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 with a patient-centered approach.

These guidelines are not intended to represent Department of Veterans Affairs or 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 by contacting your regional TRICARE Managed Care Support Contractor.

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With support from:

Office of Quality and Patient Safety, Veterans Health Administration

&

Clinical Quality Improvement Program, Defense Health Agency

Version 4.0 – 2022[a]

Based on evidence reviewed through January 2021

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I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the Health Executive Committee (HEC) "… 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 (MHS), by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.(1) Development and update of VA/DoD CPGs is funded by VA Evidence Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and well-being.

In April 2016, the VA and DoD published a CPG for the Management of Major Depressive Disorder (2016 VA/DoD MDD CPG), which was based on evidence reviewed through May 2015. Since the release of that CPG, a growing body of research has expanded the evidence base and understanding of major depressive disorder (MDD). Consequently, the VA/DoD EBPWG initiated the update of the 2016 VA/DoD MDD CPG in 2020. This updated CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations. Consequently, the strength of some recommendations may have been modified due to the confidence in the quality of the supporting evidence (see Evidence Quality and Recommendation Strength).

This CPG provides an evidence-based framework for evaluating and managing care for adults (≥18 years) who have a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) or International Classification of Diseases (ICD-9 or 10) diagnosis of MDD, including those with mild, moderate, and severe MDD, as well as those with chronic major depression diagnosed per DSM-IV criteria and those with persistent depressive disorder/chronic major depression per DSM-5 criteria. It should be noted, however, that changes in DSM diagnostic criteria for depressive disorders have affected the classification of participants in the research literature. Of note, participants diagnosed with chronic MDD under DSM-IV could be diagnosed with persistent depressive disorder under DSM-5. Thus, studies of MDD that included patients with chronic MDD (using DSM-IV criteria) could have relevance for understanding persistent depressive disorder.

Successful implementation of this CPG will:

- Assess the patient's condition and collaborate with the patient, family, and caregivers to determine optimal management of patient care
- Emphasize the use of patient-centered care and shared decision making
- Minimize preventable complications and morbidity
- Optimize individual health outcomes and quality of life (QoL)

II. Background

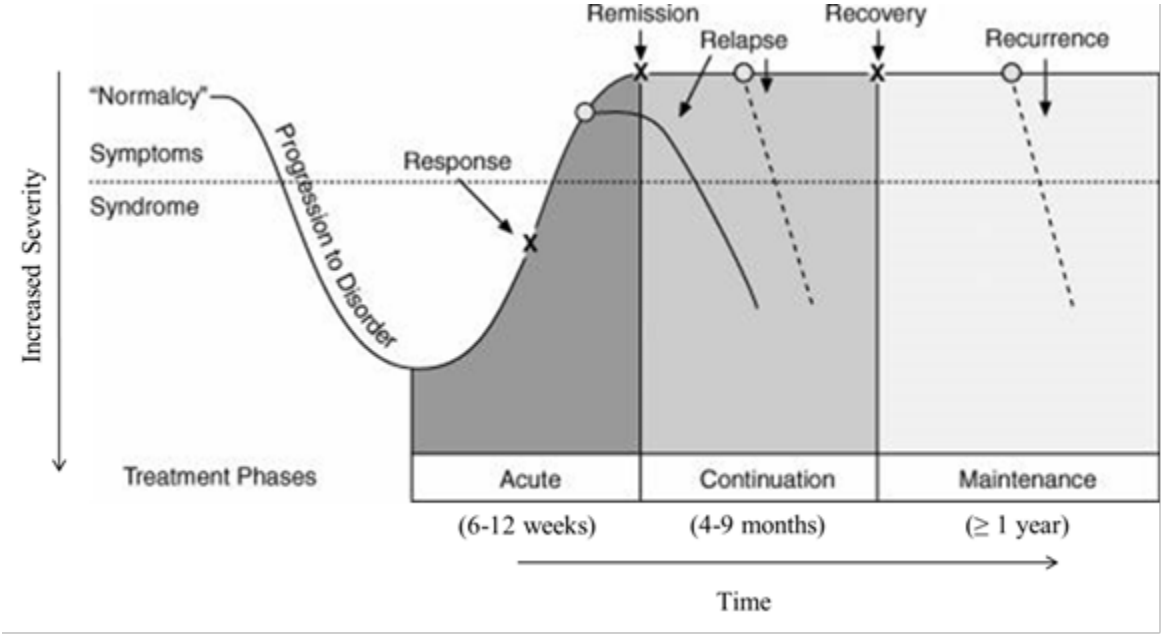
A. Description of Major Depressive Disorder (MDD)

Major depressive disorder (MDD) is a common mental disorder characterized by depressed mood, loss of interest or pleasure in regular activities, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, psychomotor changes, and poor concentration. Major depressive disorder is

the most prevalent and disabling form of depression. In addition to the immediate symptoms of depression, MDD precipitates overall poor quality of life (QoL), decreased productivity, increased obesity and sedentary behavior, and increased risk of mortality from suicide and other causes. Social difficulties potentially emerge from the condition, including stigma, loss of employment, and relationship conflict. Approaches used in the literature to categorize the severity of MDD are discussed in Section IX. Anxiety, posttraumatic stress disorder (PTSD), and substance-related disorders are common co-occurring mental illnesses that may exacerbate existing MDD and complicate treatment. Major depressive disorder also co-occurs with many medical illnesses/conditions like diabetes, hypertension, pulmonary disorders, traumatic brain injury, chronic pain, and congestive heart failure, complicating the treatment of medical disorders and MDD, and increasing morbidity and mortality.

Major depressive disorder stems from a combination of genetic, biological, environmental, and psychological factors, and therefore requires a whole person approach to care. For example, trauma, loss of a loved one, a difficult relationship, or any stressful situation may trigger MDD, but the condition may emerge void of a clear trigger.

Figure 1. Response to Acute Phases of Treatment



B. Epidemiology and Impact on the General Population

Depression is highly prevalent in the general population. The 12 month prevalence estimate is 10.4%, while the lifetime prevalence estimate is 20.6%.(2) Women are at approximately twice the risk for depression as men and the risk is higher in individuals under age 65 from lower-income groups.(2) In terms of race and ethnicity, White and Native American populations are at higher risk than African American, Asian American/Pacific Islander, or Hispanic American populations.(2)

As of 2017, depressive disorders (to include MDD and dysthymia) ranked third worldwide among disorders in terms of years lived with disability [YLD]), below back pain and headache disorders.(3) The incremental economic burden in the United States 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.(4) The rate of increase was greater from 2010 to 2018 when the economic burden increased 37.9% from $236.6 billion to $326.2 billion in 2020 values.(5) Additionally, across this period, co-occurring conditions accounted for a larger percentage of the economic burden of MDD than the MDD itself.

Although depression proves to be a devastating illness, treatment often ameliorates the condition. Various treatment options are available for people with depression, including pharmacotherapy and psychotherapy. Nonetheless, depression is frequently untreated. While a recent national survey found nearly 70% of individuals with depression had been treated in the past year,(2) a separate study showed only 28.7% of patients screening positive for depression received any treatment.(6) Being uninsured, male sex, young adult status (age 18 – 34, compared to 35 – 64), having less than a high school education, and race/ethnicity (specifically identifying as African American and Hispanic American) were associated with lower likelihood of treatment after screening positive for depression. Further evidence shows substantial disparities in access to treatment based on race and ethnicity. For example, among Medicaid beneficiaries with depression, African Americans receive treatment at half the rate of Whites, and Hispanic Americans access care at three quarters the rate of Whites.(7) These findings emphasize the need to identify effective treatments and also to determine how to increase access to care in populations that are at greatest risk for not receiving care. This means specifically addressing disparities in treatment associated with insurance status, sex, age, education, race, ethnicity, and related factors such as stigma about mental health treatment.

C. Major Depressive Disorder in the Department of Defense and the Department of Veterans Affairs Populations

Military personnel are at increased risk of depression. This is at least partially as a result of occupational stressors, such as deployment, which may involve exposure to traumatic combat experiences and separation family. A meta-analysis of 25 epidemiological studies estimated the prevalence of recent MDD based on the DSM-IV criteria at rates of 12% among currently deployed U.S. military personnel, 13.1% among previously deployed, and 5.7% among those never deployed.(8) However, these estimates were drawn from 25 studies that 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, or having had less than a college education were risk factors for depression.(8) A subsequent analysis by the same research team (The Army Study to Assess Risk and Resilience in Servicemembers [Army STARRS]) found the 30-day prevalence of MDD in a representative sample of Soldiers to be 4.8%. This figure was highly comparable to civilian prevalence figures.(9)

Major depressive disorder is a major risk factor for suicide, and the Army STARRS data revealed that prevalence estimates for lifetime suicide ideation are 12.7% among men and 20.7% among women. Lifetime suicide attempts are 2.5% among men and 12.7% among women.(9)

In the fiscal year 2020, among Veterans served by the VHA and based on electronic medical record data, the prevalence of MDD was 16.8% (just over 987,000 Veterans), with a total of 19.4% (just over 1,141,300 Veterans) having documentation of any depression diagnosis.(10) Age and sex-adjusted suicide rates in Veterans was 52% greater in Veterans than in U.S. civilian population.(11)

III. Scope of this Guideline

This CPG is based on published clinical evidence and related information available through January 31, 2021. It is intended to provide general guidance on best evidence-based practices (see Appendix A for additional information on the evidence review methodology). This CPG is not intended to serve as a standard of care.

A. Guideline Audience

This CPG is intended for use by all healthcare providers caring for patients with MDD. This version of the CPG was particularly tailored to address the needs of primary care providers (PCPs) and mental health providers.

B. Guideline Population

The patient population of interest for this CPG is adults (≥18 years) who have a DSM or ICD-9 or ICD-10 diagnosis of MDD who are eligible for care in the VA or DoD healthcare delivery systems. It includes mild, moderate, and severe MDD, as well as those with chronic major depression diagnosed per DSM-IV criteria and those with persistent depressive disorder/chronic major depression per DSM-5 criteria. It also includes adults with MDD who have either partially responded or not responded to treatment for depression. This CPG does not address patients at risk for suicide or patients with post-stroke depression or bipolar disorder I/II, as recommendations for managing these patient populations are included in the VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide, VA/DoD CPG for the Management of Stroke Rehabilitation, and the VA/DoD CPG for the Management of Bipolar Disorder).[a]

IV. Highlighted Features of this Guideline

A. Highlights in this Guideline Update

The 2022 VA/DoD MDD CPG used a more rigorous application of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, than previous iterations for rating evidence. This resulted in the exclusion or downgrading of data that was used in previous versions of this CPG. This impacted the strength of some recommendations (e.g., *Strong for* downgraded to *Weak for*) despite a similar evidence base. For additional information on GRADE or CPG methodology, see Appendix A. In an important addition, this CPG includes consumer input whereas prior versions did not.

The 2016 VA/DoD MDD CPG's management section divided treatment between "treatment of uncomplicated mild to moderate MDD" and "treatment of severe, chronic, or recurrent MDD (complex)." This CPG refers to "treatment of uncomplicated MDD" and "treatment of MDD that is severe or has partial or limited response to initial treatment" to better align with the research literature and clinical practice. The latter section now includes recommendations previously listed across several sections to improve clarity. As noted, the algorithm has been designed to better reflect this structure as well.

[a] The VA/DoD CPGs are available at: https://www.healthquality.va.gov/index.asp

Moreover, numerous interventions that previously did not meet inclusion criteria now do so or do so at a higher level of recommendation. These include:

- Short-term psychodynamic psychotherapy (STPP) (Recommendation 7)
- Trazodone (Recommendation 11)
- Repetitive transcranial magnetic stimulation (rTMS) (Recommendation 17)
- Second-generation antipsychotics (SGAs) (Recommendation 16)
- Ketamine or esketamine (Recommendation 19)

The CPG also provides expanded recommendations on research needed to strengthen future guidelines.

B. Components of the Guideline

The 2022 VA/DoD MDD CPG is the third update to this CPG. It provides clinical practice recommendations for the care of patients with MDD (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. There are several changes from the 2016 VA/DoD MDD CPG. In particular, the algorithm has been redesigned to better assist providers in decision making. The redesigned algorithm separates initial treatment for uncomplicated depression from a pathway for those patients who have a more complex presentation to better facilitate decision making. This CPG also includes expanded recommendations on Research Priorities, that the Work Group identified as crucial for improving future guidelines.

To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, patient summary, and pocket card. These can be found at https://www.healthquality.va.gov/index.asp.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency (DHA), identified the following five clinicians to serve as Champions (i.e., leaders) of this CPG's Work Group: John McQuaid, PhD and David Oslin, MD from the VA and LTC Vincent Capaldi, MD, MSc, FAPA, FACP, Fuad Issa, MD, FAPA, and LTC Scott Williams, MD, DFAPA, FACP, FAASM from the DoD.

The Work Group comprised individuals with the following areas of expertise: psychology, psychiatry, neuropsychiatry, pharmacy, sleep medicine, internal medicine, social work, and nursing. See Table 1 for a list of Work Group members.

This CPG Work Group, led by the Champions, was tasked with:

- Determining the scope of the CPG
- Crafting clinically relevant key questions (KQs) to guide the systematic evidence review
- Identifying discussion topics for the patient focus group and considering the patient perspective
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence

- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation

The Lewin Team, including The Lewin Group, ECRI, Sigma Health Consulting, and Duty First Consulting, was contracted by the VA to help develop this CPG.

Table 1. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	**John McQuaid, PhD (Champion)**
	David W. Oslin, MD (Champion)
	Andrew Buelt, DO
	Claire Collie, PhD
	Chris Crowe, PhD
	Matthew A. Fuller, PharmD, BCPP, FASHP
	Angela Giles, DBH, LCSW, BCD
	Suzanne Thorne-Odem, DNP, FNP-C
	Ilse Wiechers, MD, MPP, MHS
Department of Defense	**LTC Vincent Capaldi, MD, MSc, FAPA, FACP (Champion)**
	Fuad Issa, MD, FAPA (Champion)
	LTC Scott Williams, MD, FACP, DFAPA, FAASM (Champion)
	MAJ Rhanda Brockington, DNP, FNP-BC
	CAPT Anne Dobmeyer, PhD, ABPP
	Lt Col Nicole Garris, LCSW, DCSW
	COL (Ret.) Charles Hoge, MD
	Adam Edward Lang, PharmD, BCACP
	June Taheri, MD
Office of Quality and Patient Safety Veterans Health Administration	M. Eric Rodgers, PhD, FNP-BC
	James Sall, PhD, FNP-BC
	Rene Sutton, BS, HCA
Clinical Quality Improvement Program Defense Health Agency	Lisa D. Jones, BSN, RN, MHA, CPHQ
	Corinne K. B. Devlin, MSN, RN, FNP-BC
	Elaine P. Stuffel, MHA, BSN, RN
The Lewin Group	Clifford Goodman, PhD
	Erika Beam, MS
	Ben Agatston, JD, MPH
	Matthew Heron, BS
	Nicole Holmberg, BS
ECRI	Kris D'Anci, PhD
	Stacey Uhl, MS
	Benjamin Rouse, MHS
	Aaron Bloschichak, MPH
	Amber Moran, MA
	Joann Fontanarosa, PhD
	Megan Nunemaker, MSLS

Organization	Names*
Sigma Health Consulting	Frances Murphy, MD, MPH
	James Smirniotopoulos, MD
Duty First Consulting	Rachel Piccolino, BA
	Mary Kate Curley, BA
	Richa Ruwala, BS

*Additional contributor contact information is available in Appendix E.

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA/DoD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DoD CPGs.(12) The *Guideline for Guidelines* is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of systematic review, and external review).(13) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to craft each recommendation and determine its strength. Per GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see Determining Recommendation Strength and Direction):(14)

- Confidence in the quality of the evidence
- Balance of desirable and undesirable outcomes
- Patient values and preferences
- Other considerations, as appropriate, e.g.:
    - Resource use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). 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 incorporates the four domains.(14) A *Strong* recommendation generally indicates *High* or *Moderate* confidence in the quality of the available evidence, a clear difference in

magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility).

In some instances there is insufficient evidence on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence review may have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The manner in which this is expressed in the CPG may vary. In such instances, the Work Group may include among its set of recommendations a statement of insufficient evidence for an intervention that may be in common practice even though it is not supported by clinical evidence, particularly if there may be other risks of continuing its use (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group may decide not to include this type of statement about an intervention. For example, the Work Group may remain silent where there is an absence of evidence for a rarely used intervention. In other cases, an intervention may have a favorable balance of benefits and harms but may be a standard of care for which no recent evidence has been generated.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text (see Table 2).

Table 2. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend …
Weak for	We suggest …
Neither for nor against	There is insufficient evidence to recommend for or against …
Weak against	We suggest against …
Strong against	We recommend against …

It is important to note that a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence-based and still important to clinical care). The strength of each recommendation is shown in the Recommendations section.

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations. For instance, the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision making. The confidence in the quality of the evidence is assessed using an objective, systematic approach that is independent of the clinical topic of interest. Therefore, recommendations on topics such as psychotherapy or other interventions rely on studies that may be inherently more difficult to design and conduct rigorously (e.g., randomized controlled trials [RCTs]). These recommendations are typically supported by lower quality evidence and, in turn, *Weak* recommendations. Conversely, recommendations on topics for which rigorous studies can be designed and conducted may more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(15, 16) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of 2016 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, this typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(17) For example, the U.S. Preventive Services Task Force (USPSTF) has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(18)

Recommendation categories were used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).(19, 20) Table 3 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2022 CPG recommendation categories can be found in Recommendations. Appendix D outlines the 2016 VA/DoD MDD CPG's recommendation categories.

Table 3. Recommendation Categories and Definitions[a]

Evidence Reviewed	Recommendation Category	Definition
Reviewed[b]	New-added	New recommendation
	New-replaced	Recommendation from previous CPG was carried forward and revised
	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted
Not reviewed[c]	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted

[a] Adapted from the NICE guideline manual (2012) (19) and Garcia et al. (2014) (20)

[b] The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG.

[c] The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG.

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the *Guideline for Guidelines*.(12) Further, the *Guideline for Guidelines* refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care),(21) as well as to disclosure statements (i.e., the standard disclosure form that is completed at least twice by CPG Work Group members and the guideline development team).(12) The disclosure form inquiries regarding any relevant financial and intellectual interests or

other relationships with, e.g., manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquiries regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and the guideline development team were also subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments and/or ProPublica).

No COIs were identified among the CPG Work Group or the guideline development team. If an instance of potential or actual COI had been reported, it would have been referred to the VA and DoD program offices and reviewed with the CPG Work Group Champions. The VA and DoD program offices and the CPG Work Group Champions would have determined whether, and if so, what, further action was appropriate (e.g., excusing Work Group members from selected relevant deliberations or removal from the Work Group). Disclosure forms are on file with the VA Office of Quality and Patient Safety and are available upon request.

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.(15, 22) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DoD Leadership arranged a virtual patient focus group on January 8, 2021. The focus group aimed to gain insights of potential relevance from patients with MDD, and incorporate these into the CPG as appropriate. Topics discussed included the patients' priorities, challenges they have experienced, information they have received regarding their care, and the impacts of their care on their lives.

The patient focus group comprised a convenience sample of eight people. Three participants identified as women, and five participants identified as men. One of the women self-identified as trans-identifying. Seven participants were Veterans who received care from the VA healthcare system. One participant received care from the DoD health system; s/he is an active duty Service Member. The Work Group acknowledges this convenience sample is not representative of all patients with MDD within the VA and DoD healthcare systems and, thus, findings are not generalizable and do not comprise evidence. For more information on the patient focus group methods and findings, see Appendix B. Patient focus group participants were provided the opportunity to review the final draft and provide additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group completed a near-final draft, they identified experts from the VA and DoD healthcare systems and outside organizations generally viewed as experts in the respective field to review that draft. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review can be provided by the VA Office of Quality and Patient Safety.

F. Implementation

This CPG and algorithm are designed for adaptation by individual healthcare providers with consideration of unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care for a patient with MDD. The Work Group submits suggested performance metrics for the VA and DoD to use when assessing the implementation of this CPG. Robust implementation is identified in VA and DoD internal implementation plans and policies. Additionally, implementation would entail wide dissemination through publication in the medical literature, online access, educational programs, and, ideally, electronic medical record programming in the form of clinical decision support tools at the point of care.

VII. Approach to Care in Department of Veterans Affairs and Department of Defense

A. Patient-centered Care

Guideline recommendations are intended to consider patient needs and preferences. Guideline recommendations represent a whole/holistic health approach to care that is patient-centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. VA/DoD CPGs encourage providers to use a patient-centered, whole/holistic health approach (i.e., individualized treatment based on patient needs, characteristics, and preferences). This approach aims to treat the particular condition while also optimizing the individual's overall health and well-being.

Regardless of the care setting, all patients should have access to individualized evidence-based care as well as supportive education, peer groups, and skill-building resources to support well-being goals. Patients should be informed about all treatment options so they can make informed decisions. Patient-centered care can decrease patient anxiety, increase trust in clinicians, and improve treatment adherence.(23, 24) A whole/holistic health approach (https://www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and well-being goals. Good communication through motivational interviewing and shared goal setting is essential and should be supported by evidence-based information tailored to each patient's need. An empathetic and non-judgmental approach facilitates discussions sensitive to sex, culture, ethnicity, and other differences.

B. Shared Decision Making

This CPG encourages providers to practice shared decision making, which is a process in which providers and patients consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.(25) Shared decision making was emphasized in *Crossing the Quality Chasm,* an Institute of Medicine (IOM) (now NAM) report, in 2001 (26) and is inherent within the whole/holistic health approach. Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels and/or settings of care, especially where there may be patient heterogeneity in risks and benefits. The VHA and MHS have embraced shared decision making. Providers are encouraged to use shared decision making to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

C. Patients with Co-occurring Conditions

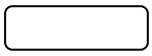
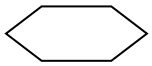
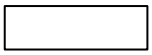
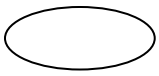
Co-occurring conditions (medical and psychiatric) can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to the management of MDD. Many Veterans, Service Members, and their families have one or more co-occurring conditions. Because MDD is sometimes accompanied by co-occurring conditions, it is often best to manage MDD collaboratively with other care providers. Some co-occurring conditions may require early specialist consultation to determine any necessary changes in treatment or to establish a common understanding of how care will be coordinated. This may entail reference to other VA/DoD CPGs (e.g., for PTSD, substance use disorders [SUD], suicide, stroke, and mild traumatic brain injury [mTBI]).[b]

VIII. Algorithm

This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision making process used in managing patients with MDD. This algorithm format represents a simplified flow of the management of patients with MDD and helps foster efficient decision making by providers. It includes:

- An ordered sequence of steps of care
- Decisions to be considered
- Recommended decision criteria
- Actions to be taken

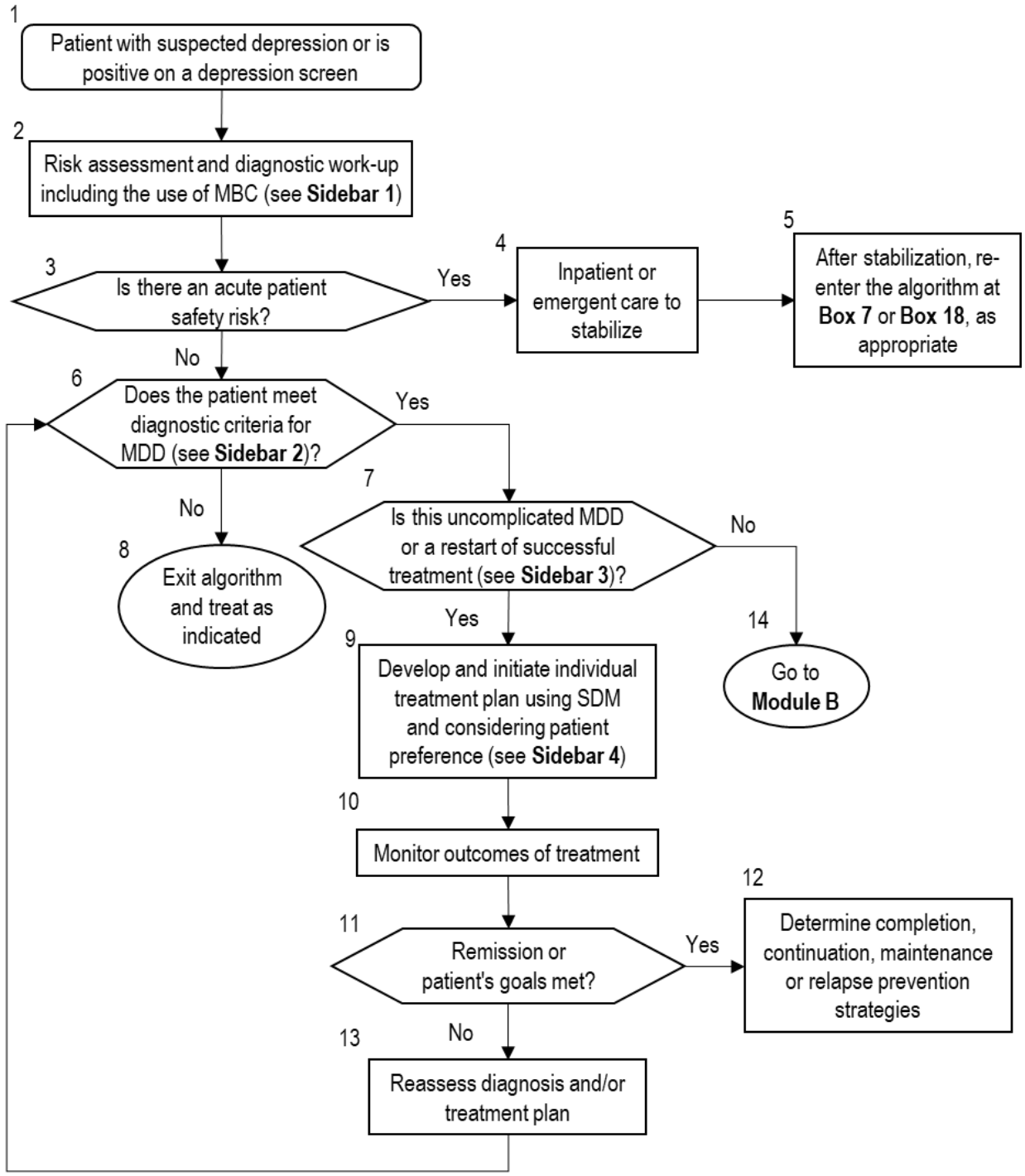
The algorithm is a step-by-step decision tree. Standardized symbols are used to display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(27) Sidebars provide more detailed information to assist in defining and interpreting elements in the boxes.

Shape	Description
	Rounded rectangles represent a clinical state or condition
	Hexagons represent a decision point in the process of care, formulated as a question that can be answered "Yes" or "No"
	Rectangles represent an action in the process of care
	Ovals represent a link to another section within the algorithm

Appendix G contains alternative text descriptions of the algorithm.

[b] The VA/DoD CPGs are available at: https://www.healthquality.va.gov/index.asp

A. Module A: Initial Assessment and Treatment



Abbreviations: MBC: measurement-based care; MDD: major depressive disorder; SDM: shared decision making

Sidebar 1: Risk Assessment and Work-up

- Functional status, medical history, past treatment history, and relevant family history
- Consider administration of PHQ-9
- Evaluate for suicidal and homicidal ideation and history of suicide attempts, and consult the VA/DoD Assessment and Management of Patients at Risk for Suicide CPG, as appropriate
- Rule out depression secondary to other causes (e.g., hypothyroidism, vitamin B-12 deficiency, syphilis, pain, chronic disease)
- Incorporate MBC principles in the initial assessment

Abbreviations: CPG: clinical practice guideline; DoD: Department of Defense; MBC: measurement-based care; MDD: major depressive disorder; PHQ-9: Patient Health Questionnaire-9; VA: Department of Veterans Affairs

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, 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

Abbreviations: DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition

Sidebar 3: Factors to be Considered in Treatment Choice

- Prior treatment response
- Severity (e.g., PHQ-9)
- Chronicity
- Comorbidity (e.g., substance use, medical conditions, other psychiatric conditions)
- Suicide risk
- Psychosis
- Catatonic or melancholic features
- Functional status
- Tolerability of prior treatments

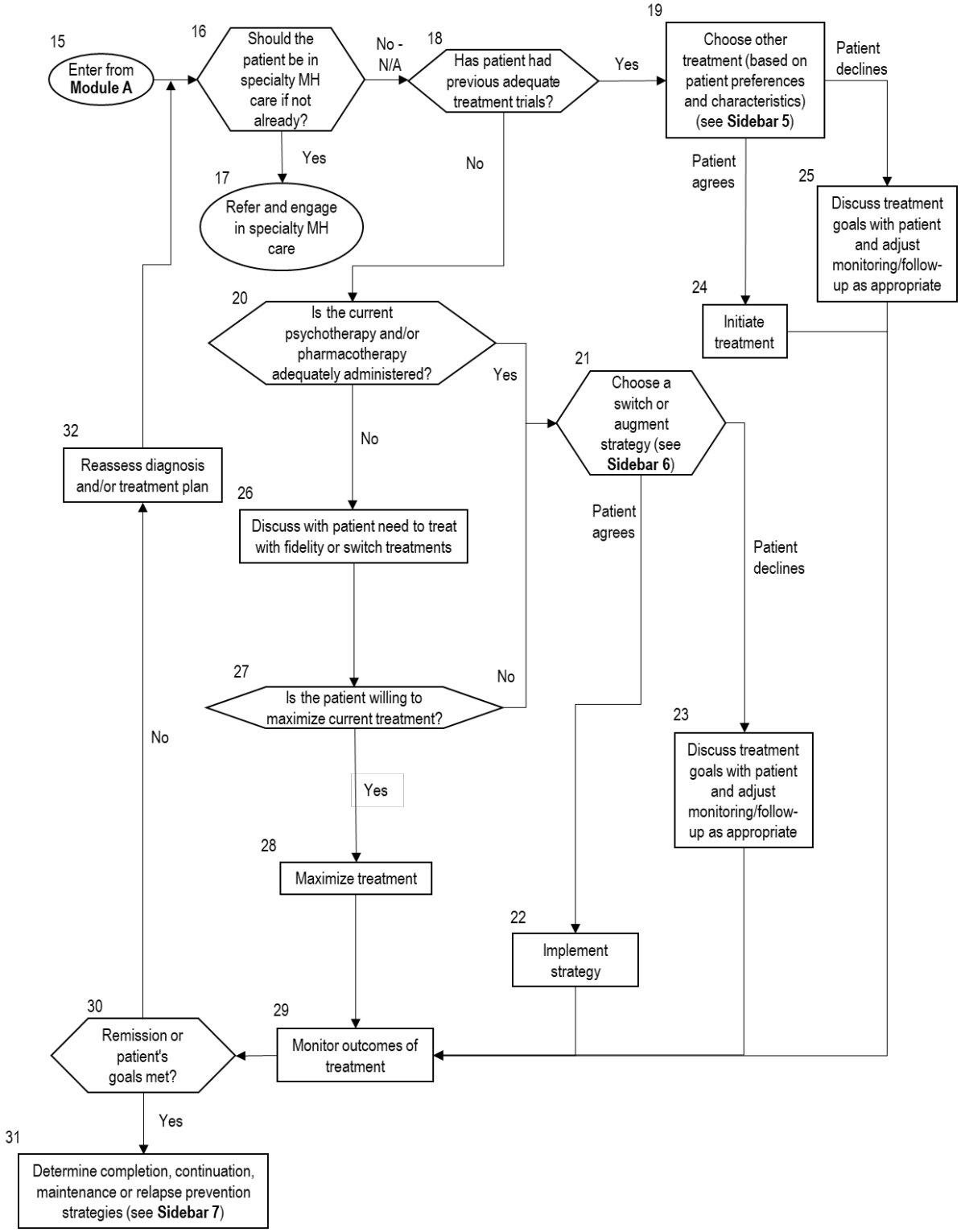
Abbreviations: MDD: major depressive disorder; PHQ-9: Patient Health Questionnaire-9

Sidebar 4: Considerations in Treatment of Uncomplicated MDD

- Consider collaborative/integrated care in primary care for appropriate patients
- For initial treatment, select pharmacotherapy or psychotherapy based on SDM
- If previous treatment was successful, consider restarting this approach
- Based on patient preferences, consider the following as an adjunct to psychotherapy or pharmacotherapy (self-help with exercise [e.g., yoga, tai chi, qi gong, resistance, aerobics], patient education, light therapy, and bibliotherapy) or as an alternative if first-line treatments are not acceptable and/or available
- Include patient characteristics (e.g., treatment of co-occurring conditions, cultural factors, social determinants, patients who are pregnant, geriatric patients) in SDM

Abbreviations: MDD: major depressive disorder; SDM: shared decision making

B. Module B: Advanced Care Management



Abbreviations: MH: mental health

Sidebar 5: Treatment Options for Patients Who Have Not Responded to Adequate Treatment Trials[a]

Consider the following treatment options:

- Consider other pharmacotherapy options (e.g., MAOIs, TCAs) (see Recommendation 16)
- ECT (see Recommendation 20)
- rTMS (see Recommendation 17)
- Ketamine/esketamine (see Recommendation 19)

[a] Patients who have demonstrated partial or no response to initial pharmacologic monotherapy (maximized) after a minimum of four to six weeks of treatment

Abbreviations: ECT: electroconvulsive therapy; MAOIs: monoamine oxidase inhibitors; rTMS: repetitive transcranial magnetic stimulation; TCAs: tricyclic antidepressants

Sidebar 6: Treatment Options for Switching or Augmenting

Consider the following treatment options:

- Adding psychotherapy or an antidepressant
- Switching to a different treatment (e.g., switch between psychotherapy or pharmacotherapy, switch to a different focus of psychotherapy or different antidepressant)
- Augmenting with a different class of medication (e.g., adding an SGA)

Abbreviations: SGA: second-generation antipsychotic

Sidebar 7: Treatment Options During Remission

Consider the following treatment options:

- For patients treated with antidepressants, consider continuation at the therapeutic dose for at least six months
- For patients with a high risk of relapse, regardless of prior treatment received, consider offering a course of CBT

Abbreviations: CBT: cognitive behavioral therapy

IX. Recommendations

The following evidence-based clinical practice recommendations were made using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Some of the recommendations use qualifier terms to denote subtypes of MDD. Specifically, the distinction between mild, moderate, and severe depression and mild, moderate, and severe MDD is clinically common yet sometimes difficult to quantify. The DSM-5 does not define MDD severity levels, but the Patient Health Questionnaire-9 (PHQ-9) defines depression severity levels as a function of the total score out of 27, largely influenced by the frequency of symptoms. A score of 5 – 9 defines mild depression, 10 – 14 defines moderate depression, 15 – 19 defines moderately severe depression, and greater than 20 defines severe depression. In contrast, 10 – 14 defines mild MDD, 15 – 19 defines moderate MDD, and >20 defines severe MDD.(28)

Hasin et al. (2018) defined MDD severity slightly differently and emphasized the number of symptoms.(2) Mild MDD was defined as having five of the cardinal symptoms, moderate MDD had 6 – 7

of the cardinal symptoms, and severe MDD had 8 – 9 cardinal symptoms. Regarding chronic depression, also termed persistent depressive disorder (or dysthymia) in DSM-5, symptoms must be present for most days over two years. Typically, symptoms do not remit for greater than two months at a time. Appendix K also describes depression subsets in detail.

Topic	#	Recommendation	Strength[a]	Category[b]
Screening	1.	We suggest that all patients not currently receiving treatment for depression be screened for depression.	Weak for	Not reviewed, Amended
Monitoring Outcomes	2.	For patients with MDD, we suggest using a quantitative measure of depression severity in the initial treatment planning and to monitor treatment progress at regular intervals to guide shared treatment decision making.	Weak for	Reviewed, New-replaced
Treatment Setting	3.	For patients with MDD who are being treated in the primary care setting, we recommend the use of collaborative/integrated care models.	Strong for	Reviewed, Amended
	4.	For patients with MDD, there is insufficient evidence to recommend for or against the use of a team-based model in specialty mental health care settings.	Neither for nor against	Reviewed, New-added
	5.	For patients with MDD, there is insufficient evidence to conclude that interventions delivered by clinicians using telehealth are either superior or inferior to in-person treatment.	Neither for nor against	Reviewed, New-added
Treatment of Uncomplicated MDD	6.	We recommend that MDD be treated with either psychotherapy or pharmacotherapy as monotherapy, based on patient preference. Factors including treatment response, severity, and chronicity may lead to other treatment strategies such as augmentation, combination treatment, switching of treatments, or use of non-first line treatments (see Recommendations 17, 18, and 20).	Strong for	Reviewed, New-replaced
	7.	When choosing psychotherapy to treat MDD, we suggest offering one of the following interventions (not rank ordered): • Acceptance and commitment therapy • Behavioral therapy/behavioral activation • Cognitive behavioral therapy • Interpersonal therapy • Mindfulness-based cognitive therapy • Problem-solving therapy • Short-term psychodynamic psychotherapy	Weak for	Reviewed, New-replaced
	8.	For patients who select psychotherapy as a treatment option, we suggest offering individual or group format based on patient preference.	Weak for	Reviewed, Not changed
	9.	There is insufficient evidence to recommend for or against combining components from different psychotherapy approaches.	Neither for nor against	Reviewed, New-added
	10.	For patients with mild to moderate MDD, we suggest offering clinician-guided computer/internet-based cognitive behavioral therapy either as an adjunct to pharmacotherapy or as a first-line treatment, based on patient preference.	Weak for	Reviewed, New-replaced

Topic	#	Recommendation	Strength[a]	Category[b]
Treatment of Uncomplicated MDD (cont.)	11.	When choosing an initial pharmacotherapy, or for patients who have previously responded well to pharmacotherapy, we suggest offering one of the following (not rank ordered): • Bupropion • Mirtazapine • A serotonin-norepinephrine reuptake inhibitor • Trazodone, vilazodone, or vortioxetine • A selective serotonin reuptake inhibitor	Weak for	Reviewed, New-replaced
	12.	When choosing an initial pharmacotherapy, we suggest against using: • Esketamine • Ketamine • Monoamine oxidase inhibitors • Nefazodone • Tricyclic antidepressants	Weak against	Reviewed, New-added
	13.	There is insufficient evidence to recommend for or against pharmacogenetic testing to help guide the selection of antidepressants.	Neither for nor against	Reviewed, New-added
	14.	For patients with mild to moderate MDD who decline pharmacotherapy and who decline or cannot access first-line evidence-based psychotherapies (either in-person or virtually), we suggest considering non-directive supportive therapy.	Weak for	Not reviewed, Amended
Treatment of MDD that is Severe or has a Partial or Limited Response to Initial Treatment	15.	We suggest offering a combination of pharmacotherapy and evidence-based psychotherapy for the treatment of patients with MDD characterized as: • Severe (e.g., PHQ-9 >20) • Persistent major depressive disorder (duration greater than two years) • Recurrent (with two or more episodes)	Weak for	Not reviewed, Amended
	16.	For patients with MDD who have demonstrated partial or no response to an adequate trial of initial pharmacotherapy, we suggest (not rank ordered): • Switching to another antidepressant (including TCAs, MAOIs, or those in Recommendation 12) • Switching to psychotherapy • Augmenting with a psychotherapy • Augmenting with a second-generation antipsychotic	Weak for	Reviewed, Amended
	17.	For patients who have demonstrated partial or no response to two or more adequate pharmacologic treatment trials, we suggest offering repetitive transcranial magnetic stimulation for treatment.	Weak for	Reviewed, Amended
	18.	There is insufficient evidence to recommend for or against theta-burst stimulation for the treatment of MDD.	Neither for nor against	Reviewed, New-added
	19.	For patients with MDD who have not responded to several adequate pharmacologic trials, we suggest ketamine or esketamine as an option for augmentation.	Weak for	Reviewed, New-replaced

Topic	#	Recommendation	Strength[a]	Category[b]
Treatment of MDD that is Severe or has a Partial or Limited Response to Initial Treatment (cont.)	20.	We recommend offering electroconvulsive therapy (ECT) with or without psychotherapy for 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 • The risks associated with other treatments are greater than the risks of ECT for this specific patient (i.e., co-occurring medical conditions make ECT the safest MDD treatment alternative) • A history of a poor response or intolerable side effects to multiple antidepressants	Strong for	Reviewed, Not changed
Relapse Prevention/Continuation Phase (All Severities and Complexities)	21.	For 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	Not reviewed, Not changed
	22.	For patients with MDD at high risk for relapse or recurrence (e.g., two or more prior episodes, unstable remission status), we suggest offering a course of cognitive behavioral therapy, interpersonal therapy, or mindfulness-based cognitive therapy during the continuation phase of treatment (i.e., after remission is achieved) to reduce the risk of subsequent relapse/recurrence. The evidence does not support recommending one of these three evidence-based psychotherapies over another.	Weak for	Not reviewed, Amended
Recommendations for Specific Populations	23.	For individuals with mild to moderate MDD who are breastfeeding or pregnant, we recommend offering an evidence-based psychotherapy as a first-line treatment (see Recommendation 7). In 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	Not reviewed, Amended
	24.	For older adults (≥65 years) with mild to moderate MDD, we suggest offering a first-line psychotherapy (see Recommendation 7). Patient preference and the additional safety risks of pharmacotherapy should be considered when making this decision.	Weak for	Not reviewed, Amended
	25.	For patients with mild to moderate MDD and significant relationship distress, we suggest offering couples-focused therapy.	Weak for	Not reviewed, Amended
	26.	For patients with mild to moderate MDD with or without a seasonal pattern (formerly seasonal affective disorder), we suggest offering light therapy.	Weak for	Reviewed, New-replaced

Topic	#	Recommendation	Strength[a]	Category[b]
Self-help, Complementary, and Alternative Treatments	27.	For patients with MDD, we suggest exercise (e.g., yoga, tai chi, qi gong, resistance, aerobics) as an adjunct.	Weak for	Reviewed, New-replaced
	28.	For patients with MDD, we suggest CBT-based bibliotherapy as an adjunct to pharmacotherapy or psychotherapy, or as an alternative when patients are unwilling or unable to engage in other treatments.	Weak for	Reviewed, Amended
	29.	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 as monotherapy.	Weak for	Not reviewed, Amended
	30.	For patients with MDD, there is insufficient evidence to recommend for or against acupuncture as an adjunct.	Neither for nor against	Reviewed, New-replaced
	31.	For patients with MDD, there is insufficient evidence to recommend for or against the addition of biofeedback.	Neither for nor against	Reviewed, New-added
	32.	For patients with MDD, there is insufficient evidence for or against the use of meditation as an adjunct.	Neither for nor against	Reviewed, New-added
Other Treatments with a Recommendation Against Use	33.	For patients with MDD, we suggest against using vagus nerve stimulation outside of a research setting.	Weak against	Reviewed, Amended
	34.	For patients with MDD, we recommend against using deep brain stimulation outside of a research setting.	Strong against	Reviewed, Not changed
	35.	Given the limited information on the safety and efficacy of psilocybin, MDMA, cannabis, and other unapproved pharmacologic treatments, we recommend against using these agents for MDD outside of a research setting.	Strong against	Reviewed, New-added
	36.	We suggest against using omega-3 fatty acids or vitamin D for treatment of MDD.	Weak against	Not reviewed, Not changed

[a] For additional information, see Determining Recommendation Strength and Direction.

[b] For additional information, see Recommendation Categorization and Appendix D.

A. Screening

Recommendation

1. We suggest that all patients not currently receiving treatment for depression be screened for depression.
   (Weak for | Not reviewed, Amended)

Discussion

Consistent with the USPSTF recommendation, screening all patients for MDD and, if the screening results are positive, follow-up should be standard clinical practice.(29) Providers may use any validated instrument for appropriate populations, but the PHQ-2 (see Table 4 and Table 5) is widely used and recommended within the VA and DoD.(30-32) The frequency of screening has not been addressed systematically in the literature, but a reasonable approach as recommended by the USPSTF is to screen annually in patients not known to have depression. All patients who screen positive on the PHQ-2

should be assessed further for symptoms and risk level, including the full PHQ-9. In addition to screening with the PHQ-2 in the general population, several high-risk subpopulations with higher prevalence rates of depression should be given special consideration for screening (e.g., patients with congestive heart failure or patients with recent significant losses).

Screening in Antenatal and Postnatal Women

Pregnant and postpartum women are at elevated risk for depression and should be screened for depression during their initial antenatal and postnatal visits. In addition, screening is typically repeated in the postpartum period at four to six weeks and three to four months after birth.(33-35) Early detection of depression during pregnancy is critical because it can adversely affect birth outcomes, neonatal health, and maternal health. Untreated postpartum depression can impair mother-infant attachments and have cognitive, emotional, and behavioral consequences for children. The Edinburgh Postnatal Depression Scale (EPDS) and the PHQ-2 are sensitive screening tools for use in postpartum women.(30, 36-40)

Screening in Individuals with Chronic Medical Illness

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

Screening in Older Adults

The PHQ-2 and PHQ-9 are the primary recommended screening and assessment tools in older populations, with comparable sensitivity but lower specificity than other screens.(41-45) The Geriatric Depression Scale, for example, employs items that are designed to be independent of physical condition for adults aged 65 and older but has more questions and is more complex to score.(46)

Summary

The Work Group considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG. Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including a lack of outcome evidence for improved health outcomes. The potential benefits of identifying patients with treatable depression slightly outweigh the potential harms, which include overtreating based solely on screening scores and the added burden and costs of conducting the screenings. Patient values and preferences varied somewhat as some patients are uncomfortable discussing their mental health. Thus, the Work Group decided upon a *Weak for* recommendation.

Table 4. Patient Health Questionnaire-2 (PHQ-2) (30)

Question #	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

Table 5. PHQ-2 Score Interpretation (30)

PHQ-2 Score	Positive Predictive Value of MDD (%)	Positive Predictive Value 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

Note that the prevalence of any depressive disorder in this primary care population, based on clinical interviews, was 18%. The positive predictive value of the PHQ-2 will change markedly based on the prevalence of depression in the screened population.

Note that the VA and DoD use a score of ≥3 to recommend further assessment.

Abbreviations: MDD: major depressive disorder; PHQ-2: Patient Health Questionnaire-2

B. Monitoring Outcomes

Recommendation

2. For patients with MDD, we suggest using a quantitative measure of depression severity in the initial treatment planning and to monitor treatment progress at regular intervals to guide shared treatment decision making.
   (Weak for | Reviewed, New-replaced)

Discussion

Evidence suggests employing measurement-based care (MBC) in the treatment of patients with major depression enhances outcomes.(47, 48) Measurement-based care operates as a treatment delivery approach involving the regular use of patient-reported outcomes in routine clinical care to track progress and allow adjustments in treatment. Measurement-based care features three key elements:

(1) Collect: use of reliable, validated, and clinically appropriate measures,

(2) Share: results are shared and discussed with the patient and other providers involved in the patient's care, and

(3) Act: the results are used by the patient and provider to make clinically appropriate adjustments in care

As of January 2018, the Joint Commission requires MBC use in all mental health treatment programs accredited under behavioral health standards.

The evidence reviewed, including a systematic review (SR), found the overall evidence for MBC was weak and recommended further research.(49) The quality of evidence was rated as poor, and none of the studies in the SR included measures of all three key elements. Thus, there was insufficient evidence to recommend any particular measure, though the Work Group recognizes that the DoD and VA promote the use of the PHQ-9 (see Appendix I for further discussion of the PHQ-9). In addition, studies used various methods, so no specific frequency of monitoring can be recommended as superior. The Work Group also acknowledges that MBC is critical in many evidence-based psychotherapies and

collaborative care programs. However, there is a limited evidence base showing the added value in these programs.

Guo et al. (2015) randomly assigned patients (n=120) being treated with pharmacotherapy to either treatment enhanced with a regular collection of self-reported rating scales provided to the physician or treatment as usual (TAU).(47) This study randomized patients and started with standard treatment across all patients. Blinded raters measured patient outcomes over 24 weeks. Outcomes favored treatment enhanced with MBC for response, remission, time to response, and time to remission. There was no measurement of fidelity to the collect, share, and act elements even though collection was done per protocol. Consistent with outcomes, patients in the MBC arm were more likely to include medication management (switches or augmentation). Similar results were shown in a pilot study of MBC (n=47 patients) in a primary care setting for patients initiating depression care.(48)

Other studies reflect supporting evidence for the use of MBC in treating depression. Chang et al. (2014) demonstrated MBC leads to a greater likelihood of continued treatment than treatment without MBC.(50) This study randomized 664 patients but did not independently measure clinical outcomes. These MBC principles are key components to all the integrated care treatment trials, including the main VA and DoD programs which consisted of 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 Solutions (TIDES).(51-54) In an SR of the effective elements of collaborative care, Williams et al. (2007) found MBC operates as a common element related to treatment outcomes.(55) Brodey et al. (2005) concluded that primary care patients experience superior outcomes when their provider receives reports on progress and treatment adherence compared to no feedback.(56)

Studies of psychotherapy illustrate similar supportive evidence. Lambert et al. (2003) conducted a meta-analysis of three trials using patient-reported outcomes as a component of psychotherapy.(57) All participants were randomly assigned to therapists who were either receiving or not receiving feedback. Feedback included the results of the patient-reported outcomes and tailored messages based on patient progress (e.g., on track, not progressing). The positive impact of MBC proved to be greater for patients who were not progressing in therapy, suggesting the value related to the act component of MBC.

The Work Group systematically reviewed new evidence related to this recommendation (48) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(47, 55-57) Therefore, this recommendation is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations (e.g., small sample sizes, lack of measurement of shared decision making, lack of reporting of sharing results with patients, and limited blinded outcomes). The potential benefits of MBC, including improved depression symptoms and remission, are balanced by the potential harms (e.g., the burden of collection and the lack of informatic support in many systems). Patient values and preferences may favor MBC though there is no strong evidence on this.(58) Thus, the Work Group decided upon a *Weak for* recommendation.

C. Treatment Setting

Recommendation

3. For patients with MDD who are being treated in the primary care setting, we recommend the use of collaborative/integrated care models.
   (Strong for | Reviewed, Amended)

Discussion

There is high confidence in the quality of evidence to recommend the use of a collaborative care model for the treatment of MDD in primary care settings. The evidence reviewed for the 2016 VA/DoD MDD CPG supported 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.(59) For this CPG, the Work Group focused on depression symptoms as the critical outcome. An SR by Hudson et al. (2019) and RCTs by Bjorkelund et al. (2018) and Curth et al. (2020) demonstrated greater reductions in depressive symptoms in collaborative care settings when compared with usual care.(60-62)

Collaborative care is often defined as meeting four criteria: a multi-professional approach to patient care, a structured management plan, scheduled patient follow-ups, and enhanced inter-professional communication.(62, 63) Collaborative care personnel include PCPs, nurses, social workers, psychologists, and mental health specialists with prescriptive authority such as clinical pharmacists, psychiatrists, advanced practice nurse practitioners, and physician assistants. The inclusion of a psychiatrist to guide MDD treatment as part of a collaborative care model was shown to have greater improvement in depressive symptoms as compared to TAU.(63, 64) In these models, psychiatrists did not directly prescribe pharmacotherapy but rather provided recommendations for treatment through supervision. For delivery of collaborative care, the SR by Hudson et al. (2019) demonstrated telephone-delivered care management had comparable effects to face-to-face management on depression symptoms.(60)

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. Evidence shows that a stepped care approach improves symptoms, response, and recovery compared to usual care.(65, 66) The benefits of collaborative care for depression outweigh the risks in primary care. Many patients prefer to receive treatment in the primary care setting, where collaborative care models are associated with increased patient satisfaction compared to usual care.(55) Several patient focus group participants noted mental health integration into primary care can be useful for identifying individuals who would benefit from further mental healthcare. Consistent with its application for other conditions and the primary care medical home model, effective collaborative care for depression calls for attention to requisite infrastructure and resources (e.g., patient registry systems, personnel, information technology).

The Work Group systematically reviewed evidence related to this recommendation (60-62) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(59, 63-67) Therefore, this is a *Reviewed*, *Amended* recommendation. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including study design and

sample size. Nevertheless, the benefits of collaborative care in the primary care setting outweighed the potential harms of increased resource use. Patient values and preferences varied somewhat because most patients prefer collaborative care. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

4. For patients with MDD, there is insufficient evidence to recommend for or against the use of a team-based model in specialty mental health care settings.
   (Neither for nor against | Reviewed, New-added)

Discussion

Strong evidence already exists in support of a collaborative care approach to managing MDD in primary care. The Work Group reviewed the evidence on whether a similar team-based approach within a specialty mental health care setting would be as beneficial. Morriss et al. (2016) conducted an RCT on a team-based approach by psychiatrists and psychotherapists of patients with MDD who had not responded to six months or more of treatment for depression.(68) For this study, a psychiatrist and psychotherapist conducted an initial joint or concurrent assessment and subsequently developed a treatment plan collaboratively. Patients followed up with each provider separately and had joint review meetings at three, six, nine, and 12 months into treatment that included the patient, psychiatrist, and psychotherapist. In addition, psychiatrists and psychotherapists held meetings every two weeks to discuss cases and share decision making. A facilitator coordinated these meetings and served as the central point of contact for patients and team members. The results suggested no difference in depression symptoms when using the Hamilton Depression Rating Scale (HDRS) and Global Assessment of Functioning (GAF) measures between team-based specialized services compared to TAU, which consisted of a consulting psychiatrist who directed treatment but did not coordinate care with a psychotherapist.(68) However, the evidence did suggest that team-based specialized services had a greater reduction of depressions symptoms as compared to TAU when measured by the Beck Depression Inventory Version I (BDI-I), PHQ-9, and the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR).(68)

The benefit of providing collaborative specialty mental health team-based care is balanced with the burdens. In consideration of providing team-based care, additional resources may be needed, such as a dedicated facilitator who serves as a central point of contact for patients and team members. Besides coordinating concurrent appointments with patients, team members must set aside time for regular meetings to collaborate. Moreover, access to team-based specialized care may vary by location, particularly between urban and rural areas, but most patients would prefer a team-based approach.

The Work Group systematically reviewed evidence related to this recommendation. Therefore, this is a *Reviewed*, *New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size and high attrition (>30%). Due to insufficient evidence, the Work Group was unable to determine the balance of benefits and harms/burdens. Patient values and preferences varied largely because some patients prefer a team-based approach while others prefer traditional care. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

5. For patients with MDD, there is insufficient evidence to conclude that interventions delivered by clinicians using telehealth are either superior or inferior to in-person treatment.
   (Neither for nor against | Reviewed, New-added)

Discussion

The use of telehealth modalities for clinician-delivered interventions to adults with MDD has been increasing and was further accelerated during the coronavirus disease 2019 (COVID-19) pandemic. However, the evidence review for the current CPG (May 1, 2015 – January 31, 2021) yielded only three RCTs (two of which originated from the other) comparing telehealth interventions to standard in-person care for the treatment of adults with MDD. All the trials focused on behavioral activation (BA) delivered via video conferencing compared with in-person delivery to a population of U.S. Veterans, focused on the use of a single modality (video conferencing or in-person), and did not address a combination of different modalities.(69-71)

Two publications showed no difference in reduction of depression symptoms between BA delivered via videoconferencing versus in person.(69, 71) Noninferiority results were mixed with noninferiority criteria for videoconferencing met in one study but not the other. Another publication found no difference between the groups in QoL scores on any of the eight domains of the Short Form 36 Health Survey Questionnaire (SF-36) at 12 months.(70) It should be noted that failing to find a statistically significant difference in outcomes between the two groups does not confirm that the two groups were equivalent, which would require an equivalence trial design. The Work Group's confidence in the quality of the evidence was very low, primarily due to inadequate sample size and unclear allocation and blinding procedures. Although there was no clear evidence of benefit related to outcomes favoring telehealth modalities over in person, there were no major harms to patients associated with telehealth care delivery documented in the reviewed studies.

Although the SR informing this recommendation focused on synchronous clinician-delivered telehealth-based interventions, other models for virtual care delivery exist. For example, Recommendation 10 addresses unguided and guided (with synchronous or asynchronous therapeutic support) internet-based cognitive behavioral therapy (iCBT).(72) Additionally, the evidence review included studies that compared the effectiveness of individual face-to-face cognitive behavioral therapy (CBT) blended with computer-assisted CBT and standard, individual face-to-face CBT.(73, 74) These studies are included as examples of other models for virtual care delivery and did not influence this recommendation's strength.

The COVID-19 pandemic necessitated rapid adoption of virtual care modalities with care delivered by telephone and video telehealth, including by providers and patients less experienced with telehealth and with interventions for which telehealth delivery was a relatively novel approach. Temporary CMS regulatory coding changes adopted early in the COVID-19 pandemic allowed for broader use of telehealth modalities, addressing reimbursement concerns. However, additional research is needed to inform patients, providers, and healthcare systems about the effectiveness of different telehealth modalities, including telephone and mixed modalities, comparative effectiveness of interventions delivered through different modalities, and test for equivalence between modalities.

Although telehealth-based interventions may improve healthcare equity by expanding the accessibility of interventions for MDD to individuals for whom travel to in-person care is a significant burden and/or who live in under-served areas, clinicians must consider patient values and preferences regarding the modality of care. For example, the patient focus group participants indicated that although telehealth modalities were considered an acceptable alternative during the COVID-19 pandemic, each stated a preference for in-person care over telehealthcare. Additionally, there is variability in patients' level of comfort and familiarity with telehealth technologies and variability in access to high-speed internet, equipment, and technologies needed to support certain telehealthcare modalities (i.e., video telehealth).

The Work Group systematically reviewed evidence related to this recommendation.(69-71) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including inadequate sample size and unclear allocation and blinding procedures. All reviewed trials focused on BA as the intervention type delivered via video conferencing versus in-person to U.S. Veterans. Although there was no clear evidence of benefit for outcomes that would favor providing services to patients with MDD through telehealth modalities over in person, there were no major harms associated with telehealth care delivery documented in the reviewed studies. Patient values and preferences vary, with some patients preferring in-person over telehealth modalities. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

D. Treatment of Uncomplicated MDD

Recommendation

6. We recommend that MDD be treated with either psychotherapy or pharmacotherapy as monotherapy, based on patient preference. Factors including treatment response, severity, and chronicity may lead to other treatment strategies such as augmentation, combination treatment, switching of treatments, or use of non-first line treatments (see Recommendations 17, 18, and 20).
   (Strong for | Reviewed, New-replaced)

7. When choosing psychotherapy to treat MDD, we suggest offering one of the following interventions (not rank ordered):
   - Acceptance and commitment therapy
   - Behavioral therapy/behavioral activation
   - Cognitive behavioral therapy
   - Interpersonal therapy
   - Mindfulness-based cognitive therapy
   - Problem-solving therapy
   - Short-term psychodynamic psychotherapy

   (Weak for | Reviewed, New-replaced)

Discussion

The evidence suggests that MDD can be treated efficaciously through the utilization of psychotherapy or pharmacotherapy as monotherapy, honoring patients' preference. Please see Recommendation 7 and Recommendation 11.

When treating patients with initial episode of MDD or for patients who have previously responded well to monotherapy in terms of symptom improvement, remission rates, or adverse effects, there was not sufficient evidence, based on the literature reviewed, to recommend one specific therapeutic modality (i.e., psychotherapy or pharmacotherapy) over another. Both modalities have established efficacy as monotherapy in RCTs.(75)

In selecting a treatment option, particularly when this is the patient's first experience with treatment, the provider should explain the risks and benefits of all treatments to achieve a shared decision on the course of treatment. While provider experience can be a factor in recommending treatments, there is limited evidence to guide the choice of a specific treatment modality. The initial choice is between a course of psychotherapy or pharmacotherapy and then within each domain, which specific treatment. Patient preference should drive the decision process. This could include referral to a different provider if the desired treatment is not in the current provider's scope of practice.

The Work Group systematically reviewed evidence related to Recommendation 6 (see the summaries related to psychotherapy and pharmacotherapy below for additional information). Therefore, this is a *Reviewed, New-replaced* recommendation. Based on the GRADE methodology, the confidence in the quality of evidence for specific treatment modalities was very low when looking at the range of outcomes considered in this evidence review (e.g., symptom improvement, remission rates). The Work Group also considered that MDD is a serious and debilitating disease that carries a high risk of disability and increased risk of suicidality. Consequently, offering either treatment modality is far superior to no treatment. The Work Group found the benefits of treatment (diminishing the risk of suicide and providing symptom relief with remission for some) outweighed the harms. Per GRADE guidelines: 15, which states, "A strong recommendation may be warranted…when low quality evidence suggests benefit in a life-threatening situation," the Work Group determined a *Strong* recommendation is warranted due to the potential catastrophic harms of untreated MDD.(14) There is variation in patient values and preferences since some patients prefer medications over psychotherapy since it is convenient, while others prefer psychotherapy to medications. Finally, the Work Group found higher feasibility for medications since medications tend to be cheaper and more available than psychotherapy. For instance, some parts of the country have limited availability of trained psychotherapists. Thus, the Work Group decided upon a *Strong for* recommendation for Recommendation 6.

Regardless of treatment choice, patients should be made aware of the risks and benefits of each option and the importance of full engagement in treatment to maximize benefit. Neither pharmacotherapy nor psychotherapy is as effective when delivered at less than the recommended frequency or dose.

Summary of Evidence on Choice of Antidepressants for Patients with an Initial Episode of MDD or for Patients who have Previously Responded Well to Monotherapy

Antidepressants have been approved and used clinically for over six decades. The exact mechanism of action is not well understood but is presumed to be mediated by changes in monoamine levels in the

brain. Newer studies have highlighted mechanisms of action that are being explored to improve response rates, lower side effect profile, or enhance remission after treatment.(76)

With the choice of pharmacotherapy, the Work Group recommends selecting any of several agents with no evidence supporting one over another (see Recommendation 11). These choices include in no specific order: bupropion, mirtazapine, serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRI), or trazodone (at recommended antidepressant doses). A review of the evidence was unable to determine a difference in risks of adverse effects that would inform choice. Some medications are not considered as initial treatment (see Recommendation 12).

Summary of Evidence on Choice of Psychotherapy for Patients with Initial Episode of MDD or for Patients who have Previously Responded Well to Monotherapy

The most recent evidence, combined with evidence collected during the 2016 VA/DoD MDD CPG, supports offering one of the following evidence-based psychotherapies, based on patient preference: CBT, interpersonal therapy (IPT), mindfulness-based cognitive therapy (MBCT), behavioral therapy (BT)/BA, acceptance and commitment therapy (ACT), problem-solving therapy (PST), or short-term psychodynamic psychotherapy (STPP).(77-86) A regimen of CBT, IPT, or MBCT is suggested for patients with MDD with an elevated risk of relapse following the achievement of remission to avoid relapse. The current evidence review emphasized comparative effectiveness trials. The most important change in this recommendation compared with the 2016 VA/DoD MDD CPG was the addition of STPP, for which there were two recent fair quality RCTs, including evidence for non-inferiority versus CBT.(87, 88)

The evidence does not suggest one specific evidence-based psychotherapy listed above is more or less effective than another in reducing depressive symptoms or achieving remission. In addition, the evidence does not suggest certain CBT treatment packages are more effective than others. For example, neither meta-cognitive therapy nor cognitive evolutionary therapy offers notable advantages (or disadvantages) in primary outcomes compared with traditional CBT approaches.(89, 90) Overall, the Work Group found consistency in evidence for efficacy and comparability of these treatments across different populations.

Upon engaging in psychotherapy as a treatment approach, the Work Group suggests that either individual or group formats be based on the patient's preference (see Recommendation 8). Other considerations include the use of computer-based psychotherapies (see Recommendation 10) and the lack of evidence to recommend combining components from different psychotherapy approaches (see Recommendation 9).

The Work Group determined that the benefits of psychotherapy outweighed harms and that there was little evidence of harm in psychotherapy studies in general. Similarly, the benefits of pharmacotherapy outweigh the risk of adverse effects. There is some variability in patient preferences regarding psychotherapy and pharmacotherapy, but variability is likely to be larger when considering decisions regarding psychotherapy versus medication. One feasibility consideration has to do with the availability of providers with adequate training in the various psychotherapies. However, CBT is a standard approach that is a routine part of training programs, and most credentialed clinicians will have experience with it. CBT is also a standard treatment often used as a comparison condition in head-to-head clinical trials of other evidence-based psychotherapies.

The Work Group systematically reviewed evidence related to Recommendation 7 (84-92) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(77-83) Therefore, this is a *Reviewed*, *New-replaced* recommendation. Based on GRADE methodology, the confidence in the quality of the evidence was very low; however, the Work Group also noted the number and breadth of studies and consistency of positive outcomes across various populations. Limitations in the body of evidence included small sample sizes, high drop-out or loss to follow-up rates, lack of intent-to-treat (ITT) analysis, and lack of blinding or assessment of allocation concealment in psychotherapy studies. Thus, the Work Group decided upon a *Weak for* recommandation for Recommendation 7.

With either pharmacotherapy or psychotherapy, self-help, complementary, and alternative treatments should be considered as a supplement or as an alternative if the former two options prove unavailable (see Recommendations 27 – 32). Non-directive supportive therapy (NDSP) is suggested for patients who decline first-line evidence-based psychotherapies (see Recommendation 14).

Recommendation

8. For patients who select psychotherapy as a treatment option, we suggest offering individual or group format based on patient preference.
   (Weak for | Reviewed, Not changed)

Discussion

Evidence suggests group psychotherapy reduces depression symptoms in patients with MDD and that group and individual psychotherapy have comparable effectiveness in reducing depression symptoms. Okumura et al. (2014) suggests group versions of CBT and MBCT are viable options for the treatment of MDD.(93) This research showed group CBT had superior efficacy in the reduction of depression symptoms compared to waitlist control, TAU, or placebo. However, there was no difference in symptom reduction when comparing group CBT to interventions such as computerized CBT or guided self-help (GSH). There was also no difference in symptom reduction with group CBT compared to psychoeducation, relaxation training, individual CBT, or other psychotherapy.

An SR by Huntley et al. (2012) showed that group CBT plus TAU led to a significant reduction in depressive symptoms compared to TAU alone.(94) When compared with individual CBT, group CBT showed no significant difference in symptom reduction.

A more recent network meta-analysis by Cuijpers et al. (2019) found group and individual CBT have comparable effectiveness in reducing depression symptoms.(95) Both group and individual formats led to a greater reduction in depression symptoms than waitlist and usual care control conditions. Of note, the authors considered an intervention to be “CBT” if it included cognitive restructuring as a core component. However, they noted that many interventions also included additional treatment components (e.g., problem-solving, BA, mindfulness-based interventions, and social skills training).

Group therapy is a modality of treatment that can be used to deliver various types of specific psychotherapies. There is a larger body of evidence for group CBT (and group interventions including cognitive restructuring as a core component) than other evidence-based group psychotherapies. The potential benefits of group therapy include improved access to care and lower costs for individuals and systems. The Work Group determined the benefits of this type of intervention outweigh the possible

harms (e.g., lack of privacy in a group setting). Additionally, there is a need for more research on other types of group therapies.

Patient values and preferences in choosing between group or individual therapy may vary greatly. For example, some patient focus group participants preferred a group format for greater interpersonal support and an opportunity to connect with and learn from others sharing similar experiences. However, some patient focus group participants noted they prefer individual therapy formats for various reasons, including feeling less comfortable in group settings. There is also a large variation in how group therapies are implemented, including group structure and size, leadership, and choice of therapies. Other considerations for providers include subgroups (e.g., women or men only, life stage), the feasibility of implementation, and the acceptability of this form of therapy in populations served.

The Work Group systematically reviewed evidence related to this recommendation (95) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(93, 94) Therefore, this is a *Reviewed*, *Not changed* recommendation. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including imprecision in specific protocol or type of therapy studied (e.g., group therapies with cognitive restructuring components versus a standardized CBT protocol), lack of data regarding potential risks, and limited evidence on group interventions using non-CBT approaches. The benefits of group psychotherapy (e.g., improved depression symptoms) slightly outweighed the potential harms (e.g., risk of adverse events or lack of privacy, which was small). Patient values and preferences varied somewhat because patients may have a preference for therapy modality (i.e., group or individual) for various reasons (e.g., cost, social support, confidentiality, convenience). Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

9. There is insufficient evidence to recommend for or against combining components from different psychotherapy approaches.
   (Neither for nor against | Reviewed, New-added)

Discussion

Few rigorous studies have examined the effectiveness of adding components from different psychotherapy approaches to established treatments for adults with MDD, or conversely, examined whether abbreviated versions of established treatments are as effective as the complete treatment. An SR by Cuijpers et al. (2019) evaluated the addition or subtraction of treatment components from psychological treatments for adults with MDD.(95) The authors hypothesized a defined treatment component as being critical to achieving successful outcomes. Overall, nine of the included studies had an additive design and 13 had a dismantling (i.e., component removed) design.

The SR by Cuijpers et al. (2019) reviewed 16 RCTs comparing adult depression outcomes for a complete psychotherapy to that psychotherapy plus or minus a treatment component or an abbreviated form of the psychotherapy.(95) Cognitive behavioral therapy was the full psychotherapy for 16 comparisons across 11 studies. The studies compared full CBT to cognitive therapy minus the BA component, BA without the cognitive component of CBT, CBT plus hypnotherapy, and CBT plus mindfulness.

Full CBT, which standardly includes the BA component, was associated with greater improvement of depression symptoms when compared to CBT without BA. No difference was found in depression outcomes when comparing CBT to BA without the cognitive component of CBT. The evidence did not indicate an advantage in depression outcomes when comparing CBT to CBT plus hypnotherapy or CBT plus a mindfulness component.

Depression outcomes from the systematic model of PST provided in a group format were compared to outcomes from a problem-focused group therapy in which subjects were encouraged to discuss current difficulties and crises. Outcomes favor the systematic model of PST. Another comparison examined depression outcomes from PST compared to PST minus the problem-orientation training component, which is described as training "geared to facilitate problem-solving skills and to feel self-efficacious in doing so."(96) Findings from this study also favored the full version of PST.

Taken together, the methodological quality of the identified studies in Cuijpers was rated as low to very low based on serious study limitations, including research methods and study execution, and an increased probability of bias across studies. Other factors limiting the quality of the evidence include wide confidence intervals (CI) and, for some studies, small to very small sample sizes. Overall, the existing evidence is characterized as very low quality, severely limiting confidence in the findings and the Work Group's ability to make *Strong* recommendations for or against modifying established treatments. There is also insufficient evidence to determine whether harms and benefits differ for combined or otherwise adapted treatments relative to research on the original protocols.

The Work Group systematically reviewed evidence related to this recommendation.(95) Therefore, this is a *Reviewed, New*-added recommendation. The Work Group's confidence in the quality of the evidence was very low. The potential benefits or harms of combining components from different psychotherapy approaches are unclear given the lack of evidence. Patient values and preferences varied somewhat because of a possible personalized approach and having a choice of effective treatments. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

10. For patients with mild to moderate MDD, we suggest offering clinician-guided computer/internet-based cognitive behavioral therapy either as an adjunct to pharmacotherapy or as a first-line treatment, based on patient preference.
    (Weak for | Reviewed, New-replaced)

Discussion

Computer/internet-based CBT in this recommendation refers to CBT delivered via a computer or internet application. These packages can be either unguided, in which the patient works through the material without the help of a clinician, or guided, involving synchronous or asynchronous support delivered by a clinical professional trained to deliver CBT. These treatments have been used in various settings, including primary care, where treatment of mild depression is more typical than in specialty care.

An SR by Karyotaki et al. (2021) found that guided computer/internet-based CBT provided greater efficacy than unguided approaches within 12 weeks of follow-up and for patients with PHQ-9 scores >9

(overall response rates 48% for guided CBT versus 37% for unguided CBT); however, differences were less apparent for patients with subthreshold symptoms or at later follow-up time periods.(72) A major limitation in these studies was the reliance on self-reported PHQ-9 scores for the primary outcome (rather than clinician-determined outcomes). The overall strength of evidence is low based on GRADE criteria.

The benefits of computer/internet-based psychotherapy over no treatment outweigh the harms. Still, there could be harms if patients decline more effective treatments in preference for a computer or internet-based modality. These treatments may also be used adjunctively with other evidence-based approaches. There is some variability in patient preferences regarding these treatments. These modalities may be less burdensome and easier to access at home, but this may pose challenges for older or homeless Veterans or individuals with limitations in internet access.

The Work Group systematically reviewed evidence related to this recommendation (72) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG. Therefore, this is a *Reviewed*, *New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. In addition to the key limitation of reliance on self-report PHQ-9 for the primary outcome, there were other limitations inherent in psychotherapy studies (small sample sizes, lack of blinding, high loss of follow-up, and other considerations). The benefits of computer/internet-based psychotherapy over no treatment outweigh the harms. Patient values and preferences varied somewhat. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

11. When choosing an initial pharmacotherapy, or for patients who have previously responded well to pharmacotherapy, we suggest offering one of the following (not rank ordered):
    - Bupropion
    - Mirtazapine
    - A serotonin-norepinephrine reuptake inhibitor
    - Trazodone, vilazodone, or vortioxetine
    - A selective serotonin reuptake inhibitor

    (Weak for | Reviewed, New-replaced)

12. When choosing an initial pharmacotherapy, we suggest against using:
    - Esketamine
    - Ketamine
    - Monoamine oxidase inhibitors
    - Nefazodone
    - Tricyclic antidepressants

    (Weak against | Reviewed, New-added)

Discussion

Evidence does not suggest one specific antidepressant medication or drug class is superior to another for the treatment of MDD in terms of symptom improvement, remission rates, or adverse effects.(91, 92) One network meta-analysis containing 522 RCTs showed a similar effect between bupropion,

mirtazapine, trazodone, nefazodone, SNRIs, SSRIs, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs) in terms of symptoms improvement and remission rates, with all being significantly more effective than placebo.(91) A network meta-analysis containing 53 RCTs showed a similar frequency of adverse events between these same agents.(92)

However, certain drug classes are associated with higher incidences of serious adverse events than others. The infrequency of these toxic events limits their appearance in clinical trials, but they must not be overlooked. To reduce the risk of toxicity in patients on antidepressants, especially those at higher risk of suicide, the Work Group recommends limiting the patient's supply of medication.(97)

While not captured in the evidence review, the Work Group considered other available literature when making these recommendations. Given the low therapeutic index of TCAs, toxicity is much more likely to occur with this class compared to other antidepressants. Therefore, TCA toxicity is a serious potential risk and can be fatal.(98) Manifestations of serious toxicity include cardiovascular, central nervous system, and anticholinergic toxicity, including refractory hypotension, ventricular arrhythmia, seizure, and coma.(99) Depending on the TCA, these significant signs of toxicity can occur at doses of 5 milligrams (mg)/kilogram (kg).(100) For this reason, TCAs should be used cautiously and dispensed in limited quantities in patients at risk for suicide.

Monoamine oxidase inhibitors also have a low therapeutic index. When combined with foods high in tyramine or certain serotonergic or sympathomimetic medications, MAOIs carry the risk of potentially life-threatening adverse effects, namely hypertensive crisis and serotonin syndrome. Severe interactions potentially leading to a hypertensive crisis can occur with tyramine intake.(101) From a drug interaction standpoint, the risk of serotonin syndrome with multiple serotonergic agents is greatest when one or both of those agents are an MAOI.(102) Additionally, sympathomimetic agents can precipitate hypertensive crisis when combined with MAOIs.(101) These serious adverse events may not occur frequently. However, all patients offered a TCA or MAOI should receive appropriate education about the medication’s safety and side effect profile, including relevant drug-drug and drug-food interactions. While not suggested as initial treatment strategies, TCAs and MAOIs continue to be effective agents in managing patients with complex MDD.

Nefazodone is associated with a significantly higher risk of hospitalizations resulting from liver toxicity compared to other antidepressants.(103, 104) The overall safety of nefazodone compared to other options led the Work Group to suggest against it as a first-line option.

Ketamine lacks long-term efficacy and safety trials in MDD, and the bulk of the short-term efficacy has been studied in patients who have previously not responded to adequate trials of antidepressants. While there is some evidence to support longer-term maintenance use of esketamine, it too has been primarily studied in patients who have previously not responded to trials of antidepressants.(105, 106) Therefore, the use of ketamine and esketamine is not recommended as initial treatment.(107) These two agents are discussed in Recommendation 19.

There is large variability in patient preferences regarding the use of any pharmacotherapy. For example, some patients are interested in trialing medication. Others may be concerned about side effects, be opposed to taking prescription medications, or prefer psychotherapy. In addition, there is some

variability in patient preferences around avoiding TCAs or MAOIs for initial treatment, as the patient may know someone who has responded well to these agents in the past, while others may prefer not to use them due to potential side effects or dietary restrictions, with MAOIs specifically.

The Work Group systematically reviewed evidence related to these recommendations.(91, 92, 107) Therefore, these recommendations are *Reviewed*, *New-replaced* and *Reviewed*, *New-added*. The Work Group rated the quality of the evidence as very low based on GRADE criteria. The body of evidence had some limitations, including concerns regarding randomization, allocation concealment, blinding of participants, personnel, and outcome assessors.(91, 92) The potential benefits of treatment with bupropion, mirtazapine, SNRIs, SSRIs, or trazodone (i.e., improvements in depressive symptoms and remission rates, reduced morbidity and mortality) outweighed the potential harms of adverse events. The potential harms (i.e., low therapeutic index resulting in increased risk for dangerous adverse events for TCAs and MAOIs, lack of long-term efficacy and safety data for ketamine, data to show efficacy after other nonresponsive options for esketamine) outweighed the potential benefits of TCAs, MAOIs, ketamine, and esketamine as initial treatment options (i.e., improvements in depressive symptoms and remission rates, reduced morbidity and mortality). Patient values and preferences around pharmacotherapy varied significantly. Thus, the Work Group decided upon a *Weak for* Recommendation 11 and a *Weak against* for Recommendation 12.

Recommendation

13. There is insufficient evidence to recommend for or against pharmacogenetic testing to help guide the selection of antidepressants.
    (Neither for nor against | Reviewed, New-added)

Discussion

There is insufficient evidence to recommend for or against the use of pharmacogenetic (PGx) testing in the selection or dosing of antidepressants or selecting specific pharmacologic strategies for the treatment of MDD. Only two studies (one SR) investigating the use of PGx testing currently exist.(108, 109) The review for this recommendation focuses on the clinical utility of PGx testing. Another set of studies was not reviewed that focuses on biological correlates.

One RCTs and one SR were evaluated. The studies were very low quality due to small sample size, and there was concern about bias given they were all commercially funded.(108, 109) When evaluating sample size for PGx studies, it is important to recognize that the test results are only helpful in a subset of patients with actionable genotypes. In Greden et al. (2019) and Ramsey et al. (2021), PGx tests were actionable in 15 – 20% of patients, meaning that the medication prescribed for that person had a gene-drug interaction.(110, 111) Thus, without an oversampling strategy, most of the studies examining PGx clinical utility have been underpowered.(110, 111)

The only study with a reasonable sample size (n=1,541) showed mixed outcomes.(110) Patients were randomly assigned to having PGx results as a guide to treatment with blinded outcome ratings. The main outcome of symptom severity showed no difference between patients who did and did not receive PGx testing to guide treatment. However, both remission and relapse showed improvement in different commercial PGx panels. A smaller trial (n=304) showed no advantage of providing PGx information to

the patient and provider.(109) The SR included four RCTs and two open-label trials with potential observational bias and small sample sizes.(112) The SR favored PGx guided treatment for symptom response and remission.

As most adverse effects of medication are dose-dependent and PGx testing almost exclusively provides information on how the patient is expected to metabolize different medication options, a reduction in adverse effects may be hypothesized. The only publication to report on adverse effects did not show a benefit from PGx testing.(110)

The current emphasis of PGx testing is on genes that influence the metabolism of medications. While not unique to antidepressants, the clinical impact of the difference in the metabolism of psychotropics is not well documented. There are some medications in which serum levels have clinical utility (e.g., lithium, TCAs), but for most antidepressants, serum levels have not been associated with clinical outcomes.

It is worth noting that the U.S. Food and Drug Administration (FDA) and non-profit organizations like the Clinical Pharmacogenetics Implementation Consortium (CPIC) have made recommendations for the use of PGx testing based on clinical utility and other available science such as basic pharmacokinetics. Thus, CPIC has made recommendations that PGx testing can be helpful in a select group of antidepressants based on evidence that some genotypes substantially alter the metabolism of these medications. However, the recommendations to date are not based on clinical outcomes. The FDA labeling of some antidepressants related to genetic testing follows this same process.

While genotyping has become a standard clinical laboratory practice, it is important to note that each medication's clinical interpretation and recommendations vary and are not governed by the FDA or other regulatory bodies.(113, 114) This lack of standardization is partly the rationale behind CPIC and other similar organizations, but clinical laboratories are not obligated to adhere to those recommendations.

The Work Group systematically reviewed evidence related to this recommendation.(108-110, 112) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The potential benefits of patient engagement and the small amount of positive evidence slightly outweighed the potential harms, which are none. Patient values and preferences varied largely. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

14. For patients with mild to moderate MDD who decline pharmacotherapy and who decline or cannot access first-line evidence-based psychotherapies (either in-person or virtually), we suggest considering non-directive supportive therapy.
    (Weak for | Not reviewed, Amended)

Discussion

Available evidence indicates NDSP yields a small, consistent, and statistically significant benefit compared to TAU, placebo controls, and other inactive control conditions. Compared to other

psychotherapies and pharmacotherapy, NDSP is less efficacious, although the effect size is small.(79, 115) For example, Cuijpers et al. (2012) found the differential effect size of NDST compared to other psychological treatments to be small (g = -.20).(115) Therefore, NDSP is not considered a first-line treatment.

The meta-analysis by Cuijpers et al. (2012) suggested the superiority of other treatments compared to NDSP may be attributed, in part, to researcher allegiance.(115) When controlling for researcher allegiance, the difference between NDSP and other interventions was non-significant. Given the totality of the evidence, it is appropriate to offer this modality to patients who decline or cannot access first-line treatments, either locally or via telehealth.

The overall quality of the evidence reviewed was low due to the limited number of studies available. Still, the possible benefits of receiving NDSP outweigh the potential harms of receiving no treatment. Providers offering NDSP should follow the principles of MBC, regularly assessing patient symptoms and functioning and revisiting the treatment plan if improvements are not demonstrated. There is some variability in patient preference regarding this treatment. For example, some patients may prefer a non-directive, unstructured therapy to first-line medications or structured first-line psychotherapies. In addition, some patients may have difficulty accessing providers trained in first-line psychotherapies for depression, either locally or via telehealth, but may have easier access to NDSP.

The Work Group considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(79, 115, 116) Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was low given the limited number of studies available. The potential benefits of NDSP (e.g., improved depression symptoms) when first-line medications and psychotherapies are declined or not accessible slightly outweighed the potential small harms of adverse events. Patient values and preferences varied somewhat. Thus, the Work Group decided upon a *Weak for* recommendation.

E. Treatment of MDD that is Severe or has a Partial or Limited Response to Initial Treatment

Recommendation

15. We suggest offering a combination of pharmacotherapy and evidence-based psychotherapy for the treatment of patients with MDD characterized as:
    - Severe (e.g., PHQ-9 >20)
    - Persistent major depressive disorder (duration greater than two years)
    - Recurrent (with two or more episodes)

    (Weak for | Not reviewed, Amended)

Discussion

An SR by Li et al. (2018), which included six RCTs evaluating the addition of a CBT intervention (e.g., CBT for depression or mindfulness-based cognitive therapy) to pharmacotherapy for patients with residual symptoms of depression after one or more adequate trials of antidepressant medication, suggests combining CBT and pharmacotherapy is more efficacious than pharmacotherapy alone in improving symptoms of depression in these patients.(117) Superior outcomes for the combination conditions were

evident immediately after treatment, six months post-treatment, and at one-year follow-up.(117) In addition to symptom improvement, the evidence also suggests the combination of pharmacotherapy and CBT results in a higher remission rate for these patients than pharmacotherapy alone. Subgroup analyses indicate that remission rates did not vary based upon the type of CBT intervention used.

Nakao et al. (2018) evaluated the efficacy of pharmacotherapy (e.g., antidepressant medications with education and medication management) alone and when combined with CBT in a sample of treatment-seeking patients with depression in Tokyo, Japan.(118) Inclusion criteria included a DSM-IV diagnosis of unipolar depression with a GRID-HAMD 17 score ≥14, despite having an adequate trial with at least one antidepressant medication for at least six weeks. The GRID-HAMD 17 is a clinician-administered measure using a semi-structured interview guide that separates the frequency of symptoms from its intensity for most items. The CBT intervention included 12 weeks of a web-based, self-administered, self-paced course of CBT with 12 concurrent face-to-face sessions with a study therapist.

Results were mixed for depressive symptoms based upon assessment method and measure. Data generated using the GRID-HAMD 17 clinician-administered depression rating scale indicated participants in the pharmacotherapy plus CBT condition had significantly lower depressive symptoms (reduction of 8.9 points) at week 12 compared to those who received pharmacotherapy alone (reduction of 3.0 points).(118) Participants were also more likely to have a treatment response, defined as a 50% or greater reduction in symptoms over baseline, at the post-treatment (12 weeks) assessment (number needed to treat [NNT] = 3, 95% CI: 1.6 to 14.2) and to have reached remission, defined as a GRID-HAMD 17 score of ≤7 (NNT = 3, 95% CI: 1.7 to 8.7) than participants in the pharmacotherapy monotherapy condition.

However, participant-rated symptoms of depression using the Beck Depression Inventory-Second Edition (BDI II) were not significantly different at each assessment point for participants in the pharmacotherapy alone and those in the pharmacotherapy plus CBT.(119) The authors suggest that because baseline sample scores on the BDI were low, a floor effect may have suppressed detection of significant differences.

There were no statistically significant differences between groups on measures of QoL (SF-36 and European Quality of Life Questionnaire-5 Dimensions, Mental and Physical subscales), and no adverse events were reported.

An RCT by Karp et al. (2018) evaluated the efficacy of a stepped-care intervention using venlafaxine XR with and without problem-solving therapy for depression and pain (PST-DP).(120) The sample of 139 older adults aged 60 or older with chronic low back pain and depression had not responded to low dose venlafaxine XR.(120) The experimental group received a higher dose of venlafaxine XR combined with PST-DP, and the control condition received a higher dose of venlafaxine XR in combination with supportive management. Treatment response was defined as a composite score of a PHQ-9 ≤5 and at least a 30% reduction in the pain Numeric Pain Rating Scale (NRS) from the score at study entry. At week 13, 36.5% (95% CI: 26.1% to 49.4%) of those in the venlafaxine XR plus PST-DP were responders compared to 37.4% (95% CI: 27.2% to 49.9%) of those in the venlafaxine XR plus supportive management condition. No significant difference was detected between groups when considering depression and pain scores independently or on all measures at a 12 month follow-up assessment.

Finally, an SR and meta-analysis by Driessen et al. (2020) evaluated three RCTs to examine the efficacy of adding STPP to antidepressants (n=244).(121) Individual patient data from three RCTs were combined to assess STPP plus an antidepressant versus antidepressant monotherapy. Results were mixed. Analyses using HAMD Z-scores as the primary outcome measure found no significant difference between groups post-treatment and at follow-up at 10 to 12 months. However, when using raw HAMD scores, the combined treatment (antidepressant + STPP) was significantly more efficacious than antidepressant monotherapy. The authors attribute the inconsistent findings to the constituent studies included in the meta-analyses. One of the RCTs enrolled patients with depression and comorbid obsessive-compulsive disorder (OCD). Results from that trial did not favor adding STPP to antidepressant therapy, while the other two studies showed more of a benefit from adding STPP.

The Work Group considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(117, 118, 120, 121) Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations. The potential benefits outweighed the potential harms. Patient values and preferences varied somewhat. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

16. For patients with MDD who have demonstrated partial or no response to an adequate trial of initial pharmacotherapy, we suggest (not rank ordered):
    - Switching to another antidepressant (including TCAs, MAOIs, or those in Recommendation 12)
    - Switching to psychotherapy
    - Augmenting with a psychotherapy
    - Augmenting with a second-generation antipsychotic

    (Weak for | Reviewed, Amended)

Discussion

Patients with MDD who have received an adequate trial (six to 12 weeks) of initial maximized pharmacotherapy 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 (see Appendix J). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that patients in primary and psychiatric care did not differ in remission or response rates; however, patients commonly required eight weeks or more to achieve response or remission.(122) An SR by Braun et al. (2020) found no clinically relevant dose-effects gradients for SSRIs and that dropout rates increased with dose, primarily due to side effects.(123) This suggests that maximizing the dose of an SSRI may not be clinically useful. Further, STAR*D demonstrated that at least one-third of patients did not achieve remission after four consecutive, highly optimized treatment steps involving either

switch or augmentation, showing the decreased likelihood of response with subsequent antidepressant trials.

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, adverse effects, and lack of clinical benefit. An SR by Bschor et al. (2018) and an RCT by Tadic et al. (2016) found no difference in antidepressant efficacy, symptom response, remission, adverse effects, and functional status between switching and continuation of antidepressant treatment.(124, 125) An SR by Davies et al. (2019) found no difference in depressive symptoms, remission, adverse events, QoL, and functional status in patients who received mirtazapine augmentation versus placebo augmentation.(126) An RCT by Xiao et al. (2021) evaluated the combination of mirtazapine and paroxetine versus either agent alone.(127) They found no difference in symptom improvement and remission at the end of the eight-week trial. Adverse effects were more common with the combination of mirtazapine and paroxetine and mirtazapine monotherapy than with paroxetine monotherapy (mirtazapine plus paroxetine 43%, mirtazapine 43%, paroxetine 22%, p=0.0153). Therefore, in patients with partial or no response to initial treatment, it is reasonable to consider switching to another first-line antidepressant (either within-class or out-of-class), psychotherapy, or augmenting current therapy with psychotherapy or an SGA.

Combined pharmacotherapy and psychotherapy are options if a response or remission is not achieved with an antidepressant as initial monotherapy. In an SR by Li et al. (2018) where the comparators were TAU (three RCTs), psychoeducation (one RCT), health enhancement program (one RCT), and medication change (one RCT), which included participants who were receiving pharmacotherapy at baseline, the addition of psychotherapy (i.e., CBT) resulted in improvement in symptoms of depression and remission.(117) Nakao et al. (2018) showed no difference in adverse events between blended CBT and antidepressant medication versus antidepressant monotherapy.(118)

Augmentation with an SGA may also be considered in patients who have demonstrated partial or no response to initial pharmacotherapy monotherapy. Three atypical antipsychotics are FDA-approved for MDD as adjunctive treatment/augmentation: aripiprazole, brexpiprazole, 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 (TRD). Other SGAs such as cariprazine and risperidone, while not indicated, are used off-label for augmentation.

Three SRs have demonstrated the significant benefit of SGAs (alone or augmentation) for remission in MDD. Komossa et al. (2010) (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).(128) Santaguida et al. (2012) (one RCT) demonstrated small significant benefit favoring augmentation with atypical antipsychotics (olanzapine, aripiprazole, risperidone, and quetiapine).(129) Dold et al. (2020) (23 RCTs) demonstrated significant improvement in depressive symptoms with SGAs (aripiprazole, brexpiprazole, cariprazine, olanzapine, quetiapine).(130) Risperidone augmentation did not differentiate from placebo augmentation.

While there is a significant benefit with augmentation using SGAs, there is also the potential for significant side effects. Fair quality evidence 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.(128) While the risk is generally lower than first-generation antipsychotics, another significant adverse effect associated with SGAs is tardive dyskinesia.(131) Due to the possibility of additional side effects and the potential for drug-drug interactions with augmentation, SGAs require appropriate monitoring (e.g., glucose, complete blood count, hepatic panel, lipid panel, body mass index, waist circumference, blood pressure, involuntary movements/tardive dyskinesia, slit lamp exam [quetiapine-only]). In the military population, the use of antipsychotics may also trigger a medical evaluation board to determine fitness for continued military service; therefore, before prescribing these medications, clinicians should carefully consider the clinical appropriateness for individual patients and the potential career impact.

Medications with Insufficient Evidence to Support For or Against

Bupropion

A common clinical practice for augmentation is the addition of bupropion-SR, where the addition of bupropion-SR to SSRI treatment significantly increased remission rate without increasing adverse events.(132) Bupropion may be considered for patients with MDD who desire to stop smoking or have experienced sexual side effects.(133, 134) However, it is contraindicated in patients with a seizure disorder, a history of anorexia nervosa, or bulimia and can potentially worsen anxiety. There was insufficient evidence to recommend bupropion even though the risks associated with augmentation are considered lower than with SGA's, and in clinical practice, bupropion is preferred over an SGA.

Buspirone

As shown in STAR*D, the addition of buspirone effectively achieved remission when combined with an SSRI.(135) 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.(136) Buspirone is generally dosed two to three times per day on a scheduled basis for full effect and generally takes two to four weeks to achieve efficacy.(137, 138) Davies et al. (2019) found no difference in depressive symptoms in patients who received buspirone augmentation versus placebo augmentation.(126)

Lithium

An SR by Nelson et al. (2014) evaluated nine RCTs of lithium augmentation of antidepressants for the treatment of MDD.(139) Dosing of lithium in the selected trials ranged from 600 mg to 900 mg per day. Lithium augmentation resulted in a reduction in depressive symptoms with a clinically meaningful NNT of five patients.(139) However, Papadimitropoulou et al. (2017) found no difference in symptom improvement and remission in patients who received lithium augmentation versus placebo augmentation.(140) In addition, lithium usage requires monitoring of lithium blood levels (therapeutic blood level is between 0.6 – <1.0 milliequivalents per liter [mEq/L] while potentially toxic blood levels are >1.5 mEq/L), and monitoring of thyroid function. Of note, in the military population, augmentation with lithium confers additional risk of toxicity secondary to potential for dehydration, which can cause

increased lithium blood levels. In the military population, the 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.(141) Liothyronine augmentation may be effective regardless of thyroid abnormalities. As with any medication, careful consideration must be given to 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 the treatment of depression in euthyroid patients due to the extended time for effectiveness to be achieved. In patients with thyroid disease, the underlying medical condition should be treated as medically appropriate.

Summary

There is some variability in patient preferences. The patient focus group participants engaged in various treatment options for MDD. However, psychotherapy can be burdensome due to a required time commitment and frequent visits. Further, there may be limited access to recommended evidence-based psychotherapies since not all providers have adequate training in them. While patients generally feel that antipsychotics could be useful, side effects may limit their acceptability. Career impact may also be a concern for active duty Service Members who are prescribed antipsychotics. Individualizing patient treatment options is important to their retention in care.

The Work Group systematically reviewed evidence related to this recommendation (117, 118, 124-127, 130, 140) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(128, 129, 132, 136, 139) Therefore, this is a *Reviewed, Amended recommendation*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations (e.g., randomization and allocation procedures, insufficient blinding of patients and/or personnel, and attrition). The potential benefits of psychotherapy or SGA augmentation resulting in improved symptoms of depression and remission slightly outweighed the potential harms (e.g., adverse events). Patient values and preferences varied somewhat because of the time commitment involved with psychotherapy and the potential for adverse effects associated with antipsychotics. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

17. For patients who have demonstrated partial or no response to two or more adequate pharmacologic treatment trials, we suggest offering repetitive transcranial magnetic stimulation for treatment.
    (Weak for | Reviewed, Amended)

Discussion

Repetitive transcranial magnetic stimulation is a somatic treatment using magnetic fields to modulate the activity of certain regions of the brain. This intervention is FDA-indicated for TRD. The evidence for this recommendation rests mostly on references identified from the CPG update in 2016 comparing

rTMS to sham treatment in participants with TRD.(142-144) One analysis found positive response rates of 25% for the intervention, significantly higher than sham; and remission rates of 17% for the intervention (also higher than sham).(144) Gaynes et al. (2014) showed clinically significant decreases in HDRS depressive severity of >4 points compared with sham.(142) Patients with TRD were found to be three times as likely to achieve a response versus sham and were five times as likely to achieve remission.(142) The NNT for response is between 3.4 and 9 patients, and the NNT for remission was between five and seven patients.(142-144) One meta-analysis found no difference between the effects of unilateral compared to bilateral rTMS in MDD,(145) a finding echoed in a more recent SR that was not identified for inclusion in this evidence synthesis.(146)

A more recent RCT, relevant to consider because it was specific to the Veteran population, suggested the considerable role of placebo effects in rTMS.(147) This study compared up to 30 treatment sessions of left prefrontal rTMS to sham control treatments in 164 Veterans with TRD. Treatment-resistant depression was defined as depression that has not responded to ≥2 adequate medication trials, and comorbidities were high, including PTSD and SUDs. The study found significant reductions in depressive symptoms and high remission rates at post-treatment (39% overall). However, there were no significant differences in these outcomes between rTMS and sham conditions reduction at treatment completion and at 24 weeks measured in ITT analyses using the clinician-administered HDRS, as well as with self-report depression symptom measures on the BDI and MADRS. There were also no significant differences when data were stratified by PTSD. Placebo effects were likely enhanced by expectancy and extensive attention provided by the study treatment team.

The benefits of rTMS outweigh the minimal risks and side effects. The most common adverse events are irritation at the stimulation site and headache. There were no significant differences in adverse events in the most recent Veteran trial.(147) One meta-analysis found no significant increase in side effects or dropouts versus sham.(144) Two meta-analyses compared electroconvulsive therapy (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%).(148) 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.(149)

The benefits of rTMS outweigh the harms. This offers an option for patients who have not responded to other treatments, and it may be viewed more favorably than ECT by patients. However, considerable limitations are feasibility and access. Repetitive transcranial magnetic stimulation is not uniformly available across all VA/DoD facilities, and access issues exist for individuals who are distant from treatment facilities. The need for daily treatments also limits many patients' ability to engage in this treatment modality.

The Work Group systematically reviewed evidence related to this recommendation (147) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(144, 145, 148, 149) Therefore, this is a *Reviewed*, *Amended* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had limitations, including small study effects, higher than optimal discontinuation, lack of measurement for allocation concealment, and/or other issues. The

benefits of rTMS for TRD in improving symptoms and facilitating remission outweigh the harms. Adverse events are generally minimal and manageable. Patient values and preferences varied somewhat. Repetitive transcranial magnetic stimulation requires a considerable time commitment for treatment. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

18. There is insufficient evidence to recommend for or against theta-burst stimulation for the treatment of MDD.
    (Neither for nor against | Reviewed, New-added)

Discussion

Theta burst stimulation (TBS) is a variation of transcranial magnetic stimulation. Chou et al. (2020) completed the first study investigating the antidepressant efficacy of bilateral TBS monotherapy, a modification of TMS using rapid, repetitive pulses.(150) The evidence was statically significant for TBS over sham stimulation after 12 weeks. However, there were no differences between TBS and sham stimulation at 24 weeks. The overall strength of the evidence for the outcomes assessed was very low due to imprecision impacted by the small sample size.(150) Patients achieving response was more common in TBS over sham stimulation. Blumberger et al. (2018) assessed the clinical effectiveness, safety, and tolerability of intermittent theta-burst stimulation (iTBS) compared with standard 10 hertz (Hz) rTMS in adults with treatment-resistant depression.(151) The study showed that iTBS was non-inferior to 10 Hz rTMS in patients with treatment-resistant depression. Clinical effectiveness was not compromised by utilizing current rTMS devices with patients treated per day using iTBS.

There is some variability in patient preferences regarding this treatment because some patients prefer non-invasive treatments. Among patients who have not responded to other treatments, people are hopeful about this option. However, some patients may view similar treatments as stigmatizing. Further, the treatment may not be available at all VA/DoD facilities. Access issues also exist for individuals who live far from facilities.

The Work Group systematically reviewed evidence related to this recommendation.(150) Therefore, this is a *Reviewed*, *New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including the methodological quality of the included studies and precision in the point estimates.(150) The benefits include the potential for symptom improvement in patients with TRD. The evidence favors TBS over sham stimulations at 12 weeks. The benefits slightly outweighed the potential harms since there were no adverse events. Patient values and preferences varied somewhat. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

19. For patients with MDD who have not responded to several adequate pharmacologic trials, we suggest ketamine or esketamine as an option for augmentation.
    (Weak for | Reviewed, New-replaced)

Discussion

Ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist that is FDA-approved for general anesthesia. Esketamine is the S-enantiomer of ketamine, and an intranasal formulation is FDA-approved, in conjunction with an oral antidepressant, for patients with MDD who have not responded to at least two prior adequate trials of antidepressant. Evidence suggests both ketamine infusion and intranasal esketamine improve depressive symptoms in patients with MDD who have not responded to at least two previous adequate trials of antidepressant medications.

An SR and meta-analysis of five RCTs (n=774; four studies required at least two previous adequate trials of antidepressant medication) found twice-weekly dosing of esketamine as augmentation to ongoing oral antidepressant use compared to placebo improved depressive symptoms and remission in patients with MDD at up to 28 days follow up.(152) An SR and meta-analysis of 20 RCTs (n=886; 10 studies required at least two previous adequate trials of antidepressant medication) studying ketamine against placebo or midazolam found improvement of depressive symptoms with ketamine augmentation in patients with MDD at up to seven days follow-up.(153) Of the studies included, 15 assessed single-dose intravenous infusions of 0.5 mg/kg, four of which also assessed different doses ranging from 0.2 mg/kg to 1.0 mg/kg. In addition, four studies assessed repeated dosing regimens (two using 0.5 mg/kg intravenous infusions, two using oral formulation ranging from 50 – 100 mg/day). Repeated dosing regimens ranged from two to three infusions per week for three to four weeks, oral dosing three days per week over three weeks, or twice daily dosing for six weeks. Pooled data showed a significant reduction of depression severity scores at two to three weeks of repeated ketamine administration compared to placebo.(153) Limitations of these findings are that 11 of the included studies had at least one domain of high risk of bias. Common sources of bias included unclear randomization, unclear allocation concealment, unclear blinding, and high attrition bias.

Other studies have been consistent with this finding for ketamine.(154) An SR and meta-analysis assessed nine studies that compared ketamine to placebo or midazolam in patients with TRD (n=192). Compared to controls, patients who received ketamine had significantly greater improvement on global depression scores within 24 hours of administration. Common side effects included dry mouth, tachycardia, increased blood pressure, and the feeling of disassociation.(154) Evidence from outside the scope of this review indicates there is a risk of a transient elevation in blood pressure in a small number of patients that resolved without significant sequelae.(155, 156) Ketamine ulcerative cystitis has been reported as an emerging problem among patients who engage in repeated recreational use of ketamine.(157) There also has been concern raised about the risk of addiction, especially with repeated dosing regimens, which are often utilized given the lack of durability in the antidepressant effect obtained from any single dose or short-course of these treatments. There is inconsistent literature on the long-term risks of harm associated with chronic or maintenance use of ketamine. Evidence from outside the scope of this review indicates safety and efficacy for esketamine for up to one year, but risks of harm associated with longer-term maintenance remain unclear.(105, 106)

The VA/DoD CPG for the Assessment and Management of Patients at Risk for Suicide suggests offering ketamine infusion as an adjunctive treatment for short-term reduction in suicidal ideation in patients with the presence of suicidal ideation and MDD (see Recommendation 10 in the Suicide CPG). This recommendation was based on studies of individuals with severe depression (mean score 33.8 on

MADRS) showing ketamine infusion of a single dose at 0.5 mg/kg provided a 10 point greater reduction in symptoms compared to the control groups 24 hours after treatment, with a moderate effect size the extends out to six weeks.(155, 158) Additionally, esketamine received a second FDA indication for the management of depressive symptoms in patients with MDD with acute suicidal ideation or behavior. However, its effectiveness in preventing suicide or reducing suicidal ideation or behavior has not been established.

There are similar values and preferences among patients regarding the use of ketamine-based antidepressant treatments. Evidence from outside the scope of this review finds most patients are willing to accept the risk of adverse events (both transient side effects, like dissociation and dizziness, as well as long-term risk, like ulcerative cystitis) for potential improvement in depression.(159) However, there may be differing patient preferences about the route of administration. Additionally, there are unique resource and feasibility challenges associated with administering these treatments, such as the need for intravenous access with ketamine infusions and the need for appropriate clinical treatment space and post-treatment monitoring for both ketamine and esketamine. These resource challenges are compounded by the lack of long term durability from these treatments, which necessitates repeated trips to a treatment facility for receiving ongoing maintenance doses in many cases. There is currently limited access in some regions (e.g., rural areas) for both treatments due to a lack of providers with adequate clinical resources, experience, and training. Further, the current evidence for efficacy is lacking for people over age 65, which is a significant portion of the Veteran population.

The Work Group systematically reviewed evidence related to this recommendation (152, 153) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(154) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including high risk of bias. The potential benefits of reduced depressive symptoms and remission slightly outweighed the potential harms and adverse events, which are largely transient and self-resolving. Patient values and preferences showed little variation. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

20. We recommend offering electroconvulsive therapy (ECT) with or without psychotherapy for 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
    - The risks associated with other treatments are greater than the risks of ECT for this specific patient (i.e., co-occurring medical conditions make ECT the safest MDD treatment alternative)
    - A history of a poor response or intolerable side effects to multiple antidepressants

    (Strong for | Reviewed, Not changed)

Discussion

An SR and meta-analysis found ECT was more efficacious than simulated (sham) ECT in 256 patients with MDD across six trials and was shown to be more efficacious than pharmacotherapy in 1,144 patients with MDD in eight trials.(160) The authors noted that the included trials were limited by small sample size. They also indicated there remains limited information regarding the degree of short-term cognitive impairment associated with ECT and evidence of the efficacy of ECT in specific subgroups, such as the elderly and patients with treatment-resistant illnesses. Despite the study limitations, the authors concluded that ECT is an important treatment option for patients with severe depression.

Although it is a common clinical practice to consider ECT in pregnant patients, no RCTs were identified specifically addressing the efficacy of ECT.(160) Evaluating the safety of ECT during pregnancy is challenging given the lack of data from controlled studies and the strong reporting bias associated with the existing literature, which is largely based on case reports and case series where there is a higher likelihood of reporting adverse or unusual outcomes (e.g., vaginal bleeding, abdominal pain, fetal bradycardia, fetal death). Nevertheless, in evidence from outside the scope of this review, an overview of published reviews addressing the safety of ECT during pregnancy supports that ECT during pregnancy is relatively safe.(161) Use of ECT in this subpopulation warrants careful discussion of risks from non-treatment versus ECT versus alternative treatments and necessitates collaboration with a multidisciplinary treatment team.

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.(162-164)

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 SRs. The UK ECT Review Group identified one RCT that found that ECT compared to simulated ECT had a greater impact on short-term cognitive functioning but not on cognitive function at six months. They identified one RCT that found ECT had a greater impact on short-term cognitive function compared to antidepressants and another RCT that found no difference in short-term cognitive function between ECT and antidepressants.(160) This treatment can be offered either as a stand-alone intervention or adjunctive treatment if a patient on combination therapy of pharmacotherapy and psychotherapy does not respond well.

The quality of evidence was rated very low. While there are some risks associated with using ECT, such as memory loss and general anesthesia risks. There are also serious risks associated with ineffectively treated or untreated severe MDD (e.g., suicide). The Work Group determined that the benefits outweigh the harms/burdens of treatment, including the possibility of changes to cognitive functioning and the risk associated with anesthesia. An exception to this is if the patient has significant co-occurring medical conditions that would increase the risks of ECT (e.g., recent myocardial infarction, intracerebral hemorrhage, or retinal detachment). There is a large variation in preferences for using ECT due to both risks and stigma associated with the treatment. The Work Group noted that resources, acceptability, and feasibility sometimes limit the ability to use this treatment and that certain areas will not have this treatment option.

While the very low quality of evidence would typically lead to a *Weak for* recommendation, the Work Group was highly confident the benefits outweigh the harm/burdens of treatment for the populations

identified (e.g., catatonia, psychotic depression, severe suicidality). The Work Group determined a *Strong for* recommendation was justified based on the GRADE 15 criteria as an intervention for treatment in a life-threatening situation (e.g., severe depression with a high risk of suicide and nonresponse to other treatment options) for the subgroups identified in the recommendation.

The Work Group systematically reviewed evidence related to this recommendation, although no new studies were found that met the search criteria. Therefore, this is a *Reviewed*, *Not changed* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size and limited assessment of appropriate burdens. However, the benefits of ECT for treating depressive symptoms in the specific populations identified in this recommendation outweigh the potential harms of cognitive functioning and risks from anesthesia due to the severe potential consequences of untreated or ineffectively treated MDD. Patient values and preferences varied largely due to preference for other forms of treatment and stigma associated with ECT. Thus, the Work Group decided upon a *Strong for* recommendation.

F. Relapse Prevention/Continuation Phase (All Severities and Complexities)

Recommendation

21. For 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 | Not reviewed, Not changed)

Discussion

The response to the acute phase of treatment ideally occurs within the six to 12 weeks of starting therapy (see Figure 1). After reaching remission, the return of symptoms of depression is called relapse and is very common. Among patients who achieve response with antidepressants, the six-month risk of relapse is approximately 41% if antidepressants are discontinued.(165, 166) Therefore, the second or continuation phase is necessary to sustain remission and prevent relapse. Three meta-analyses consistently reported that continuation treatment with antidepressants reduced relapse rates by approximately 70% compared with placebo.(165, 167, 168)

The largest meta-analysis included 54 randomized clinical trials and 9,268 randomized patients. It showed 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., nine or 12 months) did not provide additional benefit. Therefore, we recommend that antidepressant treatment be continued for at least six months after the first episode of MDD. However, for patients who have had two or more episodes of MDD or belong to high-risk subpopulations, treatment should be considered for at least 12 months and possibly indefinitely.(165, 166)

No difference in relapse prevention was noted between classes of medications or agents within classes.(168) Therefore, the same antidepressant that was initially effective in achieving response should be continued at the therapeutic dose. In the acute treatment of MDD, the therapeutic dose is the dose that results 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.

The Work Group considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(168) Therefore, this is a *Not reviewed, Not changed* recommendation. The Work Group's confidence in the quality of the evidence was moderate. The potential benefits of continued remission or response to treatment outweighed the potential harms of new adverse effects or the higher risk of relapse if medications are discontinued. Patient values and preferences were similar as most patients will want to continue effective treatments. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

22. For patients with MDD at high risk for relapse or recurrence (e.g., two or more prior episodes, unstable remission status), we suggest offering a course of cognitive behavioral therapy, interpersonal therapy, or mindfulness-based cognitive therapy during the continuation phase of treatment (i.e., after remission is achieved) to reduce the risk of subsequent relapse/recurrence. The evidence does not support recommending one of these three evidence-based psychotherapies over another.
    (Weak for | Not reviewed, Amended)

Discussion

Evidence suggests providing CBT, IPT, or MBCT after remission reduces the risk of subsequent relapse or recurrence in patients with a history of recurrent depression or other high-risk factors. Two meta-analyses demonstrated these interventions effectively reduced the risk of relapse or recurrence.(169, 170) The evidence review did not include adequate data comparing treatments to determine the superiority of one another, nor were studies of ACT, behavioral therapy/BA, PST, or STPP (the other psychotherapies recommended within this CPG) included in these analyses.

The overall quality of evidence was low. Benefits of reduced risk of relapse or recurrence slightly outweighed associated harms and burdens, which are primarily time and cost associated with the suggested treatments. There is some variability in preference for psychotherapy, in general, relative to other treatments. Further, access to specific treatments may be limited in some settings.

The Work Group considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(169, 170) Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including the limited number of studies available addressing the question. Nevertheless, the potential benefits of CBT, IPT, or MBCT for reducing the risk of relapse or recurrence of major depression slightly outweighed the potential harms and burdens. Patient values and preferences somewhat varied because some patients prefer pharmacotherapy over psychotherapy. Thus, the Work Group decided upon a *Weak for* recommendation.

G. Recommendations for Specific Populations

Recommendation

23. For individuals with mild to moderate MDD who are breastfeeding or pregnant, we recommend offering an evidence-based psychotherapy as a first-line treatment (see Recommendation 7). In 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 | Not reviewed, Amended)

Discussion

Depression can have a significant impact on the health of mother and baby during pregnancy and postpartum periods. Studies suggest antidepressants and psychotherapy effectively manage depression during pregnancy and the postpartum period.(171) Psychotherapy is recommended as a first-line treatment due to a more favorable safety profile and because patients often prefer it.

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 treating postpartum depression.(171) 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.

An additional RCT (n=192) comparing group-based CBT, group-based counseling, individual counseling, and routine primary care for postpartum MDD found group treatments were not significantly different from each other, although they were not as effective as individual counseling.(172) An SR of 40 RCTs found fair evidence supporting CBT to treat and prevent depression for women during pregnancy and one year postpartum.(173) There are no studies comparing psychotherapy to medication.

Before the initiation of medication in women of childbearing age, providers should discuss whether the individual is sexually active and may be pregnant and the potential risks to the fetus, newborn, and mother of treated and untreated depression. Medication safety should be reviewed again with pregnant or breastfeeding patients who have been prescribed antidepressant medication.

The Work Group considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(173) Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was low. Psychotherapy as a first-line treatment for pregnant or breastfeeding women with mild to moderate MDD is often preferred by patients. The benefits outweighed the potential harms/burden. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

24. For older adults (≥65 years) with mild to moderate MDD, we suggest offering a first-line psychotherapy (see Recommendation 7). Patient preference and the additional safety risks of pharmacotherapy should be considered when making this decision.
    (Weak for | Not reviewed, Amended)

Discussion

For older adults (≥65 years) with mild to moderate MDD, evidenced-based psychotherapy is preferred as a first-line treatment due to safety considerations and avoidance of the consequences of polypharmacy, which include 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.

Frazer et al. (2005) found limited evidence to support the effectiveness of IPT in the reduction of depressive symptoms.(174) Bibliotherapy for treating mild to moderate depression and CBT were treatments with the highest quality evidence of effectiveness in older adults.(174)

Gould et al. (2012) reviewed 23 studies and found no significant differences in efficacy between CBT and other treatments (medication and other psychotherapies).(175) They found CBT was an effective treatment for older patients. Cuijpers et al. (2006) reviewed 25 RCTs of various psychotherapies, 17 of which compared CBT to control groups (waitlist controls or care-as-usual).(176) Overall, the meta-analysis found no differences among psychotherapies. However, CBT specifically was found to be superior to control groups (waitlist controls, care-as-usual, no treatment, and placebo pill). An SR by Gould et al. (2012) (n=1,712) also supported the use of CBT for older adults, although the quality of the evidence was poor.(175) One study found that CBT significantly reduced symptoms of depression over non-active controls. Two 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 the risks. There is some anticipated variation in values and preferences for psychotherapy in this subpopulation. The benefits of some psychotherapies outweigh the risk of no treatment in older adults with depression.

The Work Group considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(174-176) Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was low. However, the potential benefits outweighed the potential harms. In addition, patient values and preferences varied somewhat. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

25. For patients with mild to moderate MDD and significant relationship distress, we suggest offering couples-focused therapy.
    (Weak for | Not reviewed, Amended)

Discussion

Personal relationship distress plays a role in the development and/or maintenance of depression. For patients with MDD and significant relationship distress, evidence suggests couples-focused therapy as an intervention to reduce symptoms and improve recovery. The decision to use couples-focused therapy as a treatment should come after a thorough assessment of the patient's needs and whether to include one's partner in the sessions. A meta-analysis by Barbato et al. (2008) found no significant difference between couples-focused therapy and individual therapy for the reduction of depression

symptoms.(177) However, that meta-analysis and an RCT by Cohen et al. (2010) showed significantly better recovery and improvement of symptoms for patients in couples-focused therapy compared to patients on a waitlist control or no treatment.(178)

The Work Group was unable to make recommendations related to couples-focused therapy as adjunct or augmentation strategy because no studies comparing couples-focused therapy with combined treatment were found. Current findings were limited by small sample sizes and lack of generalizability (e.g., one study did not include males with MDD). In addition, the Work Group is unable to recommend one couples-focused therapy approach over another. The meta-analysis included five CBT trials and one each of emotion-focused, interpersonal, and systemic psychotherapy, all compared to control conditions. There were no direct comparisons between types of couples-focused therapy that could inform selection between treatments.

The quality of research on the benefits, harms, and burdens of couples-focused 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-focused therapy slightly outweigh the possible harms. Consideration of the quality of the relationship should be given since not all partners may positively influence a relationship or therapy. Couples-focused therapy, in this case, could pose additional harm to the depressed patient if the partner is abusive, for example. Other considerations are that patient values and preferences for couples-focused therapy and partners willing to engage may vary. Other factors to weigh when choosing this intervention are the availability of providers trained in the couples-focused and the additional challenges with scheduling and engaging with the partner, particularly for active duty military couples where deployments and other factors can disrupt the continuity of therapy.

The Work Group considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(177, 178) Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including the limited number of studies available and lack of comparisons to key comparators such as combined treatment. The potential benefits of couples-focused therapy as a treatment for MDD slightly outweighed the potential harms, which were primarily the burden of time and cost of couples-focused therapy. Patient values and preferences were somewhat varied because some patients prefer pharmacotherapy or other therapy options (e.g., individual therapy). Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

26. For patients with mild to moderate MDD with or without a seasonal pattern (formerly seasonal affective disorder), we suggest offering light therapy.
    (Weak for | Reviewed, New-replaced)

Discussion

Evidence suggests bright light therapy improves depressive symptoms in patients with MDD. An SR by Tao et al. (2020) (n=1,120) found treatment with bright light therapy was associated with improvements in depressive symptoms in patients with mild or moderate MDD with or without a seasonal pattern compared to placebo.(179) Findings from other studies cited in the 2016 VA/DoD MDD CPG and

conducted in various patient populations are consistent with this finding in patients with depression without a seasonal component.(180, 181)

An RCT by Bais et al. (2020) showed bright light therapy was not statistically different from dim red light therapy at reducing depressive symptoms at six weeks in pregnant women with a DSM-5 diagnosis of MDD.(182) There was no documented evidence of serious harm associated with bright light therapy.

There is some variability in patient preferences regarding this treatment. Bright light therapy may be appealing to patients interested in a beneficial treatment that does not include pharmacotherapy. Some patients, however, may be sensitive to light treatment or find the time associated with this form of treatment burdensome. In addition, this treatment modality may impact health equity and may not be feasible to implement as some insurance will not cover it, and lightbox devices may be expensive.

The Work Group systematically reviewed evidence related to this recommendation (179, 182) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(180, 181) Therefore, this is a *Reviewed, New-replaced* recommendation. All evidence reviewed in this CPG and the 2016 VA/DoD MDD CPG was conducted in patients with MDD without a seasonal pattern. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including lack of blinding, unclear random sequence generation, unclear allocation concealment, small sample size, and other bias.(179, 182) The benefits of bright light therapy, including the reduction of depressive symptoms, outweigh the small risk of potential harm. These therapies may be offered as monotherapy or adjunctive to other therapeutic modalities. Patient values and preferences varied somewhat. Thus, the Work Group decided upon a *Weak for* recommendation.

H. Self-help, Complementary, and Alternative Treatments

Recommendation

27. For patients with MDD, we suggest exercise (e.g., yoga, tai chi, qi gong, resistance, aerobics) as an adjunct.
    (Weak for | Reviewed, New-replaced)

Discussion

Evidence suggests exercise such as yoga, tai chi, qi gong, resistance training, and aerobics improves symptoms in those with MDD over waitlist or usual care.(183-186) No studies meeting this CPG's systematic evidence review's inclusion criteria specifically investigated walking or group training. Moreover, most included studies had significant limitations. Despite a wide CI, point estimates for exercise interventions consistently suggested benefits. The quality of evidence was very low, and studies had significant limitations such as small sample sizes, short-term follow-up, low baseline depression scores for inclusion, variable exercise regimens and durations, and a lack of blinding of participants and assessors.

Studies with higher quality evidence showed lesser benefits than those studies with lower quality of evidence.(183) Nevertheless, the Work Group determined the benefits of exercise exceed any potential harms/burden and, therefore, justify a *Weak for* recommendation for all patients.

The Work Group acknowledges there is a large variation in patient values and preferences regarding exercise. Some patients may not be willing or able to exercise. Likewise, certain patients may lack access to a fitness center or the knowledge required to perform specialized exercises like tai chi or qi gong. The Work Group determined any exercise would benefit these individuals as the overall health benefits exceed the potential for harm. The evidence does not indicate benefits for all exercise modalities, nor does the evidence suggest specific exercise durations are necessary for the treatment of MDD.

The Work Group systematically reviewed evidence related to this recommendation.(183-186) Therefore, this is a *Reviewed, New-replaced* recommendation. The evidence from the 2016 VA/DoD MDD CPG was of limited use to the Work Group since it investigated the efficacy of exercise education (rather than physical exercise) for the treatment of MDD. Based on the known health benefits of exercise and the studies reviewed in the current and previous CPG, low quality evidence suggests an improvement in depression symptoms for individuals with MDD who add exercise to their usual depression care. The Work Group's confidence in the quality of evidence was very low. The body of evidence had numerous limitations, including small sample size, short-term follow-up, poor allocation, and lack of blinding.(183-186) The benefits of exercise outweigh the potential harms/burden. Patient values and preferences vary largely since individuals likely differ in their willingness and knowledge required to do specific exercises. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

28. For patients with MDD, we suggest CBT-based bibliotherapy as an adjunct to pharmacotherapy or psychotherapy, or as an alternative when patients are unwilling or unable to engage in other treatments.
    (Weak for | Reviewed, Amended)

Discussion

Monroy-Fraustro et. al. (2021) indicated that bibliotherapy is reading and processing literature as a non-pharmacological treatment as psychological support.(187) Naylor et al. (2010) showed physicians could practically and feasibly deliver a bibliotherapy behavioral prescription to treat depression in real-world primary care settings with medical patients.(188) However, the study reported no statistically significant differences between bibliotherapy prescription versus usual care for depression in terms of dysfunctional attitudes or QoL.(188) Cuijpers et al. (1997) conducted a meta-analysis that indicated bibliotherapy is an effective treatment modality MDD and Floyd et al. demonstrated efficacy of bibliotherapy in older adults.(189, 190) According to Campbell et al. (2003), bibliotherapy appears effective in individuals with mild to moderate depression and without suicidality.(191) Liu et al. (2009) also found evidence that CBT-based bibliotherapy reduced depressive symptoms.(192) Despite the small size (n=52), the evidence indicated that bibliotherapy grounded in the cognitive-behavioral approach lowered participants' cognitive-affective symptoms of depression, possibly by increasing their confidence in their ability to self-manage their behavior despite the experience of negative feelings.(192) The studies reviewed used cognitive-behaviorally based self-help books, including *Feeling Good: The New Mood Therapy* (193) and *Mind over Mood: Change How You Feel by Changing the Way You Think*.(194) Evidence indicates the benefits slightly outweigh harms/burden.

The Work Group systematically reviewed evidence related to this recommendation and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(188, 192) Therefore, this is a *Reviewed*, *Amended* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including small sample size.(72) Bibliotherapy can be utilized to improve depressive symptoms, which slightly outweigh the small potential harms. Patient values and preferences varied somewhat because GSH may be acceptable to patients compared to TAU but less acceptable compared to other interventions. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

29. 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 as monotherapy.
    (Weak for | Not reviewed, Amended)

Discussion

St. John's wort (SJW) (*Hypericum perforatum*) is used as an herbal remedy for a variety of maladies, including depression. The 2016 CPG analyzed a Cochrane review by Linde et al. (2008) and an SR by Maher et al. (2016).(195, 196) Both showed SJW was superior to placebo as monotherapy for mild to moderate depression when assessing depression scales and subjective symptoms and that the efficacy was similar to FDA-approved antidepressant medications.

St. John's wort is not FDA-approved, and therefore there is a risk that the dosing may not be consistent across formulations. Maher et al. (2016) found the most commonly studied extracts were standardized to hypericin (0.1 – 0.3%) or hyperforin (1 – 6%) and used at therapeutic dosages ranging from 500 – 1,800 mg daily.(196) St. John's wort is commonly given three times daily and initiated at a total daily dose of 900 mg.

Both SRs agree that SJW has fewer adverse effects than standard antidepressants.(195, 196) Adverse effects of SJW include gastrointestinal upset, mild sedation, restlessness, and increased risk of photosensitivity at higher doses. St. John's wort should not be used in pregnant or breastfeeding women because of the lack of safety data in these populations.

Patients and providers need to be aware of the potential for drug-drug interactions, and careful medication reconciliation is important. St. John's wort can result in serotonin syndrome when combined with SSRIs or other serotonergic agents. St. John's wort induces cytochrome P450 3A4 and can lead to a reduction in medication efficacy for various medications, including oral contraceptives, TCAs, and anti-epileptic drugs, as well as a variety of other medications. In addition, it is important to ensure that providers are recommending the standardized extracts that have been studied.

The Work Group considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(195, 196) Therefore, this is a *Not reviewed*, *Amended* recommendation. The Work Group's confidence in the quality of the evidence was moderate. Linde et al. (2008) was rated as high quality, and Maher et al. (2016) was rated as moderate, thus reducing the overall quality to moderate.(195, 196) The benefits of SJW for mild to moderate depression slightly outweigh the potential harms. There is

large variability in patient preference regarding this treatment. Some patients prefer herbal medication due to the perception that naturally-derived remedies are safer than manufactured pharmacotherapy, whereas some patients prefer FDA-approved therapies. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

30. For patients with MDD, there is insufficient evidence to recommend for or against acupuncture as an adjunct.
    (Neither for nor against | Reviewed, New-replaced)

Discussion

A review of the literature revealed one SR evaluating the effectiveness of acupuncture for MDD since the publication of the 2016 VA/DoD MDD CPG. The SR and meta-analysis by Smith et al. (2018) reviewed 64 RCTs with 7,104 participants.(197) When comparing acupuncture versus sham control, 14 RCTs suggest acupuncture may be associated with a small reduction in the severity of depression on the HAM-D by the end of treatment, although the quality of the evidence was low. In addition, 10 RCTs show an improvement in the rate of remission from a major depressive episode for those undergoing acupuncture compared with sham treatment within 12 months, although the quality of evidence was low.(197)

Smith et al. (2018) also found a reduction in the severity of depression with acupuncture when given alone or in conjunction with medication (31 RCTs) versus medication alone (11 RCTs).(197) However, results were questionable due to the low quality of evidence. In addition, the effect of acupuncture compared with psychotherapy was unclear.

The Work Group noted MacPherson (2013), within the Smith et al. (2018) SR, appeared to be the primary focus for the critical outcomes within this study recommending acupuncture as adjunctive treatment versus monotherapy.(197) As a result, the Work Group changed the recommendation language from the 2016 VA/DoD MDD CPG, removing the monotherapy language.

Chan et al. (2015) reviewed 13 RCTs with 1,046 patients.(198) All RCTs compared the effectiveness of antidepressants alone to antidepressants plus acupuncture. The conclusions suggest acupuncture in adjunct with antidepressants is more effective than antidepressants alone. Adjunctive acupuncture results in a significantly higher reduction of depressive symptoms, higher response rates, and fewer side effects. However, many of the RCTs included had serious quality limitations.

There appeared to be minimal potential harms to the patient, including bleeding, needling pain, or aggravation of depressive symptoms. However, the risk of adverse events with acupuncture was unclear, as most trials did not report adverse events adequately.(197) Few studies included follow-up periods or assessed important outcomes such as QoL. Smith et al. (2018) suggested high-quality RCTs were needed to examine the clinical efficacy and acceptability of acupuncture and its effectiveness, compared with acupuncture controls, medication, or psychological therapies.(197)

The Work Group noted the use of complementary and integrative health (CIH) interventions instead of an FDA-approved treatment might prevent the patient from receiving standard of care/more effective proven treatments. Providers need to consider this when determining treatment plans.

Despite the low quality of evidence supporting acupuncture, it may be offered to some patients interested in this CIH treatment. This interest may occur as a result of cultural background or a preference for CIH. However, there seemed to be variation in patient preference regarding the method and direction of acupuncture. In addition, the cost for those who do not have access to acupuncture within their healthcare system or military treatment facility may be high.

The Work Group systematically reviewed evidence related to this recommendation (197) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(198) Therefore, this is a *Reviewed*, *New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had limitations as most studies were at high risk of performance bias, in addition to being at high or unclear risk of detection bias.(197) In addition, most trials did not report adverse events adequately, and few studies included follow-up periods or assessed important outcomes such as QoL.(197) The benefits and harms were balanced. Patient values and preferences varied significantly based on the types and duration of acupuncture. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

31. For patients with MDD, there is insufficient evidence to recommend for or against the addition of biofeedback.
    (Neither for nor against | Reviewed, New-added)

Discussion

Evidence to evaluate the efficacy of biofeedback as an adjunct to treatment is limited. However, of the different types of biofeedback, two RCTs studied heart rate variability biofeedback. In Maynart et al. (2021) and Caldwell et al. (2018), patients learned optimal diaphragmatic breathing based on heart rate data from a biofeedback system.(199, 200) However, the quality of these studies was poor due to small sample sizes, moderate attrition, and unclear randomization.

Maynart et al. (2021) studied 43 adults diagnosed with MDD or dysthymia.(169) Participants in the experimental group were submitted to six weekly training exercises with biofeedback in addition to their usual treatment of care. The study used the Nexus-32 equipment for the biofeedback training exercises. Findings suggest the addition of heart rate variability biofeedback to standard treatment resulted in greater improvement in depressive symptoms after six weeks as compared to standard treatment alone. However, the overall quality rating of this study was poor because allocation was not concealed, outcome assessors were not masked, and it had a moderate attrition rate.

Caldwell et al. (2018) studied 20 female college students aged 18 to 25 years old diagnosed with MDD, comparing heart rate variability biofeedback with standard psychotherapy compared to standard psychotherapy alone.(170) Over five separate sessions, participants were trained to perform diaphragmatic breathing at a determined resonance frequency breathing rate based on their heart rate data. After each session, patients were reminded to practice breathing 15 to 20 minutes a day, four to

five times a week, using a visual pacing guide. Results demonstrated that the combination of heart rate variability biofeedback and psychotherapy increased heart rate variability and decreased depressive symptoms more effectively than psychotherapy alone. However, the overall quality rating of the study was poor due to unclear randomization, unclear allocation concealment, unclear whether outcome assessors were blinded, and no information on dropout.

There is some variability in patient preference regarding this treatment. Patients will have a varying ability to perform biofeedback, and some patients who struggle may become frustrated and stop. In addition, biofeedback requires provider training and equipment, and access to training and the cost of the equipment may be limiting factors for patients.

The Work Group systematically reviewed evidence related to this recommendation.(199, 200) Therefore, this is a *Reviewed*, *New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had several limitations, including small sample sizes, moderate attrition, unclear randomization, and unclear allocation concealment. Both studies suggested an improvement in depressive symptoms with heart rate variability feedback as an adjunct to TAU. The benefits of biofeedback remain unclear as the Work Group had very low confidence in the evidence, and any potential benefit of biofeedback improving depressive symptoms was balanced with the potential harms of patient frustration with the intervention. Patient values and preferences largely vary because some patients have a greater capacity to perform biofeedback. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

32. For patients with MDD, there is insufficient evidence for or against the use of meditation as an adjunct.
    (Neither for nor against | Reviewed, New-added)

Discussion

Two RCTs with older adult participants evaluated the effectiveness of specific types of meditation as an adjunct to TAU on depressive symptoms and remission. Ahmadpanah et al. (2017) evaluated Detached Mindfulness delivered as a group intervention to 36 older adult women aged 65 – 85 years led by trained clinical psychologists.(201) Detached Mindfulness was provided as an adjunct to TAU and was compared with TAU alone.(201) The second study by Vasudev et al. (2016) evaluated a computer-based automatic self-transcending meditation (ATSM) program.(202) The ATSM delivered Sahaj Samadhi Meditation taught by a certified instructor to 51 older adult patients (aged 60 – 85) provided as an adjunct to TAU, compared with a waitlist control receiving TAU.(202) Both studies suggested an improvement in depressive symptoms and remission with these specific forms of meditations delivered as an adjunct to TAU.

The quality of the evidence from Ahmadpanah et al. (2017) study was rated as good with adequate randomization, assessors blinded to patient allocation, low attrition rate, and the inclusion of ITT analysis.(201) The Vasudev et al. (2016) study quality was rated poor due to unclear allocation concealment among assessors and use of per-protocol analysis with a high attrition rate.(202) The overall strength of evidence was rated as very low. One of the two studies had poor methodological

quality and both exhibited imprecision in the point estimates. Examples of imprecision included small sample sizes, wide CI, and point estimates presented without statistical analyses. The use of multiple depression scales and reporting scores without statistical comparisons limited the comparability for the studies on meditation. There were no major harms to patients associated with the types of meditation documented.

There is significant variability in patient preferences regarding meditation. Meditation can be burdensome because it requires a significant time commitment from patients in session and for additional practice, and not all patients will be interested in meditation. Clinician-led meditation requires significant resources in terms of provider time and training. Additionally, providers may have variable knowledge about different types of meditation, and it may be difficult to ensure that only forms of meditation that have been evaluated through RCTs are utilized. The Work Group notes that the studies included in this evidence review evaluated only two types of meditation.

The Work Group systematically reviewed evidence related to this recommendation.(201, 202) Therefore, this is a *Reviewed*, *New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had limitations, including small sample sizes, wide CI, and point estimates presented without statistical analyses. Both studies suggested an improvement in depressive symptoms and remission with the two types of meditation delivered as an adjunct to TAU. The benefits of adjunctive meditation on depressive symptoms and remission remain unclear given the very low confidence in the quality of evidence. Any potential benefit balanced the burden of a significant time requirement on the part of patients for intervention with unclear benefit. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

I. Other Treatments with a Recommendation Against Use

Recommendation

33. For patients with MDD, we suggest against using vagus nerve stimulation outside of a research setting.
    (Weak against | Reviewed, Amended)

Discussion

The vagus nerve stimulation (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.(203)

Although VNS is FDA-approved for TRD, there is no current evidence supporting its routine use in the treatment of MDD. The FDA defines TRD and indicates the use of VNS in "patients who have been treated with, but failed to respond to, at least four adequate medication regimens and/or ECT prescribed by their physician."(203) The FDA initially approved VNS 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.(204)

A double-blind RCT of 235 outpatients found no difference between VNS and a sham placebo.(205) Other evidence stems from primarily non-blinded follow-up studies, comparing intervention group

patients to a non-concurrent cohort of TAU patients and uncontrolled observational studies.(163, 206-210)

The potential harms and burden of VNS for patients with MDD outweigh the benefits. 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 VNS. These possible adverse events include voice alteration, dysphagia, dyspnea, infection, dizziness, asthenia, chest pains, palpitations, and vocal cord paralysis.(204)

There is large variation in patient values and preferences because 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. In addition, providers or patients may try other non-pharmacological treatments for MDD over the use of VNS. Acceptability, resource availability, and risk of surgical complications are also considerations.

The Work Group systematically reviewed evidence related to this recommendation and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG. Therefore, this is a *Reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was very low. There is a lack of new or significant evidence showing the effectiveness of VNS in TRD to suggest routine use. Also, there is moderate-to-strong evidence against using VNS routinely even for severe TRD except as a possible option after exhausting other options. Thus, the Work Group decided upon a *Weak against* recommendation.

Recommendation

34. For patients with MDD, we recommend against using deep brain stimulation outside of a research setting.
    (Strong against | Reviewed, Not changed)

Discussion

The available evidence does not support the use of deep brain stimulation (DBS) as a therapy for TRD outside of a research setting. An RCT by Dougherty et al. (2014) treated 30 patients randomized to DBS (n=16) or sham DBS (n=14).(211) Active stimulation was programmed to target the ventral capsule/ventral striatum, locations identified in survey testing as having the greatest potential for an antidepressant effect. Results indicated no significant difference in the resolution of depressive symptoms between DBS and sham DBS in the resolution of depressive symptoms.

Another trial of 90 patients, including 60 randomized to subcallosal cingulate DBS and 30 randomized to sham, found no difference in clinical outcomes of symptoms resolution or remission.(212) Eight patients experienced serious adverse events related to study device or surgery. Given the lack of evidence supporting its effectiveness and 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.

The Work Group determined the potential harms/risks of DBS outweighed benefits. There is large variation in the acceptability of this treatment and considerable feasibility, acceptability, and cost considerations.

The Work Group systematically reviewed evidence related to this recommendation (212) and considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(211) Therefore, this is a *Reviewed*, *Not changed* recommendation. The Work Group's confidence in the quality of the evidence was low. The literature is limited in the number of studies and participants. The potential harms of DBS outweigh the benefits, which can be serious given the invasive nature of the treatment. Patient values and preferences may vary as many patients prefer non-invasive treatments. Thus, the Work Group decided upon a *Strong against* recommendation.

Recommendation

35. Given the limited information on the safety and efficacy of psilocybin, MDMA, cannabis, and other unapproved pharmacologic treatments, we recommend against using these agents for MDD outside of a research setting.
    (Strong against | Reviewed, New-added)

Discussion

One small study rated as low quality met inclusion criteria for psilocybin. Davis et al. (2021) compared immediate psilocybin therapy versus delayed psilocybin therapy.(213) Findings showed immediate therapy improved depressive symptoms at five and eight weeks and decreased anxiety symptoms at eight weeks. While findings suggest that psilocybin therapy may improve symptoms, it should be noted that the intervention was multi-component, and the comparator was effectively a waitlist control. No studies meeting the search criteria were identified for cannabis, cannabinol, or MDMA.

Given the lack of data, there is a concern for potential harms from treatment with psilocybin, MDMA, and cannabis, primarily risks of abuse and addiction potential. There is large variation in patient values and preferences related to the use of psychedelic treatments especially, with some patients eager to try new experimental treatments and others reluctant given risks of side effects and historical stigma associated with these agents being classified as illicit substances for many decades.

Further, there are significant resource use and feasibility challenges to implementing psilocybin and MDMA treatments since dosing protocols to date have included prolonged therapeutic interventions and monitoring (between eight to 12 hours) following administration. There are also substantial pharmacy storage and dispensing implications, with both psilocybin and MDMA currently being classified as U.S. Drug Enforcement Agency (DEA) Schedule 1 compounds. There is ongoing research in these areas, including trials recruiting from the Veteran population, the results of which may have implications for future recommendations about the potential safe and effective use of these treatments.

The Work Group systematically reviewed evidence related to this recommendation.(213) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size and the use of waitlist control.(213) The potential benefits of psilocybin to improve depressive symptoms and the lack of evidence to show benefits for cannabis, cannabinol, or MDMA were outweighed by the potential

harms of addiction and adverse events. Patient values and preferences were largely varied because of the historical stigma surrounding psychedelic treatments. Thus, the Work Group decided upon a *Strong against* recommendation.

Recommendation

36. We suggest against using omega-3 fatty acids or vitamin D for treatment of MDD.
    (Weak against | Not reviewed, Not changed)

Discussion

Omega-3 Fatty Acids

Evidence suggests no significant overall benefit when using omega-3 fatty acids for depressive symptoms.(214-216) Of the two types of omega-3 fatty acid studied, docosahexaenoic acid (DHA) had no effect on depressive symptoms. Eicosapentaenoic acid (EPA) showed a small effect. However, the methodological flaws in these studies are significant. 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.

While 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, the 2016 VA/DoD MDD CPG evidence base was not sufficient to recommend prescribing EPA instead of other validated medications or psychotherapies, and additional studies were not reviewed for this CPG.

Vitamin D

Vitamin D deficiency has been purported to induce fatigue and possibly depression. However, available evidence does not support the use of vitamin D supplementation as monotherapy for depression, especially in the absence of documented deficiency.(217, 218) One SR evaluated the efficacy of vitamin D in the treatment of mild to moderate MDD in adults with normal serum levels of vitamin D.(217) 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 et al. (2013) evaluated the efficacy of vitamin D in patients with severe MDD and concurrent vitamin D deficiency.(218) This study randomly allocated 109 participants to injections of 300,000 international units (IU) 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 poor due to a lack of ITT analysis and double-blinding, thus impacting the Work Group's ability to recommend its use as monotherapy. In addition, this dosage and route of administration are atypical for most clinical practice, which generally recommends 50,000 IU orally weekly until vitamin D levels normalize.

The Work Group considered the assessment of the evidence put forth in the 2016 VA/DoD MDD CPG.(214-218) Therefore, this is a *Not reviewed*, *Not changed* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including variability in the type of supplement and dosing regimen. The potential harms of omega-3 fatty acids

and vitamin D slightly outweigh the benefits particularly because the use of nutritional supplements instead of FDA-approved treatments may prevent or delay patients from receiving standard of care. Patient values and preferences varied largely because some patients prefer nutritional supplements to more traditional antidepressant therapies, and in the case of vitamin D, high doses can cause side effects. Thus, the Work Group decided upon a *Weak against* recommendation.

X. Research Priorities

During the development of the 2022 VA/DoD MDD CPG, the Work Group identified topics needing additional research, including areas requiring stronger evidence to support current recommendations and research exploring new areas to guide future CPGs. In general, longer term studies are required across all treatment strategies. Specifically, studies comparing treatment strategies and studies to determine which patient characteristics might differentially impact response to certain treatments are needed.

A. Access and Health Disparities

There is evidence that access to care for depression varies particularly by race and ethnicity. Simultaneously, there are limited data regarding differences by race, ethnicity, sex, and other factors predict treatment outcome.

B. Psychotherapy

Higher quality evidence on psychotherapy (in particular, larger sample sizes, using accepted diagnostic definitions of MDD for inclusion, better consistency of blinding, consistent reporting of adverse events, and stronger and better descriptions of control conditions) is needed. The Work Group identified the following psychotherapy trials as priorities:

- Comparative research on effectiveness of psychotherapy formats (individual, group, couples).
- Guided self-help compared with face-to-face CBT.
- Comparative research regarding different modalities of telehealth-based interventions (phone-only versus video, synchronous versus asynchronous) and the comparative effectiveness of telehealth-based interventions with interventions delivered in person.
- Personalized therapy by combining components of different psychotherapy approaches.
- Outcomes for case-formulation based treatment planning.
- Efficacy versus effectiveness trials (comparison of actual clinical practice versus standardized protocols).
- More research is needed to determine the management of patients with partial or limited response to psychotherapy.
- Combined treatment compared to individual treatment and the timing of when to add a second treatment.

C. Pharmacotherapy

Pharmacotherapy research priorities regarding existing treatment options include:

- Ketamine and esketamine dosing regimens and duration of treatments. Comparative efficacy of the two treatments.
- Comparative trials on the effectiveness of medication augmentation when psychotherapy does not produce a complete response.
- Effectiveness and side effects of pharmacotherapy for older adults with MDD.
- Evaluation of biomarkers for diagnosis and treatment responsiveness.
- Impact of co-morbid behavioral health disorders on pharmacologic outcomes.
- Strategies for the treatment of non-response including augmentation.
- Evaluation of psilocybin, MDMA, cannabis, and other unapproved pharmacologic treatments.

D. Nutraceuticals

In general, there is a significant gap in the quality of pharmacotherapy and psychotherapy research compared with the quality of nutraceutical research. Despite the popularity of these treatments especially in non-Western nations, trials evaluating efficacy are minimal and have serious methodologic flaws. Specific nutraceutical questions deserving of further investigation include:

- Vitamin D supplementation in nutritionally deficient individuals.
- Vitamin D supplementation in nutritionally replete individuals with specific emphasis on the role of genetics.
- Omega-3-fatty acid efficacy and dosing.
- St. John's wort with specific emphasis on dosing strategies and comparison with FDA-approved therapies.
- S-adenosyl-L-methionine (SAMe) efficacy and dosing.

E. Treatment Modalities

In addition to psychotherapeutic and pharmacologic treatments, there are a growing number of additional treatment strategies which may prove beneficial. The data thus far is scarce, so the Work Group recommends additional research in the following areas:

- Efficacy of a team-based approach within a specialty care setting.
- Larger trials assessing the value of measurement-based care.

F. Technology

While some device-based technology has been implemented in the treatment of depression for decades, there are other, newer technologies with a growing literature base. Comparative trials are needed to determine how to fit them into a treatment algorithm. Specific consideration should be given to:

- More research is needed as there is a lack of evidence in support of the routine use of VNS for TRD. Specifically, VNS should be studied in patients with recurrent seizures and depression.
- More research is needed to help compare available evidence-based treatment options for patients with difficult to treat depression who have not responded to several previous adequate antidepressant trials (e.g., ECT, rTMS, ketamine, and esketamine) and to help guide shared decision making with patients when considering the available treatment options.
- Additional research is needed on the utility of digital aids (e.g., wearables, smartphones, apps) enhancing the treatment of MDD.

G. Exercise

Although exercise is known to improve overall health, less is known about the specific role it should play in patients with MDD. Specific priorities for further research include:

- Comparison of the various types of exercise (aerobic, strength training, flexibility).
- Longer trials with longer follow-up (>10 weeks).
- Role of exercise for patients with severe MDD.

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 KQs on clinical highest priority for the VA and DoD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ) (see Table A-1).

Table A-1. PICOTS (219)

PICOTS Element	Description
Population or Patients	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.
Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic /screening test used with the patient or population.
Comparator	Treatment(s) (e.g., placebo, different drugs) or approach(es) (e.g., different dose, different frequency, standard of care) that are being compared with the intervention or exposure of interest described above.
Outcomes	Results of interest (e.g., mortality, morbidity, quality of life, complications). Outcomes can include short, intermediate, and long-term outcomes.
Timing, if applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing, and setting

Due to resource constraints, all KQs of interest to the Work Group could not be included in the systematic evidence review. Thus, the Work Group selected the 12 highest priority KQs for inclusion in the systematic evidence review (see Table A-2).

Using the GRADE approach, the Work Group rated each outcome on a 1 – 9 scale (7 – 9, critical for decision making; 4 – 6, important, but not critical, for decision making; and 1 – 3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see Outcomes); however, only critical outcomes were used to determine the overall quality of evidence (see Determining Recommendation Strength and Direction).

a. Population(s)

- Key Question 1
    - Including: Adult patients with depressive disorders, including mild, moderate, and severe depressive disorders and those with chronic major depression diagnosed per DSM-IV criteria and those with persistent depressive disorder/chronic major depression per DSM-5 criteria.
- Key Question 2
    - Including: Adults with MDD who are receiving pharmaceutical treatment for this disorder who have either partially or not responded, or have relapsed or recurred.

- Key Questions 3, 4, 6, 7, 9 – 12
    - Including: Adults with MDD, including those with chronic major depression diagnosed per DSM-IV criteria and those with persistent depressive disorder/chronic major depression per DSM-5 criteria.
- Key Question 5
    - Adults with MDD who are receiving pharmaceutical treatment or psychotherapy for this disorder who have either partially or not responded, or have relapsed or recurred.
- Key Question 8
    - Adults with MDD, including patients who are receiving treatment for this disorder who have either partially or not responded, or have relapsed or recurred.

b. Interventions

- Key Question 1: Pharmacotherapies (classes), including:
    - SSRIs, SNRIs, norepinephrine and dopamine reuptake inhibitors (NDRI), serotonin antagonist and reuptake inhibitors (SARIs), serotonin norepinephrine dopamine reuptake inhibitors (SNDRI), noradrenergic and specific serotonergic antidepressants (NaSSAs), TCAs, MAOIs, ketamine/esketamine (class: NMDA receptor antagonist), cannabis, cannabidiol (CBD), MDMA, psilocybin
- Key Question 2: Changing the drug class, or augmenting or adding to the current class, using:
    - Drug classes from KQ 1, atypical antipsychotics, lithium, triiodothyronine, buspirone
- Key Question 3: Psychotherapies, including:
    - ACT, BA/BT, client-centered counseling, CBT, computer-based cognitive behavioral therapy (CCBT), couples/marital-focused therapy (CFT), dialectical behavior therapy (DBT), emotion-focused therapy, GSH, IPT, mindfulness-based therapies (MBT), PST, STPP, group versus individual psychotherapy, any brief intervention (including motivational interviewing)
- Key Question 4: Components from the above therapies (KQ 3) alongside other psychotherapies, including:
    - Motivational interviewing, bibliotherapy, modular therapy can be used as a targeted, personalized, psychotherapy approach
- Key Question 5: Antidepressant therapy (see KQ 1) in combination with psychotherapy (see KQ 3), or vice versa
- Key Question 6: Complementary and integrative health interventions, including:
    - Acupuncture, biofeedback, light therapy (including evaluation of efficacy in non-seasonal depression), meditation
- Key Question 7: Physical activity, including:
    - TAU in addition to physical activity (guided or self-directed)

  - Aerobic
  - Resistance training
  - Tai chi/qi gong
  - Team/group activity
  - Walking
  - Yoga
- Key Question 8: Somatic interventions, including:
  - DBS, ECT, transcranial magnetic stimulation (TMS), VNS
- Key Question 9: MBC, self-monitoring, and structured monitoring
- Key Question 10: Team-based models of care, including social workers and other professionals. Models include concepts of:
  - Care management, collaborative care, co-located care, embedded mental health provider, integrated care, primary care/behavioral health (e.g., primary care/behavioral health and primary care integration)
- Key Question 11: Clinician-delivered telehealth visits (via telephone or computer). Visits should be synchronous. Content of visits can include delivery of psychotherapy and/or pharmacotherapy, using:
  - Audio/video, audio only
- Key Question 12: Biomarkers, including:
  - Electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), heart rate variability, pharmacogenetic markers, proteomics

c. Comparators

- Key Question 1: Any one of the following:
  - Another listed pharmacotherapy, placebo for newer, less established drugs, vortioxetine, vilazodone, desvenlafaxine, levomilnacipram, esketamine, ketamine, experimental applications of psychedelics, an established antidepressant medication (SSRIs, SNRIs), experimental applications of psychedelics
- Key Question 2: Not switching or changing drug class or no drug augmentation
- Key Question 3: Another current psychotherapy
- Key Question 4: Standard form of psychotherapy
- Key Question 5: Antidepressant medication alone or psychotherapy alone
- Key Question 6: Standard/usual care (active treatment) or sham (acupuncture and biofeedback)
- Key Questions 7, 9, 10: Standard/usual care (active treatment)
- Key Question 8: Sham

- Key Question 11: Standard in-person care
- Key Question 12: No use of biomarkers

d. Outcomes

- Key Questions 1, 2, 5, 8
    - Critical outcomes: Improvement of symptoms, remission rate, adverse events
    - Important outcomes: Improvement in QoL, functional status measures, relapse/ recurrence rate, suicidal behavior mortality
- Key Questions 3, 4, 6, 7, 9 – 11
    - Critical outcomes: Improvement of symptoms, remission rate
    - Important outcomes: Improvement in QoL (social and occupational functioning), functional status measures, relapse/recurrence rate, treatment adherence/ improvement of retention (keeping appointments, keeping patients engaged in the program), suicidal behavior mortality
- Key Question 12
    - Critical outcomes: Improvement of symptoms, remission rate
    - Important outcomes: Improvement in QoL (social and occupational functioning), functional status measures, relapse/recurrence rate, treatment adherence/ improvement of retention (keeping appointments, keeping patients engaged in the program), adverse events

e. Timing

- Key Questions 1, 2: Minimum of six-week follow-up, except for ketamine, psychedelics, CBD, stimulants (any follow-up)
- Key Questions 3, 4, 6, 7, 9, 10, 12: Any follow-up
- Key Questions 5, 11: Minimum of six-week follow-up for pharmacotherapies
- Key Question 8: Minimum of 12-week follow-up

f. Settings

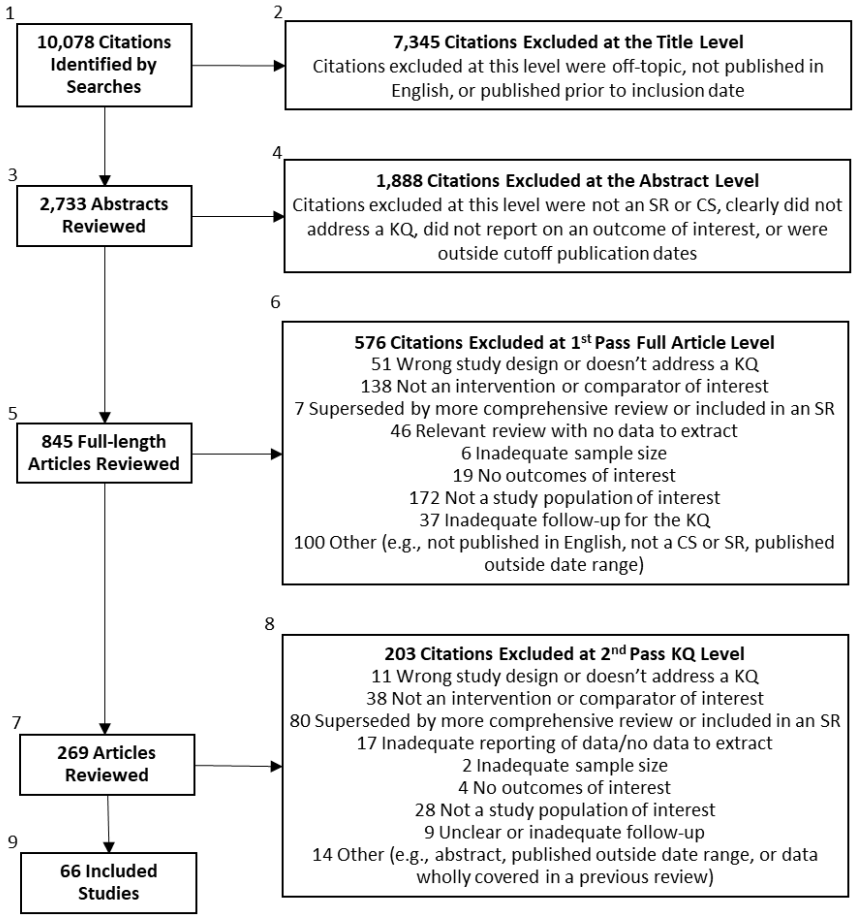
- Key Questions 1 – 12: Primary care or specialty care

B. Conducting the Systematic Review

Based on the Work Group's decisions regarding the CPG's scope, KQs, and PICOTS statements, the Lewin Team produced a systematic evidence review protocol before conducting the review. The protocol detailed the KQs, PICOTS criteria, methodology to be used during the systematic evidence review and the inclusion and exclusion criteria to be applied to each potential study, including study type and sample size. The Work Group reviewed and approved the protocol.

Figure A-1 below outlines the systematic evidence review's screening process (see also the General Criteria for Inclusion in Systematic Review and Key Question Specific Criteria). In addition, Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion/exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 10,078 citations identified by searches
    a. Right to Box 2: 7,345 citations excluded at the title level
        i. Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date
    b. Down to Box 3

2. Box 3: 2,733 abstracts reviewed
    a. Right to Box 4: 1,888 citations excluded at the abstract level
        i. Citations excluded at this level were not an SR or CS, clearly did not address a KQ, did not report on or an outcome of interest, or were outside cutoff publication dates
    b. Down to Box 5
3. Box 5: 845 full-length articles reviewed
    a. Right to Box 6: 576 citations excluded at 1st pass full article level
        i. 51 citations excluded at this level had the wrong study design or did not address a KQ
        ii. 138 citations excluded at this level did not have an intervention or comparator of interest
        iii. 7 citations excluded at this level were superseded by more comprehensive review or included in an SR
        iv. 46 citations excluded at this level had relevant reviews with no data to extract
        v. 6 citations excluded at this level had inadequate sample size
        vi. 19 citations excluded at this level had no outcomes of interest
        vii. 172 citations excluded at this level did not study a population of interest
        viii. 37 citations excluded at this level had inadequate follow-up for the KQ
        ix. 100 citations excluded at this level were excluded for another reason (e.g., not published in English, not a CS or SR, published outside date range)
    b. Down to Box 7
4. Box 7: 269 articles reviewed
    a. Right to Box 8: 203 citations excluded at 2nd pass KQ level
        i. 11 citations excluded at this level had the wrong study design or did not address a KQ
        ii. 38 citations excluded at this level did not have an intervention or comparator of interest
        iii. 80 citations excluded at this level were superseded by more comprehensive review or included in an SR
        iv. 17 citations excluded at this level had inadequate reporting of data or no data to extract
        v. 2 citations excluded at this level had an inadequate sample size
        vi. 4 citations excluded at this level had no outcomes of interest
        vii. 28 citations excluded at this level did not study a population of interest

viii. 9 citations excluded at this level had unclear or inadequate follow-up

ix. 14 citations excluded at this level were excluded for another reason (e.g., abstract, published outside date range, or data wholly covered in a previous review)

b. Down to Box 9

5. Box 9: 66 included studies

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	For adults with MDD, what is the efficacy and safety of pharmacotherapies for treating depression symptoms, including newer FDA-approved pharmacotherapies?	5 SRs*, 1 RCT
2	For adults with MDD who demonstrate no or partial benefit from initial pharmaceutical treatment, what is the efficacy of adding or changing pharmacotherapy?	6 SRs*, 2 RCTs
3	For adults with MDD, what is the comparative effectiveness of specific psychotherapies, including brief interventions, for treating depression symptoms?	5 SRs, 11 RCTs
4	For adults with MDD, what is the effectiveness of combining components from different psychotherapies (modular therapy) in a personalized manner?	1 SR
5	For patients with MDD who are partial or non-responders to initial treatment, what is the efficacy of adding pharmacotherapy to psychotherapy or psychotherapy to pharmacotherapy?	2 SRs, 2 RCTs
6	For patients with MDD, what are the benefits and harms of specific complementary and integrative health interventions in treating depression symptoms?	2 SRs, 5 RCTs
7	For patients with MDD, what is the efficacy and safety of physical activity for depression symptoms?	5 SRs, 1 RCT
8	For patients with MDD, including treatment-resistant depression, what is the effectiveness and safety of switching to or adding specific somatic interventions to current treatment to improve depression symptoms?	4 RCTs
9	In patients with MDD, does measurement-based care, including self-monitoring or structured monitoring, improve depression outcomes?	4 RCTs
10	In patients with MDD, what is the comparative effectiveness of team-based interdisciplinary models of collaborative care on depression symptoms?	1 SR, 3 RCTs
11	For adults with MDD, what is the comparative effectiveness of clinician-delivered telehealth-based interventions compared to in-person treatments?	2 RCTs** in 3 papers
12	For adults with MDD, what is the clinical utility of using selected biomarkers for improving treatment outcomes?	1 SR, 3 RCTs
	Total Evidence Base	**66 studies**

* One SR was included in both KQ 1 and KQ 2

** One study in KQ 11 was published in two papers

Abbreviations: KQ: key question; MDD: major depressive disorder; RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Evidence Review

- Systematic reviews or clinical studies published on or after May 1, 2015, to January 31, 2021. If multiple systematic reviews addressed a KQ, we selected the most recent and/or comprehensive review. Systematic reviews serve as the first line of evidence for all KQs. In the absence of an SR for an intervention, RCTs were considered for inclusion.
- Studies must be published in English.
- Publication must be a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.
- Systematic reviews must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the Strength of Evidence grading used by the Evidence-based Practice Centers of the Agency for Healthcare Research and Quality). If an existing review did not assess the overall quality of the evidence, evidence from the review must be reported in a manner that allows us to judge the overall risk of bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were not able to assess the overall quality of the evidence in the review.
- Studies must have enrolled at least 20 patients (10 per study group); small sample size is associated with increased risk of bias, and we downgraded small studies in the GRADE domain of precision: one downgrade for imprecision of a single study with <200 patients per study arm and two downgrades for imprecision for <50 total patients.
- Some older Cochrane reviews already take into account small sample size in their estimation of risk of bias. In these cases, where sample size has already contributed to the assessment of the evidence, we did not downgrade those data a second time.
- Studies must have enrolled at least 80% of patients who meet the study population criteria: adults aged 18 years or older with a diagnosis of MDD. For studies examining mixed patient populations, studies must have enrolled at least 80% of patients with the relevant condition. If the studies have presented data in a manner that ECRI can isolate the population of interest, studies with less than 80% of patients with the target condition were included.
- Studies must have reported on at least one outcome of interest.

b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

- For all KQs, except KQ 12, studies included in the SRs or independent papers must be prospective RCTs with an independent control group. As depressive disorders can worsen/improve over time independent of treatment, crossover trials were not included.
    - Key Question 12 also included prospective cohort trials that compared the use of biomarkers to no use of biomarkers on the clinical outcomes of interest.

c. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table A-3. See Appendix F for additional information on the search strategies, including topic-specific search terms and search strategies.

Table A-3. Bibliographic Database Information

Name	Date Limits	Platform/Provider
Embase (Excerpta Medica) and MEDLINE	May 1, 2015, through January 31, 2021	Elsevier
PsycINFO	May 1, 2015, through January 31, 2021	Ovid
PubMed (In-process and Publisher records)	May 1, 2015, through January 31, 2021	NLM
Agency for Healthcare Research and Quality (AHRQ)	March 2015 through January 13, 2021	AHRQ
U.S. Department of Veterans Affairs (VA) Evidence Synthesis Program	2015 through January 22, 2021	VA

d. Rating the Quality of Individual Studies and the Body of Evidence

The Lewin Team assessed the methodological risk of bias of individual diagnostic, observational, and interventional studies using the USPSTF method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(220)

Following this, the Lewin Team assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, and *Very low*.

C. Developing Evidence-based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program, DHA, the Lewin Team convened a four-day virtual recommendation development meeting on June 14 – 17, 2021, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Lewin Team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting.

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. Where appropriate, the Work Group carried forward and modified recommendations from the 2016 VA/DoD MDD CPG as necessary (see Categorization of 2016 Clinical Practice Guideline Recommendations). The Work Group also developed new recommendations not included in the 2016 VA/DoD MDD CPG based on the 2021 evidence review.

The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications (see Determining Recommendation Strength and Direction)

a. Determining Recommendation Strength and Direction

Per GRADE, each recommendation's strength and direction is determined by the following four domains:(14)

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the body of evidence supporting a recommendation (see Rating the Quality of Individual Studies and the Body of Evidence). The options for this domain include: *High*, *Moderate*, *Low*, or *Very low*. This is a direct reflection of the GRADE ratings for each relevant critical outcome in the evidence review (see Outcomes). Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(15, 16)

The recommendation strength generally aligns with the confidence in the quality of evidence. For example, *Strong* recommendations are typically supported by *High* or *Moderate* quality evidence. However, GRADE permits *Low* or *Very low* quality evidence to support a *Strong* recommendation in certain instances (e.g., life-threatening situation).(14)

2. Balance of Desirable and Undesirable Outcomes

The balance of desirable and undesirable outcomes (i.e., benefits and harms) refers to the relative magnitudes or tradeoffs of anticipated benefits (e.g., increased longevity, reduced morbidity, improved QoL, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired QoL). The options for this domain include: *benefits outweigh harms/burden*, *benefits slightly outweigh harms/burden*, *benefits and harms/burdens are balanced*, *harms/burdens slightly outweigh benefits*, and *harms/burdens outweigh benefits*. This domain assumes most clinicians will offer patients an intervention if its advantages exceed the harms. The Work Group's understanding of the benefits and harms associated with the recommendation influenced the recommendation's strength and direction.

3. Patient Values and Preferences

Patient values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life as they may apply to the intervention's potential benefits, harms, costs, limitations, and inconvenience. The options for this domain include: *similar values*, *some variation*, or *large variation*. For instance, there may be *some variation* in patient values and preferences for a recommendation on the use of acupuncture, as some patients may dislike needles. When patient values seem homogeneous, this domain may increase the recommendation's strength. Alternatively, when patient values seem heterogeneous, this domain may decrease a recommendation's strength. As part of this domain, the Work Group considered the findings from the patient focus group carried out as part of this CPG update (see Appendix B).

4. Other Implications

Other implications encompass the potential consequences or other impacts that might affect the strength or direction of the recommendation. The options for this domain include: resource use, equity, acceptability, feasibility, and subgroup considerations. The following are example implications related to equity and subgroup considerations, respectively: some of the indicated population may be

geographically remote from an intervention (e.g., complex radiological equipment); a drug may be contraindicated in a subgroup of patients.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Confidence in the quality of the evidence	Among the designated critical outcomes, what is the lowest quality of relevant evidence? How likely is further research to change the confidence in the estimate of effect?	High Moderate Low Very low
Balance of desirable and undesirable outcomes	What is the magnitude of the anticipated desirable outcomes? What is the magnitude of the anticipated undesirable outcomes? Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	Benefits outweigh harms/burdens Benefits slightly outweigh harm/burden Benefits and harms/burdens are balanced Harms/burdens slightly outweigh benefits Harms/burdens outweigh benefits
Patient values and preferences	What are the patients' values and preferences? Are values and preferences similar across the target population? Are you confident about typical values and preferences?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	What are the costs per resource unit? Is this intervention generally available? What is the variability in resource requirements across the target population and settings? Are the resources worth the expected net benefit from the recommendation? Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?	Various considerations

b. Recommendation Categorization

A summary of the recommendation categories and definitions is available in Table 3.

1. Categorizing Recommendations with an Updated Review of the Evidence

Reviewed refers to recommendations on topics included in this CPG's systematic evidence review. *Reviewed*, *New-added* recommendations are original, new recommendations (i.e., not included in the previous CPG). These recommendations are based entirely on evidence included in the current CPG's systematic evidence review.

Reviewed, *New-replaced* recommendations were in the previous CPG but revised based on the updated evidence review. These recommendations may have clinically relevant edits. *Reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. This allowed for the recommendation language to reflect GRADE approach and any other not clinically meaningful edits deemed necessary. These recommendations can be based on a combination of evidence included in the

current CPG's systematic evidence review and the evidence base that supported the recommendation in the previous CPG.

Reviewed, *Deleted* refers to recommendations from the previous CPG that were deleted after a review of the evidence. This may occur if the evidence supporting the recommendation is outdated (e.g., there is no longer a basis to recommend use of an intervention and/or new evidence suggests a shift in care), rendering the recommendation obsolete.

2. 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 CPG without an updated review of the evidence. Given time and resource constraints, the systematic evidence review carried out for this CPG update could not cover all available evidence on MDD; therefore, its KQs focused on new or updated research or areas not covered in the previous CPG.

For areas in which the relevant evidence was not changed and for which recommendations made in the previous CPG were still relevant, recommendations could have been carried forward to the updated CPG without an updated review of the evidence. The evidence supporting these recommendations was thus also carried forward from the previous CPG. These recommendations were categorized as *Not reviewed*. If evidence had not been reviewed, recommendations could have been categorized as *Not changed*, *Amended*, or *Deleted*. *Not reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Not reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. *Not reviewed*, *Deleted* recommendations were determined by the Work Group to not be relevant. A recommendation may not be relevant if it, for example, pertained to a topic (e.g., population, care setting, treatment) outside of the updated CPG's scope or if it was determined to be common practice.

The recommendation categories for the current CPG are noted in the Recommendations. The recommendation categories from the 2016 VA/DoD MDD CPG are noted in Appendix D.

D. Drafting and Finalizing the Guideline

The Work Group wrote, reviewed, and edited three drafts of the CPG using an iterative review process to solicit feedback on and make revisions to the CPG. The first and second drafts were posted online for 20 and 14 business days respectively, for the Work Group to provide feedback. Draft 3 was made available for a 14-day peer review and comment (see External Peer Review). The Work Group reviewed all feedback submitted during each review period and made appropriate revisions to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG to the VA/DoD EBPWG for approval. The Work Group considered the VA/DoD EBPWG's feedback and revised the CPG as appropriate to create the final version. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, pocket card, and patient summary. The VA/DoD EBPWG approved the final CPG and toolkit products in February 2022.

Appendix B: Patient Focus Group Methods and Findings

A. Methods

VA and DoD Leadership recruited eight participants for the focus group, with support from the Champions and other Work Group members as needed. While participant recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the CPG development process, patient focus group participants were not intended to be a representative sample of VA and DoD patients. Participants were not incentivized for their participation or reimbursed for travel expenses.

The Work Group, with support from the Lewin Team, identified topics on which patient input was important to consider in developing the CPG. The Lewin Team developed, and the Work Group approved a patient focus group guide covering these topics. The focus group facilitator led the discussion used the guide to elicit the patients' perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all questions were addressed.

B. Patient Focus Group Findings

a. Treatment initiation and retention can be challenging for individuals with MDD. Participants reported that their depression symptoms made seeking help and staying engaged difficult.

- Participants reported difficulty in seeking help for their depressive symptoms.
- Participants reported difficulty staying engaged in treatment. Two participants reported engaging in evasive behaviors to avoid therapy.
- Participants noted that care coordination and continuous engagement with providers have improved their ability to remain in treatment.

b. Participants reported that open, non-judgmental communication with their providers was a critical component of successful treatment. They want providers to see them as whole human beings and engage in shared decision making.

- Participants reported fear of judgment or stigmatization attenuated their willingness to initiate treatment for MDD.
- Participants reported open communication with their providers assuaged these fears. Participants also reported "feeling heard," is one of the most important components of a successful treatment plan.
- One participant reported fearing the implicit biases of her/his provider would adversely impact the care s/he received.

c. Participants reported that an individualized treatment approach is extremely important in identifying an optimal set of effective treatments.

- Participants shared that their MDD is influenced by several factors, including housing insecurity, abuse, and social exclusion, and that their care should be responsive to these factors.

- Participants noted that effective care is culturally sensitive, accounting for language and cross-cultural differences between patient and provider.
- Participants valued mind-body medicine, with emphasis given equally to mental and physical health.
- Participants noted that mental health integration into primary care settings can be useful for identifying individuals who would benefit from further mental healthcare.

d. Participants reported a preference for in-person and group therapies. Although participants reported use of telehealth and phone-therapy options during the pandemic, they prefer in-person therapy when possible.

- Participants reported a preference for in-person treatment over virtual care, including telehealth and phone therapy.
- Participants reported valuing group therapy as an opportunity to connect with other Veterans and share similar experiences.
- Participants reported their preferences for group therapy were impacted by various factors, including group size and relationships with the facilitator.

e. Participants valued having a range/combination of treatment options for MDD, including psychotherapy (group and individual), pharmacotherapy, complementary and integrative health interventions, peer support, intensive outpatient programs, and twelve-step programs for co-occurring alcohol use disorder (AUD).

- Participants reported engaging in a range of treatment options, including psychotherapy, pharmacotherapy, and complementary and integrative health options.
- Participants regarded psychotherapies and pharmacotherapies similarly and indicated that shared decision making is an important part of any treatment regimen.
- Participants indicated having a range of treatment options was important to their retention in care.
- Participants reported benefitting from peer activities outside of scheduled psychotherapy

Appendix C: Evidence Table

Table C-1. Evidence Table[a,b,c,d]

#	Recommendation	2016 Strength of Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
1.	We suggest that all patients not currently receiving treatment for depression be screened for depression.	Strong for	**Additional references**: (29-46)	Weak for	Not reviewed, Amended
2.	For patients with MDD, we suggest using a quantitative measure of depression severity in the initial treatment planning and to monitor treatment progress at regular intervals to guide shared treatment decision making.	Weak for	(47, 48, 55-57) **Additional references**: (49-54, 58)	Weak for	Reviewed, New-replaced
3.	For patients with MDD who are being treated in the primary care setting, we recommend the use of collaborative/integrated care models.	Strong for	(59-67)	Strong for	Reviewed, Amended
4.	For patients with MDD, there is insufficient evidence to recommend for or against the use of a team-based model in specialty mental health care settings.	Not applicable	**Additional references**: (68)	Neither for nor against	Reviewed, New-added
5.	For patients with MDD, there is insufficient evidence to conclude that interventions delivered by clinicians using telehealth are either superior or inferior to in-person treatment.	Not applicable	(69-71) **Additional references**: (72-74)	Neither for nor against	Reviewed, New-added

[a] 2016 Strength of Recommendation column: The 2016 VA/DoD MDD CPG was developed using the GRADE approach to determine the strength of each recommendation. Inclusion of more than one 2016 strength of recommendation indicates that more than one 2016 VA/DoD MDD CPG recommendation is covered by the 2022 recommendation. "Not applicable" indicates that the 2022 VA/DoD MDD CPG recommendation was a new recommendation, and therefore does not have an associated 2016 strength of recommendation.

[b] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through a systematic evidence review carried out as part of the initial development or update of this CPG. The second set of references in the evidence column (called "Additional References") includes references that provide additional information related to the recommendation, but which were not identified through a systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

[c] 2022 Strength of Recommendation column: The 2022 VA/DoD MDD CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Determining Recommendation Strength and Direction section for more information.

[d] Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

#	Recommendation	2016 Strength of Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
6.	We recommend that MDD be treated with either psychotherapy or pharmacotherapy as monotherapy, based on patient preference. Factors including treatment response, severity, and chronicity may lead to other treatment strategies such as augmentation, combination treatment, switching of treatments, or use of non-first line treatments (see Recommendations 17, 18, and 20).	Not applicable	(77-92) **Additional references:** (14, 75, 76)	Strong for	Reviewed, New-replaced
7.	When choosing psychotherapy to treat MDD, we suggest offering one of the following interventions (not rank ordered): • Acceptance and commitment therapy • Behavioral therapy/behavioral activation • Cognitive behavioral therapy • Interpersonal therapy • Mindfulness-based cognitive therapy • Problem-solving therapy • Short-term psychodynamic psychotherapy	Strong for	(77-90)	Weak for	Reviewed, New-replaced
8.	For patients who select psychotherapy as a treatment option, we suggest offering individual or group format based on patient preference.	Weak for	(93-95)	Weak for	Reviewed, Not changed
9.	There is insufficient evidence to recommend for or against combining components from different psychotherapy approaches.	Not applicable	(95) **Additional references:** (96)	Neither for nor against	Reviewed, New-added
10.	For patients with mild to moderate MDD, we suggest offering clinician-guided computer/internet-based cognitive behavioral therapy either as an adjunct to pharmacotherapy or as a first-line treatment, based on patient preference.	Strong for	(72)	Weak for	Reviewed, New-replaced
11.	When choosing an initial pharmacotherapy, or for patients who have previously responded well to pharmacotherapy, we suggest offering one of the following (not rank ordered): • Bupropion • Mirtazapine • A serotonin-norepinephrine reuptake inhibitor • Trazodone, vilazodone, or vortioxetine • A selective serotonin reuptake inhibitor	Strong for	(91, 92) **Additional references**: (97-102)	Weak for	Reviewed, New-replaced

#	Recommendation	2016 Strength of Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
12.	When choosing an initial pharmacotherapy, we suggest against using: • Esketamine • Ketamine • Monoamine oxidase inhibitors • Nefazodone • Tricyclic antidepressants	Not applicable	(91, 92, 107) **Additional references**: (97-106)	Weak against	Reviewed, New-added
13.	There is insufficient evidence to recommend for or against pharmacogenetic testing to help guide the selection of antidepressants.	Not applicable	(108-112) **Additional references**: (113, 114)	Neither for nor against	Reviewed, New-added
14.	For patients with mild to moderate MDD who decline pharmacotherapy and who decline or cannot access first-line evidence-based psychotherapies (either in-person or virtually), we suggest considering non-directive supportive therapy.	Weak for	(79, 116) **Additional references:** (115)	Weak for	Not reviewed, Amended
15.	We suggest offering a combination of pharmacotherapy and evidence-based psychotherapy for the treatment of patients with MDD characterized as: • Severe (e.g., PHQ-9 >20) • Persistent major depressive disorder (duration greater than two years) • Recurrent (with two or more episodes)	Weak for	(117, 118, 120, 121) **Additional references:** (119)	Weak for	Not reviewed, Amended
16.	For patients with MDD who have demonstrated partial or no response to an adequate trial of initial pharmacotherapy, we suggest (not rank ordered): • Switching to another antidepressant (including TCAs, MAOIs, or those in Recommendation 12) • Switching to psychotherapy • Augmenting with a psychotherapy • Augmenting with second-generation antipsychotic	Strong for	(117, 118, 124-130, 132, 136, 139, 140) **Additional references:** (122, 123, 133-135, 137, 138, 141)	Weak for	Reviewed, Amended

#	Recommendation	2016 Strength of Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
17.	For patients who have demonstrated partial or no response to two or more adequate pharmacologic treatment trials, we suggest offering repetitive transcranial magnetic stimulation for treatment.	Weak for	(144, 145, 147-149) **Additional references**: (142, 143, 146)	Weak for	Reviewed, Amended
18.	There is insufficient evidence to recommend for or against theta-burst stimulation for the treatment of MDD.	Not applicable	(150) **Additional references:** (151)	Neither for nor against	Reviewed, New-added
19.	For patients with MDD who have not responded to several adequate pharmacologic trials, we suggest ketamine or esketamine as an option for augmentation.	Strong against	(152-154) **Additional references:** (155-159)	Weak for	Reviewed, New-replaced
20.	We recommend offering electroconvulsive therapy (ECT) with or without psychotherapy for 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 • The risks associated with other treatments are greater than the risks of ECT for this specific patient (i.e., co-occurring medical conditions make ECT the safest MDD treatment alternative) • A history of a poor response or intolerable side effects to multiple antidepressants	Strong for	**Additional references**: (160-164)	Strong for	Reviewed, Not changed
21.	For 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	(168) **Additional references**: (165-167)	Strong for	Not reviewed, Not changed

#	Recommendation	2016 Strength of Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
22.	For patients with MDD at high risk for relapse or recurrence (e.g., two or more prior episodes, unstable remission status), we suggest offering a course of cognitive behavioral therapy, interpersonal therapy, or mindfulness-based cognitive therapy during the continuation phase of treatment (i.e., after remission is achieved) to reduce the risk of subsequent relapse/recurrence. The evidence does not support recommending one of these three evidence-based psychotherapies over another.	Strong for	(169, 170)	Weak for	Not reviewed, Amended
23.	For individuals with mild to moderate MDD who are breastfeeding or pregnant, we recommend offering an evidence-based psychotherapy as a first-line treatment (see Recommendation 7). In 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	(173) **Additional references**: (171, 172)	Strong for	Not reviewed, Amended
24.	For older adults (≥65 years) with mild to moderate MDD, we suggest offering a first-line psychotherapy (see Recommendation 7). Patient preference and the additional safety risks of pharmacotherapy should be considered when making this decision.	Strong for	(174-176)	Weak for	Not reviewed, Amended
25.	For patients with mild to moderate MDD and significant relationship distress, we suggest offering couples-focused therapy.	Weak for	(177, 178)	Weak for	Not reviewed, Amended
26.	For patients with mild to moderate MDD with or without a seasonal pattern (formerly seasonal affective disorder), we suggest offering light therapy.	Weak for	(179-182)	Weak for	Reviewed, New-replaced
27.	For patients with MDD, we suggest exercise (e.g., yoga, tai chi, qi gong, resistance, aerobics) as an adjunct.	Neither for nor against	(183-186)	Weak for	Reviewed, New-replaced
28.	For patients with MDD, we suggest CBT-based bibliotherapy as an adjunct to pharmacotherapy or psychotherapy, or as an alternative when patients are unwilling or unable to engage in other treatments.	Weak for	(188, 192) **Additional references**: (187, 189-191, 193)	Weak for	Reviewed, Amended
29.	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 as monotherapy.	Weak for	(195, 196) **Additional references**: (194)	Weak for	Not reviewed, Amended

#	Recommendation	2016 Strength of Recommendation	Evidence	2022 Strength of Recommendation	Recommendation Category
30.	For patients with MDD, there is insufficient evidence to recommend for or against acupuncture as an adjunct.	Neither for nor against	(197, 198)	Neither for nor against	Reviewed, New-replaced
31.	For patients with MDD, there is insufficient evidence to recommend for or against the addition of biofeedback.	Not applicable	(199, 200)	Neither for nor against	Reviewed, New-added
32.	For patients with MDD, there is insufficient evidence for or against the use of meditation as an adjunct.	Not applicable	(201, 202)	Neither for nor against	Reviewed, New-added
33.	For patients with MDD, we suggest against using vagus nerve stimulation outside of a research setting.	Strong against	**Additional references**: (163, 203-210)	Weak against	Reviewed, Amended
34.	For patients with MDD, we recommend against using deep brain stimulation outside of a research setting.	Strong against	(211, 212)	Strong against	Reviewed, Not changed
35.	Given the limited information on the safety and efficacy of psilocybin, MDMA, cannabis, and other unapproved pharmacologic treatments, we recommend against using these agents for MDD outside of a research setting.	Not applicable	(213)	Strong against	Reviewed, New-added
36.	For patients with MDD, we suggest against using omega-3 fatty acids or vitamin D for the treatment of MDD.	Weak against	(214-218)	Weak against	Not reviewed, Not changed

Appendix D: 2016 Recommendation Categorization Table

Table D-1. 2016 MDD CPG Recommendation Categorization Table[a,b,c,d,e,f]

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG 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	Not reviewed, Amended	1
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	Not reviewed, Deleted	-
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	Not reviewed, Deleted	-
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	Reviewed, New-replaced	2
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	Not reviewed, Deleted	-

[a] 2016 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2016 VA/DoD MDD CPG.
[b] 2016 CPG Recommendation Text column: This contains the wording of each recommendation from the 2016 VA/DoD MDD CPG.
[c] 2016 CPG Strength of Recommendation column: The 2016 VA/DoD MDD CPG used the GRADE approach to determine the strength of each recommendation. The strength of recommendations in the 2016 VA/DoD MDD CPG were: Strong for, Weak for, N/A, Weak against, or Strong against.
[d] 2016 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2016 VA/DoD MDD CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[e] 2022 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2022 VA/DoD MDD CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[f] 2022 CPG Recommendation # column: For recommendations that were carried forward to the 2016 VA/DoD MDD CPG, this column indicates the new recommendation(s) to which they correspond.

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG 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	Reviewed, Amended	3
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	Not reviewed, Deleted	-
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	Reviewed, New-replaced Reviewed, New-replaced Reviewed, New-replaced	6, 7, 11

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG 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	Reviewed, Amended	16
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	Reviewed, Not changed	8
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	Reviewed, New-replaced	10
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	Not reviewed, Amended	14
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	Not reviewed, Amended	15
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	Reviewed, New-replaced	2
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	Not reviewed, Not changed	21
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	Not reviewed, Deleted	-

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG 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	Not reviewed, Amended	22
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	Not reviewed, Amended	23
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	Not reviewed, Amended	24
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	Not reviewed, Amended	25
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	Reviewed, New-replaced	26
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	Not reviewed, Deleted	-

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG 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	Reviewed, New-replaced	19
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	Reviewed, Not changed	20
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	Reviewed, Amended	17
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	Reviewed, Amended	33
27	We recommend against offering deep brain stimulation (DBS) for patients with MDD outside of a research setting.	Strong against	Reviewed, New-added	Reviewed, Not changed	34
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.	N/A	Reviewed, New-replaced	Reviewed, New-replaced	30
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	Not reviewed, Deleted	-

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2022 CPG Recommendation Category	2022 CPG 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.	N/A	Reviewed, New-added	Reviewed, New-replaced	27
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	Not reviewed, Amended	29
32	For patients with MDD, we suggest against using omega-3 fatty acids or vitamin D for treatment.	Weak against	Reviewed, New-added	Not reviewed, Not changed	36
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	Reviewed, Amended	28

Appendix E: Participant List

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Appendix F: Literature Review Search Terms and Strategy

A. EMBASE and MEDLINE with EMBASE.com syntax (all questions)

Question	Set #	Concept	Strategy
KQ 1 – Pharmacotherapies KQ 2 – Adding/changing pharmacotherapies KQ 5 – Adding psychotherapy to pharmacotherapy(ies)	1	Depressive Disorders	('major depression'/de OR 'depression'/de OR 'persistent depression'/de OR 'persistent depressive disorder'/de OR 'chronic depression'/de OR 'dysthymia'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	2	Treatment Resistant Depression	('treatment resistant depression'/de OR ((((low OR no OR non OR partial) NEXT/1 respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) NEAR/2 depress*)):ti,ab) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	3	Combine Populations	#1 OR #2
	4	General Pharmacotherapy (KQ 1)	'depression'/dm_dt OR 'major depression'/dm_dt OR 'psychopharmacotherapy'/de OR pharmacotherap*.ti. OR ((medicine* OR medicat* OR drug*) NEAR/3 (therap* OR treat*)):ti OR maintenance:ti
	5	Antidepressants (KQ 1)	'antidepressant agent'/exp OR ('anti depressant*' OR (antidepress* NEAR/2 (drug* OR agent*)) OR antidepressant*):ti,ab
	6	Second Generation Antidepressants (KQ 1)	('atypical antidepressant*' OR aplenzin* OR trintellix* OR bupropion* OR forfivo* OR mirtazapine* OR nefazodone* OR oleptro* OR remeron* OR trazodone* OR wellbutrin* OR zyban*):ti,ab,tn
	7	Tricyclic Antidepressants (KQ 1)	'tricyclic antidepressant agent'/exp OR ((tricyclic NEAR/2 (antidepress*)) OR amitriptyline* OR amoxapine* OR anafranil* OR chlorimipramine* OR clomipramine* OR desipramine* OR doxepin* OR imipramine* OR maprotiline* OR mitriptyline* OR norpramin* OR nortriptyline* OR pamelor* OR protriptyline* OR prudoxin* OR silenor* OR surmontil* OR tofranil* OR trimipramine* OR vivactil* OR zonalon*):ti,ab,tn
	8	Tetracyclic Antidepressants (KQ 1)	'tetracyclic antidepressant agent'/exp OR ((tetracyclic NEAR/2 antidepress*) OR beloxepin* OR brexanolone* OR levoprotiline* OR maprotiline* OR mianserin* OR mirtazapine* OR oxaprotiline* OR teciptiline*):ti,ab,tn
	9	Atypical Antipsychotic (KQ 1)	'neuroleptic agent'/exp OR (antipsychotic* OR abilify* OR alprazolam* OR aripiprazole* OR asenapine* OR brexpiprazole* OR buspirone* OR cariprazine* OR clozapine* OR clozaril* OR fanapt* OR fazaclo* OR geodon* OR iloperidone* OR invega* OR latuda* OR lumateperone* OR lurasidone* OR molindone* OR neuroleptic* OR nialamide* OR olanzapine* OR paliperidone* OR pregabalin* OR quetiapine* OR reserpine* OR risperdal* OR risperidone* OR saphris* OR seroquel* OR spiroperidol* OR sulpiride* OR tetrabenazine* OR tranquiliz* OR tranquilliz* OR triazolam* OR ziprasidone* OR zyprexa*):ti,ab,tn

Question	Set #	Concept	Strategy
KQ 1 – Pharmacotherapies KQ 2 – Adding/changing pharmacotherapies KQ 5 – Adding psychotherapy to pharmacotherapy(ies) (cont.)	10	MAOIs (KQ 1)	'monoamine oxidase inhibitor'/exp OR ('mao inhibit*' OR 'mono amine oxidase inhibit*' OR 'monoamine oxidase a inhibitor' OR 'monoamine oxidase b inhibitor' OR 'monoamine oxidase inhibit*' OR 'monoaminoxidase inhibit*' OR mao OR maoi OR maois OR azilect* OR eldepryl* OR emsam* OR iproniazid* OR isocarboxazid* OR marplan* OR moclobemide* OR nardil* OR nialamide* OR pargyline* OR parnate* OR phenelzine* OR pheniprazine* OR rasagiline* OR selegiline* OR tranylcypromine*):ti,ab,tn
	11	Psychostimulants (KQ 1)	'psychostimulant agent'/exp OR (psychostimul* OR amphetamine* OR dexamphetamine* OR adderall* OR methylphenidate* OR modafinil*):ti,ab,tn
	12	SNRIs (KQ 1)	'serotonin noradrenalin reuptake inhibitor'/exp OR ('noradrenalin serotonin reuptake inhibitor*' OR 'noradrenalin serotonin uptake inhibitor*' OR 'norepinephrine serotonin reuptake inhibitor*' OR 'norepinephrine serotonin uptake inhibitor*' OR 'serotonin and noradrenaline reuptake inhibitor*' OR 'serotonin and noradrenaline uptake inhibitor*' OR 'serotonin and norepinephrine reuptake inhibitor*' OR 'serotonin and norepinephrine uptake inhibitor*' OR 'serotonin noradrenalin uptake inhibitor*' OR 'serotonin norepinephrine reuptake inhibitor*' OR 'serotonin norepinephrine uptake inhibitor*' OR ansofaxine* OR cymbalta* OR desvenlafaxine* OR duloxetine* OR effexor* OR fetzima* OR khedezla* OR levomilnacipran* OR milnacipran* OR pristiq* OR savella* OR snri OR snris OR ssnri OR toludesvenlafaxine* OR venlafaxine*):ti,ab,tn
	13	SSRIs (KQ 1)	'serotonin uptake inhibitor'/exp OR ('serotonin reuptake inhibitor*' OR 'serotonin specific reuptake inhibitor*' OR 'serotonin uptake inhibitor*' OR brisdelle* OR celexa* OR chlorimipramine* OR citalopram* 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 ssri OR ssris OR viibryd* OR vilazodone* OR vortioxetine* OR zimeldine* OR zoloft*):ti,ab,tn
	14	Ketamine / esketamine (KQ 1)	'ketamine'/de OR 'esketamine'/de OR (esketamine* OR ketamine* OR spravato*):ti,ab,tn
	15	Experimental drugs (KQ 1)	'cannabinoid'/exp OR 'cannabis'/de OR 'medical cannabis'/de OR 'midomafetamine'/de OR 'psilocybine'/de OR ((cbd* NEAR/2 oil*) OR bhang* OR cannabi* OR cannador OR charas OR dronabinol OR ganja* OR hashish* OR hemp* OR marihuana OR marijuana OR ecstasy OR mdma OR methylenedioxymethamphetamine OR midomafetamine OR psilocibin* OR psilocin OR psilocybin*):ti,ab,tn
	16	Drug augmentation (KQ 2)	'drug potentiation'/de OR (((drug* OR medication* OR pharm*) NEAR/5 (augment* OR potentiat* OR synerg*)) OR lithium* OR liothyronine* OR triiodothyronine*):ti,ab,tn
	17	Drug switching (KQ 2)	((chang* OR switch*) NEAR/2 ('anti depress*' OR antidepress* OR therap* OR treat*)):ti,ab
	18	Adding psychotherapy (KQ 5)	(combin* NEAR/5 (psychiatr* OR psychoanaly* OR psychodynamic OR psychotherap* OR therap* OR treat*)):ti,ab

Question	Set #	Concept	Strategy
KQ 1 – Pharmacotherapies KQ 2 – Adding/changing pharmacotherapies KQ 5 – Adding psychotherapy to pharmacotherapy(ies) (cont.)	19	Combine population & interventions (KQ 1)	#3 AND (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
	20	Combine population & interventions (KQ 2 & 5)	(#1 AND (#16 OR #17 OR #18)) OR (#2 AND (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18))
	21	Apply limits, remove unwanted publications types, limit to SRs or meta-analyses	#19 and limits
	22	Apply limits, remove unwanted publications types, limit to RCTs or SRs or meta-analyses	#20 and limits
	23	Combine results	#21 OR #22
KQ 3 – Psychotherapies KQ 4 – Combining psychotherapies KQ 5 – Adding pharmacotherapies to psychotherapies	1	Depressive Disorders	('major depression'/de OR 'depression'/de OR 'persistent depression'/de OR 'persistent depressive disorder'/de OR 'chronic depression'/de OR 'dysthymia'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	2	Treatment Resistant Depression	('treatment resistant depression'/de OR ((((low OR no OR non OR partial) NEXT/1 respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) NEAR/2 depress*)):ti,ab) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	3	Combine Populations	#1 OR #2
	4	General Psychotherapy (KQ 3)	'psychotherapy'/exp OR (psychiatr* OR psychoanaly* OR psychodynamic OR psychotherap*):ti,ab
	5	Acceptance & Commitment Therapy (KQ 3)	'acceptance and commitment therapy'/de OR (accept* NEAR/2 commitment NEAR/2 therap*):ti,ab
	6	Behavioral Therapy (KQ 3)	'behavior therapy'/exp OR ((behavior* OR behaviour* OR conditioning) NEAR/2 (activat* OR modification OR therap* OR training OR treatment*)):ti,ab
	7	Bibliotherapy (KQ 3)	'bibliotherapy'/de OR 'poetry therapy'/de OR (bibliotherap* OR (poetry NEAR/2 (psychotherap* OR therap*))):ti,ab
	8	Brief Interventions (KQ 3)	'brief intervention'/de OR 'short term psychotherapy'/de OR (((brief OR short*) NEAR/3 (intervention* OR psychotherap* OR therap*)) OR ("time limited" NEAR/3 (psychotherap* OR therap*))):ti,ab

Question	Set #	Concept	Strategy
KQ 3 – Psychotherapies KQ 4 – Combining psychotherapies KQ 5 – Adding pharmacotherapies to psychotherapies (cont.)	9	Client-Centered Counseling (KQ 3)	'client centered therapy'/de OR (('client center*' OR 'client centre*' OR nondirective OR 'person center*' OR rogerian) NEAR/2 (psychotherap* OR therap*)):ti,ab
	10	Cognitive Behavior Therapy (CBT) (KQ 3)	'cognitive behavioral therapy'/exp OR ('cognition therap*' OR (cognitive NEAR/2 (behavior* OR behaviour*) NEAR/2 (therap* OR treatment*)) OR (cognitive NEAR/2 (psychotherap* OR therap*)) OR cbt):ti,ab
	11	Computer-Based CBT (KQ 3)	'computer based cognitive training'/de OR ((computer* NEAR/5 (psychotherap* OR therap* OR train*)) OR cbt4cbt OR ccbt):ti,ab
	12	Couples Therapy (KQ 3)	'couple therapy'/de OR 'marital therapy'/de OR ((couple* OR marital OR marriage) NEAR/2 (counseling OR psychotherap* OR therap*)):ti,ab
	13	Dialectical Behavior Therapy (DBT) (KQ 3)	'dialectical behavior therapy'/de OR ((dialectical NEAR/2 (behavior* OR behaviour*)) OR dbt):ti,ab
	14	Emotion-Focused Therapy (EFT) (KQ 3)	'emotion-focused therapy'/de OR 'emotion focused coping'/de OR ((emotion* NEAR/2 focus*) OR (experiential NEAR/3 (psychotherap* OR therap*)) OR eft):ti,ab
	15	Guided Self-Help (GSH) (KQ 3)	'guided self help'/de OR ((guide* NEAR/5 ("self care" OR "self help" OR "self manag*")) OR gsh):ti,ab
	16	Interpersonal Therapy (KQ 3)	'interpersonal psychotherapy'/de OR (((interpersonal OR 'inter personal') NEAR/3 (psychotherap* OR therap*)) OR ipsrt OR ipt OR isrt):ti,ab
	17	Mindfulness-Basted Therapies (KQ 3)	'mindfulness'/exp OR (mbct OR mbsr OR mbt OR micbt OR mindful*):ti,ab
	18	Motivational Interviewing (KQ 3)	'motivational interviewing'/de OR 'motivational enhancement therapy'/de OR 'motivational intervention'/de OR 'motivational interview'/de OR 'motivational therapy'/de OR (motivational NEAR/2 (intervention* OR interview* OR therap*)):ti,ab
	19	Problem Solving (KQ 3)	'problem adaptation therapy'/de OR 'problem solving'/de OR ((problem* NEAR/3 (therap* OR psychotherap*)) OR pst):ti,ab
	20	Short-Term Psychodynamic Psychotherapy (KQ 3)	'psychodynamic psychotherapy'/de OR ((psychodynamic* NEAR/2 (psychotherap* OR therap*)) OR stpp):ti,ab
	21	Personalized Medicine (KQ 3)	'multimodal therapy'/exp OR 'personalized medicine'/de OR (((individuali* OR modular* OR personali*) NEAR/3 (medicine OR psychiatr* OR therap* OR treatment*)) OR ((integrat* OR modular* OR multimodal OR "multi modal") NEAR/2 (psychotherap* OR therap* OR treatment*)) OR 'p health' OR 'precision medicine' OR 'predictive medicine' OR theranostic*):ti,ab
	22	STAR*D Trial (KQ 3)	('sequenced treatment alternatives to relieve depression' OR 'star d' OR (sequence* NEAR/5 (psychotherap* OR therap* OR treatment*))):ti,ab OR nct00021528
	23	Combining Therapies (KQ 4)	((chang* OR switch*) NEAR/2 (psychiatr* OR psychoanaly* OR psychodynamic OR psychotherap*)):ti,ab
	24	Adding Pharmacotherapy (KQ 5)	(combin* NEAR/5 (anti-depress* OR antidepress* OR drug* OR medicine* OR medicat* OR pharmacotherap*)):ti,ab
	25	Combine Populations & Interventions (KQ 3)	#3 AND (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)

Question	Set #	Concept	Strategy
KQ 3 – Psychotherapies KQ 4 – Combining psychotherapies KQ 5 – Adding pharmacotherapies to psychotherapies (cont.)	26	Combine Populations & Interventions (KQ 4 & 5)	(#1 AND (#23 OR #24)) OR (#2 AND (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24))
	27	Apply limits, remove unwanted publications types, limit to systematic reviews or meta-analyses	#25 AND limits
	28	Apply limits, remove unwanted publications types, limit to randomized controlled trials or systematic reviews or meta-analyses	#26 AND limits
	29	Combine results	#27 OR #28
KQ 6 – Complementary & integrative health interventions KQ 7 – Efficacy & safety of physical activity	1	Depressive Disorders	('major depression'/de OR 'depression'/de OR 'persistent depression'/de OR 'persistent depressive disorder'/de OR 'chronic depression'/de OR 'dysthymia'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	2	Treatment Resistant Depression	('treatment resistant depression'/de OR ((((low OR no OR non OR partial) NEXT/1 respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) NEAR/2 depress*)):ti,ab) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	3	Combine Populations	#1 OR #2
	4	Acupuncture (KQ 6)	'acupuncture'/exp OR (acupotom* OR acupressure OR acupuncture OR electroacupuncture OR pharmacoacupuncture*):ti,ab
	5	Biofeedback (KQ 6)	'biofeedback'/de OR 'biofeedback therapy'/de OR 'biofeedback training'/exp OR 'neurofeedback'/de OR 'neurofeedback training'/de OR 'neurofeedback therapy'/de OR ('bio feed back*' OR 'bio feedback*' OR 'biofeed back*' OR biofeedback* OR feedback* OR myobiofeedback* OR myofeedback* OR neurobiofeedback* OR neurofeedback*):ti,ab
	6	Meditation (KQ 6)	'meditation'/exp OR meditat*:ti,ab
	7	Phototherapy (KQ 6)	'phototherapy'/exp OR (((color OR colour OR illumination OR light OR photoradiation) NEAR/2 (therap* OR treatment*)) OR phototherap*):ti,ab
	8	Tai-chi & Qi gong (KQ 7)	'qigong'/de OR 'tai chi'/de OR ('chi kung' OR 'ch i kung' OR chigung OR 'qi gong' OR 'tai chi' OR 't ai chi' OR taichi OR 'tai ji' OR taiji*):ti,ab

Question	Set #	Concept	Strategy
KQ 6 – Complementary & integrative health interventions KQ 7 – Efficacy & safety of physical activity (cont.)	9	Yoga (KQ 7)	'yoga'/exp OR yoga*:ti,ab
	10	Wellness & Holistic Health (KQ 6)	'psychological well-being'/de AND 'wellbeing'/de OR (((alternative* OR complement* OR holistic OR whol*) NEAR/2 (health* OR medic* OR therap* OR treatment*)) OR (health NEAR/2 promot*) OR "well being" OR wellbeing OR wellness*):ti,ab
	11	Physical Activity (KQ 7)	'dancing'/de OR 'exercise'/exp OR 'fitness'/de OR 'kinesiotherapy'/exp OR 'sport'/exp OR (((circuit* OR enduranc* OR resistance OR strength OR weight*) NEAR/5 (program* OR session* OR train)) OR (activ* NEAR/2 life*) OR (aerobic* OR athletic* OR exercis* OR fitness* OR gym* OR kinesitherap* OR sport*) OR (bicycl* OR cycl* OR danc* OR jog* OR pilate* OR row* OR run* OR sprint* OR swim* OR treadmill* OR walk* OR workout*) OR (physical* NEAR/5 (activ* OR condition* OR fit* OR movement* OR program* OR train*) OR (work* NEXT/1 out))):ti,ab
	12	Combine Interventions	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
	13	Combine Populations & Interventions	#3 AND #12
	14	Apply limits, remove unwanted publications types, limit systematic reviews or meta-analyses	#13 AND limits
KQ 8 – Somatic Interventions	1	Depressive Disorders	('major depression'/de OR 'depression'/de OR 'persistent depression'/de OR 'persistent depressive disorder'/de OR 'chronic depression'/de OR 'dysthymia'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	2	Treatment Resistant Depression	('treatment resistant depression'/de OR ((((low OR no OR non OR partial) NEXT/1 respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) NEAR/2 depress*)):ti,ab) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	3	Combine Populations	#1 OR #2
	4	Deep Brain Stimulation (DBS)	'brain depth stimulation'/de OR (brain NEAR/5 (excitation OR stimul*)):ti,ab
	5	Electroconvulsive Therapy (ECT)	'electroconvulsive therapy'/de OR 'electrostimulation'/de OR ((electr* NEAR/3 (stimul* OR therap* OR treatm*)) OR ces OR ecs OR ect OR electrotherap*):ti,ab
	6	Transcranial Magnetic Stimulation (TMS)	'transcranial magnetic stimulation'/exp OR ((transcranial NEAR/3 (electromagnet* OR "electro magnet*" OR magnet* OR stimul*)) OR rtms OR tms):ti,ab
	7	Vagus Nerve Stimulation (VNS)	'vagus nerve stimulation'/de OR (tvns OR vagal* OR vagus* OR vns):ti,ab
	8	Combine Interventions	#4 OR #5 OR #6 OR #7

Question	Set #	Concept	Strategy
KQ 8 – Somatic Interventions (cont.)	9	Combine Populations & Interventions	#3 AND #8
	10	Apply limits, remove unwanted publications types, limit to randomized controlled trials or systematic reviews or meta-analyses	#9 AND limits
KQ 9 – Measurement Based Care	1	Depressive Disorders (Broad)	('major depression'/de OR 'depression'/de OR 'persistent depression'/de OR 'persistent depressive disorder'/de OR 'chronic depression'/de OR 'dysthymia'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	2	Treatment Resistant Depression (Broad)	('treatment resistant depression'/de OR ((((low OR no OR non OR partial) NEXT/1 respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) NEAR/2 depress*)):ti,ab) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	3	Measurement-based Care (Specific)	'measurement based care'/exp OR ((measurement NEXT/3 based) OR "routine outcome monitor*" OR (structur* NEAR/3 monitor*)):ti,ab
	4	Combine Broad Populations and MBC (Specific)	(#1 OR #2) AND #3
	5	Depressive Disorders (Narrow)	('major depression'/de OR 'depression'/mj OR 'treatment resistant depression'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	6	General MBC Tools	'assessment of humans'/exp/mj OR 'depression assessment'/exp/mj OR 'patient-reported outcome'/mj OR 'psychological rating scale'/exp/mj OR 'questionnaire'/exp/mj OR 'self monitoring'/exp/mj OR (assessment* OR index* OR instrument* OR measure* OR prom OR proms OR questionnaire* OR scale OR scales OR tool*):ti

Question	Set #	Concept	Strategy
KQ 9 – Measurement Based Care (cont.)	7	Named MBC Tools	'camberwell assessment of need short appraisal schedule'/mj OR 'client satisfaction questionnaire'/mj OR 'depression anxiety stress scale'/mj OR 'european quality of life 5 dimensions questionnaire'/exp/mj OR 'generalized anxiety disorder 7'/exp/mj OR 'hamilton depression rating scale'/mj OR 'manchester short assessment of quality of life'/mj OR 'outcome questionnaire 45'/mj OR 'outcome rating scale'/mj OR 'patient health questionnaire'/exp/mj OR 'positive and negative syndrome scale'/mj OR 'quick inventory of depressive symptomatology self report'/mj OR 'session rating scale'/mj OR 'symptom checklist 90'/mj OR 'who five well being index'/mj OR ("brief addiction monitor" OR bam OR "camberwell assessment" OR cansas OR "client satisfaction questionnaire" OR csq OR "depression anxiety stress scale" OR euroqol quality of life scale OR "eq 5d 5l" OR euroqol OR ("european quality of life" near/6 questionnaire) OR "generalized anxiety disorder 7" OR "gad 7" OR "hamilton depression rating scale" OR "ham d" OR "manchester short assessment" OR mansa OR "outcome questionnaire 45" OR "oq 45" OR "outcome rating scale" OR ors OR "partners for change outcomes" OR pcoms OR "patient health questionnaire" OR "phq" OR "positive and negative syndrome scale" OR "positive and negative syndrome score" OR panss OR "quick inventory of depressive symptom*" OR "qids sr" OR "session rating scale" OR srs OR "standard for clinicians interview" OR scip OR "symptom checklist 90" OR "who five well*" OR "who 5"):ti,ab
	8	Progress Monitoring & Informing Treatment	'clinical practice'/de OR 'decision making'/exp OR 'patient monitoring'/exp/mj OR (clinical NEXT/1 (application* OR benefit* OR decision* OR effectiveness OR impact* OR implication* OR management OR outcome* OR practice OR setting* OR use OR utility)):ti,ab OR "decision making":ti,ab OR (inform* AND (drug* OR medicine OR medicat* OR psychotherapy* OR therap* OR treat)):ti,ab OR (patient NEAR/3 (monitor* OR progress* OR surveillance)):ti,ab or "personal utility":ti,ab OR (actionable OR advantag* OR benefi* OR decid* OR decision* OR efficac* OR ((guid* OR select*) AND (drug* OR medicine OR medicat* OR psychotherapy* OR therap* OR treat*)) OR inform OR informing OR outcome* OR role OR practice OR targeted OR use OR useful* OR utility OR valu*):ti
	9	Provider/Patient Feedback	('counseling'/exp OR 'physician'/exp OR 'psychotherapist'/de OR 'psychologist'/de OR 'psychotherapy'/exp OR 'treatment outcome'/exp) AND ('feedback system'/exp OR 'patient monitoring'/exp OR 'self report'/de OR ("feed back" OR feedback OR (symptom NEAR/2 monitor*)):ti,ab)
	10	Provider/Patient Feedback	((physician* OR psychiatri* OR psychotherapist* OR therapist* OR "primary care" OR "general practi*" OR psychologist*) AND ((client* OR patient* OR oupatient*) NEAR/5 ("feed back" OR feedback OR monitor*))):ti,ab
	11	Provider/Patient Outcomes	((physician* OR psychiatri* OR psychotherapist* OR therapist* OR "primary care" OR "general practi*") AND ("patient reported" NEAR/3 (information OR outcome* OR symptom*))):ti,ab
	12	Therapy Outcomes	((therap* OR psychotherap*) AND ("feed back" OR feedback OR (patient* AND (reported NEAR/3 (information OR outcome* OR symptom*))))):ti,ab

Question	Set #	Concept	Strategy
KQ 9 – Measurement Based Care (cont.)	13	Other MBC Interventions	((#6 OR #7) AND #8) OR #9 OR #10 OR #11 OR #12
	14	Combine Other MBC Interventions & Narrow Population String	#5 AND #13
	15	Combine All MBC Results	#4 OR #14
	16	Apply limits, remove unwanted publications types, limit to randomized controlled trials or systematic reviews or meta-analyses	#15 AND limits
KQ 10 – Collaborative Care	1	Depressive Disorders	('major depression'/de OR 'depression'/de OR 'persistent depression'/de OR 'persistent depressive disorder'/de OR 'chronic depression'/de OR 'dysthymia'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	2	Treatment Resistant Depression	('treatment resistant depression'/de OR ((((low OR no OR non OR partial) NEXT/1 respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) NEAR/2 depress*)):ti,ab) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	3	Combine Populations	#1 OR #2
	4	Collaborative Care Terms, controlled	'case management'/de OR 'collaborative care team'/de OR 'collaborative care'/de OR 'integrated health care system'/de OR 'interdisciplinary care'/de OR 'interdisciplinary team'/de OR 'interdisciplinary communication'/de OR 'multidisciplinary team'/de OR 'teamwork'/de
	5	Collaborative Care Terms, keywords	("team work" OR "complex intervention*" OR "cooperative behav*" OR "joint work*" OR "inter disciplin*" OR "inter professional*" OR "multi intervention*" OR "multi profession*" OR "multiple intervention*" OR ((care OR case) NEXT/1 manag*) OR ((collaborat* OR coordinat* OR "co ordinat*" OR integrat* or stepped*) NEAR/2 (care OR effort* OR health* OR inteven* OR manag* OR model* OR service* OR team* OR work*)) OR ((multidisciplinary OR "multi disciplinary") NEAR/2 team*) OR "trans disciplin*" OR (integrated NEAR/3 (deliver* OR health*))):ti,ab OR ("inter disciplin*" OR "inter professional*" OR "multi disciplin*" OR "multi profession*" OR "team work" OR "trans disciplin*" OR interdisciplin* OR interprofessional* OR multidisciplin* OR multiprofession* OR teams OR teamwork OR transdisciplin*):ti OR (("primary care" NEAR/5 ("behavioral health*" OR "behavioural health*" OR "mental health integrat*")) OR (pcbh OR pcmhi OR "pc mhi")):ti,ab,kw
	6	Combine Interventions	#4 OR #5
	7	Combine Populations & Interventions	#3 AND #6
	8	Apply limits, remove unwanted publications types, limit to randomized controlled trials or systematic reviews or meta-analyses	#7 AND limits

Question	Set #	Concept	Strategy
KQ 11 – Telehealth Interventions	1	Depressive Disorders (Broad)	('major depression'/de OR 'depression'/de OR 'persistent depression'/de OR 'persistent depressive disorder'/de OR 'chronic depression'/de OR 'dysthymia'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	2	Treatment Resistant Depression (Broad)	('treatment resistant depression'/de OR ((((low OR no OR non OR partial) NEXT/1 respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) NEAR/2 depress*)):ti,ab) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	3	Depressive Disorders (Narrow)	('major depression'/de OR 'depression'/mj OR 'treatment resistant depression'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	4	Telehealth	'online monitoring'/de OR 'teleconference'/de OR 'teleconsultation'/de OR 'telehealth'/exp OR 'telemedicine'/exp OR 'telemonitoring'/de OR 'telephone interview'/exp OR 'telepsychiatry'/de OR 'telepsychotherapy'/de OR 'videoconferencing'/exp OR ("e health*" OR "e care" OR "e consult*" OR "e medicine" OR "e mental" OR "e psych*" OR "e therap*" OR "m health*" OR ((digital OR distan* OR electronic OR mobile OR online OR "on line" OR remote* OR video* OR virtual) NEAR/2 (care OR conference* OR consult* OR monitor* OR health* OR medicine OR psychiatr* OR psycholog* OR psychotherap* OR therap* OR treatment*)) OR (tele NEXT/1 (car* OR coach* OR conferenc* OR consult* OR counsel* OR health OR homecar* OR intervention* OR manag* OR medicine OR monitor* OR psychiatr* OR psycholog* OR psychotherap* OR refer* OR support* OR therap* OR treat* OR visit*)) OR cellphone* OR ecare OR econsult* OR ehealth* OR emedicine* OR emental* OR epsych* OR etherap* OR facetime OR iphone* OR mhealth* OR phone* OR telebehavior* OR telecar* OR smartphone* OR telebehav* OR telecoach* OR teleconferenc* OR teleconsult* OR telecounsel* OR telehealth OR telehomecar* OR teleintervention* OR telemanag* OR telemed* OR telemental* OR telemonitor* OR telephone* OR telerefer* OR telerehab* OR telesupport* OR teletherap* OR teletreat* OR telypsych* OR video* OR zoom):ti,ab
	5	Broad Population Strings & Interventions, limited to systematic reviews or meta-analyses	(#1 OR #2) AND #4 AND review hedge
	6	Narrow Population String & Interventions, limited to randomized controlled trials	#3 AND #4 AND RCT hedge
	7	Combine Results	#5 OR #6
	8	Apply limits, remove unwanted publications types	#8 and limits

Question	Set #	Concept	Strategy
KQ 12 – Utility of Biomarkers	1	Depressive Disorders (broad)	('major depression'/de OR 'depression'/de OR 'persistent depression'/de OR 'persistent depressive disorder'/de OR 'chronic depression'/de OR 'dysthymia'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	2	Treatment Resistant Depression (broad)	('treatment resistant depression'/de OR ((((low OR no OR non OR partial) NEXT/1 respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) NEAR/2 depress*)):ti,ab) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	3	Depressive Disorders (Narrow)	('major depression'/de OR 'depression'/mj OR 'treatment resistant depression'/de OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*):ti) NOT (bipolar*:ti NOT ('depression'/mj OR major*:ti OR mdd:ti OR unipolar*:ti))
	4	General Biomarkers	'biological marker'/mj OR 'pharmacological biomarker'/mj OR (biomarker* OR "bio marker*" OR (biological NEAR/2 (indicator* OR marker*))):ti,ab
	5	Specific Biomarkers and Tests	'electroencephalogram'/exp/mj OR 'functional magnetic resonance imaging'/mj OR 'heart rate variability'/mj OR ("e e g" OR (brain NEAR/3 (activity OR wave*)) OR brainwave* OR eeg OR encephalogram* OR fMRI OR "functional MRI" OR (functional NEAR/5 imag*) OR rsfMRI OR ((cycle OR heart* OR rr) NEAR/3 variability)):ti,ab OR (amplichip* OR genecept* OR genesight* OR idgenetix* OR infiniti* OR millenium* OR neuroidgenetix* OR neuropharmagen* OR (pgx* AND genomind) OR rxmatch* OR spartan*)
	6	Pharmacogentic Markers	'genetic marker'/exp/mj OR 'pharmacogenetic testing'/mj OR 'pharmacogenetics'/mj OR 'pharmacogenomics'/mj OR ((genetic NEAR/2 (indicator* OR marker*)) OR pharmacogenetic* OR pharmacogenomic*):ti,ab
	7	Proteomics	'proteomics'/exp/mj OR ("prote omic*" OR "protein omic*" OR allergenomic* OR chemoproteomic* OR glycoproteomic* OR immunoproteomic* OR metalloproteomic* OR metaproteomic* OR neuroproteomic* OR pharmacoproteomic* OR phosphoproteomic* OR proteinomic* OR proteogenomic* OR proteomic* OR secretomic*):ti,ab
	8	Clinical utility or decision-making (area of interest)	'clinical practice'/de OR 'decision making'/exp OR (clinical NEXT/1 (application* OR benefit* OR decision* OR effectiveness OR impact* OR implication* OR management OR outcome* OR practice OR setting* OR use OR utility)):ti,ab OR "decision making":ti,ab OR (inform* AND (drug* OR medicine OR medicat* OR psychotherapy* OR therap* OR treat)):ti,ab OR "personal utility":ti,ab OR (actionable OR advantag* OR benefi* OR decid* OR decision* OR efficac* OR ((guid* OR select*) AND (drug* OR medicine OR medicat* OR psychotherapy* OR therap* OR treat*)) OR inform OR informing OR role OR practice OR targeted OR use OR useful* OR utility OR valu*):ti
	9	Combine Interventions with Utility	(#4 OR #5 OR #6 OR #7) AND #8
	10	Combine Broad Populations and Interventions and limit to Reviews	(#1 OR #2) AND #9 AND review hedge

Question	Set #	Concept	Strategy
KQ 12 – Utility of Biomarkers (cont.)	11	Combine Narrow Populations and Interventions and limit to RCTs & Diagnostic Studies	#3 AND #9 AND (RCT hedge OR diagnostic study hedge)
	12	Combine results	#10 OR #11
	13	Apply limits, remove unwanted publications types	#12 AND limits
Limits and hedges applied to each search strategy		Hedge to identify RCTs	'random sample'/de OR 'randomized controlled trial'/de OR randomization/de OR (random* OR RCT):ti,ab
		Hedge to identify meta-analyses and SRs	'meta analysis'/exp OR 'systematic review'/de OR [cochrane review]/lim OR systematic*:ti OR (cochrane OR metaanaly* OR “meta analy*” OR (search* AND (databases OR electronic OR methodolog* OR embase* OR ebsco* OR medline* OR ovid* OR sciencedirect* OR scopus* OR systematic OR web)) OR (systematic* NEAR/2 review*)):ti,ab
		Hedge to identify diagnostic accuracy studies	'cohort analysis'/exp OR 'diagnostic test accuracy study'/exp OR accura* OR cohort* OR diagnos* OR detect* OR negative OR positive OR predict* OR reliab* OR sensitiv* OR specific*
		Limit to English language publications	AND [english]/lim
		Exclude animal and experimental studies	NOT (([animals]/lim NOT [humans]/lim) OR (animal* OR experimental OR (vitro NOT vivo) OR canine OR dog OR dogs OR mouse OR mice OR murine:ti OR pig OR pigs OR piglet* OR porcine OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine):ti)
		Exclude studies focusing on children	NOT ((adolescen* OR baby OR babies OR boys OR child* OR girls OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR NICU OR nurser* OR paediatric* OR pediatric* OR preschool* OR school OR schools OR teen* OR toddler* OR youth*) NOT (adult* OR women OR woman OR pregnan*)):ti
		Remove undesired publication and study types (e.g., case reports, conferences, editorials)	NOT ('conference paper'/exp OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR ('case report' OR book OR editorial OR erratum OR letter OR note OR 'short survey')/de OR (book OR conference OR editorial OR erratum OR letter OR note OR 'short survey'):it OR (‘a case’ OR 'year old'):ti,ab OR (book OR 'conference proceeding'):pt OR (‘case report’ OR comment OR ((rationale OR study) NEAR/3 protocol)):ti)
		Limit to items published 2015-2021	AND [2015-2021]/py
		Limit to results added to the database between May 1, 2015, and January 31, 2021	AND [1-5-2015]/sd NOT [31-01-2021]/sd

B. PsycINFO with OVID syntax (all questions)

Question	Set #	Concept	Strategy
KQ 1 – Pharmacotherapies KQ 2 – Adding/changing pharmacotherapies KQ 5 – Adding psychotherapy to pharmacotherapy(ies)	1	Depressive Disorders	(major depression/ OR dysthymic disorder/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti
	2	Treatment Resistant Depression	(treatment resistant depression/ OR ((((low OR no OR non OR partial) ADJ respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) ADJ2 depress*)).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti
	3	Combine Populations	1 OR 2
	4	General Pharmacotherapy (KQ 1)	exp Drug Therapy/ or exp Maintenance Therapy/ or medication-assisted treatment/ or pharmacotherap*.ti. or ((medicine* or medicat* or drug*) adj3 (therap* or treat or treatment*)).ti. or maintenance.ti. or psychopharmacotherap*.ti,ab.
	5	Antidepressants (KQ 1)	antidepressant drugs/ OR ("anti depressant*" OR (antidepress* ADJ2 (drug* OR agent*)) OR antidepressant*).ti,ab.
	6	Second Generation Antidepressants (KQ 1)	("atypical antidepressant*" OR aplenzin* OR trintellix* OR bupropion* OR forfivo* OR mirtazapine* OR nefazodone* OR oleptro* OR remeron* OR trazodone* OR wellbutrin* OR zyban*).ti,ab.
	7	Tricyclic Antidepressants (KQ 1)	exp tricyclic antidepressant drugs/ OR ((tricyclic ADJ2 antidepress*) OR amitriptyline* OR amoxapine* OR anafranil* OR chlorimipramine* OR clomipramine* OR desipramine* OR doxepin* OR imipramine* OR maprotiline* OR mitriptyline* OR norpramin* OR nortriptyline* OR pamelor* OR protriptyline* OR prudoxin* OR silenor* OR surmontil* OR tofranil* OR trimipramine* OR vivactil* OR zonalon*).ti,ab.
	8	Tetracyclic Antidepressants (KQ 1)	((tetracyclic ADJ2 antidepress*) OR beloxepin* OR brexanolone* OR levoprotiline* OR maprotiline* OR mianserin* OR mirtazapine* OR oxaprotiline* OR teciptiline*).ti,ab.
	9	Atypical Antipsychotic (KQ 1)	exp neuroleptic drugs/ OR (antipsychotic* OR abilify* OR alprazolam* OR aripiprazole* OR asenapine* OR brexpiprazole* OR buspirone* OR cariprazine* OR clozapine* OR clozaril* OR fanapt* OR fazaclo* OR geodon* OR iloperidone* OR invega* OR latuda* OR lumateperone* OR lurasidone* OR molindone* OR neuroleptic* OR nialamide* OR olanzapine* OR paliperidone* OR pregabalin* OR quetiapine* OR reserpine* OR risperdal* OR risperidone* OR saphris* OR seroquel* OR spiroperidol* OR sulpiride* OR tetrabenazine* OR tranquiliz* OR tranquilliz* OR triazolam* OR ziprasidone* OR zyprexa*).ti,ab.
	10	MAOIs (KQ 1)	exp monoamine oxidase inhibitors/ OR ("mao inhibit*" OR "mono amine oxidase inhibit*" OR "monoamine oxidase A inhibitor" OR "monoamine oxidase B inhibitor" OR "monoamine oxidase inhibit*" OR "monoaminoxidase inhibit*" OR mao OR maoi OR maois OR azilect* OR eldepryl* OR emsam* OR iproniazid* OR isocarboxazid* OR marplan* OR moclobemide* OR nardil* OR nialamide* OR pargyline* OR parnate* OR phenelzine* OR pheniprazine* OR rasagiline* OR selegiline* OR tranylcypromine*).ti,ab.
	11	Psychostimulants (KQ 1)	exp amphetamine/ OR (psychostimul* OR amphetamine* OR dexamphetamine* OR adderall* OR methylphenidate* OR modafinil*).ti,ab.

Question	Set #	Concept	Strategy
KQ 1 – Pharmacotherapies KQ 2 – Adding/changing pharmacotherapies KQ 5 – Adding psychotherapy to pharmacotherapy(ies) (cont.)	12	SNRIs (KQ 1)	exp serotonin norepinephrine reuptake inhibitors/ OR ("noradrenalin serotonin reuptake inhibitor*" OR "noradrenalin serotonin uptake inhibitor*" OR "norepinephrine serotonin reuptake inhibitor*" OR "norepinephrine serotonin uptake inhibitor*" OR "serotonin and noradrenaline reuptake inhibitor*" OR "serotonin and noradrenaline uptake inhibitor*" OR "serotonin and norepinephrine reuptake inhibitor*" OR "serotonin and norepinephrine uptake inhibitor*" OR "serotonin noradrenalin uptake inhibitor*" OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR ansofaxine* OR cymbalta* OR desvenlafaxine* OR duloxetine* OR effexor* OR fetzima* OR khedezla* OR levomilnacipran* OR milnacipran* OR pristiq* OR savella* OR snri OR snris OR ssnri OR toludesvenlafaxine* OR venlafaxine*).ti,ab.
	13	SSRIs (KQ 1)	exp serotonin reuptake inhibitors/ OR ("serotonin reuptake inhibitor*" OR "serotonin specific reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR brisdelle* OR celexa* OR chlorimipramine* OR citalopram* 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 ssri OR ssris OR viibryd* OR vilazodone* OR vortioxetine* OR zimeldine* OR zoloft*).ti,ab.
	14	Ketamine / esketamine (KQ 1)	ketamine/ OR (esketamine* OR ketamine* OR spravato*).ti,ab.
	15	Experimental Drugs (KQ 1)	exp cannabis/ OR exp cannabinoids/ OR methylenedioxymethamphetamine/ OR psilocybin/ OR ((cbd* ADJ2 oil*) OR bhang* OR cannabi* OR cannador OR charas OR dronabinol OR ganja* OR hashish* OR hemp* OR marihuana OR marijuana OR ecstasy OR mdma OR methylenedioxymethamphetamine OR midomafetamine OR psilocibin* OR psilocin OR psilocybin*).ti,ab.
	16	Drug augmentation (KQ 2)	drug augmentation/ OR (((drug* OR medication* OR pharm*) ADJ5 (augment* OR potentiat* OR synerg*)) OR lithium* OR liothyronine* OR triiodothyronine*).ti,ab.
	17	Drug switching (KQ 2)	((chang* OR switch*) ADJ2 (anti-depress* OR antidepress* OR therap* OR treat*)).ti,ab
	18	Adding Psychotherapy (KQ 5)	(combin* ADJ5 (psychiatr* OR psychoanaly* OR psychodynamic OR psychotherap* OR therap* OR treat*)).ti,ab.
	19	Combine Population & Interventions (KQ 1)	3 AND (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15)
	20	Combine Population & Interventions (KQ 2 & 5)	(1 AND (16 OR 17 OR 18)) OR (2 AND (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18))
	21	Apply limits, remove unwanted publications types, limit to SRs or meta-analyses	#19 AND limits
	22	Apply limits, remove unwanted publications types, limit to RCTs or SRs or meta-analyses	#20 AND limits

Question	Set #	Concept	Strategy
KQ 3 – Psychotherapies KQ 4 – Combining psychotherapies KQ 5 – Adding pharmacotherapies to psychotherapies	1	Depressive Disorders	(major depression/ OR dysthymic disorder/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melancholic*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti
	2	Treatment Resistant Depression	(treatment resistant depression/ OR ((((low OR no OR non OR partial) ADJ respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) ADJ2 depress*)).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti
	3	Combine Populations	1 OR 2
	4	General Psychotherapy (KQ 3)	exp psychotherapy/ OR (psychiatr* OR psychoanaly* OR psychodynamic OR psychotherap*).ti,ab.
	5	Acceptance & Commitment Therapy (KQ 3)	(accept* ADJ2 commitment ADJ2 therap*).ti,ab.
	6	Behavioral Therapy (KQ 3)	exp behavior therapy/ OR ((behavior* OR behaviour* OR conditioning) ADJ2 (activat* OR modification OR therap* OR training OR treatment*)).ti,ab.
	7	Bibliotherapy (KQ 3)	bibliotherapy/ OR poetry therapy/ OR (bibliotherap* OR (poetry ADJ2 (psychotherap* OR therap*))).ti,ab.
	8	Brief Interventions (KQ 3)	brief psychotherapy/ OR (((brief OR short*) ADJ3 (intervention* OR psychotherap* OR therap*)) OR ("time limited" ADJ3 (psychotherap* OR therap*))).ti,ab.
	9	Client-Centered Counseling (KQ 3)	client centered therapy/ OR (("client center*" OR "client centre*" nondirective OR "person center*" OR rogerian) ADJ2 (psychotherap* OR therap*)).ti,ab.
	10	Cognitive behavior therapy (KQ 3)	exp cognitive behavior therapy/ OR ("cognition therap*" OR (cognitive ADJ2 (behavior* OR behaviour*) ADJ2 (therap* OR treatment*)) OR (cognitive ADJ2 (psychotherap* OR therap*)) OR cbt).ti,ab.
	11	Computer-Based CBT (KQ 3)	computer assisted therapy/ OR ((computer* ADJ5 (psychotherap* OR therap* OR train*)) OR cbt4cbt OR ccbt).ti,ab.
	12	Couples therapy (KQ 3)	exp marriage counseling/ OR couples therapy/ OR ((couple* OR marital OR marriage) ADJ2 (counseling OR psychotherap* OR therap*)).ti,ab.
	13	Dialectical behavior therapy (KQ 3)	dialectical behavior therapy/ OR ((dialectical ADJ2 (behavior* or behaviour*)) OR dbt).ti,ab.
	14	Emotion-Focused Therapy (EFT) (KQ 3)	emotion focused therapy/ OR ((emotion* ADJ2 focus*) OR (experiential ADJ3 (psychotherap* OR therap*)) OR eft).ti,ab.
	15	Guided Self-Help (KQ 3)	exp self-help techniques/ OR ((guide* ADJ5 ("self care" OR "self help" OR "self manag*")) OR gsh).ti,ab.
	16	Interpersonal therapy (KQ 3)	interpersonal psychotherapy/ OR (((interpersonal OR 'inter personal') ADJ3 (psychotherap* OR therap*)) OR ipsrt OR ipt OR isrt).ti,ab.
	17	Mindfulness-Basted Therapies (KQ 3)	mindfulness/ OR mindfulness-based interventions/ OR (mbct OR mbsr OR mbt OR micbt OR mindful*).ti,ab.
	18	Motivational Interviewing (KQ 3)	motivational interviewing/ OR (motivational ADJ2 (intervention* OR interview* OR therap*)).ti,ab.
	19	Problem solving (KQ 3)	problem solving/ or ((problem* ADJ3 (therap* or psychotherap*)) or pst).ti,ab.
	20	Short-Term Psychodynamic Psychotherapy (KQ 3)	psychodynamic psychotherapy/ OR ((psychodynamic* ADJ2 (psychotherap* OR therap*)) OR stpp).ti,ab.

Question	Set #	Concept	Strategy
KQ 3 – Psychotherapies KQ 4 – Combining psychotherapies KQ 5 – Adding pharmacotherapies to psychotherapies (cont.)	21	Personalized Medicine (KQ 3)	exp integrative psychotherapy/ OR multimodal treatment approach/ OR precision medicine/ OR (((individuali* OR modular* OR personali*) ADJ3 (medicine OR psychiatr* OR therap* OR treatment*)) OR ((integrat* OR modular* OR multimodal OR "multi modal") ADJ2 (psychotherap* OR therap* OR treatment*)) OR "p health" OR "precision medicine" OR "predictive medicine" OR theranostic*).ti,ab.
	22	STAR*D Trial (KQ 3)	("sequenced treatment alternatives to relieve depression" OR "star d" OR (sequence* ADJ5 (psychotherap* OR therap* OR treatment*))).ti,ab. OR nct00021528.mp.
	23	Combining Therapies (KQ 4)	((chang* OR switch*) ADJ2 (psychiatr* OR psychoanaly* OR psychodynamic OR psychotherap*)).ti,ab.
	24	Adding Pharmacotherapy (KQ 5)	(combin* ADJ5 (anti-depress* OR antidepress* OR drug* OR medicine* OR medicat* OR pharmacotherap*)).ti,ab.
	25	Combine Populations & Interventions (KQ 3)	3 AND (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22)
	26	Combine Populations & Interventions (KQ 4 & 5)	(1 AND (23 OR 24)) OR (2 AND (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24))
	27	Apply limits, remove unwanted publications types, limit to SRs or meta-analyses	25 AND limits
	28	Apply limits, remove unwanted publications types, limit to RCTs or SRs or meta-analyses	26 AND limits
	29	Combine results	27 OR 28
KQ 6 – Complementary & integrative health interventions KQ 7 – Efficacy & safety of physical activity	1	Depressive Disorders	(major depression/ OR dysthymic disorder/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melancholic*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	2	Treatment Resistant Depression	(treatment resistant depression/ OR ((((low OR no OR non OR partial) ADJ respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) ADJ2 depress*)).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	3	Combine Populations	1 OR 2
	4	Acupuncture (KQ 6)	acupuncture/ OR (acupotom* OR acupressure OR acupuncture OR electroacupuncture OR pharmacoacupuncture*).ti,ab.
	5	Biofeedback (KQ 6)	biofeedback/ or biofeedback training/ or neurotherapy/ OR ("bio feed back*" OR "bio feedback*" OR "biofeed back*" OR biofeedback* OR feedback* OR myobiofeedback* OR myofeedback* OR neurobiofeedback* OR neurofeedback*).ti,ab.
	6	Meditation (KQ 6)	meditation/ OR meditat*.ti,ab.
	7	Phototherapy (KQ 6)	phototherapy/ OR (((color OR colour OR illumination OR light OR photoradiation) ADJ2 (therap* OR treatment*)) OR phototherap*).ti,ab.
	8	Tai-chi & Qi gong (KQ 7)	(chi kung OR ch'i kung OR chigung OR qi gong OR tai chi OR t'ai chi OR taichi OR tai ji OR taiji*).ti,ab.
	9	Yoga (KQ 7)	yoga/ OR yoga*.ti,ab.

Question	Set #	Concept	Strategy
KQ 6 – Complementary & integrative health interventions KQ 7 – Efficacy & safety of physical activity (cont.)	10	Wellness & Holistic Health (KQ 6)	health promotion/ OR holistic health/ OR well being/ OR (((alternative* OR complement* OR holistic OR whol*) ADJ2 (health* OR medic* OR therap*OR treatment*)) OR (health ADJ2 promot*) OR "well being" OR wellbeing OR wellness*).ti,ab.
	11	Physical Activity (KQ 7)	dance therapy/ OR dance/ OR exp exercise/ OR exp sports/ OR movement therapy/ OR physical fitness/ OR (((circuit* OR enduranc* OR resistance OR strength OR weight*) ADJ5 (program* OR session* OR train)) OR (activ* ADJ2 life*) OR (aerobic* OR athletic* OR exercis* OR fitness* OR gym* OR kinesitherap* OR sport*) OR (bicycl* OR cycl* OR danc* OR jog* OR pilate* OR row* OR run* OR sprint* OR swim* OR treadmill* OR walk* OR workout*) OR (physical* ADJ5 (activ* OR condition* OR fit* OR movement* OR program* OR train*) OR (work* ADJ1 out))).ti,ab.
	12	Combine Interventions	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
	13	Combine Populations & Interventions	3 AND 12
	14	Apply limits, remove unwanted publications types, limit systematic reviews or meta-analyses	13 AND limits
KQ 8 – Somatic Interventions	1	Depressive Disorders	(major depression/ OR dysthymic disorder/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	2	Treatment Resistant Depression	(treatment resistant depression/ OR ((((low OR no OR non OR partial) ADJ respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) ADJ2 depress*)).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	3	Combine Populations	1 OR 2
	4	Deep Brain Stimulation (DBS)	deep brain stimulation/ OR (brain ADJ5 (excitation OR stimul*)).ti,ab.
	5	Electroconvulsive Therapy (ECT)	electroconvulsive shock therapy/ OR exp electrical stimulation/ OR ((electr* ADJ3 (stimul* OR therap* OR treatm*)) OR ces OR ecs OR ect OR electrotherap*).ti,ab.
	6	Transcranial Magnetic Stimulation (TMS)	transcranial magnetic stimulation/ OR ((transcranial ADJ3 (electromagnet* OR "electro magnet*" OR magnet*)) OR rtms OR tms).ti,ab.
	7	Vagus Nerve Stimulation (VNS)	nerve stimulation/ OR vagus nerve/ OR (tvns OR vagal* OR vagus* OR vns).ti,ab.
	8	Combine Interventions	4 OR 5 OR 6 OR 7
	9	Combine Populations & Interventions	3 AND 8
	10	Apply limits, remove unwanted publications types, limit to RCTs or SRs or meta-analyses	9 AND limits

Question	Set #	Concept	Strategy
KQ 9 – Measurement Based Care	1	Depressive Disorders	(major depression/ OR dysthymic disorder/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melancholl*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	2	Treatment Resistant Depression	(treatment resistant depression/ OR ((((low OR no OR non OR partial) ADJ respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) ADJ2 depress*)).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	3	Measurement-based Care (Specific)	((measurement ADJ3 based) OR "routine outcome monitor*" OR (structur* ADJ3 monitor*)).ti,ab.
	4	Combine Broad Populations and MBC (Specific)	(1 OR 2) AND 3
	5	Depressive Disorders (Narrow)	(major depression/ OR treatment resistant depression/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melancholl*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	6	General MBC Tools	*patient reported outcome measures/ OR exp *psychological assessment/ OR exp *psychometrics/ OR *"quality of life measures"/ OR exp *questionnaires/ OR *rating/ OR exp *rating scales/ OR *self-monitoring/ OR (assessment* OR index* OR instrument* OR measure* OR prom OR proms OR questionnaire* OR scale OR scales OR tool*).ti.
	7	Named MBC Tools	("brief addiction monitor" OR bam OR "camberwell assessment" OR cansas OR "client satisfaction questionnaire" OR csq OR "depression anxiety stress scale" OR euroqol quality of life scale OR "eq 5d 5l" OR euroqol OR ("european quality of life" ADJ6 questionnaire) OR "generalized anxiety disorder 7" OR "gad 7" OR "hamilton depression rating scale" OR "ham d" OR "manchester short assessment" OR mansa OR "outcome questionnaire 45" OR "oq 45" OR "outcome rating scale" OR ors OR "partners for change outcomes" OR pcoms OR "patient health questionnaire" OR "phq" OR "positive and negative syndrome scale" OR "positive and negative syndrome score" OR panss OR "quick inventory of depressive symptom*" OR "qids sr" OR "session rating scale" OR srs OR "standard for clinicians interview" OR scip OR "symptom checklist 90" OR "who five well*" OR "who 5").ti,ab,tm.
	8	Progress Monitoring & Informing Treatment	exp clinical practice/ OR exp decision making/ OR (clinical ADJ (application* OR benefit* OR decision* OR effectiveness OR impact* OR implication* OR management OR outcome* OR practice OR setting* OR "use" OR utility)).ti,ab. OR "decision making".ti,ab. OR (inform* AND (drug* OR medicine OR medicat* OR psychotherapy* OR therap* OR treat)).ti,ab. OR "personal utility".ti,ab. OR (actionable OR advantag* OR benefi* OR decid* OR decision* OR efficac* OR ((guid* OR select*) AND (drug* OR medicine OR medicat* OR psychotherapy* OR therap* OR treat*)) OR inform OR informing OR outcome* OR role OR practice OR targeted OR "use" OR "useful*" OR utility OR valu*).ti.
	9	Provider/Patient Feedback	(exp counseling/ OR exp physicians/ OR exp psychologists/ OR exp psychotherapists/ OR exp psychotherapy/ OR exp treatment outcomes/) AND (exp feedback/ OR exp monitoring/ OR self-report/ OR ("feed back" OR feedback OR (symptom ADJ2 monitor*)).ti,ab.)
	10	Provider/Patient Feedback	((physician* OR psychiatri* OR psychotherapist* OR therapist* OR "primary care" OR "general practi*" OR psychologist*) AND ((client* OR patient* OR oupatient*) ADJ5 ("feed back" OR feedback OR monitor*))).ti,ab.

Question	Set #	Concept	Strategy
KQ 9 – Measurement Based Care (cont.)	11	Provider/Patient Outcomes	((physician* OR psychiatri* OR psychotherapist* OR therapist* OR "primary care" OR "general practi*") AND ("patient reported" ADJ3 (information OR outcome* OR symptom*))).ti,ab.
	12	Therapy Outcomes	((therap* OR psychotherap*) AND ("feed back" OR feedback OR (patient* AND (reported ADJ3 (information OR outcome* OR symptom*))))).ti,ab.
	13	Other MBC Interventions	((6 OR 7) AND 8) OR 9 OR 10 OR 11 OR 12
	14	Combine Other MBC Interventions & Narrow Population String	5 AND 13
	15	Combine All MBC results	4 OR 14
	16	Apply limits, remove unwanted publications types, limit to RCTs or SRs or meta-analyses	15 AND limits
KQ 10 – Collaborative Care	1	Depressive Disorders	(major depression/ OR dysthymic disorder/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melanchol*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	2	Treatment Resistant Depression	(treatment resistant depression/ OR ((((low OR no OR non OR partial) ADJ respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) ADJ2 depress*)).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	3	Combine Populations	1 OR 2
	4	Collaborative Care Terms, controlled	case management/ OR collaboration/ OR cooperation/ OR exp Interdisciplinary Treatment Approach/ OR exp teams/ OR integrated services/ OR patient centered care/ OR teamwork/
	5	Collaborative Care Terms, keywords	("team work" OR "complex intervention*" OR "cooperative behav*" OR "joint work*" OR "inter disciplin*" OR "inter professional*" OR "multi intervention*" OR "multi profession*" OR "multiple intervention*" OR ((care OR case) ADJ manag*) OR ((collaborat* OR coordinat* OR "co ordinat*" OR integrat* or stepped*) ADJ2 (care OR effort* OR health* OR inteven* OR manag* OR model* OR service* OR team* OR work*)) OR ((multidisciplinary OR "multi disciplinary") ADJ2 team*) OR "trans disciplin*" OR (integrated ADJ3 (deliver* OR health*))).ti,ab. OR ("inter disciplin*" OR "inter professional*" OR "multi disciplin*" OR "multi profession*" OR "team work" OR "trans disciplin*" OR interdisciplin* OR interprofessional* OR multidisciplin* OR multiprofession* OR teams OR teamwork OR transdisciplin*).ti. OR (("primary care" ADJ5 ("behavioral health*" OR "behavioural health*" OR "mental health integrat*")) OR (pcbh OR pcmhi OR "pc mhi")).mp.
	6	Combine Interventions	4 OR 5
	7	Combine Populations & Interventions	3 AND 6
	8	Apply limits, remove unwanted publications types, limit to randomized controlled trials or systematic reviews or meta-analyses	7 AND limits

Question	Set #	Concept	Strategy
KQ 11 – Telehealth Interventions	1	Depressive Disorders (Broad)	(major depression/ OR dysthymic disorder/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melancholic*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	2	Treatment Resistant Depression (Broad)	(treatment resistant depression/ OR ((((low OR no OR non OR partial) ADJ respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) ADJ2 depress*)).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	3	Depressive Disorders (Narrow)	(major depression/ OR treatment resistant depression/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melancholic*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	4	Telehealth	exp computer assisted therapy/ OR exp digital interventions/ OR exp electronic health services/ OR exp teleconferencing/ OR exp telemedicine/ OR exp telephone surveys/ OR mobile health/ OR mobile phones/ OR online therapy/ OR teleconsultation/ OR telepsychiatry/ OR telepsychology/ OR video-based interventions/ OR videoconferencing/ OR ("e health*" OR "e care" OR "e consult*" OR "e medicine" OR "e mental" OR "e psych*" OR "e therap*" OR "m health*" OR ((digital OR distan* OR electronic OR mobile OR online OR "on line" OR remote* OR video* OR virtual) ADJ2 (care OR conference* OR consult* OR monitor* OR health* OR medicine OR psychiatr* OR psycholog* OR psychotherap* OR therap* OR treatment*)) OR (tele ADJ (car* OR coach* OR conferenc* OR consult* OR counsel* OR health OR homecar* OR intervention* OR manag* OR medicine OR monitor* OR psychiatr* OR psycholog* OR psychotherap* OR refer* OR support* OR therap* OR treat* OR visit*)) OR cellphone* OR ecare OR econsult* OR ehealth* OR emedicine* OR emental* OR epsych* OR etherap* OR facetime OR iphone* OR mhealth* OR phone* OR telebehavior* OR telecar* OR smartphone* OR telebehav* OR telecoach* OR teleconferenc* OR teleconsult* OR telecounsel* OR telehealth OR telehomecar* OR teleintervention* OR telemanag* OR telemed* OR telemental* OR telemonitor* OR telephone* OR telerefer* OR telerehab* OR telesupport* OR teletherap* OR teletreat* OR telypsych* OR video* OR zoom).ti,ab.
	5	Broad Population Strings & Interventions, Limited to SRs or meta-analyses	(1 OR 2) AND 4 AND review hedge
	6	Narrow Population String & Interventions, Limited to RCTs	3 AND 4 AND RCT hedge
	7	Combine Results	5 OR 6
	8	Apply limits, remove unwanted publications types	7 AND limits

Question	Set #	Concept	Strategy
KQ 12 – Utility of Biomarkers	1	Depressive Disorders (Broad)	(major depression/ OR dysthymic disorder/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melancholic*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	2	Treatment Resistant Depression (Broad)	(treatment resistant depression/ OR ((((low OR no OR non OR partial) ADJ respon*) AND depress*) OR ((nonrespon* OR recurr* OR refractory OR relaps* OR resistant) ADJ2 depress*)).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	3	Depressive Disorders (Narrow)	(major depression/ OR treatment resistant depression/ OR (depress* OR dysphor* OR dysthymi* OR mdd OR melancholic*).ti,ab.) NOT (bipolar* NOT (major* OR mdd OR unipolar*)).ti.
	4	General Biomarkers	*biological markers/ OR (biomarker* OR "bio marker*" OR (biological ADJ2 (indicator* OR marker*))).ti,ab.
	5	Specific Biomarkers	*functional magnetic resonance imaging/ OR *heart rate variability/ OR exp *electroencephalography/ OR ("e e g" OR (brain ADJ3 (activity OR wave*)) OR brainwave* OR eeg OR encephalogram* OR fMRI OR "functional MRI" OR (functional ADJ5 imag*) OR rsfMRI OR ((cycle OR heart* OR rr) ADJ3 variability)).ti,ab. OR (amplichip* OR genecept* OR genesight* OR idgenetix* OR infiniti* OR millenium* OR neuroidgenetix* OR neuropharmagen* OR (pgx* AND genomind) OR rxmatch* OR spartan*)
	6	Pharmacogentic Markers	*genetic testing/ OR ((genetic ADJ2 (indicator* OR marker*)) OR pharmacogenetic* OR pharmacogenomic*).ti,ab.
	7	Proteomics	exp *Proteomics/ OR ("prote omic*" OR "protein omic*" OR allergenomic* OR chemoproteomic* OR glycoproteomic* OR immunoproteomic* OR metalloproteomic* OR metaproteomic* OR neuroproteomic* OR pharmacoproteomic* OR phosphoproteomic* OR proteinomic* OR proteogenomic* OR proteomic* OR secretomic*).ti,ab.
	8	Clinical utility or decision-making (area of interest)	exp clinical practice/ OR exp decision making/ OR (clinical ADJ (application* OR benefit* OR decision* OR effectiveness OR impact* OR implication* OR management OR outcome* OR practice OR setting* OR "use" OR utility)).ti,ab. OR "decision making".ti,ab. OR (inform* AND (drug* OR medicine OR medicat* OR psychotherapy* OR therap* OR treat)).ti,ab. OR "personal utility".ti,ab. OR (actionable OR advantag* OR benefi* OR decid* OR decision* OR efficac* OR ((guid* OR select*) AND (drug* OR medicine OR medicat* OR psychotherapy* OR therap* OR treat*)) OR inform OR informing OR role OR practice OR targeted OR "use" OR "useful*" OR utility OR valu*).ti.
	9	Combine Interventions with Utility	(4 OR 5 OR 6 OR 7) AND 8
	10	Combine Broad Populations and Interventions and limit to Reviews	(1 OR 2) AND 9 AND review hedge
	11	Combine Narrow Populations and Interventions and limit to RCTs & Diagnostic Studies	3 AND 9 AND (RCT hedge OR diagnostic study hedge)
	12	Combine results	10 OR 11
	13	Apply limits, remove unwanted publications types	12 AND limits

Question	Set #	Concept	Strategy
Limits and hedges applied to each search strategy		Hedge to identify RCTs	random sampling/ OR (random* OR rct).ti,ab.
		Hedge to identify meta-analyses and SRs	meta analysis/ OR systematic review/ OR systematic.ti. OR (cochrane OR "meta analy*" OR metaanaly* OR (search* AND (databases OR electronic OR methodolog* OR embase* OR ebsco* OR medline* OR ovid* OR sciencedirect* OR scopus* OR systematic OR web)) OR (systematic ADJ3 review)).ti,ab.
		Hedge to identify diagnostic accuracy studies	cohort analysis/ OR accura* OR cohort* OR diagnos* OR detect* OR negative OR positive OR predict* OR reliab* OR sensitiv* OR specific*
		Limit to English language publications	limit to english language
		Exclude animal and experimental studies	NOT (animal* OR experimental OR (vitro NOT vivo) OR canine OR dog OR dogs OR mouse OR mice OR murine OR pig OR pigs OR piglet* OR porcine OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine).ti.
		Exclude studies focusing on children	NOT ((adolescen* OR baby OR babies OR boys OR child* OR girls OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR NICU OR nurser* OR paediatric* OR pediatric* OR preschool* OR school OR schools OR teen* OR toddler* OR youth*) NOT (adult* OR women OR woman OR pregnan*)).ti.
		Remove undesired publication and study types (e.g., case reports, conferences, editorials)	NOT ((chapter OR "column/opinion" OR "comment/reply" OR dissertation OR editorial OR letter OR review-book).dt. OR (book or encyclopedia OR "dissertation abstract").pt. OR ("case report" OR "a case" OR "year old").ti,ab. OR ((rationale OR study) ADJ3 protocol).ti.)
		Limit to items published 2015-2021	limit to yr="2015 - 2021"
		Limit to results added to the database between May 1, 2015, and January 31, 2021	limit to up=20150501-20210131
		Identify all items included in MEDLINE	(1* or 2* or 3* or 4* or 5* or 6* or 7* or 8* or 9*).pm.
		Remove MEDLINE citations	

Appendix G: Alternative Text Descriptions of Algorithm

The following outline narratively describes the Management of MDD CPG Algorithm. An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the Algorithm section. The sidebars referenced within this outline can also be found in the Algorithm section.

Module A: Initial Assessment and Treatment

1. The algorithm begins with Box 1, in the shape of a rounded rectangle: "Patient with suspected depression or is positive on a depression screen"
2. Box 1 connects to Box 2, in the shape of a rectangle: "Risk assessment and diagnostic work-up including the use of MBC (see **Sidebar 1**)"
3. Box 2 connects to Box 3, in the shape of a hexagon, asks the question: "Is there an acute patient safety risk?"
    a. If the answer is "Yes" to Box 3, then Box 4, in the shape of a rectangle: "Inpatient or emergent care to stabilize"
        i. Box 4 connects to Box 5, in the shape of a rectangle: "After stabilization, re-enter the algorithm at **Box 7** or **Box 18**, as appropriate"
    b. If the answer is "No" to Box 3, then Box 6
4. Box 6, in the shape of a hexagon, asks the question: "Does the patient meet diagnostic criteria for MDD (see **Sidebar 2**)?"
    a. If the answer is "Yes" to Box 6, then Box 7, in the shape of a hexagon, asks the question: "Is this uncomplicated MDD or a restart of successful treatment (see **Sidebar 3**)?"
        i. If the answer is "Yes" to Box 7, then Box 9, in the shape of a rectangle: "Develop and initiate individual treatment plan using SDM and considering patient preference (see **Sidebar 4**)"
            1. Box 9 connects to Box 10
        ii. If the answer is "No" to Box 7, then Box 14, in the shape of a circle: "Go to **Module B**"
    b. If the answer is "No" to Box 6, then Box 8, in the shape of a circle: "Exit algorithm and treat as indicated"
5. Box 10, in the shape of a rectangle: "Monitor outcomes of treatment"
6. Box 10 connects to Box 11, in the shape of a hexagon, asks the question: "Remission or patient's goals met?"
    a. If the answer is "Yes" to Box 11, then Box 12, in the shape of a rectangle: "Determine completion, continuation, maintenance of relapse prevention strategies"
    b. If the answer is "No" to Box 11, then Box 13

7. Box 13, in the shape of a rectangle: "Reassess diagnosis and/or treatment plan"
    a. Box 13 connects to Box 6

Module B: Advanced Care Management

1. The algorithm begins with Box 15, in the shape of a circle: "Enter from **Module A**"
2. Box 15 connects to Box 16, in the shape of a hexagon, asks the question: "Should the patient be in specialty MH care if not already?"
    a. If the answer is "Yes" to Box 16, then Box 17, in the shape of a circle: "Refer and engage in specialty MH care"
    b. If the answer is "No-N/A" to Box 16, then Box 18
3. Box 18, in the shape of a hexagon, asks the question: "Has patient had previous adequate treatment trials?"
    a. If the answer is "Yes" to Box 18, then Box 19, in the shape of a rectangle: "Choose other treatment (based on patient preferences and characteristics) (see **Sidebar 5**)"
        i. If the "Patient agrees" to Box 19, then Box 24, in the shape of a rectangle: "Initiate treatment"
            1. Box 24 connects to Box 29
        ii. If the "Patient declines" to Box 19, then Box 25, in the shape of a rectangle: "Discuss treatment goals with patient and adjust monitoring/follow-up as appropriate"
            1. Box 25 connects to Box 29
    b. If the answer is "No" to Box 18, then Box 20
4. Box 20, in the shape of a hexagon, asks the question: "Is the current psychotherapy and/or pharmacotherapy adequately administered?"
    a. If the answer is "Yes" to Box 20, then Box 21, in the shape of a hexagon: "Choose a switch or augment strategy (see **Sidebar 6**)"
        i. If the "Patient agrees" to Box 21, then Box 22, in the shape of a rectangle: "Implement strategy"
            1. Box 22 connects to Box 29
        ii. If the "Patient declines" to Box 21, then Box 23, in the shape of a rectangle: "Discuss treatment goals with patient and adjust monitoring/follow-up as appropriate"
            1. Box 23 connects to Box 29
    b. If the answer is "No" to Box 20, then Box 26
5. Box 26, in the shape of a rectangle: "Discuss with patient need to treat with fidelity or switch treatments"

6. Box 26 connects to Box 27, in the shape of a hexagon, asks the question: "Is the patient willing to maximize current treatment?"
    a. If the answer is "Yes" to Box 27, then Box 28, in the shape of a rectangle: "Maximize treatment"
        i. Box 28 connects to Box 29
    b. If the answer is "No" to Box 27, then Box 21
7. Box 29, in the shape of a rectangle: "Monitor outcomes of treatment"
8. Box 29 connects to Box 30, in the shape of a hexagon, asks the question: "Remission or patient's goals met?"
    a. If the answer is "Yes" to Box 30, then Box 31, in the shape of a rectangle: "Determine completion, continuation, maintenance or relapse prevention strategies (see **Sidebar 7**)"
    b. If the answer is "No" to Box 30, then Box 32, in the shape of a rectangle: "Reassess diagnosis and/or treatment plan"
        i. Box 32 connects to Box 16

Appendix H: Abbreviations

Abbreviation	Definition
BA	behavioral activation
BCT	behavioral couples therapy
CBT	cognitive behavioral therapy
CI	confidence intervals
COI	conflict of interest
DEA	U.S. Drug Enforcement Administration
DoD	U.S. Department of Defense
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBPWG	Evidence-Based Practice Work Group
ECT	electroconvulsive therapy
FDA	U.S. Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSH	guided self-help
IOM	Institute of Medicine
ITT	intent to treat
KQ	key question
MAOI	monoamine oxidase inhibitors
MBC	measurement-based care
MDD	major depressive disorder
NDSP	non-directive supportive therapy
PGx	pharmacogenetic
PHQ	Patient Health Questionnaire
PICOTS	population, intervention, comparison, outcome, timing, and setting
PST	problem-solving therapy
PTSD	posttraumatic stress disorder
QoL	quality of life
RCT	randomized controlled trial
SGA	second-generation antipsychotic
SNRI	serotonin-norepinephrine reuptake inhibitors
SR	systematic review
SSRI	selective serotonin uptake inhibitors
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
STPP	short-term psychodynamic psychotherapy
SUD	substance use disorders
TAU	treatment as usual
TCA	tricyclic antidepressants
TMS	transcranial magnetic stimulation
TRD	treatment-resistant depression

Abbreviation	Definition
U.S.	United States
VA	U.S. Department of Veterans Affairs
VHA	Veterans Health Administration
VNS	vagus nerve stimulation

Appendix I: Quick Guide to the Patient Health Questionnaire in Clinical Practice

A. Purpose

The PHQ facilitates the recognition and diagnosis of depressive disorders.(221) The PHQ-2 functions 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.(222) Although the instrument can be used to align with diagnostic criteria, it 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).

The PHQ-9 can also be used as a continuous measure of severity in the practice of MBC. Measurement-based care emphasizes the use of assessments to help personalize care and guide treatment decisions. As a standard part of clinical care, it aids in identifying intervention targets, assessing progress over time, and guiding treatment decisions. Measurement-based care also has a positive impact on the clinical relationship between patient and provider by validating the patient's experience, empowering them as an active partner in their overall wellness, and prioritizing what matters most to the patient regarding their care.

B. Scoring the PHQ-9 (223)

a. PHQ-9 Scoring Instructions

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. A blank assessment can be found in Table I-1, while an example of this scored assessment can be found in Table I-3.

Table I-1. 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 of these challenges, how difficult (not difficult at all, somewhat difficult, very difficult, extremely difficult) have these issues made it for you to perform your work, manage your domestic life, or negotiate social dynamics with other people?

b. 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 two weeks, how often have you been bothered by any of the following?" Scores of 10, 15, and 20 represent cut-points for mild, moderate, and severe MDD, respectively (see Table I-2). A score of 10 or more has a sensitivity of 88% and a specificity of 88% for MDD.(28) All clinically significant responses are found in the column farthest to the right in the PHQ-9.

Table I-2. Classification of MDD Symptoms Severity

Severity Level	PHQ-9 Total Score	Number of Symptoms According to DSM-5	Functional Impairment
Mild	10 – 14	5	Mild
Moderate	15 – 19	6 to 7	Moderate
Severe	≥20	8 to 9	Severe

Note that these cut scores related to classification of MDD. Another use of the PHQ-9 is as a marker of severity of depressive symptoms. The cut scores as a marker of severity of symptoms is 0-5 none, 6-9 mild, 10-15 moderate, 16 and above severe. This addresses two different uses of the instrument.

Abbreviations: DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

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

Since the questionnaire relies on patient self-reporting, the clinician must verify the definitive diagnosis, whereby considering how well the patient understood the questions in the questionnaire as well as other relevant information from the patient, support network, or other sources. While the PHQ-9 can be used to supplement the clinical exam, the use of the PHQ-9 as a diagnostic tool is discouraged.

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

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.(51)

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 (Table I-1 and Table I-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.

C. Using the PHQ-9 in Measurement-Based Care

Enhancing the clinical partnership leads to improved collaboration between patient and provider regarding next steps in care as MBC helps create a shared language to discuss treatment. The tenets of MBC include collect, share, and act.

a. Collect

Routine collection of the PHQ-9 is relevant to treatment as it aids in the management of depression and engages the patient in their care from the very start. When discussing the use of PHQ-9 with patients, it is important to communicate the rationale of MBC, the process of regular administration, as well as the information that will be gained towards the identification of treatment goals and targets. After initiation of therapy or a change in treatment, providers should monitor patients at least monthly to track response/progress. At a minimum, assessments should include the PHQ-9, adherence to the medication and psychotherapy treatment plan, and emergence of adverse effects.

b. Share

Sharing results of PHQ-9 with a patient facilitates a discussion regarding their subjective experiences with depression and any potential discrepancies that may impact the achievement of their healthcare goals. This also provides an opportunity to educate on depression symptoms, clarify any misunderstandings regarding the questions being asked in PHQ-9, and discuss progress towards treatment goals. Using graphs is an important way to share information with patients regarding how their symptoms are progressing and how they are doing over time.

Documentation of the results into the medical record is a vital step in the sharing process. Not only does it allow for tracking of scores over time for the episode of care, but it also benefits other providers of the care team who are working with the patient, again providing a universal language of symptom changes.

c. Act

Data collected from the PHQ-9 is used to inform the next steps in care in collaboration with the patient's input regarding their goals for wellness. In reviewing the scores, providers can offer personalized treatment intervention options and engage patients in shared decision making to determine the next steps in care. See Recommendations for details on the treatment for uncomplicated mild to moderate MDD (PHQ-9 score of 10 – 19) and the treatment of severe, chronic, or recurrent MDD (PHQ-9 score >20) at initial assessment as well as guidance regarding the use of PHQ-9 scores in determining partial response, remission, and recovery.

D. Example of Using the PHQ-9 in Clinical Practice

The following is an example of how MDD can be assessed in a patient using the PHQ-9 for a presumptive diagnosis to calculate depression severity and symptom monitoring over time.

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

Table I-3. PHQ-9 Screening Example

Over the last 2 weeks, how often have you been bothered by any of the following?		Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (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. Utilizing 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 I-3. Note that #i, suicidal ideation, is counted whenever indicated.

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.

As part of the treatment plan, the provider would explain the rationale of MBC and repeat the PHQ-9, regularly. At each collection point, the provider would share with the patient their progress over time, as an educational tool when reviewing with the patient. In collaboration with the patient, the provider would engage in shared decision making to identify target goals, discuss treatment interventions (e.g., change in medication, change in psychotherapy), and assess next steps in care, including developing a maintenance plan if scores indicate clinically significant recovery. Special attention should be given to item nine at each collection point to determine the need for further risk assessment and/or safety planning.

E. Additional Clinical Considerations

After completing a provisional diagnosis with the PHQ-9, additional clinical considerations exist that may shape management and treatment options.(224)

- Has a psychosocial stressor(s) triggered current symptoms?
- What is the duration of the current disturbance, and has the patient received any treatment for it?
- To what extent are the symptoms of the patient impairing their capacity to complete daily work and life duties and responsibilities?
- Is there a history of similar episodes, and were they treated?
- Is there a family history of similar conditions?(225)

Appendix J: Pharmacotherapy

Table J-1. Antidepressant Dosing and Monitoring[a,b]

Class	Agent	Initial Dose	Titration Schedule	Max. Dose/day	Initial Dose or Guidance: Special Populations		
					Geriatric	Renal	Hepatic
SSRIs	Citalopram	20 mg once daily	20 mg weekly	40 mg; 20 mg geriatric	10-20 mg once daily	CrCl <20 ml/min: 10 mg daily	10-20 mg daily
	Escitalopram	10 mg once daily	10 mg weekly	20 mg	5-10 mg once daily	CrCl <20 ml/min: 5 mg daily	5-10 mg once daily
	Fluoxetine	20 mg once daily	20 mg every 2 weeks	80 mg	10 mg once daily	↓ dose and/or ↓ frequency	↓ dose 50%
	Fluoxetine weekly	90 mg once a week	N/A	90 mg	90 mg once a week	No change	Avoid
	Paroxetine	20 mg once daily	10-20 mg weekly	50 mg; 40 mg geriatric	10 mg once daily	10 mg once daily	10 mg once daily
	Paroxetine CR	25 mg once daily	12.5 mg weekly	62.5 mg; 50 mg geriatric	12.5 mg; once daily	12.5 mg once daily	12.5 mg once daily
	Sertraline	50 mg once daily	25-50 mg weekly	200 mg	25 mg once daily	No change	↓ dose 50%/avoid
	Vilazodone	10 mg once daily	10 mg weekly	20-40 mg	10 mg	No change	No change
	Vortioxetine	5-10 mg once daily	5-10 mg weekly	20 mg	5-10 mg once daily	No change	No change
SNRIs	Desvenlafaxine	50 mg once daily	Unnecessary	100 mg; no additional benefit at doses >50 mg per day	Consider CrCl	CrCl <30 ml/min, 25 mg once daily	50 mg once daily
	Duloxetine	20-30 mg twice daily	20-30 mg weekly	120 mg; no additional benefit at doses >60 mg per day	20 mg once or twice daily	Avoid if CrCl <30 ml/min	Avoid

[a] All doses oral except selegiline patch, esketamine nasal, ketamine infusion
[b] Titration Schedule column: Recommended minimum time between dose increases

Class	Agent	Initial Dose	Titration Schedule	Max. Dose/day	Initial Dose or Guidance: Special Populations		
					Geriatric	Renal	Hepatic
SNRIs (cont.)	Levomilnacipran	20 mg once daily	20-40 mg every 2 days	120 mg	Refer to adult dosing, consider CrCl	Max doses less if CrCl <60 ml/min	No change
	Venlafaxine IR	37.5 mg once or twice daily	75 mg weekly	375 mg	37.5 mg once or twice daily	↓ dose based on CrCl	↓ dose 50%
	Venlafaxine XR	37.5-75 mg once daily	75 mg weekly	225 mg	37.5-75 mg once daily	↓ dose based on CrCl	↓ dose 50%
NDRIs	Bupropion IR	100 mg twice daily	100 mg weekly	150 mg three times daily	Refer to adult dosing	Max dose 150 mg/day	Severe: 75 mg/day
	Bupropion SR	150 mg once daily	150 mg weekly	200 mg twice daily	Refer to adult dosing		100 mg once daily or 150 mg every other day; Mod to severe: use with extreme caution
	Bupropion XR	150 mg once daily	150 mg weekly	450 mg	Refer to adult dosing		
5-HT2 receptor antagonist	Trazodone	50 mg three times daily	50 mg weekly to usual dosage range of 200-400 mg per day	600 mg	25-50 mg at bedtime	No change	Unknown
	Nefazodone	100 mg twice daily	100 mg weekly	600 mg	50 mg twice daily	No change	Avoid
Noradrenergic antagonist	Mirtazapine	15 mg daily at bedtime	15 mg weekly	45 mg	7.5 mg at bedtime	CrCl <30 ml/min, 7.5-15 mg once daily	↓ dose 50%
TCAs	Amitriptyline	25-50 mg daily single dose at bedtime or in divided doses	25-50 mg weekly	300 mg	10-25 mg at bedtime	No change	Lower dose and slower titration recommended
	Amoxapine	25-50 mg 1-3 times daily	25-50 mg weekly	600 mg	25 mg 2-3 times daily	No change	
	Clomipramine	12.5-50 mg daily at bedtime	50 mg every 1-3 days	250 mg	Refer to adult dosing	No change	

Class	Agent	Initial Dose	Titration Schedule	Max. Dose/day	Initial Dose or Guidance: Special Populations		
					Geriatric	Renal	Hepatic
TCAs (cont.)	Desipramine	25-50 mg once daily or in divided doses	25-50 mg weekly	300 mg; 150 mg geriatric	10-25 mg once daily	No change	Lower dose and slower titration recommended
	Doxepin	25-50 mg daily at bedtime	25-50 mg weekly	300 mg	Low dose, once daily	No change	
	Imipramine	25 mg 1-4 times daily	25-50 mg weekly	300 mg	10-25 mg at bedtime	No change	
	Nortriptyline	25 mg once daily	25-50 mg weekly	150 mg	10-25 mg/day	No change	
	Protriptyline	10-20 mg daily in divided doses	10-20 mg weekly in divided doses	60 mg	5 mg three times daily	No change	
	Trimipramine	25-50 mg at bedtime or in divided doses	25-50 mg weekly	300 mg	12.5-50 mg/day	No change	
MAOIs	Isocarboxazid	10 mg twice daily	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 daily	Avoid in any renal impairment; contraindicated in severe	Contraindicated in patients with a history of liver disease or abnormal LFTs
	Phenelzine	15 mg 3 times daily	Increase rapidly, based on patient tolerance, to 60-90 mg/day	90 mg; 60 mg geriatric	7.5 mg once daily	Contraindicated in severe	Contraindicated
	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
	Tranylcypromine	10-30 mg/day in divided doses	10 mg every 1-3 weeks	60 mg	10 mg twice daily	Use caution	Use caution

Class	Agent	Initial Dose	Titration Schedule	Max. Dose/day	Initial Dose or Guidance: Special Populations		
					Geriatric	Renal	Hepatic
NMDA Antagonists	Esketamine	56-84 mg intranasally twice weekly for 4 weeks in conjunction with an oral antidepressant	56-84 mg weekly or every 2 weeks	84 mg	28-84 mg twice weekly for 4 weeks	No change in PK parameters	Severe; avoid
	Ketamine	0.5 mg/kg infusion over 40 min 2-3 times weekly	Weekly	1 mg/kg	Refer to adult dosing	No change	No change

Note that for individuals with reproductive potential or who are lactating, please see FDA guidance.

Abbreviations: 5-HT: serotonin; CR: controlled release; CrCl: creatinine clearance; IR: immediate release; kg: kilograms; LFT: liver function test; MAOI: monoamine oxidase inhibitor; max: maximum; mg: milligrams; min: minutes; ml: milliliters; N/A: not applicable; NMDA: N-methyl-D-aspartate; NDRI: norepinephrine and dopamine reuptake inhibitor; PK: pharmacokinetic; SNRI: serotonin-norepinephrine reuptake inhibitor; SR: sustained-release; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; XR: extended-release

Table J-2. Antidepressant Adverse Event Profiles

Drug Class or Drug	Amine Reuptake Inhibitor		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/+	• Sexual dysfunction common • Citalopram and escitalopram dose-related conduction effects • Paroxetine most anticholinergic; avoid in elderly • Paroxetine and fluoxetine CYP2D6 inhibitor
SNRIs	++/+++	++/+++	0/+	0/+	0/++	0/+	++/+++	0/+	• Sexual dysfunction common • Venlafaxine norepinephrine activity dose-related • Desvenlafaxine active metabolite of venlafaxine • Withdrawal syndrome
Bupropion	0/+	0/+	0	0	0	0/+	+	0	• Risk of seizures is dose-related; avoid if seizure history, bulimia, or eating disorder • CYP2D6 inhibitor
Trazodone, Nefazodone	+++	0/+	0/+	++/+++	0/+	0/+	+	0/+	• Very sedating • Nefazodone is associated witha higher risk of hepatotoxicity • Nefazodone CYP3A4 inhibitor
Mirtazapine	0/+	0/+	0	+++	0/+	0/+	0/+	++	• Doses >15 mg less sedating • May stimulate appetite

Drug Class or Drug	Amine Reuptake Inhibitor		Anti-cholinergic Activity	Sedation (H1 activity)	Orthostatic Hypotension (alpha-1 act.)	Cardiac Conduction Effects	GI Effects	Weight Gain	Comments
	5HT	NE							
Vortioxetine	+++	++	0	0	0	0/+	+++	0	• Sexual dysfunction common
TCAs	+/+++	+/+++	+/+++	0/+++	+/+++	++	0/+	+/+++	• Among TCAs, desipramine and nortriptyline are more tolerable; least sedating, anticholinergic and orthostatic hypotension • Desipramine may cause agitation • Therapeutic blood concentrations established for desipramine, imipramine, and nortriptyline
MAOIs	0	0	0/+	0/+	+/++	0/+	0/+	0/+	• 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: act: activity; GI: gastrointestinal; MAOI: monoamine oxidase inhibitor; mg: milligrams; NE: norepinephrine; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; 5HT: serotonin

Table J-3. Augmentation, Adjunct, and Alternative Pharmacotherapy[c]

Class	Agent	Initial Dose	Titration Schedule	Max. Dose/day	Initial Dose or Guidance: Special Populations		
					Geriatric	Renal	Hepatic
SGAs	Aripiprazole	2-5 mg once daily	5 mg after ≥1 week	15 mg	2 mg once daily	No change	No change
	Asenapine	5 mg twice daily	5 mg weekly	20 mg	Refer to adult dosing	No change	Severe; contraindicated
	Brexpiprazole	0.5-1 mg daily	1 mg weekly	3 mg	Refer to adult dosing	CrCl < 60 ml/min; 2 mg once daily	Mod-severe; 2 mg once daily
	Cariprazine	0.5 mg daily	0.5 mg weekly	4.5 mg	Refer to adult dosing	CrCl <30 ml/min; avoid	Severe; avoid
	Clozapine	12.5 mg once or twice daily	25-50 mg daily	900 mg	12.5 mg once daily	↓ dose	↓ dose
	Iloperidone	1 mg twice daily	1-2 mg twice daily	24 mg	Refer to adult dosing	No change	Severe; avoid
	Lumateperone	42 mg once daily	None	42 mg	Refer to adult dosing	No change	Mod-severe; avoid
	Lurasidone	20 mg once daily with food	20 mg weekly	60 mg	Refer to adult dosing	CrCl <50 ml/min; 20 mg daily	Severe; 20 mg daily
	Olanzapine	2.5-5 mg once daily	2.5-5 mg weekly	20 mg	2.5 mg once daily	No change	No change
	Olanzapine/ fluoxetine	6 mg/25 mg once daily	Weekly	18 mg/50 mg	3-6 mg/25 mg once daily	No change	3-6 mg/25 mg once daily
	Paliperidone	6 mg once daily	3 mg weekly	12 mg	Refer to adult dosing	CrCl 50-79 ml/min; 3 mg once daily	No change
	Quetiapine	50 mg once daily for 1-2 days	150 mg daily on day 3	300 mg	50 mg once daily	No change	Initial 25 or 50 mg once daily
	Risperidone	0.25-0.5 mg once daily	0.25-1 mg weekly	3 mg	0.25 mg once daily	CrCl <30 ml/min; 0.5 mg twice daily	Severe; 0.5 mg twice daily
	Ziprasidone	20 mg twice daily with food	20 mg twice daily	160 mg	20 mg twice daily	No change	Caution

[c] Titration Schedule column: Recommended minimum time between dose increases

Class	Agent	Initial Dose	Titration Schedule	Max. Dose/day	Initial Dose or Guidance: Special Populations		
					Geriatric	Renal	Hepatic
5-HT1A & -HT2 agonist	Buspirone	7.5-10 mg twice a day	10-15 mg weekly	60 mg	Refer to adult dosing	Avoid if severe	Avoid ifsevere
Lithium	Lithium	300-600 mg in 1-2 divided doses	300 mg weekly	1200 mg	150mg once or twice a day	CrCl <30 ml/min; avoid	No change
Thyroid Hormone	Liothyronine	25 µg once aday	May be increased to 50 µg/day after ~1 week	62.5 µg	5 µg once a day; increase by 5 µg/day every 2 weeks	No change	No change
Herbal	St. John's Wort	300 mg 2-3 times a day	Unknown	1800 mg	Unknown	Has not been studied	Has not been studied

Note that for individuals with reproductive potential or who are lactating, please see FDA guidance.

Abbreviations: 5-HT: serotonin; CrCl: creatinine clearance; FDA: U.S. Food and Drug Administration; mg: milligram; min: minutes; ml: milliliter; mod: moderate; µg: microgram; SGA: second-generation antipsychotic

Appendix K: Definitions

A. Major Depressive Disorder

A diagnosis of MDD generally occurs 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 ICD-10 (226) and DSM-5,(227) though some individuals demonstrate an atypical presentation with reactive mood, increased appetite, weight gain, and excessive sleepiness.(228)

Diagnosis of MDD results from the presence of depressed mood or loss of interest or pleasure, along with at least four additional MDD diagnosis criteria symptoms for at least two weeks (see Table K-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 K-1. Diagnosis of MDD (229)

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 every, or nearly all, activities for most of the day, principally on a daily basis
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

Abbreviations: MDD: major depressive disorder

In addition, individuals demonstrating more severe or atypical presentations, 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 negative, self-blaming cognitions and low mood typically encountered in major depression. Conversely, others may develop psychotic symptoms unrelated to the mood of the patient. In the latter case, the mood-incongruent psychotic symptoms prove difficult to distinguish from those that occur in other psychoses such as schizophrenia.

Severe Major Depressive Disorder Symptoms

- 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 ADLs (e.g., grooming, eating, catatonia)

Abbreviations: ADLs: activities of daily living

Table I-2 describes the classification of MDD based on the PHQ-9 symptom scores. The classification highlights the different symptoms that depressed individuals experience, depending on the characteristics of the depression experienced, the personal and social circumstances, as well as the responses required from services. Though the DSM-IV and Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria validate the PHQ-9, no changes exist in the diagnostic criteria for MDD from DSM-IV to DSM-5. Therefore, the PHQ-9 remains a valid screening tool.

The general categories of severity prove applicable as a basis for initial classification while benefiting from further characterization by any of the modifiers. This includes the existence of co-occurring mental health disorders and the duration of symptoms despite treatment. For most patients, an improvement of symptoms follows an untreated first episode of MDD. Although some patients return to pre-episode mood and function levels, many continue to experience residual subsyndromal symptoms. In a minority of patients, an MDD episode persists for over two years and is defined as chronic MDD. Treatment-resistant depression emerges after at least two adequate treatment trials and lack of full response to each.(51)

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

a. Onset Response to Treatment

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

b. Remission

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

c. Recovery

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

d. Partial Response

- <50% improvement in symptoms

e. Recurrence

- Recurrence stems from the appearance of another new episode of MDD after remission of a previous episode occurs. The literature often defines a complex case as three or more major depressive episodes.

B. Treatments

Acceptance and commitment therapy (ACT) is a psychotherapy intervention derived from relational frame theory that emphasizes accepting emotional distress and engagement in goal-directed behaviors based on individual values. A key feature of these interventions pivots on the acceptance rather than avoidance of emotional pain. The acceptance conceivably reduces affective symptom severity. To facilitate effective behavior change, ACT emphasizes the identification of personal values and learning to act based on those values, despite inevitable distress, as opposed to focusing on behavior pain and adversity avoidance.

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. Behavior therapy 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 behaviors and objectively assess the benefit of engaging in them) 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 behavioral therapies (CBT) are interventions that treat MDD by teaching patients to modify both thinking and behavior. Patients learn to track thinking and activities while identifying the affective and behavioral consequences of those thoughts and activities. Patients then learn techniques to examine, and when indicated, modify thinking that contributes to depression and identify, schedule, and engage in rewarding 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, developing experiments to test the accuracy of such thoughts, and the use of guided discovery (facilitating the ability of the patient to identify alternative beliefs through the use of questions designed to explore current thought processes that exacerbate depression). In addition, treatment incorporates structured practice outside of the session, including scheduled activities, mood tracking, thought recording, challenging, and interpersonal skills practice. Cognitive behavioral therapy can also be administered via computer-based programs designated as computer-based cognitive behavioral therapy (CCBT).

Interpersonal psychotherapy (IPT) is derived from attachment theory and treats MDD by improving interpersonal functioning and exploring relationship-based difficulties. Interpersonal psychotherapy addresses the connection between patients' feelings and current difficulties in relationships with people by targeting four primary areas: (1) interpersonal loss, (2) role conflict, (3) role change, and (4) interpersonal skills.

Problem-solving therapy (PST) is defined as a discrete, time-limited, structured psychological intervention, focusing on learning to cope with specific problem areas. The therapist and patient work collaboratively to identify and prioritize key problem areas, break problems down into specific,

manageable tasks, problem solve, and develop appropriate coping behaviors for challenges. The intervention operates as a short-term approach. The mode of action is hypothesized as skills acquisition. The intervention has been delivered effectively in 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 effect without necessarily attempting to change it. Regarding cognition, compared to cognitive therapy, MBCT emphasizes individuals learning to become more detached and able to observe thoughts as objects, with less focus on modifying or eliminating dysfunctional thought.

Non-directive supportive psychotherapy (NDSP) refers to a broad range of treatments that tend not to be structured or manualized and emphasize listening skills and the 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. Short-term psychodynamic psychotherapy refers to psychodynamic psychotherapy of approximately 10 to 20 weeks duration. The approach focuses on the patient gaining insight into unconscious conflicts, as the challenges manifest in the life and relationships of the patient. Examined relationships include the patient's relationship with the therapist (i.e., transference). This therapy assesses the conflicts that originate from the past, usually within childhood relationships to parental figures. Patients gain insight into and work through such conflicts through exploration of feelings along with interpretations offered by the therapist. The development of insight is theorized to be a core requirement for behavior change and symptom improvement. Of note, while some label IPT as an STPP, others argue the approach serves as a distinct model, as the technique features a distinct body of literature (see IPT above).

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