



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

**Department of Veterans Affairs  
Department of Defense**

## **Clinician Guideline 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 recommendations.

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

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

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## **I. Introduction**

### **A. Major Depressive Disorder**

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

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

### **B. Depression in the General Population**

According to the National Alliance on Mental Illness, an estimated 16 million American adults—almost 7% of the population—had at least one major depressive episode in the past year. Women are 70% more likely than men to experience depression, and young adults aged 18–25 are 60% more likely to have depression than people aged 50 or older.[1] Depressive disorders often start at a young age; they reduce people’s functioning and often recur.[2] According to the World Health Organization (WHO), MDD (identified as unipolar depressive disorders by WHO) ranked first worldwide among the leading causes of disability (i.e., aggregate years lived with disability [YLD]).[3]

The incremental economic burden of individuals with MDD was \$210.5 billion in 2010, in both direct and indirect costs, compared to \$173.2 billion in 2005, an increase of 21.5% over this period.[4] Additionally, co-occurring conditions accounted for a larger percentage of the economic burden of MDD than the MDD itself.

Although depression can be a devastating illness, it often responds to treatment. There are a variety of treatment options available for people with depression including drugs and psychotherapy. Depression is frequently underdiagnosed, however; among people with severe depressive symptoms, for example, only about one-third (35%) had seen a mental health professional for treatment in the past year.[5]

### **C. Depression in the VA/DoD Populations**

Military personnel are prone to depression, at least partially as a result of exposure to traumatic experiences, including witnessing combat, and separation from family during deployment or military trainings.[6,7] For example, based on data collected in 2011 from a de-identified cross-sectional survey of active duty soldiers, The Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) described the 30-day prevalence of MDD as 4.8% compared to less than 1%—five times higher— among a civilian comparison group.[8] A meta-analysis of 25 epidemiological studies estimated the prevalence of recent major depression based on the DSM-IV criteria at rates of 12.0% among currently deployed U.S. military personnel, 13.1% among previously deployed, and 5.7% among those never deployed.[9]

However, the 25 studies from which these estimates are drawn described a wide range of prevalences depending on the screening or diagnostic instrument, population, and time period used. Being female, enlisted, 17-25 years old, unmarried, and having had less than a college education were risk factors for depression.<sup>[9]</sup> In an analysis among current and former U.S. military personnel who were included in the Millennium Cohort Study and observed from July 1, 2001 to December 31, 2008, the risk of suicide increased in men and in those who were depressed.<sup>[10]</sup>

In fiscal year 2015, among Veterans served by the Veterans Health Administration (VHA), the documented prevalence of any depression (including depression not otherwise specified) was 19.8% while the documented prevalence of MDD only was 6.5%.<sup>[11]</sup>

## **II. Scope of the Guideline**

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

### III. Guideline Working Group




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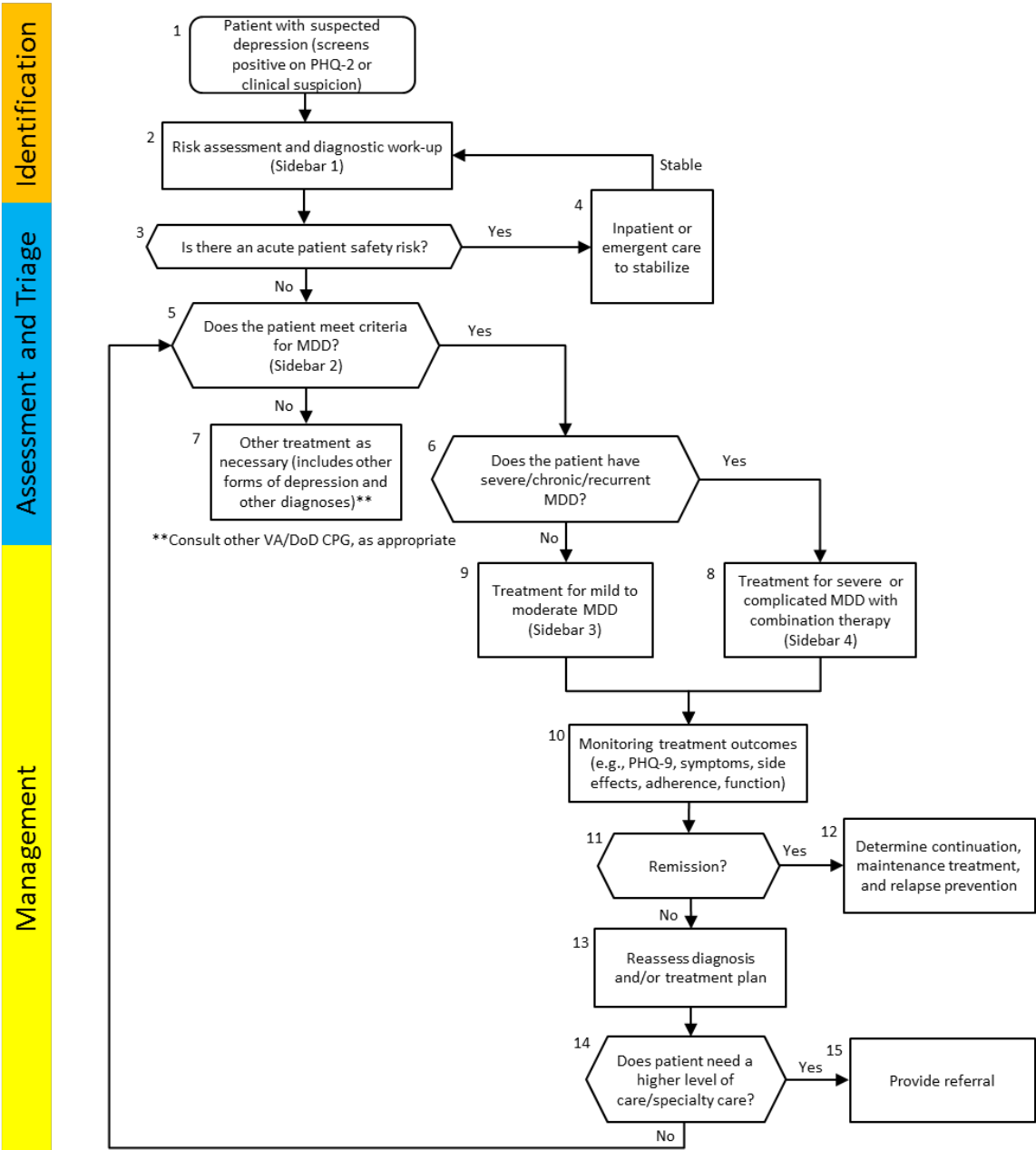
## IV. Algorithm

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

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

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed.<sup>[12]</sup>

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



**Sidebar 1 - Risk Assessment and Work-up**

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

**Sidebar 3 - Considerations in Treatment of Mild/Moderate MDD**

For example:

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

**Sidebar 2 - DSM-5 Criteria**

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

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

**Criterion B:** The symptoms cause significant distress or functional impairment

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

**Sidebar 4 - Considerations in Treatment of Severe MDD**

For example:

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

## V. Recommendations

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

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



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

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

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

## VI. Identification

**Table 1: Patient Health Questionnaire-2 (PHQ-2) [13]**

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

**Table 2: PHQ-2 Score Interpretation [13]**

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

## VII. Assessment and Triage

**Table 3: Diagnostic Criteria for Major Depressive Episode based on DSM-5 [14]**

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

**Table 4: Nine Symptom Checklist (PHQ-9)**

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

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

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

**PHQ-9 Scoring Instructions:**

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

- Not at all (#) \_\_\_\_ x 0 = \_\_\_\_
- Several days (#) \_\_\_\_ x 1 = \_\_\_\_
- More than half the days (#) \_\_\_\_ x 2 = \_\_\_\_
- Nearly every day (#) \_\_\_\_ x 3 = \_\_\_\_
- Total score: \_\_\_\_

## VIII. Treatment Setting

**Table 5: Summary of Evidence-based Elements of the Collaborative Care Model for MDD\* [15-21]**

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

\*Work Group’s synthesis of collaborative care model for MDD based on literature available through January 2015.

Abbreviations: CBT: Cognitive Behavioral Therapy, CRNP: Certified Registered Nurse Practitioner

## IX. Management

**Table 6: Classification of MDD Symptoms Severity and Risk Modifiers**

Severity Level	PHQ-9 Total Score	Number of Symptoms According to DSM-5	Functional Impairment
Mild	10-14	2	Mild
Moderate	15-19	3	Moderate
Severe	≥20	4 or 5	Severe
Modifiers			
Complications	Co-occurring PTSD, substance use disorder (SUD), psychosis, suicide risk, mania, significant social stressors, war-related conditions, significant anxiety		
Chronicity	More than two years of symptoms despite treatment		
Treatment-Resistant Depression	At least two adequate treatment trials and lack of full response to each [22]		

**Table 7: Definitions of Evidence-based Psychotherapy**

Evidence-based Psychotherapy	Definition
Cognitive behavioral therapy (CBT)	Interventions that treat MDD by teaching patients to modify both thinking and behavior. Patients learn to track their thinking and activities and identify the affective and behavioral consequences of those thoughts and activities. Patients then learn techniques to change thinking that contributes to depression and schedule activities to improve mood. CBT can also be administered via computer-based programs in which case it is known as computer-based cognitive behavioral therapy (CCBT).
Interpersonal therapy (IPT)	IPT is derived from attachment theory and treats MDD by focusing on improving interpersonal functioning and exploring relationship-based difficulties. IPT addresses the connection between patients’ feelings and current difficulties in their relationships with people in their life by targeting four primary areas - interpersonal loss, role conflict, role change, and interpersonal skills.
Mindfulness-based cognitive therapy (MBCT)	MBCT integrates traditional CBT interventions with mindfulness-based skills, including and mindfulness meditation, imagery, experiential exercises, and other techniques that aid patients in experiencing affect without necessarily attempting to change it. With regard to cognitions, unlike cognitive therapy, MBCT does not so much seek to modify or eliminate dysfunctional thoughts as to become more detached and able to observe thoughts as objects.
Behavioral therapy (BT)	BT for major depression refers to a class of psychotherapy interventions which treat MDD by teaching patients to increase rewarding activities. Patients learn to track their activities and identify the affective and behavioral consequences of those activities. Patients then learn techniques to schedule activities to improve mood. BT emphasizes training patients to monitor their symptoms and behaviors to identify the relationships between them.
Behavioral activation (BA)	BA is a particular version of BT which targets the link between avoidant behavior and depression and expands the treatment component of BT.
Acceptance and commitment therapy (ACT)	ACT is a manualized psychotherapy intervention derived from relational frame theory that emphasizes acceptance of emotional distress and engagement in goal directed behaviors. A key feature of these interventions is acceptance rather than avoidance of emotional pain. This acceptance is thought to reduce affective symptom severity. To facilitate effective behavior change, ACT emphasizes identification of personal values and learning to act based on those values in spite of inevitable distress as opposed to having behaviors be focused on avoiding pain and adversity.
Problem-solving therapy (PST)	PST is defined as a discrete, time-limited, structured psychological intervention that focuses on learning to cope with specific problem areas and where therapist and patient work collaboratively to identify and prioritize key problem areas; to break problems down into specific, manageable tasks; to problem solve; and to develop appropriate coping behaviors for problems. The intervention is short-term and the mode of action is hypothesized as skills acquisition.

**Table 8: Antidepressant Dosing<sup>1</sup> and Monitoring [23]**

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

<sup>1</sup> All dose oral except selegiline patch

<sup>2</sup> Recommended minimum time between dose increases



Class	Agent	Initial Dose	Titration Schedule <sup>2</sup>	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
SNRIs	Duloxetine	20-30 mg twice a day	20-30 mg weekly	60 mg	20 mg once or twice a day	Avoid if CrCl <30 ml/min	Avoid	C
	Venlafaxine IR	37.5 mg twice a day	75 mg weekly	225-375 mg	25mg once or twice a day	↓dose based on CrCl	↓ dose 50%	C
	Venlafaxine XR	75 mg once a day	75 mg weekly	225 mg	37.5-75 mg once a day	↓dose based on CrCl	↓ dose 50%	C
	Levomilnacipran	20 mg once a day	20-40 mg every 2 days	120 mg	Refer to adult dosing, Consider CrCl	Max doses less if CrCl <60ml/min	No change	C
	Desvenlafaxine	50 mg once a day	Unnecessary	100 mg; no benefit at doses >50 mg per day	Consider CrCl	CrCl <30 ml/min, 25mg once daily	No change	C
5-HT <sub>3</sub> receptor antagonist	Vortioxetine	10 mg once a day	10 mg once daily	5-20mg	5-20 mg once a day	No change	Severe: not recommended	C
NDRIs	Bupropion IR	100 mg twice a day	100 mg weekly	450 mg	37.5mg twice a day	Has not been studied	Severe: 75 mg/day	C
	Bupropion SR	150 mg once a day	150 mg weekly	200 mg twice daily	100 mg once a day		100 mg once a day	C
	Bupropion XR	150 mg once a day	150 mg weekly	450 mg	150 mg once a day		or 150 mg every other day; Mod to severe: use with extreme caution	C

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

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

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

**Table 9: Antidepressant Adverse Event Profiles [23]**

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

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

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

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

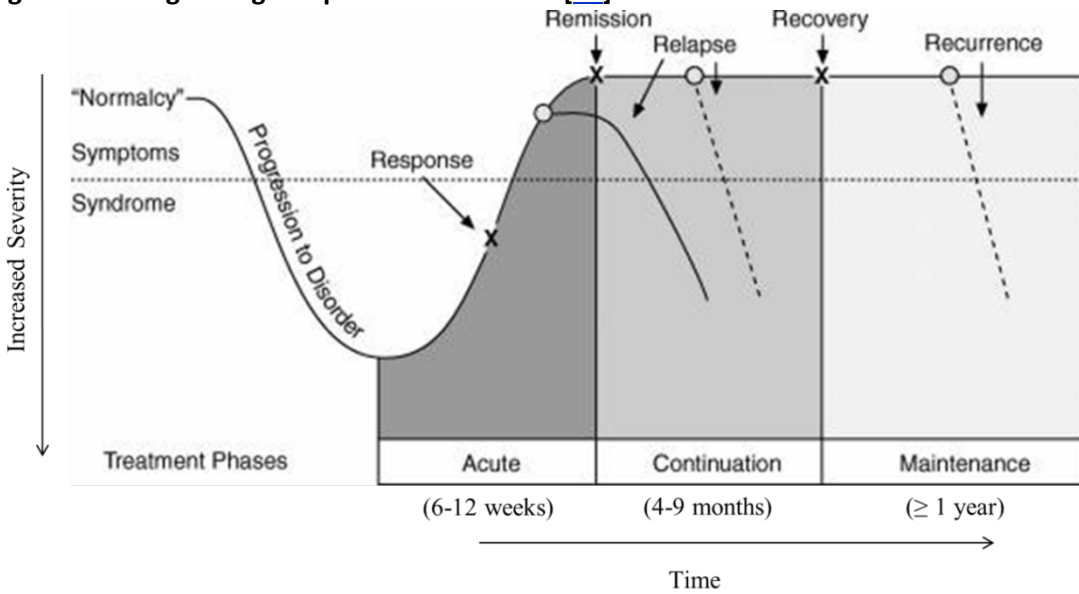
**Table 10: Augmentation, Adjunct and Alternative Pharmacotherapy [23]**

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

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

<sup>3</sup> Recommended minimum time between dose increases

Figure 1: Distinguishing Relapse and Recurrence [24]



## X. Methods

### A. Strength of Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation: [25]

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

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

**Table 11. Evidence to Recommendation Framework**

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

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains.<sup>[25]</sup> GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low.<sup>[26]</sup> In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

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

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



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

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

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

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

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

## **B. Recommendation Categorization**

For use in the 2016 MDD CPG, a set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE, UK). These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated. The categories and definitions can be found in Table 12.

**Table 12: Recommendation Categories and Definitions**

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

\*Adapted from the NICE guideline manual (2012) [27] and Garcia et al. (2014) [28]

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