Clinical Practice Guideline SUMMARY

Management of Major Depressive Disorder (MDD)

May, 2009

VA/DoD Evidence Based Practice

VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT

OF

MAJOR DEPRESSIVE DISORDER (MDD)

Department of Veterans Affairs

Department of Defense

SUMMARY

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and The Department of Defense (DoD) guidelines are based on the best information available at the time of publication. They are designed to provide information and assist in decision-making. They are not intended to define a standard of care and should not be construed as one. Also, they should not be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when providers 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 any particular clinical situation.

Version 2.0 – 2008

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Introduction

Major Depressive Disorder (MDD)

Depression is a major cause of disability worldwide. Evidence for the effectiveness of various pharmacological and psychological treatments is abundant, yet outcomes are often disappointing. This may reflect poor patient understanding of the illness, poor adherence to treatment or inadequate systems to support high quality care.

Given the low detection and recognition rates, it is essential that primary care and mental health practitioners have the required skills to assess patients with depression, their social circumstances and relationships, and the risk they may pose to themselves and to others. This is especially important in view of the fact that depression is associated with an increased suicide rate, a strong tendency for recurrence and high personal and social costs. The effective assessment of a patient, including risk assessment, and the subsequent coordination of the patient's care, is likely to improve outcomes and should therefore be comprehensive.

- Depression is a major cause of impaired quality of life, reduced productivity, and increased mortality.
    - Social difficulties are common (e.g. social stigma, loss of employment, marital break-up).
    - Associated problems, such as anxiety symptoms and substance misuse, may cause further disability.
- People with depression are at increased risk of suicide. Mortality from suicide is reported to be as high as 15% among people hospitalized for severe depression. In primary care populations, the prevalence of suicidal ideation is approximately 20-30% among depressed patients, but serious suicide attempts (7/10,000) and completed suicides (4/10,000) are relatively infrequent [Simon GE, 2006]
- Depression is a significant independent risk factor for both first myocardial infarction and cardiovascular mortality. In people with ischemic heart disease, depression has been found to be associated with a three- to fourfold increase in cardiovascular morbidity and mortality.
- **Depression in VA population:**

  Major depressive disorder, diagnosed by structured psychiatric interviews and specific diagnostic criteria, is present in 5-13% of patients seen by primary care physicians. The prevalence of this disorder in the general population is about 3-5%. The annual economic burden of depression in the U.S. (including direct care costs, mortality costs, and morbidity costs) has been estimated to total almost $83.1 billion in year 2000 dollars [Greenberg PE, 2003]. The suicide rate in depressed persons is at least 8 times higher than that of the general population. (VA Tech-manual 1999)

- **Depression in DoD Population:**

  A triservice population-based study of military personnel found 3.2% of personnel met survey criteria for major depressive disorder, 5.1% of women and 2.8% of men (Riddle et al., 2008). Hoge and colleagues (2004) found that 8 to 15% of combat soldiers returning from Operation Iraqi Freedom (OIF) met survey criteria for major depression compared to 7 to 14% in combat soldiers returning from Operation Enduring Freedom (OEF). The prevalence of major depression before OIF/OEF was 5 to 11%. An analysis of DoD post-deployment health assessment screening results found that 5.2% of Army soldiers and Marines screened positive for depression (6.1% after OIF, 3/5% after OEF, and 2.7% after other deployments) (Hoge et al, 2006).

  Provider diagnosis of depression underestimates the true occurrence of the disorder, because many individuals with the disorder never seek care for it and primary care providers often do not recognize or diagnose it. In a study of automated DoD health care data, the 12-month prevalence of a provider diagnosis of depression was 1.9 percent among active-duty military personnel, 1.5 percent among reserve component personnel, and 3.9 percent among family member and retirees.

Of those with new depression diagnoses in acute phase treatment, 49% of active duty personnel, 58percent of reserve component personnel, and 32 percent of family member/retirees received associated mental health specialty care (NQMP 2004).

Scope of Guideline

Target population:

Adult patients with Major Depressive Disorder

This guideline applies to patients presenting with symptoms of depression, and to patients being followed for major depressive disorder. (This includes those newly diagnosed, those receiving ongoing treatment and those with chronic depression).

Audiences:

The guideline is relevant to all healthcare professionals who have direct contact with patients with MDD, and who make decisions about their care. This version of the guideline was specifically tailored to what would be of greatest value to the primary care provider.

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Key Elements Addressed by the Guideline

1. Depression is common, underdiagnosed and undertreated.

2. Depression is frequently a recurrent/chronic disorder, with a 50% recurrence rate after the first episode, 70% after the second, and 90% after the third.

3. Most depressed patients will receive most or all of their care through primary care physicians.

4. Depressed patients frequently present with somatic complaints to their primary care doctor rather than complaining of depressed mood**.**

5. Annual screening for MDD is recommended in the primary care setting as an important mechanism for reducing morbidity and mortality. Screeening should be done using a standardized tool such as the Patient Health Questionnaire (PHQ-2), a 2 item screen

6. A standardized assessment tool such as the PHQ-9 should be used as an aid for diagnosis, measurement of symptom severity and to assess treatment response.

7. Mild depression can be effectively treated with either medication or psychotherapy. Moderate to severe depression may require an approach combining medication and psychotherapy.

8. Selective Serotonin Reuptake Inhibitors (SSRIs) along with the Seratonin Norepinephrine reuptake inhibitors (SNRIs), bupropion, or mirtazapine are considered a first-line treatment option for adults with Major Depressive Disorder (MDD).

9. No particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patients' symptoms to side effect profile, presence of medical and psychiatric co-morbidity, and prior response.

10. Patients treated with antidepressants should be closely observed for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose increases or decreases

11. Evidence-based short-term psychotherapies, such as Cognitive Behavioral Therapy (CBT), Interpersonal Therapy (IPT) and Problem Solving Therapy (PST) are recommended treatment options for major depression. Other psychotherapies are treatment options for specific populations or are based on patient preference.

12. Patients require frequent visits early in treatment to assess response to intervention, suicidal ideation, side effects, and psychosocial support systems

13. Continuation therapy (9-12 months after acute symptoms resolve) decreases the incidence of relapse of major depression

14. Long term maintenance or life-time drug therapy should be considered for selected patients based on their history of relapse and other clinical factors

15. Patient education and support are essential. Care management may be considered to improve outcome.

STRUCTURE OF THE GUIDELINE

The algorithms describe the step-by-step process of clinical decision-making and intervention that should occur when managing patients with MDD. General and specific recommendations for each step in the algorithm are included in an annotation section following the algorithm. The links to these recommendations are embedded in the relevant specific steps in the algorithm.

Each annotation includes a brief discussion of the research supporting the recommendations and the rationale behind the grading of the evidence and determination of the strength of the recommendations.

In annotations for which there are studies to support the evidence-based recommendations the Strength of Recommendation [SR] based on the level of evidence is presented in brackets for these recommendations. Recommendations that are not based on evidence were derived by consensus of experts. No SR is presented for these recommendations.

Evidence Rating System

SR	
A	A strong recommendation that clinicians provide the intervention to eligible patients. *Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.*
B	A recommendation that clinicians provide (the service) to eligible patients. *At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.*
C	No recommendation for or against the routine provision of the intervention is made. *At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. *At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.*
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. *Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

SR = Strength of recommendation

Lack of Evidence – Consensus of Experts

Where existing literature was ambiguous or conflicting, or where scientific data was lacking on an issue, recommendations were based on the clinical experience of the Working Group. These recommendations are indicated in the evidence tables as based on "Working Group Consensus."

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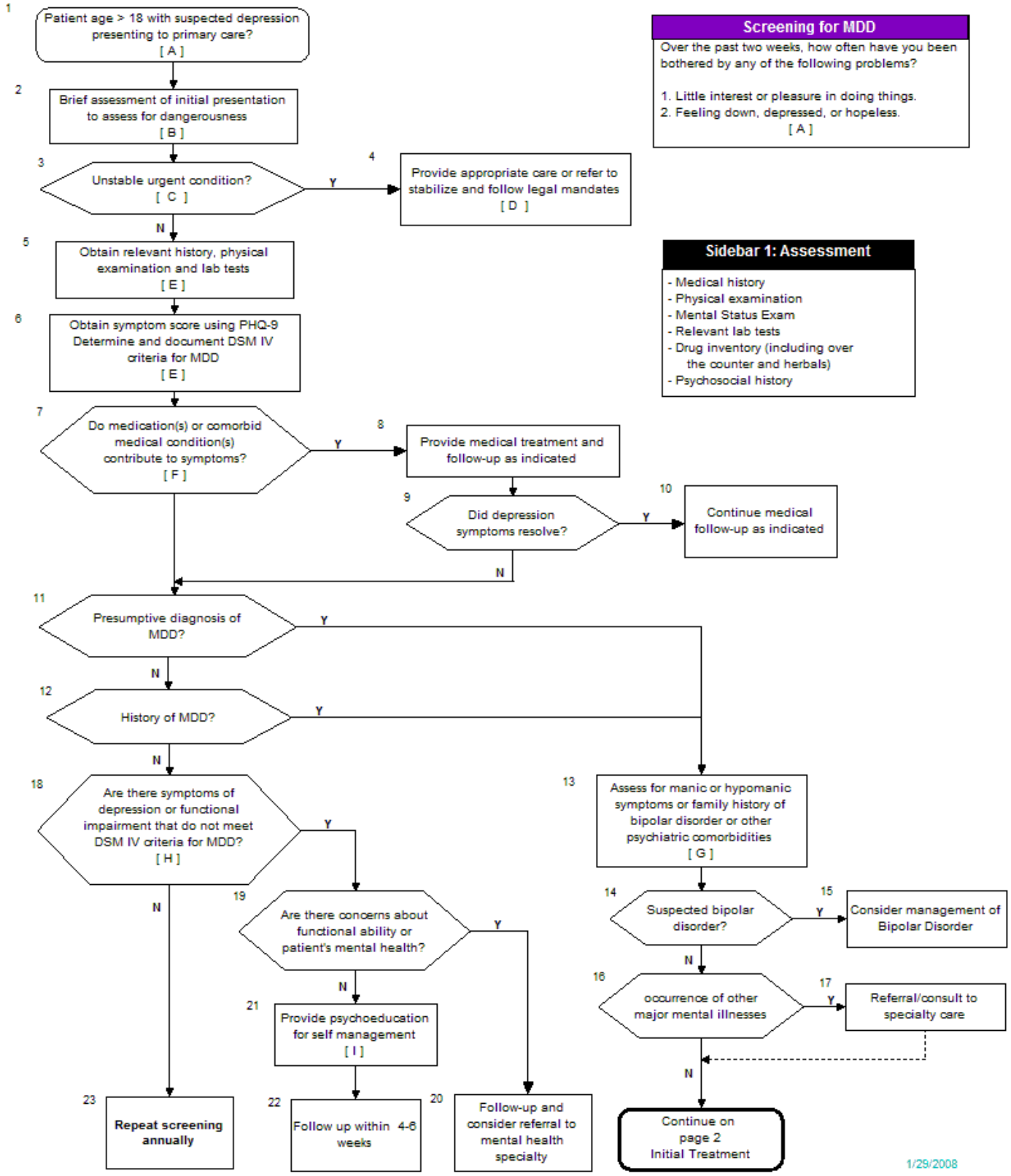
Management of Major Depressive Disorder in Adults

Primary Care Initial Assessment and Diagnosis

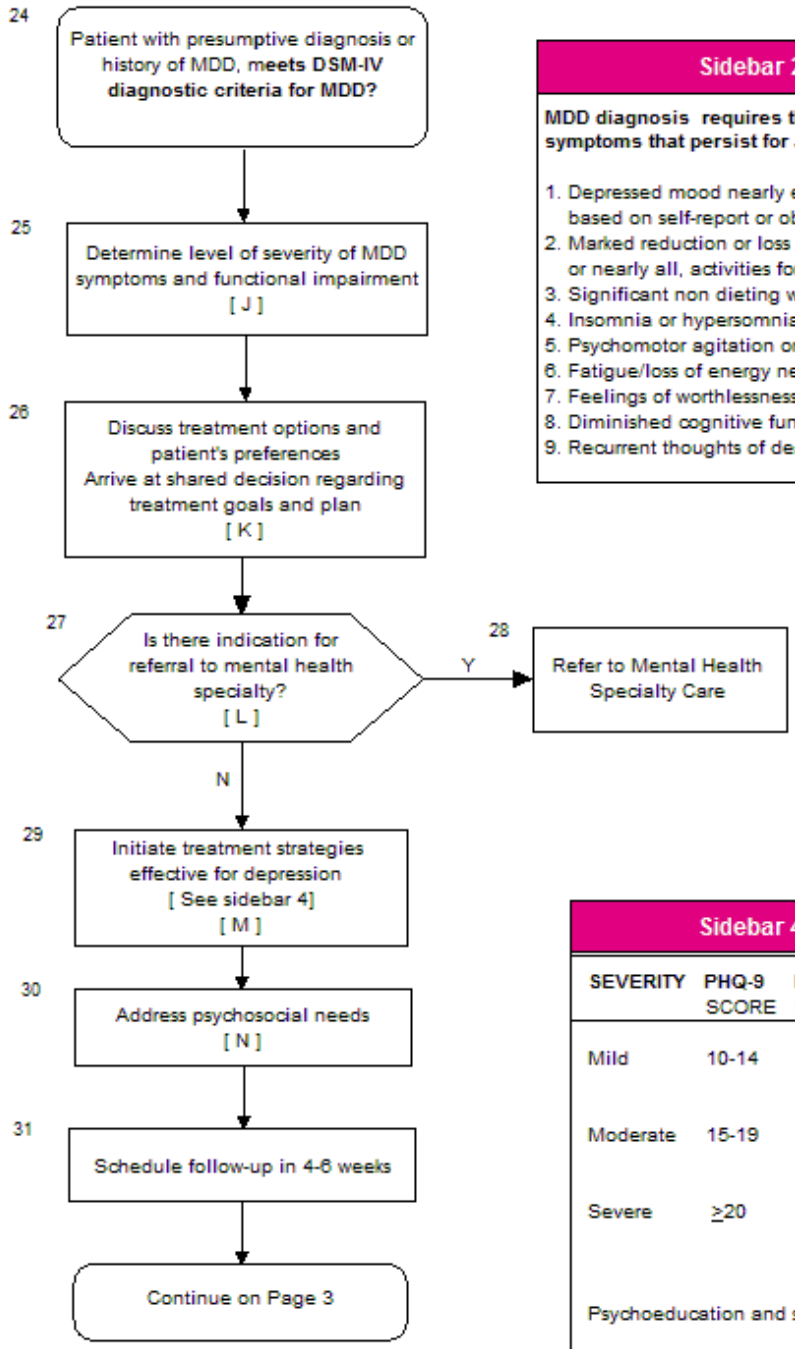
1



Management of Major Depressive Disorder in Adults

Primary Care -Initial Treatment

2



Sidebar 2: DSM-IV Diagnostic Criteria for MDD

MDD diagnosis requires the presence of symptom 1, 2, or both; and at least 5 of 9 symptoms that persist for at least 2 weeks:

1. Depressed mood nearly every day for most of the day, based on self-report or observation of others
2. Marked reduction or loss of interest or pleasure in all, or nearly all, activities for most of the day, nearly every day
3. Significant non dieting weight loss or weight gain (>5% change in body weight)
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation (should be observable by others)
6. Fatigue/loss of energy nearly every day
7. Feelings of worthlessness or excessive/inappropriate guilt nearly every day
8. Diminished cognitive function (reduced ability to think or concentrate) nearly every day
9. Recurrent thoughts of death and/or suicide, suicide planning, or a suicide attempt

Sidebar 3: Indications for Referral to Mental Health

- Unclear diagnosis
- Evidence of psychotic features, past-mania or hypomania
- Signs of comorbid psychiatric conditions
- Unable to treat patient in primary care
- Need for psychosocial interventions
- Patient preference

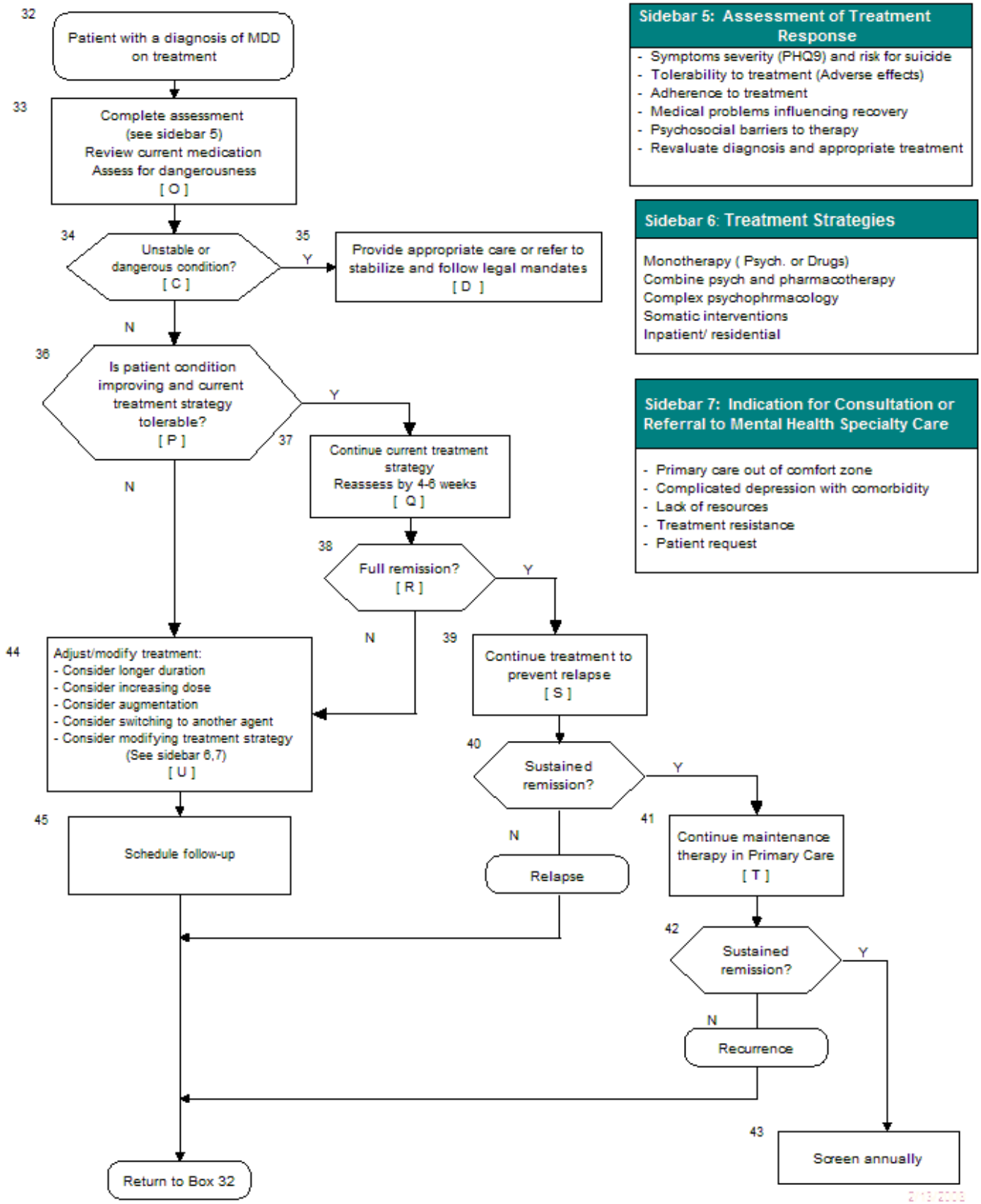
Sidebar 4 : Initial Treatment Strategies for MDD

SEVERITY	PHQ-9 SCORE	FUNCTIONAL IMPAIRMENT	INITIAL STRATEGY
Mild	10-14	Mild	Monotherapy - antidepressants or psychotherapy or, possibly combination
Moderate	15-19	Moderate	Antidepressants or psychotherapy or, combination
Severe	≥20	Severe	May start with antidepressants or psychotherapy but should prefer combination or multiple antidepressants

Psychoeducation and self-management should be provided for all severity levels

Management of Major Depressive Disorder in Adults

Primary Care - Treatment Management and Follow-up



1. DEFINITIONS

Major Depressive Disorder (MDD):

Major depression is generally diagnosed when a persistent low mood and an absence of positive affect are accompanied by a range of symptoms. The number and combination of symptoms needed to make a diagnosis is operationally defined by ICD-10 (WHO, 1992) and DSM-IV-TR (APA, 2000); although some people will show an atypical presentation with reactive mood, increased appetite, weight gain and excessive sleepiness (Quitkin et al, 1991).

- Diagnosis of a major depressive disorder (MDD) is based on the presence of depressed mood or loss of interest or pleasure, along with at least 4 additional MDD diagnosis criteria symptoms for a duration of at least 2 weeks (See Table 1).

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

Table 1. Diagnosis of MDD

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

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th ed, Text Revision. Washington, DC: American Psychiatric Association; 2000.

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

People with severe depressions may also develop psychotic symptoms (hallucinations and/or delusions), most commonly thematically consistent with the negative, self-blaming cognitions and low mood typically encountered in major depression, although others may develop psychotic symptoms unrelated to the patients' mood. In the latter case, these mood-incongruent psychotic

symptoms can be hard to distinguish from those that occur in other psychoses such as schizophrenia.

Severe Major Depressive Disorder (MDD)

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

Table 2 describes the classification of MDD based on the symptoms score obtained with the Patient Health Questionnaire-9 (PHQ-9). The classification may be helpful for emphasizing the different needs that depressed individuals have - depending on the characteristics of their depression and their personal and social circumstances - and the responses that are required from services.

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

The general categories of severity should be used as a basis for initial classification and should be further characterized by any of the modifiers. These will include the existence of co-occurring mental health disorders and the duration of symptoms despite treatment. For most patients, an untreated first episode of MDD is followed by improvement of symptoms; although some patients return to pre-episode mood and function levels, many continue to experience residual sub-syndromal symptoms. In a minority of patients, a MDD episode persists for over 2 years, and is defined as chronic MDD.

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

Table 2. Classification of MDD Symptoms Severity

Severity Level	Patient Health Questionnaire (PHQ-9) Total Score	Functional Impairment
Mild	10-14	Mild
Moderate	15-19	Moderate
Severe	$\geq$ 20	Severe
Modifiers		
Complications	Co-occurring post traumatic stress disorder (PTSD), substance use disorder (SUD), psychosis, suicide risk, mania, significant social stressors, war-related conditions	
Chronicity	More than 2 years of symptoms despite treatment	

Onset Response to Treatment

- Minimal clinically significant: a change in PHQ score of 25 percent
- Response to treatment: PHQ score improvement of 50 percent from baseline

Full Remission

- PHQ score of 4 or less, maintained for at least 1 month, OR
- Beck Depression Inventory (BDI) score of 10 or less, maintained for at least 1 month, OR
- Hamilton Rating Scale for Depression (HRSD-17 or HAM-D) score of 7 or less, maintained for at least 1 month.

Recovery

- PHQ score of 4 or less, maintained for at least 6 months, OR
- BDI score of 10 or less, maintained for at least 6 months, OR
- HRSD-17 score of 7 or less, maintained for at least 6 months.

2. SCREENING

2.1. Screening Adults

BACKGROUND

The U.S. Preventive Services Task Force (USPSTF) has concluded that routine screening for depressive disorders is an important mechanism for reducing morbidity and mortality. Depressive disorders are highly prevalent and are often not detected unless systematic screening efforts are implemented. Brief screens (e.g., PHQ-2) appear to perform comparably to longer screens (e.g., Geriatric Depression Scale [GDS] or Patient Health Questionnaire [PHQ-9]). Although depression questionnaires may perform more poorly in adults > 75 years, the performance is adequate to improve initial recognition of depression. Patients with severe chronic medical illness are at higher

risk for depression than the average patient seen in primary care. The PHQ-9 appears to have adequate performance characteristics in medically ill patients; the PHQ-2 appears promising but is less-well studied in these groups.

In addition to new case identification, systematic screening provides a platform for:

- Identification of patients who are depressed and no longer engaged in treatment
- Promotion of integrated care programs
- Promotion of early intervention programs such as watchful waiting or targeted symptom management.

ACTION STATEMENT

Identify patients who are depressed and are no longer engaged in treatment.

RECOMMENDATIONS

1. The Patient Health Questionnaire (PHQ) 2-item should be completed annually by all patients seen in primary care settings. [A]

2. Patients who screen positive on the Patient Health Questionnaire (PHQ) 2-item should have both a documented assessment using a quantitative questionnaire to further assess whether the patient has sufficient symptoms to warrant a diagnosis of clinical major depression and a full clinical interview that includes evaluation for suicide risk. [B]

3. In patients at particularly high risk for depression based on medical illness (e.g., hepatitis C starting interferon treatment or post-myocardial infarction), clinicians should have a high index of suspicion for depression and use a diagnostic assessment tool (e.g., Patient Health Questionnaire (PHQ) 9-item) when depression is suspected. [I]

4. Caution should be used in screening patients older than 75 years since screening instruments may not perform as well as in patients 65 to 75 years old. [C]

See Appendix B: Screening and Assessment Instruments

Patient Health Questionnaire-2 (PHQ-2):

Over the past two weeks, how often have you been bothered by any of the following problems?

Little interest or pleasure in doing things.
0 = Not at all
1 = Several days
2 = More than half the days
3 = Nearly every day

Feeling down, depressed, or hopeless.
0 = Not at all
1 = Several days
2 = More than half the days
3 = Nearly every day

Score Interpretation:

PHQ-2 score	*Probability of major depressive disorder (%)*	*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

Information from Kroenke et al., 2003

2.2. Screening/Assessment for Depression in Pregnancy and in the Postpartum Period

BACKGROUND

Depression in pregnancy in general, and in the postpartum period in particular, is a well-recognized problem. Although estimates vary, in the first 3 months after childbirth, 14.5 percent of women have a new episode of major or minor depression; 10 to 20 percent of mothers are believed to suffer with depression sometime during their postpartum course, making postpartum depression the most common serious postpartum disorder. In addition, it is an under-recognized entity, with 50 percent of cases undetected in some series. This rate of under-detection can be reduced by the use of a screening instrument, administered during the course of pre- and postnatal visits. This detection can lead to further diagnostic interviews and to appropriate treatment, lessening the deleterious effects of depression on both the mother and child.

ACTION STATEMENT

To identify women who are depressed during pregnancy or in the postpartum period.

RECOMMENDATIONS

1. Women should be screened for depression at their first contact with healthcare services in both the antenatal and the postnatal periods. [B]

2. Depression screening should be performed with either the Edinburgh Postnatal Depression Scale (EDPS) or the PHQ-2. [B]

3. In the postpartum period, recommended screening is typically at 4 to 6 weeks and 3 to 4 months. [C]

RATIONALE

Early detection of depression during pregnancy is critical because depression can adversely affect birth outcomes and neonatal health and, if left untreated, can persist after the birth. Untreated postpartum depression can impair mother-infant attachments and have cognitive, emotional, and behavioral consequences for children. The best studied of these screening instruments is the EDPS.

ANNOTATIONS

Annotation A	*Patient Age > 18 With Suspected Depression Presenting to Primary Care*

This guideline and algorithms should be used in the primary care setting for assessment and diagnosis of adult patients who are suspected to have MDD.

Algorithm A describes the screening strategy for MDD in primary care, using standardized screening tools. Adult patients that screen positive for depression should be assessed and evaluated using standardized assessment tools. Other possible causes for a patient's symptoms should be considered and psychiatric and/or medical comorbidities should be identified. Patients diagnosed with mild or moderate MDD (based on DSM-IV-TR) may be treated in primary care. Patients with severe MDD or any complicated MDD and comorbidities should be referred to specialty care for treatment.

Annotation B	*Brief Assessment of Initial Presentation to Assess for Dangerousness*

3. DANGEROUS CONDITIONS

3.1. Assess for Dangerousness

BACKGROUND

Unstable conditions, whether psychiatric or physiologic, represent situations that require immediate attention. Whatever the cause, the following situations may serve as warning signs of violence:

- Ideas about, or intent to, harm others
- Verbal escalation or inability to be redirected
- History of violent behavior
- Severe agitation or hostility
- Active psychosis
- Intoxication or withdrawal from alcohol or drugs.

Immediate attention and intervention, including referral or consultation with a mental health professional, may be required in order to stave off the potential for escalation of agitation or violent impulses.

ACTION STATEMENT

Identify patients who are at high risk of harm to self or others.

RECOMMENDATIONS

1. A referral to emergency services and/or consultation with a mental health professional is indicated for patients presenting with any of the following unstable conditions:

    a. Delirium

b. Marked psychotic symptoms

c. Severe depressive symptoms/depression (e.g., catatonia, malnourishment, severe disability)

d. Suicidality or homicidality

e. Potential for violence (e.g., ideas about or intent to harm others; history of violent behavior; severe agitation or hostility; active psychosis)

f. Substance withdrawal or intoxication

2. Any patient with suicidal ideation or attempts necessitating psychiatric hospitalization should be considered for referral to mental health specialty care.

DISCUSSION

- **Delirium** – Delirium (also known as organic brain syndrome, organic psychosis, acute confusional state, acute brain syndrome and various other names) is a very common disorder of cognition and consciousness, with an abrupt onset that is commonly unrecognized. This is especially true in the elderly and chronically ill.
- **Marked psychotic symptoms** – "Psychosis," in and of itself, is not a disorder. Rather, it is a symptom, which may present in a variety of conditions. Psychotic patients have an impaired sense of reality, which may manifest in several ways (hallucinations, delusions, mental confusion, or disorganization).
- **Severe depressive symptoms/depression** (e.g., catatonia, malnourishment, severe disability) – The clinical presentation of depressed patients is marked by considerable variation, not only in the expression of various neurovegetative symptoms themselves, but also in the magnitude of severity of these symptoms. While many mild to moderate illnesses may not necessarily present situations requiring immediate attention, the presence of severe depressive symptoms may represent an urgent condition, even in the absence of suicidal ideation.
- **Suicidality** – Suicidal behavior is best assessed with the following criteria: current suicidal ideas or plans, presence of active mental illness (severe depression or psychosis), presence of substance use disorder, past history of suicidal acts, formulation of plan, availability of means for suicide (firearms, pills, etc.), disruption of important personal relationships, or failure at important personal endeavors.
- **Potential for violence** – Violence often emerges as a response to a perceived threat or as marked frustration resulting from the inability to meet goals by nonviolent means. Specific factors that contribute to violent behavior include psychiatric, medical, environmental, and situational/social factors.
- **Unstable urgent medical conditions** – Any condition immediately threatening to life, limb, or eye sight, or requiring emergency medical care. These may include acute myocardial infarction, respiratory failure, hypertensive crisis, diabetic ketoacidosis, crushing radiating chest pain, etc.

For more information on these conditions see:

Appendix C: Suicidality

Annotation C	*Unstable Urgent Condition?*

3.2. Is Patient a Threat to Self or Others?

BACKGROUND

Direct and nonjudgemental questioning regarding suicidal and/or homicidal ideation/intent is indicated in all cases where MDD is suspected. A significant number of patients who contemplate suicide are seen by a physician within a month prior to their attempt. Medical providers often express concern regarding this line of questioning in the fear that it may actually stimulate the thought in the patient. However, evidence shows that direct assessment of suicidal ideation and intent does not increase the risk of suicide. Consider gathering collateral information from a third party, if possible. Homicidal ideation and suicidal ideation may co-occur. Risk of violence towards others should be assessed by asking directly whether the patient has thoughts of harming anyone.ACTION STATEMENT

Identify patients who pose a threat to self or others and initiate appropriate intervention.

RECOMMENDATIONS

1. Patients with a presumptive diagnosis of MDD should be assessed for suicidality by using a direct line of questioning. One recommended line of questioning uses the following (modified from Hirschfeld & Russell, 1997):

    a. "Have you had thoughts about death or about killing yourself?"

    b. "Tell me about your hopes for the future."

    c. "Do you have a plan for how you would kill yourself?"

    d. "Are there means available (e.g., pills, a gun and bullets, or poison)?"

    e. "Have you actually rehearsed or practiced how you would kill yourself?"

    f. "Do you tend to be impulsive?"

    g. "How strong is your intent to do this?"

    h. "Can you resist the impulse to do this?"

    i. "Have you heard voices telling you to hurt or kill yourself?"

    j. Ask about previous attempts, especially the degree of intent.

    k. Ask about suicide of family members or significant others.

2. Risk of violence towards others should be assessed by asking directly whether or not the patient has thoughts of harming anyone:

    a. Assess whether the patient has an active plan and method/means (e.g., weapons in the home)

    b. Assess whom the patient wishes to harm

c. Assess whether the patient has ever lost control and acted violently

d. Assess seriousness/severity of past violent behavior.

3. In the event of expressed dangerousness to self or others by a person with possible MDD, steps must be taken to insure patient safety until further evaluation and a referral or consultation with a mental health professional has taken place.

DISCUSSION

While the PHQ-2 or PHQ-9 is a valid and important screening tool for MDD, it is not sufficient to effectively assess whether the patient is a threat to self or others. This assessment requires a structured line of questioning designed to elicit responses specific to the issues of potential suicide. Hirschfeld & Russell (1997) put forth a line of questioning which is recommended in an adapted form for this guideline. In addition, homicidal ideation also needs to be explored from the perspectives of whether the patient has an active plan and the method/means are at hand.

3.3. Is There Evidence of Psychosis?

BACKGROUND

Psychosis is defined as a mental state in which the patient is significantly out of touch with reality to the extent that it impairs functioning. Patients with psychotic symptoms may present in an acutely agitated state with a recent onset of disturbed and/or disturbing symptoms. However, patients may also present with enduring, chronic symptoms which are long-standing and to which patients have made a reasonably comfortable adaptation.

In particular, paranoid concerns that others wish to harm the patient and voices (especially command hallucinations) telling the patient to hurt him or herself or someone else, are indications for an immediate mental health consultation or referral. Patients who have longstanding psychotic illness and who are able to attend to present circumstances without responding to their psychosis may be evaluated and treated for a co-morbid depression in the primary care setting.

It is important to bear in mind that psychotic symptoms may be the direct result of an underlying medical condition, toxic state, alcohol or substance use disorder, or may be associated with a mental health condition such as schizophrenia or affective illness.

ACTION STATEMENT

Identify patients who have acute or chronic psychosis and treat accordingly.

RECOMMENDATIONS

1. Patients with a possible diagnosis of MDD should be assessed for acute or chronic psychosis.

2. Patients with a possible diagnosis of MDD who exhibit any of the following characteristics related to psychosis need to be referred for urgent/emergent mental health intervention as these are inappropriate for care in the primary care setting:

   a. Serious delusions (e.g., fixed false beliefs)

   b. Visual or (typically) auditory hallucinations

c. Confusion (incoherence)

d. Catatonic behavior (e.g., motoric immobility or excessive agitation)

e. Extreme negativism or mutism

f. Peculiar voluntary movement

g. Inappropriate affect of a bizarre or odd quality.

3. Patients who have longstanding psychotic illness and who are able to attend to present circumstances without responding to their psychosis, may be evaluated and treated for a co-morbid depression in the primary care setting.

Annotation D	*Provide Appropriate Care or Refer to Stabilize and Follow Legal Mandates*

3.4. Provide Appropriate Care or Refer to Stabilize and Follow Legal Mandates

BACKGROUND

Initial steps in assessing and caring for dangerous conditions in patients with MDD include the provision of appropriate care to stabilize the situation. Depending on the seriousness of the condition and the resources at hand, this will be accomplished on-site or through urgent/emergent referral to mental health. However, it is also essential that primary care providers and their administrative staffs have an understanding of, and ability to access local, state and federal regulations/policies/procedures and guidelines relating to danger to self or others. If patients represent a risk to others, additional notifications may be required by state or federal laws and/or regulations. When making notifications, it is wise to consult a peer and/or medical law consultant on the legal and ethical requirements.

For VA patients, these procedures should also reflect the opinion and guidance of the VHA District Council. For DoD patients, these procedures are directed by DoD Directive 6490.1, "Mental Health Evaluation of Members of the Armed Forces," DoD Instruction 6490.4, "Requirements for Mental Health Evaluations of Members of the Armed Forces," and related Service regulations/instructions. These regulations/instructions may require a number of notifications (e.g., commanders) which would not be made in a civilian practice.

ACTION STATEMENT

Ensure that appropriate care, protocols and regulatory/policy mandates are followed during diagnosis and stabilization of the patient with MDD with an unstable condition.

RECOMMENDATIONS

1. Local, state, and federal regulations/mandates as well as guidelines should be followed if the patient represents a risk to self or others.

2. In managing patients who pose a risk, mental health providers need to be prepared to consult with primary care and other medical specialties concerning patients who may be encountered in their clinics.

3. Patient care management plans must reflect the realities of local resources, staffing, and transportation.

4. Consultation with a peer and/or medical law consultant on the legal and ethical requirements is recommended as it relates to notifications regarding the patient who represents a risk to others.

Annotation E	*Obtain Relevant History, Physical Examination and Laboratory Tests* *Obtain Symptom Score Using PHQ-9* *Determine and Document DSM-IV-TR Criteria for MDD*

4. ASSESSMENT

4.1. Obtain History, Physical Examination and Laboratory Tests

BACKGROUND

After determining that the patient is stable, the goal is to gain a complete understanding of the patient's medical, social, and mental health history and recognize current signs and symptoms of depression for diagnostic and treatment purposes.

The diagnosis of Major Depressive Disorder includes:

- A clinical course that is characterized by one or more major depressive episodes without a history of manic, mixed, or hypomanic episodes, or without being attributed to other medical or mental disorders
- Presence of depressed mood or loss of interest or pleasure, along with at least 4 additional symptoms as defined by the DSM-IV-TR criteria for MDD
- Symptoms have been present during the same 2-week period, nearly every day, and represent a change from previous functioning
- Symptoms cause clinically significant distress or impairment in social and occupational functioning
- Symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

Key elements in the clinical assessment include:

- A clinical interview focusing on past medical history and a brief review of systems is generally sufficient to rule out medical disorders causing major depression
- Focused physical examination and laboratory testing as indicated by the review of systems
- Findings of depression in Mental Status Exams including slow speech, sighing, psychomotor retardation or agitation, downcast eyes, and little or no smiling are important indicators
- Determination of medication history and substance abuse/dependence that may contribute to the symptoms or cause the depression

- Laboratory testing directed toward detection of associated general medical conditions.

Clinical Assessment of the Patient with MDD
• Medical history • Physical examination • Mental status examination (MSE) • Relevant laboratory tests • Drug inventory, including over-the-counter (OTC) drugs and herbals • Psychosocial history • Comorbid conditions

ACTION STATEMENT

Complete a thorough medical and mental health history and examination to develop an appropriate clinical understanding of the patient's condition and arrive at a diagnosis.

RECOMMENDATIONS

1. Once the patient is stable, the clinical assessment should be completed by the primary care provider, including a relevant history, physical examination, and laboratory tests as indicated. [I]

2. Relevant history may include the following:

   a. Review of the impact of depressive symptoms on functional status. Typical questions include:

      - "During the past few weeks, have any physical or emotional problems interfered with your typical daily activities?"
      - "Has it been more difficult to do things on your own or with your (family, friends, neighbors, church, etc.)?"
      - If positive, areas for brief inquiry include: job, pleasurable hobbies, social activities, and important personal relationships.

   b. Review of psychiatric, marital, family, and military service history, past physical or sexual abuse, and medication or substance use.

   c. Treatment for any prior mental health problems, past psychiatric hospitalizations, or inability to function in usual life roles.

   d. Additional information to the PHQ-9 that may help diagnose depression and determine severity of symptoms, such as:

      - Medically unexplained physical symptoms
      - Chronic, debilitating medical conditions
      - Current substance abuse/use

- Decrease in sensory, physical, or cognitive function
- Victim of current or past physical or sexual abuse or emotional neglect
- Family history of major depression
- Loss of significant relationship, primary support system, or economic status
- Neurological disorder (e.g., multiple sclerosis, Parkinson's disease, stroke) or history of closed head injury
- Protracted care-giving role for a family member with a chronic, disabling condition
- Spousal bereavement and widowhood
- Symptoms or signs of post traumatic stress disorder
- Mania/hypomania.

e. Review of medications, including prescription drugs and over-the-counter drugs (herbals, nutritionals, vitamins, and body building supplements).

3. Physical examination

   a. Appropriate physical examination including mental status exam; in certain subpopulations (e.g., elderly, traumatic brain injury), a screen for cognitive impairment is appropriate.

4. Laboratory tests as clinically indicated, e.g., complete blood count (CBC), chemistry profile, thyroid studies, B12 and folate assessments, pregnancy screen and toxicology screen and an ECG for patients over the age of 40.

DISCUSSION

Obtain a Psychiatric History

Key elements of the past history of depression include: prior antidepressant use, past hospitalization for depression or suicidality, and inability to function in usual life roles. Substance use and misuse can cause and/or exacerbate depression. Use of screening tools (such as the Alcohol Use Disorders Identification Test [AUDIT-C]) can improve detection of substance use disorders (see the VA/DoD Guideline on Substance Use Disorder).

There is a high likelihood of depression among individuals with past or present physical or sexual abuse or a history of substance use disorders. Primary care physicians should respectfully ask each patient direct and specific questions about physical or sexual abuse during the history.

Physical Examination

A brief screening physical examination may uncover endocrine, cardiac, cerebrovascular, or neurologic disease that may be exacerbating or causing depressive symptoms. Particularly in the elderly patient, a full Mental Status Examination (MSE) includes a cognitive screening assessment that may consist of a standardized instrument such as the Folstein Mini-Mental State Examination (MMSE) (Crum et al., 1993; Cummings et al., 1993; Folstein et al., 1975) (see the VA/DoD Guideline on Psychoses). If screening is suggestive of cognitive impairment and the patient is not delirious, then a laboratory evaluation to assess for reversible causes of dementia is appropriate. The depression assessment should be continued (Forsell, et al., 1993). If delirium is present, consider it an emergency and stabilize the patient before returning to the algorithm to continue with depressive assessment. Other MSE findings of importance in depression include slow speech, sighing, psychomotor retardation or agitation, downcast eyes, and little or no smiling.

Laboratory Evaluation

Use the history and physical examination findings to direct a conservative laboratory evaluation. There is no biomarker test for depression, so testing is directed toward detection of associated general medical conditions. Appropriate laboratory studies to rule out medical disorders that may cause symptoms of depression include complete blood count (CBC), chemistry profile, thyroid studies, and toxicology screen (Rosse et al., 1995). For patients over the age of 40, an ECG may be useful. In female patients of childbearing age, consider a pregnancy test to guide treatment decisions.

Diagnostic imaging and neuropsychological or psychological testing is not a part of the standard laboratory evaluation for depression. Proceed with the algorithm while awaiting the completion of the laboratory evaluation.

4.2. Symptom Score (PHQ-9)

BACKGROUND

Brief 2-item depression screens have high sensitivity but poor specificity for MDD, leading to high false positive rates. Further evaluation is required to establish an accurate diagnosis. Unipolar depressive disorders may be classified by DSM-IV-TR criteria into: major depressive disorder (MDD), dysthymic disorder, and depressive disorder not otherwise specified (DNOS). Since treatment is linked to diagnosis, it is important to determine whether a clinically significant mood disorder is present and, if so, to classify the patients accurately into the correct DSM-IV-TR category.

The nine-item Patient Health Questionnaire (PHQ-9) is a validated self- or interviewer-administered instrument that assesses DSM-IV-TR criterion symptoms and effects on functioning. In addition, it can be scored as a continuous measure to assess severity and monitor treatment response. The PHQ-9 can be administered in less than 2 minutes, is simple to score, is easily understood, and is available in multiple languages.

ACTION STATEMENT

Use a standardized instrument (PHQ-9) to document baseline depressive symptoms, measure symptom severity, and assist in evaluating treatment response and future progress.

RECOMMENDATIONS

1. For patients with a positive depression screen or in whom depression is suspected, administer the PHQ-9 as a component of the initial assessment. [B]

2. DSM-IV-TR criteria should be used to diagnose depression. The PHQ-9 assessment tool combined with a clinical interview should be used to obtain the necessary information about symptoms, symptom severity, and effects on daily functioning, that is required to diagnose MDD based on DSM-IV-TR criteria.

3. The PHQ-9 should be used to monitor treatment response at 4 to 6 weeks, after each change in treatment, and to periodically assess the patient's response to treatment until full remission is achieved.

(See Appendix B: Screening and Assessment Instruments)

Annotation F	*Do Medications or Comorbid Medical Conditions Contribute to Symptoms?*

5. DIAGNOSTIC WORK-UP

5.1. Do Medications Cause or Contribute to Symptoms?

BACKGROUND

Many prescription or over-the-counter (OTC) drugs contribute to depression. Although there is little published information on alternative medicines causing depression, consideration should also be given to herbal, nutritional, vitamin and body building supplements, particularly when consumed in large doses.

ACTION STATEMENT

Identify patients who may be experiencing depressed symptoms as a side effect of medication.

RECOMMENDATIONS

1. The diagnostic work-up for MDD should include a review of all prescription or over-the-counter (OTC) medications as they may cause or contribute to the depressive symptoms.

2. Consideration should also be given to herbals, nutritionals, vitamins, and body building supplements, particularly when consumed in large doses.

3. Consider discontinuing the offending medication as clinically indicated.

Common medications that contribute to or may cause depressive symptoms are presented in Table 3Table 3.

Table 3. Medication-induced Depression or Depressive Symptoms

Medication/ Class	Association	Comment
Beta-blockers	+/-	Recent, better designed investigations have not supported earlier findings that beta-blockers increase the risk of depression. Propranolol and soltalol have side effects labeled as depression.
Calcium channel blockers	+/-	An association between CCBs and depression or suicide has been reported in some studies; other studies have not found an association.
ACE-inhibitors	+/-	Conflicting reports of an association; some trials have reported an improvement in mood
Lipid-lowering agents	+/-	A meta-analysis reported an association between cholesterol lowering and suicide, violent, and accidental deaths. It is not clear whether the increased risk of mortality was secondary to the lowered cholesterol or the intervention(s). No such association has been found with the newer lipid-lowering agents (i.e., the statins)

Medication/ Class	Association	Comment
Reserpine Clonidine Methyldopa	+	Reserpine and the other rauwolfia alkaloids have long been associated with depression. The frequency and strength of association may have been exaggerated by the high doses used in the past. Clonidine and methyldopa may also cause sedation and symptoms of depression.
Corticosteroids	+	The majority of studies support an association. Corticosteroids, particularly higher doses, are associated with psychosis and mania.
Selective estrogen receptor modulators (SERM)	+/-	Data primarily suggest a lack of relationship between SERMs and depression. Confounding by diagnosis (usually breast cancer) may account for positive links.
NSAIDs	+	Rare psychiatric symptoms, not limited to depression, have been seen.
H_2-antagonists	-	No association found in small studies.
Benzodiazepines	+	Primarily a concern in older patients who use benzodiazepines chronically or those who abuse benzodiazepines. Benzodiazepine toxicity, namely sedation, may be mistaken for depressive symptoms.
Barbiturates	+	See benzodiazepines.
Topiramate	+	Known to have CNS effects (confusion and poor concentration) which may be mistaken for depressive symptoms.
Progesterone implants	+/-	Levonorgestrel has not been associated with depression. Medroxyprogesterone acetate has been reported to slightly increase the risk for depression in one study.
Interferon-ά	+/-	Mixed findings, although it appears that patients with hepatitis C may be at the greater risk.
Interferon-β	-	No evidence to support interferon-β causes depression in patients with multiple sclerosis.
Interleukin-2	+	Depressive symptoms along with cognitive problems, fatigue and appetite changes have been observed and usually appear early in the course of treatment.
Isotretinoin	-	A systematic review of nine studies did not find an association between the use of isotretinoin and depression. Data were insufficient to establish a relationship between isotretinoin and suicide.
Vareniciline (Chantix)	+	Chantix is a medicine used to help patients stop smoking. Chantix may cause worsening of a current psychiatric illness. Symptoms may include anxiety, nervousness, tension, depressed mood, unusual behaviors and thinking about or attempting suicide

Kotlyar et al., 2005; Marqueling et al., 2005; Patten et al., 2004

5.2. Do Medical Conditions Contribute to Symptoms?

BACKGROUND

Major depression may also be associated with medical illnesses or the patient's perception of his or her condition. Depressive symptoms may be a manifestation of an emergent medical condition, such as systemic lupus erythematosis (SLE) and clinical evaluation is needed to evaluate for these emergent conditions. Depression may be caused by some medical illnesses (e.g., profound hypothyroidism) and the depression may respond to treatment of the medical condition. More commonly, medical conditions and depressive disorders co-exist. Additionally, there is often a strong association between the level of disability from the medical condition and the depressive symptom requiring treatment.

ACTION STATEMENT

Identify patients who may be experiencing depressed symptoms as a result of an underlying medical condition.

RECOMMENDATIONS

1. The diagnostic work-up for MDD should include evaluation for existing or emerging medical conditions that may exacerbate the depression. These may include:
    a. Cardiovascular diseases
    b. Chronic pain syndrome
    c. Degenerative diseases
    d. Immune disorders
    e. Metabolic endocrine conditions (including kidney and lung diseases)
    f. Neoplasms
    g. Trauma
2. Simultaneous treatment is often required for both the medical problem and psychiatric symptoms and can lead to overall improvement in function.

Table 4 includes many of the pathobiologies associated with depression.

Table 4. Pathobiologies Related to Depression

Pathology	Disease
Cardiovascular diseases	Coronary artery disease Congestive heart failure Stroke Vascular dementias
Chronic pain syndrome	Fibromyalgia Reflex sympathetic dystrophy Low back pain (LBP) Chronic pelvic pain Bone or disease related pain
Degenerative diseases	Hearing loss Alzheimer's disease Parkinson's disease

	Huntington's disease Other neurodegenerative diseases
Immune disorders	HIV (both primary and infection-related) Multiple sclerosis Systemic lupus erythematosis (SLE) Sarcoidosis
Metabolic/endocrine conditions (including renal and pulmonary)	Malnutrition, vitamin deficiencies Hypo/hyperthyroidism Addison's disease Diabetes mellitus Hepatic disease (cirrhosis) Chronic obstructive pulmonary disease - (COPD) or asthma Kidney disease
Neoplasms	Of any kind, especially pancreatic or central nervous system
Trauma	Traumatic Brain Injury Amputation Burn injuries

Annotation G	*Are There Other Co-Occurring Mental Health Illnesses?*

5.3. Other Co-Morbid Psychiatric Conditions

BACKGROUND

Other common psychiatric conditions may complicate treatment or put the patient at increased risk for adverse outcomes. These conditions include bipolar disorder, post traumatic stress disorder (PTSD), substance use disorder (SUD), suicidality/homicidality, and psychosis.

ACTION STATEMENT

Determine whether other psychiatric conditions are present and may complicate treatment.

RECOMMENDATIONS

1. Patients presenting to primary care with evidence or suspicion of co-occurring psychiatric disorders should be offered referral to mental health specialty for evaluation and treatment. Conditions that should prompt the primary care provider to consider referral include:

    a. Extreme weight loss suggestive of anorexia nervosa

    b. Extensive history of childhood abuse, unstable or broken relationships, or criminal behavior starting before or during adolescence, that is suggestive of a personality disorder

    c. A pattern of "binging" (rapid and excessive consumption of food) and/or "purging" (use of self-induced vomiting, laxatives, or diuretics) to control weight that may suggest bulimia nervosa

d. Frequent and disabling nightmares or flashbacks suggestive of post traumatic stress disorder

e. Other major mental disorders (e.g., schizophrenia or bipolar disorder) likely to significantly complicate the primary care management of depression symptoms.

2. Patient presenting with unexplained physical symptoms and depression should be offered referral to a mental health specialist as these may represent a somatoform disorder.

5.4. Assessment for Bipolar Disorder

BACKGROUND

Some patients presenting with a major depressive episode have bipolar disorder, for which effective treatment may differ significantly from that for other depressed patients. A past history of mania or hypomania excludes a patient from a diagnosis of MDD. These patients may require referral to a mental health professional. These patients often need a specialist's treatment and follow-up, since initiating or titrating routine antidepressant medication can precipitate a manic episode.

ACTION STATEMENT

Determine if the patient has bipolar disorder.

RECOMMENDATIONS

1. The possible existence of bipolar disorder should be assessed in patients presenting with depressive symptoms, using a clinical interview or a bipolar questionnaire.

2. Patients suspected to have bipolar disorder should be referred to mental health for diagnosis and management.

Further information on assessment and screening tools for Bipolar Disorder – see: http://www.cqaimh.org/stable.html, and VA/DoD Clinical Practice Guideline for Bipolar Disorder

5.5. Substance Use Disorder

BACKGROUND

Alcoholism and major depressive disorder are distinct clinical entities and are not different expressions of the same underlying condition. Current alcohol consumption can be screened by asking a few questions that can be easily integrated into a clinical interview.

ACTION STATEMENT

Identify patients who require evaluation and treatment for substance use disorder (SUD).

RECOMMENDATIONS

1. Patients should be asked about any current or recent use of caffeine, nicotine, alcohol, or other psychoactive substances. [I]

2. Patients with current alcohol or other drug dependence should be managed according to the VA/DoD Guideline for Substance Use Disorder. [I]

5.6. Unexplained Symptoms

BACKGROUND

Medically unexplained symptoms of autonomic excitation such as cardiac (chest pain, atypical chest pain, palpitations, shortness of breath, hyperventilation), gastrointestinal (epigastric distress, irritable bowel syndrome), neurologic (headache, dizziness, paresthesias), panic attacks and frequent emergency room visits for medically unexplained somatic symptoms may be presented with depressive symptoms. These can cause significant impairment, suffering, and disability.

When considering depression, the clinician should assess whether the symptoms are causing the depression or the depression is resulting in physical complaints. Physical illness may cause psychosocial distress through a direct biological link, such as through neurotransmitters involved in both pain and mental disorders. Physical symptoms may cause emotional distress by overwhelming an individual's ability to cope. Distress may increase unhealthy behaviors that increase the risk of such symptoms. The disordered sleep and changes in autonomic nervous system functioning associated with stress may cause these symptoms. Finally, both mental disorders and medically unexplained symptoms (MUS) may be found together in some people, simply by chance.

Patients diagnosed with MDD may also present with complaints of pain. Patients presenting in primary care may initially complain of pain. After further assessment, the provider may identify an underlying diagnosis of MDD. The reverse is also true; patients diagnosed with MDD may experience and report symptoms of pain.

ACTION STATEMENT

Determine if the patient has other somatoform disorders.

RECOMMENDATIONS

1. Patients presenting with unexplained physical symptoms and depression should be offered referral to a mental health specialist as these may represent a somatoform disorder.

2. When referring a patient with possible MDD and unexplained physical symptoms to a mental health specialist, the primary care provider needs to:

    a. Build a trust relationship with the patient

    b. Carefully explain the reason for referral before and after it is recommended

    c. Set a follow-up appointment for after the referral.

Annotation H	*Are There Symptoms of Depression or Functional Impairment That Do Not Meet DSM IV-TR Criteria For MDD?*

6. DEPRESSION NOT OTHERWISE SPECIFIED

BACKGROUND

Depression not otherwise specified (NOS) includes depressive syndromes with fewer than 5 symptoms or of less than 2 weeks duration, thereby failing to meet major depression criteria (DSM-IV-TR). Although disorders categorized as depression NOS fail to meet specific diagnostic requirements for major depression or dysthymia, they, by definition, still cause "clinically significant distress or impairment in social, occupational, or other important areas of functioning." These depressive states are often referred to as "minor," "subthreshold," or "subsyndromal" depression (see Table 6).

ACTION STATEMENT

Identify patients with a diagnosis of depression not otherwise specified (NOS) and treat accordingly.

RECOMMENDATIONS

1. Patients with depressive symptoms who do not meet the diagnostic criteria of MDD (less than 5 symptoms and duration of less than two weeks) should be diagnosed with depression not otherwise specified (NOS.

2. If the diagnosis of depression NOS is made, the primary care provider may consider an initial approach of "watchful waiting" or a 4 to 8 week trial of support, psychoeducation, self-help, and exercise.

Table 5. Diagnostic Nomenclature for Clinical Depressive Conditions

DSM-IV-TR	Diagnostic Criteria	Duration
Major depression	≥ 5 depressive symptoms* (must include either depressed mood or anhedonia)	≥ 2 weeks
Dysthymia	3 or 4 dysthymic symptoms† (must include depressed mood)	≥ 2 years
Depression NOS	Variables: all included disorders must cause clinically significant impairment of daily functioning but fail to meet the classification for major depression or dysthymia. Example: minor depression with 2 to 4 depressive symptoms	≥ 2 weeks

*Depressive symptoms are 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.
†Dysthymic symptoms are generally the same as major depressive symptoms, with the addition of feelings of hopelessness and the omission of suicidal ideation.

7. DYSTHYMIA

BACKGROUND

Diagnosis and Relation to Major Depression

Dysthymia is a chronic mood disorder. To be diagnosed with dysthymia, an individual must report at least a two-year period during which, for most days, the individual experiences depressed mood for more than half of the day, along with at least two of the following symptoms:

- Increased or decreased appetite
- Insomnia or hypersomnia
- Fatigue or low energy
- Poor self-image
- Reduced concentration or indecisiveness
- Hopelessness.

Dysthymia is distinct from major depression due to the longer course (a minimum of two years as opposed to 2 weeks of symptoms) and lower severity (3 or more symptoms, most days, most of the time, versus 5 or more symptoms nearly every day). However, the two disorders are often difficult to distinguish in clinical settings. Some specific areas of differential diagnosis are chronic depression, double depression, and depression in partial remission. Depressive episodes lasting more than two years are defined as chronic depression. In this case, the higher severity of symptoms indicates a diagnosis of major depression rather than dysthymia. Double depression refers to comorbid diagnoses of both dysthymia and major depression. In this situation, a patient initially meets criteria for dysthymia (i.e., two years of symptoms that do not meet MDD criteria), and then develops an episode of major depression in the context of the dysthymic disorder. For diagnostic purposes, a separate dysthymic disorder is not diagnosed if a patient initially experiences a depressive episode, and continues to experience subsyndromal symptoms following recovery, even if those symptoms last more than two years. In this case, a diagnosis of major depression in partial remission is appropriate.

ACTION STATEMENT

Identify patients with a diagnosis of dysthymia and treat accordingly.

RECOMMENDATIONS

1. The diagnosis of dysthymia may be considered in patients who experienced a two-year period during which, for most days, the individual experiences depressed mood for more than half the of the day, along with at least two of the following symptoms:

    a. Increased or decreased appetite

    b. Insomnia or hypersomnia

    c. Fatigue or low energy

    d. Poor self-image

    e. Reduced concentration or indecisiveness

f. Hopelessness.

2. Patients who initially experienced a depressive episode and continue to experience subsyndromal symptoms following recovery, should be diagnosed as MDD in partial remission, even if those symptoms last more than two years.

3. Primary care providers may consider antidepressant pharmacotherapy or a combined course of pharmacotherapy and psychotherapy if the patient is diagnosed with dysthymia, though the evidence suggests that the benefits of psychotherapy, and possibly pharmacotherapy, are lower than those found in treatment of major depression.

4. In treating an elderly patient with dysthymia, psychotherapy should be considered, as some evidence suggests this is more effective than pharmacotherapy in this age group.

Annotation I	*Provide Psychoeducation for Self-Management*

(See Section 11)

Annotation J	*Determine Level of Symptoms Severity of MDD and Functional Impairment*

8. SEVERITY CLASSIFICATION OF MDD SYMPTOMS

ACTION STATEMENT

Use evaluation of PHQ-9 scores and functional impairment to determine the level of severity of MDD symptoms for a patient with MDD

RECOMMENDATIONS

1. The level of symptoms severity of MDD should be determined for the patient with diagnosed MDD based on the patient's symptoms score (PHQ-9) and level of functional impairment ascertained in the clinical psychiatric interview.

2. The classification of mild, moderate, or severe MDD should be used to establish a baseline and track progress as treatment is initiated (see Table 6).

3. Key symptoms that may have impact on a patient's functional impairment should be considered when using the following classification and may indicate assigning a higher level of severity than is determined by the PHQ-9 score.

Table 6. Symptom Severity Classification

Severity Level	PHQ-9 Total Score	Functional Impairment
Mild MDD	10-14	Mild
Moderate MDD	15-19	Moderate
Severe MDD	≥ 20	Severe
Modifiers		
Complications	Co-occurring PTSD, SUD, psychosis, suicide risk, mania, significant social stressors, war-related conditions	
Chronicity	More than 2 years of symptoms despite treatment	

Annotation K	Discuss Treatment Options and Patient's Preferences; Arrive at Shared Decision Regarding Treatment Goals and Plan

9. SHARED DECISION AND TREATMENT PLAN

BACKGROUND

Informed decision making is the collaboration between patient and healthcare provider to come to an agreement about a healthcare decision. Informed decision-making explains the medical condition, outlines treatment options, and walks the patient through what to consider about their own care. Prior to the initiation of treatment, the healthcare provider offers the patient information that will help him or her make a decision about treatment options. The discussion should include:

- Describe the likely outcomes of the various treatment options
- Discuss what is personally important about the risks and benefits of each option
- Encourage the patient to participate in the decisions about his/her medical care
- Emphasize that no one medical answer is right for all people and that the decisions that will best serve a particular patient often critically depends on the patient's own preferences and values.

ACTION STATEMENT

Including the patient in decisions about their medical care may increase adherence to treatment.

RECOMMENDATIONS

1. Patients should receive information that is reasonable for them about their treatment options.

2. Patients should be informed about the risks and benefits of each treatment option.

3. Patients should be assessed for their understanding of the ramifications of their choice.

RATIONALE

Selection of an initial treatment for depressed patients should be influenced by both clinical factors (e.g., severity of symptoms) and the patient's preferences.

Annotation L	*Is there Indication for Referral to Mental Health Specialty?*

10. MENTAL HEALTH REFERRAL/CONSULTATION

BACKGROUND

Approximately 10 to 20 percent of patients in primary care settings suffer from depressive disorders. Many patients with MDD can be effectively treated in primary care settings. Many patients with MDD prefer treatment by their primary care providers. However, some patients present with severe symptoms, co-morbid mental health disorders, or other complications that require referral and/or consultation with mental health providers. An important issue in referring patients to mental health specialists is the communication and coordination of care between primary care and mental health care providers to assure that patients receive high quality care.

ACTION STATEMENT

Appropriately refer patients with MDD or related disorders to mental health professionals.

RECOMMENDATIONS

1. Patients with severe or complicated depressive disorder should be referred to mental health specialty care.

2. Patients with depressive disorders may need more advanced specialized management if any of the following complicating factors that may influence treatment decisions exist:

    a. Failure to respond to adequate depression treatment or otherwise complicating treatment

    b. A co-existing mental health disorder that significantly complicates treatment (e.g., a history of hypomania or a manic episode, post traumatic stress disorder [PTSD], psychosis, substance use disorder [SUD])

    c. A co-existing medical condition that significantly complicates the treatment planning for depression

    d. Urgent or unstable psychiatric conditions

    e. Personal or family history of suicide attempts or suicidal ideas necessitating psychiatric hospitalization

    f. A past depressive episode involving severe loss of functioning or other life threatening consequences.

3. The primary care provider should consider consultation with mental health specialists in the following circumstances:

a. Unclear diagnosis

b. Failure to respond to 2 or more antidepressants

c. Three months of treatment without desired clinical improvement

d. Need for, or patient request for, psychotherapy or combination of both medication and psychotherapy

e. Concerns about patient's adherence to treatment

f. Extreme levels of distress and/or extremely impaired functioning that, in the primary care provider's judgment, seem beyond the capabilities of the primary care setting.

4. When weighing the need for consultation, the primary care provider should take into account the patient's preferences and common barriers to effective mental health consultation such as:

a. Patient reluctance to see a mental health care specialist

b. Feasibility for the patient

c. Geographical distance from consultants

d. Length of time to consultant availability.

11. INITIAL TREATMENT

Annotation M	*Initiate Treatment Strategies Effective for Depression*

Table 7. Treatment Strategies

	Level	PHQ Total Score	Functional Impairment	Initial Treatment Strategies *
Severity	Mild	5-14	Mild	Watchful waiting, supportive counseling; if no improvement after one or more months, consider use of an antidepressant or brief psychological counseling
	Moderate	15-19	Moderate	Start with monotherapyof either antidepressants or psychotherapy, or a combination of both
	Severe	≥ 20	Severe	May start with monotherapy of either antidepressants or psychotherapy, but should emphasize combinationof both or multiple drug therapy
Modifiers	Complicated	Co-occurring PTSD, SUD, mania, or significant social stressors		Start with combination of medications and somatic interventions
	Chronicity	> 2 years of symptomatology despite treatment		For mild -start with monotherapy of either antidepressants or psychotherapy,, or a combination of both For Mod/Severe - combination of antidepressants and psychotherapy or multiple drug therapy

*Treatment strategy options include:

1. Psychoeducation and self-management (provided to all MDD patients)
2. Watchful waiting
3. Monotherapy (psychotherapy or pharmacotherapy)
4. Combination psychotherapy and antidepressants
5. Treatment of complex patients
6. Somatic treatment
7. Inpatient and residential

11.1. Psychoeducation and Self-Management

BACKGROUND

The major goals of patient education are improved adherence to treatment and improved outcomes by eliciting the patient's active engagement in treatment. There should be 3 focus areas for patient education: education on the nature of depression, including its course and various treatment alternatives, education focused on adherence-enhancement strategies, and education focused on other self-management strategies.

ACTION STATEMENT

All patients, and when appropriate, family members, should be provided education regarding depression, its treatment options, and self-management strategies.

RECOMMENDATIONS

1. Psychoeducation should be provided for individuals with depression at all levels of severity and in all care settings and should be provided both verbally and with written educational materials. [I]

2. There should be education on the nature of depression and its treatment options and should include the following: [I]

    a. Depression is a medical illness, not a character defect

    b. Education on the causes, symptoms, and natural history of major depression

    c. Treatment is often effective and is the rule rather than the exception

    d. The goal of treatment is complete remission; this may require several treatment trials

    e. Treatment of depression can lead to decreased physical disability and longer life

    f. Education about various treatment options, including the advantages and disadvantages of each, side effects, what to expect during treatment, and the length of treatment

3. When antidepressant pharmacotherapy is used, the following key messages should be given to enhance adherence to medication: [B]

    a. Side effects often precede therapeutic benefit, but typically recede over time while benefits increase

    b. A slight increase in suicidal ideation in the first month may occur and patients should contact their provider if this does occur.

    c. Successful treatment often entails medication and/or dosage adjustments in order to maximize response while minimizing side effects

    d. Most people need to be on medication for at least 6 to 12 months after adequate response

e. It usually takes 2 to 6 weeks before improvements are seen

f. Continue to take the medication even after feeling better

g. Do not discontinue taking medications without first discussing with your provider

4. Education focused on treatment adherence should focus on the following: [I]

   a. Education on the risk of relapse in general; essentially, that relapse risk is high, particularly as the frequency of prior episodes increases

   b. Education on how to monitor symptoms and side effects

   c. Education on early signs and symptoms of relapse or recurrence, along with encouragement to seek treatment early in the event these signs or symptoms occur.

5. A major goal for the use of self-management strategies is to enhance the patient's active engagement in treatment. A common strategy is for a patient to collaboratively select one or two self-management goals at a time to pursue during treatment. Education should incorporate principles of self-management and may include information and goals related to:

   a. *Nutrition* – Often patients with MDD do not have a balanced diet. Expert opinion suggests that diet should be included in the therapeutic content. However, there is not a robust evidence base that improving diet impacts treatment outcomes. [I]

   b. *Exercise* (see Section 23.1 on Exercise) – MDD is associated with low levels of exercise. There is fairly strong evidence that exercise often has significant antidepressant effects. [B]

   c. *Bibliotherapy* (see Section 22.11 on Guided Self-Help) - Bibliotherapy (the use of self-help texts) may be helpful to patients for understanding their illness and developing self management skills. Guided self-help programs which entail a cognitive behavioral focus and intermittent monitoring and oversight by a health care professional are significantly more effective than no treatment control and as effective as more traditionally delivered modes (e.g., individual or group cognitive behavioral therapy [CBT]). [B]

   d. *Sleep hygiene* – Patients with MDD often have substantial sleep problems including insomnia, hypersomnia, and disturbances of sleep maintenance. Education regarding appropriate sleep hygiene should be included for patients exhibiting any sleep disturbances. [I]

   e. *Tobacco use* – Tobacco use has been demonstrated to impact on the recovery of depression; therefore, patients being treated for depression should be advised to abstain until their symptoms remit. Referral or treatment of nicotine dependence should be considered in patients treated for depression. [I]

   f. *Caffeine use* – Expert opinion suggests that excessive caffeine use may exacerbate some symptoms of depression such as sleep problems or anxiety symptoms. [I]

   g. *Alcohol use and abuse* – Even low levels of alcohol use have been demonstrated to impact on the recovery of depression; therefore, patients being treated for depression should be advised to abstain until their symptoms remit. [I]

h. *Pleasurable activities* (see Section 21.5 on Behavioral Activation) - Depression has been conceptualized by behavioral theorists as the loss or significant decrement of reinforcing activities. Behavioral activation (the systematic scheduling and monitoring of pleasurable or reinforcing activities) has been shown to have significant antidepressant effects. [B]

6. Psychoeducational strategies should be incorporated into structured and organized treatment protocols, which entail structured systematic monitoring of treatment adherence and response and self-management strategies. [B]

RATIONALE

The evidence suggests that the use of psychoeducation and self-management strategies lead to improvements in patient active involvement and adherence to treatment.

11.2. Watchful Waiting

BACKGROUND

Watchful Waiting (WW) is defined as prospective monitoring (i.e., 4-8 weeks) of symptoms and disability and is a strategy to be used in mild cases of depression to differentiate a diagnosis of major depression from an adjustment disorder, uncomplicated bereavement, or minor depression.

In patients with relatively few depressive symptoms, the diagnosis of major depression or dysthymia may not be self evident.

ACTION STATEMENT

Careful prospective monitoring of symptoms to determine if they persist or abate is a supported strategy in patients with relatively few depressive symptoms, prior to initiation of medication or psychotherapy.

RECOMMENDATIONS

1. In patients with likely adjustment disorder, bereavement or subsyndromal depression rather than major depression, a period of Watchful Waiting (WW) should be initiated. WW should only be considered when systematic follow-up assessments can be conducted.

2. Watchful Waiting should incorporate psychoeducation, general support, and prospective symptom monitoring over a 4 to 8 week period.

RATIONALE

There is an evidence base that a substantial number of patients with minor or subsyndromal depression will improve without formal treatments such as antidepressants or psychotherapy. Therefore, it is important not to expose patients to the expense or burden of treatments that are not recommended.

11.3. Monotherapy

BACKGROUND

MDD or mild-moderate MDD, necessitates the initiation of treatment in order to prevent further disability, psychic pain and mortality. A thorough and heartfelt discussion with the patient may delineate the proper therapy (either the use of an antidepressant or psychotherapeutic intervention).

ACTION STATEMENT

The initial treatment strategy for patients diagnosed with MDD, mild or moderate, should start with either psychotherapy or a single antidepressant.

RECOMMENDATIONS

1. Patients who are diagnosed with mild-moderate MDD should receive an initial trial of monotherapy that incorporates either an antidepressant medication or psychotherapy (see Table 7).

    a. Patient preferences, resources, and tolerability of treatment should be considered in determining the choice between an antidepressant and psychotherapy.

    b. Monotherapy should be optimized before proceeding to subsequent strategies by monitoring outcomes, maximizing dosage (medication or psychotherapy), and allowing sufficient response time (8-12 weeks).

11.4. Combination Psychotherapy and Antidepressants

BACKGROUND

In the initial treatment of moderate to severe MDD, the concurrent use of psychotherapy and antidepressant medication demonstrated statistically significant improvements in outcomes relative to monotherapy. Combining psychotherapy and antidepressant medication is also one of several legitimate alternative strategies to partial response or treatment non-response.

ACTION STATEMENT

Combination treatment of antidepressant medication and psychotherapy should be used for moderate to severe MDD or as a potential strategy for managing patients who have had partial or non-response to monotherapy.

RECOMMENDATIONS

1. In patients with moderate to severe MDD, the initial treatment strategy should include both empirically validated psychotherapy and an antidepressant medication.

2. Patient preferences, resources, and tolerability of treatment may override this recommendation in certain circumstances. In these circumstances, more aggressive monotherapy should be considered as well as adapting treatment when response is not robust.

11.5. Treatment of Complex Patients

BACKGROUND

Complex or refractory MDD may require the use of multiple psychotropic medications and ancillary services in order to maximize symptom reduction and enhance function. This level of care is often required in patients with concurrent anxiety or addictive disorders or other mental health problems. This may include the use of mood-stabilizing medications, antipsychotics, multiple antidepressants, benzodiazepines, case management, family support, peer support, group therapy, or mobile treatment units.

ACTION STATEMENT

Certain antidepressants or combinations of psychotropic medications may be required in severe or refractory cases of MDD.

RECOMMENDATIONS

1. More complex treatment strategies should be limited to patients with a diagnosis of MDD who are refractory to the above treatment strategies or in complex cases such as patients with psychiatric comorbidity.

2. The use of complex treatment strategies should be limited to those with expertise, such as a mental health provider.

3. The use of complex strategies increases the burden to patients, the chance of adverse events, and costs. Therefore, structured monitoring and assessment is critical in the management of these patients.

11.6. Somatic Treatment

BACKGROUND

There is evidence to support the efficacy of electro-convulsive therapy (ECT) for patients with refractory MDD. While ECT is efficacious in MDD in general, it is often reserved for more severe cases based on patient preference, safety, residual side effects and stigma. Vagus nerve stimulation (VNS) is a relatively novel treatment and lacks a strong evidence base that allows recommendations in specific patients. At the time of this guideline update, transcranial magnetic stimulation (TMS) is not FDA approved, and will not be addressed in this text.

ACTION STATEMENT

Certain somatic therapies (e.g., ECT, VNS) may be required in severe or refractory cases of MDD (i.e., during pregnancy, in catatonic patients, and in elderly patients diagnosed with psychotic depression).

RECOMMENDATIONS

1. Somatic treatment strategies should be prescribed and monitored only by physicians who have specific training and expertise in the management of treatment-resistant depression and the use of these devices.

a. Electro-convulsive therapy (ECT) is a recommended treatment strategy for patients who have failed multiple other treatment strategies.

b. Electro-convulsive therapy (ECT) may be a *first* line treatment for pregnant women, patients with psychotic depression, catatonic patients, or patients who have severe self-neglect issues.

c. Vagus nerve stimulation (VNS) is currently FDA approved only for treatment of resistant depression for patients who have failed to respond to at least 4 adequate medications and/or electro-convulsive therapy (ECT) trials.

11.7. Inpatient and Residential Settings

BACKGROUND

Inpatient or residential care settings can be useful in the acute stabilization of patients who have suicidal or homicidal thoughts or those with self-care or neglect concerns, by providing a non-threatening and safe environment. Inpatient and residential settings often incorporate all of the available treatment strategies including psychoeducation, pharmacotherapy, psychotherapy, somatic therapies, and case management.

ACTION STATEMENT

Severely impaired patients with MDD may require acute or subacute stabilization.

RECOMMENDATIONS

1. Patients who express suicidal or homicidal thoughts or who are unable to provide basic self-care should be considered for admission to an inpatient psychiatric unit.

2. Patients with unstable social networks or who lack significant support in the community may require subacute care in a residential setting.

RATIONALE

Inpatient and residential settings are used to provide acute stabilization and to provide a safe environment. Inpatient care usually lasts no more than 2 weeks and should be linked to ongoing outpatient or residential care. Residential care can last up to 6 to 12 months and provide a therapeutic environment in which the patient can develop a social network, work toward independence, and learn sufficient coping skills. Residential settings may be particularly warranted for patients who are homeless.

Annotation N	*Address Psychosocial Needs*

11.8. Psychosocial Issues

BACKGROUND

Psychosocial Rehabilitation services facilitate an individual's restoration to an optimal level of independent functioning in the community. This involves identifying and accessing resources for vocational, residential, social/recreational, educational and personal adjustment services. The

nature of the process and the methods used differ between settings and the individual's needs. Despite these variations, psychosocial rehabilitation is based on a strengths perspective which encourages persons to participate as actively as possible in determining and attaining their psychosocial goals.

ACTION STATEMENT

Psychosocial rehabilitation services should be offered to individuals with MDD who have significant, unmet psychosocial needs.

RECOMMENDATIONS

1. Individuals with MDD should be assessed for any significant, unmet psychosocial needs or situational stressors. These include, but are not limited to: [B]
    a. Inadequate or no housing
    b. Financial difficulties, especially if unable to meet basic needs
    c. Problematic family relationships or situations (including caregiver burden or domestic violence)
    d. Poor social support
    e. Religious and spiritual problems
    f. Occupational problems
    g. Difficulties with activities of daily living or instrumental activities of daily living
    h. Any other acute or chronic situational stressors
2. If unmet psychosocial needs are identified, psychosocial rehabilitation services should be offered to individuals with MDD at all levels of severity, regardless of population or setting, and regardless of the type of pharmacotherapy or psychotherapy being administered. [B]
3. Psychosocial rehabilitation services may include, but are not limited to, referrals to community social service agencies, emergency and transitional housing programs, vocational rehabilitation, agencies providing financial assistance, support groups, senior centers, and supervised living situations (e.g., foster homes, assisted living facilities). [C]

Annotation O	*Complete Assessment of Treatment Response; Review Current Medication; Assess for Dangerousness*

12. TREATMENT RESPONSE

12.1. Assess Depressive Symptoms, Functional Status and Suicide Risk

BACKGROUND

To assess response to treatment, depressive symptoms should be carefully assessed at follow-up visits. The PHQ-9 is a validated self- or interviewer-administered instrument that assesses DSM-IV-TR criterion symptoms, effects on functioning, and suicidal ideation. In addition, it can be scored as a continuous measure to assess severity and monitor treatment response. The PHQ-9 can

be administered in < 2 minutes, is simple to score, has an average reading level, and is available in multiple languages.

ACTION STATEMENT

Assess depressive symptoms, functional status, and suicide risk to determine treatment effects.

RECOMMENDATIONS

1. The PHQ-9 should be used to monitor treatment response at 4 to 6 weeks after initiation of treatment, after each change in treatment, and periodically until full remission is achieved. [B]

2. In patients who reach full remission, assessment of symptoms should be continued periodically to monitor for relapse or recurrence. [B]

3. Patients with suicidal ideation should have a careful evaluation of suicide risk. [A]

RATIONALE

The PHQ-9 is a validated instrument that is responsive to clinically important changes and aids treatment decisions by quantifying symptom severity. Assessing treatment response is critical to making informed modifications to the treatment plan.

12.2. Tolerability of Treatment

BACKGROUND

Antidepressant medications commonly have adverse effects that may interfere with adherence and successful treatment.

ACTION STATEMENT

Assess for adverse effects and tolerability after any change of treatment strategy.

RECOMMENDATIONS

1. Using a clinical interview, assess for treatment burden (e.g., medication side effects or adverse effects, attending appointments) after initiating or changing treatment, when the patient is non-adherent to treatment, or when the patient is not responding to treatment.

2. Identified side effects should be managed to minimize or alleviate the side effects.

(See Appendix D-2. Antidepressant Adverse Drug Effects: Receptor Affinities and Relative Comparisons.)

12.3. Adherence to Treatment

BACKGROUND

Poor adherence to treatment and/or premature discontinuation of treatment for depression is common and is associated with poorer outcomes and recurrence. Improved adherence improves treatment outcomes, but there is insufficient evidence to determine if it reduces recurrence. Several interventions have been shown to enhance adherence and improve symptom outcomes.

ACTION STATEMENT

> Systematically assess adherence to treatment with all depressed patients. Employ educational and systems interventions to enhance adherence for patients at high risk of poor adherence. Consider evidence-based psychotherapy in combination with antidepressant medications.

RECOMMENDATIONS

1. Adherence should be assessed directly and routinely, targeting common reasons for non-adherence (e.g., side effects, lack of efficacy, feeling better). [B]

2. Providers should give simple educational messages regarding antidepressant use (e.g., take daily, understand gradual nature of benefits, continue even when feeling better, do not stop without checking with the provider, and specific instructions on how to address issues or concerns) in order to increase adherence to treatment in the acute phase of treatment. [B]

3. In primary care, utilize collaborative care personnel (e.g., nurses, social workers, psychologists) and systems strategies to enhance adherence to treatment beyond the acute phase. Collaborative care strategies used by mental health specialists focus on patient education via systematic in-person or telephonic follow-up/monitoring to address adherence, relapse prevention issues and self-management strategies. [B]

4. For patients who are at high risk for non-adherence to antidepressant medication, refer for psychotherapy to increase medication adherence and decrease the chance of treatment discontinuation. [B]

12.4. Re-Evaluate Diagnoses and Treatment Strategy for Non-Response

BACKGROUND

In patients who do not respond to an adequate trial of empirically proven depression treatment, potential causes for non-response should be investigated. These may include poor treatment adherence, inaccurate diagnosis, psychiatric or medical comorbidity, or psychsocial stressors.

ACTION STATEMENT

> In patients who do not respond to an adequate treatment trial, reconfirm the diagnoses and assess for concurrent problems that may adversely affect treatment.

RECOMMENDATIONS

1. In treatment of non-responders, the diagnosis of MDD should be reconfirmed and the patient should be assessed for factors that may contribute to non-response. Referral to mental health specialty for a comprehensive assessment may be considered. Evaluation should include:

    a. Assessment for existence of psychiatric conditions that may present initially with depressive symptoms or adversely affect treatment response, including bipolar disorder, substance abuse, post traumatic stress disorder, generalized anxiety or panic disorder and in older adults, dementia.

    b. Assessment for medical conditions that may present with depressive symptoms. This may require additional history, physical examination, and laboratory testing. Poorly controlled medical conditions (e.g., chronic pain, congestive heart failure [CHF]) that may potentiate depression should be treated aggressively).

    c. Assessment for psychosocial problems that may contribute to treatment non-response. Domains assessed may include financial, legal, relationship, work, or negative life events.

Annotation P	*Is the Patient's Condition Improving and is the Current Treatment Strategy Tolerable?*

13. SYMPTOM IMPROVEMENT

BACKGROUND

The goal of treatment should be to achieve remission. Remission is defined as the absence of depressive symptoms or the presence of minimal depressive symptoms. Response is defined as a 50 percent or greater reduction in symptoms (as measured on a standardized rating scale) and partial response is typically defined as a 25 to 50 percent reduction in symptoms. For some standardized questionnaires (e.g., PHQ-9), specific changes in scores have been defined for the minimum clinically important improvement. Patients who have not shown at least a partial response by 4 to 6 weeks are unlikely to respond to that treatment. Therefore, a reasonable criterion for extending the initial treatment is if the patient is tolerating the treatment and experiencing clinically significant improvement at 4 weeks of therapeutic dose. For psychological treatments, response may be delayed, so the decision point for continued treatment may be delayed to 6 to 8 weeks.

ACTION STATEMENT

Determine if depressive symptoms are significantly improved, defined as a:
- Five-point reduction OR score <10 on the PHQ-9
- Twenty-five % or greater reduction in score on an accepted standardized instrument.

RECOMMENDATIONS

1. If the patient has shown clinically significant improvement in depressive symptoms, but is not yet at remission, and if medication has been well tolerated, then continuing to prescribe and raising the dose is recommended.

2. Improvement with psychotherapy is often slower than with pharmacotherapy. A decision regarding progress with psychotherapy and the need to change or augment this type of treatment may require 8 to 10 weeks before evaluation.

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Annotation Q	*Continue Current Treatment Strategy; Reassess By 4-6 Weeks*

14. CONTINUE CURRENT TREATMENT STRATEGY/REASSESS BY 4-6 WEEKS

ACTION ITEM

Ensure patient remains on treatment with desired outcome.

BACKGROUND

A large body of literature studying the effectiveness of either pharmacotherapy or psychotherapy or both, typically report at least a partial remission (50 percent symptom reduction) within four to six weeks of treatment. Full response, defined as minimal or no symptoms, often requires a longer duration of treatment and full restoration of psychosocial functioning may take several months.

Patients may discontinue treatment at the four to six week interval if either the symptoms are not improving or the symptoms have remitted somewhat despite the natural course of the illness. The four to six week patient visit is an important time to reinforce the need for continued treatment, possible treatment modification, patient education and assessment of adherence.

RECOMMENDATIONS

1. After initiation of therapy or change in medication or dose adjustment, patients should be monitored in person or by phone on a monthly basis. Clinicians can use these encounters to assess adherence to medication and psychotherapy, emergence of adverse effects, symptom breakthrough, suicidality, and psychosocial stress.

Annotation R	*Full Remission?*

15. FULL REMISSION

BACKGROUND

Remission of depressive symptoms is the goal of all antidepressant therapy. Although remission is recognized as the optimal outcome of treatment for depression, remission lacks a universally accepted definition. This is partly due to the lack of objective biologic markers or tests that confirm a response to treatment and no well-defined end points of treatment. Significant symptoms may still exist even though patients may have a full response as measured by currently available standardized psychiatric rating scales. In addition, many patients may experience marked improvement in depressive symptoms, but still have impaired psychosocial and work function. Rating scales define remission in clinical trials, but it is unclear how well these definitions predict risk of later relapse.

ACTION STATEMENT

The goal of antidepressant therapy should be the lowest possible degree of depressive symptomatology in order to minimize risk of later relapse.

RECOMMENDATIONS

1. Full remission in defined as:
   - PHQ-9 score of 4 or less, maintained for at least 1 month, OR
   - Beck Depression Inventory (BDI) score of 10 or less, maintained for at least 1 month, OR
   - Hamilton Rating Scale for Depression (HRSD) of 7 or less, maintained for at least 1 month.

Annotation S	*Continue Treatment to Prevent Relapse*

16. CONTINUATION TREATMENT

BACKGROUND

The conclusion of the acute phase of treatment is remission, which ideally occurs within the first 6 to 12 weeks of therapy. The primary goal of the second phase, the continuation phase, is to sustain remission and prevent relapse. Recurrence of depression after a first episode is common. Clinicians should educate patients and their families to self-assess for symptoms and risk for recurrent episodes. Surveillance for recurrence or relapse should continue indefinitely.

ACTION STATEMENT

Continue antidepressant treatment for at least six months to decrease the risk of relapse after initial remission is achieved.

RECOMMENDATIONS

1. In patients with MDD who achieve remission with antidepressant medication, treatment should be continued at the same dose for an additional 6 to 12 months to decrease the risk of relapse. [A]

2. In patients who achieve remission with psychotherapy, continuation phase psychotherapy should be considered for patients at higher risk for relapse, taking into account personal history, family history, and severity of current illness.

3. Cognitive behavioral therapy (CBT), Cognitive Therapy (CT), or Mindfulness-Based Cognitive Therapy (MBCT) should be used during the continuation phase of treatment with patients at high risk for relapse (i.e., two or more prior episodes, double depression, unstable remission status) to reduce the risk of subsequent relapse/recurrence. This can

occur after pharmacotherapy has ended or as a combined intervention for patients continuing pharmacotherapy. [A]

4. Depressive symptoms and functional status should be assessed periodically, more frequently early in the continuation phase, as this corresponds to the highest risk period for relapse. [C]

5. A relapse prevention plan should be developed that addresses duration of treatment, prognosis, self-management goals, and self-monitoring. [B]

Annotation T	*Continue Maintenance Therapy in Primary Care*

17. MAINTENANCE TREATMENT TO PREVENT RECURRENCE

BACKGROUND

The third phase, maintenance, targets patients who are at high risk for recurrent depressive episodes. The maintenance phase begins at the time that the physician considers the patient to be recovered but still at a risk for recurrence, and it may last many years, perhaps even indefinitely.

Upon complete remission of depressive symptoms, patients who receive continuation phase treatment of antidepressants (lasting at least 6 months) are less likely to suffer a relapse. Patients at high risk for recurrence are less likely to recur if treatment is continued beyond the continuation phase. Preventing relapse and recurrence is important. Beyond the patient/family suffering, additional episodes increase the risk for future episodes.

ACTION STATEMENT

Continue antidepressant treatment in patients who recover from depression but are at high risk for recurrence.

RECOMMENDATIONS

1. Patients should be assessed for risk of recurrence after completing the continuation phase treatment. [I]

2. Indications for Maintenance:

    a. Two or more prior episodes [B], chronic major (> 1 year), or double depression

    b. A family history of bipolar disorder and more severe depression as defined by: the need for hospitalization, strong suicidal ideation or behaviors, longer duration of symptoms, and more residual symptoms after response to treatment [C]

    c. Co-morbid substance abuse/dependence, anxiety disorders [C]

    d. Ongoing psychosocial stressors: low socioeconomic status, acrimonious relationship, chronic/severe medical illness [C].

3. Maintenance treatment should be continued at the same dosage that was used during the continuation phase, and continued for at least 12 months and possibly indefinitely. [A]

4. Consider maintenance phase psychotherapy for a very select population. [B]

Annotation U	*Adjust/Modify Treatment*

18. ADJUST/MODIFY TREATMENT FOR PARTIAL OR NO RESPONSE

BACKGROUND

The treatment options for patients presenting with MDD include pharmacotherapy, psychological and behavioral interventions, or a combination of the two. All available antidepressants have been shown to have superior efficacy compared to placebo. It is widely accepted that there are no differences in overall efficacy between antidepressants.

Onset Response to Treatment

Minimal clinically significant: a change in PHQ score of 25 percent

Response to treatment: PHQ score improvement of 50 percent from baseline

Full Remission

PHQ score of 4 or less, maintained for at least 1 month, OR

Recovery

PHQ score of 4 or less, maintained for at least 6 months

ACTION STATEMENT

The selection of an antidepressant for a patient with MDD should be based on safety, co-morbid conditions, symptoms, concurrent medication, and previous antidepressant response.

RECOMMENDATIONS

1. The choice of antidepressant should be based on safety, the patient's co-morbid conditions, symptoms, concurrent medication, and previous response: [I]
    a. Antidepressants in dosage forms that are taken once or twice a day should be prescribed to enhance patient adherence
    b. Antidepressant doses should be increased based on patient tolerance and response
    c. An adequate trial to response of an antidepressant is a therapeutic dose for 4 to 6 weeks.

Onset Response

2. Patients who do not tolerate an initial antidepressant prior to responding, should be switched to a different first-line antidepressant.

3. Patients who demonstrate a 25 percent improvement or greater, without achieving remission, from their baseline PHQ-9 score after 6 weeks of treatment have the following options:
    a. Continue present management and reassess in 4-6 weeks
    b. Consider raising the dose in patients who tolerate to accelerate remission

4. Patients who do not achieve a 25 percent improvement from their baseline PHQ-9 after 6 weeks of medication have the following options:
    a. Consider raising the dose in patients who tolerate to accelerate remission
    b. Switch to a different first line antidepressant and repeat the process starting at Box 32 of the clinical algorithm

Treatment Response-Remission

5. Patients who do not achieve remission (a PHQ-9 score < 5) after 8 to 12 weeks with an initial antidepressant have the following options:
    a. Increase in the dose, provided the dose has not already been maximized and is tolerable
    b. Current medication could be augmented with another medication (see #8) or combined with psychotherapy
    c. Switch to a different first line antidepressant and repeat the process starting at Box 32 of the clinical algorithm

6. Patients who do not achieve remission after 8 to 12 weeks of a second treatment trial using a first-line antidepressant have the following options available:
    a. Current medication could be augmented with another medication (see #8) or combined with psychotherapy (if not already tried)
    b. Consider modifying therapy and restarting the course of therapy with a different drug, following the steps and options discussed above starting at Box 32
    c. Consider a referral to mental health services.

7. Patients who do not achieve remission after adequate trials of two first-line antidepressants should either be switched to a new antidepressant from a different class (consider venlafaxine if not already tried) or receive augmentation with either medications or psychotherapy.

8. Patients who do not achieve remission after adequate trials of three different antidepressants should either receive augmentation with either medications or psychotherapy or receive combination antidepressant treatment or electro-convulsive therapy (ECT).

For a discussion of the evidence regarding antidepressants, see Section 20.

Table 8. Treatment Response and Follow-up

Step	Patient Condition	Options	Reassess at:
1	Initial Treatment		2 weeks *
2	Non response to initial low dose *	• Increase dose • Consider longer duration • Switch • Consider referral to specialty care	4 to 6 weeks
3	Failed second trial of antidepressant	• Switch • Augment or combine • Consider referral to specialty care	8 to 12 weeks
4	Failed 3 trials including augmentation	• Re- evaluate diagnosis and treatment • Consider referral to specialty care	12 to 18 weeks

**If treatment is not tolerable, switch to another antidepressant.*

19. CARE MANAGEMENT

ACTION STATEMENT

Care management should be considered for patients with MDD who are treated in primary care settings.

BACKGROUND

Many patients with mild to moderate major depression prefer treatment by their primary care clinician or will not follow-up for care when referred to specialty mental health care settings. Care management improves a range of outcomes for these patients

RECOMMENDATIONS

1. Consider 6 to 12 months of care management for patients with mild to moderate major depression. [B]

2. Care management components may be delivered by telephone, should be delivered by individuals with the relevant training and skill set, and should include: [B]

    a. Depression symptom monitoring using a validated instrument (e.g., PHQ-9) at each contact

    b. Depression education (illness, course, treatments, timing of expected treatment response, active coping strategies such as exercise and leisure planning)

    c. Antidepressant medication monitoring to include tolerability and adherence

    d. Initiation of crisis assessment and intervention as needed

    e. Care coordination with primary care and mental health clinicians as needed.

3. Care managers should:

a. Encourage and support regular attendance for scheduled visits with medical or mental health care providers and adherence to psychotherapies or antidepressant therapies as appropriate

b. Look for possible manic or hypomanic episodes or alcohol/substances abuse to facilitate referral to mental health

c. Participate in routine clinical review of the care manager caseload and facilitate feedback of mental health specialist recommendations

20. PHARMACOLOGIC TREATMENT

20.1. General

RECOMMENDATIONS

1. There is insufficient evidence to recommend one antidepressant medication over another for all patients.

    a. The choice of medication is based on side effect profiles (see Appendix D-2), history of prior response, family history of response, type of depression, concurrent medical illnesses, concurrently prescribed medications, and cost of medication

    b. Generally, selective serontonin reuptake inhibitors (SSRIs) or venlafaxine are first line antidepressants for patients in the primary care setting because of their low toxicity and ease of administration relative to other antidepressants

    c. Generally, initial doses used for the elderly should be lower than in healthy adults

    d. Prior to discontinuing an antidepressant as a failure, providers should ensure that an appropriate dose titration and target dose range has been achieved and an adequate response period allowed (a minimum of four to six weeks)

    e. Discontinuation of antidepressant maintenance therapy should be done with a slow taper, as it may result in adverse withdrawal symptoms or return of original depressive symptoms. Tapering should be guided by the elimination half-life of the parent compound and metabolites, and by close monitoring of depressive symptoms (see Appendix D-3).

20.2. Selective Serotonin Reuptake Inhibitors (SSRIs)

BACKGROUND

All selective serotonin reuptake inhibitors (SSRIs) work at the level of the synapse by blocking serotonin reuptake but are structurally distinct and have differences in receptor binding characteristics, pharmacokinetics, and side effect profiles. Consideration of these differences may guide the practitioner in selecting one of the SSRIs over another for an individual patient. All SSRIs are effective treatments for MDD and, excluding fluvoxamine, FDA approved for such.

ACTION STATEMENT

Selective serotonin reuptake inhibitors (SSRIs) along with the serotonin norepinephrine reuptake inhibitors (SNRIs), such as bupropion and mirtazapine are considered a first-line treatment option for adults with MDD.

RECOMMENDATIONS

1. All of the selective serotonin reuptake inhibitors (SSRIs), excluding fluvoxamine, may be used as first-line agents in the treatment of adults with MDD.

2. Patients who do not remit or are intolerant of one SSRI may be switched to another SSRI or to another class of antidepressant.

3. Patients who do not remit or are intolerant to two or more SSRIs should be switched to a different class of antidepressant.

4. Maximizing the dose of an SSRI should be considered for patients who show no response or partial response.

5. Augmentation may be considered for those who show only partial response to an SSRI.

6. When SSRIs are prescribed, the following should be considered:

    a. The potential for pharmacokinetic and pharmacodynamic drug interactions

    b. The potential for discontinuation symptoms particularly for the shorter-half life SSRIs

    c. Drug specific side effects in selecting specific SSRI for patients who may be sensitive to these effects (See Appendix D-2).

7. Avoid paroxetine in pregnant women.

8. When using SSRIs in pregnant women, the potential for increased risk of persistent pulmonary hypertension of the newborn should be considered.

20.3. SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

BACKGROUND

The serotonin norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. SNRIs, along with the SSRIs, bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.

ACTION STATEMENT

SNRIs, along with the selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, are considered a first line treatment option for adults with MDD.

RECOMMENDATIONS

1. Serotonin norepinephrine reuptake inhibitors (SNRIs) may be used as first line agents in the treatment of adults with MDD.

2. Patients who do not remit or are intolerant of an SNRI may be switched to another class of antidepressants.

3. SNRIs may be considered as a treatment option in patients who have not remitted to treatment with one or more second generation antidepressants (SSRIs, bupropion, or mirtazapine).

4. SNRIs should be initiated at a low dose to improve tolerability and then increased to an effective dose.

5. Maximizing the dose of venlafaxine may be considered for patients who show no response or a partial response to antidepressant treatment.

6. Augmentation may be considered for patients who show no response or a partial response to antidepressant treatment.

7. Consider the potential for drug interactions with this class.

8. Consider the potential for discontinuation symptoms with this class.

9. Avoid duloxetine in patients with substantial alcohol use or evidence of chronic liver disease.

20.4. Buproprion

BACKGROUND

Bupropion's mechanism of action differs from other antidepressants since it primarily affects dopamine and norepinephrine pathways. Because of its unique mechanism of action, bupropion's adverse event profile differs from other antidepressants. Bupropion can also be used to augment (in combination with) other antidepressants and is a treatment option for smoking cessation.

ACTION STATEMENT

Bupropion, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, is considered a first-line treatment option for MDD.

RECOMMENDATION

1. Bupropion is a treatment option for patients with MDD for whom a first-line antidepressant is appropriate.

2. Bupropion is an augmentation option for patients who have partially responded to a different antidepressant but have not achieved remission.

3. Patients should be titrated to the dose of bupropion that is effective and tolerable without exceeding the maximum recommended daily dose. (See Appendix D-1)

4. Bupropion should be considered as an alternative antidepressant for patients who have experienced intolerable sexual side effects with other antidepressants.

5. Bupropion may be considered for patients for whom weight gain would be problematic or for patients who experienced intolerable weight gain with another antidepressant.

6. Bupropion may be considered for patients with MDD who desire to stop smoking.

7. Bupropion should not be prescribed to patients with a history of seizure disorder or anorexia nervosa or bulimia.

20.5. Mirtazapine

BACKGROUND

Mirtazapine increases the release of norepinephrine and serotonin via its action as a central presynaptic alpha$_2$-adrenergic agonist. Mirtazapine also antagonizes 5-HT$_3$ serotonin, H$_1$ histamine, and peripheral alpha$_1$-adrenergic and muscarinic receptors. Because of its unique mechanism of action and pharmacologic profile, mirtazapine's adverse event profile differs from other antidepressants, most notably in its sedative properties at lower doses.

ACTION STATEMENT

Mirtazapine, along with the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and bupropion, is considered a first-line treatment option for MDD. Mirtazapine can also be used in combination with other antidepressants.

RECOMMENDATION

1. Mirtazapine is a treatment option for patients with MDD for whom a first-line antidepressant is appropriate.

2. Mirtazapine in combination with another antidepressant is a treatment option for patients who have not achieved remission after several trials with a first-line antidepressant.

3. Mirtazapine's dose should be titrated to a dose that is effective and tolerated without exceeding the maximum recommended daily dose. (See Appendix D-1)

4. Mirtazapine is a treatment option for patients who have experienced intolerable sexual side effects with other antidepressants.

5. Mirtazapine should be avoided in patients for whom weight gain would be problematic.

20.6. Tricyclic & Tetracyclic Antidepressants (TCAs)

BACKGROUND

TCAs inhibit reuptake of norepinephrine and/or serotonin at the presynaptic neuron, but are predominately adrenergic reuptake inhibitors. TCAs appear to be equally efficacious, but have major differences in their side-effect profile.

Contraindications to TCAs include:

- Hypersensitivity to any tricyclic drug (cross-reactivity may occur within a chemically related group such as TCAs)
- Acute recovery phase following myocardial infarction (MI).

TCAs should be avoided for patients with the following clinical conditions unless consultation from an appropriate specialist guides therapy:

- Angle-closure glaucoma or increased intraocular pressure
- History of urinary retention or urethral spasm
- Cardiovascular disease (CVD) including coronary heart disease (CHD) with ECG abnormalities, conduction abnormalities including bundle branch block, paroxysmal tachycardia and/or orthostatic hypotension
- Patients at risk for suicide
- Patients with cognitive impairment (anticholinergic effects may slow cognition or cause delirium)
- Concomitant use of TCAs and MAOIs.

The most common side effects of the TCAs include anticholinergic effects (dry mouth, blurred vision, increased intraocular pressure, constipation, urinary retention); cardiovascular effects (orthostatic hypotension, syncope, tachycardia, arrhythmias), CNS effects (sedation, confusion); weight gain (especially with amitriptyline and doxepin); and sexual dysfunction. TCAs can also decrease seizure threshold.

RECOMMENDATIONS

1. TCAs may be considered agents for certain patients who do not respond to two or more trials with first line antidepressants or who have previously achieved remission with TCA. [B]
2. TCAs should be used cautiously in the elderly. If the use of TCAs is necessary, nortriptyline and desipramine should be considered first. Due to increased side effects (e.g., CNS, anticholinergic, cardiovascular effects) associated with amitriptyline, imipramine and doxepin, the primary care physician should avoid the use of these agents in elderly patients.
3. TCAs should be used cautiously in patients who are at high risk for suicide.
4. Therapeutic response and dosing with a TCA may vary among patients due to both pharmacokinetic (e.g., enzyme induction by smoking), and pharmacodynamic (e.g., increased sensitivity in the elderly) differences.
5. Therapeutic plasma concentrations should be monitored. Of the various TCAs, plasma concentration for desipramine, imipramine, and nortriptyline are best established. Although amitriptyline has been extensively studied, no clear relationship between response and plasma level has emerged. The use of therapeutic blood concentration can be of value in

particular clinical instances, such as in patients who do not respond to or comply with therapy, patients on combination therapy, elderly patients, or patients with suspected drug toxicity.

20.7. Monoamine Oxidase Inhibitors (MAOIs)

ACTION STATEMENT

Monoamine oxidase inhibitors (MAOIs) are considered a treatment option for adults with MDD who have not achieved remission after trials with other antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).

BACKGROUND

While the mechanism of action of MAOIs as antidepressants is not completely understood, down regulation of β-adrenoreceptors, α1 and α2 adrenoreceptors, and serotonin-1 and serotonin-2 receptors as a result of MAO-B blockade are likely responsible for their antidepressant effects. MAOIs may be effective in patients who do not respond to treatment with other antidepressants, but their requirement for dietary restrictions, adverse effect profile and propensity for drug interactions limit their use. The MAOIs include three oral agents (isocarboxazid, phenelzine, and tranylcypromine) first introduced to the market in the late 1950s or early 1960s and a transdermal formulation of selegiline first marketed in 2006.

RECOMMENDATIONS

1. MAOIs may be considered a treatment option for adults with MDD who have not achieved remission on other antidepressants.
2. Patient education must include dietary and drug restrictions, including the requirement for a tyramine-restricted diet with all monoamine oxidase inhibitors (MAOIs) (with the exception of the lowest strength of the selegiline transdermal patch) to avoid a hypertensive crisis.
3. Avoid concurrent use with other medications with serotonergic effects (e.g., other antidepressants, triptans, meperidine, tramadol, propoxyphene, dextromethorphan) due to the risk of serotonin syndrome.
4. Avoid concurrent use with stimulants, vasoconstrictors and other medications with adrenergic effects due to the potential for hypertensive crisis.
5. Allow adequate wash-out periods following treatment with other antidepressants or other drugs that interact with MAOIs based on half-life (e.g., 5 weeks after stopping fluoxetine therapy before starting an MAOI).

20.8. Augmentation

ACTION STATEMENT

Augmentation with medication may be considered for patients who have had a partial response to antidepressant monotherapy at a therapeutic dose after at least 6 weeks. The augmenting medication selected should be based on the patient's current medications (including antidepressants), co-morbid conditions, and adverse effect profile.

BACKGROUND

Augmentation is useful for patients who have demonstrated a partial response tolerance to an antidepressant and wish to remain on that agent instead of switching to a different agent. Augmentation can be introduced at any place in therapy, after a partial response to an initial agent or a partial response after several trials of monotherapy. Clinicians may want to consider augmentation prior to trials with a tricyclic antidepressant or monoamine oxidase inhibitor.

RECOMMENDATIONS

1. Augmentation can be introduced at any point in therapy, provided the patient has demonstrated a partial response to an existing antidepressant

2. Bupropion SR and anxiolytic buspirone are the preferred initial augmentation strategies given their ease of use and lower risk of toxicity.

3. The atypical antipsychotics, with the exception of clozapine, can be considered as an alternative augmentation strategy, but should only be considered when other more established augmentation agents have either failed to result in remission or are contraindicated.

20.9. Psychostimulants

BACKGROUND

The psychostimulants, including the amphetamines and methylphenidate, are believed to exert their pharmacologic effects through neuronal release of dopamine and norepinephrine and by blocking the re-uptake of catecholamines. Methylphenidate and the amphetamines are available in a variety of controlled-release, sustained-release formulations designed to extend the dosing interval to every 12 or 24 hours; however, these formulations have not been studied in patients with MDD or depressive syndromes and are primarily intended for children with ADD or ADHD. All of the psychostimulants can increase heart rate or blood pressure, or provoke or induce anxietyand abuse. All are Schedule II drugs with the exception of modafanil which is Schedule IV.

ACTION STATEMENT

The psychostimulants including the amphetamines are not appropriate as monotherapy for the treatment of MDD. Psychostimulants may have a role as augmentation agents or in the treatment of other forms of depression such as in the medically-ill elderly or post-stroke patients.

RECOMMENDATIONS

1. The psychostimulants may have a role as augmentation agents, although the evidence is stronger in support of other augmentation agents.

2. The psychostimulants may be useful as monotherapy for patients who are demoralized, apathetic or physically inactive; specific patient populations are the medically ill elderly or post-stroke patients.

3. Methylphenidate is the most studied and preferred psychostimulant.

4. Only the immediate-release formulations of psychostimulants should be prescribed.

5. Patients receiving psychostimulants should have their heart rate and blood pressure monitored. Psychostimulants should not be prescribed for patients with uncontrolled hypertension or cardiovascular disease.

6. Psychostimulants are best avoided in patients with a co-morbid anxiety or for those in whom anxiety is a significant symptom of their depression.

21. PSYCHOTHERAPY

21.1. General Approach

BACKGROUND

There are several short term psychotherapy interventions that have evidence of efficacy in the treatment of major depression. The most well studied interventions are cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), and problem-solving therapy (PST). In addition, classes of treatment related to CBT have recently begun to be tested. Behavioral activation (BA) is derived both from CBT and from earlier behavioral therapy (BT) models, while mindfulness-based therapies (MBT) have evolved from an integration of cognitive and behavioral interventions with mindfulness and acceptance techniques.

ACTION STATEMENT

Evidence-based short-term psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended treatment options for major depression. Other psychotherapies are treatment options for specific populations or are based on patient preference.

RECOMMENDATIONS

1. First-line psychotherapies (cognitive behavioral therapy [CBT], interpersonal psychotherapy [IPT], and problem-solving therapy [PST]) are recommended for the treatment of uncomplicated major depression: [A]

    a. PST is recommended for psychotherapy provided in a primary care setting [A]

    b. Treatments should be delivered by providers trained in the specific technique [B]

    c. For severe depression (Hamilton rating scale for depression [HRSD] ≥20 or equivalent):

        - Behavioral Activiation (BA) is a recommended treatment [B]
        - CBT is a treatment option [B]

2. The recommended courses for first line psychotherapies (CBT, IPT, PST) are:

    a. CBT and IPT: 16 to 20 sessions over approximately 16 weeks [A]

    b. PST: six sessions over 3 months [A]

3. In patients with a history of suicide attempts, CBT is a recommended treatment for reducing risk of suicide attempts. [B]

4. For patients with severe, recurrent or chronic major depression, or double depression combination, CBT and pharmacotherapy are recommended treatments. [A]

5. For older patients with chronic MDD, combination dialectical behavior therapy (DBT) and pharmacotherapy is the recommended first-line treatment intervention. [B]

6. For older patients who have recently become caregivers for a disabled family member, short-term psychodynamic psychotherapy (SDPP) is the recommended first-line treatment intervention. [C]

7. For pregnant and postpartum women, CBT and IPT are the recommended first-line treatment interventions. [B]

8. For patients with comorbid depression and relationship distress, couples/marital-focused therapy (CFT) is the recommended first-line treatment intervention. [B]

21.2. Cognitive Behavioral Therapy (CBT)

BACKGROUND

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

ACTION STATEMENT

Individual CBT is a recommended treatment option for adults with major depression. CBT may be combined with pharmacotherapy for patients who do not respond to monotherapy.

RECOMMENDATIONS

1. Sixteen to 20 sessions of individual CBT for major depression is a recommended treatment option, including postpartum or older patients. [A]

2. CBT group is an option for treatment of major depression. [B]

3. For severe major depression, CBT alone is a treatment option. [B]

4. For severe, recurrent (3 or more episodes) or chronic major depression, CBT in combination with pharmacotherapy is a recommended treatment option. [A]

21.3. Interpersonal Psychotherapy (IPT)

BACKGROUND

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

ACTION STATEMENT

Individual Interpersonal Psychotherapy (IPT) is a recommended treatment option for adults (including older adults and pregnant women) with uncomplicated mild to moderate major depression.

RECOMMENDATIONS

1. Sixteen to 20 sessions of interpersonal psychotherapy (IPT) is a recommended treatment option for mild to moderate MDD. [A]

2. IPT in the treatment of mild to moderate MDD should be delivered by clinicians trained specifically in the delivery of IPT. [C]

3. IPT combined with pharmacotherapy is a treatment option for patients who do not respond to either monotherapy. [B]

21.4. Problem-Solving Therapy (PST)

BACKGROUND

Problem-solving therapy (PST) is defined as a discrete, time limited, structured psychological intervention that focuses on learning to cope with specific problem areas and where:

- Therapist and patient work collaboratively to identify and prioritize key problem areas, to break problems down into specific, manageable tasks, to problem solve, and to develop appropriate coping behaviors for problems. The intervention is short-term and the mode of action is hypothesized as skills acquisition. The intervention can be delivered effectively in primary care settings by general practitioners or nurses. This treatment modality is, in fact, where there is the strongest quality evidence.

ACTION STATEMENT

Problem-solving therapy (PST) is the recommended treatment for uncomplicated mild to moderate major depression particularly in primary care settings.

RECOMMENDATIONS

1. Six sessions of individual problem-solving therapy (PST), administered over 3 months, in a primary care setting, with or without antidepressant therapy (depending on other factors) is a recommended treatment option for patients with uncomplicated mild to moderate MDD, including older adults. [A]

21.5. Behavior Therapy/Behavioral Activation (BT/BA)

BACKGROUND

Behavior therapy (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. Primary therapeutic techniques of BT include collaborative empiricism (the therapist and patient working together to increase rewarding behaviors) and functional analysis of obstacles to activities. In addition, treatment incorporates structured practice outside of the session, including scheduled activities, mood tracking and interpersonal skills practice. Behavioral Activation (BA) is a particular version of BT which targets the link between avoidant behavior and depression and expands the treatment component of behavioral activation.

ACTION STATEMENT

Behavior Therapy (BT), including Behavioral Activation (BA), is a recommended treatment option for adults with major depression. It may be considered as a first line treatment for patients with severe depression who do not tolerate pharmacotherapy.

RECOMMENDATIONS

1. Individual Behavior Therapy/Behavioral Activation (BT/BA), is a treatment option for patients with mild to moderate MDD. [A]

2. Sixteen to 24 sessions of individual Behavior Therapy/Behavioral Activation (BT/BA) may be offered to patients with severe MDD, especially if they are not able to tolerate pharmacotherapy (including pregnant, postpartum, or older patients). [B]

3. Individual Behavior Therapy/Behavioral Activation (BT/BA) may be particularly useful in primary care settings, due to the potentially brief nature of the approach and the relative ease in learning how to effectively implement it. [I]

21.6. Couple/Marital-Focused Therapies

BACKGROUND

Couple/marital-focused therapy (CFT) is a theory-based time-limited psychological intervention that aims to help participants understand the effects of their actions on one another, on their relationship, and on depression symptoms and other problems. CFT aims to change interactions to be more supportive and less conflictual. Candidates for CFT for depression are couples who have at least one partner who has depression as well as marital distress. CFT is often variable, but often entails 15 to 20 sessions delivered over 5 to 6 months.

ACTION STATEMENT

Couple-focused therapy (CFT) is a recommended treatment option for mild to moderate, uncomplicated depression for patients concurrently experiencing marital distress.

RECOMMENDATIONS

1. Couple-focused therapy (CFT) is a treatment option for MDD if at least one member of the couple is experiencing depression as well as marital distress. [C]

21.7. Client-Centered Counseling

BACKGROUND

The term counseling has historically been synonymous with patient or client-centered, non-directive therapy that had its origins with Carl Rogers (has also been known as Rogerian, non-directive, supportive, and/or Humanistic psychotherapy). The approach posits that people can self-heal and/or solve their problems on their own under the right conditions; conditions provided by the therapist. These "necessary and sufficient conditions for therapeutic change" espoused by Rogers include high positive regard for the patient, therapist sincerity and genuineness, and empathic understanding of the patient's concerns. Patient-centered or non-directive therapists demonstrate these therapeutic conditions by actively listening to the patient's problems and helping him/her clarify major areas of concern, but leaving decisions to the patient without giving advice or providing interpretations. Over time, the term counseling has come to have a more generic meaning for a variety of short-term psychological interventions that may utilize other therapeutic strategies or techniques (e.g., psychodynamic and cognitive behavioral). There does, however, tend to be a retained emphasis on self-healing and patient empowerment.

ACTION STATEMENT

Consider the use of counseling for adults with mild to moderate MDD for short-term symptom reduction.

RECOMMENDATIONS

1. Counseling may be considered for achieving short term reduction in depressive symptoms for adults with mild to moderate MDD of recent onset. [C]

21.8. Acceptance and Mindfulness

BACKGROUND

Mindfulness-based or acceptance-based interventions (referred to subsequently as Mindfulness-based interventions or MBIs) for major depression are treatments that emphasize non-judgmental awareness of both internal experiences and external factors, in addition to behavioral and cognitive interventions to reduce distress. Specific versions of MBI include dialectical behavior therapy (DBT), mindfulness-based cognitive therapy for relapse prevention (MBCT), and acceptance and commitment therapy (ACT). While these models integrate techniques that are derived from spiritual practices (particularly Zen Buddhism), the models themselves have arisen from behavioral (DBT, ACT) or MBCT theories of psychopathology, and are not inherently spiritual practices. Models vary on the level of integration between traditional CBT interventions and mindfulness-

based skills, but in general there is training in mindfulness meditation, imagery, experiential exercises, and other techniques that aid patients in experiencing effect without necessarily attempting to change it. A key feature of these interventions is acceptance rather than avoidance of emotional pain. This acceptance is thought to reduce affective symptom severity. With regard to cognitions, unlike cognitive therapy, MBCT does not so much seek to modify or eliminate dysfunctional thoughts as to become more detached or less wrapped up in them. To facilitate effective behavior change, MBIs emphasize identification of personal values and learning to act based in pursuit of those values in spite of inevitable distress as opposed to having behaviors be focused on avoiding pain and adversity.

ACTION STATEMENT

Modified dialectical behavioral therapy (DBT) is an option for an adjunctive treatment to pharmacotherapy for major depression in older patients. [C]

RECOMMENDATIONS

1. Twenty-eight sessions of dialectical behavioral therapy (DBT) skills training class, supplemented by weekly phone coaching, may be offered as an augmentation strategy to pharmacotherapy for older patients with MDD. [C]

21.9. Short-Term Psychodynamic Psychotherapy

BACKGROUND

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

ACTION STATEMENT

Short-term psychodynamic psychotherapy (SDPP) is an option for treating mild to moderate MDD in an outpatient mental health setting.

RECOMMENDATIONS

1. Short-term psychodynamic psychotherapy (SDPP) may be considered for achieving reduction in depressive symptoms for mild to moderate MDD in adults, depending on patient preference and on the presence of other complex comorbidities. [C]

21.10. Computer-Based Cognitive Behavioral Therapy (CCBT)

BACKGROUND

Computer-based cognitive behavioral therapy (CCBT) is a structured program of care which seeks to replicate the care provided by a therapist following a standard CBT program. The standard structure typically includes an introduction to the program, including how to progress through it, systematic brief monitoring contacts (6 - 12 weekly sessions), to include telephoni, and general availability for consultation as needed. This intervention can be offered alone or as an adjunctive intervention to traditional psychotherapy or pharmacotherapy.

ACTION STATEMENT

Computer-based cognitive behavioral therapy (CCBT) may be an effective alternative option to traditional individual or group psychotherapy. [B]

RECOMMENDATIONS

1. Consider offering computer-based cognitive behavioral therapy (CCBT) to adults with mild to moderate depression as an alternative to standard psychotherapy, particularly when the latter is not readily accessible, or as an adjunctive intervention combined with standard psychotherapy or pharmacotherapy, with the goal of reducing depressive symptoms and achieving remission. [B]

21.11. Guided Self-Help

BACKGROUND

Guided self-help (GSH) is defined as a self-administered intervention designed to treat depression; it makes use of a range of books or a self-help manual, which are based on an evidence-based intervention and designed specifically for self-help utilization. A healthcare professional or paraprofessional could facilitate its utilization by introducing it and monitoring the patient's use and response to it. Contact is limited, usually not lasting beyond 3 contacts.

ACTION STATEMENT

Consider guided self-help (GSH) interventions for mild to moderate depression.

RECOMMENDATIONS

1. Guided cognitive-behavioral-based self-help interventions of 6 to 9 weeks duration, entailing brief monitoring and oversight by a healthcare professional or paraprofessional, may be offered to adult patients with mild to moderate major depression in order to reduce depressive symptoms and hopefully achieve remission, particularly if traditional cognitive-behavioral treatment options are not conveniently accessible. [B]

22. SOMATIC TREATMENT INTERVENTIONS

22.1. Electroconvulsive Therapy (ECT)

BACKGROUND

Electroconvulsive therapy (ECT) has advanced in terms of its importance in treating severe MDD, especially in its psychotic and treatment-resistant forms. Refinements in anesthetic, physiologic monitoring, stimulus control, and neuromuscular blockade techniques are largely responsible for the advances and have contributed to ECT's improved safety profile.

ACTION STATEMENT

Electroconvulsive therapy (ECT) should be considered in patients with severe MDD who cannot tolerate, or have not responded to, several trials of antidepressant treatment, unless the patient has significant co-morbid medical conditions that would increase the risks of ECT (e.g., recent myocardial infarction or intracerebral hemorrhage, currently taking MAOIs, or retinal detachment).

RECOMMENDATIONS

1. Electroconvulsive therapy (ECT) should be considered in patients with severe MDD and any of the following conditions: [A]
    a. Catatonia or other psychotic symptoms
    b. Severe suicidality
    c. A history of prior good response to ECT
    d. Need for rapid, definitive treatment response on either medical or psychiatric grounds
    e. Risks of other treatments outweigh the risks of ECT (i.e., comorbid medical conditions make ECT the safest treatment alternative)
    f. A history of poor response to multiple antidepressants
    g. Intolerable side effects to all classes of antidepressant medications (e.g., seizures, hyponatremia, severe anxiety)
    h. Patient preference.
2. In patients with the following potential contraindications for electroconvulsive therapy (ECT), the trade-off between risk and benefit must be weighed for each individual: [**B**]
    a. Space-occupying cerebral lesion or other conditions resulting in elevated intracranial pressure confers added risk of brainstem herniation
    b. Significant cardiovascular problems such as recent myocardial infarction, severe cardiac ischemic disease or profound hypertensive illness
    c. Recent intracerebral hemorrhage, or patients with bleeding or unstable vascular aneurysms or malformations

d. Degenerative diseases of the axial or appendicular skeleton - use of anesthetic and muscle relaxant techniques have added to the safety profile of ECT in these individuals.

e. Patient currently taking monoamine oxidase inhibitor medication (MAOI). MAOIs should be discontinued two weeks prior to initiating ECT in order to prevent a possible hypertensive crisis.

f. Patient currently taking lithium may develop a neurotoxic syndrome marked by increased mental confusion, disorientation, and unresponsiveness

g. Retinal detachment

h. Pheochromocytoma

i. High anesthesia risk – American Society of Anesthesiologists level 4 or 5.

3. Electroconvulsive therapy (ECT) should be considered a short-term therapy that requires maintenance treatment with antidepressants or if antidepressants are not tolerated, repeated treatment with ECT. [A]

4. There is insufficient evidence to recommend for or against ECT in the elderly. [I]

22.2. Vagus Nerve Stimulation (VNS)

BACKGROUND

Vagus nerve stimulation (VNS) for treatment of depression involves implanting a device that sends electrical pulses to the brain. The device consists of three parts: 1) a pulse generator implanted under the skin in the chest wall, 2) two electrodes that are wrapped around the vagus nerve, and 3) a programming wand for non-invasive programming of the device. This device was first approved by the FDA for treatment of refractory epilepsy. In patients with refractory epilepsy who received a VNS, it was noted that their mood improved, thus leading to consideration of VNS for depression.

ACTION STATEMENT

Vagus nerve stimulation (VNS) has not been demonstrated to be safe and effective and should not be routinely considered in patients with treatment resistant depression.

RECOMMENDATIONS

1. Vagus nerve stimulation (VNS) should not be routinely considered for patients with severe treatment resistant depression. [D]

23. OTHER TREATMENT INTERVENTIONS

23.1. Use of Exercise to Reduce Depression

BACKGROUND

Exercise has been associated with health and improvements in well-being. There is evidence to support the use of exercise as an adjunct to treatment for major depression. Patients under

treatment for MDD should be encouraged to fully participate in their own health maintenance, including diet and exercise.

ACTION STATEMENT

Providers should consider prescribing exercise to patients with mild to severe depression, if there are no medical contraindications.

RECOMMENDATIONS

1. Consider the use of exercise as an adjunct to other empirically supported treatments for depression, particularly antidepressant medication. [A]

2. Consider exercise as a monotherapy for depression, only if there are contraindications to other empirically supported treatments. [B]

23.2. Light Therapy

BACKGROUND

Originally linked with seasonal affective disorder (SAD), light therapy has evolved over the past twenty years to be used to treat a variety of non-seasonal disorders as well. There has been an increased amount of research and public awareness regarding light therapy unequaled by that taught in clinical training programs or covered by insurance.

ACTION STATEMENT

Consider light therapy for some patients with MDD, particularly if they have seasonal affective disorder (SAD).

RECOMMENDATIONS

1. Light therapy, including dawn simulation, may be considered an effective treatment for the patient with seasonal affective disorder (SAD). [B]

2. Light therapy may be considered in the treatment of MDD during pregnancy, in postpartum depression or for geriatric patients when more established treatments have increased risk of harm or are unavailable. [C]

3. A 2,500-Lux white light for two hours/day or treatment with 10,000-Lux for 30 minutes/day is recommended as these are equally efficacious and better than control treatments done with dim light. [C]

4. Light therapy may be considered for patients with MDD who don't want to take medications. [I]

5. Patients being treated for MDD with light therapy need to be monitored for safety. [C]

23.3. St. John's Wort

BACKGROUND

St. John's Wort (SJW) (hypericum perforatum) has been used in Europe for its antidepressant and its anti-inflammatory and wound healing properties. It is a popular natural product in the United States. SJW has many pharmacologically active compounds, but most studies have focused on defining the neuropharmacology of hyperforin and hypericin. It appears that hyperforin and related compounds are mostly responsible for SJW's effect on mood through their effects on neurotransmitter levels including serotonin, norepinephrine and dopamine.

ACTION STATEMENT

St. John's Wort (SJW) may be used for patients with mild major depression who have a strong preference for herbal treatments.

RECOMMENDATIONS

1. St. John's Wort may be used by patients with mild MDD who have a strong preference for herbal treatments. [B]

2. St John's Wort is not recommended for patients with moderate to severe major depression. [D]

3. St John's Wort should not be used by patients taking medication whose clearance is substantially dependent on the Cytochrome P450 (CYP) 3A4 isoenzyme. [D]

4. St. John's Wort is contraindicated in pregnancy [D]

5. Patient's taking St John's Wort should be informed of potential drug-drug interactions and advised to inform all prescribing clinicians that they are using this herbal treatment. [C]

23.4. Acupuncture

BACKGROUND

There is widespread community interest concerning complementary therapies, including acupuncture, in the treatment of MDD. Acupuncture has been investigated as an intervention for the treatment of major depressive disorder, but the trials have been small and methodological quality has varied.

ACTION STATEMENT

Acupuncture should not be recommended as a treatment for MDD.

RECOMMENDATIONS

1. There is insufficient evidence to determine the efficacy of acupuncture compared to medication, wait list control, or sham acupuncture in the management of major depressive disorder; therefore, it is not recommended as a treatment for MDD. [I]

Appendix B: Screening and Assessment Instruments

Appendix B-1: Quick Guide to the Patient Health Questionnaire (PHQ)

Purpose. The Patient Health Questionnaire (PHQ) is designed to facilitate the recognition and diagnosis of depressive disorders in primary care patients. For patients with a depressive disorder, a PHQ Depression Severity Index score can be calculated and repeated over time to monitor change.

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

Interpreting the PHQ. To facilitate interpretation of the patient's responses, all clinically significant responses are found in the column farthest to the right. (The only exception is for suicidal ideation when diagnosing a depressive syndrome.)

DSM-IV-TR Diagnostic Criteria

Major Depressive Syndrome 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).

Note: The diagnoses of Major Depressive Disorder and Other Depressive Disorder require ruling out normal **bereavement (mild symptoms, duration less than 2 months),** a history of a manic episode (Bipolar Disorder) and a **physical disorder, medication or other drug** as the biological cause of the depressive symptoms.

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

- *Have current symptoms been triggered by psychosocial **stressor(s)**?*
- *What is the **duration** of the current disturbance and has the patient received any **treatment** for it?*
- *To what extent are the patient's symptoms **impairing** his or her usual work and activities?*
- *Is there a **history** of similar episodes, and were they **treated**?*
- *Is there a **family history** of similar conditions?*

Interpreting the PHQ to Make a Provisional Diagnosis. To facilitate interpretation of patient responses, all clinically significant responses are found in the columns farthest to the right. Any symptom endorsed as being present at least "more than half the days" counts toward a DSM-IV-TR

diagnosis. (The only exception is for suicidal ideation which counts toward a DSM-IV-TR diagnosis if endorsed as being present "several days" or more.)

Appendix B-2. Example of Diagnosing Major Depressive Disorder & Calculating PHQ-9 Depression Severity

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

	Over the last 2 weeks, how often have you been bothered by any of the following?	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
		(0)	**(1)**	**(2)**	**(3)**
a	Little interest or pleasure in doing things?	☐	☐	☐	☒
b	Feeling down, depressed, or hopeless?	☐	☒	☐	☐
c	Trouble falling or staying asleep, or sleeping too much?	☐	☐	☒	☐
d	Feeling tired or having little energy?	☐	☐	☐	☒
e	Poor appetite or overeating?	☐	☒	☐	☐
f	Feeling bad about yourself—or that you are a failure or have let yourself or your family down?	☐	☐	☒	☐
g	Trouble concentrating on things, such as reading the newspaper or watching television?	☐	☐	☐	☒
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?	☒	☐	☐	☐
i	Thoughts that you would be better off dead or of hurting yourself in some way?	☐	☒	☐	☐
FOR OFFICE CODING: Maj Dep Syn 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 Dep Syn 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).					

Major Depressive Disorder Diagnosis. The criteria for Major Depressive Syndrome 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". Note that #i, suicidal ideation, is counted whenever it is present.

In this case, the diagnosis of Major Depressive *Disorder* (not Syndrome) 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.

PHQ-9 Depression Severity. This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. The Index is the sum of the scores for the nine items, and ranges from 0 to 27. In the above case, the PHQ-9 depression severity score is 16 (3 items scored 1, 2 items scored 2, and 3 items scored 3). Scores of 5, 10, 15, and 20 represent cutpoints for mild, moderate, moderately severe and severe depression, respectively. Sensitivity to change has also been confirmed.

Appendix B-3. PHQ-9 Scores and Proposed Treatment Actions *

PHQ-9 Score	DSM-IV-TR Criterion Symptoms	Depression Severity	Proposed Treatment Action
1 – 4	Few	None	None
5 – 9	<5	Mild depressive symptoms	Watchful waiting; repeat PHQ-9 at follow-up
10 – 14	5-6	Mild Major Depression	Treatment plan, considering counseling, follow-up and/or pharmacotherapy
15 – 19	6-7	Moderately Major depression	Immediate initiation of pharmacotherapy and/or psychotherapy
20 – 27	>7	Severe Major depression	Immediate initiation of pharmacotherapy and, if severe impairment or poor response to therapy, expedited referral to a mental health specialist for psychotherapy and/or collaborative management

** From Kroenke K, Spitzer RL, Psychiatric Annals 2002;32:509-521*

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr. Spitzer at rls8@columbia.edu or Dr. Kroenke at kkroenke@regenstrief.org. The names PRIME-MD® and PRIME-MD TODAY® are trademarks of Pfizer Inc.

Appendix B-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**
1	Little interest or pleasure in doing things?	**0**	**1**	**2**	**3**
2	Feeling down, depressed, or hopeless?	**0**	**1**	**2**	**3**
3	Trouble falling or staying asleep, or sleeping too much?	**0**	**1**	**2**	**3**
4	Feeling tired or having little energy?	**0**	**1**	**2**	**3**
5	Poor appetite or overeating?	**0**	**1**	**2**	**3**
6	Feeling bad about yourself—or that you are a failure or have let yourself or your family down?	**0**	**1**	**2**	**3**
7	Trouble concentrating on things, such as reading the newspaper or watching television?	**0**	**1**	**2**	**3**
8	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**
9	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 <u>any</u> problems, how <u>difficult</u> 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**
☐	☐	☐	☐

From the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues. For research information, contact Dr. Spitzer at rls8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc. Copyright© 1999 Pfizer Inc. All rights reserved. Reproduced with permission.

Appendix D: Pharmacotherapy

Appendix D-1. Antidepressant Dosing and Monitoring

	Class Agent	Initial Dose	Titration Schedule [1]	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
SSRI	Citalopram	20 mg once a day	20 mg weekly	60 mg	10-20 mg	Avoid: CrCl <20 ml/min	↓ dose	C
	Escitalopram	10 mg once a day	10 mg weekly	40 mg	5-10 mg	Avoid: CrCl <20 ml/min	10 mg	C
	Fluoxetine	20 mg once a day	20 mg 2weeks	80 mg	10 mg	No change	↓dose 50%	C
	Fluoxetine weekly	90 mg once a week	NA	90 mg	90 mg	Avoid	Avoid	C
	Paroxetine	20 mg once a day	20 mg weekly	50 mg	10 mg	10 mg	10 mg	D
	Paroxetine CR	25 mg once a day	12.5 mg weekly	62.5 mg	12.5 mg	12.5mg	12.5 mg	D
	Sertraline	50 mg once a day	50 mg weekly	200 mg	25 mg	No change	↓ dose	C
SNRIs	Duloxetine	20-30 mg twice a day		60 mg	20 – 40mg	Avoid if CrCl<30	Avoid	C
	Venlafaxine IR	37.5 mg twice a day	75 mg weekly	225-375 mg	25-50 mg	CrCl = 10-70, ↓ dose 50%	↓ dose 50%	C
	Venlafaxine XR	75 mg once a day	75 mg weekly	225 mg	37.5-75 mg			C
DNRI	Bupropion IR	100 mg twice a day	100mg weekly	450 mg	37.5mg BID	Has not been studied	Severe: 75 mg/day	C
	Bupropion SR	150 mg once a day	150mg weekly	400 mg	100 mg QD		100 mg QD or 150mg QOD	C
	Bupropion XR	150 mg once a day	150mg weekly	450 mg	150 mg QD			C
SARIs	Trazodone	50 mg three times a day	50 mg weekly	600 mg	25- 50 mg	No change	Unknown	C
	Nefazodone	100 mg twice a day	100 mg weekly	600 mg	50 mg BID	No change	Avoid	C
NaSSA	Mirtazapine	15 mg daily at bedtime	15 mg weekly	45 mg	7.5 mg QHS	CrCl <40 mL/min	Cl ↓ 30%	C
TCAs	Amitriptyline	50 mg once to – three times a day	Weekly	300 mg	10–25 mg HS	No change	Lower dose and slower titration recommended	C
	Impramine	25 mg once a day – four times a day	Weekly	300 mg	10-25 mg HS	No change		D
	Nortriptyline	25 mg three to four times a day	Weekly	150 mg	10-25 mg HS	No change		
	Desipramine	25 mg three times or- 75 mg once a day	Weekly	300 mg	10-25 mg QD	No change		
	Doxepin	25-75 mg daily at bedtime or twice a day	Weekly	300 mg	1-25 mg QHS	No change		C
MAOIs	Isocarboxazid	10 mg twice to three times a day			10 mg BID	No change	No change	C
	Phenelzine	15 mg three times a day	Weekly	90 mg	7.5 mg QD			C
	Selegiline patch	6mg/24hours	3 mg/24h 2 weeks	12 mg/24h	6 mg/24h			C
	Tranylcypromine	10 mg twice a day	10 mg weekly	60 mg/day	10 mg BID			C

TDM = Therapeutic Drug Monitoring;
[1]Recommended minimum time between dose increases.
NA = not applicable

Appendix D-2. Antidepressant Adverse Drug Effects: Receptor Affinities and Relative Comparisons

	Amine uptake inhibition		**Adverse Effects**							
	5HT	NE	Anticholinergic Activity (muscarinic)	Sedation (H_1)	Orthostatic Hypotension ($alpha_1$)	Cardiac Effects	GI Effects	Seizures	Weight Gain	Sexual Dysfunction
SSRIs										
Citalopram	+++	0/+	0	0/+	0	0	+++	0	0	+++
Escitalopram	+++	0/+	0	0/+	0	0	+++	0	0	+++
Fluoxetine	+++	0/+	0	0/+	0	0/+	+++	0/+	0/+	+++
Paroxetine	+++	0/+	0/+	0/+	0	0	+++	0	0/+	+++
Sertraline	+++	0/+	0	0/+	0	0	+++	0	0	+++
SNRIs										
Duloxetine	+++	+++	0	0/+	0/+	0/+	+++	0	0/+	+++
Venlafaxine	+++	+++	0	0	0	0/+	+++	0	0	+++
NDRIs										
Bupropion*	0/+	0/+	0	0	0	0	++	+++	0	0
SARIs										
Nefazodone	+++	0/+	0	+++	0	0/+	++		0/+	0/+**
Trazodone	+++	0	0	+++	0	0/+	++	0	+	+**
NaSSAs										
Mirtazapine	-	-	0	+++	0/+	0	0/+	0	0/+	0

	Amine uptake inhibition		**Adverse Effects**							
	5HT	NE	Anticholinergic Activity (muscarinic)	Sedation (H_1)	Orthostatic Hypotension ($alpha_1$)	Cardiac Effects	GI Effects	Seizures	Weight Gain	Sexual Dysfunction
TCAs										
Tertiary *Amines*										
Amitriptyline	+++	++	+++	+++	+++	+++	0/+	++	++	++
Clomipramine	+++	++	+++	++	++	+++	+		++	+++
Doxepin	++	+	++	+++	++	+++	0/+	++	++	++
Imipramine	+++	++	++	++	++	+++	0/+	++	++	++
Trimipramine	+	+	+++	+++	++	+++	0/+	++	++	++
Secondary Amines										
Desipramine	++	+++	+	0/+	+	++	0/+	+	+	++
Nortriptyline	+++	++	+	+	+	++	0/+	+	+	++
Protriptyline	++	+++	++	0/+	+	+++	0/+	++	0	++
Others										
Amoxapine*	++	+++	+	+	++	++	0/+	++	+	++
Maprotiline	+++	+++	++	++	++	++	0/+	+++	+	++
MAOIs										
Phenelzine	-	-	0	+	+	0	0/+	0	+	+++
Selegiline*	-	-	0	0	0	0	0	0	0	+
Tranylcypromine	-	-	0	0	+	0	0/+	0	+	++

*Inhibits dopamine receptors

**Nefazodone: also impotence (+) and risk of hepatotoxicity; trazodone: priapism (+)

Adapted from Baldessarini R. Drug therapy of depression and anxiety disorders. In: Brunton L, ed. Goodman & Gilman's Pharmacological Basis of Therapeutics. 11th ed. New York: McGraw Hill, 2006: 429-60; gastrointestinal and sexual effects for duloxetine updated based on recent clinical evidence.

Appendix F: Acronyms

ACT	Acceptance and Commitment Therapy
ADLs	Activities of Daily Living
ADM	Antidepressant Medication
AUC	Area Under the Curve
AUDIT-C	Alcohol Use Disorders Identification Test
BA	Behavioral Activation
BDI	Beck Depression Inventory
BT	Behavioral Therapy
CBC	Complete Blood Count
CBT	Cognitive Behavioral Therapy
CCBT	Computer-Based Cognitive Behavioral Therapy
CFT	Couples/Marital-Focused Therapy
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
DBT	Dialectical Behavior Therapy
DNOS	Depressive Disorder Not Otherwise Specified
ECT	Electro-Convulsive Therapy
EDPS	Edinburgh Postnatal Depression Scale
GDS	Geriatric Depression Scale
GSH	Guided Self-Help
HAM-D	Hamilton Depression Scale
HRSD	Hamilton Rating Scale for Depression
ICSI	Institute for Clinical Systems Improvement
IPT	Interpersonal Psychotherapy
LBP	Low Back Pain
MAOI	Monoamine Oxidase Inhibitor Medication
MBCT	Mindfulness-Based Cognitive Therapy
MBI	Mindfulness-Based Interventions
MBT	Mindfulness-Based Therapy
MDD	Major Depressive Disorder
MMSE	Mini-Mental State Examination
MAOIs	Monamine Oxidase Inhibitors
MSE	Mental Status Examination
MUS	Medially Unexplained Symptoms
NOS	Not Otherwise Specified
OTC	Over-the-Counter
PHQ-9	Patient Health Questionnaire-9 items
PST	Problem-solving Therapy
RCT	Randomized Controlled Trial
SAD	Seasonal Affective Disorder
SDPP	Short-Term Psychodynamic Psychotherapy
SLE	Systemic Lupus Erythematosis
SNRI	Serotonin Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
SDPP	Short Term Psychodynamic Psychotherapy
TAU	Treatment AS Usual
TCAs	Tricyclic & Tetracyclic Antidepressants
TMS	Transcranial Magnetic Stimulation
USPSTF	U.S Preventive Services Task Force
VNS	Vagus Nerve Stimulation
WW	Watchful Waiting