowledge related to somatic treatments (e.g., deep brain stimulation, electroconvulsive therapy) and newer treatments (e.g., ketamine) for depression for which there is evidence of benefit as well as significant risks. Much of the research on nutritional supplements, exercise and related behavioral interventions is sparse and poorly conducted. Finally, it continues to be very important to continue to look for new mechanisms for the treatment of this important condition.

F. Implementation

This CPG and algorithm are designed to be adaptable by individual healthcare providers with consideration of local needs and resources. The algorithm serves as a guide that providers can use to determine the best interventions and timing of care for their patients in order to optimize quality and improve clinical outcomes.

Although this CPG represents practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. New technology and more research will improve patient care in the future. The CPG can assist in identifying priority areas for

research and optimal allocation of resources. Future studies examining the results of CPG implementation may lead to the development of new evidence particularly relevant to the development and dissemination of guidelines.

V. Guideline Working Group

Guideline Working Group*	
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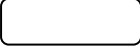
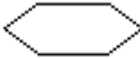

* Additional contributor contact information is available in [Appendix G](#).

VI. Algorithm

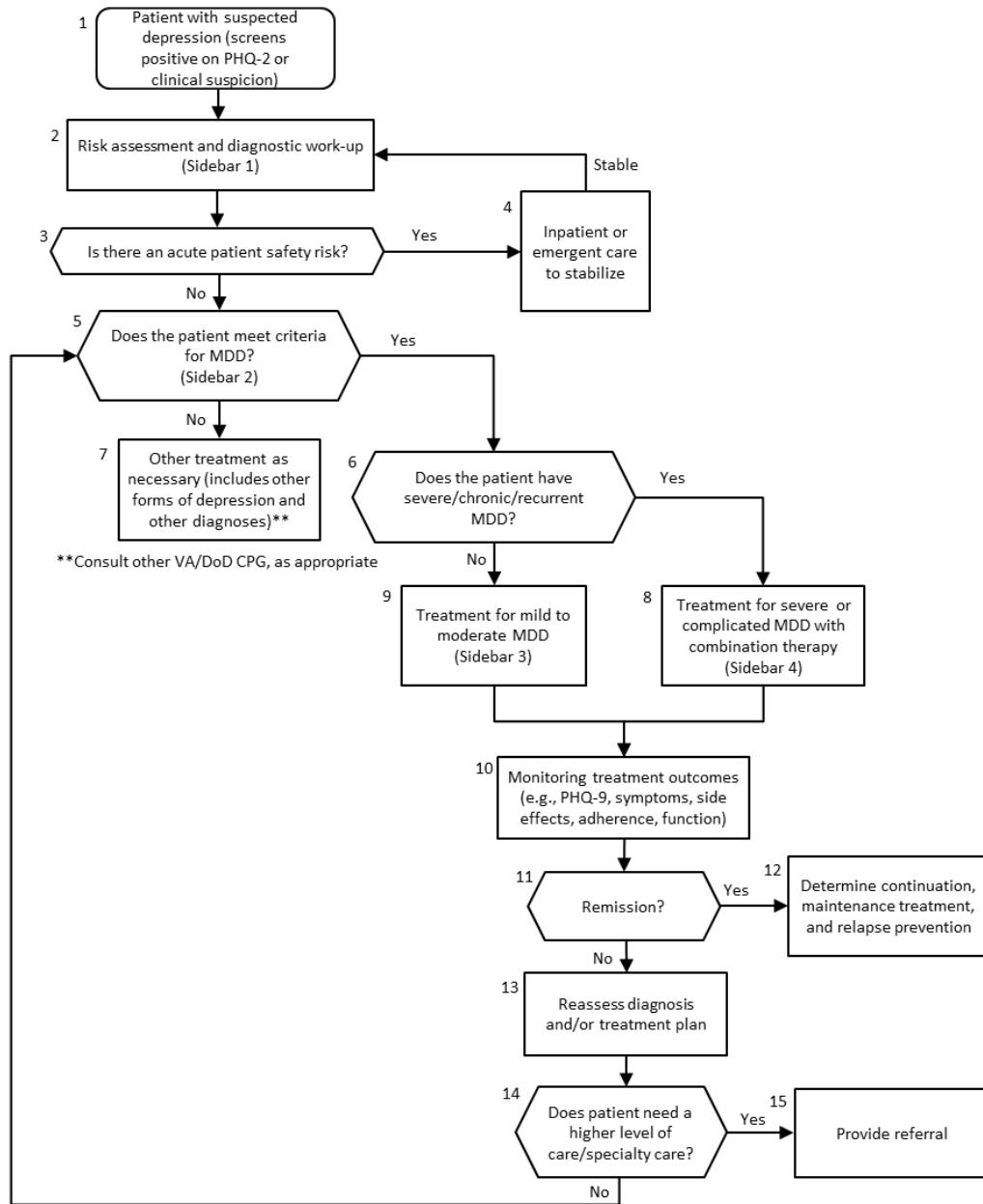
This CPG includes an algorithm that is designed to facilitate clinical decision making for the management of MDD. The use of the algorithm format as a way to represent patient management was chosen based on the understanding that such a format can facilitate efficient diagnostic and therapeutic decision making and has the potential to affect patterns of resource use. The algorithm format allows the provider to follow a linear approach in assessing the critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Recommended observations and examinations
- Decisions to be considered
- Actions to be taken

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed.[\[21\]](#)

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No.
	Rectangles represent an action in the process of care.

Identification
Assessment and Triage
Management



Sidebar 1 - Risk Assessment and Work-up

- Consider administration of PHQ-9
- Evaluate for (1) suicidal and homicidal ideation, (2) history of suicide attempts, (3) presence of psychotic features
- Rule out causes of secondary MDD (e.g., hypothyroidism, B-12 deficiency, syphilis, chronic disease)

Sidebar 3 - Considerations in Treatment of Mild/Moderate MDD

For example:

- Select monotherapy or combination therapy: pharmacotherapy/psychotherapy
- Treatment for special populations (e.g., treatment of co-occurring conditions, pregnant patients, geriatric patients)
- Patient preferences (treatment refusers)
- Consider referral

Sidebar 2 - DSM-5 Criteria

Criterion A: Five or more of the following symptoms present during the same 2-week period; at least one of the symptoms is either (1) depressed mood or (2) loss of interest/pleasure:

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day
- Significant weight loss when not dieting or weight gain
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy every day
- Feelings of worthlessness or excessive inappropriate guilt
- Diminished ability to think, concentrate, or indecisiveness, nearly every day
- Recurrent thought of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Criterion B: The symptoms cause significant distress or functional impairment

Criterion C: The episode is not attributable to the physiological effects of a substance or another medical condition

Sidebar 4 - Considerations in Treatment of Severe MDD

For example:

- Recommend referral to specialty level care
- Select combination therapy: pharmacotherapy/psychotherapy
- Treatment for special populations (e.g., treatment of co-occurring conditions, pregnant patients, geriatric patients)
- Patient preferences (treatment refusers)

VII. Recommendations

The following recommendations are organized into sections reflecting both the typical clinical approach to patients as well as grouped according to the severity of the major depressive disorder. The first four sections (Identification, Assessment and Triage, Treatment Setting, and Management) represent the core activities and decisions involved in caring for an individual with MDD. The last section (Other Treatment Considerations) addresses specific populations, complementary alternatives, and secondary treatment options.

#	Recommendation	Strength*	Category†
A. Identification			
1.	We recommend that all patients not currently receiving treatment for depression be screened for depression using the Patient Health Questionnaire-2 (PHQ-2).	Strong For	Not Reviewed, Amended
B. Assessment and Triage			
2.	For patients with suspected depression, we recommend an assessment for acute safety risks (e.g., harm to self or others, psychotic features) during the initial assessment and periodically thereafter as needed.	Strong For	Not Reviewed, Amended
3.	For patients with suspected depression, we recommend an appropriate diagnostic evaluation that includes a determination of functional status, medical history, past treatment history, and relevant family history.	Strong For	Not Reviewed, Amended
4.	For patients with a diagnosis of MDD, we suggest using the Patient Health Questionnaire-9 (PHQ-9) as a quantitative measure of depression severity in the initial treatment planning and to monitor treatment progress (see Recommendation 14).	Weak For	Not Reviewed, Amended
C. Treatment Setting			
5.	We recommend that patients with complex MDD (severe, chronic or recurrent) be offered specialty care by providers with mental health expertise in order to ensure better outcomes and effective delivery of evidence-based treatment strategies.	Strong For	Reviewed, New-replaced
6.	We recommend the use of the collaborative care model for the treatment of MDD within a primary care setting.	Strong For	Reviewed, New-replaced
D. Management			
a. Treatment for Uncomplicated Mild to Moderate MDD			
7.	We recommend that treatment planning include patient education about the condition and treatment options, including risks and benefits. The individualized treatment plan should be developed using shared decision-making principles, and should define the provider, patient, and support network's roles.	Strong For	Not Reviewed, Amended

#	Recommendation	Strength*	Category†
8.	<p>As first-line treatment for uncomplicated mild to moderate MDD (see Recommendation 17 for complex cases), we recommend offering one of the following treatments based on patient preference, safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications, cost of medication and provider training/competence:</p> <ul style="list-style-type: none"> ▪ Evidence-based psychotherapy: <ul style="list-style-type: none"> • Acceptance and commitment therapy (ACT) • Behavioral therapy/behavioral activation (BT/BA) • Cognitive behavioral therapy (CBT) • Interpersonal therapy (IPT) • Mindfulness-based cognitive therapy (MBCT) • Problem-solving therapy (PST) ▪ Evidence-based pharmacotherapy: <ul style="list-style-type: none"> • Selective serotonin reuptake inhibitor (except fluvoxamine) (SSRIs) • Serotonin–norepinephrine reuptake inhibitor (SNRIs) • Mirtazapine • Bupropion ▪ The evidence does not support recommending a specific evidence-based psychotherapy or pharmacotherapy over another. 	Strong For	Reviewed, New-replaced
9.	In patients who have demonstrated partial or no response to initial pharmacotherapy monotherapy (maximized) after a minimum of four to six weeks of treatment, we recommend switching to another monotherapy (medication or psychotherapy) or augmenting with a second medication or psychotherapy.	Strong For	Reviewed, New-replaced
10.	For patients who select psychotherapy as a treatment option, we suggest offering individual or group format based on patient preference.	Weak For	Reviewed, New-replaced
11.	For patients with mild to moderate MDD, we recommend offering computer-based cognitive behavioral therapy (CCBT) either as an adjunctive intervention or, based on patient preference, as a first-line treatment.	Strong For	Reviewed, Amended
12.	For patients with mild to moderate MDD who decline pharmacotherapy and who decline or cannot access first-line evidence-based psychotherapies, we suggest offering non-directive supportive therapy or short-term psychodynamic psychotherapy.	Weak For	Reviewed, New-replaced
b. Treatment of Severe, Chronic or Recurrent MDD (Complex)			
13.	<p>We suggest offering a combination of pharmacotherapy and evidence-based psychotherapy for the treatment of patients with MDD during a new episode of care when the MDD is characterized as:</p> <ul style="list-style-type: none"> ▪ Severe (i.e., PHQ-9 >20) ▪ Chronic (duration greater than two years) ▪ Recurrent (with three or more episodes) 	Weak For	Reviewed, New-replaced
c. Monitoring (All Severities and Complexities of MDD)			
14.	After initiation of therapy or a change in treatment, we recommend monitoring patients at least monthly until the patient achieves remission. At minimum, assessments should include a measure of symptoms, adherence to medication and psychotherapy, and emergence of adverse effects.	Strong For	Reviewed, Amended

#	Recommendation	Strength*	Category†
d. Continuation and Maintenance Treatments (All Severities and Complexities of MDD)			
15.	In patients with MDD who achieve remission with antidepressant medication, we recommend continuation of antidepressants at the therapeutic dose for at least six months to decrease risk of relapse.	Strong For	Reviewed, New-replaced
16.	In patients at high risk for recurrent depressive episodes (see Discussion) and who are treated with pharmacotherapy, we recommend offering maintenance pharmacotherapy for at least 12 months and possibly indefinitely.	Strong For	Reviewed, New-replaced
17.	For patients at high risk for relapse (e.g., two or more prior episodes, unstable remission status), we recommend offering a course of cognitive behavioral therapy (CBT), interpersonal therapy (IPT) or mindfulness-based cognitive therapy (MBCT) during the continuation phase of treatment (after remission is achieved) to reduce the risk of subsequent relapse/recurrence. <ul style="list-style-type: none"> ▪ The evidence does not support recommending a specific evidence-based psychotherapy over another. 	Strong For	Reviewed, Amended
E. Other Treatment Considerations			
a. Recommendations for Specific Populations With Mild to Moderate MDD			
18.	For initiation of treatment in pregnant or breastfeeding women with mild to moderate MDD, we recommend offering an evidence-based psychotherapy (i.e., ACT, BA/BT, CBT, IPT, MBCT, PST) as a first-line treatment. <ul style="list-style-type: none"> ▪ The evidence does not support recommending a specific evidence-based psychotherapy over another. ▪ In pregnant patients with a history of MDD prior to pregnancy who responded to antidepressant medications, and are currently stable on pharmacotherapy, weigh risk/benefit balance to both mother and fetus in treatment decisions. 	Strong For	Reviewed, New-replaced
19.	For older adults (≥65 years) with mild to moderate MDD, we recommend offering an evidence-based psychotherapy (i.e., ACT, BT/BA, CBT, IPT, MBCT, PST) as a first-line treatment. Patient preference and the additional safety risks of pharmacotherapy should be considered when making this decision. <ul style="list-style-type: none"> ▪ The evidence does not support recommending a specific evidence-based psychotherapy over another. 	Strong For	Reviewed, New-replaced
20.	In patients with mild to moderate MDD and significant relationship distress, we suggest offering couples-focused therapy, either as monotherapy or in combination with pharmacotherapy.	Weak For	Reviewed, New-replaced
21.	We suggest offering light therapy for adult patients with mild to moderate MDD with a seasonal pattern (formerly seasonal affective disorder [SAD]).	Weak For	Reviewed, Amended
b. Other Considerations for the Treatment of Severe, Chronic or Recurrent MDD (Complex)			
22.	For patients with treatment-resistant MDD who had at least two adequate pharmacotherapy trials, we recommend offering monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs) along with patient education about safety and side effect profiles of these medications.	Strong For	Reviewed, New-replaced
23.	Given the limited information on ketamine’s safety and duration of effect, we recommend against the use of ketamine to treat MDD outside of a research setting.	Strong Against	Reviewed, New-added

#	Recommendation	Strength*	Category†
24.	We recommend offering electroconvulsive therapy (ECT) with or without psychotherapy in patients with severe MDD and any of the following conditions: <ul style="list-style-type: none"> ▪ Catatonia ▪ Psychotic depression ▪ Severe suicidality ▪ A history of a good response to ECT ▪ Need for rapid, definitive treatment response on either medical or psychiatric grounds ▪ Risks of other treatments outweigh the risks of ECT (i.e., co-occurring medical conditions make ECT the safest treatment alternative) ▪ A history of a poor response to multiple antidepressants ▪ Intolerable side effects to all classes of antidepressant medications (e.g., seizures, hyponatremia, severe anxiety) ▪ Patient preference ▪ Pregnancy 	Strong For	Reviewed, Amended
25.	We suggest offering treatment with repetitive transcranial magnetic stimulation (rTMS) for treatment during a major depressive episode in patients with treatment-resistant MDD.	Weak For	Reviewed, New-added
26.	We recommend against offering vagus nerve stimulation (VNS) for patients with MDD, including patients with severe treatment-resistant depression outside of a research setting.	Strong Against	Reviewed, Amended
27.	We recommend against offering deep brain stimulation (DBS) for patients with MDD outside of a research setting.	Strong Against	Reviewed, New-added
c. Self-help and Complementary and Alternative Treatments			
28.	For patients with MDD, there is insufficient evidence to recommend for or against acupuncture either as monotherapy or as an adjunctive treatment to pharmacotherapy.	Not Applicable	Reviewed, New-replaced
29.	For patients with MDD, we suggest offering patient education on the benefits of exercise as an adjunct to other evidence-based treatments for depression or as monotherapy when patients are unwilling or unable to engage in first-line evidence-based psychotherapy or pharmacotherapy.	Weak For	Reviewed, New-replaced
30.	For patients with MDD, there is insufficient evidence to recommend for or against yoga, tai chi, or qi gong either as monotherapy or as an adjunctive treatment to pharmacotherapy.	Not Applicable	Reviewed, New-added
31.	For patients with mild MDD who are not pregnant or breastfeeding and who prefer herbal treatments to first-line psychotherapy or pharmacotherapy, we suggest standardized extract of St. John's wort (SJW) as a medication monotherapy.	Weak For	Reviewed, Amended
32.	For patients with MDD, we suggest against using omega-3 fatty acids or vitamin D for treatment.	Weak Against	Reviewed, New-added
33.	For patients with mild MDD, we suggest patient education about the benefits of bibliotherapy based on cognitive-behavioral principles as adjunctive treatment or an alternative to pharmacotherapy or psychotherapy based on patient preference.	Weak For	Reviewed, New-replaced

*For additional information, please refer to [Grading Recommendations](#).

†For additional information, please refer to [Recommendation Categorization](#) and [Appendix F](#).

A. Identification

Recommendation

1. We recommend that all patients not currently receiving treatment for depression be screened for depression using the Patient Health Questionnaire-2 (PHQ-2).

(Strong For | Not Reviewed, Amended)

Discussion

Consistent with the USPSTF recommendation, screening for MDD and follow-up of a positive screen should be standard clinical practice. The current policy for VA and DoD recommends annual screening for MDD. The PHQ-2 ([Tables 1](#) and [2](#)) is the recommended screening tool for this purpose.[\[22-24\]](#) All patients who screen positive on the PHQ-2 should have a further assessment of symptoms and assessment of risk ([Recommendations 2](#) and [3](#)). In addition to screening with the PHQ-2 in the general population, several high risk subpopulations require a more frequent or rigorous screening (e.g., patients with congestive heart failure, patients with recent significant losses). Any validated instrument may be used in appropriate populations but the PHQ-2 is widely used and recommended within the VA and DoD health centers.

Screening in Antenatal and Postnatal Women

Pregnant and postpartum women are at elevated risk for depression, and should be screened for depression in their first contact with their healthcare provider in both the antenatal and the postnatal periods. In addition, screening is typically repeated in the postpartum period at four to six weeks and three to four months after birth.[\[25-27\]](#) Early detection of depression during pregnancy is critical because depression can adversely affect both birth outcomes and neonatal health in addition to its effects on the mother. Untreated postpartum depression can impair mother-infant attachments and have cognitive, emotional, and behavioral consequences for children. Both the Edinburgh Postnatal Depression Scale (EPDS) and the PHQ-2 are sensitive screening tools for use in postpartum women.[\[22,28-32\]](#)

Screening in Individuals with Chronic Medical Illness

In patients at particularly high risk for depression because of chronic medical illness (e.g., hepatitis C, chronic pain, post-myocardial infarction), clinicians should have a high index of suspicion for depression and screen accordingly.

Screening in Older Adults

The PHQ-2 and PHQ-9 are still the primary recommended screening and assessment tools in elderly populations, with comparable sensitivity, but lower specificity, than a longer screen.[\[33-37\]](#) The Geriatric Depression Scale, for example, includes items that are less somatically based to identify depression independent of physical condition for adults aged 65 and older.[\[38\]](#)

Table 1: Patient Health Questionnaire-2 (PHQ-2) [22]

Question Number	Over the past two weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed, or hopeless	0	1	2	3

For office coding: Total Score = ____ + ____

Table 2: PHQ-2 Score Interpretation [22]

PHQ-2 Score	Probability of MDD (%)	Probability of any depressive disorder (%)
1	15.4	36.9
2	21.1	48.3
3	38.4	75.0
4	45.5	81.2
5	56.4	84.6
6	78.6	92.9

B. Assessment and Triage

Recommendation

- For patients with suspected depression, we recommend an assessment for acute safety risks (e.g., harm to self or others, psychotic features) during the initial assessment and periodically thereafter as needed.

(Strong For | Not Reviewed, Amended)

Discussion

With high confidence in the overall evidence, we recommend that patients with a presumed diagnosis of MDD be initially and periodically assessed for acute safety risks. The benefits significantly outweigh the harms/burdens, as not assessing for suicidal or homicidal ideation can result in death.

With a significant number of patients who complete suicide having been seen by a clinician in the month prior to their attempt, [39,40] assessment should not be relegated to mental health specialists only, but is also recommended in primary care medical settings. Evidence reveals that the assessment of suicidal ideation (i.e., asking about suicide intentions) does not increase the risk of suicide. Hirschfeld and Russell reinforced this concept and recommended that assessment for the presence of acute safety risks be done through the use of non-judgmental, direct questioning. [41] When using the PHQ-9, attention should be paid to the last item (“Thoughts that you would be better off dead or of hurting yourself in some way?”), as it has been associated with increased risk for a suicide attempt. [42] When managing a patient’s acute safety risks, attention should be paid to the setting that provides the most safety for the patient in addition to consideration of the risk and protective factors that will support the patient. A formal risk assessment and safety plan have been shown to be effective strategies for assessing and mitigating risk. Any patient with suicidal ideation or suicide attempts necessitating psychiatric hospitalization should be considered for referral to mental health specialty care. For further information

on evaluation of suicidality, please see the VA/DoD Assessment and Management of Patients at Risk for Suicide CPG.¹

Homicidal ideation should be assessed from the perspective of whether the patient has an active plan and/or the method and means of carrying out the plan. It might be necessary to seek consultation or ethics advice regarding the requirement to warn any people identified by the patient to be at risk. Hirschfeld and Russell gave the following example to assess for the presence of homicidal thoughts or intent:[\[41\]](#)

1. Assess whether the patient has an active plan and method/means (e.g., weapons in the home)
2. Assess whom the patient wishes to harm
3. Assess whether the patient has ever lost control and acted violently
4. Assess seriousness/severity of past violent behavior

Patients with a possible diagnosis of MDD who exhibit any of the following characteristics associated with psychosis need to be referred for an urgent/emergent mental health intervention, as these patients are inappropriate for management of care in the primary care setting:[\[41\]](#)

1. Serious delusions (e.g., fixed false beliefs)
2. Visual or (typically) auditory hallucinations
3. Confusion (incoherence)
4. Catatonic behavior (e.g., motoric immobility or excessive agitation)
5. Extreme negativism or mutism
6. Peculiar movements
7. Inappropriate affect of a bizarre or odd quality
8. Severe symptoms

In the event of expressed danger to self or others by a person with possible MDD, steps must be taken to ensure patient and others' safety until further evaluation and a referral or consultation with a mental health professional has taken place. Providers should ensure that protocols and system policies are followed in these acute safety situations. Local, state, and federal regulations/mandates as well as guidelines should be followed, and consultation with a peer or other medical law consultant on the legal and ethical requirements is recommended (as it relates to notifications regarding the patient who presents a risk to others). In managing patients who pose a risk, mental health providers need to be prepared to consult with primary care and other medical specialties concerning patients who may appear in their clinics. Patient care management plans must also reflect the realities of local resources, staffing, and transportation. Patients who express suicidal or homicidal thoughts or who are unable to provide basic self-care should be considered for admission to an inpatient psychiatric unit. Patients with unstable social networks or who lack significant support in the community may require sub-acute care in a residential setting.

¹ See the VA/DoD Clinical Practice Guideline on the Assessment and Management of Patients at Risk for Suicide. Available at: <http://www.healthquality.va.gov/guidelines/MH/srb/>

Recommendation

3. For patients with suspected depression, we recommend an appropriate diagnostic evaluation that includes a determination of functional status, medical history, past treatment history, and relevant family history.

(Strong For | Not Reviewed, Amended)

Discussion

Clinical evaluation of a patient who screens positive for depressive symptoms should include an evaluation that establishes: (1) a working diagnosis of (or rules out) MDD; (2) a patient-centered approach to education about depression; (3) expectations for recovery; and (4) ascertainment of preferences for treatment. If a diagnosis of MDD is established, appropriate care consistent with this CPG can commence, built on the foundation of the initial provider interaction that fosters an informed choice by the patient and identification of the available system resources (e.g., psychotherapy services, collaborative care management) that the provider needs to engage.[\[43\]](#)

Establishing a working diagnosis in a patient with depressive symptoms entails a focused clinical interview, physical examination, and pertinent laboratory and other testing with an eye toward identifying remediable co-occurring conditions or alternative diagnoses. DSM-5 criteria should be used to diagnose MDD ([Table 3](#)).[\[44\]](#) Alternative diagnoses may be suggested by a history of substance use disorder (SUD); decrease in cognitive function; symptoms of a neurologic disorder or history of closed head injury; symptoms or signs of PTSD; history of mania or hypomania; or use of prescription, over-the-counter or other psychoactive substances (including caffeine and nicotine) that may exacerbate or alter depressive symptoms. Co-occurring conditions or experiences do not preclude a diagnosis of MDD yet are important in treatment planning or may require attention in their own right, such as current or past physical or sexual abuse or emotional neglect, chronic pain syndromes, sleep disorders, extreme weight loss or gain or other gastrointestinal symptoms suggestive of an eating disorder, spousal bereavement or loss of significant relationships or economic status, or a protracted caregiving role. Other important considerations may include the patient's medical, psychiatric, marital, family, occupational and military service history. Physical examination supports the clinical interview and mental status exam with attention to any neurologic deficits, evidence of endocrine or other metabolic disease or systemic illness. Laboratory testing is performed as clinically indicated. Useful tests may include thyroid studies (thyroid-stimulating hormone [TSH]), complete blood count (CBC), chemistry profile, pregnancy screen, and/or toxicology panel. Use of a structured instrument such as the PHQ-9 facilitates collection of the information required to diagnosis MDD based on DSM criteria, ascertains the baseline severity of symptoms, and helps to determine their impact on daily functioning.[\[45\]](#) Furthermore, a brief test for cognitive impairment is likely appropriate in the elderly and in those with a history of traumatic brain injury.

Table 3: Diagnostic Criteria for Major Depressive Episode based on DSM-5 [46]

Criterion A	Five or more of the following symptoms present during the same two-week period; at least one of the symptoms is either (1) depressed mood or (2) loss of interest/ pleasure: a. Depressed mood most of the day, nearly every day b. Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day c. Significant weight loss when not dieting or weight gain d. Insomnia or hypersomnia nearly every day e. Psychomotor agitation or retardation nearly every day f. Fatigue or loss of energy every day g. Feelings of worthlessness or excessive inappropriate guilt h. Diminished ability to think, concentrate, or indecisiveness, nearly every day i. Recurrent thought of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
Criterion B	The symptoms cause significant distress or functional impairment.
Criterion C	The episode is not attributable to the physiological effects of a substance or another medical condition

Patients with alternative diagnoses, severe or complicated presentations (e.g., mania, depression with psychosis or coexisting cognitive impairment), or suicidality should receive acute intervention and/or specialty referral as appropriate. Patients with unexplained physical symptoms and depression suggestive of a somatoform disorder may also benefit from a referral to a mental health specialist. Regardless of the venue and modalities for mental health treatment, care coordination around chronic medical conditions and heightened attention to unmet psychosocial needs or situational stressors are important elements of effective care.[47]

Recommendation

4. For patients with a diagnosis of MDD, we suggest using the Patient Health Questionnaire-9 (PHQ-9) as a quantitative measure of depression severity in the initial treatment planning and to monitor treatment progress (see [Recommendation 14](#)).
(Weak For | Not Reviewed, Amended)

Discussion

As a component of a full assessment for MDD, the PHQ-9 is recommended for use as a patient self-reported assessment and outcome measure. A core set of common symptom measures is recommended by the Interagency Task Force Work Group on Common Mental Health Measures for use in the provision of mental health services and outcomes tracking for Service Members and Veterans across the VA and DoD. Common measures were felt to help drive coordination across DoD, VA and civilian clinical settings in a way that will improve coordination and care. The agreed upon measure for depression was the PHQ-9.[48]

The PHQ-9 ([Appendix B](#)) is a validated, nine-item questionnaire that can be self- or interviewer-administered to ascertain depressive symptoms and symptom severity within the previous two weeks. It is readily available in the VA and DoD and takes as little as two minutes to complete. The PHQ-9 aligns with the diagnostic criteria for MDD, thus making it a good assessment tool; however, it is not meant to replace a clinical interview/assessment/judgment to establish a diagnosis of MDD. A PHQ-9 score

greater than or equal to 10 has a sensitivity of 88% and a specificity of 88% for major depression.[45,49,50] Furthermore, a study of 6,000 patients validated different PHQ cut-points as representing mild, moderate, and severe depression.[45] Since treatment is guided by the severity of depression, the PHQ-9 score can be very helpful to the clinician in monitoring the response to treatment. Systematic measurement of treatment response has also been found to increase the likelihood of response to treatment [51-53]; therefore, we suggest using the PHQ-9 at least monthly (see [Recommendation 14](#)) to track response/progress.

C. Treatment Setting

Recommendation

5. We recommend that patients with complex MDD (severe, chronic or recurrent) be offered specialty care by providers with mental health expertise in order to ensure better outcomes and effective delivery of evidence-based treatment strategies.

(Strong For | Reviewed, New-replaced)

Discussion

The delivery of complex treatment strategies requires specialized education and training. We did not find evidence that supports the use of treatments by clinicians who determine that the patient's needs are outside of their scope of practice or training. However, patients may resist going to specialty care settings because of perceived stigma associated with a mental health diagnosis. In cases when a patient with complex MDD is not amenable to specialty mental healthcare, the additional benefit of specialty care should be emphasized. Complex MDD includes severe, chronic or recurrent MDD. Severe MDD (i.e., PHQ-9 >20) is defined as the need for hospitalization, strong suicidal ideation or behaviors, longer duration of symptoms, and more residual symptoms after response to treatment (see [Appendix D](#)). Chronic MDD is characterized as MDD with duration greater than two years and recurrent MDD is defined by three or more episodes.

When a patient with complex MDD is amenable, clinicians who determine that the patient's needs are outside of their scope of practice should refer patients requiring complex evidence-based treatment to a behavioral health specialist. Two studies support this recommendation. Cuijpers found that combination treatments were more effective in managing depression when delivered in an outpatient mental health setting.[54] Krahn found that referral of patients with more severe depressive symptoms to specialty mental health settings yielded significantly better outcomes than referral to integrated primary care.[55] Additionally, in these patients with complex MDD, providers should assess for presence of psychosis and treat appropriately.

Recommendation

6. We recommend the use of the collaborative care model for the treatment of MDD within a primary care setting.

(Strong For | Reviewed, New-replaced)

Discussion

There is very good evidence to recommend the use of the collaborative care model for treatment of MDD in primary care settings. This includes data supporting the effectiveness of collaborative care versus usual

care for the outcomes of clinically significant reduction in depressive symptoms, improved treatment adherence, symptom remission at six month follow-up, and more favorable rates of recovery from symptoms at 12 month follow-up.[\[56\]](#) For depression, remission is defined as the significant reduction of symptoms such that the PHQ-9 score is four or less, maintained for at least one month.

Collaborative care interventions for MDD include the involvement of dedicated clinical support for the care of the patients (e.g., care manager, behavioral health specialist), a structured approach to treatment frequently involving patient education and behavioral therapy (BT) or behavioral activation (BA), systematic and scheduled follow-up (in person or by telephone), use of validated instruments such as the PHQ-9 to guide care, and enhanced interdisciplinary communication through methods such as shared medical record systems and case supervision.[\[57\]](#) Collaborative care personnel include primary care providers, nurses, social workers, psychologists, and mental health specialists with prescriptive authority such as clinical pharmacists, psychiatrists and advanced practice nurse practitioners.

Although collaborative care interventions themselves sometimes differ between studies, there is evidence supporting the effectiveness of specific elements, as well as evidence showing the ineffectiveness of other possible elements. [Table 4](#) outlines the consensus by the panel of the optimal and non-critical elements of collaborative care.

There is evidence to support the effectiveness of interventions that include a psychological component (e.g., behavioral activation, problem solving therapies) for the outcome of improvement in depressive symptoms compared to medical management alone. Mavandadi et al. showed in a randomized controlled trial (RCT) that, in addition to the benefit of the monitoring component, the presence of the psychological component was critical to recovery.[\[58\]](#) Systematic identification of patients, a focus on including individuals with a chronic physical health condition, and scheduled care manager supervision were also significant predictors—in both univariate and multivariate analyses—of improved symptom outcomes.

There is substantial evidence supporting the use of virtual visits in the context of collaborative care models. Using virtual visits, such as by telephone, increases the ability to be flexible with scheduling clinical contacts and allows for cost sharing between several clinics. Tutty et al. demonstrated that those patients identified by a primary care provider and randomly assigned to telephone case management doubled their chance of receiving at least a moderate dose of an antidepressant and doubled their chance of a 50% reduction in depressive symptoms compared with usual care.[\[59\]](#) Other studies demonstrate similar efficacy.[\[60-66\]](#)

There is also evidence showing the ineffectiveness of strategies that do not have a structured approach to assessment and follow-up for depression treatment in primary care. For example, in a systematic review of five available relevant studies, Cape et al. found that consultation liaison by mental health professionals did not improve antidepressant use or short- or long-term depression outcomes compared to usual care.[\[67\]](#)

Collaborative care for depression is consistent with primary care medical home models, and with stepped care for depression in which treatment intensity progresses, as needed for individual patients. There is fair evidence that this stepped care approach improves symptoms, response, and recovery

compared to usual care.^[68,69] The benefits of collaborative care for depression usually outweigh risks in the primary care setting where cases tend to be less complex than those seen by specialists. Many patients prefer to be treated in the primary care setting, where collaborative care models have been shown to be associated with increased patient satisfaction compared to usual care.^[56] Consistent with its application for other conditions and with the primary care medical home model, effective implementation of collaborative care for depression calls for attention to requisite infrastructure and resources (e.g., patient registry systems, personnel, information technology) and accompanying process redesign.

**Table 4: Summary of Evidence-based Elements of the Collaborative Care Model for MDD*
[39,56,57,67-70]**

Essential	Optimal	Equivocal	Not Recommended
Interdisciplinary, team approach to brief, problem-focused care	Access to evidence-based psychosocial services (e.g., behavioral activation, motivational interviewing, problem solving therapy, brief CBT)	Requiring or focusing on direct hand-offs from the primary care provider to the team	Consultation-liaison or co-located care without systematic follow-up
Structured protocols, including screening, case identification, and longitudinal measurement	Availability to provide crisis intervention	Acceptance of stable patients from specialty care	Assessment and triage (i.e., walk-in) model (no follow up)
Systematic follow-up (registries, measure-guided treatment)	Facilitated self-management		
Patient education and activation including adherence monitoring	A program that offers additional behavioral health services including brief alcohol interventions	Use of a prescribing provider (psychiatrists, certified registered nurse practitioner [CRNP]) for psychotropic medications (separate from supervision)	
Supervision by psychiatrist/prescriber	Open accessibility to primary care providers and patients		
Data-driven quality improvement	Referral management for more severe symptoms		

*Work Group’s synthesis of collaborative care model for MDD based on literature available through January 2015.
Abbreviations: CBT - Cognitive Behavioral Therapy, CRNP - Certified Registered Nurse Practitioner

D. Management

a. Treatment for Uncomplicated Mild to Moderate MDD

Recommendation

- We recommend that treatment planning include patient education about the condition and treatment options, including risks and benefits. The individualized treatment plan should be developed using shared decision-making principles, and should define the provider, patient, and support network’s roles.

(Strong For | Not Reviewed, Amended)

Discussion

Even though a new systematic literature review was not conducted for this recommendation, we continue to support this recommendation, which was carried over from the 2009 MDD CPG. Patients should receive tailored information regarding their treatment options with the goal of a shared decision about treatment. This includes informing them about the risks and benefits of their treatment options and ensuring they understand the ramifications of their choice. In addition, the following communication can enhance adherence to medication in the acute phase of treatment:

- a. Education regarding common symptoms and relapsing nature of MDD. Relapse risk increases as the number of prior MDD episodes increases.
- b. The patient should take the medication daily or as directed by the prescribing provider.
- c. It usually takes four to six weeks before improvements are seen.
- d. The patient should continue to take the medication even after feeling better. Most people need to be on medication for at least 6 to 12 months after adequate response to prevent relapses.
- e. Education on early signs and symptoms of relapse or recurrence, along with encouragement to seek treatment early in the event these signs or symptoms occur.
- f. Reminding the patient that successful treatment often entails medication and/or dosage adjustments in order to maximize response while minimizing side effects.
- g. Education on side effects, which can precede therapeutic benefit, but may recede over time and can be addressed if the prescriber is informed.
- h. A slight increase in suicidal ideation in the first month can occur and patients should contact their provider if this does occur.
- i. Education to not discontinue taking medications without first discussing with their provider.

Psychoeducational strategies can be incorporated into treatment protocols, which entail systematic monitoring of treatment adherence and response, and self-management strategies. A major goal for the use of self-management strategies is to enhance the patient's active engagement in treatment. A common strategy is for a patient to collaboratively select one or two self-management goals at a time to pursue during treatment. Education should incorporate principles of self-management and may include information and goals related to:

- a. Nutrition – Often patients with MDD do not have a balanced diet. Expert opinion suggests that diet should be included in the therapeutic content. However, there is not a robust evidence base that improving diet impacts treatment outcomes.
- b. Bibliotherapy – The use of self-help texts may be helpful to patients for understanding their illness and developing self-management skills. Although there is mixed evidence regarding the use of guided self-help (GSH) interventions such as bibliotherapy, bibliotherapy with a cognitive behavioral focus and intermittent monitoring and oversight by a healthcare professional may be a useful alternative for patients with mild MDD as adjunctive treatment or an alternative to pharmacotherapy or psychotherapy based on patient preference (see [Recommendation 33](#)).

- c. Exercise – Patient education on the benefits of exercise for psychological health should be offered. Exercise is safe, acceptable, and shows good adherence in patients with major depression.^[71] In patients with mild depression who are not currently undergoing medical treatment, exercise is an excellent self-management and preventive strategy. Exercise can also be used when patients are unwilling, unable, or have contraindications to taking first-line treatments. We suggest that exercise be used adjunctively with a first-line evidence-based treatment (see [Recommendation 29](#)).
- d. Sleep hygiene – Patients with MDD often have substantial sleep problems, including insomnia, hypersomnia, and disturbances of sleep maintenance. Education regarding appropriate sleep hygiene should be included for patients exhibiting any sleep disturbances.^[72]
- e. Tobacco use – Tobacco use has been demonstrated to impact the recovery of depression; therefore, patients being treated for depression should be advised to abstain until their symptoms remit. Referral or treatment of nicotine dependence should be considered in patients treated for depression.
- f. Caffeine use – Expert opinion suggests that excessive caffeine use may exacerbate some symptoms of depression such as sleep problems or anxiety symptoms.
- g. Alcohol use and abuse – Even low levels of alcohol use have been demonstrated to impact the recovery of depression; therefore, patients being treated for depression should be advised to abstain until their symptoms remit.
- h. Pleasurable activities – Depression has been conceptualized by behavioral theorists as the loss or significant decrement of reinforcing activities. Behavioral activation (the systematic scheduling and monitoring of pleasurable or reinforcing activities) has been shown to have significant antidepressant effects.

The benefits of educating and involving patients in their treatment greatly outweigh any harms or burdens. Furthermore, these practices reflect the typical standard of care shared by most providers. With this being said, situations where time is more limited might not be conducive to time-intensive or extreme patient involvement. Until further evidence is reviewed in this area, our confidence in the literature remains low to moderate with the recommendation primarily based on expert recommendations and standard of care.

Recommendation

8. As first-line treatment for uncomplicated mild to moderate MDD (see [Recommendation 17](#) for complex cases), we recommend offering one of the following treatments based on patient preference, safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications, cost of medication and provider training/competence:
 - Evidence-based psychotherapy:
 - Acceptance and commitment therapy (ACT)
 - Behavioral therapy/behavioral activation (BT/BA)
 - Cognitive behavioral therapy (CBT)
 - Interpersonal therapy (IPT)

- Mindfulness-based cognitive therapy (MBCT)
- Problem-solving therapy (PST)
- Evidence-based pharmacotherapy:
 - Selective serotonin reuptake inhibitor (except fluvoxamine) (SSRIs)
 - Serotonin–norepinephrine reuptake inhibitor (SNRIs)
 - Mirtazapine
 - Bupropion
- The evidence does not support recommending a specific evidence-based psychotherapy or pharmacotherapy over another.

(Strong For | Reviewed, New-replaced)

Discussion

When MDD severity is determined to be mild to moderate (PHQ-9 score of 10-19, see [Table B-1](#)) the initial treatment should consist of an evidence-based monotherapy. The evidence does not suggest that one specific evidence-based psychotherapy or pharmacotherapy listed above is more effective than another. When the patient prefers psychotherapy, one of the following evidence-based interventions can be offered based on patient preference and availability: CBT, IPT, MBCT, BT/BA, ACT, or PST. Further, patients and providers may want to consider that there is some evidence that treatment benefits for CBT and possibly BA may be more enduring than for pharmacotherapy.[\[73\]](#) If the shared decision is made to initiate antidepressant monotherapy, we recommend starting with an SSRI, SNRI, mirtazapine, or bupropion. Their efficacies are comparable, and therefore selection should be based on the antidepressant's safety and side effect profile.

Although combination therapy has the strongest evidence base for individuals who did not respond to an appropriate trial of monotherapy, or patients with severe MDD as discussed in [Recommendation 17](#), there are several possible indications for initial combination therapy in moderate or moderately severe MDD. For example, a combination of psychotherapy and pharmacotherapy may be indicated in a patient with moderate MDD in the presence of additional risk factors such as suicidality [\[74\]](#) or because of patient preference.

The DoD and VA have adapted procedures (including assessment, pharmacotherapy and psychotherapy) for delivery of services via telehealth (e.g., videoconferencing, telephone care). However, the current review did not evaluate the literature on such uses of telehealth for major depression, and therefore we do not have a specific recommendation regarding their implementation. The review did evaluate the literature on a particular form of telehealth, i.e., CCBT. Nevertheless, given the need to improve the access of Veterans, Service Members and dependents to adequate mental healthcare, we strongly recommend that the next revision of the guideline formally review the literature on the broader array of telehealth approaches and incorporate this information into the guideline as supported by the evidence. The panel recognizes that some recent literature indicates that telehealth approaches are acceptable to patients and are not significantly less effective than traditional approaches.[\[19,20\]](#) The use of telephone visits in collaborative care models is a well-evidenced component as outlined in [Recommendation 6](#).

Summary of Evidence on Choice of Psychotherapy for Mild to Moderate MDD

The psychotherapies that were included in our evidence review were (in alphabetical order) ACT,[[75](#)] BT/BA,[[76](#)] CBT,[[73,74,77,78](#)] IPT,[[79](#)] MBCT,[[80](#)] and PST.[[81](#)] Certain psychotherapies demonstrate a small, consistent, and statistically significant superiority to treatment as usual, placebo controls, and other inactive control conditions for depression. However, there is no evidence of superiority among these psychotherapies or between a particular psychotherapy and pharmacotherapy. Notwithstanding their substantial bodies of evidence, CBT and IPT exhibited no difference in efficacy versus each other or the other interventions listed above for the treatment of depression.

Direct comparisons between pharmacotherapy and psychotherapy have generally demonstrated no differences in outcomes for mild to moderate depression. Combination pharmacotherapy and psychotherapy has, in general, shown no additional benefit for treating mild depression. The overall confidence in the quality of the evidence reviewed was moderate, given the number of treatment studies upon which the conclusions are based.

The recommendations on the use of psychotherapy are based on clinician fidelity to the particular manual or protocol being implemented. Selection of the specific intervention should be accompanied by appropriate patient education and patient-centered shared decision-making. The availability of appropriately trained staff should also be considered.

Summary of Evidence on Choice of Antidepressants for Mild to Moderate MDD

There is no evidence to suggest that one antidepressant drug class is superior to another for the treatment of MDD in terms of response and remission rates.[[82-87](#)] Initial monotherapy with bupropion, mirtazapine, an SNRI, or an SSRI provide the best options for patients who do not have absolute contraindications to these medications (e.g., drug-drug interactions, allergies, co-occurring medical conditions). [Appendix C](#) provides details regarding individual agents and their corresponding warnings, precautions, and contraindications.

All of the SSRIs, except fluvoxamine, may be used as first-line agents in the treatment of adults with MDD.[[82,83](#)] Fluvoxamine is not a Food and Drug Administration (FDA) approved drug for the treatment of MDD.

When prescribing SSRIs, the dose should be maximized in patients that show no response or a partial response using an appropriate titration schedule. The provider should consider the potential for pharmacokinetic and pharmacodynamic drug interactions as well as the potential for the appearance of symptoms that warrant a tapered-dose discontinuation, especially for the antidepressants with shorter half-lives (e.g., paroxetine, venlafaxine). Sertraline may be the best choice for pregnant women. Sertraline may also be the most appropriate medication in postpartum women who intend to breastfeed, due to the lower levels of medication transmitted to infants via breast milk. Fluoxetine has a long half-life and therefore may not be the best SSRI during pregnancy, in women planning to breastfeed, or in the elderly.[[88](#)] SNRIs should be initiated at a low dose to ensure tolerability and then titrated to an effective dose.

Bupropion and mirtazapine are also first-line treatment options for patients with MDD. Patients should be titrated to the dose that is effective and tolerable without exceeding the maximum recommended

daily dose. Bupropion may be considered for patients with MDD who desire to stop smoking, although it is contraindicated in patients with a seizure disorder or history of anorexia nervosa or bulimia and can potentially worsen anxiety. Bupropion and mirtazapine are treatment options for patients who have experienced intolerable sexual side effects with other antidepressants (e.g., decreased desire). Mirtazapine should be avoided in patients for whom weight gain or sedation would be problematic.[\[83,84\]](#)

Most studies assessed outcomes after 6 to 12 weeks. Given the lack of evidence demonstrating distinct differences in clinical outcomes between different drug classes, we recommend basing treatment choices on collaborative decision making between the patient and the provider with consideration of safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications and cost of medication. Antidepressants in dosage forms that are taken once or twice daily (rather than more frequently) should be prescribed to reduce patient burden. Generally, initial doses in the frail elderly should be lower than in healthy adults. Providers should ensure that an appropriate dose titration and target dose range has been achieved and an adequate trial period allowed (a minimum of four to six weeks) prior to considering discontinuing an antidepressant as a treatment failure.

Recommendation

9. In patients who have demonstrated partial or no response to initial pharmacotherapy monotherapy (maximized) after a minimum of four to six weeks of treatment, we recommend switching to another monotherapy (medication or psychotherapy) or augmenting with a second medication or psychotherapy.

(Strong For | Reviewed, New-replaced)

Discussion

Patients with MDD who have received an adequate trial of initial maximized pharmacotherapy or psychotherapy monotherapy but have achieved partial (<50% improvement in symptoms) or no response should be reassessed for possible diagnostic error, the presence of co-occurring conditions, and treatment adherence. Once diagnosis and treatment adherence are confirmed, treatment should be adjusted to achieve remission.

Maximized pharmacotherapy is defined as an antidepressant dose advanced to either the FDA maximum recommended dose and/or maximum dose tolerated by the patient for a minimum of four to six weeks. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found the average time to remission was 44 days in primary care and 49 days in psychiatric care; however, patients commonly required eight weeks or more to achieve remission, a time period that also allows sufficient time for initial antidepressant dose titration.[\[89\]](#)

Changing treatment regimen may improve outcomes and long-term prognosis. However, there is little evidence of a demonstrable difference between specific augmentation or switching strategies in regard to achieving remission.[\[90\]](#)

In general, monotherapy with first-line antidepressants (e.g., SSRIs, SNRIs, bupropion, mirtazapine) is preferable to combination treatment with two antidepressants because of the increased potential for

drug-drug interactions and adverse effects. Therefore, it is reasonable to consider switching to another first-line antidepressant (either within-class or out-of-class), or augmenting current therapy with psychotherapy, or switching to psychotherapy.

However, in cases of severe MDD, combined pharmacotherapy and psychotherapy is recommended if initial monotherapy with an antidepressant does not achieve a response or remission (see [Recommendation 13](#)). In patients who have demonstrated partial response and are tolerating the current antidepressant, augmentation with another medication or psychotherapy is reasonable.

STAR*D Study Design

This is a brief synopsis of the STAR*D Study using National Institute of Mental Health (NIMH) information found in “Questions and answers about the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study – All Medication Levels,” to assist the clinician in understanding how the below treatment strategies were developed.^[1] Over a seven year period, STAR*D enrolled 4,041 outpatients (ages 18-75 years old) from 41 clinical sites (specialty care and primary care settings) around the country and followed a stepped approach to treating MDD. Participants were started out with citalopram for 12-14 weeks. If symptom-free at this level of treatment, patients were continued on citalopram and moved on to a 12 month follow-up period for monitoring. For patients who could not tolerate side effects or did not become symptom-free, they progressed to level 2, which allowed patients the options of switching to a different medication or adding on to citalopram. Patients in the “switch” group were randomly assigned to sertraline, bupropion sustained-release (SR), or venlafaxine extended-release (XR). The “add-on” group was prescribed either bupropion-SR or buspirone, or could switch to, or add on, cognitive psychotherapy. If level 2 patients became symptom-free, they continued their current treatment and moved into the follow-up period. If not symptom-free or unable to tolerate side effects, they progressed to level 3. In level 3, patients had the option to switch medications or add-on to their current treatment. “Switch” group patients were randomly assigned to either mirtazapine or nortriptyline. “Add-on” group patients were randomly assigned to receive lithium or triiodothyronine in addition to the medication they were already taking. If patients did not become symptom-free in previous levels, they progressed to level 4 and were taken off all other medications then randomly switched to tranylcypromine or the combination of venlafaxine-XR with mirtazapine.

Augmentation Strategies

The following augmentation strategies are presented to assist the clinician in reasoning through treatment choices. They are not intended to be used in a step-wise manner. When considering a particular augmenting medication, the choice of augmentation or switching strategy should be based on safety, patient’s comorbid conditions, symptoms, drug-drug interactions, previous response, and patient preference. For example, in a patient who is still having difficulty with insomnia, the addition of mirtazapine or a second generation atypical antipsychotic, such as olanzapine or quetiapine, may be helpful in achieving symptom resolution secondary to the side effect of sedation often associated with

these medications. However, many of these same drugs cause weight gain, which is a concern for patients who are obese or otherwise at risk of metabolic side effects.

Bupropion

A common starting place for augmentation is the addition of bupropion-SR, as implemented in STAR*D, where the addition of bupropion-SR to SSRI treatment significantly increased remission rate without increasing adverse events.[91] Of note, when using bupropion, the clinician needs to consider a history of seizures, risks for seizures (e.g., brain injury, eating disorders), hypertension, and co-occurring anxiety disorders. Bupropion can lower the seizure threshold, increase blood pressure secondary to the norepinephrine effect, and may be activating in some patients and increase anxiety/irritability.

Buspirone

As shown in STAR*D, the addition of buspirone was effective at achieving remission when combined with an SSRI.[92] Buspirone dosing was started at 15 mg/day for one week, raised to 30 mg/day for one to two weeks and then to 45 mg/day by week four, with a maximum dose of 60 mg/day. The mean dose of buspirone in STAR*D was 45 mg/day.[93] In clinical practice, buspirone is typically started between 7.5 to 15 mg by mouth two to three times per day depending on patient's sensitivity/susceptibility to medication side effects. The dose may be increased by 2.5 mg twice a day every two to three days until desired efficacy, or the maximum dose of 60 mg/day, is reached. Buspirone needs to be dosed two to three times per day on a scheduled basis for full effect and generally takes two to four weeks to achieve efficacy. In STAR*D, the mean time to remission (of those remitting) was 4.8 weeks while time to response (of those responding) was 6.2 weeks.[94]

Lithium

Lithium augmentation requires proper dosing (typically 600 to 900 mg/day), monitoring of lithium blood levels (therapeutic blood level is between 0.6 – <1.0 mEq/L while potentially toxic blood levels are > 1.5 mEq/L), and monitoring of thyroid functioning. In a meta-analysis of nine RCTs, the number needed to treat for lithium augmentation was clinically meaningful at five patients.[95] Of note, in the military population and in physical laborers, augmentation with lithium confers additional risk of toxicity secondary to potential for dehydration, which can cause increased lithium blood levels. In the military population, use of mood stabilizers and antipsychotics may trigger the need for a medical evaluation board and fitness for duty evaluation.

Liothyronine

Liothyronine (synthetic T3) has also been studied as part of augmentation strategies and was found to be effective. Liothyronine augmentation at the dose of 50 µg/day resulted in a remission rate of 25.7% with a mean time to remission of 5.3 weeks in the STAR*D study.[94] Liothyronine augmentation may be effective regardless of thyroid abnormalities. As with any medication, careful consideration must be given to patient comorbidities and medication side effect profiles. Liothyronine should be prescribed with caution in patients with cardiovascular disease/arrhythmias, diabetes, renal impairment, or untreated adrenal insufficiency. Levothyroxine is not used as an augmentation for treatment of depression in euthyroid patients due to the long time for effectiveness to be achieved. In patients with thyroid disease, the underlying medical condition should be treated as medically appropriate.

Second Generation Antipsychotics

Although the literature on the second generation antipsychotics (SGAs) or atypical antipsychotics for augmentation in the treatment of MDD has grown since the 2009 MDD CPG, SGAs should be considered only when other strategies have failed because of their significant side effects. Only two atypical antipsychotics are FDA approved for MDD as adjunctive treatment/augmentation: aripiprazole and quetiapine-XR. Olanzapine is approved for the treatment of acute treatment-resistant MDD when used in combination with fluoxetine but olanzapine by itself is not indicated for the treatment of treatment-resistant depression (FDA prescribing guide for olanzapine). Brexpiprazole is newly approved and was not included in the evidence review search strategy of the current CPG.

Note: Treatment resistance is defined as a lack of full response despite at least two adequate treatment trials (see [Appendix D](#)).^[96]

Two systematic reviews have demonstrated significant benefit of SGAs (alone or augmentation) for remission in MDD. Komossa et al. (28 RCTs) demonstrated significant improvement in remission with aripiprazole (mean doses = 11-12 mg/day,) olanzapine (mean doses = 8-14 mg/day), quetiapine (mean doses = 180 mg/day), and risperidone (mean doses = 1.2-1.6 mg/day).^[97] Santaguida et al. (one RCT) demonstrated small significant benefit favoring augmentation with atypical antipsychotics (olanzapine, aripiprazole, risperidone, and quetiapine).^[90]

While there is significant benefit with augmentation using SGAs, there are also significant side effects. Evidence of fair quality found that compared to placebo, aripiprazole had a significantly higher incidence of akathisia and weight gain; olanzapine had a significantly higher incidence of weight gain and sedation; quetiapine had significantly greater weight gain and sedation; and risperidone had greater, but not statistically significant, weight gain when compared to antidepressants plus placebo.^[97] Due to the possibility for side effects, SGAs require appropriate monitoring (e.g., glucose, CBC, hepatic panel, lipid panel, body mass index, waist circumference, blood pressure, involuntary movements/tardive dyskinesia, slit lamp exam [quetiapine-only]). In the military population, use of antipsychotics may also trigger a medical evaluation board to determine fitness for continued military service; therefore, the clinician should carefully consider the clinical appropriateness of these medications for individual patients and potential related career impact prior to prescribing them.

Recommendation

10. For patients who select psychotherapy as a treatment option, we suggest offering individual or group format based on patient preference.
(Weak For | Reviewed, New-replaced)

Discussion

Group versions of CBT and MBCT are viable options for the treatment of MDD, based on a study conducted by Okumara.^[98] This research showed substantial evidence that group CBT had superior efficacy in the reduction of depression symptoms as compared to waitlist control, treatment as usual, or placebo. When comparing group CBT to interventions such as computerized CBT or GSH, there was no difference in the reduction of symptoms. There was also no difference in the reduction of symptoms

when group CBT was compared to interventions such as psychoeducation, relaxation training, individual CBT or other psychotherapy.

A systematic review conducted by Huntley showed that group CBT plus treatment as usual led to significant reduction in depressive symptoms when compared to treatment as usual alone.[\[99\]](#) When group CBT was compared with individual CBT, this review also showed no significant difference in the reduction of symptoms. There is a larger body of evidence for group CBT than other evidence-based group psychotherapies, which raises confidence in the evidence for group CBT. We believe that the benefits of this type of intervention outweigh the possible harms, although the lack of privacy in a group setting could impose potential harms.

Patient values and preferences should be a consideration in the choice between group or individual therapy as these may vary greatly. There is also a large variation in how group therapies are implemented, including, e.g., group structure, leadership, and choice of therapies. Group therapy should not be a default intervention to address limited provider resources. Other considerations are: subgroups (e.g., women or men only, life stage) and feasibility of this form of therapy in terms of being implemented with minimal difficulty and acceptability.

As a larger body of evidence exists for group CBT compared to other group psychotherapies, there is a need for more evidence for other types of group therapies.

Recommendation

11. For patients with mild to moderate MDD, we recommend offering computer-based cognitive behavioral therapy (CCBT) either as an adjunctive intervention or, based on patient preference, as a first-line treatment.

(Strong For | Reviewed, Amended)

Discussion

CCBT for adults with mild to moderate depression is a viable treatment option when standard psychotherapy is not readily accessible or if used as an adjunctive treatment combined with standard psychotherapy or pharmacotherapy.

Two meta-analyses and one systematic review confirmed the effectiveness of CCBT.[\[100-102\]](#) The review by Arnberg et al. included five RCTs enrolling a total of 489 patients with mostly mild-to-moderate depression.[\[100\]](#) Patients in the studies included in this review were allocated to CCBT or waitlist. A second systematic review and meta-analysis by So et al. included 14 RCTs (16 comparisons were used for the meta-analysis) enrolling 2,807 depressed patients.[\[101\]](#) The review compared CCBT to waitlist or treatment as usual. The third systematic review and meta-analysis by Richards and Richardson included 19 RCTs that randomly allocated 2,996 patients to treatment or waitlist/treatment as usual.[\[102\]](#) These studies showed a significant change in depression severity for patients accessing CCBT compared to patients on a waitlist control or receiving treatment as usual.

Despite moderate confidence in the quality of the studies, the evidence shows that benefits of CCBT outweigh harms. In a study conducted by the VA Evidence-based Synthesis Program, Dedert et al. found that CCBT was effective but there was insufficient data to compare CCBT and in-person treatment for

depression.[103] Patients' values and preferences regarding the use of CCBT will be highly variable since access to and competence with computers may be a barrier to some patients while preferable for others. Because CCBT requires less real-time engagement of providers it may enable more efficient allocation of their time.

Recommendation

12. For patients with mild to moderate MDD who decline pharmacotherapy and who decline or cannot access first-line evidence-based psychotherapies, we suggest offering non-directive supportive therapy or short-term psychodynamic psychotherapy.

(Weak For | Reviewed, New-replaced)

Discussion

Available evidence indicates that non-directive supportive psychotherapy (NDSP) and short-term psychodynamic psychotherapy (STPP) yield a small, consistent, and statistically significant benefit compared to treatment as usual, placebo controls and other inactive control conditions. When compared to other psychotherapies and pharmacotherapy, NDSP and STPP are significantly less efficacious, although the effect size is small.[77,104] Therefore, they are not considered first-line treatments. A meta-analysis by Cuijpers et al. suggests that the superiority of other treatments compared to NDSP may be attributed, in part, to researcher allegiance. When controlling for that, the difference between interventions was non-significant.[105] Further, a limited number of lower-quality studies suggest that the difference between STPP and CBT becomes non-significant over time.[104] Given the totality of the evidence, it is therefore appropriate to offer these modalities to patients who decline first-line treatments or prefer NDSP or STPP. The overall quality of the evidence reviewed was judged to be low due to the limited number of studies available, but the benefits of receiving NDSP and/or STPP outweigh the potential harms of offering no treatment.

b. Treatment for Severe, Chronic, or Recurrent MDD (Complex)

Recommendation

13. We suggest offering a combination of pharmacotherapy and evidence-based psychotherapy for the treatment of patients with MDD during a new episode of care when the MDD is characterized as:

- Severe (i.e., PHQ-9 >20)
- Chronic (duration greater than two years)
- Recurrent (with three or more episodes)

(Weak For | Reviewed, New-replaced)

Discussion

A systematic review of RCTs suggests very poor long-term outcomes with relapse rates as high as 80% in one year after achieving remission.[106] Given the high morbidity and mortality of the more severe forms of depression, it is suggested that a combination of an evidence-based psychotherapy and evidenced-based pharmacotherapy be used as initial treatment. The quality of evidence for this recommendation is considered low because there are few trials comparing combination treatment to monotherapy, and the studies reflect a lack of consensus on the inclusion criteria for patients with

severe, chronic and/or recurrent depression (although the studies have been limited to recurrent depression with three or more episodes). There is one systematic review of the literature on this topic that includes only one RCT of treatment for chronic depression and one RCT for treatment-resistant depression.^[54] In this review, the studies demonstrated superiority of the combination treatment versus monotherapy for patients with chronic depression or treatment-resistant depression. A large RCT (n=452) of antidepressants alone or in combination with cognitive therapy found that the combination treatment was more effective in severe but non-chronically depressed individuals compared to monotherapy.^[107] Nevertheless, the quality of the evidence pertaining to the use of combination treatment versus monotherapy in these patient groups remains low.

In general, however, the available evidence indicates that the benefits for combination therapy outweigh the risks, including the risk of non-response to monotherapy. Hollon et al. found few adverse effects in the combination group versus monotherapy.^[107] In the shared decision-making process for choosing combination therapy versus monotherapy, issues of availability, acceptance, and burden should be factored into treatment planning. There are likely wide variations in provider and patient acceptance of this choice.

Determining the effectiveness and safety of combination treatment versus monotherapy alone should be a high research priority given the potential costs and other burden differences in the two treatment options versus the high burden of illness in patients with severe or recurrent or treatment-resistant depression.

c. Monitoring (All Severities and Complexities of MDD)

Recommendation

14. After initiation of therapy or a change in treatment, we recommend monitoring patients at least monthly until the patient achieves remission. At minimum, assessments should include a measure of symptoms, adherence to medication and psychotherapy, and emergence of adverse effects.

(Strong For | Reviewed, Amended)

Discussion

Monitoring of treatment progress is a critical component to the delivery of care. Monitoring should include assessment of symptomatology using the PHQ-9 (see [Recommendation 4](#) and [Appendix B](#) for further discussion of the PHQ-9), adherence to medication and psychotherapy, emergence of adverse effects, symptom breakthrough, suicidality, and psychosocial stress. Monitoring is the responsibility of all providers involved in the patient's care and the results of monitoring should be shared with the patient and other providers. Ideally, the PHQ-9 score will be graphed over time and provided to the patient as an educational tool. The consensus on the frequency of assessment was monthly, which is consistent with the new Agency for Healthcare Research and Quality (AHRQ) guidelines but is not otherwise evidence-based. More research as to the ideal frequency of visits for monitoring and for psychopharmacology management is justified.

As noted above, the PHQ-9 is a validated instrument that assesses depressive symptoms and suicidal ideation. In addition, it can be scored as a continuous measure to assess depression severity and

monitor treatment response. The PHQ-9 should be used to monitor response after initiation of treatment, after each change in treatment, and at least monthly until remission is achieved. Remission is defined as a PHQ-9 score of four or less, maintained for at least one month. In patients who reach remission, assessment of symptoms should be continued periodically to monitor for relapse or recurrence, and potential suicide risk.[\[51-53\]](#)

The concept of measurement-based care for the treatment of depression is not new but has struggled to catch on.[\[108,109\]](#) Results from the STAR*D study found that management of depression was the most critical issue in treatment. Active management includes switching or augmenting treatments when there is partial or no response. In the STAR*D study, this management was facilitated by active monitoring of symptoms.[\[96\]](#) This approach is also referred to as stepped care. This principle has been a key component to all the integrated care treatment trials including Re-Engineering Systems of Primary Care for PTSD and Depression in the Military (RESPECT-Mil), Behavioral Health Laboratory (BHL), and Translating Initiatives in Depression into Effective Solution (TIDES), the main VA and DOD programs.[\[96,110-112\]](#) Finally, Guo et al. conducted an RCT in which patients were either monitored using a DSM checklist or not monitored. Not only did the monitored group have greater improvement in symptoms, there was evidence for greater management of treatment.[\[113\]](#) Monitoring has also been shown to improve outcomes when communicating by telephone and feeding back to providers.[\[114\]](#)

The Work Group rated the confidence in this evidence as moderate and found that the benefits of monitoring care outweigh any potential harms or burdens. Based on what we suspect are similar value systems regarding the importance of quality care, the Work Group determined that there may be little variation among either patients or providers regarding the value of close monitoring, especially early in the course of treatment.

d. Continuation and Maintenance Treatments (All Severities and Complexities of MDD)

Recommendation

15. In patients with MDD who achieve remission with antidepressant medication, we recommend continuation of antidepressants at the therapeutic dose for at least six months to decrease risk of relapse.

(Strong For | Reviewed, New-replaced)

Discussion

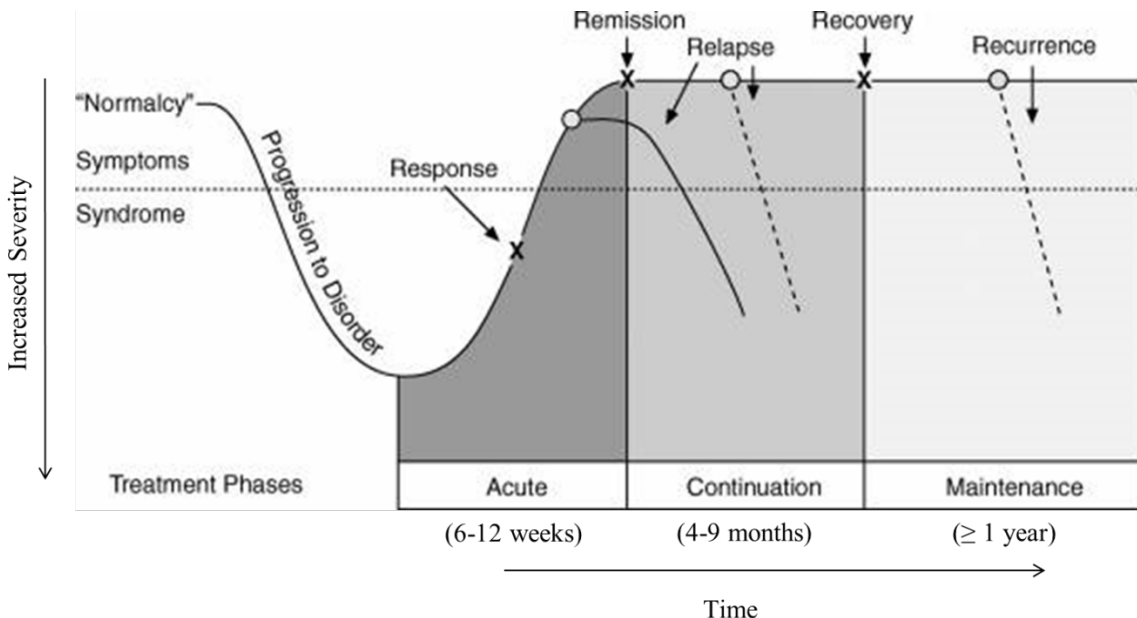
The response to the acute phase of treatment ideally occurs within the first 6 to 12 weeks of therapy ([Figure 1](#)). The return of symptoms of depression after a remission has been reached is called relapse, and is very common. Among patients who achieve response with antidepressants, the six-month risk of relapse is about 41% if antidepressants are discontinued.[\[115,116\]](#) Therefore, the second phase, the continuation phase, is necessary to sustain remission and prevent relapse. Three recent meta-analyses consistently reported that continuation treatment with antidepressants reduced relapse rates by approximately 70% compared with placebo.[\[115,117,118\]](#)

The most recent and largest meta-analysis included 54 randomized clinical trials, and 9,268 randomized patients. It showed that patients enrolled in the briefest trials of continuation treatment (e.g., six

months) received treatment long enough to demonstrate the benefits of relapse prevention, and that longer durations of treatment (e.g., 9 or 12 months) did not provide additional benefit. Therefore, we recommend that continuation antidepressant treatment is continued for at least six months after a first episode of MDD. However, for patients who had two or more episodes of MDD, or belong to high risk subpopulations, antidepressants should be continued longer (see Maintenance Treatment [Recommendations 16](#) and [17](#)).

No difference in relapse prevention was noted between classes of medications or for agents within classes.[\[118\]](#) Therefore, we recommend that the same antidepressant that was initially effective to achieve response is continued at the therapeutic dose. The therapeutic dose is the dose used in the acute treatment of depressive disorder that resulted in maximum response or remission. Clinicians should educate patients and their families to self-assess for symptoms (e.g., use of the PHQ-9) and about the importance of continuation treatment for relapse prevention. Surveillance for recurrence or relapse should continue indefinitely.

Figure 1: Distinguishing Relapse and Recurrence [\[119\]](#)



Recommendation

16. In patients at high risk for recurrent depressive episodes (see [Discussion](#)) and who are treated with pharmacotherapy, we recommend offering maintenance pharmacotherapy for at least 12 months and possibly indefinitely.

(Strong For | Reviewed, New-replaced)

Discussion

The third phase, maintenance treatment, targets patients who are at high risk for recurrent depressive episodes. Recurrence is the appearance of another new episode of MDD, while in the maintenance phase, after remission of a previous episode has been achieved. Preventing recurrence is important,

since each additional episode increases the risk of future episodes. The maintenance phase begins after six months of continuation treatment if the physician considers the patient to be recovered but still at a risk for recurrence. In high risk subpopulations, maintenance antidepressant treatment decreases the absolute risk of recurrence by 25%, with demonstrated benefits up to 36 months.[\[115,116\]](#) Maintenance treatment should be continued at the same dosage used during the continuation phase for at least 12 months and possibly indefinitely.[\[115,116,120\]](#)

Discontinuation of antidepressant therapy should be done with a slow taper since withdrawal done too rapidly may result in adverse withdrawal symptoms or return of the original depressive symptoms. Tapering should be guided by the elimination half-life of the medication and by close monitoring of the depressive symptoms.

Indications for Maintenance Therapy:

1. Two or more prior episodes, chronic major depression (greater than one year), or a major depressive episode in a patient with persistent depressive disorder
2. A family history of bipolar disorder and more severe depression as defined by: the need for hospitalization, strong suicidal ideation or behaviors, longer duration of symptoms, and more residual symptoms after response to treatment
3. Co-occurring SUD or anxiety disorders
4. Ongoing psychosocial stressors such as inadequate financial resources, significant relationship difficulties, poor social support, and chronic/severe medical illness

Recommendation

17. For patients at high risk for relapse (e.g., two or more prior episodes, unstable remission status), we recommend offering a course of cognitive behavioral therapy (CBT), interpersonal therapy (IPT) or mindfulness-based cognitive therapy (MBCT) during the continuation phase of treatment (after remission is achieved) to reduce the risk of subsequent relapse/recurrence.
 - The evidence does not support recommending a specific evidence-based psychotherapy over another.

(Strong For | Reviewed, Amended)

Discussion

Relapse and recurrence are associated with a history of previous episodes of depression and/or a chronic course (greater than two years of depressive symptoms during the index episode). A specific course of time-limited CBT, IPT or MBCT for relapse prevention following response to acute treatment for an episode produces a small, statistically significant reduction in the risk of depression relapse or recurrence.[\[121,122\]](#) The benefits of reducing the risks of subsequent depressive episodes outweigh the modest additional burden of psychotherapies to most patients.

E. Other Treatment Considerations

a. Recommendations for Specific Populations with Mild to Moderate MDD

Recommendation

18. For initiation of treatment in pregnant or breastfeeding women with mild to moderate MDD, we recommend offering an evidence-based psychotherapy (i.e., ACT, BA/BT, CBT, IPT, MBCT, PST) as a first-line treatment.
- The evidence does not support recommending a specific evidence-based psychotherapy over another.
 - In pregnant patients with a history of MDD prior to pregnancy who responded to antidepressant medications, and are currently stable on pharmacotherapy, weigh risk/benefit balance to both mother and fetus in treatment decisions.

(Strong For | Reviewed, New-replaced)

Discussion

Depression can have significant impact on the health of mother and baby in pregnancy and postpartum time periods. Antidepressants and psychotherapy have both been found to be effective in managing depression during pregnancy and the postpartum period.[\[123\]](#) However, psychotherapy is recommended as a first-line treatment due to a more favorable safety profile and because it is often preferred by patients. The evidence does not support recommending any specific evidence-based psychotherapy over another. A meta-analysis found fair evidence that CBT and IPT are efficacious for treatment of postpartum depression.[\[123\]](#) Group and individual treatments were equivalent to other treatments and superior to control groups. Combined CBT and medication had the largest effect size in this meta-analysis. Prior to the initiation of medication in women of childbearing age, potential risks to the fetus, newborn, and mother of treated and untreated depression should be discussed. Medication safety should be reviewed again with pregnant or breastfeeding patients who were prescribed antidepressant medication. An additional RCT (n=192) comparing group-based CBT, group-based counseling, individual counseling and routine primary care for postpartum MDD found that group treatments were not significantly different from each other, although they were not as effective as individual counseling.[\[124\]](#) A systematic review of 40 RCTs found fair evidence supporting CBT to treat and prevent depression for women during pregnancy and one year postpartum.[\[125\]](#) There are no studies comparing psychotherapy to medication.

Recommendation

19. For older adults (≥65 years) with mild to moderate MDD, we recommend offering an evidence-based psychotherapy (i.e., ACT, BT/BA, CBT, IPT, MBCT, PST) as a first-line treatment. Patient preference and the additional safety risks of pharmacotherapy should be considered when making this decision.
- The evidence does not support recommending a specific evidence-based psychotherapy over another.

(Strong For | Reviewed, New-replaced)

Discussion

In the elderly with depression, psychotherapy is preferred as a first-line treatment because of safety considerations, and to avoid the consequences of polypharmacy, including potential increased toxicity and drug-drug interactions, in elderly patients with lower distribution volume and declining liver or kidney function. This recommendation applies despite the misconception that older adults may not be good candidates for psychotherapy. The evidence does not support recommending any specific evidence-based psychotherapy over another.

Two systematic reviews addressed psychotherapy treatment with older adults with acute depression.[\[126,127\]](#) Psychotherapies in general led to reductions in depressive symptoms and increased the likelihood of recovery. Psychotherapy did not differ from pharmacotherapy for reducing depression and, in three reviewed studies, there was no evidence that IPT differed from other psychotherapies.[\[127\]](#) CBT was found to be an effective treatment for older patients.[\[126,127\]](#) Cuijpers et al. reviewed 25 RCTs of various psychotherapies, 17 of which compared CBT to control groups (waitlist controls or care-as-usual).[\[127\]](#) No differences were found among psychotherapies generally, however CBT specifically was found to be superior to control groups (wait list controls, care-as-usual, no treatment and placebo pill). A recent systematic review (n=1,712) also supported the use of CBT for older adults, although the quality of the evidence was poor. One study found that CBT significantly reduced symptoms of depression over non-active controls. Two of the studies found no significant difference in effect between CBT versus active control and CBT alone versus CBT plus another treatment. As with younger populations, the benefits of psychotherapy treatment outweigh risks. There is some anticipated variation in values and preferences for psychotherapy in this subpopulation.[\[128\]](#) The benefits of some type of psychotherapy outweigh the risk of no treatment in older adults with depression.

Recommendation

20. In patients with mild to moderate MDD and significant relationship distress, we suggest offering couples-focused therapy, either as monotherapy or in combination with pharmacotherapy.
(Weak For | Reviewed, New-replaced)

Discussion

Personal relationship distress plays a role in the development and/or maintenance of depression. For patients with mild to moderate MDD and significant relationship distress, we suggest couples-focused therapy to reduce symptoms and improve recovery. The decision to use couples therapy as a treatment should come after a thorough assessment of patient's needs and the decision about whether to include one's partner in the sessions. A systematic review conducted by Barbato et al. found no significant difference between couples therapy and individual therapy for the reduction of depression symptoms.[\[129\]](#) However, Barbato et al. [\[129\]](#) and an RCT conducted by Cohen et al. [\[130\]](#) showed significantly better recovery and improvement of symptoms for patients in couples therapy compared to patients on a waitlist control or no treatment. While we are not aware of studies comparing couples therapy with combined treatment, we recommend that couples therapy be combined with pharmacotherapy for the patient with depression in situations when one would do so with other psychotherapies.

The quality of research on the benefits, harms and burdens of couples therapy compared with individual therapy for MDD is limited. Despite low confidence in the quality of the studies, the evidence suggests that the benefits of couples therapy outweigh the possible harms. Consideration of the quality of the relationship should be given since not all partners may be a positive influence in a relationship or as part of therapy. Couples therapy in this case could pose additional harm to the depressed patient if the partner is abusive, addicted to substances, or has other negative influences. Other considerations are that patient values and preferences for couples therapy vary largely. Additional variation among partners willing to engage in this treatment also impacts patient choice. Other factors to weigh when choosing this intervention are the availability of trained providers who are able to target the couple rather than the individual, and the additional challenges with scheduling and engaging with the partner.

Current findings were weakened by small sample sizes and lack of generalizability (e.g., one study did not include males with MDD). Additional studies with larger sample sizes and more heterogeneity are research priorities for understanding this treatment intervention.

Recommendation

21. We suggest offering light therapy for adult patients with mild to moderate MDD with a seasonal pattern (formerly seasonal affective disorder [SAD]).
(Weak For | Reviewed, Amended)

Discussion

There is limited evidence in support of the use of bright light therapy for patients with depression that includes a seasonal component.[\[131\]](#) This includes short-term data supporting its potential effectiveness in improving depressive symptoms and response in both elderly patients [\[132\]](#) and antepartum women [\[133\]](#) who have a seasonal pattern to their MDD. Studies do not extend evidence of a treatment benefit to depressed patients without a seasonal component. In addition to limitations in the quality of existing evidence in favor of a treatment effect, there is a lack of information on long-term clinical outcomes.

On a practical level, however, benefits often outweigh risks in considering a trial of bright light therapy for depressed patients with a seasonal component. The particulars of dosing (exposure time and intensity) are important in undertaking such a trial, as is the incorporation of patient preferences for this modality within the overall plan of depression treatment. Use of a light box is the standard method of assuring adequate delivery of bright light therapy. Specifically, most trials have employed treatment with 6,000-Lux to 10,000-Lux for 30 to 60 minutes/day in demonstrating favorable short-term outcomes, compared to control treatments using dim light.[\[131\]](#)

b. Other Considerations for the Treatment of Severe, Chronic, or Recurrent MDD (Complex)

Recommendation

22. For patients with treatment-resistant MDD who had at least two adequate pharmacotherapy trials, we recommend offering monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs) along with patient education about safety and side effect profiles of these medications.
(Strong For | Reviewed, New-replaced)

Discussion

Overall, the efficacy of TCAs and MAOIs is equivalent to other antidepressants and has been reported superior for the MDD subtypes of melancholia and atypical depression, respectively. Their tolerability, adverse effects, and safety profiles, however, make them less acceptable than first-line antidepressants, such as the SSRIs.

A systematic review of depression treatment comparing antidepressants with placebo summarized results from 10 studies comparing TCA use to placebo in primary care. The number needed to treat for TCAs was approximately four, and for SSRIs it was six. The numbers needed to harm (for stopping use as a result of side effects) ranged from 5 to 11 for TCAs and 21 to 94 for SSRIs.[\[134\]](#) In STAR*D, TCAs were used as an alternative to mirtazapine when patients did not respond to first-line antidepressants. Response and remission rates did not differ significantly by treatment: nortriptyline 16.5% and 19.8%, and mirtazapine 13.4% and 12.3%, respectively.[\[135\]](#)

TCAs' tolerability is limited by sedation and anticholinergic effects such as dry mouth and eyes, constipation, cognitive slowing or impairment, and urinary retention. These properties are greater with tertiary (dimethylated) amine TCAs (e.g., amitriptyline, imipramine) than secondary (monomethylated) amines (e.g., desipramine, nortriptyline). Safety concerns also include increased intraocular pressure in persons with angle-closure glaucoma, orthostatic hypotension, syncope, tachycardia and arrhythmias. Despite the side effects of TCAs, they may be considered in certain patients with co-occurring conditions. In terms of potential for overdose, TCAs have a lower lethal dose threshold compared to SSRIs. A single TCA dose of 35-50 mg/kg of body weight or even lower, which corresponds to roughly a one to two week supply of a therapeutic dose, is lethal.[\[136\]](#) For this reason, TCAs should be used cautiously and dispensed in limited quantities in patients at risk for suicide. Death following overdose is usually due to arrhythmias.

Therapeutic plasma concentrations have been determined for desipramine (125-300 ng/mL), imipramine (200-350 ng/mL), and nortriptyline (50-175 ng/mL) and levels should be monitored to determine the right therapeutic dose and limit the risk of toxicity.[\[137-139\]](#)

The MAOIs consist of oral formulations of isocarboxazid, phenelzine, and tranylcypromine, and a transdermal formulation of selegiline. MAOIs may be effective in patients who do not respond to treatment with other antidepressants, but their requirement for dietary restrictions of tyramine and other highly concentrated amine containing foods (e.g., dopamine in fava beans, large quantities of coffee or other caffeine containing beverages), adverse effect profile, and propensity for drug interactions limit their use although these may be less important for the lowest dose of the transdermal form.

A meta-analysis reported overall response rates of 57.9% with phenelzine, 60.1% with isocarboxazid, and 52.6% with tranylcypromine for outpatients with depressive disorders.[\[140\]](#) The meta-analysis did not perform statistical tests to determine whether there are significant differences between the three drugs, but the overall response rates appear similar. The meta-analysis suggests that the MAOIs may be more effective for patients with atypical features, but not as effective as TCAs for patients with more severe or melancholic depression.

A review of 59 charts of patients who had received at least one trial of another antidepressant found that 24 patients (41%) had not responded to ≥ 4 adequate antidepressant trials.^[141] After switching to a MAOI, 56% had a change in their Clinical Global Impression score of “much or very much improved” relative to the treatment immediately prior to the MAOI. In the STAR*D trial, remission rates were not significantly different between tranylcypromine (6.9%) and venlafaxine plus mirtazapine (13.7%).^[142] Tranylcypromine was associated with significantly less symptom reduction and greater attrition due to intolerance. In other words, those who were treated with tranylcypromine were more likely to discontinue the treatment, citing side effects as the reason. It is also possible that the dietary restrictions associated with taking an MAOI could have limited its acceptability as a treatment.^[142] In three placebo-controlled clinical trials selegiline response rates were relatively low with only small advantages compared to placebo and low response rates (30-40%) relative to those reported with other antidepressants (50-60%).^[143-145] Selegiline has not yet been studied in treatment-resistant depression. Limitations of the available evidence include that in some trials the comparator drugs used are not available in the U.S.

Patient education must include discussion about dietary and drug restrictions, including the requirement for a tyramine-restricted diet with all MAOIs (with the exception of the lowest strength of the selegiline transdermal patch) to avoid a hypertensive crisis. Foods containing large amounts of tyramine include aged cheeses, red wine, sherry, liqueurs, yeast-containing products, bottled or canned beer, smoked or pickled meats and fish, and fermented sausages such as salami, pepperoni, and bologna. Restricted fruits and vegetables include avocados, canned or overripe figs, and fermented bean curd such as soy beans, soy paste, and soy sauce. Concurrent use with other medications with serotonergic effects (e.g., other antidepressants, triptans, meperidine, tramadol, dextromethorphan) is also to be avoided due to the risk of serotonin syndrome. Concurrent use with stimulants, vasoconstrictors, or other medications with adrenergic effects is also to be avoided due to the potential for hypertensive crises. It is essential to have an adequate wash-out period following treatment with other antidepressants or other drugs that interact with MAOIs based on half-life (e.g., five weeks after stopping fluoxetine therapy before starting an MAOI).

Recommendation

23. Given the limited information on ketamine’s safety and duration of effect, we recommend against the use of ketamine to treat MDD outside of a research setting.

(Strong Against | Reviewed, New-added)

Discussion

Ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist approved for general anesthesia. Ketamine has demonstrated a rapid response in persons with MDD following a single infusion. A systematic review and meta-analysis assessed nine, non-electroconvulsive therapy studies that compared ketamine to placebo or midazolam in patients with treatment-resistant depression (n=192).^[146] Compared to controls, patients who received ketamine had significantly greater improvement on global depression scores within 24 hours of administration. Suicidal ideation was reduced in the two studies in which it was assessed. Ketamine’s efficacy was maintained in patients on or off antidepressants in all subgroups and sensitivity analyses. Common side effects included dry mouth, tachycardia, increased blood pressure and the feeling of disassociation.^[146]

Despite these preliminary positive findings in a limited number of studies, many questions remain unanswered. The studies to date have given a single dose of ketamine leaving the number and frequency of doses needed to treat an episode of MDD undetermined. The most common dose has been 0.5 mg/kg of body weight.^[146] Higher doses may be more likely to result in cardiovascular adverse effects and no dose ranging studies have been conducted. Ketamine has also not been studied in persons with co-occurring conditions. Thus, the identification of patients who would most benefit from ketamine and the best approach to dosing has not been established.

Ketamine has shown promise as a treatment for patients with treatment-resistant MDD. Until the practical questions and long-term safety and efficacy concerns are addressed, ketamine should be reserved for investigational clinical trials. The panel encourages such clinical trials within and supported by the VA and DoD.

Recommendation

24. We recommend offering electroconvulsive therapy (ECT) with or without psychotherapy in patients with severe MDD and any of the following conditions:

- Catatonia
- Psychotic depression
- Severe suicidality
- A history of a good response to ECT
- Need for rapid, definitive treatment response on either medical or psychiatric grounds
- Risks of other treatments outweigh the risks of ECT (i.e., co-occurring medical conditions make ECT the safest treatment alternative)
- A history of a poor response to multiple antidepressants
- Intolerable side effects to all classes of antidepressant medications (e.g., seizures, hyponatremia, severe anxiety)
- Patient preference
- Pregnancy

(Strong For | Reviewed, Amended)

Discussion

Electroconvulsive therapy should be considered in patients with severe MDD who cannot tolerate, or have not responded to, several trials of antidepressant treatment, unless the patient has significant co-occurring medical conditions that would increase the risks of ECT (e.g., recent myocardial infarction or intracerebral hemorrhage, currently taking MAOIs, or retinal detachment). While there are some risks associated with using ECT, such as memory loss and anesthesia, there are also risks associated with severe MDD that is otherwise untreated (e.g., suicide). Although there is large variation in preferences for using ECT, we are highly confident that the benefits outweigh the harm/burdens of treatment. We are aware that resources, acceptability and feasibility sometimes limit the ability to use this treatment and realize that certain areas will not have this treatment option.

ECT was more efficacious than simulated (sham) ECT in a total of 256 patients with MDD across six trials. ECT was also shown to be more efficacious than pharmacotherapy in a total of 1,144 patients with MDD involved in eight trials.^[147] The authors of the study note that the trials included in the review were

small, and there still remains limited information regarding the degree of short-term cognitive impairment associated with ECT as well as evidence of the efficacy of ECT in specific subgroups, such as the elderly and patients with treatment-resistant illnesses. The UK ECT Review Group states, however, that ECT is an important treatment option for patients with severe depression.

Regimens of ECT have variable effects on depression symptoms:[\[147\]](#)

- Bilateral ECT, compared with unilateral electrode placement ECT, improved symptoms (22 trials involving 1137 patients)
- High dose ECT, compared with low dose ECT, significantly improved symptoms. High dose and low dose definitions varied based on the trial. Two trials reported the low dose as being 2.5 times above the convulsive threshold and the high dose as fixed at 0.8 A, 403 mC, 90 Hz for two seconds and pulse width of 1-4 ms. Another trial reported the lower dose group at 7-10 J in five seconds and the higher dose group at 40-55 J in eight seconds, and another trial as low dose being at 50% or 150% of seizure threshold and the higher dose as greater than 500% of the seizure threshold (6 trials involving 337 patients).
- There was no significant difference in outcomes between twice weekly and three times weekly treatment (4 trials involving 159 patients) or between brief pulse waveform and sine waveform (8 trials involving 296)

Symptom improvement with ECT is short term and should be followed by maintenance treatment with antidepressants, or if antidepressants are not tolerated, repeated treatment with ECT.[\[148-150\]](#)

ECT is effective in the treatment of severe depression in pregnant women and may be a safer option than other possible treatments.

The negative impact of ECT on short- and long-term cognitive functioning was inconsistently assessed across studies and reported results varied across studies included in the systematic reviews. One RCT found that ECT compared to simulated ECT had a greater impact on short-term cognitive functioning, but not on cognitive function at six months. Compared to antidepressants, one RCT found ECT had a greater impact on short-term cognitive function and another RCT found there was no difference in short-term cognitive function between ECT and antidepressants.[\[147\]](#) ECT can be offered as adjunctive treatment if patients on combination therapy of pharmacotherapy and psychotherapy are not responding well.

Recommendation

25. We suggest offering treatment with repetitive transcranial magnetic stimulation (rTMS) for treatment during a major depressive episode in patients with treatment-resistant MDD.
(Weak For | Reviewed, New-added)

Discussion

Repetitive transcranial magnetic stimulation is a somatic treatment that uses magnetic fields to modulate the activity of certain regions of the brain. This intervention is FDA-indicated for treatment-resistant depression. The research demonstrating its efficacy has dramatically improved since publication of the 2009 MDD CPG.

Three meta-analyses compared rTMS to a sham treatment in patients with treatment-resistant depression.[151-153] One analysis found positive response rates of 25% [153] for the intervention, significantly higher than sham; and remission rates of 17% [153] for the intervention (also higher than sham). A study by Gaynes et al. showed clinically significant decreases in HDRS (Hamilton Depression Rating Scale) depressive severity of >4 points compared with sham.[151] Patients with treatment-resistant depression were found to be three times as likely to achieve a response versus sham and were five times as likely to achieve a remission.[151] The number needed to treat for response is between 3.4 and 9 patients, [151-153] and the number needed to treat for remission was between 5 and 7 patients.[152,153] One meta-analysis found no difference between the effects of unilateral compared to bilateral rTMS in MDD.[154]

Perspectives regarding the use of rTMS vary. Similar to other somatic treatments, it is not available in all locations. It normally requires several weeks of consecutive daily treatments for effectiveness. Compared to basic psychotherapy or treatment with pharmacological approaches, it is resource intensive but may be less burdensome compared to augmentation strategies or an adverse outcome such as a psychiatric hospitalization. Its favorable side effect profile may also encourage its use over augmentation with additional medications (e.g., SGAs) or treatment with ECT.

The benefits of rTMS outweigh the minimal risks and side effects. The most common adverse events are irritation at the stimulation site and headache. One meta-analysis found no significant increase in side effects or drop outs versus sham.[153] Two meta-analyses compared ECT with TMS. One analysis showed significantly more responders and remitters with ECT compared to TMS but no difference in mental status outcomes, cognitive function, or adverse events. A subgroup analysis showed that ECT was more effective in psychotic depression but rTMS was as effective as ECT in patients without psychosis (with a response rate of 52.5%).[155] The other analysis showed no difference between the two treatments and described mixed results as to whether ECT has a deleterious impact on cognitive functioning compared with rTMS.[156]

As rTMS is an emerging technology, additional research is needed. Most importantly, the duration of the treatment effect and the long-term safety profile of the intervention need to be demonstrated. More evidence is needed to determine the best approach to using rTMS for treatment-resistant depression and if TMS should be a standalone or augmentation therapy. Head-to-head studies comparing rTMS to pharmacotherapy or psychotherapy were not found in our literature search. It has also not been studied in pregnant women. Therefore, our confidence in the literature remains only moderate at this time.

Recommendation

26. We recommend against offering vagus nerve stimulation (VNS) for patients with MDD, including patients with severe treatment-resistant depression outside of a research setting.
(Strong Against | Reviewed, Amended)

Discussion

Although vagus nerve stimulation is FDA approved for treatment-resistant depression, there is no current evidence that supports its routine use in the treatment of MDD. The FDA defines treatment-resistant depression and indicates the use of VNS in “patients who have been treated with, but failed to

respond to, at least 4 adequate medication and/or ECT treatment regimens prescribed by their physician.”[157] VNS was initially approved by the FDA for the treatment of refractory epilepsy. In patients with refractory epilepsy who received VNS, it was noted that their mood improved, thus leading to consideration of VNS for depression.[158]

The VNS device involves sending electrical pulses to the brain and consists of a pulse generator, similar to a pacemaker, implanted under the skin in the chest wall that has an electrical lead connecting to the vagus nerve.[157] Safety considerations must be evaluated and discussed before utilizing VNS, for which the harms and burdens appear to outweigh the benefits for routine treatment. Evidence indicates a greater than 5% chance of significant adverse events for patients who have been implanted with a VNS. These possible adverse events include voice alteration, dysphagia, dyspnea, infection, dizziness, asthenia, chest pains, palpitations, and vocal cord paralysis.[159]

The lack of new or significant evidence showing effectiveness of VNS in treatment-resistant depression is the reason for the strong recommendation against its routine use. Also, there is moderate-to-strong evidence against using VNS routinely even for severe treatment-resistant depression, except as a possible last resort.

A double-blind RCT of 235 outpatients found no difference between VNS and a sham placebo.[160] Other evidence stems from primarily non-blinded follow up studies,[161] a comparison between intervention group patients to a non-concurrent cohort of treatment as usual patients,[162], and uncontrolled observational studies.[149,163-165]

There may also be a large variation in patients’ values and preferences in the use of VNS for treatment-resistant depression. Some patients may not wish to undergo such an invasive procedure while others might prefer to have the VNS implanted if it means they would no longer have to take daily medications. Providers or patients may try other non-pharmacological treatments for MDD over the use the VNS. Acceptability and resource availability are also a consideration as the device costs approximately \$25,000 and requires surgical implantation.

As there is a lack of evidence in support of the routine use of VNS for treatment-resistant depression, more research is needed. Specifically, VNS should be studied in patients with recurrent seizures and depression.

Recommendation

27. We recommend against offering deep brain stimulation (DBS) for patients with MDD outside of a research setting.

(Strong Against | Reviewed, New-added)

Discussion

The available evidence does not support the use of deep brain stimulation as a therapy for treatment-resistant depression. Dougherty et al. conducted the only completed RCT.[166] Thirty patients were randomized to DBS (n=16) or sham DBS (n=14). Active stimulation was programmed to target the ventral capsule/ventral striatum, locations identified in survey testing as having the greatest potential for antidepressant effect. Results indicated no significant difference in response rate between DBS and

sham DBS. According to the authors the trial was underpowered (n=30) and, perhaps, unable to detect between group differences. Also, suicidal ideation, hypomania, worsening depression and insomnia occurred more frequently in the active DBS group.

Given the lack of evidence in support of its effectiveness, and its potential harms and burdens, there is no basis upon which to recommend the use of DBS, which should be considered experimental until further evidence becomes available.

c. Self-help and Complementary and Alternative Treatments

The following approaches are, in general, most relevant and appropriate for mild or moderate MDD rather than more severe or complex forms of depression. Even for milder forms of MDD, they should be considered secondary rather than first-line treatments as they are less supported by evidence.

Recommendation

28. For patients with MDD, there is insufficient evidence to recommend for or against acupuncture either as monotherapy or as an adjunctive treatment to pharmacotherapy.

(Not Applicable | Reviewed, New-replaced)

Discussion

There are two systematic reviews that evaluate acupuncture effectiveness for MDD.[\[167,168\]](#) In the 2015 systematic review and meta-analysis, Chan et al. reviewed 13 RCTs with a total of 1,046 patients.[\[167\]](#) All RCTs compared effectiveness of antidepressants alone to antidepressant plus acupuncture. The conclusions suggest that acupuncture used adjunctively with antidepressants is more effective than antidepressants alone. Adjunctive acupuncture results in significantly higher reduction of depressive symptoms, higher response rates, and fewer side effects. Only 3 of 13 included RCTs reported adverse events. Although this was a well done systematic review and meta-analysis, many of the RCTs included had serious quality limitations such as lack of blinding of outcome assessors, intention-to-treat (ITT) analysis, or allocation concealment.

Another 2015 systematic review and meta-analysis by Sorbero et al. identified 18 RCTs that examined acupuncture in the treatment of MDD.[\[168\]](#) Eleven RCTs assessed acupuncture as monotherapy, and seven as adjunctive MDD treatment. Among the seven RCTs that assessed effectiveness of adjunctive acupuncture, five looked at acupuncture plus antidepressants versus antidepressants alone, and two looked at acupuncture plus treatment as usual versus treatment as usual alone. The authors conclude that adjunctive acupuncture is more effective in decreasing depressive symptoms, but the effect of acupuncture on relapse rate could not be determined. Reported adverse events were typically mild in nature, but the studies were not designed to detect rare events.

Four out of 11 RCTs investigating acupuncture monotherapy in the review by Sorbero et al. used antidepressants as a control condition.[\[168\]](#) Although two of the four reported no statistically significant difference in reducing MDD symptoms, none of these four RCTs reported a statistical power calculation to determine whether the studies were sufficiently powered to detect differences. Five acupuncture monotherapy RCTs used massage, or sham acupuncture as controls, but the results were conflicting. Two remaining RCTs showed that acupuncture was superior to a waitlist control at reducing depressive

symptoms, but the size of the effect could not be determined. The higher quality RCTs in this review still suffered from limited blinding, limited use of ITT analysis, and high attrition.

Two other reviews evaluated acupuncture monotherapy effectiveness for depressive disorders, but did not limit their inclusion criteria to MDD specifically, and therefore may not be generalizable for the MDD population. A 2010 review by Fan et al. included 13 RCTs (2,787 patients) with a mixture of depressive disorder diagnoses.[\[169\]](#) It suggests that acupuncture monotherapy shows similar effect as antidepressants or other conventional treatments. However, 40% of the included studies did not report the randomization procedure, and did not provide information on blinding. A 2014 review by Zhang et al. (17 RCTs, 1,132 patients) concludes that in treatment of post-stroke depression acupuncture monotherapy was more effective than antidepressants.[\[170\]](#) Based on these reviews, the evidence is insufficient to recommend for or against acupuncture monotherapy in treatment of MDD.

Despite the lack of strong evidence in support of acupuncture, it may be offered to some patients who seek it. This may arise from factors such as cultural background or a preference for complementary and integrative modalities. For those who do not have access to acupuncture care within their healthcare system or military treatment facility and who seek acupuncture care at their own expense, cost burden may also be high. Treatment may also be burdensome with regard to time and transportation depending on the duration and frequency.

More rigorous studies using specific active controls, blinding of outcome assessors, allocation concealment, and ITT analysis are needed to fully understand the effectiveness and value of acupuncture in the treatment of MDD. RCTs that compare acupuncture monotherapy to first-line treatments should be sufficiently powered to detect a superior treatment or establish equivalency. Because MDD is a common co-occurring condition among those with chronic pain, and acupuncture is a common treatment modality within integrative military health clinics, additional assessment of depression outcomes in that population should be specifically investigated.

Recommendation

29. For patients with MDD, we suggest offering patient education on the benefits of exercise as an adjunct to other evidence-based treatments for depression or as monotherapy when patients are unwilling or unable to engage in first-line evidence-based psychotherapy or pharmacotherapy.

(Weak For | Reviewed, New-replaced)

Discussion

The benefits of exercise for weight management, cardiovascular health, diabetes, bone density, cancer risk, fall risk and longevity are well documented in the medical literature. With respect to psychological health, exercise has been shown to increase positive emotions,[\[171\]](#) reduce negative emotions,[\[171\]](#) and increase self-efficacy.[\[172\]](#) The neural changes that result from regular exercise are increases in the brain's blood circulation, endorphins, and monoamines, and reduction in cortisol.[\[173\]](#)

A 2013 Cochrane systematic review and meta-analysis by Cooney et al. evaluated the effectiveness of exercise in the treatment of adults with major depression, and included 39 RCTs and 2,326 patients.[\[71\]](#) Cooney et al. defined exercise as the "planned, structured and repetitive bodily movement done to

improve or maintain one or more components of physical fitness” based on American College of Sports Medicine criteria.[174] It suggests that compared to control groups (i.e., waitlist control, placebo or other intervention) exercise monotherapy was more effective at reducing depressive symptoms (moderate effect size). The same review showed no difference in efficacy of exercise monotherapy and either psychotherapy or antidepressants in reducing depressive symptoms and improving quality of life. All three interventions had similar treatment adherence, but participants in the medication groups reported more side effects than individuals in the exercise groups. The duration of intervention among the trials included in this review ranged from 10 days to 16 weeks, and follow-up ranged from 4 to 26 months. The depression severity was not reported. Most of the included trials evaluated exercise monotherapy, with the exception of three RCTs that looked at exercise adjunctive to CBT versus CBT alone, and one trial compared exercise alone to exercise plus sertraline to sertraline alone.

Although Cooney et al. suggests that exercise monotherapy is effective for major depression, the methodological quality of the included RCTs was low. Of the 39 included trials, only 14 trials achieved adequate concealment for randomization, 15 performed ITT analysis, and 12 blinded outcome assessors.[71] A future systematic review that includes only high-quality RCTs is necessary to provide more confidence in exercise efficacy as monotherapy.

Because of the methodological limitations described above, we suggest that exercise be used adjunctively with a first-line evidence-based treatment, especially for moderate and severe MDD. In those patients with mild depression who are not currently undergoing medical treatment, exercise is an excellent self-management and preventative strategy. Exercise can also be used as monotherapy when patients are unwilling, unable, or have contraindications to taking first-line treatments. As shown in the trial by Dunn et al., the type of exercise (e.g., aerobic, strength training) does not influence efficacy, but total energy expenditure positively correlates with symptom improvement.[175]

In conclusion, exercise is safe, acceptable, and shows good adherence in patients with major depression.[71] The self-care nature of exercise allows patients to feel more in control, and empowers them to take an active central role in the therapeutic process. As with any treatment, patients should be instructed not to discontinue psychotherapy and/or pharmacotherapy without consulting a physician, and to follow up regularly.

Recommendation

30. For patients with MDD, there is insufficient evidence to recommend for or against yoga, tai chi, or qi gong either as monotherapy or as an adjunctive treatment to pharmacotherapy.

(Not applicable | Reviewed, New-added)

Discussion

According to the 2012 National Health Interview Survey, over 10% of Americans had used yoga, tai chi, or qi gong as a complementary health strategy within the past year.[176] From 2002-2012, yoga by itself had seen a two-fold increase in the number of Americans who are practicing for health reasons. Military Service Members have been shown to utilize complementary modalities at a rate 2.5 times that of their civilian counterparts.[177] While the widespread practice of these mind-body modalities have demonstrated

significant merit as adjunctive approaches in managing certain disease conditions and health risks, the current state of the evidence regarding their effectiveness in the treatment of MDD is weak.

In reviewing the literature of yoga, tai chi, and qi gong as they relate to the treatment of MDD, the quality of the evidence was found to be very low. Two systematic reviews of yoga and three RCTs of tai chi were identified. [178-182] In most cases, the target populations were highly specialized, limiting generalizability of the results. Selection bias, issues with blinding, not using ITT analysis, and poorly described methodology contributed to the low quality ratings.

Gong conducted an analysis of six RCTs examining yoga as a treatment for depression in pregnant women. While the findings showed a significantly favorable difference in depression symptoms in those using yoga over controls, there were significant flaws with regards to blinding, allocation concealment, and the lack of ITT analysis.[178] The Klainin-Yobas systematic review included 12 studies of interventions to treat depression in older adults, of which four included yoga.[179] While benefits were reported in yoga groups, the quality of the research was low due to the lack of ITT and a lack of identifying confounding factors.

Three RCTs of tai chi were reviewed and deemed to be of good quality. In obese patients with moderate co-occurring depression, tai chi significantly improved symptoms at 12 and 24 weeks as compared to controls. However, another RCT in Chinese Americans that compared tai chi to controls for the treatment of MDD showed no change in depression severity or quality of life at 12 weeks.[182] In a study by Lavretsky et al., an escitalopram plus tai chi intervention was compared to escitalopram plus health education.[181] While there was a decrease in depression severity in the tai chi group, there were no significant differences between groups with regard to treatment response, remission, and physical functioning.

While the authors acknowledge that specific values and preferences of patients may strongly favor the use of these mind-body modalities as an adjunctive treatment to other care, there is currently insufficient evidence to guide clinical decision-making with regard to their role in treating MDD. More methodologically rigorous research, particularly studies of mind-body modalities for depression in more generalized populations, is needed.

Recommendation

31. For patients with mild MDD who are not pregnant or breastfeeding and who prefer herbal treatments to first-line psychotherapy or pharmacotherapy, we suggest standardized extract of St. John's wort (SJW) as a medication monotherapy.

(Weak For | Reviewed, Amended)

Discussion

St. John's wort, or *Hypericum perforatum*, is a flowering plant that has antidepressant properties. It is classified as a dietary supplement and thus is not examined and regulated by FDA. As a result, there is not good evidence that dosing of SJW is consistent across formulations from different manufacturers. There are two systematic reviews and meta-analyses that evaluated the efficacy of SJW monotherapy in management of MDD.

A Cochrane review examined 29 studies of 5,489 patients with depression.[\[183\]](#) The included trials compared efficacy of the standardized extract of SJW with placebo or conventional antidepressant medications. For patients with mild and moderate major depression, SJW was shown to be superior to placebo, and its efficacy was similar to that of standard antidepressants. Maher et al. reproduced these results in their 2015 systematic review and meta-analysis that included 35 RCTs, and also showed that SJW monotherapy for mild and moderate depression was superior to placebo in improving symptoms and not significantly different from antidepressant medications.[\[184\]](#)

It should be noted that efficacy of SJW for MDD is established for standardized extracts only, and not for other preparations (e.g., tinctures, infusions, dry herb capsules). Maher et al. analyzed 35 RCTs and found that the most commonly studied extracts were standardized to either hypericin (0.1-0.3%) or hyperforin (1-6%), and used at therapeutic dosages ranging from 500-1800 mg daily. Thus, starting a patient on a SJW extract standardized to 0.3% hypericin at 300 mg three times daily, and titrating the dose up to 1200 mg a day is consistent with the evidence.

Both systematic reviews agree that SJW has fewer adverse effects than standard antidepressants.[\[183,184\]](#) Adverse effects of SJW include gastrointestinal upset, mild sedation, restlessness, and increased risk of photosensitivity at higher doses. SJW should not be used in pregnant or breastfeeding women because of lack of safety data in these populations.

Providers need to be mindful of potential herb-drug interactions of SJW, and carefully review patient's drug profile before prescribing. Taking SJW in combination with SSRIs increases the risk of serotonin syndrome and serotonergic adverse events, and is not recommended. SJW induces the cytochrome P450 3A4 enzyme, thereby posing a high risk of drug interactions. For example, SJW can decrease the effectiveness of contraceptives, tricyclic antidepressant drugs, cyclosporine, and antiepileptic drugs. Patients taking clopidogrel should avoid SJW because of an increased risk of bleeding.

Recommendation

32. For patients with MDD, we suggest against using omega-3 fatty acids or vitamin D for treatment.
(Weak Against | Reviewed, New-added)

Discussion

We only reviewed omega-3 fatty acids and vitamin D use for this CPG. Other nutritional or dietary supplements were not considered. The decision to only review the evidence on omega-3 fatty acids and vitamin D was made based on the clinical uncertainty surrounding the efficacy of these two substances.

Omega-3 Fatty Acids

Omega-3 fatty acids are found in certain types of fish (e.g., herring, tuna, sardines), nuts, and seeds. The two types of the omega-3 fatty acids that are most commonly studied for psychological health are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Three recent systematic reviews evaluate the efficacy of omega-3 fatty acids in treatment of depression.[\[185-187\]](#)

A 2015 review by Newberry et al. included 24 RCTs, and 20 out of 24 studies reported efficacy outcomes for placebo comparisons.[\[187\]](#) The review suggests that DHA had no effect on depressive symptoms, while EPA showed a small but significant effect on reducing depressive symptoms compared to placebo.

However, the authors reported evidence of publication bias. Also, no statistically significant effect was found for the proportion of patients in remission compared to placebo.

Two earlier systematic reviews reported conflicting conclusions. A 2010 meta-analysis by Jans et al. reported no statistically significant effect of omega-3 fatty acids on depressive symptoms in a subgroup analysis of three small RCTs (n=110).^[186] Appleton et al., on the other hand, reported that their meta-analysis of 16 RCTs suggested that omega-3 fatty acids were more effective than placebo in patients with more severe depression.^[185] However, they also suggest that significant heterogeneity and possible publication bias prevented clinically meaningful conclusions.

The quality of evidence was rated as poor due to lack of allocation concealment, or ITT analysis in many included trials, and blinding in some trials. In conclusion, the omega-3 fatty acid EPA may have a small benefit in improving depression symptoms compared to placebo with relatively minor gastrointestinal adverse events for adults with MDD but the existing evidence base is weak at this time.^[187] We suggest that practitioners and policymakers wait until future research in this field is conducted before recommending omega-3 fatty acids in treatment of MDD.

Vitamin D

Vitamin D is found in such foods as fish, dairy products, and dietary supplements and can also be obtained through exposure to the sun. One systematic review evaluated efficacy of vitamin D in treatment of mild to moderate MDD in adults with normal serum levels of vitamin D.^[188] The review included nine RCTs that randomly allocated 4,923 patients to vitamin D or placebo, and indicated a non-significant difference favoring placebo.

Another RCT by Mozaffari-Khosravi evaluated efficacy of vitamin D in patients with severe MDD and concurrent vitamin D deficiency.^[189] This study randomly allocated 109 participants to injections of 300,000 IU (International units) vitamin D3, injections of 150,000 IU vitamin D3, or no treatment, and followed them for three months. The investigators concluded that 300,000 IU of vitamin D3 was more effective at reducing MDD severity than no treatment. No significant between group difference was reported for injections of 150,000 IU vitamin D3 versus no treatment. The quality of this study was reported as poor due to lack of ITT analysis and double-blinding, and therefore its conclusions are hard to translate to clinical practice.

It is important to note that the effective dose suggested by Mozaffari-Khosravi is much higher than standard treatment for simple vitamin D deficiency (i.e., 50,000 IU vitamin D3 orally once a week), and therefore should be studied further.^[189] Future well designed adequately powered double-blind RCTs in severely depressed patients with concurrent vitamin D deficiency that utilize allocation concealment and ITT analysis are needed to guide clinical decisions in this particular subpopulation.

Recommendation

33. For patients with mild MDD, we suggest patient education about the benefits of bibliotherapy based on cognitive-behavioral principles as adjunctive treatment or an alternative to pharmacotherapy or psychotherapy based on patient preference.

(Weak For | Reviewed, New-replaced)

Discussion

There is mixed evidence regarding the use of guided self-help (GSH) interventions, including bibliotherapy. While Naylor et al. [190] reported no statistically significant differences between bibliotherapy prescription versus usual care for depression, dysfunctional attitudes, or quality of life, Liu et al. [191] found preliminary evidence that CBT-based bibliotherapy reduced depressive symptoms. Results from Naylor et al. suggest that a bibliotherapy behavioral prescription can be practically and feasibly delivered by physicians as a treatment for depression in real world primary care settings with medical patients. Considering the expense of antidepressant medication, its association with aversive side effects, the contraindications for some patients, and its limited effectiveness for others, these results suggest that patients' use of GSH, such as bibliotherapy, may be a useful alternative.

Despite the small size of the Liu et al. study (n= 52), the preliminary evidence for the utility of bibliotherapy grounded in the cognitive-behavioral approach was found to lower participants' cognitive-affective symptoms of depression, possibly by increasing their confidence in their ability to self-manage his or her behavior despite the experience of negative feelings.[191]

Both studies incorporated the use of evidence-based, recommended self-help books including *Feeling Good: The new mood therapy* [192] and *Mind over Mood: Change How You Feel by Changing the Way You Think*. [193] Cognitive bibliotherapy appears to be a promising treatment option for depressed, non-suicidal adults who are interested in this treatment modality. Given the high accessibility and cost effectiveness of this accessible treatment, it may be an effective option for some.

The results of these studies are promising enough to warrant using bibliotherapy for some patients, especially if primary treatment modalities are not available. The current findings warrant further research on physician-delivered behavioral prescriptions for depression that could be effective, and, therefore, be expanded in a number of ways to include interactive websites, DVDs, and other media.

Appendix A: Evidence Review Methodology

A. Developing the Scope and Key Questions

The Clinical Practice Guideline (CPG) Champions, along with the Work Group, were tasked with identifying key evidence questions to guide the systematic review of the literature on MDD. These questions, which were developed in consultation with the Lewin team, addressed clinical topics of the highest priority for the VA and DoD populations. The key questions follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 provides a brief overview of the PICOTS typology.

Table A-1. PICOTS [194]

P	Patients, Population, or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
I	Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
C	Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
O	Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
(T)	Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
(S)	Setting, of applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Table A-2 contains the final set of key questions used to guide the systematic review for this CPG.

a. Population(s)

The key questions are specific to adults 18 years or older with MDD treated in any VA/DoD clinical setting, including patients being followed for MDD. This includes those newly diagnosed, those receiving ongoing treatment, and those with chronic depression. Evidence was also considered from studies assessing treatment of MDD among the following subpopulations: elderly (including very elderly), women of childbearing potential, pregnant or breastfeeding women and patients with the following comorbid medical conditions: coronary artery disease, arrhythmias, seizure disorders, hypertension, lower back pain, dementia, Alzheimer’s, or stroke.

b. Interventions

Pharmacotherapies included: selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), serotonin antagonist and reuptake inhibitors (SARIs), noradrenergic and specific serotonergic antidepressants

(NaSSAs), tricyclic and tetracyclic antidepressants, monoamine oxidase inhibitors (MAOIs), psychostimulants, atypical antipsychotics, drugs for antidepressant augmentation (i.e., lithium, triiodothyronine, bupropion, and other (ketamine)).

Psychotherapies included: behavioral activation/behavioral therapy (BA/BT), client-centered counseling, cognitive behavioral therapy (CBT), computer-based cognitive behavioral therapy (CCBT), couples/marital-focused therapy (CFT), dialectical behavior therapy (DBT), guided self-help (GSH), interpersonal psychotherapy (IPT), mindfulness-based therapies (MBT), problem-solving therapy (PST), short-term psychodynamic psychotherapy (STPP), acceptance and commitment therapy (ACT), and evidence-based group psychotherapies.

Somatic interventions included: ablative limbic system surgery, deep brain stimulation (DBS), electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulation (VNS).

Collaborative care models included: collaborative care management, embedded mental health providers, co-located care, and integrated care.

Complementary and alternative interventions included: light therapy, St. John's wort, acupuncture, omega-3 fatty acids, meditation, vitamin D, exercise, and bibliotherapy.

c. Outcomes

Treatment and management outcomes included: improvement in quality of life (social and occupational functioning), improvement of symptoms, remission rate, relapse and recurrence rate, medication adherence and dropout, improvement of retention (keeping patients engaged in programs), improvement in co-occurring conditions, and adverse events (i.e., behavioral: agitation, anxiety, irritability, hostility, impulsivity; mortality/suicide; sexual side effects; weight gain; cardiovascular symptoms; worsening of depression; fatigue/sleepiness; insomnia; nausea, vomiting, diarrhea; neurological symptoms; and urological symptoms).

d. Timing

Timing for most interventions included a follow-up period of 6 to 12 weeks. There were some exceptions for treatments which may have more immediate effects (e.g., somatic interventions) or if the treatment is intended to be brief (e.g., brief psychotherapy).

B. Conducting the Systematic Review

Extensive literature searches identified 4,601 citations potentially addressing the key questions of interest to this evidence review. Of those, 2,470 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, not a full-length article). Overall, 2,131 abstracts were reviewed with 1,089 of those being excluded for the following reasons: not a systematic review or clinical study, did not address a key question of interest to this review, did not enroll a population of interest, or was published prior to January 2006. A total of 1,042 full-length articles were reviewed. Of those, 520 were excluded at a first pass review for the following reasons: not addressing a key question of interest, not enrolling the population of interest, not meeting inclusion criteria for a clinical study or systematic review, not meeting inclusion criteria for any key question, or being a duplicate. A table listing all studies excluded at

the full-article level is included as a separate file to this report. A total of 522 full-length articles were thought to address one or more key questions. However, upon further review, 398 additional studies were excluded. Reasons for their exclusion are presented in Figure A-1 below. Overall, 124 studies addressed one or more of the key questions and were considered as evidence in this review. Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram

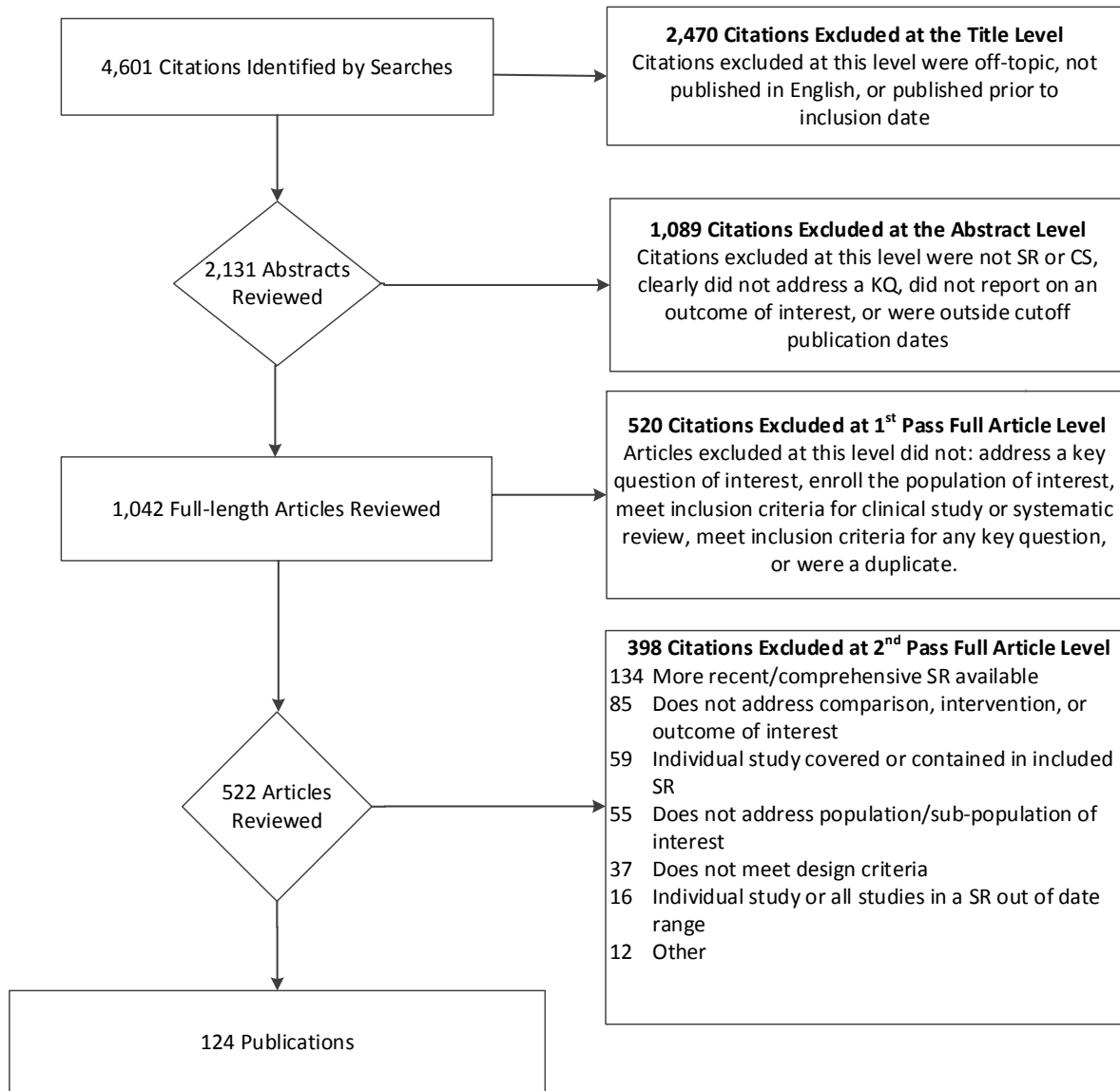


Table A-2. Evidence Base for Key Questions

Question Number	Key Question	Number and Type of Studies
1	For adults with MDD, what drug classes (e.g., SSRIs, SNRIs, and TCAs) alone or in combination are safe and effective for treating depressive symptoms? a. Do medications differ in effectiveness and safety among the following subpopulations: elderly (including very elderly), women of childbearing potential, pregnant or lactating women and patients with co-occurring medical conditions?	43 (40 systematic reviews with 2 contributing evidence to 2 subsections, 2 RCTs, and 1 pooled analysis)
2	For partial or non-responders to initial antidepressant medication, what is the effectiveness of switching medications within or across drug class or augmenting treatment with a medication from a different class (e.g., lithium, buspirone, atypical or second generation antipsychotics)?	4 (3 systematic reviews and 1 RCT)
3	For patients with MDD who have achieved remission of symptoms, how long should pharmacotherapy be continued to reduce the incidence of recurrence? a. Are there risk factors that discriminate effectively between patients who benefit from longer- versus shorter-term treatment?	2 (1 large meta-regression; 1 systematic review)
4	For adults with MDD, are psychotherapies (e.g., CBT, IPT, PST-PC), including brief interventions, effective for treating depressive symptoms?	33 (29 systematic reviews and 4 RCTs)
5	For partial or non-responders to initial antidepressant therapy does the addition of brief behavioral interventions or other psychotherapies improve response?	6 (2 systematic reviews and 4 RCTs)
6	Are there subpopulations (e.g., patients who have been refractory, patients who have relapsed or patients with higher severity of diagnosis) which are more likely to respond to initial combination therapy?	2 (1 systematic review and 1 RCT)
7	Are there collaborative, team-based models other than collaborative care management which are more effective than usual care for MDD in primary care settings?	5 systematic reviews
8	For patients newly diagnosed with MDD, what is the evidence to support a specific frequency of follow up or number of contacts, either in person or over the phone, within a designated time frame following the start of pharmacotherapy? a. Does this vary by severity (mild, moderate, severe) of diagnosis? Does this follow-up vary based on risk factors and co-occurring conditions?	2 (1 systematic review and 1 RCT)
9	For patients with treatment-resistant depression, what is the effectiveness and safety of adding or switching to somatic interventions, such as vagal nerve stimulation, ECT, or transcranial magnetic stimulation to current treatment to improve depressive symptoms?	7 (6 systematic reviews and 1 RCT)
10	For patients with MDD, are complementary and alternative treatments (e.g., light therapy, SJW, acupuncture, Omega-3, meditation and vitamin D) and lifestyle interventions (e.g., exercise and bibliotherapy) effective and safe in treating depressive symptoms?	20 (14 systematic reviews and 6 RCTs)
Total Evidence Base		124 publications

a. Criteria for Study Inclusion/Exclusion

i. General Criteria

- Systematic reviews published on or after January 1, 2008 and individual clinical studies published on or after January 1, 2006. Including previous systematic reviews published

on or after 2008 will ensure that the reviews include individual studies within the date range for this report.

- Studies must be published in English.
- Publication must be a full-length clinical study, systematic review, or meta-analysis; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length, clinical studies were not accepted as evidence.
- Study must have enrolled a patient population in which at least 80% of patients had MDD. Studies enrolling more than 20% of patients with one or more of the following disorders will be excluded: mild depression, dysthymia, psychotic depression, or bipolar disorder.
- Studies must have enrolled adults 18 years or older. In studies that mix adults and children, at least 80% of the enrolled patients had to have been 18 years or older.

ii. Treatment Studies

- Study must have evaluated a pharmacological or non-pharmacological treatment of interest to this review.
- Study must have been a prospective RCT with an independent control group.
- Crossover trials considered only if data from the first treatment period were reported separately.
- Study must have enrolled ≥10 patients per treatment arm.
- The study must report data on at least one of the included outcomes.
- Study must have followed patients for 6 to 12 weeks.
- All subjective outcomes (e.g., depressive symptoms, quality of life) must have been measured using a validated instrument.

b. Literature Search Strategy

ECRI Institute information specialists searched the following databases for relevant information. Search terms and strategies for the bibliographic databases appear below.

Name	Date Limits	Platform/Provider
Bibliographic Databases		
Cochrane Library	2006 through January 2015	Wiley
EMBASE	2006 through April 2015	Elsevier
Health Technology Assessment Database (HTA)	2006 through January 2015	Wiley
Medline	2006 through April 2015	Elsevier
PsycINFO	2006 through April 2015	OVIDSP
PubMed (In-process, Publisher, and PubMed-Not-Medline records)	2006 through April 2015	NLM
Gray Literature Resources		
Agency for Healthcare Research and Quality (AHRQ)	2006 through February 2015	AHRQ

c. Topic-specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

EMTREE, Medical Subject Headings (MeSH), PsycInfo, and Keywords

Concept	Controlled Vocabulary	Keywords
Depression	EMBASE (EMTREE) 'depression'/exp MEDLINE (MESH) Depressive Disorder, Major/ Depressive disorder/ PsycINFO major depression/	depress* dysphor* mdd melanchol*
Collaborative Care	EMBASE (EMTREE) cooperation/exp/mj 'health care delivery'/exp/mj 'integrated health care system'/mj 'mental health service'/mj 'patient care'/exp 'patient care planning'/de 'Primary Health Care'/mj 'total quality management'/mj MEDLINE (MESH) *Cooperative Behavior/ *Delivery of Health Care, Integrated/og *Health Services Accessibility/ *Mental Health Services/og *Primary Health Care/og *Quality Control/ *Quality Improvement/og PsycINFO Collaboration/ *Cooperation/ Interdisciplinary Treatment Approach/ Integrated Services/ *"Quality of Care"/ *"Quality of Services"/ Treatment Planning/	co-located collaborative embed* integrat* team AND care model* system* "Collaborative depression care management" depression care model*
Pharmacotherapies - General	EMBASE (EMTREE) 'antidepressant agent'/de depression/dd_dt	antidepressant* anti-depressant* drug therap*

Concept	Controlled Vocabulary	Keywords
	'major depression'/dd_dt MEDLINE (MeSH) exp antidepressant agents/ *depression/dt *'major depression'/dt PsycINFO exp Antidepressant Drugs/	nct00021528 pharmacotherap* "sequenced treatment alternatives to relieve depression" star*d star-d
Pharmacotherapies – Tricyclic Antidepressants	EMBASE (EMTREE) 'tricyclic antidepressant agent'/de MEDLINE (MeSH) exp antidepressant agents/ Antidepressive Agents, Tricyclic/ *depression/dt *'major depression'/dt PsycINFO exp Antidepressant Drugs/ exp Tricyclic Antidepressant Drugs/	amitriptyline amoxapine anafranil antidepressant* anti-depressant* clomipramine desipramine doxepin imipramine maprotiline norpramin nortriptyline pamelor prudoxin protriptyline silenor Surmontil tofranil tricyclic AND antidepressant* trimipramine vivactil zonalon
Pharmacotherapies – Selective serotonin reuptake inhibitors	EMBASE (EMTREE) 'serotonin uptake inhibitor'/de MEDLINE (MESH) exp serotonin uptake inhibitors/	brisdelle celexa citalopram desvenlafaxine escitalopram fluoxetine fluvoxamine Lexapro Luvox milnacipran mirtazapine nefazodone paroxetine paxil pexeva Prozac remeron sarafem selective serotonin reuptake inhibitor* selfemra sertraline SSRI

Concept	Controlled Vocabulary	Keywords
		viibryd vilazodone Zoloft
Pharmacotherapies – Serotonin– norepinephrine reuptake inhibitors	EMBASE (EMTREE) 'serotonin noradrenalin reuptake inhibitor'/de	Cymbalta duloxetine Effexor fetzima khedezla pristiq savella Serotonin–norepinephrine reuptake inhibitor* SNRI* venlafaxine
Pharmacotherapies – Atypical antipsychotics	EMBASE (EMTREE) 'atypical antipsychotic agent'/de MEDLINE(MESH) Antipsychotic Agents/ PsycINFO exp Neuroleptic Drugs/	abilify atypical antipsychotic* clozapine clozaril fanapt fazaclo Geodon invega latuda olanzapine Risperdal saphris Seroquel ziprasidone zyprexa
Pharmacotherapies – Atypical antidepressants	MEDLINE(MESH) Antidepressive Agents, Second-Generation/	aplenzin atypical antidepressant* brintellix bupropion forfivo mirtazapine nefazodone oleptro remeron trazodone Wellbutrin zyban
Pharmacotherapies – Monoamine oxidase inhibitor	EMBASE (EMTREE) 'monoamine oxidase inhibitor'/de MEDLINE (MeSH) exp Monoamine Oxidase Inhibitors/ PsycINFO	azilect "beta-phenethylhydrazine" eldepryl emsam isocarboxazid marplan monoamine oxidase inhibitor*

Concept	Controlled Vocabulary	Keywords
		MAO MAOI* "MAO inhibitor" "MAO inhibitors" monoamine oxidase A inhibitor monoamine oxidase B inhibitor nardil parnate phenelzine rasagiline selegiline tranylcypromine
Drug Augmentation	PsycINFO Drug Augmentation/	augment*
Pharmacotherapy Follow-Up	EMBASE(EMTREE) 'follow up'/de/mj 'patient care'/exp/mj 'patient scheduling'/de/mj planning'/de/mj 'Treatment Planning'/mj MEDLINE (MeSH) *Continuity of Patient Care/ PsycINFO *"Continuum of Care"/ *Treatment Planning/	(Continuation or Continuum) AND care "follow up" "followed up" "Primary Care-Mental Health Integration" (visit* AND frequen*)
Psychotherapy	EMBASE(EMTREE) 'acceptance and commitment therapy'/de 'behavior therapy'/exp 'cognitive therapy'/exp 'dialectical behavior therapy'/de 'marital therapy'/de 'problem solving'/de 'psychiatric treatment'/exp 'psychotherapy'/exp MEDLINE (MeSH) Acceptance and Commitment Therapy/ exp behavior therapy/ exp Cognitive Therapy/ Couples Therapy/ Problem Solving/ exp Psychotherapy/ PsycINFO exp Cognitive Behavior Therapy/ Dialectical Behavior	"acceptance and commitment" AND therap* ACT behavior* AND therap* behaviour* AND therap* CBT Cognitive* cognitive AND therap* (couple* OR marriage OR marital) AND (therap* OR counseling) dialectical behavior therapy dialectical behaviour therapy dialectical AND therap* Interpersonal AND therap* IPSRT IPT ISRT "problem adaptation" AND therap* "problem solving" AND therap* psychoanalysis* psychodynamic psychotherap*

Concept	Controlled Vocabulary	Keywords
	Therapy/ Interpersonal Psychotherapy/ Exp Marriage Counseling/	
Other Treatments	EMBASE(EMTREE) Ayurveda/de 'bibliotherapy'/de exercise/exp 'herbal medicine'/de 'hypericum perforatum extract'/de hypnosis/de meditation/de mindfulness/de 'phototherapy'/exp 'physical activity'/exp 'recreational therapy'/de 'transcendental meditation'/de 'transcranial magnetic stimulation'/de 'vagus nerve stimulation'/de yoga/de MEDLINE (MeSH) Bibliotherapy/ exp Complementary Therapies/ exp Electric Stimulation Therapy/ exp exercise/ Hypericum/ hypnosis/ Meditation/ Mindfulness/ phototherapy/ transcranial magnetic stimulation/ Vagus Nerve/ Vagus Nerve Stimulation/ yoga/ PsycINFO Alternative Medicine/ bibliotherapy/ exp Creative Arts Therapy/ exp Electrical Brain Stimulation/ exp exercise/ Hypericum Perforatum/ hypnosis/	art AND therap* Ayurved* bibliotherap* CES color therap* colour therap* Cranial electrotherapy stimulation creative AND therap* dance AND therap* education* AND therap* exercis* gestalt AND therap* herbal hypericum hypnosis hypnotic klamath weed light therapy mantra* meditat* meditation* MET microcurrent cranial stimulation milieu AND therap* mindful* mind-body motivational AND therap* movement AND therap* music AND therap* phototherap* play AND therap* psychodrama relaxation rTMS saint johns wort saint john`s wort sjw st johns wort st. john`s wort supportive AND therap* TMS transcranial AND magnetic vagal vagus

Concept	Controlled Vocabulary	Keywords
	exp Medicinal Herbs and Plants/ phototherapy/ physical activity/ transcranial magnetic stimulation/ Vagus Nerve/ yoga/	vns walk* yoga
Limbic System Surgery	EMBASE(EMTREE) 'ablation therapy'/de 'capsulotomy'/de 'limbic system'/de surgery/de MEDLINE (MeSH) exp limbic system/ exp Neurosurgery/ PsycINFO exp limbic system/ exp Neurosurgery/ surgery/	ablative capsulotomy cingulotomy leucotomy limbic surg* tractotomy

d. Search Strategies

Medline/PsycINFO (presented in OVID syntax)

Set Number	Concept	Search Statement
1	MDD	*major depression/ or *Depressive Disorder, Major/ or (depress\$ or melanchol\$ or dysphor\$ or MDD).ti,ab.
2	Collaborative Care	Treatment Planning/ OR Collaboration/ OR Integrated Services/ OR Interdisciplinary Treatment Approach/ OR 'collaborative care' OR (collaborative adj5 care) OR (collaborative adj5 system*) OR (collaborative adj5 model*) OR (integrate* adj5 care) OR (integrate* adj5 system*) OR (integrate* adj5 model*) OR (team* adj5 care) OR (team* adj5 system*) OR (team* adj5 model*) OR (embed* adj5 care) OR (embed* adj5 system*) OR (embed* adj5 model*) OR (co-located adj5 care) OR (co-located adj5 system*) OR (co-located adj5 model*)
3		1 AND 2
4		*Delivery of Health Care, Integrated/og OR *Mental Health Services/og OR *Primary Health Care/og OR *Quality Improvement/og OR *Cooperative Behavior/ OR *Health Services Accessibility/
5		*Quality Control/ or *"Quality of Care"/ or *"Quality of Services"/ OR *Cooperation/
6		"depression care model" OR "depression care models" OR "Collaborative depression care management"
7		(Collocat* adj3 care) OR (integrat* adj3 care)

Set Number	Concept	Search Statement	
8		4 or 5 or 6 or 7	
9		1 and 8	
10	Pharmacotherapy	*depression/dt or *'major depression'/dt	
11		exp Antidepressant Drugs/ OR exp antidepressant agents/ OR antidepressant* OR 'anti-depressant' OR 'anti-depressants'	
12		exp Tricyclic Antidepressant Drugs/ OR Antidepressive Agents, Tricyclic/ OR (tricyclic AND antidepressant*) OR amitriptyline OR amoxapine OR anafanil OR clomipramine OR desipramine OR doxepin OR imipramine OR maprotiline OR norpramin OR nortriptyline OR pamelor OR prudoxin OR protriptyline OR silenor OR Surmontil OR tofranil OR trimipramine OR vivactil OR zonalon	
13		exp serotonin uptake inhibitors/ OR 'selective serotonin reuptake inhibitor' OR 'selective serotonin reuptake inhibitors' OR SSRI OR SSRIs OR brisdelle OR celexa OR citalopram OR desvenlafaxine OR escitalopram OR fluoxetine OR fluvoxamine OR lexapro OR Luvox OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR paxil OR pexeva OR prozac OR remeron OR sarafem OR selfemra OR sertraline OR viibryd OR vilazodone OR zoloft	
14		("Serotonin–norepinephrine reuptake inhibitor" or "Serotonin–norepinephrine reuptake inhibitors" or SNRI or SNRIs or Cymbalta or duloxetine or Effexor or fetzima or khedezla or pristiq or savella or venlafaxine).mp.	
15		exp Neuroleptic Drugs/ or Antipsychotic Agents/ or "atypical antipsychotic".mp. or "atypical antipsychotics".mp. or abilify.mp. or clozapine.mp. or clozaril.mp. or fanapt.mp. or fazaclo.mp. or geodon.mp. or invega.mp. or latuda.mp. or olanzapine.mp. or risperdal.mp. or saphris.mp. or seroquel.mp. or ziprasidone.mp. or zyprexa.mp.	
16		Antidepressive Agents, Second-Generation/ or "atypical antidepressant".mp. or "atypical antidepressants".mp. or aplenzin.mp. or britellix.mp. or bupropion.mp. or forfivo.mp. or mirtazapine.mp. or nefazodone.mp. or oleptro.mp. or remeron.mp. or trazodone.mp. or wellbutrin.mp. or zyban.mp.	
17		exp Monoamine Oxidase Inhibitors/ or "monoamine oxidase inhibitor".mp. or "monoamine oxidase inhibitors".mp. or MAO.mp. or MAOI*.mp. or "MAO inhibitor".mp. or "MAO inhibitors".mp. or "beta-phenethylhydrazine".mp. or "monoamine oxidase A inhibitor".mp. or "monoamine oxidase B inhibitor".mp. or azilect.mp. or eldepryl.mp. or emsam.mp. or isocarboxazid.mp. or marplan.mp. or nardil.mp. or parnate.mp. or phenelzine.mp. or rasagiline.mp. or selegiline.mp. or tranlycypromine.mp.	
18		Drug Augmentation/ OR augment*	
19		10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	
20		1 and 19	
21		Pharmacotherapy Follow-Up	"Primary Care-Mental Health Integration".mp. or *"Continuum of Care"/ or *Continuity of Patient Care/ or ((Continuation or Continuum) adj3 care).mp. or *Treatment Planning/ or "follow up".mp. or "followed up".mp. or (visit* adj3 frequen*).mp.
22			20 and 21

Set Number	Concept	Search Statement	
23	Psychotherapy	exp behavior therapy/ OR (behavior* adj3 therap*) OR (behaviour* adj3 therap*)	
24		exp Cognitive Behavior Therapy/ OR exp Cognitive Therapy/ OR (Cognitive adj3 therap*) OR CBT OR Cognitive*.ti.	
25		Interpersonal Psychotherapy/ OR (Interpersonal adj3 therap*) OR IPSRT OR IPT OR ISRT	
26		exp Psychotherapy/ OR psychotherap* OR psychodynamic OR psychoanalys* OR psychiatr*	
27		Acceptance and Commitment Therapy/ OR "Acceptance and Commitment Therapy" OR ACT OR (acceptance adj2 commitment adj2 therap*)	
28		Problem Solving/ or ("problem solving" adj2 therap*).mp. or ("problem adaptation" adj2 therap*).mp.	
29		Dialectical Behavior Therapy/ OR "dialectical behavior therapy" OR "dialectical behaviour therapy" OR (dialectical adj2 therap*) OR DBT	
30		Couples Therapy/ OR Exp Marriage Counseling/ OR ((couple* OR marriage OR marital) adj2 (therap* OR counseling))	
31		23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	
32		1 and 31	
33		Other Treatments	exp exercise/ OR exercis* OR physical activity/ OR yoga OR walk*
34			exp Electrical Brain Stimulation/ OR microcurrent cranial stimulation OR exp Electric Stimulation Therapy/ OR Cranial electrotherapy stimulation OR MET OR CES
35	(art adj3 therap*) OR (dance adj3 therap*) OR (play adj3 therap*) OR (motivational adj3 therap*) OR exp Creative Arts Therapy/ OR exp Complementary Therapies/ OR (creative adj3 therap*) OR (education* adj3 therap*) OR (gestalt adj3 therap*) OR hypnosis/ OR hypnosis OR hypnotic OR meditat* OR (milieu adj3 therap*) OR (motivational adj3 therap*) OR (movement adj3 therap*) OR (music adj3 therap*) OR psychodrama OR relaxation OR (supportive adj3 therap*)		
36	transcranial magnetic stimulation/ OR (transcranial adj3 magnetic) OR TMS OR rTMS		
37	Alternative Medicine/ OR exp Medicinal Herbs and Plants/ OR herbal OR Hypericum Perforatum OR (john* adj2 wort) OR SJW		
38	Vagus Nerve/ OR Vagus Nerve Stimulation/ OR vagus OR vagal OR vns		
39	33 or 34 or 35 or 36 or 37 or 38		
40	1 and 39		
41	STAR*D Trial		("Sequenced Treatment Alternatives to Relieve Depression" or NCT00021528 or "star-d" or star*d).mp.
42			1 and 41

Set Number	Concept	Search Statement
43	Meditation	Meditation/ OR meditat\$ OR Mindfulness/ OR Mindful\$ OR "mindbody" OR ayurved\$ OR yoga OR yoga/ OR mantra*
44		1 and 43
45	Bibliotherapy	Bibliotherapy/ OR Bibliotherap\$
46		1 and 45
47	St. John's wort	Hypericum Perforatum/ OR sjw OR "klamath weed" OR "saint johns wort" OR "st johns wort" OR "st. johns wort" OR "saint john's wort" OR "st john's wort" OR "st. john's wort" OR hypericum
48		1 and 47
49	Light Therapy	phototherapy/ OR phototherap* OR 'light therapy' OR (color adj3 therap*) OR (colour adj3 therap*) OR (light adj3 therap*)
50		1 and 49
51	Limbic System Surgery	exp limbic system/ OR limbic.mp.
52		surgery/ OR exp Neurosurgery/ OR surg* OR ablative
53		1 and 51 and 52
54		capsulotomy OR cingulotomy OR tractotomy OR leucotomy
55		1 and 54
56		53 or 55
57	Randomized Controlled Trials Search Hedge	((Randomized controlled trials or random allocation or doubleblind method or single-blind method or placebos or cross-over studies).de. or placebo\$.mp. or random\$.ti. or crossover\$.mp. or cross over.mp. or ((singl* or doubl* or tripl* or trebl*) and (blind* or mask* or sham*)),mp. or latin square.mp. or ISRCTN.mp. or ACTRN*.mp. or (NCT* not NCT).mp. or (clinical trials/ and random*.ti.))
58	Systematic Reviews & Meta Analyses Search Hedge	((research synthesis or pooled).mp. or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base\$ or methodol\$ or systematic or quantitative\$ or studies or search\$).mp. and (review/ or review.pt. or literature review/)))
59	RCTs Or Reviews Hedge	57 or 58
60	Combined Interventions for Reviews Search (Collaborative Care, Pharmacotherapy, Psychotherapy, Other Treatments)	9 or 20 or 32 or 40
61		58 and 60

Set Number	Concept	Search Statement
62	Combined Interventions for Trials & Reviews Search (Collaborative Care, Pharmacotherapy Follow-Up, Acceptance & Commitment Therapy, Problem Solving Therapy, Dialectical Therapy, Couples Therapy, Star*D, Meditation, Bibliotherapy, St. John's wort, Light Therapy)	3 or 22 or 27 or 28 or 29 or 30 or 42 or 44 or 46 or 48 or 50
63	Combined Interventions for Trials & Reviews Search (Collaborative Care, Pharmacotherapy Follow-Up, Acceptance & Commitment Therapy, Problem Solving Therapy, Dialectical Therapy, Couples Therapy, Star*D, Meditation, Bibliotherapy, St. John's wort, Light Therapy)	#56 AND #59
64	Limbic System Surgery	56
65	Combine Results Sets	61 or 63 or 64
66	Remove Publication Types	65 not (((("column/opinion" OR "comment/reply" OR dissertation OR editorial OR letter OR book).dt. OR book.pt.) OR (letter/ or editorial/ or news/ or comment/ or case report or case reports/ or note/ or conference paper/) or (letter or editorial or news or comment or case reports or conference abstract\$.pt.)
67	English	limit 66 to english language
68	Date	limit 67 to yr="2006 - 2015"
69	Humans	limit 68 to humans [Limit not valid in PsycINFO; records were retained]
70	Dedupe	remove duplicates from 69

OVID syntax:

- \$ or * = truncation character (wildcard)
- ADJn = search terms within a specified number (n) of words from each other in any order
- / = search as a subject heading (note that terms preceded by an asterisk are searched as a major subject headings)
- exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
- .de. = limit controlled vocabulary heading
- .fs. = floating subheading
- .hw. = limit to heading word
- .md. = type of methodology (PsycINFO)
- .mp. = combined search fields (default if no fields are specified)
- .pt. = publication type
- .ti. = limit to title
- .tw. = limit to title and abstract fields

EMBASE

Set Number	Concept	Search Statement
1	MDD	'depression'/exp/mj OR depress*:ti OR melanchol*:ti OR dysphor*:ti OR mdd:ti,ab
2	Collaborative Care	'patient care'/exp OR 'collaborative care' OR 'patient care planning'/de OR collaborative NEAR/5 care OR collaborative NEAR/5 system* OR collaborative NEAR/5 model* OR integrate* NEAR/5 care OR integrate* NEAR/5 system* OR integrate* NEAR/5 model* OR team* NEAR/5 care OR team* NEAR/5 system* OR team* NEAR/5 model* OR embed* NEAR/5 care OR embed* NEAR/5 system* OR embed* NEAR/5 model* OR 'co-located' NEAR/5 care OR 'co-located' NEAR/5 system* OR 'co-located' NEAR/5 model*
3		#1 AND #2
4	Pharmacotherapy	depression/dd_dt OR 'major depression'/dd_dt
5		'antidepressant agent'/de OR antidepressant* OR 'anti-depressant' OR 'anti-depressants'
6		'tricyclic antidepressant agent'/de OR (tricyclic AND antidepressant*) OR amitriptyline OR amoxapine OR anafranil OR clomipramine OR desipramine OR doxepin OR imipramine OR maprotiline OR norpramin OR nortriptyline OR pamelor OR prudoxin OR protriptyline OR silenor OR Surmontil OR tofranil OR trimipramine OR vivactil OR zonalon
7		'serotonin uptake inhibitor'/de OR 'selective serotonin reuptake inhibitor' OR 'selective serotonin reuptake inhibitors' OR brisdelle OR celexa OR citalopram OR desvenlafaxine OR escitalopram OR fluoxetine OR fluvoxamine OR lexapro OR Luvox OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR paxil OR peveva OR prozac OR remeron OR sarafem OR selfemra OR sertraline OR viibryd OR vilazodone OR zolof
8		'serotonin noradrenalin reuptake inhibitor'/de OR 'Serotonin–norepinephrine reuptake inhibitor' OR 'Serotonin–norepinephrine reuptake inhibitors' OR Cymbalta OR duloxetine OR Effexor OR fetzima OR khedezla OR pristin OR savella OR venlafaxine
9		'atypical antipsychotic agent'/de OR 'atypical antipsychotic' OR 'atypical antipsychotics' OR abilify OR clozapine OR clozaril OR fanapt OR fazaclo OR geodon OR invega OR latuda OR olanzapine OR risperdal OR saphris OR seroquel OR ziprasidone OR zyprexa
10		'atypical antidepressant' OR 'atypical antidepressants' OR aplenzin OR brintellix OR bupropion OR forfivo OR mirtazapine OR nefazodone OR oleptro OR remeron OR trazodone OR wellbutrin OR zyban
11		'monoamine oxidase inhibitor'/de OR 'monoamine oxidase inhibitor' OR 'monoamine oxidase inhibitors' OR MAO OR MAOI* OR "MAO inhibitor" OR "MAO inhibitors" OR "beta-phenethylhydrazine" OR 'monoamine oxidase A inhibitor' OR 'monoamine oxidase B inhibitor' OR azilect OR eldepryl OR emsam OR isocarboxazid OR marplan OR nardil OR parnate OR phenelzine OR rasagiline OR selegiline OR tranlylcypromine
12		#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13		#1 AND #12

Set Number	Concept	Search Statement	
14	Psychotherapy	'behavior therapy'/exp OR (behavior* NEAR/3 therap*):ab,ti OR (behaviour* NEAR/3 therap*):ab,ti	
15		'cognitive therapy'/exp OR (Cognitive NEAR/3 therap*):ti,ab OR CBT:ti,ab OR Cognitive*:ti	
16		(Interpersonal NEAR/3 therap*):ti,ab OR IPSRT OR IPT OR ISRT	
17		'psychiatric treatment'/exp OR 'psychotherapy'/exp OR psychotherap*:ab,ti OR psychodynamic:ab,ti OR psychoanalys*:ab,ti	
18		'behavior therapy'/exp OR (behavior* NEAR/3 therap*):ab,ti OR (behaviour* NEAR/3 therap*):ab,ti	
19		'cognitive therapy'/exp OR (Cognitive NEAR/3 therap*):ti,ab OR CBT:ti,ab OR Cognitive*:ti	
20		(Interpersonal NEAR/3 therap*):ti,ab OR IPSRT OR IPT OR ISRT	
21		'psychiatric treatment'/exp OR 'psychotherapy'/exp OR psychotherap*:ab,ti OR psychodynamic:ab,ti OR psychoanalys*:ab,ti	
22		'acceptance and commitment therapy'/de OR "acceptance and commitment" NEAR/3 therap* OR "problem solving" NEAR/3 therap* OR "problem adaptation" NEAR/3 therap*	
23		'problem solving'/de OR 'problem solving' NEAR/2 therap* OR 'problem adaptation' NEAR/2 therap* AND [2008-2015]/py	
24		'dialectical behavior therapy'/de OR "dialectical behavior therapy" OR "dialectical behaviour therapy" OR dialectical NEAR/2 therap* OR DBT AND [2007-2015]/py	
25		'marital therapy'/de OR ((couple* OR marriage OR marital) NEAR/2 (therap* OR counseling)) AND [2008-2015]/py	
26		'acceptance and commitment therapy'/de OR "Acceptance and Commitment Therapy" OR ACT OR (acceptance NEAR/2 commitment NEAR/2 therap*) AND [2007-2015]/py	
27		#14 OR #15 OR #16 OR #17 OR #18 OR 19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	
28		#1 AND #27	
29		MCS	microcurrent cranial stimulation OR Cranial electrotherapy stimulation
30			#1 AND #29
31		STAR*D Trial	star*d OR 'sequenced treatment alternatives to relieve depression' OR nct00021528
32		#1 AND #31	
33	Meditation	'transcendental meditation'/de OR meditation/de OR mindfulness/de OR meditat* OR meditation* OR mindful* OR "mind-body" OR Ayurved* OR Ayurveda/de OR yoga OR yoga/de OR mantra*	
34		#1 AND #33	
35	Bibliotherapy	'bibliotherapy'/de OR bibliotherap*	
36		#1 AND #35	
37	St. John's wort	'hypericum perforatum extract'/de OR sjw OR 'klamath weed' OR 'saint johns wort' OR 'st johns wort' OR 'st. johns wort' OR 'saint john's wort' OR 'st john's wort' OR 'st. john's wort' OR hypericum	

Set Number	Concept	Search Statement
38		#1 AND #37
39	Light Therapy	'phototherapy'/exp OR phototherap* OR 'light therapy' OR color NEAR/3 therap* OR colour NEAR/3 therap* OR light NEAR/3 therap*
40		#1 AND #39
41	Pharmacotherapy Follow-up	'follow up'/de/mj OR 'patient care planning'/de/mj OR 'patient scheduling'/de/mj OR 'follow up' OR 'followed up' OR "Primary Care-Mental Health Integration" OR 'patient care'/exp/mj OR 'Treatment Planning'/mj OR (visit* NEAR/3 frequen*) OR ((Continuity OR Continuation or Continuum) NEAR/3 care)
42		#13 AND #41
43	Limbic System Surgery	'limbic system'/de OR limbic
44		surgery/de OR 'ablation therapy'/de OR surg* OR ablative
45		#1 AND #43 AND #44
46		'capsulotomy'/de OR capsulotomy OR cingulotomy OR tractotomy OR leucotomy
47		#1 AND #46
48		#45 OR #47
49	Collaborative Care Models	'integrated health care system'/mj OR 'mental health service'/mj OR 'Primary Health Care'/mj OR 'total quality management'/mj OR cooperation/exp/mj OR 'health care delivery'/exp/mj
50		"depression care model" OR "depression care models" OR "Collaborative depression care management"
51		collocat* NEAR/3 care OR integrat* NEAR/3 care
52		#49 OR #50 OR #51
53		#1 AND #52
54	Other Treatments	exercise/exp OR exercis* OR 'physical activity'/exp
55		'bibliotherapy'/de OR bibliotherap*
56		'phototherapy'/exp OR phototherap* OR 'light therapy' OR color NEAR/3 therap* OR colour NEAR/3 therap*
57		'vagus nerve stimulation'/de OR vagus OR vagal OR vns
58		'herbal medicine'/de OR herbal OR 'hypericum perforatum extract'/de OR john* NEAR/2 wort OR SJW
59		'transcranial magnetic stimulation'/de OR transcranial NEAR/3 magnetic OR TMS OR rTMS
60		art NEAR/3 therap* OR dance NEAR/3 therap* OR play NEAR/3 therap* OR motivational NEAR/3 therap* OR 'recreational therapy'/de OR creative NEAR/3 therap* OR education* NEAR/3 therap* OR gestalt NEAR/3 therap* OR hypnosis/de OR hypnosis OR hypnotic OR meditat* OR milieu NEAR/3 therap* OR motivational NEAR/3 therap* OR movement NEAR/3 therap* OR music NEAR/3 therap* OR psychodrama OR relaxation OR supportive NEAR/3 therap*
61		#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60
62		#1 AND #61

Set Number	Concept	Search Statement
63	Randomized Controlled Trials Search Hedge	'randomized controlled trial'/exp OR 'randomization'/de OR 'double blind procedure'/de OR 'single blind procedure'/de OR 'placebo'/de OR 'latin square design'/de OR 'crossover procedure'/de OR 'triple blind procedure'/de OR 'controlled study'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'intermethod comparison'/de OR 'parallel design'/de OR 'control group'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'major clinical study'/de OR 'evaluation study'/exp OR random*:de OR random*:ti OR placebo* OR (singl* OR doubl* OR tripl* OR trebl* AND (dummy OR blind OR sham)) OR 'latin square' OR isrctn* OR actrn* OR (nct* NOT nct)
64	Systematic Reviews & Meta Analyses Search Hedge	'research synthesis' OR pooled OR 'systematic review'/de OR 'meta analysis'/de OR ('evidence base' OR 'evidence based' OR methodol* OR systematic OR quantitative* OR studies OR search* AND ('review'/de OR review/it))
65	RCTs Or Reviews Hedge	#64 OR #65
66	Combined Interventions for Reviews Search (Collaborative Care, Pharmacotherapy, Psychotherapy, Other Treatments)	#3 OR #13 OR #28 OR #53 OR #62
67		#64 AND #66
68	Combined Interventions for Trials & Reviews Search (Problem Solving Therapy, Dialectical Behavioral Therapy, Couples Therapy, Acceptance & Commitment Therapy, Bibliotherapy, Meditation, STAR*D trial, MCS, St. John's wort)	#23 OR #24 OR #25 OR #30 OR #31 OR #34 OR #36 OR #38
69		#65 AND #68
70	Light Therapy & Follow-Up RCTs	#40 OR #42
71		#63 AND #70
72	Combine Results Sets	#48 OR #67 OR #69 OR #71
73	Remove Publication Types	#72 NOT ('conference paper'/exp OR 'case study'/exp AND ('case report'/de OR 'book'/de OR 'editorial'/de OR 'erratum'/de OR 'letter'/de OR 'note'/de OR 'short survey'/de) OR book:it OR conference:it OR editorial:it OR erratum:it OR letter:it OR note:it OR 'short survey':it OR book:pt OR 'conference proceeding':pt)
74	Limits	#73 AND [humans]/lim AND [english]/lim AND [2006-2015]/py

EMBASE.com Syntax:

- * = truncation character (wildcard)
- NEAR/n = search terms within a specified number (n) of words from each other in any order
- NEXT/n = search terms within a specified number (n) of words from each other in the order specified
- / = search as a subject heading

- exp = “explodes” controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary’s hierarchy)
- mj = denotes a term that has been searched as a major subject heading
- :de = search in the descriptors field (controlled terms and keywords)
- :lnk = floating subheading
- :it,pt. = source item or publication type
- :ti. = limit to title
- :ti,ab. = limit to title and abstract fields

PUBMED (PreMEDLINE)

Set Number	Concept	Search Statement
1	MDD	"depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms] OR depress*[ti] OR melanchol*[ti] OR dysphor*[ti] OR MDD[tiab]
2	Pharmacotherapy	antidepressant* OR antidepressants OR antidepressant OR anti-depressants
3		amitriptyline OR amoxapine OR anafranil OR clomipramine OR desipramine OR doxepin OR imipramine OR maprotiline OR norpramin OR nortriptyline OR pamelor OR prudoxin OR protriptyline OR silenor OR Surmontil OR tofranil OR trimipramine OR vivactil OR zonalon
4		selective serotonin reuptake inhibitor OR selective serotonin reuptake inhibitors OR brisdelle OR celexa OR citalopram OR desvenlafaxine OR escitalopram OR fluoxetine OR fluvoxamine OR lexapro OR Luvox OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR paxil OR pexeva OR prozac OR remeron OR sarafem OR selfemra OR sertraline OR viibryd OR vilazodone OR zoloft
5		Serotonin–norepinephrine reuptake inhibitor OR Serotonin–norepinephrine reuptake inhibitors OR Cymbalta OR duloxetine OR Effexor OR fetzima OR khedezla OR pristiq OR savella OR venlafaxine
6		atypical antipsychotic OR atypical antipsychotics OR abilify OR clozapine OR clozaril OR fanapt OR fazaclo OR geodon OR invega OR latuda OR olanzapine OR risperdal OR saphris OR seroquel OR ziprasidone OR zyprexa
7		atypical antidepressant OR atypical antidepressants OR aplenzin OR britellix OR bupropion OR forfivo OR mirtazapine OR nefazodone OR oleptro OR remeron OR trazodone OR wellbutrin OR zyban
8		monoamine oxidase inhibitor OR monoamine oxidase inhibitors OR MAO OR MAOI* OR "MAO inhibitor" OR "MAO inhibitors" OR "betaphenethylhydrazine" OR 'monoamine oxidase A inhibitor' OR "monoamine oxidase B inhibitor" OR azilect OR eldepryl OR emsam OR isocarboxazid OR marplan OR nardil OR parnate OR phenelzine OR rasagiline OR selegiline OR tranylcypromine

Set Number	Concept	Search Statement
9		drug OR drugs OR pharmacotherap* OR pharmacologic*
10		#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11		#1 AND #10
12	Psychotherapy	((behavior* OR behaviour*) AND (therapy OR therapies OR therapist OR therap*)) OR dialect*
13		(cognitive AND (therapy OR therapies OR therapist OR therap*)) OR CBT
14		(Interpersonal AND (therapy OR therapies OR therapist OR therap*)) OR IPSRT OR IPT OR ISRT
15		psychiatric OR psychotherapy OR psychodynamic OR psychoanalysis
16		#12 OR #13 OR #14 OR #15
17		#1 AND #16
18	Other Therapies	("problem solving" AND therap*) OR ("problem adaptation" AND therap*) AND 2008:2015[dp]
19		("dialectical behavior therapy" OR "dialectical behaviour therapy" OR (dialectical AND therap*) OR DBT) AND 2007:2015[dp]
20		((couple* OR marriage OR marital) AND (therap* OR counseling)) AND 2008:2015[dp]
21		(Acceptance and Commitment Therapy/ OR "Acceptance and Commitment Therapy" OR ACT OR (acceptance AND commitment AND therap*)) AND 2007:2015[dp]
22		#18 OR #19 OR #20 OR #21 OR #22
23		#1 AND #22
24	Other Treatments	exercis* OR physical activity OR yoga OR walk*
25		bibliotherap*
26		phototherapy OR light therapy OR color therapy OR colour therapy
27		vagus OR vagal OR vns
28		herbal OR hypericum perforatum OR (john* AND wort) OR SJW
29		Vagus Nerve/ OR Vagus Nerve Stimulation/ OR vagus OR vagal OR vns
30		(transcranial AND magnetic) OR TMS OR rTMS
31		((art OR dance OR family OR play OR motivational OR recreational OR creative OR education* OR gestalt OR milieu OR motivational OR movement OR music OR relaxation OR supportive) AND (therapy OR therap*)) OR psychodrama OR relaxation OR hypnosis OR hypnotic OR meditation OR transactional OR "problem solving"
32		#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
33		#1 AND #32

Set Number	Concept	Search Statement
34	Cranial Electric Stimulation	"skull"[MeSH Terms] OR "skull"[All Fields] OR "cranial"[All Fields]
35		"electric stimulation"[MeSH Terms] OR ("electric"[All Fields] AND "stimulation"[All Fields]) OR "electric stimulation"[All Fields] OR ("electrical"[All Fields] AND "stimulation"[All Fields]) OR "electrical stimulation"[All Fields] OR ("electrotherapy"[All Fields] AND "stimulation"[All Fields]) OR "electrotherapy stimulation"[All Fields] OR "CES"[All Fields]
36		#1 AND #34 AND #35
37	Limbic System Surgery	limbic system
38		Neurosurg* OR surg* OR ablative
39		#1 AND #37 AND #38
40		capsulotomy OR cingulotomy OR tractotomy OR leucotomy
41		#1 AND #40
42		#39 OR #41
43	Randomized Controlled Trials Search Hedge	(Random*[tiab] OR randomized[tiab] OR RCT*[tiab])
44	Other Therapies RCTs Set	#23 AND #43
45	Combined Interventions for Reviews Search (Pharmacotherapy, Psychotherapy, Other Treatments)	#11 OR #17 OR #33
46		#45 AND Filters activated: Meta-Analysis, Review, Systematic Reviews
47	Limbic System Surgery & Cranial Electric Stimulation	#42 OR #36
48	Combine Results Sets	#44 OR #46 OR #47
49	Remove Publication Types	#48 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR "Textbooks" [pt] OR "Book Reviews"[pt] OR "Book Illustrations"[pt])
50	English	#49 AND Filters activated: Publication date from 2006/01/01 to 2015/12/31, English
51	Subsets	#50 AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb])

PubMed syntax:

- [Mesh] = search as a subject heading
- [majr] = search as a major subject heading
- * = truncation character (wildcard)
- [ti] = limit to title field
- [tiab] = limit to title and abstract fields
- [tw] = text word

C. The Face-to-Face Meeting

In consultation with the COR, the Champions, the Work Group, and the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group members on June 2-5, 2015. These experts were gathered to develop and draft the clinical recommendations for an update to the 2009 MDD CPG. Lewin presented findings from the evidence review of the key questions in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to categorize recommendations from the 2009 MDD CPG. The members also developed new clinical practice recommendations not presented in the 2009 MDD CPG, based on the 2015 evidence review. The subject matter experts were divided into two smaller subgroups at this meeting.

As the Work Group members drafted clinical practice recommendations, they also assigned a grade for each recommendation based on a modified GRADE and USPSTF methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

In addition to developing recommendations during the face-to-face meeting, the Work Group members also revised the 2009 MDD CPG algorithms to reflect the new and amended recommendations. They discussed the available evidence as well as changes in clinical practice since 2009, as necessary, to update the algorithms.

D. Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[\[195\]](#)

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate:
 - Resource Use
 - Equity
 - Acceptability
 - Feasibility
 - Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life, decreased

resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations for MDD, conducted by ECRI, assessed the confidence in the quality of the evidence base and assigned a rate of “High,” “Moderate,” “Low,” or “Very Low.”

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients’ perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term “values” has the closest connotation to these processes. For others, the connotation of “preferences” best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having “similar values,” “some variation,” or “large variation” in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient’s values and preferences?

- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example statin use in the frail elderly and others with multiple co-occurring conditions may not be effective and depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility and subgroup considerations require similar judgments around the practicality of the recommendation.

The framework below was used by the Work Group to guide discussions on each domain.

Table A-3. Evidence to Recommendation Framework

Decision Domain	Judgment
Balance of desirable and undesirable outcomes	
<ul style="list-style-type: none"> ▪ Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? ▪ Are the desirable anticipated effects large? ▪ Are the undesirable anticipated effects small? ▪ Are the desirable effects large relative to undesirable effects? 	<ul style="list-style-type: none"> ▪ Benefits outweigh harms/burden ▪ Benefits slightly outweigh harms/burden ▪ Benefits and harms/burden are balanced ▪ Harms/burden slightly outweigh benefits ▪ Harms/burden outweigh benefits
Confidence in the quality of the evidence	
<ul style="list-style-type: none"> ▪ Is there high or moderate quality evidence that answers this question? ▪ What is the overall certainty of this evidence? 	<ul style="list-style-type: none"> ▪ High ▪ Moderate ▪ Low ▪ Very low
Values and preferences	
<ul style="list-style-type: none"> ▪ Are you confident about the typical values and preferences and are they similar across the target population? What are the patient’s values and preferences? Are the assumed or identified relative values similar across the target population? 	<ul style="list-style-type: none"> ▪ Similar values ▪ Some variation ▪ Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	
<ul style="list-style-type: none"> ▪ Are the resources worth the expected net benefit from the recommendation? ▪ What are the costs per resource unit? ▪ Is this intervention generally available? ▪ Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? ▪ Is there lots of variability in resource requirements across settings? 	<ul style="list-style-type: none"> ▪ Various considerations

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains.^[195] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is

low.[196] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, “Strong” or “Weak.” A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or “We recommend offering this option ...”)
- Weak For (or “We suggest offering this option ...”)
- Weak Against (or “We suggest not offering this option ...”)
- Strong Against (or “We recommend against offering this option ...”)

Note that weak (For or Against) recommendations may also be termed “Conditional,” “Discretionary,” or “Qualified.” Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

E. Recommendation Categorization

a. Recommendation Categories and Definitions

For use in the 2016 MDD CPG, a set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE, UK). These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated. The categories and definitions can be found in Table A-4.

Table A-4. Recommendation Categories and Definitions

Evidence Reviewed*	Recommendation Category*	Definition*
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012) [16] and Garcia et al. (2014) [17]

b. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether or not they were based on an updated review of the evidence. If evidence was reviewed, recommendations could be categorized as “New-added,” “New-replaced,” “Not changed,” “Amended,” or “Deleted.”

“Reviewed, New-added” recommendations were original, new recommendations that were not in the 2009 MDD CPG. “Reviewed, New-replaced” recommendations were in the previous version of the guideline, but were modified to align with the updated review of the evidence. These recommendations could have also included clinically significant changes to the previous version. Recommendations categorized as “Reviewed, Not changed” were carried forward from the previous version of the CPG unchanged.

To maintain consistency between 2009 recommendations, which were developed using the USPSTF methodology, and 2016 recommendations, which were developed using the GRADE methodology, it was necessary to modify the 2009 recommendations to include verbiage to signify the strength of the recommendation (e.g., “We recommend” vs. “We suggest”). Because the 2009 recommendations inherently needed to be modified at least slightly to include this language, the “Not changed” category was not used. For recommendations carried forward to the updated CPG with review of the evidence and slightly modified wording, the “Reviewed, Amended” recommendation category was used. This allowed for the wording of the recommendation to reflect GRADE methodology as well as for any other non-substantive (i.e., not clinically meaningful) language changes deemed necessary.

Recommendations could have also been designated “Reviewed, Deleted.” These were recommendations from the previous version of the CPG that were not brought forward to the updated guideline after review of the evidence. This occurred if the evidence supporting the recommendations was out of date, to the extent that there was no longer any basis to recommend a particular course of care and/or new evidence suggests a shift in care, rendering recommendations in the previous version of the guideline obsolete.

c. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous version of the CPG without a systematic review of the evidence. Due to time and budget constraints, the update of the MDD CPG could not review all available evidence on management of MDD, but instead focused its key questions on areas of new or updated scientific research or areas that were not previously covered in the CPG.

For areas of research that have not changed, and for which recommendations made in the previous version of the guideline were still relevant, recommendations could have been carried forward to the updated guideline without an updated systematic review of the evidence. These recommendations were categorized as “Not reviewed.” If evidence was not reviewed, recommendations could have been categorized as “Not changed,” Amended,” or “Deleted.”

“Not reviewed, Not changed” recommendations refer to recommendations from the previous version of the MDD CPG that were carried forward unchanged to the updated version. The category of “Not reviewed, Amended” was used to designate recommendations that were modified from the 2009 CPG with the updated GRADE language, as explained above.

Recommendations could also have been categorized as “Not reviewed, Deleted” if they were determined to be out of scope. A recommendation was out of scope if it pertained to a topic (i.e., population, care setting, treatment, condition) outside of the scope for the updated CPG as defined by the Work Group. Deleted recommendations from the previous version of the guideline should no longer be followed once the updated version of the guideline has been published.

The categories for the recommendations included in the 2016 version of the guideline are noted in the Recommendations. The categories for the recommendations from the 2009 MDD CPG are noted in [Appendix F](#).

F. Drafting and Submitting the Final Clinical Practice Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations and/or to update discussion sections from the 2009 MDD CPG to support the amended “carried forward” recommendations. The Work Group also considered tables, appendices, and other sections from the 2009 MDD CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithms, as necessary.

After developing the initial draft of the updated CPG, an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG

were posted on a wiki website for a period of 14-20 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group and appropriate revisions were made to the CPG.

Draft 3 of the CPG was made available for peer review and comment. This process is described in [Peer Review Process](#). After revisions were made based on the feedback received during the peer review and comment period, the Champions presented the CPG to the EBPWG for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The Work Group also produced a set of guideline toolkit materials which included a provider summary, pocket card, and a patient summary. The final 2016 MDD CPG was submitted to the EBPWG in April 2016.

Appendix B: Quick Guide to the Patient Health Questionnaire (PHQ)

A. Purpose

The Patient Health Questionnaire (PHQ) is designed to facilitate the recognition and diagnosis of depressive disorders in primary care patients. The PHQ-2 is used as a screening tool for depression whereas the PHQ-9 serves as an indicator of depression severity or response to treatment for patients with a depressive disorder. The instrument can be used both as a continuous measure of severity but also to align with diagnostic criteria. The instrument should not be used in isolation to make a diagnosis without considering other aspects of the assessment including whether the symptoms are better accounted for by another disorder (e.g., PTSD, hypothyroidism).

B. Scoring the PHQ-9

a. Using the PHQ-9 as a Measure of Severity

This is calculated by assigning scores to the response categories for the question, “Over the last 2 weeks, how often have you been bothered by any of the following?” A blank assessment can be found in [Table B-2](#), while an example of this scored assessment can be found in [Table B-3](#). The response categories “not at all,” “several days,” “more than half the days,” and “nearly every day,” correspond to scores of 0, 1, 2, and 3 respectively. The Index is the sum of the scores for the nine items, and ranges from 0 to 27. Scores of 10, 15, and 20 represent cut-points for mild, moderate, and severe MDD, respectively ([Table B-1](#)). Sensitivity to change has also been confirmed. A score of 10 or more has a sensitivity of 88% and a specificity of 88% for major depression.^[45]

b. PHQ-9 Scoring Instructions:

Count the number (#) of boxes checked in a column. Multiply those numbers by the value indicated below, and then add the subtotal to produce a total score. The possible range is 0-27. Use the table below to interpret the PHQ-9 score.

Not at all (#) _____ x 0 = _____

Several days (#) _____ x 1 = _____

More than half the days (#) _____ x 2 = _____

Nearly every day (#) _____ x 3 = _____

Total score: _____

Table B-1: Classification of MDD Symptoms Severity and Risk Modifiers

Severity Level	PHQ-9 Total Score	Number of Symptoms According to DSM-5	Functional Impairment
Mild	10-14	2	Mild
Moderate	15-19	3	Moderate
Severe	≥20	4 or 5	Severe
Modifiers			
Complications	Co-occurring PTSD, SUD, psychosis, suicide risk, mania, significant social stressors, war-related conditions, significant anxiety		
Chronicity	More than two years of symptoms despite treatment		
Treatment-Resistant Depression	At least two adequate treatment trials and lack of full response to each [96]		

c. Using the PHQ-9 as a Presumptive Diagnostic Tool

Since the questionnaire relies on patient self-report, definitive diagnoses must be verified by the clinician, taking into account how well the patient understood the questions in the questionnaire, as well as other relevant information from the patient, his or her family, or other sources.

d. Interpreting the PHQ

To facilitate interpretation of the patient's responses, all clinically significant responses are found in the column farthest to the right in the PHQ-9 (the only exception is for suicidal ideation when diagnosing a depressive syndrome). Using the PHQ-9 to help determine symptom severity can serve as a good assessment tool, as it aligns with the DSM-5 diagnostic criteria for MDD.

PHQ-9 Consistent with DSM-5

Major Depressive Episode if #a or b and five or more of #a-i are at least “more than half the days” (count #i if present at all) in the PHQ-9 nine symptom checklist (Tables B-1 and B-3)

Other Depressive Syndrome if #a or b and two, three, or four of #a-i are at least “more than half the days” (count #i if present at all) in the PHQ-9 nine symptom checklist (Tables B-1 and B-3)

Note: The diagnoses of MDD requires ruling out a history of a manic episode (Bipolar Disorder) and a physical disorder, medication or other drug as the biological cause of the depressive symptoms. In the context of bereavement or other significant loss, symptoms consistent with a major depression can occur, and the diagnosis of MDD is considered if there is indication the symptoms are distinguished from normal response to loss given the individual's history, cultural norms, and the context of the loss.

e. Additional Clinical Considerations

After making a provisional diagnosis with the PHQ-9, there are additional clinical considerations that may affect decisions about management and treatment.

- Have current symptoms been triggered by a psychosocial stressor(s)?

- What is the duration of the current disturbance and has the patient received any treatment for it?
- To what extent are the patient’s symptoms impairing his or her usual work and activities?
- Is there a history of similar episodes, and were they treated?
- Is there a family history of similar conditions?

f. Interpreting the PHQ-9 to Make a Provisional Diagnosis

To facilitate interpretation of patient responses, all clinically significant responses in [Tables B-2](#) and [B-3](#) are found in the columns farthest to the right. Any symptom endorsed as being present at least “more than half the days” counts toward a DSM-5 diagnosis. (The only exception is for suicidal ideation which counts toward a DSM-5 diagnosis if endorsed as being present “several days” or more.)

[Table B-2](#) includes an unscored PHQ-9 assessment with the corresponding point values for each response. Underneath [Table B-2](#) is a follow-up question included in the assessment.

Table B-2: Nine Symptom Checklist (PHQ-9)

	Over the last 2 weeks, how often have you been bothered by any of the following?	Not at all	Several days	More than half the days	Nearly every day
a	Little interest or pleasure in doing things?	0	1	2	3
b	Feeling down, depressed, or hopeless?	0	1	2	3
c	Trouble falling or staying asleep, or sleeping too much?	0	1	2	3
d	Feeling tired or having little energy?	0	1	2	3
e	Poor appetite or overeating?	0	1	2	3
f	Feeling bad about yourself—or that you are a failure or have let yourself or your family down?	0	1	2	3
g	Trouble concentrating on things, such as reading the newspaper or watching television?	0	1	2	3
h	Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual?	0	1	2	3
i	Thoughts that you would be better off dead or of hurting yourself in some way?	0	1	2	3
For office coding: Total Score = ____ + ____ + ____ + ____					

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

g. Example of Diagnosing Major Depressive Disorder and Calculating PHQ-9 Depression Severity

The following is an example of how MDD can be assessed in a patient using the PHQ-9 to calculate depression severity.

Patient: A 43-year-old woman who looks sad and complains of fatigue for the past month.

Table B-3. PHQ-9 Screening Example

	Over the last 2 weeks, how often have you been bothered by any of the following?	Not at all	Several days	More than half the days	Nearly every day
		(0)	(1)	(2)	(3)
a	Little interest or pleasure in doing things?				X
b	Feeling down, depressed, or hopeless?		X		
c	Trouble falling or staying asleep, or sleeping too much?			X	
d	Feeling tired or having little energy?				X
e	Poor appetite or overeating?		X		
f	Feeling bad about yourself—or that you are a failure or have let yourself or your family down?			X	
g	Trouble concentrating on things, such as reading the newspaper or watching television?				X
h	Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual?	X			
i	Thoughts that you would be better off dead or of hurting yourself in some way?		X		
FOR OFFICE CODING: Major Depressive Episode if #a or b and five or more of #a-i are at least “More than half the days” (count #i if present at all). Other Depressive Syndrome if #a or b and two, three, or four of #a-i are at least “More than half the days” (count #i if present at all).					

Interpretation: The severity score = 16 and represents moderately severe depression likely requiring treatment. Using the answers as a diagnostic tool, the criteria for a presumed Major Depressive Episode are met since she checked #a “nearly every day” and five of items #a to i were checked “more than half the days” or “nearly every day”, as indicated in [Table B-3](#). Note that #i, suicidal ideation, is counted whenever it is present.

In this case, the diagnosis of MDD was made since questioning by the physician indicated no history of a manic episode; no evidence that a physical disorder, medication, or other drug caused the depression; and no indication that the depressive symptoms were normal bereavement. Questioning about the suicidal ideation indicated no significant suicidal potential.

Appendix C: Pharmacotherapy

Table C-1: Antidepressant Dosing¹ and Monitoring [197]

Class	Agent	Initial Dose	Titration Schedule ²	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
SSRIs	Citalopram	20 mg once a day	20 mg weekly	40 mg; 20 mg geriatric	10-20 mg once a day	Avoid: CrCl <20 ml/min	↓ dose	C
	Escitalopram	10 mg once a day	10 mg weekly	20 mg	5-10 mg once a day	Avoid: CrCl <20 ml/min	10 mg once a day	C
	Fluoxetine	20 mg once a day	20 mg every 2 weeks	80 mg	10 mg once a day	↓ dose and/or ↓ frequency	↓ dose 50%	C
	Fluoxetine weekly	90 mg once a week	N/A	90 mg	90 mg once a week	No change	Avoid	C
	Paroxetine	20 mg once a day	20 mg weekly	50 mg	10 mg once a day	10 mg once a day	10 mg once a day	D
	Paroxetine CR	25 mg once a day	12.5 mg weekly	62.5 mg; 50 mg geriatric	12.5 mg; once a day	12.5 mg once a day	12.5 mg once a day	D
	Sertraline	50 mg once a day	50 mg weekly	200 mg	25 mg once a day	25 mg once a day	↓ dose	C
	Vilazodone	10 mg once a day	10 mg weekly	20-40 mg	5 mg	No change	No change	C

¹ All doses oral except selegiline patch

² Recommended minimum time between dose increases

Class	Agent	Initial Dose	Titration Schedule ²	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
SNRIs	Duloxetine	20-30 mg twice a day	20-30 mg weekly	60 mg	20 mg once or twice a day	Avoid if CrCl <30 ml/min	Avoid	C
	Venlafaxine IR	37.5 mg twice a day	75 mg weekly	225-375 mg	25mg once or twice a day	↓ dose based on CrCl	↓ dose 50%	C
	Venlafaxine XR	75 mg once a day	75 mg weekly	225 mg	37.5-75 mg once a day	↓ dose based on CrCl	↓ dose 50%	C
	Levomilnacipran	20 mg once a day	20-40 mg every 2 days	120 mg	Refer to adult dosing, Consider CrCl	Max doses less if CrCl <60ml/min	No change	C
	Desvenlafaxine	50 mg once a day	Unnecessary	100 mg; no benefit at doses >50 mg per day	Consider CrCl	CrCl <30 ml/min, 25mg once daily	No change	C
5-HT3 receptor antagonist	Vortioxetine	10 mg once a day	10 mg once daily	5-20mg	5-20 mg once a day	No change	Severe: not recommended	C
NDRIs	Bupropion IR	100 mg twice a day	100 mg weekly	450 mg	37.5mg twice a day	Has not been studied	Severe: 75 mg/day	C
	Bupropion SR	150 mg once a day	150 mg weekly	200 mg twice daily	100 mg once a day		100 mg once a day or 150 mg every other day; Mod to severe: use with extreme caution	C
	Bupropion XR	150 mg once a day	150 mg weekly	450 mg	150 mg once a day		C	

Class	Agent	Initial Dose	Titration Schedule ²	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
5-HT ₂ receptor antagonist	Trazodone	50 mg three times a day	50 mg weekly	600 mg	25-50 mg at bedtime	Has not been studied	Unknown	C
	Nefazodone	100 mg twice a day	100 mg weekly	600 mg	50 mg twice a day	No change	Avoid	C
Noradrenergic antagonist	Mirtazapine	15 mg daily at bedtime	15 mg weekly	45 mg	7.5 mg at bedtime	Caution in renal impairment	Cl ↓ 30%	C
TCAs	Amitriptyline	25-50 mg daily single dose at bedtime or in divided doses	Weekly	300 mg	10-25 mg at bedtime	No change	Lower dose and slower titration recommended	C
	Imipramine	25 mg 1- 4 times a day	Weekly	300 mg	10-25 mg at bedtime	No change		Unclassified
	Nortriptyline	25 mg 3-4 times a day	Weekly	150 mg	30-50 mg/day	No change		Unclassified
	Desipramine	25-50 mg once daily or in divided doses	Weekly	300 mg; 150 mg geriatric	10-25 mg once a day	No change		Unclassified
	Doxepin	25-50 mg daily at bedtime or twice a day	Weekly	300 mg	Low dose, once daily	No change		C

Class	Agent	Initial Dose	Titration Schedule ²	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
MAOIs	Isocarboxazid	10 mg twice a day	10 mg/day every 2-4 days to 40 mg/day. After first week, may increase by up to 20 mg/week to a maximum of 60 mg/day.	60 mg	10 mg twice a day	Avoid in any renal impairment. Contraindicated in severe	Contraindicated in patients with a history of liver disease or abnormal LFTs	C
	Phenelzine	15 mg 3 times a day	Increase rapidly, based on patient tolerance, to 60-90 mg/day	90 mg; 60 mg geriatric	7.5 mg once a day	Avoid if severe	Avoid	Undetermined
	Selegiline patch	6 mg/24 hours	3 mg/24 hours every 2 weeks	12 mg/24 hours	6 mg/24 hours	Use in patients with a CrCl <15 ml/min has not been studied	Mild to mod: no adjustment; Severe: not studied	C
	Tranylcypromine	10 mg twice a day	10 mg weekly	60 mg	10 mg twice a day	No change	Avoid	C

Abbreviations: 5-HT = serotonin, BID = twice a day, CrCl = creatinine clearance, CR = controlled release, IR = immediate release, LFT = liver function test, MAOI = monoamine oxidase inhibitor, mg = milligram, min = minute, ml = milliliter, N/A= not applicable, NDRI= norepinephrine and dopamine reuptake inhibitor, QD = once a day, QHS = once before bedtime, QID = four times a day, QOD = every other day, SNRI = serotonin norepinephrine reuptake inhibitor, SR = sustained-release, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TDM = therapeutic drug monitoring, XR = extended-release

Table C-2: Antidepressant Adverse Event Profiles [197]

Drug Class or Drug	Amine Update		Anti-cholinergic Activity	Sedation (H1 activity)	Orthostatic Hypotension (alpha-1 act.)	Cardiac Conduction Effects	GI Effects	Weight Gain	Comments
	5HT	NE							
SSRIs	+++	0/+	0/++	0/+	0	0/+	+++	0/+	<ul style="list-style-type: none"> ▪ Sexual dysfunction common ▪ Citalopram and escitalopram dose-related conduction effects ▪ Paroxetine most anticholinergic; avoid in elderly ▪ Paroxetine and fluoxetine CYP2D6 and CYP2B6 inhibitors ▪ Vilazodone CYP2C8 2C1 and 2D6 inhibitor
SNRIs	++/+++	++/+++	0/+	0/+	0/++	0/+	++/+++	0/+	<ul style="list-style-type: none"> ▪ Sexual dysfunction common ▪ Venlafaxine NE activity dose-related ▪ Desvenlafaxine active metabolite of venlafaxine
Bupropion	0/+	0/+	0	0	0	0	++	0	<ul style="list-style-type: none"> ▪ Risk of seizures is dose-related; avoid if seizure history, bulimia or eating disorder ▪ CYP2D6 inhibitor
Trazodone Nefazodone	+++	0/+	0	+++	0	0/+	++	0/+	<ul style="list-style-type: none"> ▪ Very sedating ▪ Nefazodone associated with a higher risk of hepatotoxicity ▪ Nefazodone CYP3A4 inhibitor
Mirtazapine	0/+	0/+	0	+++	0/+	0	0/+	+++	<ul style="list-style-type: none"> ▪ Doses >15 mg less sedating ▪ May stimulate appetite
Vortoxetine	+++	++	0	0	0	0	+++	0	

Drug Class or Drug	Amine Update		Anti-cholinergic Activity	Sedation (H1 activity)	Orthostatic Hypotension (alpha-1 act.)	Cardiac Conduction Effects	GI Effects	Weight Gain	Comments
	5HT	NE							
TCAs	+ /+++	+ /+++	+ /+++	0 /+++	+ /+++	++ /+++	0 /+	0 /++	<ul style="list-style-type: none"> Desipramine and nortriptyline more tolerable; least sedating, anticholinergic and orthostatic hypotension Therapeutic blood concentrations established for desipramine, imipramine, and nortriptyline
MAOIs	0	0	0	0 /+	0 /+	0	0 /+	0 /+	<ul style="list-style-type: none"> Requires a low tyramine diet except selegiline 6 mg/24 hours patch Contraindicated with sympathomimetics and other antidepressants Observe appropriate washout times when switching from or to another class of antidepressant

Key: +++ = strong effect, ++ = moderate effect, + = minimal effect, 0 = no effect

Abbreviations: MAOI = monoamine oxidase inhibitor, SNRI = serotonin norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant

Table C-3: Augmentation, Adjunct and Alternative Pharmacotherapy [197]

Class	Agent	Initial Dose	Titration Schedule ³	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
SGAs	Aripiprazole	2-5 mg once a day	2-5 mg after ≥1 week	15 mg	2 mg once a day	No change	No change	C
	Olanzapine	2.5-5 mg once a day	2.5-5 mg weekly	20 mg	2.5 mg once a day	No change	No change	C
	Quetiapine	50 mg once a day for 1 day	100 mg daily as tolerated	300 mg	50 mg once a day	No change	Initial 25 or 50 mg once a day	C
	Risperidone	0.25-0.5 mg once a day	0.5 mg daily	3 mg	0.25 mg once a day	Adjust if CrCl <30 ml/min	Severe: Caution	C
	Ziprasidone	20 mg twice a day	20 mg twice a day every 2-4 days	160 mg	20 mg twice a day	No change	Caution	C
5-HT1A & -HT2 agonist	Buspirone	7.5 mg twice a day	7.5 mg twice a day weekly	60 mg	7.5 mg twice a day	Avoid if severe	Avoid if severe	B
Lithium	Lithium	300 mg 1-2 times a day	300 mg weekly	1200 mg	150mg once or twice a day	↓ dose 25% - 75%	No change	D
Thyroid hormone	Liothyronine	25 µg once a day	May be increased to 50 µg/day after ~1 week	50 µg	5 µg once a day; increase by 5 µg/day every 2 weeks	No change	No change	A
Herbal	St. John's wort	300 mg 2-3 times a day	Unknown	1200 mg	Unknown	Has not been studied	Has not been studied	Avoid

Abbreviations: 5-HT = serotonin, CrCl = creatinine clearance, mg = milligram, µg = microgram, SGA = Second Generation Antipsychotic

³ Recommended minimum time between dose increases

Appendix D: Definitions

A. Major Depressive Disorder

Major depression is generally diagnosed when a persistent low mood or lack of interest in activity plus impairment in functional areas of life persists. The number and combination of symptoms needed to make a diagnosis is operationally defined by International Classification of Diseases (ICD)-10 [198] and DSM-5 [199]; although some people will show an atypical presentation with reactive mood, increased appetite, weight gain and excessive sleepiness.[200]

Diagnosis of MDD is based on the presence of depressed mood or loss of interest or pleasure, along with at least four additional MDD diagnosis criteria symptoms for duration of at least two weeks (See [Table D-1](#)).

Depressive symptoms include depressed mood, loss of interest in most activities (anhedonia), significant change in weight or appetite, insomnia or hypersomnia, decreased concentration, decreased energy, inappropriate guilt or feelings of worthlessness, psychomotor agitation or retardation, and suicidal ideation.

Table D-1. Diagnosis of MDD [46]

Symptom	MDD diagnosis is based on the following list of symptoms, and requires the presence of symptom 1, 2, or both; and at least five of nine symptoms overall; these symptoms must persist for at least two weeks
1	Depressed mood nearly every day for most of the day, based on self- report or observation of others
2	Marked reduction or loss of interest or pleasure in all, or nearly all, activities for most of the day, nearly every day
3	Significant non-dieting weight loss or weight gain (> 5% change in body weight)
4	Insomnia or hypersomnia nearly every day
5	Psychomotor agitation or retardation (should be observable by others)
6	Fatigue/loss of energy nearly every day
7	Feelings of worthlessness or excessive/inappropriate guilt (possibly delusional) nearly every day
8	Diminished cognitive function (reduced ability to think or concentrate, or indecisiveness) nearly every day
9	Recurrent thoughts of death and/or suicide, suicide planning, or a suicide attempt

In addition, those with a more severe or atypical presentation, including marked physical slowness (or marked agitation) and a range of somatic symptoms, are often referred to as melancholic depressions, or depression with melancholia.

People with severe depressive episodes may also develop psychotic symptoms (hallucinations and/or delusions), most commonly thematically consistent with the negative, self-blaming cognitions and low mood typically encountered in major depression, although others may develop psychotic symptoms unrelated to the patient's mood. In the latter case, these mood-incongruent psychotic symptoms can be hard to distinguish from those that occur in other psychoses such as schizophrenia.

Severe Major Depressive Disorder

- Active suicidal ideation with either intent or plan, or suicide attempt
- Active homicidal ideation
- Psychotic symptoms
- Severe anorexic symptoms (including loss of weight that poses health risk)
- Inability to maintain activities of daily living (ADLs) (e.g., grooming, feeding, catatonia)

[Table B-1](#) describes the classification of MDD based on the symptoms score obtained with the PHQ-9. The classification may be helpful for emphasizing the different needs that depressed individuals have, depending on the characteristics of their depression and their personal and social circumstances, and the responses that are required from services. While the PHQ-9 has been validated with DSM-IV and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria, there were no changes in the diagnostic criteria for MDD from DSM-IV to DSM-5 and therefore the PHQ-9 should remain a valid screening tool.

Defining severity levels of MDD requires “categorization” of continuous measures of symptom presentation and functional impairment, and the “cut-off levels” between scores are quite arbitrary. Nonetheless, the classification of severity of MDD may be used as a framework to facilitate the organization of care services supporting both patients and family members, and healthcare professionals in identifying and accessing the most effective interventions.

The general categories of severity should be used as a basis for initial classification and should be further characterized by any of the modifiers. These will include the existence of co-occurring mental health disorders and the duration of symptoms despite treatment. For most patients, an untreated first episode of MDD is followed by improvement of symptoms; although some patients return to pre-episode mood and function levels, many continue to experience residual subsyndromal symptoms. In a minority of patients, a MDD episode persists for over two years, and is defined as chronic MDD. Treatment-resistant depression is defined as at least two adequate treatment trials and lack of full response to each.[\[96\]](#)

The nature and course of depression is significantly affected by psychological, social and physical characteristics of the patient and their circumstances. These factors have a significant impact upon both the initial choice of treatment and the probability of a patient benefiting from that intervention.

Onset Response to Treatment

- Response to treatment: PHQ score improvement of >50% from baseline

Remission

- PHQ score of ≤ 4 , maintained for at least one month

Recovery

- PHQ score of ≤ 4 , maintained for at least six months

Partial Response

- <50% improvement in symptoms

Recurrence

- Recurrence is the appearance of another new episode of MDD after remission of a previous episode has been achieved. The literature often defines a complex case as three or more major depressive episodes.

B. Treatments

Acceptance and Commitment Therapy (ACT) is a manualized psychotherapy intervention derived from relational frame theory that emphasizes acceptance of emotional distress and engagement in goal directed behaviors. A key feature of these interventions is acceptance rather than avoidance of emotional pain. This acceptance is thought to reduce affective symptom severity. To facilitate effective behavior change, ACT emphasizes identification of personal values and learning to act based on those values in spite of inevitable distress as opposed to having behaviors be focused on avoiding pain and adversity.

Behavior Therapy (BT) for major depression refers to a class of psychotherapy interventions that treat MDD by teaching patients to increase rewarding activities. Patients learn to track their activities and identify the affective and behavioral consequences of those activities. Patients then learn techniques to schedule activities to improve mood. BT emphasizes training patients to monitor their symptoms and behaviors to identify the relationships between them. Primary therapeutic techniques of BT include collaborative empiricism (the therapist and patient working together to increase rewarding behaviors) and functional analysis of obstacles to activities. In addition, treatment incorporates structured practice outside of the session, including scheduled activities, mood tracking and interpersonal skills practice.

Behavioral Activation (BA) is a particular version of BT that targets the link between avoidant behavior and depression and expands the treatment component of BT.

Cognitive Behavior Therapies (CBT) are interventions that treat MDD by teaching patients to modify both thinking and behavior. Patients learn to track their thinking and activities and identify the affective and behavioral consequences of those thoughts and activities. Patients then learn techniques to change thinking that contributes to depression and schedule activities to improve mood. Primary therapeutic techniques of CBT include education of the patient about the treatment model, collaboration between the patient and therapist to choose goals, identifying unhelpful thoughts and developing experiments to test the accuracy of such thoughts, and guided discovery (facilitating the patient in identifying alternative beliefs through the use of questions designed to explore current beliefs that exacerbate depression). In addition, treatment incorporates structured practice outside of the session, including scheduled activities, mood tracking, thought recording and challenging, and interpersonal skills practice. CBT can also be administered via computer-based programs, in which case it is known as computer-based cognitive behavioral therapy (CCBT).

Interpersonal Psychotherapy (IPT) is derived from attachment theory and treats MDD by focusing on improving interpersonal functioning and exploring relationship-based difficulties. IPT addresses the connection between patients' feelings and current difficulties in their relationships with people in their life by targeting four primary areas: (1) interpersonal loss, (2) role conflict, (3) role change, and (4) interpersonal skills. However, psychotherapy research is not clear on the classification of interpersonal therapy. In some systematic reviews, it is classified as a psychodynamic intervention and in others as a cognitive behavioral intervention.

Problem-solving Therapy (PST) is defined as a discrete, time-limited, structured psychological intervention that focuses on learning to cope with specific problem areas and where therapist and patient work collaboratively to identify and prioritize key problem areas; to break problems down into specific, manageable tasks; to problem solve; and to develop appropriate coping behaviors for problems. The intervention is short-term and the mode of action is hypothesized as skills acquisition. The intervention can be delivered effectively in primary care settings by general practitioners or nurses.

Mindfulness-based Cognitive Therapy (MBCT) integrates traditional CBT interventions with mindfulness-based skills, including mindfulness meditation, imagery, experiential exercises, and other techniques that aid patients in experiencing affect without necessarily attempting to change it. With regard to cognitions, unlike cognitive therapy, MBCT does not so much seek to modify or eliminate dysfunctional thoughts as to become more detached and able to observe thoughts as objects.

Non-directive Supportive Psychotherapy (NDSP) refers to a broad range of treatments that tend to not be manualized, and emphasize listening skills and development of a strong therapeutic alliance as the primary strategies for symptom management.

Short-term Psychodynamic Psychotherapy (STPP) is derived from psychoanalysis and longer-term psychodynamic psychotherapy. STPP is defined as psychodynamic psychotherapy of approximately 10 to 20 weeks duration. It focuses on the patient gaining insight into unconscious conflicts as they are manifested in the patient's life and relationships, including his/her relationship with his/her therapist (i.e., transference). It is thought that these conflicts have their origin in the past, usually childhood relationships to parental figures. Patients gain insight into and work through such conflicts through exploration of their feelings along with interpretations offered by his/her therapist. Of note, while some label IPT as an STPP, others argue that it is a distinct model and is described in a separate annotation because it has a distinct body of literature (see IPT above).

Appendix E: Evidence Table

Recommendation	2009 Grade ¹	Evidence ²	Strength of Recommendation ³	Recommendation Category ⁴
1. We recommend that all patients not currently receiving treatment for depression be screened for depression using the Patient Health Questionnaire-2 (PHQ-2).	A, I	[22-37] Additional References: [38]	Strong For	Not Reviewed, Amended
2. For patients with suspected depression, we recommend an assessment for acute safety risks (i.e., harm to self or others, psychotic features) during the initial assessment and periodically thereafter as needed.	A	[41] Additional References: [39,40,42]	Strong For	Not Reviewed, Amended
3. For patients with suspected depression, we recommend an appropriate diagnostic evaluation that includes a determination of functional status, medical history, past treatment history, and relevant family history.	I	[45] Additional References: [43,44,46,47]	Strong For	Not Reviewed, Amended
4. For patients with a diagnosis of MDD, we suggest using the Patient Health Questionnaire-9 (PHQ-9) as a quantitative measure of depression severity in the initial treatment planning and to monitor treatment progress (see Recommendation 14).	B	[45,49-53] Additional References: [48]	Weak For	Not Reviewed, Amended

¹ The 2009 VA/DoD MDD CPG used the USPSTF evidence grading system (<http://www.uspreventiveservicestaskforce.org>). Inclusion of more than one 2009 Grade indicates that more than one 2009 CPG recommendation is covered under the 2015 recommendation. The strength of recommendations were rated as follows: A- a strong recommendation that the clinicians provide the intervention to eligible patients; B- a recommendation that clinicians provide (the service) to eligible patients; C- no recommendation for or against the routine provision of the intervention is made; D- recommendation is made against routinely providing the intervention; I- the conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention.

² The evidence column indicates studies that support each recommendation. For new recommendations, developed by the 2015 guideline Work Group, the literature cited corresponds directly to the 2015 evidence review. For recommendations that have been carried over from the 2009 VA/DoD MDD CPG, slight modifications were made to the language in order to better reflect the current evidence and/or the change in grading system used for assigning the strength of each recommendation (USPSTF to GRADE). For these “modified” recommendations, the evidence column indicates “additional evidence,” which can refer to either 1) studies that support the recommendation and which were identified through the 2015 evidence review, or 2) relevant studies that support the recommendation, but which were not systematically identified through a literature review.

³ Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

⁴ Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

Recommendation	2009 Grade ¹	Evidence ²	Strength of Recommendation ³	Recommendation Category ⁴
5. We recommend that patients with complex MDD (severe, chronic or recurrent) be offered specialty care by providers with mental health expertise in order to ensure better outcomes and effective delivery of evidence-based treatment strategies.	None	[54] Additional References: [55]	Strong For	Reviewed, New-replaced
6. We recommend the use of the collaborative care model for the treatment of MDD within a primary care setting.	B, B	[56,57,67-70] Additional References: [39,58-66]	Strong For	Reviewed, New-replaced
7. We recommend that treatment planning include patient education about the condition and treatment options, including risks and benefits. The individualized treatment plan should be developed using shared decision-making principles, and should define the provider, patient, and support network’s roles.	B, I	[71] Additional References: [72]	Strong For	Not Reviewed, Amended
<p>8. As first-line treatment for uncomplicated mild to moderate MDD (see Recommendation 17 for complex cases), we recommend offering one of the following treatments based on patient preference, safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications, cost of medication and provider training/competence:</p> <ul style="list-style-type: none"> ▪ Evidence-based psychotherapy: <ul style="list-style-type: none"> • Acceptance and commitment therapy (ACT) • Behavioral therapy/behavioral activation (BT/BA) • Cognitive behavioral therapy (CBT) • Interpersonal therapy (IPT) • Mindfulness-based cognitive therapy (MBCT) • Problem-solving therapy (PST) ▪ Evidence-based pharmacotherapy: <ul style="list-style-type: none"> • Selective serotonin reuptake inhibitor (except fluvoxamine) (SSRIs) • Serotonin–norepinephrine reuptake inhibitor (SNRIs) • Mirtazapine • Bupropion ▪ The evidence does not support recommending a specific evidence-based psychotherapy or pharmacotherapy over another. 	A, B	[73-87] Additional References: [19,20,88]	Strong For	Reviewed, New-replaced

Recommendation	2009 Grade ¹	Evidence ²	Strength of Recommendation ³	Recommendation Category ⁴
9. In patients who have demonstrated partial or no response to initial pharmacotherapy monotherapy (maximized) after a minimum of four to six weeks of treatment, we recommend switching to another monotherapy (medication or psychotherapy) or augmenting with a second medication or psychotherapy.	None	[90,91,94,95,97] Additional References: [1,89,92,93,96]	Strong For	Reviewed, New-replaced
10. For patients who select psychotherapy as a treatment option, we suggest offering individual or group format based on patient preference.	B	[98] Additional References: [99]	Weak For	Reviewed, New-replaced
11. For patients with mild to moderate MDD, we recommend offering computer-based cognitive behavioral therapy (CCBT) either as an adjunctive intervention or, based on patient preference, as a first-line treatment.	B	[100-102] Additional References: [103]	Strong For	Reviewed, Amended
12. For patients with mild to moderate MDD who decline pharmacotherapy and who decline or cannot access first-line evidence-based psychotherapies, we suggest offering non-directive supportive therapy or short-term psychodynamic psychotherapy.	C	[77,104,105]	Weak For	Reviewed, New-replaced
13. We suggest offering a combination of pharmacotherapy and evidence-based psychotherapy for the treatment of patients with MDD during a new episode of care when the MDD is characterized as: <ul style="list-style-type: none"> ▪ Severe (e.g., PHQ-9 >20) ▪ Chronic (duration greater than two years) ▪ Recurrent (with three or more episodes) 	A	[54,107] Additional References: [106]	Weak For	Reviewed, New-replaced
14. After initiation of therapy or a change in treatment, we recommend monitoring patients at least monthly until the patient achieves remission. At minimum, assessments should include a measure of symptoms, adherence to medication and psychotherapy, and emergence of adverse effects.	C, B	[51-53] Additional References: [96,108-114]	Strong For	Reviewed, Amended
15. In patients with MDD who achieve remission with antidepressant medication, we recommend continuation of antidepressants at the therapeutic dose for at least six months to decrease risk of relapse.	A, I	[115,116,118] Additional References: [117,119]	Strong For	Reviewed, New-replaced

Recommendation	2009 Grade ¹	Evidence ²	Strength of Recommendation ³	Recommendation Category ⁴
16. In patients at high risk for recurrent depressive episodes (see Discussion) and who are treated with pharmacotherapy, we recommend offering maintenance pharmacotherapy for at least 12 months and possibly indefinitely.	B, C	[115,116,120]	Strong For	Reviewed, New-replaced
17. For patients at high risk for relapse (e.g., two or more prior episodes, unstable remission status), we recommend offering a course of cognitive behavioral therapy (CBT), interpersonal therapy (IPT) or mindfulness-based cognitive therapy (MBCT) during the continuation phase of treatment (after remission is achieved) to reduce the risk of subsequent relapse/recurrence. <ul style="list-style-type: none"> The evidence does not support recommending a specific evidence-based psychotherapy over another. 	A	[121,122]	Strong For	Reviewed, Amended
18. For initiation of treatment in pregnant or breastfeeding women with mild to moderate MDD, we recommend offering an evidence-based psychotherapy (i.e., ACT, BA/BT, CBT, IPT, MBCT, PST) as a first-line treatment. <ul style="list-style-type: none"> The evidence does not support recommending a specific evidence-based psychotherapy over another. In pregnant patients with a history of MDD prior to pregnancy who responded to antidepressant medications, and are currently stable on pharmacotherapy, weigh risk/ benefit balance to both mother and fetus in treatment decisions. 	B, A, A, C, A, B	[123-125]	Strong For	Reviewed, New-replaced
19. For older adults (≥65years) with mild to moderate MDD, we recommend offering an evidence-based psychotherapy (i.e., ACT, BT/BA, CBT, IPT, MBCT, PST) as a first-line treatment. Patient preference and the additional safety risks of pharmacotherapy should be considered when making this decision. <ul style="list-style-type: none"> The evidence does not support recommending a specific evidence-based psychotherapy over another. 	B, A, A, C, A, B	[126-128]	Strong For	Reviewed, New-replaced
20. In patients with mild to moderate MDD and significant relationship distress, we suggest offering couples-focused therapy, either as monotherapy or in combination with pharmacotherapy.	B, C	[129,130]	Weak For	Reviewed, New-replaced
21. We suggest offering light therapy for adult patients with mild to moderate MDD with a seasonal pattern (formerly seasonal affective disorder [SAD]).	B, C, I	[132,133] Additional References: [131]	Weak For	Reviewed, Amended

Recommendation	2009 Grade ¹	Evidence ²	Strength of Recommendation ³	Recommendation Category ⁴
22. For patients with treatment-resistant MDD who had at least two adequate pharmacotherapy trials, we recommend offering monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs) along with patient education about safety and side effect profiles of these medications.	B, None	[134,137-145] Additional References: [135,136]	Strong For	Reviewed, New-replaced
23. Given the limited information on ketamine’s safety and duration of effect, we recommend against the use of ketamine to treat MDD outside of a research setting.	B, None	[146]	Strong Against	Reviewed, New-added
24. We recommend offering electroconvulsive therapy (ECT) with or without psychotherapy in patients with severe MDD and any of the following conditions: <ul style="list-style-type: none"> ▪ Catatonia ▪ Psychotic depression ▪ Severe suicidality ▪ A history of a good response to ECT ▪ Need for rapid, definitive treatment response on either medical or psychiatric grounds ▪ Risks of other treatments outweigh the risks of ECT (i.e., co-occurring medical conditions make ECT the safest treatment alternative) ▪ A history of a poor response to multiple antidepressants ▪ Intolerable side effects to all classes of antidepressant medications (e.g., seizures, hyponatremia, severe anxiety) ▪ Patient preference ▪ Pregnancy 	A	[148-150] Additional References: [147]	Strong For	Reviewed, Amended
25. We suggest offering treatment with repetitive transcranial magnetic stimulation (rTMS) for treatment during a major depressive episode in patients with treatment-resistant MDD.	None	[151-156]	Weak For	Reviewed, New-added
26. We recommend against offering vagus nerve stimulation (VNS) for patients with MDD, including patients with severe treatment-resistant depression outside of a research setting.	D	[149,159-165] Additional References: [157,158]	Strong Against	Reviewed, Amended
27. We recommend against offering deep brain stimulation (DBS) for patients with MDD outside of a research setting.	None	[166]	Strong Against	Reviewed, New-added

Recommendation	2009 Grade ¹	Evidence ²	Strength of Recommendation ³	Recommendation Category ⁴
28. For patients with MDD, there is insufficient evidence to recommend for or against acupuncture either as monotherapy or as an adjunctive treatment to pharmacotherapy.	I	[167,169,170] Additional References: [168]	Not Applicable	Reviewed, New-replaced
29. For patients with MDD, we suggest offering patient education on the benefits of exercise as an adjunct to other evidence-based treatments for depression or as monotherapy when patients are unwilling or unable to engage in first-line evidence-based psychotherapy or pharmacotherapy.	B, B	[71,175] Additional References: [171-174]	Weak For	Reviewed, New-replaced
30. For patients with MDD, there is insufficient evidence to recommend for or against yoga, tai chi, or qi gong either as monotherapy or as an adjunctive treatment to pharmacotherapy.	None	[178-182] Additional References: [176,177]	Not Applicable	Reviewed, New-added
31. For patients with mild MDD who are not pregnant or breastfeeding and who prefer herbal treatments to first-line psychotherapy or pharmacotherapy, we suggest standardized extract of St. John’s wort (SJW) as a medication monotherapy.	B	[183] Additional References: [184]	Weak For	Reviewed, Amended
32. For patients with MDD, we suggest against using omega-3 fatty acids or vitamin D for treatment.	None	[185,186,188,189] Additional References: [187]	Weak Against	Reviewed, New-added
33. For patients with mild MDD, we suggest patient education about the benefits of bibliotherapy based on cognitive-behavioral principles as adjunctive treatment or an alternative to pharmacotherapy or psychotherapy based on patient preference.	B	[190,191] Additional References: [192,193]	Weak For	Reviewed, New-replaced

Appendix F: 2009 Recommendation Categorization

2009 CPG Location ¹			2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement	2009 Rec Number				
A	Identify patients who are depressed and are no longer engaged in treatment.	1	The Patient Health Questionnaire (PHQ) 2-item should be completed annually by all patients seen in primary care settings.	A	Not Reviewed, Amended	Recommendation 1
A	Identify patients who are depressed and are no longer engaged in treatment.	2	Patients who screen positive on the Patient Health Questionnaire (PHQ) 2-item should have both a documented assessment using a quantitative questionnaire to further assess whether the patient has sufficient symptoms to warrant a diagnosis of clinical major depression and a full clinical interview that includes evaluation for suicide risk.	B	Not Reviewed, Deleted	--
A	Identify patients who are depressed and are no longer engaged in treatment.	3	In patients at particularly high risk for depression based on medical illness (e.g., hepatitis C starting interferon treatment or post-myocardial infarction), clinicians should have a high index of suspicion for depression and use a diagnostic assessment tool (e.g., Patient Health Questionnaire (PHQ) 9-item) when depression is suspected.	I	Not Reviewed, Amended	Recommendation 1
A	Identify patients who are depressed and are no longer engaged in treatment.	4	Caution should be used in screening patients older than 75 years since screening instruments may not perform as well as in patients 65 to 75 years old.	C	Not Reviewed, Deleted	--

¹ The first three columns indicate the location of each recommendation within the 2009 MDD CPG.

² The 2009 Recommendation Text column contains the wording of each recommendation from the 2009 MDD CPG. In some cases, the recommendations were graded. In these cases, the Grade is contained in following column (2009 Grade).

³ The 2009 VA/DoD MDD CPG used the USPSTF evidence grading system (<http://www.uspreventiveservicestaskforce.org>). The strength of recommendations were rated as follows: A= a strong recommendation that the clinicians provide the intervention to eligible patients; B= a recommendation that clinicians provide (the service) to eligible patients; C= no recommendation for or against the routine provision of the intervention is made; D= recommendation is made against routinely providing the intervention; I= the conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention.

⁴ The Category column indicates the way in which each 2009 MDD CPG recommendation was updated.

⁵ For recommendations that were carried forward to the 2015 MDD CPG, this column indicates the new recommendation(s) to which they correspond.

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
A	To identify women who are depressed during pregnancy or in the postpartum period.	1	Women should be screened for depression at their first contact with healthcare services in both the antenatal and the postnatal periods.	B	Not Reviewed, Deleted	--
A	To identify women who are depressed during pregnancy or in the postpartum period.	2	Depression screening should be performed with either the Edinburgh Postnatal Depression Scale (EDPS) or the PHQ-2.	B	Not Reviewed, Deleted	--
A	To identify women who are depressed during pregnancy or in the postpartum period.	3	In the postpartum period, recommended screening is typically at 4 to 6 weeks and 3 to 4 months.	C	Not Reviewed, Deleted	--
B	Identify patients who are at high risk of harm to self or others.	1	A referral to emergency services and/or consultation with a mental health professional is indicated for patients presenting with any of the following unstable conditions: <ul style="list-style-type: none"> a. Delirium b. Marked psychotic symptoms c. Severe depressive symptoms/depression (e.g., catatonia, malnourishment, severe disability) d. Suicidality or homicidality e. Potential for violence (e.g., ideas about or intent to harm others; history of violent behavior; severe agitation or hostility; active psychosis) f. Substance withdrawal or intoxication 	None	Not Reviewed, Amended	Recommendation 2
B	Identify patients who are at high risk of harm to self or others.	2	Any patient with suicidal ideation or attempts necessitating psychiatric hospitalization should be considered for referral to mental health specialty care.	None	Not Reviewed, Deleted	--

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
C	Identify patients who pose a threat to self or others and initiate appropriate intervention.	1	<p>Patients with a presumptive diagnosis of MDD should be assessed for suicidality by using a direct line of questioning. One recommended line of questioning uses the following (modified from Hirschfeld & Russell, 1997):</p> <ol style="list-style-type: none"> “Have you had thoughts about death or about killing yourself?” “Tell me about your hopes for the future.” “Do you have a plan for how you would kill yourself?” “Are there means available (e.g., pills, a gun and bullets, or poison)?” “Have you actually rehearsed or practiced how you would kill yourself?” “Do you tend to be impulsive?” “How strong is your intent to do this?” “Can you resist the impulse to do this?” “Have you heard voices telling you to hurt or kill yourself?” Ask about previous attempts, especially the degree of intent. Ask about suicide of family members or significant others. 	None	Not Reviewed, Deleted	--
C	Identify patients who pose a threat to self or others and initiate appropriate intervention.	2	<p>Risk of violence towards others should be assessed by asking directly whether or not the patient has thoughts of harming anyone:</p> <ol style="list-style-type: none"> Assess whether the patient has an active plan and method/means (e.g., weapons in the home) Assess whom the patient wishes to harm Assess whether the patient has ever lost control and acted violently Assess seriousness/severity of past violent behavior. 	None	Not Reviewed, Deleted	--

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C	Identify patients who pose a threat to self or others and initiate appropriate intervention.	3	In the event of expressed dangerousness to self or others by a person with possible MDD, steps must be taken to insure patient safety until further evaluation and a referral or consultation with a mental health professional has taken place.	None	Not Reviewed, Deleted	--
C	Identify patients who have acute or chronic psychosis and treat accordingly.	1	Patients with a possible diagnosis of MDD should be assessed for acute or chronic psychosis.	None	Not Reviewed, Deleted	--
C	Identify patients who have acute or chronic psychosis and treat accordingly.	2	Patients with a possible diagnosis of MDD who exhibit any of the following characteristics related to psychosis need to be referred for urgent/emergent mental health intervention as these are inappropriate for care in the primary care setting: a. Serious delusions (e.g., fixed false beliefs) b. Visual or (typically) auditory hallucinations c. Confusion (incoherence) d. Catatonic behavior (e.g., motoric immobility or excessive agitation) e. Extreme negativism or mutism f. Peculiar voluntary movement g. Inappropriate affect of a bizarre or odd quality.	None	Not Reviewed, Deleted	--
C	Identify patients who have acute or chronic psychosis and treat accordingly.	3	Patients who have longstanding psychotic illness and who are able to attend to present circumstances without responding to their psychosis, may be evaluated and treated for a comorbid depression in the primary care setting.	None	Not Reviewed, Deleted	--
D	Ensure that appropriate care, protocols and regulatory/policy mandates are followed during diagnosis and stabilization of the patient with MDD with an unstable condition.	1	Local, state, and federal regulations/mandates as well as guidelines should be followed if the patient represents a risk to self or others.	None	Not Reviewed, Deleted	--

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D	Ensure that appropriate care, protocols and regulatory/policy mandates are followed during diagnosis and stabilization of the patient with MDD with an unstable condition.	2	In managing patients who pose a risk, mental health providers need to be prepared to consult with primary care and other medical specialties concerning patients who may be encountered in their clinics.	None	Not Reviewed, Deleted	--
D	Ensure that appropriate care, protocols and regulatory/policy mandates are followed during diagnosis and stabilization of the patient with MDD with an unstable condition.	3	Patient care management plans must reflect the realities of local resources, staffing, and transportation.	None	Not Reviewed, Deleted	--
D	Ensure that appropriate care, protocols and regulatory/policy mandates are followed during diagnosis and stabilization of the patient with MDD with an unstable condition.	4	Consultation with a peer and/or medical law consultant on the legal and ethical requirements is recommended as it relates to notifications regarding the patient who represents a risk to others.	None	Not Reviewed, Deleted	--
E	Complete a thorough medical and mental health history and examination to develop an appropriate clinical understanding of the patient's condition and arrive at a diagnosis.	1	Once the patient is stable, the clinical assessment should be completed by the primary care provider, including a relevant history, physical examination, and laboratory tests as indicated.	I	Not Reviewed, Amended	Recommendation 4
E	Complete a thorough medical and mental health history and examination to develop an appropriate clinical understanding of the patient's condition and arrive at a diagnosis.	2	Relevant history may include the following: a. Review of the impact of depressive symptoms on functional status. Typical questions include: i. "During the past few weeks, have any physical or emotional problems interfered with your typical daily activities?" ii. "Has it been more difficult to do things on your own or with your (family, friends, neighbors, church, etc.)?" iii. If positive, areas for brief inquiry include: job, pleasurable hobbies, social activities, and important personal relationships.	None	Not Reviewed, Deleted	--

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			<ul style="list-style-type: none"> b. Review of psychiatric, marital, family, and military service history, past physical or sexual abuse, and medication or substance use. c. Treatment for any prior mental health problems, past psychiatric hospitalizations, or inability to function in usual life roles. d. Additional information to the PHQ-9 that may help diagnose depression and determine severity of symptoms, such as: <ul style="list-style-type: none"> i. Medically unexplained physical symptoms ii. Chronic, debilitating medical conditions iii. Current substance use iv. Decrease in sensory, physical, or cognitive function v. Victim of current or past physical or sexual abuse or emotional neglect vi. Family history of major depression vii. Loss of significant relationship, primary support system, or economic status viii. Neurological disorder (e.g., multiple sclerosis, Parkinson’s disease, stroke) or history of closed head injury ix. Protracted care-giving role for a family member with a chronic, disabling condition x. Spousal bereavement and widowhood xi. Symptoms or signs of post-traumatic stress disorder xii. Mania/hypomania. e. Review of medications, including prescription drugs and over-the-counter drugs (herbals, nutritionals, vitamins, and body building supplements). 			

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E	Complete a thorough medical and mental health history and examination to develop an appropriate clinical understanding of the patient's condition and arrive at a diagnosis.	3	Appropriate physical examination including mental status exam; in certain subpopulations (e.g., elderly, traumatic brain injury), a screen for cognitive impairment is appropriate.	None	Not Reviewed, Deleted	--
E	Complete a thorough medical and mental health history and examination to develop an appropriate clinical understanding of the patient's condition and arrive at a diagnosis.	4	Laboratory tests as clinically indicated, e.g., complete blood count (CBC), chemistry profile, thyroid studies, B12 and folate assessments, pregnancy screen and toxicology screen and an ECG for patients over the age of 40.	None	Not Reviewed, Deleted	--
E	Use a standardized instrument (PHQ-9) to document baseline depressive symptoms, measure symptom severity, and assist in evaluating treatment response and future progress.	1	For patients with a positive depression screen or in whom depression is suspected, administer the PHQ-9 as a component of the initial assessment.	B	Not Reviewed, Amended	Recommendation 3
E	Use a standardized instrument (PHQ-9) to document baseline depressive symptoms, measure symptom severity, and assist in evaluating treatment response and future progress.	2	DSM-IV-TR criteria should be used to diagnose depression. The PHQ-9 assessment tool combined with a clinical interview should be used to obtain the necessary information about symptoms, symptom severity, and effects on daily functioning that is required to diagnose MDD based on DSM-IV-TR criteria.	None	Not Reviewed, Deleted	--
E	Use a standardized instrument (PHQ-9) to document baseline depressive symptoms, measure symptom severity, and assist in evaluating treatment response and future progress.	3	The PHQ-9 should be used to monitor treatment response at 4 to 6 weeks, after each change in treatment, and to periodically assess the patient's response to treatment until full remission is achieved.	None	Not Reviewed, Deleted	--
F	Identify patients who may be experiencing depressed symptoms as a side effect of medication.	1	The diagnostic work-up for MDD should include a review of all prescription or over-the-counter (OTC) medications as they may cause or contribute to the depressive symptoms.	None	Not Reviewed, Deleted	--
F	Identify patients who may be experiencing depressed symptoms as a side effect of medication.	2	Consideration should also be given to herbals, nutritional, vitamins, and body building supplements, particularly when consumed in large doses.	None	Not Reviewed, Deleted	--

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F	Identify patients who may be experiencing depressed symptoms as a side effect of medication.	3	Consider discontinuing the offending medication as clinically indicated.	None	Not Reviewed, Deleted	--
F	Identify patients who may be experiencing depressed symptoms as a result of an underlying medical condition.	1	The diagnostic work-up for MDD should include evaluation for existing or emerging medical conditions that may exacerbate the depression. These may include: a. Cardiovascular diseases b. Chronic pain syndrome c. Degenerative diseases d. Immune disorders e. Metabolic endocrine conditions (including kidney and lung diseases) f. Neoplasms g. Trauma	None	Not Reviewed, Deleted	--
F	Identify patients who may be experiencing depressed symptoms as a result of an underlying medical condition.	2	Simultaneous treatment is often required for both the medical problem and psychiatric symptoms and can lead to overall improvement in function.	None	Not Reviewed, Deleted	--
G	Determine whether other psychiatric conditions are present and may complicate treatment.	1	Patients presenting to primary care with evidence or suspicion of co-occurring psychiatric disorders should be offered referral to mental health specialty for evaluation and treatment. Conditions that should prompt the primary care provider to consider referral include: a. Extreme weight loss suggestive of anorexia nervosa b. Extensive history of childhood abuse, unstable or broken relationships, or criminal behavior starting before or during adolescence, that is suggestive of a personality disorder c. A pattern of "binging" (rapid and excessive consumption of food) and/or "purging" (use of self-induced vomiting, laxatives, or diuretics) to control weight that may suggest bulimia nervosa	None	Not Reviewed, Deleted	--

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			d. Frequent and disabling nightmares or flashbacks suggestive of post-traumatic stress disorder e. Other major mental disorders (e.g., schizophrenia or bipolar disorder) likely to significantly complicate the primary care management of depression symptoms.			
G	Determine whether other psychiatric conditions are present and may complicate treatment.	2	Patient presenting with unexplained physical symptoms and depression should be offered referral to a mental health specialist as these may represent a somatoform disorder.	None	Not Reviewed, Deleted	--
G	Determine if the patient has bipolar disorder.	1	The possible existence of bipolar disorder should be assessed in patients presenting with depressive symptoms, using a clinical interview or a bipolar questionnaire.	None	Not Reviewed, Deleted	--
G	Determine if the patient has bipolar disorder.	2	Patients suspected to have bipolar disorder should be referred to mental health for diagnosis and management.	None	Not Reviewed, Deleted	--
G	Identify patients who require evaluation and treatment for substance use disorder (SUD).	1	Patients should be asked about any current or recent use of caffeine, nicotine, alcohol, or other psychoactive substances.	I	Not Reviewed, Deleted	--
G	Identify patients who require evaluation and treatment for substance use disorder (SUD).	2	Patients with current alcohol or other drug dependence should be managed according to the VA/DoD Guideline for Substance Use Disorder.	I	Not Reviewed, Deleted	--
G	Determine if the patient has other somatoform disorders.	1	Patients presenting with unexplained physical symptoms and depression should be offered referral to a mental health specialist as these may represent a somatoform disorder.	None	Not Reviewed, Deleted	--
G	Determine if the patient has other somatoform disorders.	2	When referring a patient with possible MDD and unexplained physical symptoms to a mental health specialist, the primary care provider needs to: a. Build a trust relationship with the patient b. Carefully explain the reason for referral before and after it is recommended c. Set a follow-up appointment for after the referral.	None	Not Reviewed, Deleted	--

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H	Identify patients with a diagnosis of depression not otherwise specified (NOS) and treat accordingly.	1	Patients with depressive symptoms who do not meet the diagnostic criteria of MDD (less than 5 symptoms and duration of less than two weeks) should be diagnosed with depression not otherwise specified (NOS).	None	Not Reviewed, Deleted	--
H	Identify patients with a diagnosis of depression not otherwise specified (NOS) and treat accordingly.	2	If the diagnosis of depression NOS is made, the primary care provider may consider an initial approach of “watchful waiting” or a 4 to 8 week trial of support, psychoeducation, self-help, and exercise.	None	Not Reviewed, Deleted	--
H	Identify patients with a diagnosis of dysthymia and treat accordingly.	1	The diagnosis of dysthymia may be considered in patients who experienced a two-year period during which, for most days, the individual experiences depressed mood for more than half the of the day, along with at least two of the following symptoms: a. Increased or decreased appetite b. Insomnia or hypersomnia c. Fatigue or low energy d. Poor self-image e. Reduced concentration or indecisiveness f. Hopelessness.	None	Not Reviewed, Deleted	--
H	Identify patients with a diagnosis of dysthymia and treat accordingly.	2	Patients who initially experienced a depressive episode and continue to experience subsyndromal symptoms following recovery, should be diagnosed as MDD in partial remission, even if those symptoms last more than two years.	None	Not Reviewed, Deleted	--
H	Identify patients with a diagnosis of dysthymia and treat accordingly.	3	Primary care providers may consider antidepressant pharmacotherapy or a combined course of pharmacotherapy and psychotherapy if the patient is diagnosed with dysthymia, though the evidence suggests that the benefits of psychotherapy, and possibly pharmacotherapy, are lower than those found in treatment of major depression.	None	Reviewed, Deleted	--

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H	Identify patients with a diagnosis of dysthymia and treat accordingly.	4	In treating an elderly patient with dysthymia, psychotherapy should be considered, as some evidence suggests this is more effective than pharmacotherapy in this age group.	None	Reviewed, Deleted	--
J	Use evaluation of PHQ-9 scores and functional impairment to determine the level of severity of MDD symptoms for a patient with MDD	1	The level of symptoms severity of MDD should be determined for the patient with diagnosed MDD based on the patient's symptoms score (PHQ-9) and level of functional impairment ascertained in the clinical psychiatric interview.	None	Not Reviewed, Amended	Recommendation 3
J	Use evaluation of PHQ-9 scores and functional impairment to determine the level of severity of MDD symptoms for a patient with MDD	2	The classification of mild, moderate, or severe MDD should be used to establish a baseline and track progress as treatment is initiated.	None	Not Reviewed, Deleted	--
J	Use evaluation of PHQ-9 scores and functional impairment to determine the level of severity of MDD symptoms for a patient with MDD	3	Key symptoms that may have impact on a patient's functional impairment should be considered when using the following classification and may indicate assigning a higher level of severity than is determined by the PHQ-9 score.	None	Not Reviewed, Deleted	--
K	Including the patient in decisions about their medical care may increase adherence to treatment.	1	Patients should receive information that is reasonable for them about their treatment options.	None	Not Reviewed, Deleted	--
K	Including the patient in decisions about their medical care may increase adherence to treatment.	2	Patients should be informed about the risks and benefits of each treatment option.	None	Not Reviewed, Deleted	--
K	Including the patient in decisions about their medical care may increase adherence to treatment.	3	Patients should be assessed for their understanding of the ramifications of their choice.	None	Not Reviewed, Deleted	--
L	Appropriately refer patients with MDD or related disorders to mental health professionals.	1	Patients with severe or complicated depressive disorder should be referred to mental health specialty care.	None	Not Reviewed, Deleted	--

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L	Appropriately refer patients with MDD or related disorders to mental health professionals.	2	<p>Patients with depressive disorders may need more advanced specialized management if any of the following complicating factors that may influence treatment decisions exist:</p> <ul style="list-style-type: none"> a. Failure to respond to adequate depression treatment or otherwise complicating treatment b. A co-existing mental health disorder that significantly complicates treatment (e.g., a history of hypomania or a manic episode, post-traumatic stress disorder [PTSD], psychosis, substance use disorder [SUD]) c. A co-existing medical condition that significantly complicates the treatment planning for depression d. Urgent or unstable psychiatric conditions e. Personal or family history of suicide attempts or suicidal ideas necessitating psychiatric hospitalization f. A past depressive episode involving severe loss of functioning or other life threatening consequences. 	None	Reviewed, Deleted	--
L	Appropriately refer patients with MDD or related disorders to mental health professionals.	3	<p>The primary care provider should consider consultation with mental health specialists in the following circumstances:</p> <ul style="list-style-type: none"> a. Unclear diagnosis b. Failure to respond to 2 or more antidepressants c. Three months of treatment without desired clinical improvement d. Need for, or patient request for, psychotherapy or combination of both medication and psychotherapy e. Concerns about patient's adherence to treatment f. Extreme levels of distress and/or extremely impaired functioning that, in the primary care provider's judgment, seem beyond the capabilities of the primary care setting. 	None	Not Reviewed, Deleted	--

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L	Appropriately refer patients with MDD or related disorders to mental health professionals.	4	When weighing the need for consultation, the primary care provider should take into account the patient's preferences and common barriers to effective mental health consultation such as: a. Patient reluctance to see a mental health care specialist b. Feasibility for the patient c. Geographical distance from consultants d. Length of time to consultant availability.	None	Not Reviewed, Deleted	--
M	All patients, and when appropriate, family members, should be provided education regarding depression, its treatment options, and self-management strategies.	1	Psychoeducation should be provided for individuals with depression at all levels of severity and in all care settings and should be provided both verbally and with written educational materials.	I	Not Reviewed, Deleted	--
M	All patients, and when appropriate, family members, should be provided education regarding depression, its treatment options, and self-management strategies.	2	There should be education on the nature of depression and its treatment options and should include the following: a. Depression is a medical illness, not a character defect b. Education on the causes, symptoms, and natural history of major depression c. Treatment is often effective and is the rule rather than the exception d. The goal of treatment is complete remission; this may require several treatment trials e. Treatment of depression can lead to decreased physical disability and longer life f. Education about various treatment options, including the advantages and disadvantages of each, side effects, what to expect during treatment, and the length of treatment	I	Not Reviewed, Deleted	--

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M	All patients, and when appropriate, family members, should be provided education regarding depression, its treatment options, and self-management strategies.	3	<p>When antidepressant pharmacotherapy is used, the following key messages should be given to enhance adherence to medication:</p> <ul style="list-style-type: none"> a. Side effects often precede therapeutic benefit, but typically recede over time while benefits increase b. A slight increase in suicidal ideation in the first month may occur and patients should contact their provider if this does occur. c. Successful treatment often entails medication and/or dosage adjustments in order to maximize response while minimizing side effects d. Most people need to be on medication for at least 6 to 12 months after adequate response e. It usually takes 2 to 6 weeks before improvements are seen f. Continue to take the medication even after feeling better g. Do not discontinue taking medications without first discussing with your provider 	B	Not Reviewed, Amended	Recommendation 7
M	All patients, and when appropriate, family members, should be provided education regarding depression, its treatment options, and self-management strategies.	4	<p>Education focused on treatment adherence should focus on the following:</p> <ul style="list-style-type: none"> a. Education on the risk of relapse in general; essentially, that relapse risk is high, particularly as the frequency of prior episodes increases b. Education on how to monitor symptoms and side effects c. Education on early signs and symptoms of relapse or recurrence, along with encouragement to seek treatment early in the event these signs or symptoms occur. 	I	Not Reviewed, Amended	Recommendation 7

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M	All patients, and when appropriate, family members, should be provided education regarding depression, its treatment options, and self-management strategies.	5	<p>A major goal for the use of self-management strategies is to enhance the patient’s active engagement in treatment. A common strategy is for a patient to collaboratively select one or two self-management goals at a time to pursue during treatment. Education should incorporate principles of self-management and may include information and goals related to:</p> <ul style="list-style-type: none"> a. Nutrition – Often patients with MDD do not have a balanced diet. Expert opinion suggests that diet should be included in the therapeutic content. However, there is not a robust evidence base that improving diet impacts treatment outcomes. b. Exercise – MDD is associated with low levels of exercise. There is fairly strong evidence that exercise often has significant antidepressant effects. c. Bibliotherapy - Bibliotherapy (the use of self-help texts) may be helpful to patients for understanding their illness and developing self-management skills. Guided self-help programs which entail a cognitive behavioral focus and intermittent monitoring and oversight by a health care professional are significantly more effective than no treatment control and as effective as more traditionally delivered modes (e.g., individual or group cognitive behavioral therapy d. Sleep hygiene – Patients with MDD often have substantial sleep problems including insomnia, hypersomnia, and disturbances of sleep maintenance. Education regarding appropriate sleep hygiene should be included for patients exhibiting any sleep disturbances. e. Tobacco use – Tobacco use has been demonstrated to impact on the recovery of depression; therefore, patients being treated for depression should be advised to abstain until their symptoms remit. 	I, B, C	Not Reviewed, Deleted	--

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			<p>Referral or treatment of nicotine dependence should be considered in patients treated for depression.</p> <p>f. Caffeine use – Expert opinion suggests that excessive caffeine use may exacerbate some symptoms of depression such as sleep problems or anxiety symptoms.</p> <p>g. Alcohol use and abuse – Even low levels of alcohol use have been demonstrated to impact on the recovery of depression; therefore, patients being treated for depression should be advised to abstain until their symptoms remit.</p> <p>h. Pleasurable activities – Depression has been conceptualized by behavioral theorists as the loss or significant decrement of reinforcing activities. Behavioral activation (the systematic scheduling and monitoring of pleasurable or reinforcing activities) has been shown to have significant antidepressant effects.</p>			
M	All patients, and when appropriate, family members, should be provided education regarding depression, its treatment options, and self-management strategies.	6	Psychoeducational strategies should be incorporated into structured and organized treatment protocols, which entail structured systematic monitoring of treatment adherence and response and self-management strategies.	B	Not Reviewed, Amended	Recommendation 7
M	Careful prospective monitoring of symptoms to determine if they persist or abate is a supported strategy in patients with relatively few depressive symptoms, prior to initiation of medication or psychotherapy.	1	In patients with likely adjustment disorder, bereavement or subsyndromal depression rather than major depression, a period of Watchful Waiting (WW) should be initiated. WW should only be considered when systematic follow-up assessments can be conducted.	None	Not Reviewed, Deleted	--

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M	Careful prospective monitoring of symptoms to determine if they persist or abate is a supported strategy in patients with relatively few depressive symptoms, prior to initiation of medication or psychotherapy.	2	Watchful Waiting should incorporate psychoeducation, general support, and prospective symptom monitoring over a 4 to 8 week period.	None	Not Reviewed, Deleted	--
M	The initial treatment strategy for patients diagnosed with MDD, mild or moderate, should start with either psychotherapy or a single antidepressant.	1	<p>Patients who are diagnosed with mild-moderate MDD should receive an initial trial of monotherapy that incorporates either an antidepressant medication or psychotherapy (see Table 7).</p> <p>a. Patient preferences, resources, and tolerability of treatment should be considered in determining the choice between an antidepressant and psychotherapy.</p> <p>b. Monotherapy should be optimized before proceeding to subsequent strategies by monitoring outcomes, maximizing dosage (medication or psychotherapy), and allowing sufficient response time (8-12 weeks).</p>	None	Reviewed, New-replaced	Recommendation 8
M	Combination treatment of antidepressant medication and psychotherapy should be used for moderate to severe MDD or as a potential strategy for managing patients who have had partial or non-response to monotherapy.	1	In patients with moderate to severe MDD, the initial treatment strategy should include both empirically validated psychotherapy and an antidepressant medication.	None	Reviewed, New-replaced	Recommendation 13
M	Combination treatment of antidepressant medication and psychotherapy should be used for moderate to severe MDD or as a potential strategy for managing patients who have had partial or non-response to monotherapy.	2	Patient preferences, resources, and tolerability of treatment may override this recommendation in certain circumstances. In these circumstances, more aggressive monotherapy should be considered as well as adapting treatment when response is not robust.	None	Reviewed, Deleted	--

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M	Certain antidepressants or combinations of psychotropic medications may be required in severe or refractory cases of MDD.	1	More complex treatment strategies should be limited to patients with a diagnosis of MDD who are refractory to the above treatment strategies or in complex cases such as patients with psychiatric comorbidity.	None	Reviewed, Deleted	--
M	Certain antidepressants or combinations of psychotropic medications may be required in severe or refractory cases of MDD.	2	The use of complex treatment strategies should be limited to those with expertise, such as a mental health provider.	None	Reviewed, New-replaced	Recommendation 5
M	Certain antidepressants or combinations of psychotropic medications may be required in severe or refractory cases of MDD.	3	The use of complex strategies increases the burden to patients, the chance of adverse events, and costs. Therefore, structured monitoring and assessment is critical in the management of these patients.	None	Reviewed, Deleted	--
M	Certain somatic therapies (e.g., ECT, VNS) may be required in severe or refractory cases of MDD (i.e., during pregnancy, in catatonic patients, and in elderly patients diagnosed with psychotic depression).	1	<p>Somatic treatment strategies should be prescribed and monitored only by physicians who have specific training and expertise in the management of treatment-resistant depression and the use of these devices.</p> <p>a. Electro-convulsive therapy (ECT) is a recommended treatment strategy for patients who have failed multiple other treatment strategies.</p> <p>b. Electro-convulsive therapy (ECT) may be a first line treatment for pregnant women, patients with psychotic depression, catatonic patients, or patients who have severe self-neglect issues.</p> <p>c. Vagus nerve stimulation (VNS) is currently FDA approved only for treatment of resistant depression for patients who have failed to respond to at least 4 adequate medications and/or electro-convulsive therapy (ECT) trials.</p>	None	Reviewed, Deleted	--
M	Severely impaired patients with MDD may require acute or subacute stabilization.	1	Patients who express suicidal or homicidal thoughts or who are unable to provide basic self-care should be considered for admission to an inpatient psychiatric unit.	None	Not Reviewed, Deleted	--

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M	Severely impaired patients with MDD may require acute or subacute stabilization.	2	Patients with unstable social networks or who lack significant support in the community may require subacute care in a residential setting.	None	Not Reviewed, Deleted	--
N	Psychosocial rehabilitation services should be offered to individuals with MDD who have significant, unmet psychosocial needs.	1	Individuals with MDD should be assessed for any significant, unmet psychosocial needs or situational stressors. These include, but are not limited to: <ul style="list-style-type: none"> a. Inadequate or no housing b. Financial difficulties, especially if unable to meet basic needs c. Problematic family relationships or situations (including caregiver burden or domestic violence) d. Poor social support e. Religious and spiritual problems f. Occupational problems g. Difficulties with activities of daily living or instrumental activities of daily living h. Any other acute or chronic situational stressors 	B	Not Reviewed, Deleted	--
N	Psychosocial rehabilitation services should be offered to individuals with MDD who have significant, unmet psychosocial needs.	2	If unmet psychosocial needs are identified, psychosocial rehabilitation services should be offered to individuals with MDD at all levels of severity, regardless of population or setting, and regardless of the type of pharmacotherapy or psychotherapy being administered.	B	Not reviewed, Deleted	--
N	Psychosocial rehabilitation services should be offered to individuals with MDD who have significant, unmet psychosocial needs.	3	Psychosocial rehabilitation services may include, but are not limited to, referrals to community social service agencies, emergency and transitional housing programs, vocational rehabilitation, agencies providing financial assistance, support groups, senior centers, and supervised living situations (e.g., foster homes, assisted living facilities).	C	Not Reviewed, Deleted	--

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O	Assess depressive symptoms, functional status, and suicide risk to determine treatment effects.	1	The PHQ-9 should be used to monitor treatment response at 4 to 6 weeks after initiation of treatment, after each change in treatment, and periodically until full remission is achieved.	B	Not Reviewed, Deleted	--
O	Assess depressive symptoms, functional status, and suicide risk to determine treatment effects.	2	In patients who reach full remission, assessment of symptoms should be continued periodically to monitor for relapse or recurrence.	B	Not Reviewed, Deleted	--
O	Assess depressive symptoms, functional status, and suicide risk to determine treatment effects.	3	Patients with suicidal ideation should have a careful evaluation of suicide risk.	A	Not Reviewed, Amended	Recommendation 2
O	Assess for adverse effects and tolerability after any change of treatment strategy.	1	Using a clinical interview, assess for treatment burden (e.g., medication side effects or adverse effects, attending appointments) after initiating or changing treatment, when the patient is non-adherent to treatment, or when the patient is not responding to treatment.	None	Reviewed, Deleted	--
O	Assess for adverse effects and tolerability after any change of treatment strategy.	2	Identified side effects should be managed to minimize or alleviate the side effects.	None	Reviewed, Deleted	--
O	Systematically assess adherence to treatment with all depressed patients. Employ educational and systems interventions to enhance adherence for patients at high risk of poor adherence. Consider evidence-based psychotherapy in combination with antidepressant medications.	1	Adherence should be assessed directly and routinely, targeting common reasons for nonadherence (e.g., side effects, lack of efficacy, feeling better).	B	Not Reviewed, Deleted	--

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O	Systematically assess adherence to treatment with all depressed patients. Employ educational and systems interventions to enhance adherence for patients at high risk of poor adherence. Consider evidence-based psychotherapy in combination with antidepressant medications.	2	Providers should give simple educational messages regarding antidepressant use (e.g., take daily, understand gradual nature of benefits, continue even when feeling better, do not stop without checking with the provider, and specific instructions on how to address issues or concerns) in order to increase adherence to treatment in the acute phase of treatment.	B	Not Reviewed, Amended	Recommendation 7
O	Systematically assess adherence to treatment with all depressed patients. Employ educational and systems interventions to enhance adherence for patients at high risk of poor adherence. Consider evidence-based psychotherapy in combination with antidepressant medications.	3	In primary care, utilize collaborative care personnel (e.g., nurses, social workers, psychologists) and systems strategies to enhance adherence to treatment beyond the acute phase. Collaborative care strategies used by mental health specialists focus on patient education via systematic in-person or telephonic follow-up/monitoring to address adherence, relapse prevention issues and self-management strategies.	B	Reviewed, New-replaced	Recommendation 6
O	Systematically assess adherence to treatment with all depressed patients. Employ educational and systems interventions to enhance adherence for patients at high risk of poor adherence. Consider evidence-based psychotherapy in combination with antidepressant medications.	4	For patients who are at high risk for non-adherence to antidepressant medication, refer for psychotherapy to increase medication adherence and decrease the chance of treatment discontinuation.	B	Not Reviewed, Deleted	--

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O	In patients who do not respond to an adequate treatment trial, reconfirm the diagnoses and assess for concurrent problems that may adversely affect treatment.	1	<p>In treatment of non-responders, the diagnosis of MDD should be reconfirmed and the patient should be assessed for factors that may contribute to non-response. Referral to mental health specialty for a comprehensive assessment may be considered. Evaluation should include:</p> <ol style="list-style-type: none"> Assessment for existence of psychiatric conditions that may present initially with depressive symptoms or adversely affect treatment response, including bipolar disorder, substance use disorder, post-traumatic stress disorder, generalized anxiety or panic disorder and in older adults, dementia. Assessment for medical conditions that may present with depressive symptoms. This may require additional history, physical examination, and laboratory testing. Poorly controlled medical conditions (e.g., chronic pain, congestive heart failure [CHF]) that may potentiate depression should be treated aggressively). Assessment for psychosocial problems that may contribute to treatment nonresponse. Domains assessed may include financial, legal, relationship, work, or negative life events. 	None	Not Reviewed, Deleted	--
P	<p>Determine if depressive symptoms are significantly improved, defined as a:</p> <ul style="list-style-type: none"> ▪ Five-point reduction OR score <10 on the PHQ-9 ▪ Twenty-five % or greater reduction in score on an accepted standardized instrument. 	1	If the patient has shown clinically significant improvement in depressive symptoms, but is not yet at remission, and if medication has been well tolerated, then continuing to prescribe and raising the dose is recommended.	None	Reviewed, Deleted	--

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Annotation	Action Statement					
P	Determine if depressive symptoms are significantly improved, defined as a: <ul style="list-style-type: none"> Five-point reduction OR score <10 on the PHQ-9 Twenty-five % or greater reduction in score on an accepted standardized instrument. 	1	Improvement with psychotherapy is often slower than with pharmacotherapy. A decision regarding progress with psychotherapy and the need to change or augment this type of treatment may require 8 to 10 weeks before evaluation.	None	Reviewed, Deleted	--
Q	Ensure patient remains on treatment with desired outcome.	1	After initiation of therapy or change in medication or dose adjustment, patients should be monitored in person or by phone on a monthly basis. Clinicians can use these encounters to assess adherence to medication and psychotherapy, emergence of adverse effects, symptom breakthrough, suicidality, and psychosocial stress.	None	Reviewed, Deleted	--
R	The goal of antidepressant therapy should be the lowest possible degree of depressive symptomatology in order to minimize risk of later relapse.	1	Full remission is defined as: <ul style="list-style-type: none"> PHQ-9 score of 4 or less, maintained for at least 1 month, OR Beck Depression Inventory (BDI) score of 10 or less, maintained for at least 1 month, OR Hamilton Rating Scale for Depression (HRSD) of 7 or less, maintained for at least 1 month. 	None	Not Reviewed, Deleted	--
S	Continue antidepressant treatment for at least six months to decrease the risk of relapse after initial remission is achieved.	1	In patients with MDD who achieve remission with antidepressant medication, treatment should be continued at the same dose for an additional 6 to 12 months to decrease the risk of relapse.	A	Reviewed, New-replaced	Recommendation 15
S	Continue antidepressant treatment for at least six months to decrease the risk of relapse after initial remission is achieved.	2	In patients who achieve remission with psychotherapy, continuation phase psychotherapy should be considered for patients at higher risk for relapse, taking into account personal history, family history, and severity of current illness.	None	Not Reviewed, Deleted	--

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Annotation	Action Statement					
S	Continue antidepressant treatment for at least six months to decrease the risk of relapse after initial remission is achieved.	3	Cognitive behavioral therapy (CBT), Cognitive Therapy (CT), or Mindfulness-Based Cognitive Therapy (MBCT) should be used during the continuation phase of treatment with patients at high risk for relapse (i.e., two or more prior episodes, double depression, unstable remission status) to reduce the risk of subsequent relapse/recurrence. This can occur after pharmacotherapy has ended or as a combined intervention for patients continuing pharmacotherapy.	A	Reviewed, Amended	Recommendation 17
S	Continue antidepressant treatment for at least six months to decrease the risk of relapse after initial remission is achieved.	4	Depressive symptoms and functional status should be assessed periodically, more frequently early in the continuation phase, as this corresponds to the highest risk period for relapse.	C	Reviewed, Amended	Recommendation 14
S	Continue antidepressant treatment for at least six months to decrease the risk of relapse after initial remission is achieved.	5	A relapse prevention plan should be developed that addresses duration of treatment, prognosis, self-management goals, and self-monitoring.	B	Reviewed, Amended	Recommendation 14
T	Continue antidepressant treatment in patients who recover from depression but are at high risk for recurrence.	1	Patients should be assessed for risk of recurrence after completing the continuation phase treatment.	I	Reviewed, New-replaced	Recommendation 15
T	Continue antidepressant treatment in patients who recover from depression but are at high risk for recurrence.	2	<p>Indications for Maintenance:</p> <ul style="list-style-type: none"> a. Two or more prior episodes, chronic major (> 1 year), or double depression b. A family history of bipolar disorder and more severe depression as defined by: the need for hospitalization, strong suicidal ideation or behaviors, longer duration of symptoms, and more residual symptoms after response to treatment c. Co-morbid substance use disorder, anxiety disorders d. Ongoing psychosocial stressors: low socioeconomic status, acrimonious relationship, chronic/severe medical illness. 	B, C, C, C	Reviewed, Deleted	--

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T	Continue antidepressant treatment in patients who recover from depression but are at high risk for recurrence.	3	Maintenance treatment should be continued at the same dosage that was used during the continuation phase, and continued for at least 12 months and possibly indefinitely.	A	Reviewed, New-replaced	Recommendation 16
T	Continue antidepressant treatment in patients who recover from depression but are at high risk for recurrence.	4	Consider maintenance phase psychotherapy for a very select population.	B	Reviewed, Deleted	--
U	The selection of an antidepressant for a patient with MDD should be based on safety, comorbid conditions, symptoms, concurrent medication, and previous antidepressant response.	1	The choice of antidepressant should be based on safety, the patient's co-morbid conditions, symptoms, concurrent medication, and previous response: a. Antidepressants in dosage forms that are taken once or twice a day should be prescribed to enhance patient adherence b. Antidepressant doses should be increased based on patient tolerance and response c. An adequate trial to response of an antidepressant is a therapeutic dose for 4 to 6 weeks.	I	Reviewed, Deleted	--
U	The selection of an antidepressant for a patient with MDD should be based on safety, comorbid conditions, symptoms, concurrent medication, and previous antidepressant response.	2	Patients who do not tolerate an initial antidepressant prior to responding, should be switched to a different first-line antidepressant.	None	Reviewed, New-replaced	Recommendation 9
U	The selection of an antidepressant for a patient with MDD should be based on safety, comorbid conditions, symptoms, concurrent medication, and previous antidepressant response.	3	Patients who demonstrate a 25 percent improvement or greater, without achieving remission, from their baseline PHQ-9 score after 6 weeks of treatment have the following options: a. Continue present management and reassess in 4-6 weeks b. Consider raising the dose in patients who tolerate to accelerate remission	None	Reviewed, Deleted	--

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U	The selection of an antidepressant for a patient with MDD should be based on safety, comorbid conditions, symptoms, concurrent medication, and previous antidepressant response.	4	<p>Patients who do not achieve a 25 percent improvement from their baseline PHQ-9 after 6 weeks of medication have the following options:</p> <ol style="list-style-type: none"> Consider raising the dose in patients who tolerate to accelerate remission Switch to a different first line antidepressant and repeat the process starting at Box 32 of the clinical algorithm 	None	Reviewed, Deleted	--
U	The selection of an antidepressant for a patient with MDD should be based on safety, comorbid conditions, symptoms, concurrent medication, and previous antidepressant response.	5	<p>Patients who do not achieve remission (a PHQ-9 score < 5) after 8 to 12 weeks with an initial antidepressant have the following options:</p> <ol style="list-style-type: none"> Increase in the dose, provided the dose has not already been maximized and is tolerable Current medication could be augmented with another medication (see #8) or combined with psychotherapy Switch to a different first line antidepressant and repeat the process starting at Box 32 of the clinical algorithm 	None	Reviewed, Deleted	--
U	The selection of an antidepressant for a patient with MDD should be based on safety, comorbid conditions, symptoms, concurrent medication, and previous antidepressant response.	6	<p>Patients who do not achieve remission after 8 to 12 weeks of a second treatment trial using a first-line antidepressant have the following options available:</p> <ol style="list-style-type: none"> Current medication could be augmented with another medication (see #8) or combined with psychotherapy (if not already tried) Consider modifying therapy and restarting the course of therapy with a different drug, following the steps and options discussed above starting at Box 32 Consider a referral to mental health services. 	None	Reviewed, New-replaced	Recommendation 9

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U	The selection of an antidepressant for a patient with MDD should be based on safety, comorbid conditions, symptoms, concurrent medication, and previous antidepressant response.	7	Patients who do not achieve remission after adequate trials of two first-line antidepressants should either be switched to a new antidepressant from a different class (consider venlafaxine if not already tried) or receive augmentation with either medications or psychotherapy.	None	Reviewed, New-replaced	Recommendation 9
U	The selection of an antidepressant for a patient with MDD should be based on safety, comorbid conditions, symptoms, concurrent medication, and previous antidepressant response.	8	Patients who do not achieve remission after adequate trials of three different antidepressants should either receive augmentation with either medications or psychotherapy or receive combination antidepressant treatment or electro-convulsive therapy (ECT).	None	Reviewed, Deleted	--
U	Care management should be considered for patients with MDD who are treated in primary care settings.	1	Consider 6 to 12 months of care management for patients with mild to moderate major depression.	B	Reviewed, New-replaced	Recommendation 6
U	Care management should be considered for patients with MDD who are treated in primary care settings.	2	Care management components may be delivered by telephone, should be delivered by individuals with the relevant training and skill set, and should include: <ul style="list-style-type: none"> a. Depression symptom monitoring using a validated instrument (e.g., PHQ-9) at each contact b. Depression education (illness, course, treatments, timing of expected treatment response, active coping strategies such as exercise and leisure planning) c. Antidepressant medication monitoring to include tolerability and adherence d. Initiation of crisis assessment and intervention as needed e. Care coordination with primary care and mental health clinicians as needed. 	B	Reviewed, Deleted	--

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U	Care management should be considered for patients with MDD who are treated in primary care settings.	3	<p>Care managers should:</p> <ol style="list-style-type: none"> Encourage and support regular attendance for scheduled visits with medical or mental health care providers and adherence to psychotherapies or antidepressant therapies as appropriate Look for possible manic or hypomanic episodes or alcohol/substances abuse to facilitate referral to mental health Participate in routine clinical review of the care manager caseload and facilitate feedback of mental health specialist recommendations 	None	Reviewed, Deleted	--
U		1	<p>There is insufficient evidence to recommend one antidepressant medication over another for all patients.</p> <ol style="list-style-type: none"> The choice of medication is based on side effect profiles, history of prior response, family history of response, type of depression, concurrent medical illnesses, concurrently prescribed medications, and cost of medication Generally, selective serotonin reuptake inhibitors (SSRIs) or venlafaxine are first line antidepressants for patients in the primary care setting because of their low toxicity and ease of administration relative to other antidepressants Generally, initial doses used for the elderly should be lower than in healthy adults Prior to discontinuing an antidepressant as a failure, providers should ensure that an appropriate dose titration and target dose range has been achieved and an adequate response period allowed (a minimum of four to six weeks) Discontinuation of antidepressant maintenance therapy should be done with a slow taper, as it may result in adverse withdrawal symptoms or return of original depressive symptoms. Tapering should be 	None	Reviewed, New-replaced	Recommendation 8

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			guided by the elimination half-life of the parent compound and metabolites, and by close monitoring of depressive symptoms.			
U	Selective serotonin reuptake inhibitors (SSRIs) along with the serotonin norepinephrine reuptake inhibitors (SNRIs), such as bupropion and mirtazapine are considered a first-line treatment option for adults with MDD.	1	All of the selective serotonin reuptake inhibitors (SSRIs), excluding fluvoxamine, may be used as first-line agents in the treatment of adults with MDD.	None	Reviewed, New-replaced	Recommendation 8
U	Selective serotonin reuptake inhibitors (SSRIs) along with the serotonin norepinephrine reuptake inhibitors (SNRIs), such as bupropion and mirtazapine are considered a first-line treatment option for adults with MDD.	2	Patients who do not remit or are intolerant of one SSRI may be switched to another SSRI or to another class of antidepressant.	None	Reviewed, New-replaced	Recommendation 9
U	Selective serotonin reuptake inhibitors (SSRIs) along with the serotonin norepinephrine reuptake inhibitors (SNRIs), such as bupropion and mirtazapine are considered a first-line treatment option for adults with MDD.	3	Patients who do not remit or are intolerant to two or more SSRIs should be switched to a different class of antidepressant.	None	Reviewed, New-replaced	Recommendation 9
U	Selective serotonin reuptake inhibitors (SSRIs) along with the serotonin norepinephrine reuptake inhibitors (SNRIs), such as bupropion and mirtazapine are considered a first-line treatment option for adults with MDD.	4	Maximizing the dose of an SSRI should be considered for patients who show no response or partial response.	None	Reviewed, Deleted	--
U	Selective serotonin reuptake inhibitors (SSRIs) along with the serotonin norepinephrine reuptake inhibitors (SNRIs), such as bupropion and mirtazapine are considered a first-line treatment option for adults with MDD.	5	Augmentation may be considered for those who show only partial response to an SSRI.	None	Reviewed, New-replaced	Recommendation 9

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U	Selective serotonin reuptake inhibitors (SSRIs) along with the serotonin norepinephrine reuptake inhibitors (SNRIs), such as bupropion and mirtazapine are considered a first-line treatment option for adults with MDD.	6	When SSRIs are prescribed, the following should be considered: a. The potential for pharmacokinetic and pharmacodynamic drug interactions b. The potential for discontinuation symptoms particularly for the shorter half-life SSRIs c. Drug specific side effects in selecting specific SSRI for patients who may be sensitive to these effects.	None	Reviewed, New-replaced	Recommendation 8
U	Selective serotonin reuptake inhibitors (SSRIs) along with the serotonin norepinephrine reuptake inhibitors (SNRIs), such as bupropion and mirtazapine are considered a first-line treatment option for adults with MDD.	7	Avoid paroxetine in pregnant women.	None	Reviewed, Deleted	--
U	Selective serotonin reuptake inhibitors (SSRIs) along with the serotonin norepinephrine reuptake inhibitors (SNRIs), such as bupropion and mirtazapine are considered a first-line treatment option for adults with MDD.	8	When using SSRIs in pregnant women, the potential for increased risk of persistent pulmonary hypertension of the newborn should be considered.	None	Reviewed, Deleted	--
U	SNRIs, along with the selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.	1	Serotonin norepinephrine reuptake inhibitors (SNRIs) may be used as first line agents in the treatment of adults with MDD.	None	Reviewed, New-replaced	Recommendation 8
U	SNRIs, along with the selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.	2	Patients who do not remit or are intolerant of an SNRI may be switched to another class of antidepressants.	None	Reviewed, New-replaced	Recommendation 9

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U	SNRIs, along with the selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.	3	SNRIs may be considered as a treatment option in patients who have not remitted to treatment with one or more second generation antidepressants (SSRIs, bupropion, or mirtazapine).	None	Reviewed, New-replaced	Recommendation 9
U	SNRIs, along with the selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.	4	SNRIs should be initiated at a low dose to improve tolerability and then increased to an effective dose.	None	Reviewed, Deleted	--
U	SNRIs, along with the selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.	5	Maximizing the dose of venlafaxine may be considered for patients who show no response or a partial response to antidepressant treatment.	None	Reviewed, Deleted	--
U	SNRIs, along with the selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.	6	Augmentation may be considered for patients who show no response or a partial response to antidepressant treatment.	None	Reviewed, New-replaced	Recommendation 9
U	SNRIs, along with the selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.	7	Consider the potential for drug interactions with this class.	None	Reviewed, New-replaced	Recommendation 8
U	SNRIs, along with the selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.	8	Consider the potential for discontinuation symptoms with this class.	None	Reviewed, New-replaced	Recommendation 8

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U	SNRIs, along with the selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.	9	Avoid duloxetine in patients with substantial alcohol use or evidence of chronic liver disease.	None	Reviewed, Deleted	--
U	Bupropion, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, is considered a first-line treatment option for MDD.	1	Bupropion is a treatment option for patients with MDD for whom a first-line antidepressant is appropriate.	None	Reviewed, New-replaced	Recommendation 8
U	Bupropion, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, is considered a first-line treatment option for MDD.	2	Bupropion is an augmentation option for patients who have partially responded to a different antidepressant but have not achieved remission.	None	Reviewed, New-replaced	Recommendation 9
U	Bupropion, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, is considered a first-line treatment option for MDD.	3	Patients should be titrated to the dose of bupropion that is effective and tolerable without exceeding the maximum recommended daily dose.	None	Reviewed, Deleted	--
U	Bupropion, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, is considered a first-line treatment option for MDD.	4	Bupropion should be considered as an alternative antidepressant for patients who have experienced intolerable sexual side effects with other antidepressants.	None	Reviewed, New-replaced	Recommendation 9

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U	Bupropion, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, is considered a first-line treatment option for MDD.	5	Bupropion may be considered for patients for whom weight gain would be problematic or for patients who experienced intolerable weight gain with another antidepressant.	None	Reviewed, Deleted	--
U	Bupropion, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, is considered a first-line treatment option for MDD.	6	Bupropion may be considered for patients with MDD who desire to stop smoking.	None	Reviewed, Deleted	--
U	Bupropion, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, is considered a first-line treatment option for MDD.	7	Bupropion should not be prescribed to patients with a history of seizure disorder or anorexia nervosa or bulimia.	None	Reviewed, Deleted	--
U	Mirtazapine, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and bupropion, is considered a first-line treatment option for MDD. Mirtazapine can also be used in combination with other antidepressants.	1	Mirtazapine is a treatment option for patients with MDD for whom a first-line antidepressant is appropriate.	None	Reviewed, New-replaced	Recommendation 8

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U	Mirtazapine, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and bupropion, is considered a first-line treatment option for MDD. Mirtazapine can also be used in combination with other antidepressants.	2	Mirtazapine in combination with another antidepressant is a treatment option for patients who have not achieved remission after several trials with a first-line antidepressant.	None	Reviewed, New-replaced	Recommendation 9
U	Mirtazapine, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and bupropion, is considered a first-line treatment option for MDD. Mirtazapine can also be used in combination with other antidepressants.	3	Mirtazapine's dose should be titrated to a dose that is effective and tolerated without exceeding the maximum recommended daily dose.	None	Reviewed, Deleted	--
U	Mirtazapine, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and bupropion, is considered a first-line treatment option for MDD. Mirtazapine can also be used in combination with other antidepressants.	4	Mirtazapine is a treatment option for patients who have experienced intolerable sexual side effects with other antidepressants.	None	Reviewed, Deleted	--
U	Mirtazapine, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and bupropion, is considered a first-line treatment option for MDD. Mirtazapine can also be used in combination with other antidepressants.	5	Mirtazapine should be avoided in patients for whom weight gain would be problematic.	None	Reviewed, Deleted	--

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U		1	TCA's may be considered agents for certain patients who do not respond to two or more trials with first line antidepressants or who have previously achieved remission with TCA.	B	Reviewed, New-replaced	Recommendation 22 Recommendation 23
U		2	TCA's should be used cautiously in the elderly. If the use of TCA's is necessary, nortriptyline and desipramine should be considered first. Due to increased side effects (e.g., CNS, anticholinergic, cardiovascular effects) associated with amitriptyline, imipramine and doxepin, the primary care physician should avoid the use of these agents in elderly patients.	None	Reviewed, Deleted	--
U		3	TCA's should be used cautiously in patients who are at high risk for suicide.	None	Reviewed, Deleted	--
U		4	Therapeutic response and dosing with a TCA may vary among patients due to both pharmacokinetic (e.g., enzyme induction by smoking), and pharmacodynamic (e.g., increased sensitivity in the elderly) differences.	None	Reviewed, Deleted	--
U		5	Therapeutic plasma concentrations should be monitored. Of the various TCA's, plasma concentration for desipramine, imipramine, and nortriptyline are best established. Although amitriptyline has been extensively studied, no clear relationship between response and plasma level has emerged. The use of therapeutic blood concentration can be of value in particular clinical instances, such as in patients who do not respond to or comply with therapy, patients on combination therapy, elderly patients, or patients with suspected drug toxicity.	None	Reviewed, Deleted	--
U		1	MAOIs may be considered a treatment option for adults with MDD who have not achieved remission on other antidepressants.	None	Reviewed, New-replaced	Recommendation 22 Recommendation 23

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U		2	Patient education must include dietary and drug restrictions, including the requirement for a tyramine-restricted diet with all monoamine oxidase inhibitors (MAOIs) (with the exception of the lowest strength of the selegiline transdermal patch) to avoid a hypertensive crisis.	None	Reviewed, Deleted	--
U		3	Avoid concurrent use with other medications with serotonergic effects (e.g., other antidepressants, triptans, meperidine, tramadol, propoxyphene, dextromethorphan) due to the risk of serotonin syndrome.	None	Reviewed, Deleted	--
U		4	Avoid concurrent use with stimulants, vasoconstrictors and other medications with adrenergic effects due to the potential for hypertensive crisis.	None	Reviewed, Deleted	--
U		5	Allow adequate wash-out periods following treatment with other antidepressants or other drugs that interact with MAOIs based on half-life (e.g., 5 weeks after stopping fluoxetine therapy before starting an MAOI).	None	Reviewed, Deleted	--
U	Augmentation with medication may be considered for patients who have had a partial response to antidepressant monotherapy at a therapeutic dose after at least 6 weeks. The augmenting medication selected should be based on the patient's current medications (including antidepressants), co-morbid conditions, and adverse effect profile.	1	Augmentation can be introduced at any point in therapy, provided the patient has demonstrated a partial response to an existing antidepressant.	None	Reviewed, New-replaced	Recommendation 9
U	Augmentation with medication may be considered for patients who have had a partial response to antidepressant monotherapy at a therapeutic dose after at least 6 weeks. The augmenting medication selected should be based on the	2	Bupropion SR and anxiolytic buspirone are the preferred initial augmentation strategies given their ease of use and lower risk of toxicity.	None	Reviewed, Deleted	--

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	patient's current medications (including antidepressants), co-morbid conditions, and adverse effect profile.					
U	Augmentation with medication may be considered for patients who have had a partial response to antidepressant monotherapy at a therapeutic dose after at least 6 weeks. The augmenting medication selected should be based on the patient's current medications (including antidepressants), co-morbid conditions, and adverse effect profile.	3	The atypical antipsychotics, with the exception of clozapine, can be considered as an alternative augmentation strategy, but should only be considered when other more established augmentation agents have either failed to result in remission or are contraindicated.	None	Reviewed, Deleted	--
U	The psychostimulants including the amphetamines are not appropriate as monotherapy for the treatment of MDD. Psychostimulants may have a role as augmentation agents or in the treatment of other forms of depression such as in the medically-ill elderly or poststroke patients.	1	The psychostimulants may have a role as augmentation agents, although the evidence is stronger in support of other augmentation agents.	None	Reviewed, New-replaced	Recommendation 9
U	The psychostimulants including the amphetamines are not appropriate as monotherapy for the treatment of MDD. Psychostimulants may have a role as augmentation agents or in the treatment of other forms of depression such as in the medically-ill elderly or poststroke patients.	2	The psychostimulants may be useful as monotherapy for patients who are demoralized, apathetic or physically inactive; specific patient populations are the medically ill elderly or post-stroke patients.	None	Reviewed, Deleted	--

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
U	The psychostimulants including the amphetamines are not appropriate as monotherapy for the treatment of MDD. Psychostimulants may have a role as augmentation agents or in the treatment of other forms of depression such as in the medically-ill elderly or poststroke patients.	3	Methylphenidate is the most studied and preferred psychostimulant.	None	Reviewed, Deleted	--
U	The psychostimulants including the amphetamines are not appropriate as monotherapy for the treatment of MDD. Psychostimulants may have a role as augmentation agents or in the treatment of other forms of depression such as in the medically-ill elderly or poststroke patients.	4	Only the immediate-release formulations of psychostimulants should be prescribed.	None	Reviewed, Deleted	--
U	The psychostimulants including the amphetamines are not appropriate as monotherapy for the treatment of MDD. Psychostimulants may have a role as augmentation agents or in the treatment of other forms of depression such as in the medically-ill elderly or poststroke patients.	5	Patients receiving psychostimulants should have their heart rate and blood pressure monitored. Psychostimulants should not be prescribed for patients with uncontrolled hypertension or cardiovascular disease.	None	Reviewed, Deleted	--
U	The psychostimulants including the amphetamines are not appropriate as monotherapy for the treatment of MDD. Psychostimulants may have a role as augmentation agents or in the treatment of other forms of depression such as in the medically-ill elderly or poststroke patients.	6	Psychostimulants are best avoided in patients with a co-morbid anxiety or for those in whom anxiety is a significant symptom of their depression.	None	Reviewed, Deleted	--

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
U	Evidence-based short-term psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended treatment options for major depression. Other psychotherapies are treatment options for specific populations or are based on patient preference.	1	<p>First-line psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended for the treatment of uncomplicated major depression: [A]</p> <ul style="list-style-type: none"> a. PST is recommended for psychotherapy provided in a primary care setting [A] b. Treatments should be delivered by providers trained in the specific technique [B] c. For severe depression (Hamilton rating scale for depression [HRSD] ≥ 20 or equivalent): <ul style="list-style-type: none"> i. Behavioral Activation (BA) is a recommended treatment [B] ii. CBT is a treatment option [B] 	A, B	Reviewed, New-replaced	Recommendation 8
U	Evidence-based short-term psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended treatment options for major depression. Other psychotherapies are treatment options for specific populations or are based on patient preference.	2	<p>The recommended courses for first line psychotherapies (CBT, IPT, PST) are:</p> <ul style="list-style-type: none"> a. CBT and IPT: 16 to 20 sessions over approximately 16 weeks b. PST: six sessions over 3 months 	A	Reviewed, Deleted	--
U	Evidence-based short-term psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended treatment options for major depression. Other psychotherapies are treatment options for specific populations or are based on patient preference.	3	In patients with a history of suicide attempts, CBT is a recommended treatment for reducing risk of suicide attempts.	B	Reviewed, Deleted	--

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	2009 Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
U	Evidence-based short-term psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended treatment options for major depression. Other psychotherapies are treatment options for specific populations or are based on patient preference.	4	For patients with severe, recurrent or chronic major depression, or double depression combination, CBT and pharmacotherapy are recommended treatments.	A	Reviewed, New-replaced	Recommendation 13
U	Evidence-based short-term psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended treatment options for major depression. Other psychotherapies are treatment options for specific populations or are based on patient preference.	5	For older patients with chronic MDD, combination dialectical behavior therapy (DBT) and pharmacotherapy is the recommended first-line treatment intervention.	B	Reviewed, New-replaced	Recommendation 18
					Reviewed, New-replaced	Recommendation 19
U	Evidence-based short-term psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended treatment options for major depression. Other psychotherapies are treatment options for specific populations or are based on patient preference.	6	For older patients who have recently become caregivers for a disabled family member, short-term psychodynamic psychotherapy (SDPP) is the recommended first-line treatment intervention.	C	Reviewed, Deleted	--

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
U	Evidence-based short-term psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended treatment options for major depression. Other psychotherapies are treatment options for specific populations or are based on patient preference.	7	For pregnant and postpartum women, CBT and IPT are the recommended first-line treatment interventions. [B]	B	Reviewed, New-replaced	Recommendation 18
U	Evidence-based short-term psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended treatment options for major depression. Other psychotherapies are treatment options for specific populations or are based on patient preference.	8	For patients with comorbid depression and relationship distress, couples/marital-focused therapy (CFT) is the recommended first-line treatment intervention.	B	Reviewed, New-replaced	Recommendation 20
U	Individual CBT is a recommended treatment option for adults with major depression. CBT may be combined with pharmacotherapy for patients who do not respond to monotherapy.	1	Sixteen to 20 sessions of individual CBT for major depression is a recommended treatment option, including postpartum or older patients.	A	Reviewed, New-replaced	Recommendation 18 Recommendation 19
U	Individual CBT is a recommended treatment option for adults with major depression. CBT may be combined with pharmacotherapy for patients who do not respond to monotherapy.	2	CBT group is an option for treatment of major depression.	B	Reviewed, New-replaced	Recommendation 10

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
U	Individual CBT is a recommended treatment option for adults with major depression. CBT may be combined with pharmacotherapy for patients who do not respond to monotherapy.	3	For severe major depression, CBT alone is a treatment option.	B	Reviewed, Deleted	--
U	Individual CBT is a recommended treatment option for adults with major depression. CBT may be combined with pharmacotherapy for patients who do not respond to monotherapy.	4	For severe, recurrent (3 or more episodes) or chronic major depression, CBT in combination with pharmacotherapy is a recommended treatment option.	A	Reviewed, New-replaced	Recommendation 13
U	Individual Interpersonal Psychotherapy (IPT) is a recommended treatment option for adults (including older adults and pregnant women) with uncomplicated mild to moderate major depression.	1	Sixteen to 20 sessions of interpersonal psychotherapy (IPT) is a recommended treatment option for mild to moderate MDD.	A	Reviewed, New-replaced	Recommendation 18
						Recommendation 19
U	Individual Interpersonal Psychotherapy (IPT) is a recommended treatment option for adults (including older adults and pregnant women) with uncomplicated mild to moderate major depression.	2	IPT in the treatment of mild to moderate MDD should be delivered by clinicians trained specifically in the delivery of IPT.	C	Reviewed, New-replaced	Recommendation 18
						Recommendation 19
U	Individual Interpersonal Psychotherapy (IPT) is a recommended treatment option for adults (including older adults and pregnant women) with uncomplicated mild to moderate major depression.	3	IPT combined with pharmacotherapy is a treatment option for patients who do not respond to either monotherapy.	B	Reviewed, Deleted	--

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
U	Problem-solving therapy (PST) is the recommended treatment for uncomplicated mild to moderate major depression particularly in primary care settings.	1	Six sessions of individual problem-solving therapy (PST), administered over 3 months, in a primary care setting, with or without antidepressant therapy (depending on other factors) is a recommended treatment option for patients with uncomplicated mild to moderate MDD, including older adults.	A	Reviewed, New-replaced	Recommendation 8
U	Behavior Therapy (BT), including Behavioral Activation (BA), is a recommended treatment option for adults with major depression. It may be considered as a first line treatment for patients with severe depression who do not tolerate pharmacotherapy.	1	Individual Behavior Therapy/Behavioral Activation (BT/BA), is a treatment option for patients with mild to moderate MDD.	A	Reviewed, New-replaced	Recommendation 8
						Recommendation 18
						Recommendation 19
U	Behavior Therapy (BT), including Behavioral Activation (BA), is a recommended treatment option for adults with major depression. It may be considered as a first line treatment for patients with severe depression who do not tolerate pharmacotherapy.	2	Sixteen to 24 sessions of individual Behavior Therapy/Behavioral Activation (BT/BA) may be offered to patients with severe MDD, especially if they are not able to tolerate pharmacotherapy (including pregnant, postpartum, or older patients).	B	Reviewed, New-replaced	Recommendation 18
						Recommendation 19
U	Behavior Therapy (BT), including Behavioral Activation (BA), is a recommended treatment option for adults with major depression. It may be considered as a first line treatment for patients with severe depression who do not tolerate pharmacotherapy.	3	Individual Behavior Therapy/Behavioral Activation (BT/BA) may be particularly useful in primary care settings, due to the potentially brief nature of the approach and the relative ease in learning how to effectively implement it.	I	Reviewed, Deleted	--

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
U	Couple-focused therapy (CFT) is a recommended treatment option for mild to moderate, uncomplicated depression for patients concurrently experiencing marital distress.	1	Couple-focused therapy (CFT) is a treatment option for MDD if at least one member of the couple is experiencing depression as well as marital distress.	C	Reviewed, New-replaced	Recommendation 20
U	Consider the use of counseling for adults with mild to moderate MDD for short-term symptom reduction.	1	Counseling may be considered for achieving short term reduction in depressive symptoms for adults with mild to moderate MDD of recent onset.	C	Reviewed, New-Replaced	Recommendation 11
U	Modified dialectical behavioral therapy (DBT) is an option for an adjunctive treatment to pharmacotherapy for major depression in older patients.	1	Twenty-eight sessions of dialectical behavioral therapy (DBT) skills training class, supplemented by weekly phone coaching, may be offered as an augmentation strategy to pharmacotherapy for older patients with MDD.	C	Reviewed, Deleted	--
U	Short-term psychodynamic psychotherapy (SDPP) is an option for treating mild to moderate MDD in an outpatient mental health setting.	1	Short-term psychodynamic psychotherapy (SDPP) may be considered for achieving reduction in depressive symptoms for mild to moderate MDD in adults, depending on patient preference and on the presence of other complex comorbidities.	C	Reviewed, New-Replaced	Recommendation 11
U	Computer-based cognitive behavioral therapy (CCBT) may be an effective alternative option to traditional individual or group psychotherapy.	1	Consider offering computer-based cognitive behavioral therapy (CCBT) to adults with mild to moderate depression as an alternative to standard psychotherapy, particularly when the latter is not readily accessible, or as an adjunctive intervention combined with standard psychotherapy or pharmacotherapy, with the goal of reducing depressive symptoms and achieving remission.	B	Reviewed, Amended	Recommendation 12
U	Consider guided self-help (GSH) interventions for mild to moderate depression.	1	Guided cognitive-behavioral-based self-help interventions of 6 to 9 weeks duration, entailing brief monitoring and oversight by a healthcare professional or paraprofessional, may be offered to adult patients with mild to moderate major depression in order to reduce depressive symptoms and hopefully achieve remission, particularly if traditional cognitive behavioral treatment options are not conveniently accessible.	B	Reviewed, New-replaced	Recommendation 33

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
U	Electroconvulsive therapy (ECT) should be considered in patients with severe MDD who cannot tolerate, or have not responded to, several trials of antidepressant treatment, unless the patient has significant co-morbid medical conditions that would increase the risks of ECT (e.g., recent myocardial infarction or intracerebral hemorrhage, currently taking MAOIs, or retinal detachment).	1	<p>Electroconvulsive therapy (ECT) should be considered in patients with severe MDD and any of the following conditions:</p> <ul style="list-style-type: none"> a. Catatonia or other psychotic symptoms b. Severe suicidality c. A history of prior good response to ECT d. Need for rapid, definitive treatment response on either medical or psychiatric grounds e. Risks of other treatments outweigh the risks of ECT (i.e., comorbid medical conditions make ECT the safest treatment alternative) f. A history of poor response to multiple antidepressants g. Intolerable side effects to all classes of antidepressant medications (e.g., seizures, hyponatremia, severe anxiety) h. Patient preference. 	A	Reviewed, Amended	Recommendation 24
U	Electroconvulsive therapy (ECT) should be considered in patients with severe MDD who cannot tolerate, or have not responded to, several trials of antidepressant treatment, unless the patient has significant co-morbid medical conditions that would increase the risks of ECT (e.g., recent myocardial infarction or intracerebral hemorrhage, currently taking MAOIs, or retinal detachment).	2	<p>In patients with the following potential contraindications for electroconvulsive therapy (ECT), the trade-off between risk and benefit must be weighed for each individual:</p> <ul style="list-style-type: none"> a. Space-occupying cerebral lesion or other conditions resulting in elevated intracranial pressure confers added risk of brainstem herniation b. Significant cardiovascular problems such as recent myocardial infarction, severe cardiac ischemic disease or profound hypertensive illness c. Recent intracerebral hemorrhage, or patients with bleeding or unstable vascular aneurysms or malformations d. Degenerative diseases of the axial or appendicular skeleton - use of anesthetic and muscle relaxant 	B	Reviewed, Deleted	--

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
			<p>techniques have added to the safety profile of ECT in these individuals.</p> <p>e. Patient currently taking monoamine oxidase inhibitor medication (MAOI). MAOIs should be discontinued two weeks prior to initiating ECT in order to prevent a possible hypertensive crisis.</p> <p>f. Patient currently taking lithium may develop a neurotoxic syndrome marked by increased mental confusion, disorientation, and unresponsiveness</p> <p>g. Retinal detachment</p> <p>h. Pheochromocytoma</p> <p>i. High anesthesia risk – American Society of Anesthesiologists level 4 or 5.</p>			
U	Electroconvulsive therapy (ECT) should be considered in patients with severe MDD who cannot tolerate, or have not responded to, several trials of antidepressant treatment, unless the patient has significant co-morbid medical conditions that would increase the risks of ECT (e.g., recent myocardial infarction or intracerebral hemorrhage, currently taking MAOIs, or retinal detachment).	3	Electroconvulsive therapy (ECT) should be considered a short-term therapy that requires maintenance treatment with antidepressants or if antidepressants are not tolerated, repeated treatment with ECT.	A	Reviewed, Deleted	--
U	Electroconvulsive therapy (ECT) should be considered in patients with severe MDD who cannot tolerate, or have not responded to, several trials of antidepressant treatment, unless the patient has significant co-morbid medical conditions that would increase the risks of ECT (e.g., recent myocardial infarction or intracerebral	4	There is insufficient evidence to recommend for or against ECT in the elderly.	I	Reviewed, Deleted	--

2009 CPG Location ¹		2009 Rec Number	2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement					
	hemorrhage, currently taking MAOIs, or retinal detachment).					
U	Vagus nerve stimulation (VNS) has not been demonstrated to be safe and effective and should not be routinely considered in patients with treatment-resistant depression.	1	Vagus nerve stimulation (VNS) should not be routinely considered for patients with severe treatment-resistant depression.	D	Reviewed, Amended	Recommendation 26
U	Providers should consider prescribing exercise to patients with mild to severe depression, if there are no medical contraindications.	1	Consider the use of exercise as an adjunct to other empirically supported treatments for depression, particularly antidepressant medication.	B	Reviewed, New-replaced	Recommendation 29
U	Providers should consider prescribing exercise to patients with mild to severe depression, if there are no medical contraindications.	2	Consider exercise as a monotherapy for depression, only if there are contraindications to other empirically supported treatments.	B	Reviewed, New-replaced	Recommendation 29
U	Consider light therapy for some patients with MDD, particularly if they have seasonal affective disorder (SAD).	1	Light therapy, including dawn simulation, may be considered an effective treatment for the patient with seasonal affective disorder (SAD).	B	Reviewed, Amended	Recommendation 21
U	Consider light therapy for some patients with MDD, particularly if they have seasonal affective disorder (SAD).	2	Light therapy may be considered in the treatment of MDD during pregnancy, in postpartum depression or for geriatric patients when more established treatments have increased risk of harm or are unavailable.	C	Reviewed, Amended	Recommendation 21
U	Consider light therapy for some patients with MDD, particularly if they have seasonal affective disorder (SAD).	3	A 2,500-Lux white light for two hours/day or treatment with 10,000-Lux for 30 minutes/day is recommended as these are equally efficacious and better than control treatments done with dim light.	C	Reviewed, Amended	Recommendation 21
U	Consider light therapy for some patients with MDD, particularly if they have seasonal affective disorder (SAD).	4	Light therapy may be considered for patients with MDD who don't want to take medications.	I	Reviewed, Amended	Recommendation 21

2009 CPG Location ¹			2009 Recommendation Text ²	2009 Grade ³	Category ⁴	2016 Recommendation ⁵
Annotation	Action Statement	2009 Rec Number				
U	Consider light therapy for some patients with MDD, particularly if they have seasonal affective disorder (SAD).	5	Patients being treated for MDD with light therapy need to be monitored for safety.	C	Reviewed, Amended	Recommendation 21
U	St. John's wort (SJW) may be used for patients with mild major depression who have a strong preference for herbal treatments.	1	St. John's wort may be used by patients with mild MDD who have a strong preference for herbal treatments.	B	Reviewed, Amended	Recommendation 31
U	St. John's wort (SJW) may be used for patients with mild major depression who have a strong preference for herbal treatments.	2	St John's wort is not recommended for patients with moderate to severe major depression.	D	Reviewed, Deleted	--
U	St. John's wort (SJW) may be used for patients with mild major depression who have a strong preference for herbal treatments.	3	St John's wort should not be used by patients taking medication whose clearance is substantially dependent on the Cytochrome P450 (CYP) 3A4 isoenzyme.	D	Reviewed, Deleted	--
U	St. John's wort (SJW) may be used for patients with mild major depression who have a strong preference for herbal treatments.	5	Patient's taking St John's wort should be informed of potential drug-drug interactions and advised to inform all prescribing clinicians that they are using this herbal treatment.	C	Reviewed, Deleted	--
U	Acupuncture should not be recommended as a treatment for MDD.	1	There is insufficient evidence to determine the efficacy of acupuncture compared to medication, wait list control, or sham acupuncture in the management of major depressive disorder; therefore, it is not recommended as a treatment for MDD. [I]	I	Reviewed, New-replaced	Recommendation 28

Appendix G: Participant List

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<p>Karin Glenn, DNP, RN, PMHNP-BC Nurse Practitioner – Mental Health Clinic ONS CPP MH Field Advisory Committee Member Edward Hines Jr. VA Hospital Hines, IL</p>	<p>Janet L. Henderson, MD, PharmD, FACEP Acting Chief of Staff Chief, Medicine Service Director, Emergency Department VAMC Hampton 100 Emancipation Drive Hampton, VA</p>
<p>Marina Khusid, MD, ND, MSA Chief of Integrative Medicine Research Directorate Deployment Health Clinical Center Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury Silver Spring, MD</p>	<p>Timothy Lacy, MD Tri-Service Work Flow Team BH Lead Contract Support (EHRTS) Defense Health Headquarters Office of the Chief Information Officer Silver Spring, MD</p>
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<p>Edward P. Post, MD, PhD, FACP National Medical Director, Primary Care-Mental Health Integration Office of Primary Care Services, VA Central Office Staff Physician Ann Arbor VAMC Ann Arbor, MI</p>	<p>M. Eric Rodgers, PhD, FNP, BC Director, VA/DoD Evidence-Based CPG Program Office of Quality, Safety and Value Department of Veterans Affairs Veterans Health Administration - Virtual Glendale, CO</p>
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<p>Maj Lucretia Vaughan, MD (Co-Chair) Psychiatry Davis-Monthan AFB Tucson, Arizona</p>	<p>LTC Terri L. Yost, PhD, FNP-BC Nursing Research Walter Reed National Military Medical Center Bethesda, MD</p>

Appendix H: Abbreviation List

Abbreviation	Definition
ACT	Acceptance and Commitment Therapy
AHRQ	Agency for Healthcare Research and Quality
Army STARRS	Army Study to Assess Risk and Resilience in Servicemembers
BA	Behavioral Activation
BDI	Beck Depression Inventory
BHL	Behavioral Health Laboratory
BID	Twice a day
BT	Behavioral Therapy
CBT	Cognitive Behavioral Therapy
CBC	Complete Blood Count
CCBT	Computer-based Cognitive Behavioral Therapy
CFT	Couples/marital-focused Therapy
COR	Contracting Officer's Representative
CPG	Clinical Practice Guideline
CR	Controlled Release
CrCl	Creatinine Clearance
CRNP	Certified Registered Nurse Practitioner
DBS	Deep Brain Stimulation
DBT	Dialectical Behavior Therapy
DHA	Docosahexaenoic acid
DoD	Department of Defense
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EBPWG	Evidence-Based Practice Working Group
ECT	Electroconvulsive Therapy
EPDS	Edinburgh Postnatal Depression Scale
EPA	Eicosapentaenoic acid
FDA	Food and Drug Administration
GSH	Guided Self-Help
HDRS	Hamilton Depression Rating Scale
HRSD	Hamilton Rating Scale for Depression
HTA	Health Technology Assessment
ICD	International Classification of Diseases
IPT	Interpersonal Therapy
IR	Immediate Release
ITT	Intention-to-treat
IU	International Unit

Abbreviation	Definition
MAOI	Monoamine Oxidase Inhibitor
MBCT	Mindfulness-based Cognitive Therapy
MBT	Mindfulness-based Therapy
MDD	Major Depressive Disorder
NaSSA	Noradrenergic and Specific Serotonergic Antidepressant
NDRI	Norepinephrine and Dopamine Reuptake Inhibitor
NDSP	Non-directive Supportive Psychotherapy
NICE	National Institute for Health and Care Excellence
NIMH	National Institute of Mental Health
NMDA	N-methyl-D-aspartate
PHQ	Patient Health Questionnaire
PICOTS	Population, Intervention, Comparison, Outcome, Timing and Setting
PST	Problem-solving Therapy
PTSD	Posttraumatic Stress Disorder
QD	Once a day
QHS	Once before bedtime
QID	Four times a day
QOD	Every other day
RESPECT-Mil	Re-Engineering Systems of Primary Care for PTSD and Depression in the Military
RCT	Randomized Controlled Trial
rTMS	Repetitive Transcranial Magnetic Stimulation
SAD	Seasonal Affective Disorder
SARI	Serotonin Antagonist and Reuptake Inhibitors
SGA	Second Generation Antipsychotic
SJW	St. John's wort
SNRI	Serotonin–norepinephrine Reuptake Inhibitor
SR	Sustained-Release
SSRI	Selective Serotonin Reuptake Inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
STPP	Short-term Psychodynamic Psychotherapy
SUD	Substance Use Disorder
T3	Triiodothyronine
TCA	Tricyclic Antidepressants
TDM	Therapeutic Drug Monitoring
TMS	Transcranial Magnetic Stimulation
TSH	Thyroid-stimulating Hormone
USPSTF	United States Preventive Services Task Force
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
VNS	Vagus Nerve Stimulation

Abbreviation	Definition
WHO	World Health Organization
XR	Extended-Release
YLD	Years lived with disability

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