VA/DoD Clinical Practice Guidelines

VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder

Provider Summary

Version 4.0 | 2022

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

Department of Veterans Affairs

Department of Defense

Provider Summary

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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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 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 Methods).

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)

The full VA/DoD MDD CPG, as well as additional toolkit materials including a pocket card and patient summary, can be found at: https://www.healthquality.va.gov/.

Recommendations

The following evidence-based clinical practice recommendations were made using a systematic approach considering four domains as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (see Methods). 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.(2)

Hasin et al. (2018) defined MDD severity slightly differently and emphasized the number of symptoms.(3) 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. The Definitions section also describes depression subsets in detail.

Table 1. Recommendations

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

Topic	#	Recommendation	Strength[a]	Category[b]
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
	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

Topic	#	Recommendation	Strength[a]	Category[b]
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
	20.	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 • 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

Topic	#	Recommendation	Strength[a]	Category[b]
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
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

Topic	#	Recommendation	Strength[a]	Category[b]
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 in the full VA/DoD MDD CPG.

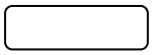
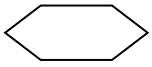
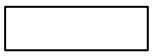
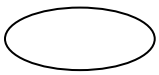
[b] For additional information, see Recommendation Categorization and Appendix D in the full VA/DoD MDD CPG.

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:

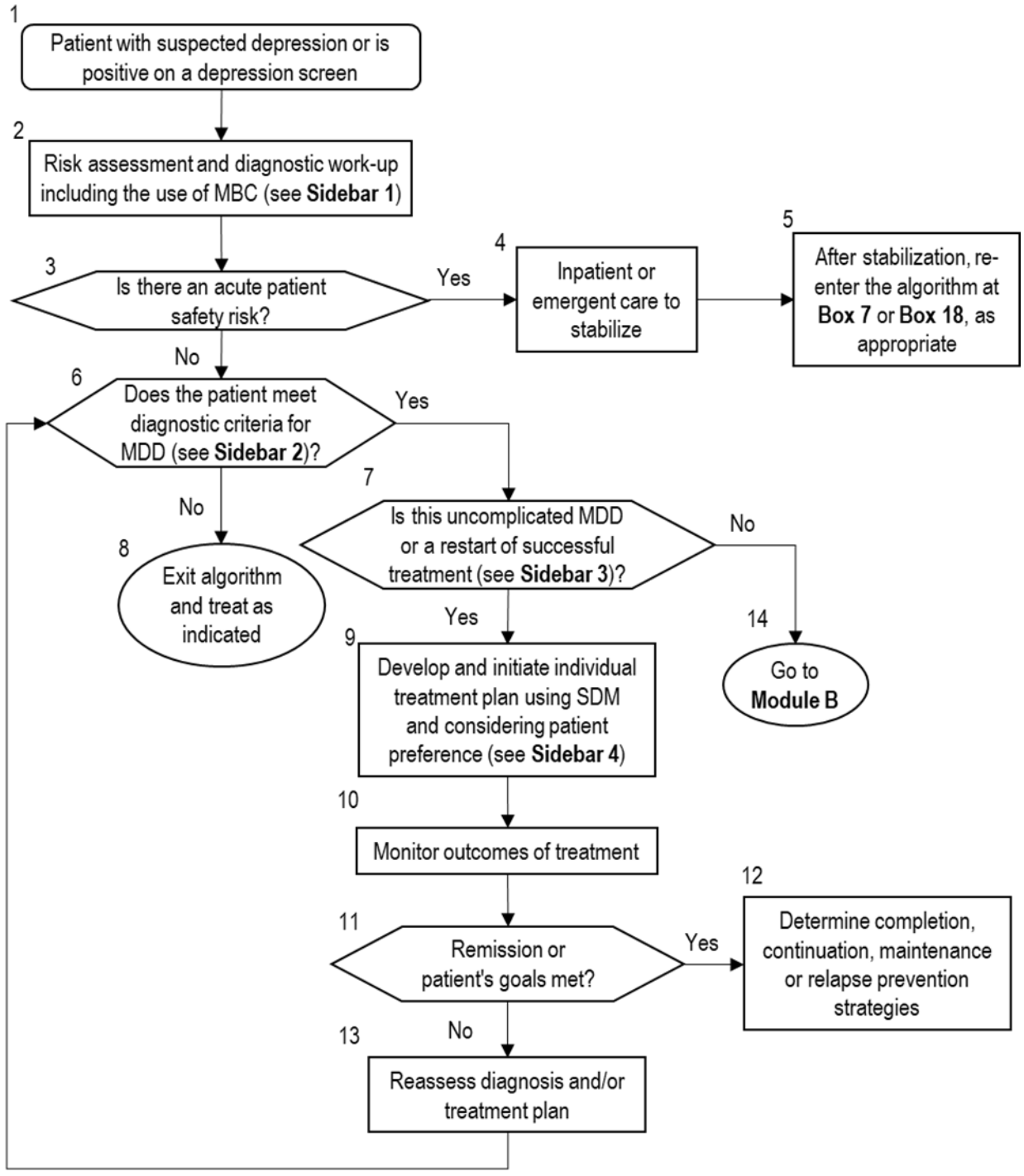
- An ordered sequence of steps of care
- Decisions to be considered
- Recommended decision criteria
- Actions to be taken

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.(4) 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

For alternative text descriptions of the algorithm, please refer to Appendix G in the full VA/DoD MDD CPG.

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

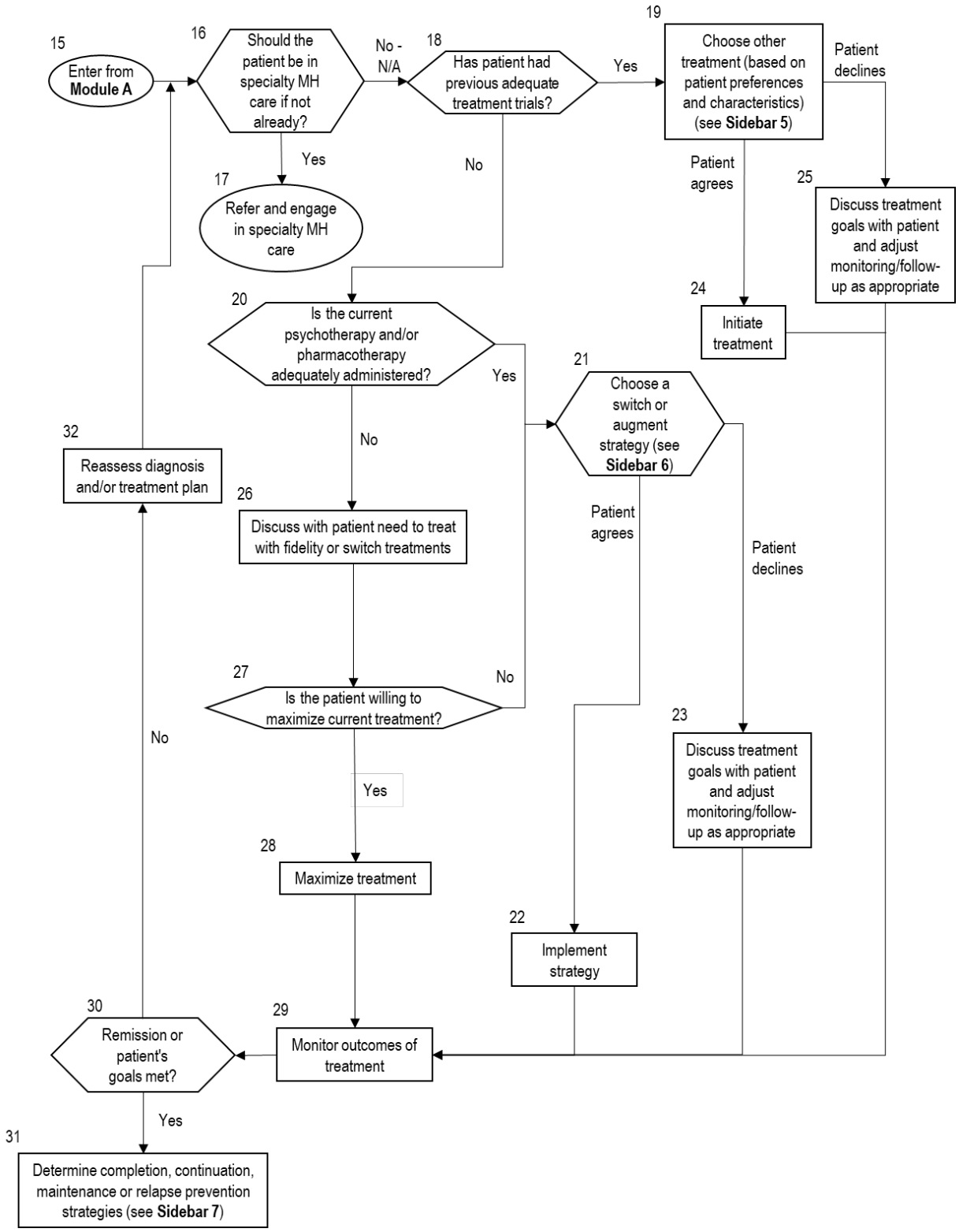
Abbreviations: MDD: major depressive disorder; PHQ-9: Patient Health Questionnaire-9

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

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

Scope of the CPG

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 in the full VA/DoD MDD CPG for additional information on the evidence review methodology). This CPG is not intended to serve as a standard of care.

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.

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]

Highlighted Features of this Guideline

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 the full VA/DoD MDD CPG. 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.

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.

Methods

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.(5) 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).(6) Appendix A in the full VA/DoD MDD CPG provides a detailed description of the CPG development methodology.

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

The Work Group used the 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: 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) (see Determining Recommendation Strength and Direction in the full VA/DoD MDD CPG).(7)

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.(7) 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 to not 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.

The GRADE of each recommendation made in the 2022 CPG can be found in the section on Recommendations. Additional information regarding the use of the GRADE system can be found in Appendix A in the full VA/DoD MDD CPG.

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).(8, 9) 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 in the full VA/DoD MDD CPG. The 2022 CPG recommendation categories can be found in Recommendations. Appendix D in the full VA/DoD MDD CPG 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) (8) and Garcia et al. (2014) (9)

[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

Guideline Work Group

Table 4. Guideline Work Group and Guideline Development Team

Organization	Names*
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Organization	Names*
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	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
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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.(10, 11) 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 gender, culture, ethnicity, and other differences.

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.(12) Shared decision making was emphasized in *Crossing the Quality Chasm,* an Institute of Medicine (IOM) (now NAM) report, in 2001 (13) 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.

Quick Guide to the Patient Health Questionnaire in Clinical Practice

A. Purpose

The PHQ facilitates the recognition and diagnosis of depressive disorders.(14) 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.(15) 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 (16)

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 5, while an example of this scored assessment can be found in Table 7.

Table 5. 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 6). A score of 10 or more has a sensitivity of 88% and a specificity of 88% for MDD.(2) All clinically significant responses are found in the column farthest to the right in the PHQ-9.

Table 6. 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.(17)

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 5 and Table 7).

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 7. 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			

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)
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.(18)

- 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?(19)

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 (20) and DSM-5,(21) though some individuals demonstrate an atypical presentation with reactive mood, increased appetite, weight gain, and excessive sleepiness.(22)

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 8).

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 8. Diagnosis of MDD (23)

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 6 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.(17)

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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Access to the full guideline and additional resources are available at the following link:
https://www.healthquality.va.gov/guidelines/MH/mdd/