Clinical Practice Guideline

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

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The Management of MDD Working Group

With support from:

The Office of Quality and Performance, VA, Washington, DC

&

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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

Table of Contents

Page

Introduction **1**

Guideline Update Working Group **5**

Key Elements Addressed by the Guideline **6**

Algorithms and Annotations **11**

Appendices

Appendix A: Guideline Development Process

Appendix B: Screening and Assessment Instruments

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

B-2. Example of Diagnosing MDD & Calculating PHQ-9 Depression Severity

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

B-4. Nine Symptom Checklist (PHQ-9)

Appendix C: Suicidality

Appendix D: Pharmacotherapy

D-1. Antidepressant Dosing and Monitoring

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

D-3. Drug-Drug Interaction

Appendix E: Participant List

Appendix F: Acronym List

Appendix G: Bibliography

Tables

page

Table 1. Diagnosis of MDD (DSM-IV-TR Criteria, 2000) 15
Table 2. Classification of MDD Symptoms Severity 17
Table 3. Medication-induced Depression or Depressive Symptoms 35
Table 4. Pathobiologies Related to Depression 37
Table 6. Diagnostic Nomenclature for Clinical Depressive Conditions 42
Table 7. Symptom Severity Classification 46
Table 8. Treatment Strategies 51
Table 9. Treatment Response and Follow-up 80

Introduction

The Clinical Practice Guideline for the Management of Major Depressive Disorder (MDD) was developed under the auspices of the Veterans Health Administration (VHA) and the Department of Defense (DoD) pursuant to directives from the Department of Veterans Affairs (VA). VHA and DoD define clinical practice guidelines as:

> "Recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes:
> - Determination of appropriate criteria such as effectiveness, efficacy, population benefit, or patient satisfaction; and
> - Literature review to determine the strength of the evidence in relation to these criteria."

The intent of the guideline is to:

- Reduce current practice variation and provide facilities with a structured framework to help improve patient outcomes
- Provide evidence-based recommendations to assist providers and their patients in the decision-making process for patients with MDD
- Identify outcome measures to support the development of practice-based evidence that can ultimately be used to improve clinical guidelines.

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.

The guideline:

- Offers best practice advice on the care of adults who have a clinical working diagnosis of MDD.
- Covers diagnostic criteria for MDD.
- Focuses on identification of susceptibility factors (i.e., adult patients at increased risk for developing MDD).

- Specifies key elements in the evaluation of patients with MDD.
- Addresses pharmacotherapy and management of comorbidities in patients with MDD.
- Addresses psychological treatments for acute phase treatment and relapse prevention
- Addresses indications for consultation and referral to specialty care
- Does ***not*** cover the management of patients with minor depression or dysthymia and is limited to depression in adults only.

Development Process

The development process of this guideline follows a systematic approach described in "Guideline-for-Guidelines," an internal working document of VHA's National Clinical Practice Guideline Counsel. Appendix A clearly describes the guideline development process.

In the development of this guideline, the Working Group relied heavily on the following evidence-based guidelines:

- Management of Major Depressive Disorder in Adults in the Primary Care Setting. Washington, DC: VA/DoD Evidence Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs, and Health Affairs, Department of Defense, May 2000. Office of Quality and Performance publication 10Q-CPG/MDD-00

- National Collaborating Centre for Mental Health. Depression: management of depression in primary and secondary care. London (UK): National Institute for Clinical Excellence (NICE) 2004; Clinical Practice Guideline 23. (Referred to throughout this document as NICE-2004)

Search for additional research published since the previous 2000 VHA/DoD guideline reveals that considerable progress has been made in depression research over the brief period separating these two works. The literature was critically analyzed and evidence was graded using a standardized format. The evidence rating system for this document is based on the system used by the U.S. Preventive Services Task Force (USPSTF).

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."

This Guideline is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VA, DoD, and academia, and a guideline facilitator from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The draft document was discussed in 3 face-to-face group meetings. The content and validity of each section was thoroughly reviewed in a series of conference calls. The final document is the product of those discussions and has been approved by all members of the Working Group.

The list of participants is included in Appendix E to the guideline.

Implementation

The guideline and algorithms are designed to be adapted by individual facilities in considering needs and resources. The algorithms serve as a guide that providers can use to determine best interventions and timing of care for their patients to optimize quality of care and clinical outcomes. This should not prevent providers from using their own clinical expertise in the care of an individual patient. Guideline recommendations are intended to support clinical decision-making and should never replace sound clinical judgment.

Although this guideline represents the state of the art practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating of published information. New technology and more research will improve patient care in the future. The clinical practice guideline can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of clinical practice guidelines such as these may lead to the development of new practice-based evidence.

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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.

Table of Contents

By Annotations

Page

Annotation A: Patient Age > 18 With Suspected Depression Presenting to Primary Care 24

Annotation B: Brief Assessment of Initial Presentation to Assess for Dangerousness 24

Annotation C: Unstable Urgent Condition? 26

Annotation D: Provide Appropriate Care or Refer to Stabilize and Follow Legal Mandates 29

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 30

Annotation F: Do Medications or Comorbid Medical Conditions Contribute to Symptoms? 34

Annotation G: Are There Other Co-Occurring Mental Health Illnesses? **Error! Bookmark not defined.**

Annotation H: Are There Symptoms of Depression or Functional Impairment That Do Not Meet DSM-IV-TR Criteria For MDD? 41

Annotation I: Provide Psychoeducation for Self-Management 45

Annotation J: Determine Level of Symptoms Severity of MDD and Functional Impairment 45

Annotation K: Discuss Treatment Options and Patient's Preferences; Arrive at Shared Decision Regarding Treatment Goals and Plan 49

Annotation L: Is there Indication for Referral to Mental Health Specialty? 49

Annotation M: Initiate Treatment Strategies Effective for Depression 51

Annotation N: Address Psychosocial Needs 60

Annotation O: Complete Assessment of Treatment Response; Review Current Medication; Assess for Dangerousness 64

Annotation P: Is the Patient's Condition Improving and is the Current Treatment Strategy Tolerable? 69

Annotation Q: Continue Current Treatment Strategy; Reassess By 4-6 Weeks 70

Annotation R: Full Remission? 71

Annotation S: Continue Treatment to Prevent Relapse 73

Annotation T: Continue Maintenance Therapy in Primary Care 74

Annotation U: Adjust/Modify Treatment 78

By Topics

Page

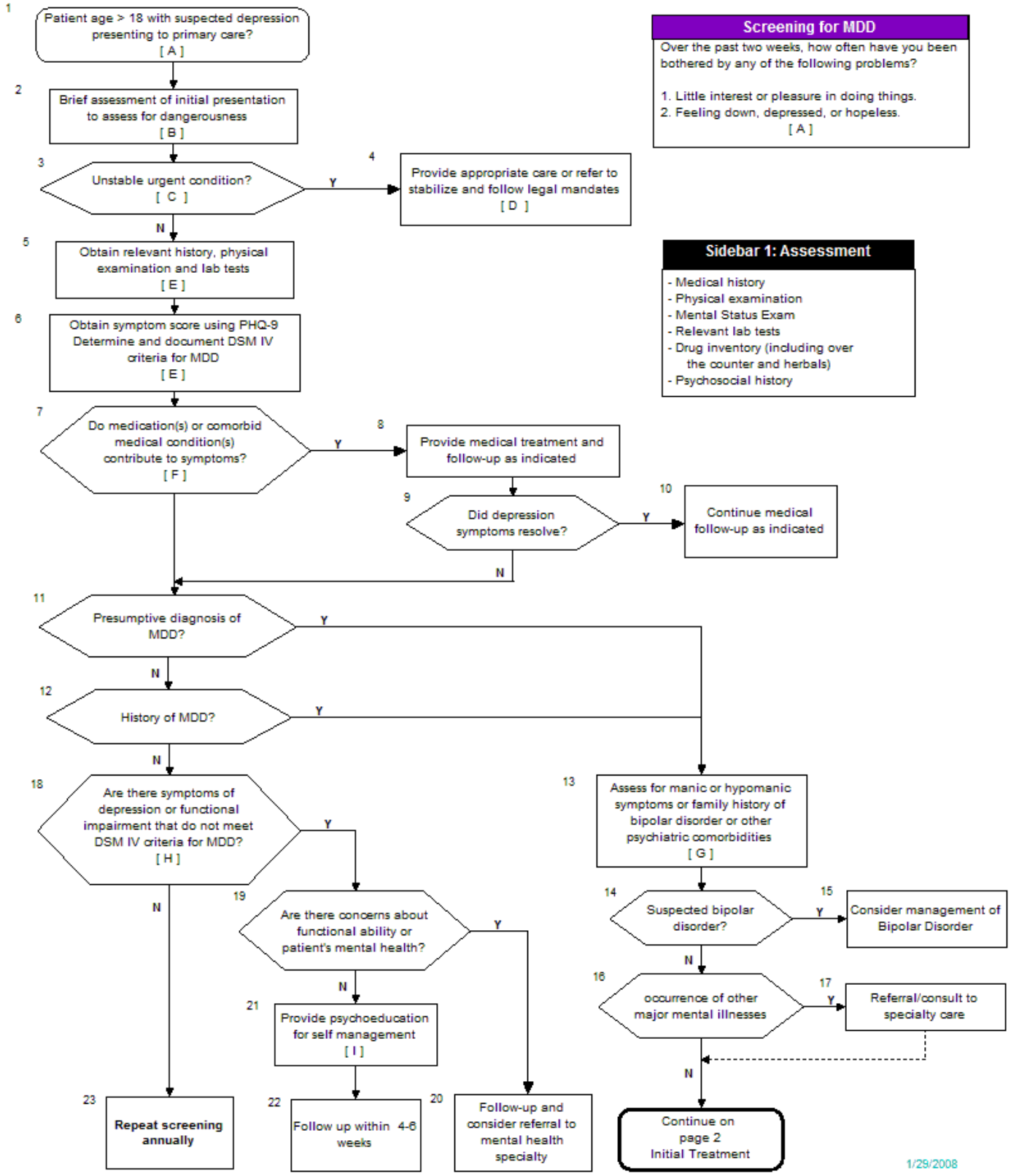
1. DEFINITIONS 15
2. SCREENING 17
   - *2.1. Screening Adults* *17*
   - *2.2. Screening/Assessment for Depression in Pregnancy and in the Postpartum Period* *21*
3. DANGEROUS CONDITIONS 24
   - *3.1. Assess for Dangerousness* *24*
   - *3.2. Is Patient a Threat to Self or Others?* *26*
   - *3.3. Is There Evidence of Psychosis?* *27*
   - *3.4. Provide Appropriate Care or Refer to Stabilize and Follow Legal Mandates* *29*
4. ASSESSMENT 30
   - *4.1. Obtain History, Physical Examination and Laboratory Tests* *30*
   - *4.2. Symptom Score (PHQ-9)* *33*
5. DIAGNOSTIC WORK-UP 35
   - *5.1. Do Medications Cause or Contribute to Symptoms?* *35*
   - *5.2. Do Medical Conditions Contribute to Symptoms?* *36*
   - *5.3. Other Co-Morbid Psychiatric Conditions* *38*
   - *5.4. Assessment for Bipolar Disorder* *39*
   - *5.5. Substance Use Disorder* *40*
   - *5.6. Unexplained Symptoms* *40*
6. DEPRESSION NOS 41
7. DYSTHYMIA 43
8. SEVERITY CLASSIFICATION OF MDD SYMPTOMS 45
9. SHARED DECISION AND TREATMENT PLAN 49
10. MENTAL HEALTH REFERRAL/CONSULTATION 49
11. INITIAL TREATMENT 51
    - *11.1. Psychoeducation and Self-Management* *52*
    - *11.2. Watchful Waiting* *55*
    - *11.3. Monotherapy* *56*
    - *11.4. Combination Psychotherapy and Antidepressants* *57*
    - *11.5. Treatment of Complex Patients* *58*
    - *11.6. Somatic Treatment* *58*
    - *11.7. Inpatient and Residential Settings* *59*
    - *11.8. Psychosocial Issues* *60*
12. TREATMENT RESPONSE 64
    - *12.1. Assess Depressive Symptoms, Functional Status and Suicide Risk* *64*
    - *12.2. Tolerability of Treatment* *65*
    - *12.3. Adherence to Treatment* *65*
    - *12.4. Re-Evaluate Diagnosis and Treatment Strategy for Non-Response* *68*
13. SYMPTOM IMPROVEMENT 69

14. CONTINUE CURRENT TREATMENT STRATEGY/REASSESS BY 4-6 WEEKS 70
15. FULL REMISSION 71
16. CONTINUATION TREATMENT 73
17. MAINTENANCE TREATMENT TO PREVENT RECURRENCE 74
18. ADJUST/MODIFY TREATMENT FOR PARTIAL OR NO RESPONSE 78
19. CARE MANAGEMENT 81
20. PHARMACOLOGIC TREATMENT 83
20.1. General 83
20.2. Selective Serotonin Reuptake Inhibitors (SSRIs) 83
20.3. SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs) 87
20.4. Buproprion 89
20.5. Mirtazapine 91
20.6. Tricyclic & Tetracyclic Antidepressants (TCAs) 93
20.7. Monoamine Oxidase Inhibitors (MAOIs) 95
20.8. Augmentation 97
20.9. Psychostimulants 99
21. PSYCHOTHERAPY 101
21.1. General Approach 101
21.2. Cognitive Behavioral Therapy (CBT) 108
21.3. Interpersonal Psychotherapy (IPT) 111
21.4. Problem-Solving Therapy (PST) 113
21.5. Behavior Therapy/Behavioral Activation (BT/BA) 115
21.6. Couple/Marital-Focused Therapies 118
21.7. Client-Centered Counseling 119
21.8. Acceptance and Mindfulness 121
21.9. Short-Term Psychodynamic Psychotherapy 123
21.10. Computer-Based Cognitive Behavioral Therapy (CCBT) 125
21.11. Guided Self-Help 127
22. SOMATIC TREATMENT INTERVENTIONS 130
22.1. Electroconvulsive Therapy (ECT) 130
22.2. Vagus Nerve Stimulation (VNS) 132
23. OTHER TREATMENT INTERVENTIONS 134
23.1. Use of Exercise to Reduce Depression 134
23.2. Light Therapy 136
23.3. St. John's Wort 137
23.4. Acupuncture 139

Management of Major Depressive Disorder in Adults

Primary Care Initial Assessment and Diagnosis

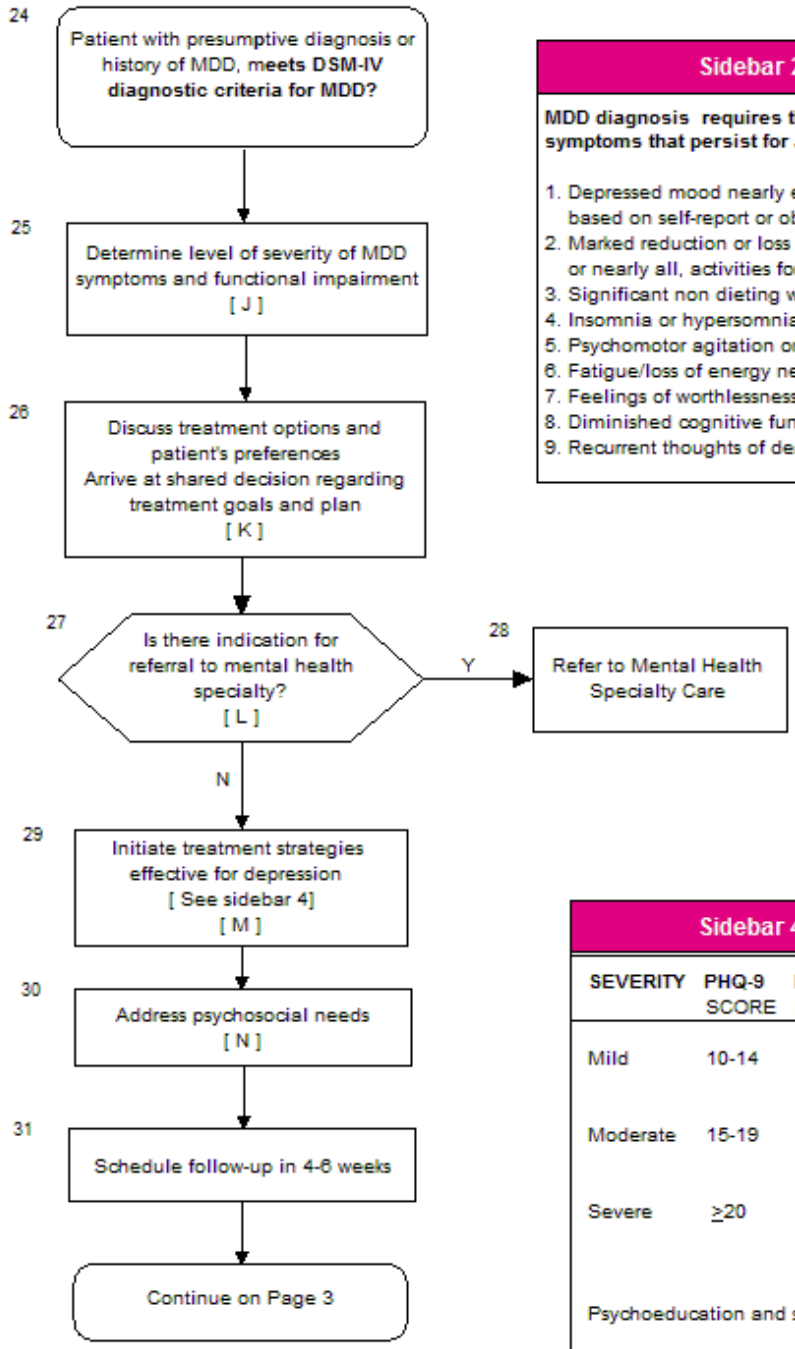
1



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

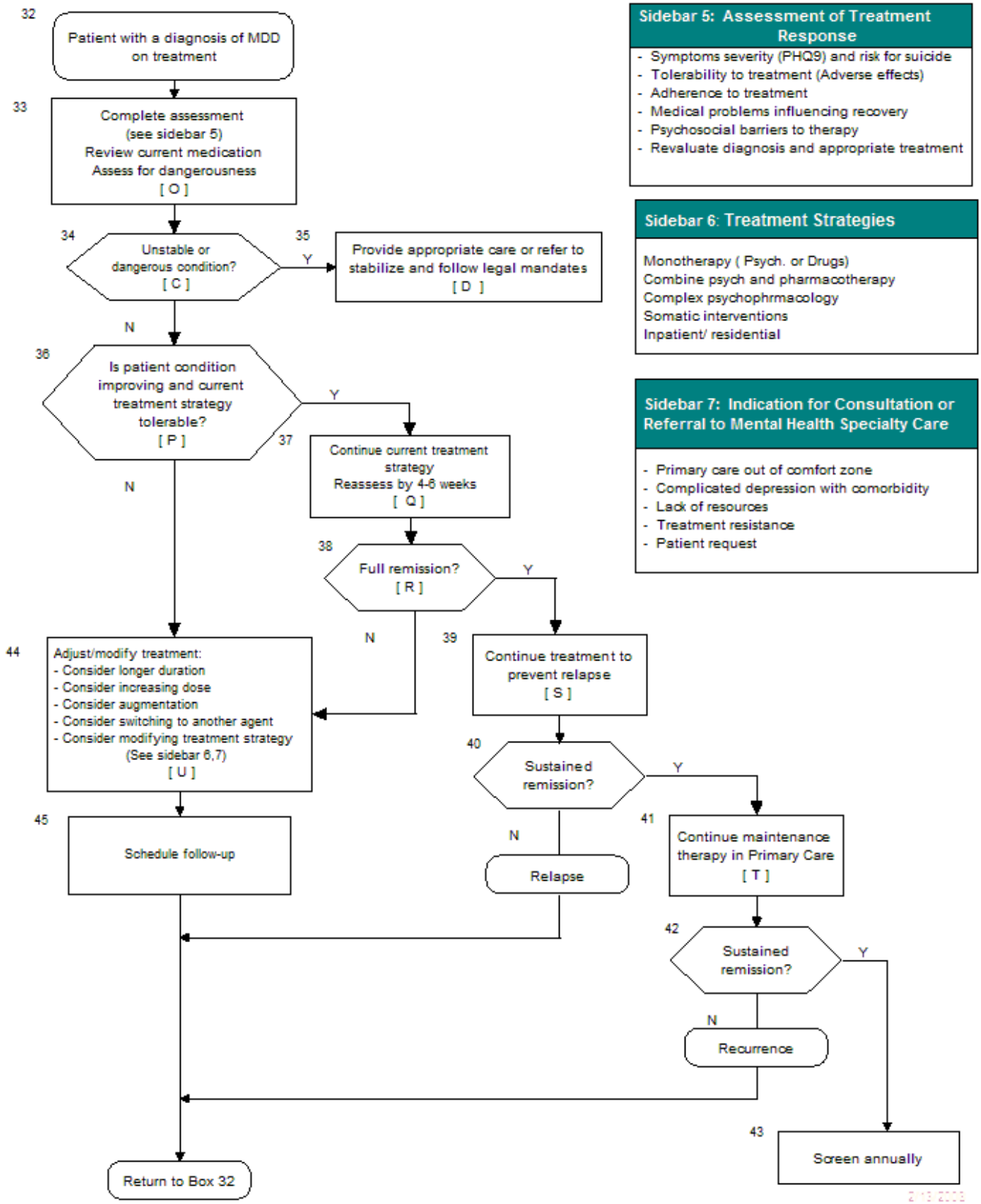
Sidebar 4 : Initial Treatment Strategies for MDD

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

DISCUSSION

Despite its high prevalence and substantial economic impact, depression often goes unrecognized or undertreated. Depressed patients have increased disability, healthcare utilization, and mortality from suicide and other causes, as well as reduced productivity and health-related quality of life.

Why Screening?

In the absence of systematic screening and treatment planning, less than half of the patients with depression will be identified and, of those identified, only a proportion will be adequately treated (Balestrieri et al., 2002; Katon & Schulberg, 1992; Olfson et al., 2000; Wells et al., 1989). Screening for depression provides a rapid method for identifying high-risk patients for whom a treatment plan can be formulated. In non-specialty care settings, including within the VA, approximately 13 percent of primary care patients will screen positively for depression (Foster et al., 1999).

Screening is an important component of integrated care programs that are effective models for managing patients with depression in primary care settings (Bruce et al., 2004; Levkoff et al., 2004; Oslin et al., 2003; Simon et al., 2001 & 2002; Unutzer et al., 2002). These studies demonstrated significant improvement in outcomes of depressed patients relative to usual care, including significantly reduced long-term morbidity (Simon et al., 2001 & 2002).

While screening for depression is an important public health policy, the USPSTF is clear that screening is valuable only when assessment, treatment, and monitoring are available (AHRQ, 2002).

Why PHQ-2?

There is a need for a screening instrument with a high sensitivity in order to identify the broader spectrum of depressive disorders. The choice of screening instruments is dependent upon the intent. A screening with high specificity will undoubtedly identify true cases of major depression but will likely miss some cases and will not detect cases of minor depression. The evidence shows that asking the two-question screen about mood and anhedonia may be as effective as using longer questionnaires. The PHQ-2 is effective for initial screening and is feasible, practical, at the appropriate reading level, and easy to score. This approach requires greater attention to a more in-depth systematic assessment of patients who screen positive, in order to develop an appropriate treatment plan.

EVIDENCE STATEMENTS

- 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 (AHRQ, 2002). The task force further states that "most instruments are easy to use and can be administered in less than 5 minutes. Shorter screening tests, including simply asking questions about depressed mood and anhedonia, appear to detect a majority of depressed patients and, in some cases, perform better than the original instrument from which they were derived (Whoolley et al., 1997)."

- The PHQ-2 has a reported sensitivity and specificity of between 82 to 97 and 78 to 91 percent, respectively, for major depression using a cut off score of > 2 (Corson et al., 2004; Kroenke et al., 2003; Lowe et al., 2005).

- Using the PHQ-9 algorithm for major depression as the reference standard, the VA single-item screen was specific (88 percent) but less sensitive (78 percent). A PHQ-2 score of 3 or more demonstrated similar specificity (91%) with high sensitivity (97%) (Corson et al., 2004).

- The PHQ has also been demonstrated to be an effective screening tool in patients after a cardiovascular disease, cerebrovascular event, or with significant cognitive impairment (McManus et al., 2005; Thibault & Steiner, 2004; Williams et al., 2005).

- There is evidence that the PHQ-2 can also be used to measure outcomes of treatment (Lowe et al., 2005).

- Discriminating between depressed and nondepressed patients is exemplified by the PHQ-2's higher area under the curve (AUC) for major depression of 0.93 compared with 0.82 for the 2-item PRIME-MD as reported by Whooley et al. (1997). The PHQ-2 is scored 0 to 6 and it has superior performance over the PRIME-MD 2-item screen, which is scored 0 to 2 (Kroenke et al., 2003). (Note: this is based on two different studies and not on a head-to-head comparison in the same population.)

Screening in the Elderly

- Two-item screens based on the PHQ (written format; rating scale ranging from 0 – 3 for each item and verbal format; "yes" or "no" response for each item) compare favorably with longer screens in elderly patients. These screens have good sensitivity (range 0.79 – 0.97), but lower specificity (range 0.58 - 0.67) than longer screens (Alessi et al., 2003; Arroll et al., 2003; Blank et al., 2004; Corson et al., 2004; Li et al., 2007).

- Depression questionnaires, including longer instruments such as the Geriatric Depression Scale (GDS) may not perform as well in individuals > 75 years old compared to younger individuals (Watson et al., 2004).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Two-item screens based on the PHQ have good sensitivity in mid-life, postpartum women, and older patients	Kroenke et al., 2003 Whooley et al., 1997 Williams et al., 2002	I	Good	A
	Studies targeting or including elderly patients	Arroll et al., 2003 Blank et al., 2004 Corson et al., 2004 Kroenke et al., 2003 Li et al., 2007 Whooley et al., 1997	I II II II II I	Fair	B
	Studies done with VA patients	Corson et al., 2004 Whooley et al., 1997	II I	Fair	B
2	Studies in postpartum patients	Kroenke et al., 2003	II	Fair	B
3	Two-item screens perform better than single item screens addressing mood only	Alessi et al., 2003 Blank et al., 2004 Corson et al., 2004	II	Fair	B
4	Depression questionnaires, including longer instruments such as the GDS may not perform as well in individuals > 75 years old	Watson et al., 2004	II	Fair	C
5	Screening should be done annually	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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.

EVIDENCE STATEMENTS

- Women are at elevated risk for depression during the antenatal and postpartum periods. The point prevalence of depression is 10 to 15 percent during pregnancy and 5 to 31 percent in the postpartum period (Gaynes et al., 2005).
- In addition to adverse effects on the mother, depression has adverse effects on the fetus and infants (Epperson et al., 1999). The presence of maternal depressive symptoms at a critical time for infant and family has additional adverse effects, such as marital distress (Beck, 2001), problems with mother-infant interaction and attachment (Righetti-Veltema et al., 2003) and adverse behavioral and cognitive effects in the child (Grace et al., 2003).
- In a systematic review of the evidence for depression screening during pregnancy, only one study reported on screening accuracy in a population, with 6 patients with major depression and 14 patients with either major or minor depression. For major depression, sensitivities for the Edinburgh Postnatal Depression Scale (EPDS) at all thresholds evaluated (12, 13, 14, 15) were 1.0, underscoring the markedly small number of depressed patients involved; specificities ranged from 0.79 (at EPDS >12) to 0.96 (at EPDS >15). For major or minor depression, sensitivity was much poorer (0.57 to 0.71), and specificity remained high (0.72 to 0.95) (Gaynes et al., 2005).
- For postpartum depression screening, the systematic review (Gaynes et al., 2005) reported that the small number of depressed patients involved in the studies precluded identifying an optimal screener or an optimal threshold for screening. "Our ability to combine the results of different studies in a meta-analysis was limited by the use of multiple cutoffs and other differences in the studies that would have made the pooled estimate hard to interpret. Where we were able to combine the results through meta-analysis, the pooled analysis did not add to what one could conclude from individual studies" (Gaynes et al., 2005).
- Three systematic reviews evaluated screening tools for postpartum depression, used either in the prenatal or postpartum period.
    - In the first review (Austin & Lumley, 2003), 16 studies evaluating screening tools prenatally were included. Outcome assessments used the Edinburgh Postnatal Depression Scale (EPDS) or standardized diagnostic psychiatric interviews, or both. However, most of the studies were small - only 4 studies had adequate sample sizes to assess the sensitivity and specificity of postpartum depression screens. In the two largest population-based studies the positive predictive value was low. The authors

concluded that no screening instruments were appropriate for prenatal prediction of postpartum postpartum depression.

- A second review (Boyd et al., 2005) included 36 studies of self-reported scales for postpartum depression screens 2 weeks after labor. Out of eight tools that have been evaluated, results suggested that the EPDS is the most extensively studied postpartum measure with moderate psychometric soundness. However, as in the other reviews, most of the studies included had small sample sizes.

- The evidence report/technology assessment (Gaynes et al., 2005) also looked at the predictive value of different screening tools for detecting depression during the perinatal period. Although the EPDS and the postpartum depression Screening Scale (PDSS) seemed to have higher sensitivities than the BDI (with estimates ranging from 0.75 to 1.0 at different thresholds), the author questioned the external validity of the studies and the accuracy given the small sample sizes in several studies.

- A recent review of the literature (Gjerdingen et al., 2007) concluded that postpartum depression screening improves recognition of the disorder but, additional studies with large, representative samples are needed to help identify the ideal postpartum depression screening tool.
- Although there are no published reports on the validity of the PHQ-9 in screening for postpartum depression, it has been used as a screen in obstetrics/gynecology practices that include both women of childbearing age and older women (Scholle et al., 2003). The PHQ-2 was studied in 8 primary care clinics and 7 obstetrical/gynecology clinics, where construct and criterion validity were found to be very good, and sensitivity and specificity high (83% and 92%, respectively) (Kronke et al., 2003). A single study (done in Europe and with no control group) showed that a 2-item questionnaire, substantially the same as the PHQ-2, performs comparably to longer instruments (Jesse & Graham, 2005).
- Studies that have addressed postpartum depression screening demonstrate that screening is feasible in the outpatient setting and can improve the rates of detection and treatment (Georgiopoulos et al., 2001; NICE, 2004).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	Women are at increased risk for depressive disorders during pregnancy and postpartum periods	Gaynes et al., 2005	I	Good	A
2	Depression screening improves detection during pregnancy and during the postpartum period	Georgiopoulos et al., 2001 Gjerdingen et al., 2007 NICE, 2004	I	Good	B
3	PHQ-2 is a sensitive screen for depression in postpartum women	Kronke et al., 2003 Spitzer et al., 2000	II I	Fair	B
4	Edinburgh Postnatal Depression Scale (EDPS) is a sensitive and valid screen for depression in the antepartum and postpartum period	Adouard et al., 2005 Evins et al., 2000 Peindl et al., 2004 Boyd et al., 2005	II	Good	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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.

EVIDENCE STATEMENTS

- Evidence shows that in the presence of certain risk factors and related conditions, the risk of suicide is increased in the patient with MDD. (e.g., psychiatric illness, serious medical illness, persons with social adjustment problems, living alone, recent bereavement, personal/family history of suicide attempts, family history of completed suicide, divorce/separation, unemployment, Caucasian race, male gender, advanced age, family or personal history of substance abuse) (USPSTF, 1996).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	Suicide risk factors and related conditions	USPSTF, 1996	I	Fair	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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.

DISCUSSION

Psychosis is defined as a mental state in which the patient is significantly out of touch with reality to the extent that it impairs function. 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 (Kaplan & Sadock, 1996).

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)

RATIONALE

Non-standardized assessments lead to frequent diagnostic misclassification. The PHQ-9 improves diagnostic accuracy and aids treatment decisions by quantifying symptom severity.

EVIDENCE STATEMENTS

- PHQ-9 scores have been validated against DSM-IIIR, DSM-IV-TR, and functional status measures. Validity has been assessed against an independent structured mental health professional interview. PHQ-9 score ≥10 had a sensitivity of 88 percent and a specificity of 88 percent for major depression (Dietrich et al., 2003; Kroenke et al., 2001; Löwe, Gräf et al., 2004).

- In head-to-head comparisons and across studies, the PHQ-9 gives better discriminate power than other instruments of comparable length. A study in 6,000 patients validated different PHQ cut-points representing mild, moderate, and severe depression (Kroenke et al., 2001).

- Comparisons of the PHQ-9 to other comparable instruments in patients with severe or multiple chronic medical illnesses are not available.

- PHQ-9 is self-administered and can even be used over the telephone (Pinto-Mexa et al., 2005).

- In a systematic review of randomized trials comparing enhanced primary care to usual care, systematic measurement of response to treatment was a common component of enhanced care (24 of 28 trials). Enhanced care roughly doubled the likelihood of response to treatment (Bower et al., 2006; Gilbody et al., 2006; Williams et al., 2007).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	Depression questionnaires are useful for identifying major depressive disorder and dysthymic disorder	Williams et al., 2002	I	Good	A
2	PHQ-9 performed better than other self-administered instruments for identifying major depressive disorder	Henkel et al., 2003 Kroenke et al., 2001 Löwe, Gräf et al., 2004 Williams et al., 2002	I	Good	B
3	PHQ-9 is responsive to change in clinical status	Löwe, Unutzer et al., 2004 Löwe, Kroenke et al., 2004	II	Fair	A
4	Systematic assessment of treatment response is a component of efficacious primary care treatment models	Bower et al., 2006 Gilbody et al., 2006 Williams et al., 2007	I	Good	A

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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)
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

Medication/ Class	Association	Comment
		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-α	+/-	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

DISCUSSION

Some depressed patients manifest periods of mania. According to DSM-IV-TR, a manic episode is a distinct period of persistently elevated, expansive, or irritable mood, lasting at least four days (hypomanic episode) or at least one week (manic episode), that is clearly different from the usual nondepressed mood and is observable by others.

During this period of abnormal mood, at least three of the following symptoms need to be present and persistent to a significant degree.

- Inflated self esteem or grandiosity
- Decreased need for sleep
- Pressure to keep talking
- Flight of ideas or subjective experience that thoughts are racing
- Distractibility
- Increase in goal-directed activity or psychomotor agitation
- Excessive involvement in pleasurable activities that have a high potential for painful consequences.

These symptoms need to be severe enough to cause marked impairment in social or occupational functioning or require hospitalization. The clinician also needs to determine that symptoms are not secondary to a substance use or general medical condition. Hypomania is characterized by a manic episode without accompanying impairment or psychosis.

An alternative to the clinical interview is to use a structured questionnaire (see the Mood Disorders Questionnaire at: http://www.cqaimh.org/pdf/tool_interview.pdf).

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]

DISCUSSION

The discussion of the literature regarding the best way(s) to treat patients who are diagnosed with both major depression and substance abuse/dependence is beyond the scope of this guideline.

See the VA/DoD Guideline for Substance Use Disorder for further diagnosis and treatment.

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.

DISCUSSION

Studies of patients with MUS indicate high rates of major depression and panic disorder and several mechanisms that might account for this correlation (Engel & Katon, 1999). (For discussion of MUS – see the VA/DoD Guideline for Medically Unexplained Symptoms.)

Patients with medically unexplained physical symptoms suggestive of a somatoform disorder may sometimes require referral to a mental health specialist. However, patients with unexplained physical symptoms often resent psychiatric referral and fail to follow through. Primary care providers should initiate MDD treatment if possible by building a trusting relationship with the patient. The practitioner should carefully explain the reason for referral before and after it is recommended, and schedule a follow-up appointment after the referral. These measures will help to allay patient concerns that their physical symptoms are being addressed, yet they require more specialized attention to their state of well-being and, therefore, are being referred for consultation.

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.

EVIDENCE STATEMENTS

- Patients with depression NOS may recover spontaneously, progress to major depression (about 10 to 20 percent at one year), or continue to experience low level depressive symptoms (Ackerman et al., 2002; Hermens et al., 2004).

- High quality, randomized trials of antidepressants or psychotherapy are limited for this condition. These data suggest that antidepressant medications or empirically-based psychotherapy may have small beneficial effects (Ackerman et al., 2002; Cuijpers et al., 2007; Judd et al., 2004).

- Care enhancements such as telephone care management have typically failed to improve outcomes. Weighing risks and benefits of treatment, appropriate treatment strategies include: a 4 to 8 week trial of support, education, and self-help strategies such as exercise; antidepressant medication, or psychological treatments – particularly for patients with more severe functional impairment. Care management programs are not routinely indicated for these patients.

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.

EVIDENCE STATEMENTS

Treatment of Dysthymia

There is limited evidence regarding treatment for dysthymia, and treatment studies of dysthymia often include other disorders as well (e.g., chronic depression, minor depression). Most studies have examined the same interventions that have been studied for major depression.

- Reviews of psychotherapy and pharmacotherapy indicate that there is good evidence that antidepressant medications are efficacious for reducing dysthymia, and there is some evidence that psychotherapy is beneficial as well, although it appears that the benefits of psychotherapy, and possibly pharmacotherapy, are lower than those found in treatment of major depression (Arnow & Constantino, 2003; Koscis, 2003).

- Studies of combined pharmacotherapy and psychotherapy found that combined sertraline and interpersonal psychotherapy (IPT) was not superior to sertraline alone, and either medication was superior to IPT alone. A comparison of sertraline with or without group cognitive behavioral therapy (CBT) found some evidence that combined treatment may improve functioning over medication alone, but did not find group CBT alone superior to placebo. In the context of major depression, some studies suggest that combined treatment may lead to better treatment response for double depression. These results suggest that either medication or psychotherapy may be beneficial for patients with dysthymia, and combined treatment may be of value in patients with major depression and comorbid dysthymia. However, the variability in findings and limited number of studies prevent definitive conclusions (Koscis, 2003).

- In contrast, a meta-analysis of later life major depression treatments found that in studies that included patients with either minor depression or dysthymia, psychotherapy had a greater effect than pharmacotherapy (Pinquart et al., 2006).

- In general, the course of dysthymia appears to be relatively stable, and individuals who recover from dysthymic episodes had a 71.4 percent likelihood of recurrence of some depressive disorder. Patients with a dysthymic disorder had a slower rate of symptom recovery over time, and had higher rates of depression after 10 years when compared to patients with nonchronic major depression (Klein et al., 2006).

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	

DISCUSSION

Example 1: Upgrading Severity

Patient: 63 year old man who screens positive on the PHQ-2. Per protocol, a PHQ-9 is given to the patient by the intake staff and is available to you.

	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).					

Add function impairment item as "very difficult."

On follow-up questioning, the clinician discovers that the patient's anhedonia is profound and that he spends much of the day in bed, giving up his regular Wednesday night card game and Sunday afternoon golf outing. In addition to a poor appetite, he has lost 15 pounds since his visit six months ago. Physical examination and laboratory evaluation do not suggest any other cause of weight loss.

Conclusion: Although this patient's PHQ-9 score is 17, placing him in the "moderate major depression category," his significant weight loss, marked anhedonia, and marked functional impairment would warrant an assessment of "severe" functional impairment and a treatment plan corresponding to this severity.

Example 2: Downgrading Severity

Patient: 78 year old man who complains of insomnia. To evaluate for depression, you administer the PHQ-9 and obtain the following results.

	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).					

Add function impairment item as "somewhat difficult."

The PHQ score is 15 with "somewhat difficult" function. On follow-up questioning, the clinician discovers that the patient is having depressive symptoms. However, he has chronic low back pain and significant knee osteoarthritis. Item "h" – moving slowly – is related to his arthritis, does not represent any change in baseline, and has not worsened since he began to notice depressed mood. The other symptoms are reported accurately and represent a change from baseline. You discount the "moving slowly" symptom and characterize the patient's MDD as mild.

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.

EVIDENCE STATEMENTS

- The evidence stems primarily from consensus opinions on patient education derived from the 2006 Institute for Clinical Systems Improvement (ICSI) Health Care Guideline for Major Depressive Disorder. Some studies focused on the relationships between patient education, self-management, and treatment adherence; other studies focused on specific self-management strategies.
  - There is strong evidence that providing key educational messages at the beginning of treatment can enhance treatment adherence, particularly with regard to antidepressant medication use; assessing adherence systematically adds to this effectiveness (Katon et al., 2001; Lin et al., 1995 & 2003; Vergouwen et al., 2003; Williams et al., 2007).
  - There is strong evidence that structured and organized protocols that focused on a systematic monitoring of adherence, treatment response, self-management strategies, relapse prevention, as well as ongoing patient education, enhances both adherence and treatment response (Katon et al., 2001, Lin et al., 2003, Vergouwen et al., 2003, Williams et al., 2007).
  - The ICSI guideline recommends universal and ongoing patient and family education for all patients with major depression. It recommends that such education should focus on the nature and course of depression, the various treatment options, including advantages and disadvantages of each, the typical treatment course and side effects for treatment options, the importance of treatment adherence, and strategies of relapse prevention (ICSI, 2006).
  - Regarding self-management strategies, the strongest empirical support is for exercise (Baybak et al., 2000; Blumenthal et al., 1999; Carlson, 1991; Craft & Landers, 1998; Dunn et al., 2005; Harris et al., 2006; Knubben et al., 2007; Lawlor & Hopker, 2001; Mather et al., 2002; North et al., 1990; Trivedi et al., 2006), guided self-help or bibliotherapy (Cuijpers, 1997; Lewis et al., 2003; NICE, 2004), and behavioral activation (Dimidjian et al., 2006; Jacobson et al., 1996).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Adherence to treatment should be directly and routinely assessed	Katon et al., 2001 Lin et al, 2003 Vergouwen et al., 2003 Williams et al., 2007	I	Good	B
2	Initial brief educational messages addressing medication adherence issues to enhance acute phase adherence	Lin et al., 1995	I	Good	B
3	In primary care settings, use of collaborative care or other structured protocol approaches enhances adherence.	Katon et al., 2001 Lin et al., 2003 Vergouwen et al., 2003 Williams et al., 2007	I	Good	B
4	Patient education should focus on the nature and course of depression, treatment options, the importance of adherence, and relapse prevention strategies	ICSI, 2006	III	Fair	C
5	Exercise is an effective self-management strategy	Baybak et al., 2000 Blumenthal et al., 1999 Carlson, 1991 Craft & Landers, 1998 Dunn et al., 2005 Harris et al., 2006 Knubben et al., 2007 Lawlor & Hopker, 2001 Mather et al., 2002 North et al., 1990 Trivedi et al., 2006	I	Good	B
6	Guided self-help or bibliotherapy is an effective self-management strategy	Cuijpers, 1997 Lewis et al., 2003 NICE, 2004	I	Good	B
7	Behavioral activation is an effective self-management strategy	Dimidjian et al., 2006	I	Good	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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.

EVIDENCE STATEMENTS

- In a review, Ackermann & Williams (2002) identified six clinical trials of specific treatments, and two controlled studies of multifaceted interventions for minor depression. They conclude that, "Collectively, these studies provide only mixed support for a small to moderate benefit for the antidepressant medications and psychological treatments tested (relative to responses in the placebo or control conditions)." Moreover, the PROSPECT primary care based integrated care study failed to demonstrate an effect for algorithm-based treatment for those with minor depression relative to usual primary care (Bruce et al., 2004).

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).

RATIONALE

Treatment of MDD has demonstrated improvements in the overall well-being of patients, reductions in suicide ideation, and improvements in occupational and social functioning when adequate monotherapy is provided.

(See Section 21: Psychotherapy for discussion and evidence grading)

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.

RATIONALE

With MDD that is moderate to severe, the evidence suggests that combination treatment leads to more rapid response, less disability, and greater symptom improvement.

(See Section 21: Psychotherapy for discussion and evidence grading)

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.

RATIONALE

The ultimate goal of treatment is to reduce disability and maximize functional recovery. In complex patients or patients with refractory MDD, the use of multiple pharmacotherapeutic strategies and additional supportive therapies may be used to achieve this goal.

(See Section 21: Psychotherapy for discussion and evidence grading)

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.

RATIONALE

The ultimate goal of somatic treatment strategies is to reduce occupational and social disability and maximize functional recovery in a timely manner.

At this time, there is not sufficient evidence to support the use of ECT or VNS as an initial treatment strategy in less severe MDD, where self-neglect is not an issue.

(See Section 22: Somatic Treatment for discussion and evidence grading)

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.

EVIDENCE STATEMENTS

- Due to the nature and severity of patients admitted to the hospital, there is not a literature base that supports the efficacy of inpatient care for acute stabilization. The paramount issue is patient safety; thus a trial comparing inpatient treatment to no treatment would not be ethical. There are studies involving specific strategies within inpatient settings such as the use of intramuscular (IM) formulations of antipsychotics for acute agitation or mania.

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]

RATIONALE

Negative life events and circumstances may contribute to the onset of an episode of MDD. They may also influence treatment adherence and outcome. Psychosocial rehabilitation services therefore can be an important part of the treatment of MDD when indicated.

EVIDENCE STATEMENTS

There is evidence that psychosocial stressors may be etiological factors for MDD:

- Tennant (2002) completed a systematic literature search focusing on predictive studies between 1980 to early 2001 using Medline, EMBASE, and PsychInfo. This search revealed that environmental stressors are just as significant as genetics in the etiology of MDD.

- Paykel et al. (1996) studied a group of predominantly recurrent inpatient sample of individuals with MDD. The patients were followed-up longitudinally every 3 months to remission and up to 15 months thereafter. The results demonstrated that life events, social support and marital relationships appeared to play a role in the onset of MDD.

- Monroe et al. (2006) noted that it is widely accepted in the literature that major life stress is often an important factor in the first episode of MDD. In their 3-year, longitudinal study of 126 individuals with a history of MDD, they found that non-severe life events are capable of triggering a recurrence of depression.

There is evidence that psychosocial circumstances can be barriers to adherence to treatment for MDD:

- Miranda et al. (2006) found low-income, minority women have increased difficulty with adherence to treatment. In an RCT comparing antidepressant medication (ADM), CBT, and standard supportive psychotherapy in the community, only 35 percent completed six or more sessions of CBT and only 67 percent received nine or more weeks of medication (N=267). This is in stark contrast to DeRubeis and colleagues' study (2005) which included primarily white, educated participants: at eight weeks, 89 percent of the ADM cohort and 85 percent of the CBT cohort remained in care (N=240).

There is evidence that psychosocial circumstances and stressors influence the outcome of patients with MDD:

- Leskelä et al. (2006) studied 193 individuals with MDD over the course of 18 months. Using several measure instruments, including interviews and the Hamilton Depression Scale (HAM-D), they found that adverse life events and/or perceived poor social support influence the medium-term outcome of all psychiatric patients with MDD. Psychosocial factors appear to

play a role in the outcome of mild depressions; in contrast, psychosocial factors are relatively unimportant in the subsequent course of severe and recurrent depressions.

- There is insufficient literature on the effect of psychosocial rehabilitation services on persons with MDD. However, according to consensus, psychosocial rehabilitation services may lessen vulnerability to MDD, improve treatment adherence, and improve outcome. In addition, expert opinion has found psychosocial rehabilitation services to be important in treating other serious psychiatric conditions (seeVA/DoD Clinical Practice Guidelines for Management of Psychosis:Schizophrenia). This Work Group therefore, has decided to strongly recommend psychosocial rehabilitation services, as the potential benefit to the individual seems to outweigh any costs to the system.

Limitations of the literature:

- Due to the nature of the research question, there are no RCTs available on the impact of psychosocial stressors on the etiology of MDD, adherence to treatment, or outcome.

- The literature varies in what it includes in "negative life events."

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Benefit	SR
1	Psychosocial stressors as etiological factors for MDD:					
	a. Environmental stressors are just as significant as genetics in the etiology of MDD	Tennant, 2002	II-2	Fair	Moderate	B
	b. Life events, social support and marital relationships play a role in the onset of MDD	Paykel et al., 1996	II-2	Fair	Moderate	B
	c. Major life stress is often an important factor in the first episode of MDD d. Non-severe life events are capable of triggering a recurrence of depression	Monroe et al., 2006	I	Good	Moderate	A
2	Barriers to adherence to treatment for MDD: Low-income minority women may have increased difficulty with adherence to treatment, antidepressant medications (ADM) or cognitive behavioral therapy (CBT)	Miranda et al., 2006	I	Fair	Moderate	C
3	Influencing treatment outcome:					
	Adverse life events and/or perceived poor social support influence the medium-term outcome of all psychiatric patients with MDD.	Leskelä, et al, 2006	II-2	Fair	Moderate	B
	Psychosocial factors appear to play a role in the outcome of mild depressions; however, they areunimportant in the subsequent course of severe and recurrent depressions.	Paykel et al., 1996	II-2	Fair	Moderate	B
4	Psychosocial rehabilitation services may lessen vulnerability to MDD, resulting in improved treatmentadherence and improved outcomes.	Working Group Consensus	III	Poor	N/A	I

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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.

EVIDENCE STATEMENTS

- In randomized trials comparing enhanced primary care to usual care, systematic measurement of response to treatment was a common component of enhanced care (24 of 28 trials). Enhanced care roughly doubled the likelihood of response to treatment (Bower et al., 2006; Gilbody et al., 2006; Williams et al., 2007).

(See also Annotation E Section 4.2.)

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Systematic assessment of treatment response is a component of efficacious primary care treatment models	Bower et al., 2006 Gilbody et al., 2006 Williams et al., 2007	I	Good	A

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

Non-adherence to treatment is very common and a major reason for inadequate response to treatment and recurrence of symptoms (de Jonghe et al., 2001; Haslom et al., 2003; Lin et al., 1995; Manning & Marr, 2003; Pampallona et al., 2002). Because depression is increasingly conceptualized and treated as a recurrent and/or chronic disease (Lin et al., 2003, Williams et al., 2007), it makes sense to extend concerted effort into enhancing treatment adherence. Additionally, a number of interventions have been shown to be effective in enhancing adherence as well as in reducing symptom severity.

EVIDENCE STATEMENTS

- Lin et al. (1995) found that 5 simple education messages (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) improve adherence. In addition, assessing for previous use of antidepressant medication and prescribing scheduled pleasant activities enhances medication adherence during the first month of treatment, but not at the three-month point.

- In a systematic review of studies examining adherence to depression treatment, Pampallona et al. (2002) concluded that non-adherence was indeed a major problem and that there was ample evidence that interventions could enhance adherence, but that there was inconsistent evidence (i.e., mixed results) as to which interventions were effective in doing so. In a systematic review of interventions designed to enhance antidepressant medication adherence, Vergouwen et al. (2003) found that there was a lack of consistent support for educational interventions alone toward enhancing adherence, but they did find that collaborative care approaches consistently enhanced adherence during both the acute and continuation phase of treatments, as well as led to improved clinical benefits.

- In a systematic review of 28 RCTs of multifaceted interventions in primary care (i.e., particular kinds of collaborative care), Williams et al. (2007) found that these multifaceted interventions typically achieved greater symptom improvement and commonly had improved treatment adherence as compared to usual care. All interventions utilized care management. The most commonly used interventions were patient education and self-management,

monitoring of depressive symptoms and treatment adherence, decision support for medication management, a patient registry and mental health supervision of care managers.

- In an RCT comparing a collaborative care approach to usual primary care, Katon et al. (2001) and Lin et al. (2003) assessed the effectiveness of a collaborative care relapse prevention program on treatment adherence, clinical outcome, and relapse. Components of the approach included two in-person contacts with "depression specialist" treatment extenders (i.e., nurse, social worker, and psychologist), three telephonic follow-ups, and four individualized mailings over the course of a year. Contacts focused specifically on enhancing medication adherence, enhancing use of self-monitoring and responding to early warning signs of relapse, utilizing self-management strategies such as pleasant activity and social event scheduling, exercise, identifying high risk situations and utilizing problem solving. The interventions specifically focusing on medication adherence entailed somewhat intensive evidence-based education on the advantages and disadvantages of adherence with regard to both symptom management and recurrence and individualized problem solving of patients' own barriers to adherence. Collectively, these methods led to improved treatment adherence, relative to usual care for up to 12 months after initiation of treatment, and better treatment outcomes. They did not, however, lead to lower rates of relapse. The intervention also led to significantly more favorable attitudes toward medication use, self-confidence in managing medication side effects, depressive symptom monitoring, checking for early warning signs, and planful coping. The more favorable attitudes toward use of medication and increased confidence in managing medication side effects were significant predictors of increased adherence.

- In a systematic review of combined treatments (medication and psychotherapy), Pampallona et al. (2004) found that adding psychotherapy of longer than 12 weeks duration to antidepressant treatment significantly increased the chances of patients remaining in treatment. In an RCT of combined antidepressant and psychotherapy (16 weeks of short-term psychodynamic psychotherapy) versus pharmacotherapy alone, de Jonghe et al. (2001) found that combination therapy significantly enhanced patients' acceptance of pharmacotherapy after randomization. At 24 weeks, significantly fewer combined therapy patients had stopped taking medication (22% versus 40%). There were also significantly improved clinical outcomes for the combined therapy group at 8, 16, and 24 weeks of treatment.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Assess adherence to treatment directly and routinely	Katon et al., 2001 Lin et al., 2003 Vergouwen et al., 2003 Williams et al., 2007	I	Good	B
2	Brief educational messages at the beginning of treatment, given by providers, addressing medication adherence issues enhance acute phase adherence	Lin et al., 1995	I	Good	B
3	In primary care settings, utilize collaborative care approaches to enhance adherence. These approaches should use education and systematic monitoring, specifically addressing adherence and self-management strategies	Katon et al., 2001 Lin et al., 2003 Vergouwen et al., 2003 Williams et al., 2007	I	Good	B
4	For patients who are willing, refer patients taking antidepressant medication to psychotherapy to increase adherence and decrease treatment discontinuation	de Jonghe et al., 2001 Pampallona et al., 2004	I	Good	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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.

RATIONALE

Recognizing factors that cause or contribute to poor treatment response can help clinicians formulate an effective treatment plan.

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.

RATIONALE

Patients who show little to no response to antidepressant medication at a therapeutic dose after 4 to 6 weeks are unlikely to benefit from that medication.

EVIDENCE STATEMENTS

- A response is generally identified as significant improvement in depressive symptoms, ie, a ≥50% reduction in baseline symptom severity, although residual symptoms may still be present. It is estimated that approximately 50% of outpatients with nonpsychotic major depressive disorder (MDD) in efficacy trials respond to treatment with one antidepressant. (Kupfer D, 1991)

- PHQ-9 scores have been validated against DSM-IIIR, DSM-IV-TR, and functional status measures. Scores of < 5 are community norms for no impairment (R=0.04 for MDD); scores of 5 to 9 are consistent with mild depressive symptoms (Kroenke et al., 2001).

- In the IMPACT trial of late-life depression, psychometric analysis showed that a conservative estimate of Minimal Clinically Important Difference (MCID) was 5 points on the 0 to 27 point PHQ-9 scale. A 5-point change was also suggested in another study (Lowe et al., 2004).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	Five-point reduction OR score <10 on the PHQ-9 indicates improvement in MDD symptoms	Kroenke et al., 2001 Lowe et al., 2004	I	Good	A

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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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.

EVIDENCE STATEMENTS

- AHCPR and American Psychiatric Association Practice Guidelines for Depression recommend a four to six week reassessment for treatment response (Schulberg et al., 1998; Shelton, 1999).

- Rate of response for individuals with MDD who show no improvement by week four will be very low and no better than placebo, and a change in treatment regimen is indicated (Quitkin et al., 1996).

- Patients tolerant of an adequate dose, whose conditions have never been at least minimally improved by the end of week 4, should have their treatment regimen altered. Patients whose conditions minimally improve at some prior week but not after week 5 should have their treatment changed. Patients whose conditions minimally improve in week 5 should continue treatment until week 6 (Quitkin et al., 1996).

- In a blinded, placebo-controlled discontinuation study following an open trial of fluoxetine, patients unimproved at week 6 had a remission rate at week 12 of 31 to 41 percent. For patients with remission at week 12, level of improvement at week 6 did not affect prognosis in weeks 13 to 26. Of the unimproved patients at week 8, 23 percent had remissions by week 12 (Quitkin et al, 2003).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	Four to six week reassessment for treatment response	Schulberg et al., 1998 Shelton, 1999	I	Fair	B
2	Rate of response for individuals with MDD who show no improvement by week four is low and no better than placebo; change treatment regimen	Quitkin et al., 1996	I	Good	A
3	Nonresponse to fluoxetine should not be declared until 8 weeks of treatment have elapsed	Quitkin et al., 2003	I	Good	A

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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

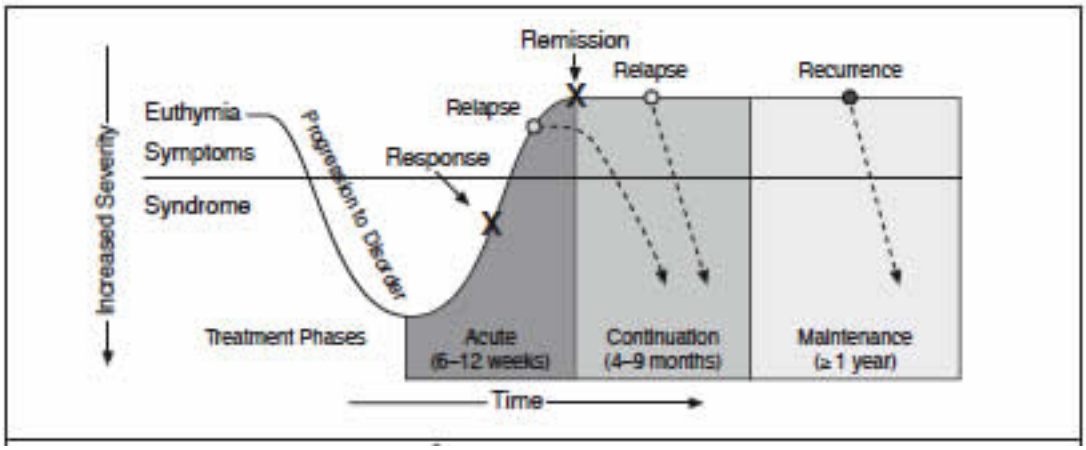
The goal of antidepressant therapy should be the lowest possible degree of depressive symptomatology in order to minimize risk of later relapse.

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.

Figure 1. Distinguishing Relapse and Recurrence *



*Kupfer DJ. Recurrent depression: challenges and solutions. J Clin Psychiatry. 1991;52:28-34

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.

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]

RATIONALE

Among patients who achieve remission from MDD, the risk of relapse is about 41 percent (range 15% to 52%) if antidepressant medications are discontinued (Gartlehner et al., 2007; Geddes et al., 2003). Randomized discontinuation trials have shown that continuing antidepressants for at least 6 months following remission decreases the risk of relapse by approximately 70 percent (Gartlehner et al., 2007; Geddes et al., 2003). The risk of relapse appears lower in patients who achieve remission after a course of empirically-based psychotherapy, so continuation phase psychotherapy is not routinely indicated for patients at average risk of relapse. Among patients at higher than average risk for relapse, continued psychotherapy or the addition of psychotherapy to antidepressant medication, decreases the risk of relapse.

EVIDENCE STATEMENTS

- Among patients who achieve remission with antidepressant medication, the six-month risk of relapse is about 41 percent if antidepressants are discontinued (Gartlehner et al., 2007; Geddes et al., 2003; Limosin et al., 2004; Oldehinkel et al., 2000).

- High quality evidence demonstrates that continuing antidepressants for at least six months following remission decreases the absolute risk of relapse by approximately 23 percent (relative risk reduction 70%) (Gartlehner et al., 2007; Geddes et al., 2003).

For discussion of Psychotherapy for Relapse/Recurrence Prvention – See discussion of section 17

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	The median six-month risk of relapse is 40% (range 11% to 52%)	Gartlehner et al., 2007 Geddes et al., 2003 Limosin et al., 2004 Oldehinkel et al., 2000	I	Good	A
2	Continuation phase antidepressant treatment decreases relapse by 70%	Gartlehner et al., 2007 Geddes et al., 2003	I	Good	A

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

Relapse and recurrence is a significant problem, as many patients who achieve remission are likely to relapse or experience recurrence of depression without ongoing treatment. The most effective protection against relapse/recurrence for patients achieving remission from pharmacological treatment is ongoing pharmacological treatment. For patients at high risk of recurrence, maintenance phase treatment decreases the recurrence risk.

Relapse is less likely with acute stage psychotherapy than pharmacotherapy when both treatments are withdrawn. Psychotherapy applied as a relapse prevention intervention at the end of acute stage pharmacological remission may build on the acute efficiency and efficacy of pharmacotherapy in achieving remission, while avoiding the potential long term use of medication, which is a major concern for many patients. CBT relapse prevention interventions after treatment remission via pharmacotherapy may have a cumulative effect with continuation and maintenance antidepressant treatment.

EVIDENCE STATEMENT

- In patients at high risk of relapse, maintenance phase antidepressant treatment decreases the absolute risk of recurrence by about 25 percent (Gartlehner et al., 2007; Geddes et al., 2003).

- The benefits of maintenance phase treatment have been demonstrated for up to 36 months (Gartlehner et al., 2007; Geddes et al., 2003).

- The benefits of decreased recurrence should be weighed against the possible adverse effects of long-term antidepressant treatment including increased risk of GI bleeding with concurrent NSAIDs (Dalton et al., 2003; Yuan et al., 2006), sexual dysfunction (Gregorian et al., 2002) and osteoporosis (Diem et al., 2007; Haney et al., 2007).

- The strongest evidence for the use of psychotherapy to prevent relapse or recurrence comes from two major lines of studies involving behavioral therapy. 1) Studies demonstrating that particular dysfunctional cognitive patterns and/or styles (patterns and styles that are the target of CBT interventions) are more predictive of relapse/recurrence and 2) studies demonstrating that CBT applied in the acute stage of treatment and/or in the continuation phase help prevent relapse/recurrence. A number of these studies specifically examine CBT, or closely related therapies, as relapse/recurrence prevention interventions.

- **Association of cognitive style and patterns**: Alloy et al. (2006), in a prospective study over 2.5 years of 347 college freshman at high or low risk for depression based on psychometrically measured dysfunctional cognitive styles who had no diagnosis at baseline, demonstrated that high risk individuals were 3.5 to 6.8 times more likely than low risk individuals to develop both first onset and recurrent episodes of minor, major, and "hopelessness" depression, while controlling for both initial depressive symptom severity and history of previous depression. From the same subject pool, Iacoviello et al (2006) studied the frequency, severity, chronicity, and duration of depressive episode course for the 159 subjects who experienced at least one episode of depression following baseline assessment. Subjects at high cognitive risk (based on psychometrically measured negative cognitive style), experienced significantly more frequent, more severe, and more chronic courses than subjects at low cognitive risk. In a study of 97 graduate students with a least one prior episode of major depression, Mongrain & Blackburn (2006) demonstrated that dysfunctional cognitive attitudes, negative attributional style, and cognitive vulnerability in the achievement domain were associated with a greater number of prior episodes, while controlling for current mood and neuroticism. Negative attributional style and autonomous personality style predicted recurrence of disorder, while controlling for history of depression and related variables. In a study of 53 initially hospitalized depressed patients over one year who had demonstrated a 50% or greater reduction in symptom severity after six months of treatment, Beevers, et al. (2003) demonstrated that poor changes in psychometrically measured dysfunctional attitudes and extreme thinking patterns significantly predicted shorter return to depression. Initial degree of depressive symptoms and history of depression was statistically controlled for. Segal et al. (2006) demonstrated that remitted depressed patients who displayed greater dysfunctional cognitions in response to negative mood provocation were at significantly greater risk for relapse during the subsequent 18 months. The patients who achieved remission through antidepressant treatment demonstrated significantly greater cognitive reactivity than those who achieved remission through Cognitive Therapy (CT). Collectively, these studies suggest that CT, which is aimed at altering cognitive variables which make patients vulnerable to relapse, may be effective in reducing relapse/recurrence over time. Petersen et al (2004) demonstrated that gains in positive attributional style achieved during pharmacotherapy for depression were significantly more effectively maintained for patients receiving a pharmacotherapy plus CBT continuation intervention versus pharmacotherapy alone. However, symptom severity or rates of relapse did not differ between the two groups. Teasdale et al. (2001) demonstrated that patterns of extreme thinking as indicated by frequency of "totally agree" or "totally disagree" responses, rather than the thought content of the items themselves, predicted relapse and response to CT in 158 recurrently depressed patients. Teasdale et al. (2002) demonstrated that accessibility to "metacognitive sets" (an ability to step back and view one's thoughts in a detached manner) was increased by CT and this in turn significantly reduced the risk of relapse.

- There is evidence that CT has enduring effects that reduce the risk of relapse once treatment has ended and that it has more enduring effects than pharmacotherapy when it is discontinued (Hollon & Shelton, 2001). In a randomized control trial Hollon et al. (2005) examined the durability of CT treatment responders with moderate to severe depression who were withdrawn from treatment versus pharmacotherapy responders who entered continuation treatment of either placebo pharmacotherapy withdrawal or active pharmacotherapy for 12 months. CT responders were allowed up to 3 booster sessions over the 12 months. Patients withdrawn from CT were significantly less likely to relapse during continuation than patients withdrawn from medication (30.8% vs 76.2%; P=.004) and were not significantly more likely to relapse than patients who continued on active medication (30.8% vs 47.2%; P=.20). Rohan et al. (2004) demonstrated that CBT, with and without light therapy, was significantly more effective than light therapy alone in preventing relapse among patients with Seasonal Affective Disorder.

- A number of relatively older studies have demonstrated the efficacy of CBT and Interpersonal Psychotherapy (IPT) adapted for the 4-6 month continuation phase of treatment for the prevention of depressive relapse and recurrence (Fava et al. 1994, 1996, 1998 a, b, 1999;

Jarrett et al 1998, Fava, 1999; Paykel et al. 1999; Frank et al. 1991). In a more recent study, Teasdale et al. (2000) studied the relapse prevention efficacy of Mindfullness-Based Cognitive Therapy (MBCT), an eight week group intervention designed to train recovered depressed patients to disengage from the dysphoria-activated depressogenic thinking that appears to mediate relapse/recurrence. In a multi-site randomized controlled trial, 145 recurrently depressed patients, who were not currently taking medications, were randomly assigned to treatment as usual (TAU), which could include reinstitution of antidepressant medication, or MBCT, which could also include reinstitution of medications. For patients with three or more previous episodes (77% of sample), Mindfulness-Based Cognitive Therapy (MBCT) significantly reduced the risk for relapse/recurrence (37% versus 66%). This preventive effect did not hold for patients with only two prior episodes. Ma and Teasdale (2004) replicated this study with 73 recurrently depressed patients. MBCT reduced relapse from 78% to 36% in the 55 patients with three or more episodes, whereas for the 18 patients with only two prior episodes, the corresponding figures were 20% and 50%. MBCT was most effective in preventing relapses not preceded by aversive life events which were more common in the two-episode group. This group also reported less childhood adversity and later first episode onset than the 3-or-more episode group, suggesting these groups may represent distinct populations. Bockting et al (2005) demonstrated that the CT augmentation achieved a significant protective effect against future relapse/recurrence, which intensified with the number of previous episodes experienced. For patients with 5 or more previous episodes (41% of the sample), CT reduced relapse/recurrence from 72% to 46%. Jarrett et al (2001) examined the efficacy of a CT continuation phase intervention (10 sessions over 8 months) for 84 patients who had responded successfully to an acute phase of CT (20 sessions over 12-14 weeks). The continuation phase intervention significantly reduced relapse versus control (10% versus 31%). Over 24 months, including a CT-free period, age of onset and quality of remission during the late phase of acute treatment interacted with condition in influencing duration of effects. In patients with early onset MDD, continuation treatment significantly reduced relapse/recurrence (16% versus 67% for control) and it significantly reduced relapse for those with unstable remission at late acute phase (37% versus 62%). As with other studies described above, this demonstrated that CT may be most efficacious in preventing relapse for patients who are most vulnerable for it, based on other factors (e.g., early onset, number of prior episodes, instability of remission). In studies examining more specifically the durability of relapse/recurrence prevention effects, in Fava et al's (2004) randomized control trial, 40 patients with recurrent major depression who had been successfully treated with pharmacotherapy were randomly assigned to either cognitive behavior treatment (CBT) of residual symptoms (supplemented by lifestyle modification and well-being therapy) or clinical management and followed up for relapse/recurrence for six years. In both groups, pharmacotherapy was tapered and discontinued and not reinstituted unless relapse occurred. CBT resulted in significantly lower relapse (40%) than clinical management (90%). The CBT group also experienced significantly fewer episodes of relapse over the six years. In a study examining the long term durability of CBT as a relapse prevention intervention, Paykel et al. (2005) followed 158 patients for six years after randomization (4.5 years after completion of CBT) who had been randomly assigned to CBT plus medication and clinical management versus medication and clinical management alone. Effects in prevention of relapse and recurrence were found to persist, with weakening, and were not fully lost until 3.4 years after the end of CBT.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Continued antidepressants have been demonstrated to be effective in reducing risk of relapse/recurrence	Gartlehner et al., 2007 Geddes et al., 2003	I	Good	A
2	Continuation phase CBT, CT, or MBCT reduces the risk of relapse/recurrence with recurrently depressed patients who have or have not discontinued medication and who are at higher risk of relapse (i.e., 3 or more prior episodes, earlier onset, unstable remission)	Bockting et al. 2005 Jarrett et al., 2001 Ma & Teasdale, 2004 Teasdale et.al, 2000	I	Good	A
3	Relapse/recurrence prevention effects appear to be fairly durable	Fava et al., 2004 Paykel et al. 2005	I	Good	A
4	A variety of dysfunctional cognitive variables, which are typically targets of CT and respond favorably to CT, significantly predict relapse/recurrence	Alloy et al., 2006 Beevers et al., 2003 Iacoviello et al., 2006 Mongrain & Blackburn, 2006 Petersen et al., 2004 Segal et al., 2006 Teasdale, et al., 2001, 2002	III	Fair	C

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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

RATIONALE

Patients appropriate for care management may have a range of medical and psychiatric co-morbid conditions that require integrated care. Care management is a flexible clinical approach to the management of several chronic health conditions that may be integrated into primary care settings.

The care manager implements specific strategies on behalf of the treating provider. These strategies include adherence, side effect and relapse monitoring, assessment of symptom and functional status response, and giving timely feedback of pertinent clinical data to treating providers to affect their approach to depression management. Care management also facilitates the interface between patients and the specialty mental health setting through regular reviews of those patients receiving care. For those patients preferring primary care treatment, care management sometimes leads to complete depression symptom remission as well as timely referrals to specialty mental health care

Systematic reviews of several randomized trials have demonstrated strong evidence specifically supporting the benefits of care management and multifaceted interventions on depression outcomes. (Willimas et al., 2007, Gilbody et al., 2006). An Evidence Synthesis Report prepared by VA has shown that at least 16 weeks is effective in treating depression in a collaborative care model. (VA Evidence Synthesis, 2009).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**R**
1	Compared to usual primary care, care management improves depression outcomes for patients with mild to moderate MDD	Bower et al., 2006 Gilbody et al., 2006 Williams 2007	I	Good	A
2	Care management appears more effective when continued for at least six months	Williams et al., 2007	II	Fair	B
3	Care management is effective when delivered by telephone	Gilbody et al., 2006 Williams 2007	I	Good	A
4	Essential elements of care management are: prospective follow-up to include symptom monitoring and treatment adherence, patient education, and coordination of primary care and mental health services	Gilbody et al., 2006 Williams 2007	II	Fair	B
5	In efficacious studies, care management functions routinely included general support	Gilbody et al., 2006 Williams et al., 2007	I	Fair	B
7	In almost all studies, care managers participated in case reviews with a mental health professional who typically was a psychiatrist	Williams et al., 2007	I	Good	A

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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.

RATIONALE

SSRIs are more effective than placebo and comparable to each other as first-line therapy for MDD. Individuals who fail or are intolerant to one SSRI can be switched to another SSRI or other first-line antidepressant. However, there is little evidence to support the use of a third SSRI after unsuccessful trials with two SSRIs. Rather, such individuals should be switched to another class of antidepressant. After sufficient length of time, dose should be increased based on tolerability and efficacy for those who show no or partial response. Augmentation may be considered for those with partial response. In selecting or switching to another SSRI, clinicians should be aware of variability in side effect profiles among the SSRIs (e.g., higher risk of diarrhea with sertraline, more sedation, weight gain and sexual dysfunction with paroxetine). Practitioners should be aware of potential drug interactions (e.g., CYP450 2D6 inhibition by fluoxetine and paroxetine or serotonin syndrome) for patients on concomitant medications. As the only FDA Pregnancy Category D agent with a higher risk of cardiovascular malformation, paroxetine should be avoided in pregnant women. All other SSRIs are FDA Pregnancy Category C agents and generally considered safe in pregnancy. However, SSRIs as a class have been associated with risk of miscarriage, preterm labor, and an increase in persistent pulmonary hypertension in the newborn. The SADHEART (Glassman et al., 2002), ENRICHED, and CREATE (Lespérance et al, 2007) studies indicate that SSRIs are safe medications in cardiac patients.

EVIDENCE STATEMENTS

- A systematic review of 8 RCT studies and 3 meta-analyses examined dose escalation of SSRIs. There was no evidence of increased efficacy within the first 4 weeks and limited efficacy for dose escalation after 8 weeks (Rue HG, Trivedi MH, et al. 2006).

- In a case-controlled study of 337 pregnant women on SSRIs compared to 836 matched control women, use of SSRIs after the 20th week of gestation led to a 6 fold increase in the risk for

persistent pulmonary hypertension of the newborn although a crude risk of only 1 percent (Chambers CD, et al. 2006) was noted.

- Two epidemiological studies, one in Sweden (Kallen B, et al. 2006) and one in the US, found a 2-fold and 1.5 fold, respectively, increased risk of cardiac defect in the infant with paroxetine use in the first trimester. A case-control using US data reported a greater than 3 fold increased risk of right ventricular outflow tract obstruction in infants with first trimester exposure to paroxetine (Louik C, et al. 2007). Using data from a Canadian population-based registry, two nested case-control studies determined that the risk of cardiac malformations did not differ significantly after first trimester exposure to paroxetine or other SSRIs compared to non-SSRI antidepressants. A dose response relationship was observed with infants whose mothers took >25 mg per day of paroxetine having a 2.23 times greater risk for any major congenital malformations and a 3.07 fold increased risk for major cardiac malformations (Berard A, et al. 2007). A meta-analysis concluded that first trimester exposure to paroxetine conveyed a 72percent greater risk of cardiac malformation compared to controls. This meta-analysis was conducted prior to the publication of the above trials (Bar-Oz B, et al. 2007).

- For initial treatment of major depression, 55 head-to-head studies comparing SSRIs to another SSRI or second-generation antidepressant found no evidence of significant difference in efficacy or effectiveness (Gartlehner G, et al. 2007).

- An analysis of 72 head-to-head efficacy studies of second-generation antidepressants and an additional 39 observational/experimental studies (with 5 RCT studies designed to detect differences in adverse events) found 8 percent higher rates of diarrhea with sertraline than comparison drugs (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine). Paroxetine had higher weight gains than fluoxetine and sertraline. Of the SSRIs, paroxetine had the highest incidence of discontinuation/withdrawal syndrome and fluoxetine had the lowest (Gartlehner G, et al. 2007).

- A systematic review of 8 RCTs and 23 open studies found that after failure on one SSRI, patients may still respond to another SSRI, although results from the Star*D trial indicated that only 25 percent of such patients may remit (Rue HG, et al. 2006b; Rush AJ, et al. 2006a).

- Although several clinical guidelines suggest SSRIs be considered first line for atypical depression, empirical evidence to support this is weak. There are 3 RCTs comparing fluoxetine to imipramine or phenelzine in atypical depression. While the two smaller RCTs found fluoxetine equal to phenelzine (n=22) (Pande AC, et al. 1996) and superior to imipramine (n=28) (Reimherr FW, et al. 1984), the largest RCT to date (n=145) found fluoxetine and imipramine were equally effective although fluoxetine was better tolerated (McGrath MF, et al. 2000).

- Despite the FDA warning about increased suicidal ideation and behaviors on antidepressants, ecological studies in developed countries have shown either decreased rates or no increase of suicide with SSRI use (Grunebaum MF, et al. 2004; Khan A, et al. 2003; Korkeila J et al., 2007). However, analysis of a Finnish cohort study noted increased risk of suicide attempt despite decreased completed suicide (Tiihonen J, et al. 2006).

- Analysis of FDA summary reports of controlled clinical trials (77 suicides out of 48,277 subjects) did not demonstrate an increased risk of suicide for SSRIs compared to other antidepressants or placebo (Khan A, et al. 2003).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	No evidence of increased efficacy by dose escalation within first 4 weeks. Dose escalation after 6 weeks appeared less effective than continuing same dose. Limited efficacy for dose escalation after 8 weeks	Ruhe et al., 2006a	I	Poor	I
2	SSRIs used in the later half of pregnancy increase the risk of persistent pulmonary hypertension compared to non-SSRI antidepressants	Chambers, 2006	II	Fair	B
3	All SSRIs are equally effective for initial treatment of Major Depression	DERP, 2006 Hansen et al., 2005	I	Good	A
4.	Sertraline has higher rates of diarrhea than citalopram, fluoxetine, fluvoxamine, and paroxetine	AHRQ, 2007 DERP, 2006	I	Fair	B
5	Of the SSRIs, paroxetine has the highest reported rate discontinuation syndrome and fluoxetine the lowest.	AHRQ, 2007 DERP, 2006	I	Fair	B
6	Among the SSRIs, paroxetine has the highest rate of sexual dysfunction and weight gain.	AHRQ, 2007 DERP, 2006	I	Fair	B
7	After failure on one SSRI, patients may still respond to another SSRI	Ruhe et al., 2006b Rush et al., 2006a	I	Good	A
8	Fluoxetine is equal in efficacy to imipramine for atypical depression, although more tolerable	McGrath, 2000	I	Good	A
9	In an analysis of epidemiological databases in various developed countries, SSRIs are associated with lower suicide rates	Gibbons et al., 2005 Korkeila et al., 2007 Tiihonen et al., 2006	II	Fair	B
10	Initiation of SSRIs may increase suicidal ideation or behaviors	Tiihonen et al., 2006	II	Fair	B

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.

RATIONALE

The SNRIs' pharmacologic and adverse effect profiles should be considered along with patient co-morbidities and past experience with other antidepressants. Response and remission rates with venlafaxine may be slightly higher than with the SSRIs, although this is balanced by higher rates of nausea and vomiting and discontinuation due to adverse effects. There is no evidence supporting increased efficacy with duloxetine relative to the SSRIs.

EVIDENCE STATEMENTS

- Systematic reviews (AHRQ, 2007; NICE, 2007) support the use of SNRIs for the treatment of adults with MDD, based on results of numerous placebo- and active-controlled RCTs.

- Few of the head-to-head RCTs comparing venlafaxine and various SSRIs have reported significant differences between SSRIs and venlafaxine, although efficacy results tended to favor venlafaxine. Three meta-analyses comparing venlafaxine and fluoxetine (AHRQ, 2007; Hansen et al., 2005; Smith, 2002) have reported slightly greater efficacy with venlafaxine than with fluoxetine. This is counterbalanced by a higher incidence of nausea and vomiting (about 10% higher, 95% CI: 4-17%) and higher discontinuation rates compared to SSRIs (RR 1.5; 95-% CI: 1.2-1.8%) (AHRQ, 2007).

- Duloxetine RCTs have included SSRIs (fluoxetine or paroxetine) as active comparators, but were not designed to directly compare active treatments. There are no consistent data supporting greater efficacy with duloxetine compared to SSRIs.

- There is insufficient evidence to prefer one SNRI over another. One meta-analysis comparing placebo-controlled trials with venlafaxine and duloxetine (Vis et al., 2005) and pooled results of two similar double-blind RCTs comparing duloxetine and venlafaxine (Perahia et al., 2008) reported no statistically significant differences in treatment effects between the two SNRIs. A second meta-analysis that used meta-regression techniques to make indirect comparisons (Eckert & Lancon, 2006) reported a significantly greater treatment effect with venlafaxine than with duloxetine, with similar dropout rates.

- A systematic review (Ruhe et al., 2006b) identified three RCTs evaluating the efficacy of switching to venlafaxine vs. other antidepressants after initial failure on an SSRI (Baldomero et al., 2005; Poirier & Boyer, 1999; STAR*D, 2006). A meta-analysis of remission rates and response in these three trials (Ruhe et al., 2006b) favored venlafaxine, with a weighted difference in remission rate of 8 percent (95% CI: 4-11%) and response rate of 6 percent (95%CI: 1-10%). The Level II STAR*D trial (2006), which compared a switch after citalopram to venlafaxine, bupropion, or sertraline, did not find significant differences in response rates (28.2%, 26.1%, and 26.7%, respectively), remission rates (24.8%, 21.3%, 17.6%), or discontinuation rates due to adverse effects (21.2%, 27.2%, 21.0%) between these agents.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	SNRIs have been shown to be superior to placebo for the treatment of adults with MDD	AHRQ, 2007 NICE, 2007	I	Good	A
2	Response and remission rates with venlafaxine may be slightly higher than with the SSRIs, although this is balanced by higher rates of nausea and vomiting and discontinuation due to adverse effects	AHRQ, 2007 Hansen et al., 2005 Smith, 2002	I	Good	C
3	Although one meta-analysis reported a significantly greater treatment effect with venlafaxine than with duloxetine, another meta-analysis and pooled results of two similar double-blind RCTs report no statistically significant differences in treatment effect between the two SNRIs.	Eckert & Lancon, 2006 Perahia et al., 2008 Vis et al., 2005	I	Good	C
4	SNRIs are effective in treating adult patients with MDD who have not responded to one or more trials with other second generation antidepressants (SSRIs, bupropion, or mirtazapine)	Ruhe et al., 2006b Level II STAR*D, 2006 Baldomero et al., 2005 Poirier & Boyer, 1999	I	Good	A

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.

RATIONALE

Bupropion's unique pharmacologic and adverse effect profiles should be considered along with a patient's co-morbidities and past experience with other antidepressants. Response and remission rates with bupropion are similar to other first-line antidepressants. Bupropion can be added to existing antidepressant treatment for patients who have had a partial response but have not achieved remission.

EVIDENCE STATEMENTS

- Bupropion's response rate has not been shown to differ from to the SSRIs in 6 comparative trials (fluoxetine, 2; paroxetine, 1; and sertraline, 3) included in a systematic review that rated the quality of the trials as fair. Bupropion had the highest mean incidence of insomnia (16%) and headache (27.2%) in clinical trials relative to the other second-generation antidepressants (AHRQ, 2007; Hansen et al., 2005). Bupropion is associated with modest weight loss rather than weight gain (Hansen et al., 2005).

- Bupropion is a switching option for patients who have not responded or remitted to other first-line antidepressants. Data supporting bupropion as a switching option is limited to 1 RCT and 2 small open-label trials. The STAR*D trial did not find a statistically significant difference in remission rates in patients switched from citalopram to bupropion (21.3%), venlafaxine (24.8%) or sertraline (17.6%). Patients switched from their STAR*D Step II treatment did not differ in their response rates between bupropion (6.7%) and venlafaxine (6.3%) in STEP III. Bupropion's rate of intolerability was greater (nonsignificant) compared to other switching options in STEPS II and III (Rush et al., 2006). An open-label trial that recruited patients who had failed to respond to fluoxetine reported a 34.6percent response rate with bupropion (Ruhe et al., 2006b).

- Another open-label trial recruited patients who had intolerable sexual side effects to fluoxetine and reported a 10.3% drop-out rate attributed to side effects with bupropion (Ruhe et al., 2006b)

- AHRQ 2007 determined that bupropion was associated with great satisfaction with respect to sexual activity compared to sertraline or fluoxetine with a Number Needed to Treat (NNT) = 7.

- Bupropion SR is equivalent to buspirone in achieving remission when used to augment initial antidepressant treatment.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Bupropion's response and remission rates are comparable to other first-line antidepressants	AHRQ, 2007 DERP, 2006 Hansen et al, 2005	I	Good	A
2	Bupropion is a switching option for patients who have not responded or remitted to other first-line antidepressants	Ruhe et al., 2006b Rush et al., 2006	I	Good	A
3	Bupropion can be used to augment existing antidepressant treatment	Trivedi et al., 2006	I	Fair	B
4	Bupropion has a lower incidence of sexual side effects than the SSRIs	AHRQ, 2007 DERP, 2006	I	Fair	B

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 $5\text{-}HT_3$ 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.

RATIONALE

Mirtazapine's unique pharmacologic and adverse effect profiles should be considered along with a patient's co-morbidities and past experience with other antidepressants. Response and remission rates with mirtazapine are similar to other first-line antidepressants. Mirtazapine can be combined with existing antidepressant treatment for patients who have had a partial response but have not achieved remission.

EVIDENCE STATEMENTS

- Systematic reviews and meta-analyses have found no difference in response rates between mirtazapine and the other first-line antidepressants bupropion, citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine. The percent of patients who experienced weight gain was greater with mirtazapine than all the other first-line antidepressants (AHRQ, 2007; DERP, 2006).

- Mirtazapine in combination with venlafaxine (n=51) resulted in a remission rate that was not different statistically from remission after treatment with tranylcypromine (n=58) in patients who had not achieved remission after trials of three different antidepressants, 13.7% vs. 6.9%. Symptom reduction was greater with the combination (25%) than with tranylcypromine alone (6.2%). Significantly, fewer patients withdrew from the study in the combination group (22.6%) than did those taking tranylcypromine alone (41.4%) (McGrath et al., 2006).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	Mirtazapine's response and remission rates are comparable to other first-line antidepressants	AHRQ, 2007 DERP, 2006	I	Good	A
2	Mirtazapine is a switching option for patients who have not responded or remitted to other first-line antidepressants	Ruhe et al., 2006b	I	Good	A
3	Mirtazapine can be used in combination with existing antidepressant treatment	McGrath et al., 2006	I	Good	A
4	Mirtazapine has a lower incidence of sexual side effects than the SSRIs	AHRQ, 2007 DERP, 2006	I	Good	A
5	Mirtazapine is associated with weight gain more often than other first-line antidepressants	AHRQ, 2007	I	Good	A

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.

EVIDENCE STATEMENTS

In general, the secondary amine TCAs (i.e., nortriptyline, desipramine) have equal efficacy and fewer side effects than the parent tertiary amines (i.e., amitriptyline, imipramine) .

- With the exception of clomipramine, the available TCAs are listed in Table 1 and Table 5. Clomipramine is approved only for the treatment of obsessive-compulsive disorder (OCD) and is not discussed in these guidelines. Patients with obsessive-compulsive disorder should be referred to a psychiatrist.
- A systematic review of depression treatment comparing antidepressants with placebo summarized results from 10 studies comparing TCA to placebo in primary care. The number needed to treat for TCAs was about 4, and for SSRIs it was 6. The numbers needed to harm (for withdrawal caused by side effects) ranged from 5 to 11 for TCAs and 21 to 94 for SSRIs. Low-dose (100 mg or 75 mg) as well as high-dose TCAs were effective. (Arroll et al., 2005)
- A Cochrane review (Mottram, 2006) suggests that SSRIs and TCAs are of the same efficacy. However, Mottram found some evidence suggesting that TCA related antidepressants and classical TCAs may have different side effect profiles and are associated with differing withdrawal rates when compared with SSRIs. The review suggests that classical TCAs are associated with a higher withdrawal rate due to side effect experience, although these results must be interpreted with caution due to the relatively small size of the review and the heterogeneity of the drugs and patient populations. TCAs are more lethal in overdose than SSRIs.
- In STAR*D, TCAs were used as an alternative to mitrazapine when patients did not respond to first line antidepressants. When treated with nortriptyline, 13percent of these patients achieved remission.

Therapeutic Drug Monitoring of TCA [a-c]

- Therapeutic plasma concentrations for desipramine, imipramine, and nortriptyline can be used to guide treatment for patients that do not respond to or comply with therapy, for individuals on combination therapy, in elderly patients, or when ruling out toxicity
- Therapeutic plasma concentrations should be drawn after 1 week of therapy, when the majority of patients will be in steady state
- Draw blood sample 10-12 hours after the last dose to ensure that absorption and distribution of the drug are complete
- Nortriptyline plasma concentrations demonstrate a curvilinear concentration-response relationship and therefore the dose should be adjusted to obtain concentrations within a therapeutic range window (50-175 ng/mL); concentrations above the upper limit are associated with a declining (but not necessarily toxic) response
- Imipramine (plus metabolite desipramine) plasma concentrations demonstrate a linear concentration-response relationship and therefore the upper limit is a function of toxicity rather than reduced efficacy (200-350 ng/mL); raising serum concentrations above threshold may convert nonresponders into responders;

monitor for signs and symptoms of toxicity

- The relationship between response and plasma desipramine concentrations is less clear; in general, a minimum concentration of 125 ng/mL should be obtained if tolerated; concentrations over 300 ng/mL may increase the risk of toxicity

[a] *DeVane LC, Jarecke RC. (1992). Chapter 33: Cyclic Antidepressants. pharmacokinetics, Principles of therapeutic drug monitoring, 3rd ed., Evans WE, Schentag JJ, Jusko WJ, eds. Vancouver, WA: Applied Therapeutics, Inc. 1-47.*
[b] *Preskorn SH, Burke MJ, Fast GA. Therapeutic Drug Monitoring: Principals and Practice. (1993). Psychiatric Clinics of North America. 16(3):611-645.*
[c] *Charney D, Miller H, Licinio J, Salomon R. (1995). Chapter 28: Treatment of depression. From: Schatzberg A, Nemeroff C, ed. Textbook of psychopharmacology. American psychiatric press; 575-601.*

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	Remission when treated with nortriptyline, for patient who failed two trials of first line antidepressants.	STAR*D DERP	I	Fair	B
2	Low-dose as well as high-dose TCAs are effective compared to placebo, with higher rates of withdrawal caused by side effects compared to first line antidepressants	Arroll et al., 2005 Mottram et al., 2006	I	Fair	B

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).

RATIONALE

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.

EVIDENCE STATEMENTS

- For the oral MAOIs, a meta-analysis (Thase et al., 1995) reported overall efficacy rates of 57.9 percent with phenelzine, 60.1 percent with isocarboxazid, and 52.6 percent with tranylcypromine in the outpatient setting. The meta-analysis did not perform statistical tests to determine absolute differences between the three drugs, but the overall efficacy rates appear similar. The meta-analysis supports that the MAOIs may be more effective for patients with atypical features, but not as effective as TCAs for patients with more severe or melancholic depression.
- Moreover, the MAOIs may be beneficial for outpatients with treatment resistant depression, though this is less well established and, in some cases, based on comparisons with drugs not available in the U.S. A recent chart review (Amsterdam et al., 2005) reviewed 59 charts of patients who had received at least one trial of another antidepressant; 24 (41%) patients had not responded to ≥4 adequate antidepressant trials. Overall, 56 percent of MAOI trials had a CGI-change score indicating that patients were "much or very much improved" relative to the treatment immediately prior to the MAOI.
- In level 4 of the STAR*D trial, remission rates were not significantly different between the two treatment groups (6.9% for the tranylcypromine group and 13.7% for the venlafaxine plus mirtazapine group). The mean daily dose at exit for tranylcypromine was 36.9 mg (SD=18.5); for venlafaxine, 210.3 mg (SD=95.2); and for mirtazapine, 35.7 mg (SD=17.6). Tranylcypromine was associated with significantly less symptom reduction and greater attrition due to intolerance. Those who were treated with tranylcypromine were more likely to discontinue the treatment, citing side effects as the reason. It is also possible that the dietary restrictions associated with taking an MAOI could have limited its acceptability as a treatment. (McGrath PJ et al., 2006)
- Selegiline transdermal patch has only been studied in three placebo-controlled clinical trials (Amsterdam, 2003; Bodkin & Amsterdam, 2002; Feiger, 2006) and has not been studied in treatment resistant depression. The response rates have been relatively low with small advantages compared with placebo and low response rates (30-40%) relative to those reported with other antidepressants (50-60%).

- Dietary restrictions are required with all the MAOIs with the exception of the lowest dose of the selegiline transdermal formulation, though it is unclear what percent of patients will achieve remission at this dose.

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.

RATIONALE

Bupropion SR and buspirone are equally effective at achieving remission when used to augment first-line antidepressant treatment (SSRIs). Bupropion SR and buspirone are recommended as initial choices for augmentation since their efficacy has been demonstrated in at least one randomized clinical trial and their safety and tolerability profiles are more favorable than lithium.

a. Bupropion SR: Initial dose 100 mg twice a day, increasing after 2 weeks to 150 mg twice daily, and then again in another 2 weeks, if necessary, to 200 mg twice daily: Maximum dose: 400 mg/day.

b. Buspirone: Initial dose 7.5 mg twice a day, increasing to 15 mg twice a day after 1 week, then increasing the dose by 15 mg/day every 2 to 3 additional weeks; Maximum dose: 60 mg/day.

Dose adjustments may be necessary based on age, renal or hepatic function, or concurrent drug therapy.

Lithium and triiodothyronine (T3) have been studied as augmentation strategies for first-line and tricyclic antidepressants. Lithium is the best-studied augmentation strategy with more than 10 controlled clinical trials. Response has been more consistent when combined with a TCA or MAOI, than an SSRI. Triiodothyronine is preferred to thyroxine (T4) due to its quicker onset and offset of action.

a. Lithium: Initial dose: 300 milligrams or 450 milligrams as a single daily dose or in divided doses. The dose can be increased by 50 to 100 percent every 1 to 2 weeks depending on the patient's tolerability and renal function. Target lithium plasma concentration is >0.5 and <1 milliequivalents/L; Maximum dose 900milligrams/day.

b. T3: Initial dose: 25 micrograms daily, increase to 50 micrograms daily after 1-week. Maximum dose: 50 micrograms per day.

Dose adjustments may be necessary based on age, renal or hepatic function, or concurrent drug therapy.

All the atypical antipsychotics, with the exception of clozapine, have been reported to improve response or remission rate when used to augment an antidepressant.

EVIDENCE STATEMENTS

- Augmentation can be introduced at any point in therapy, provided the patient has demonstrated a partial response to an existing antidepressant.
- Augmentation was a treatment option in Steps 2, 3 and 4 of the STAR*D trial. Augmenting citalopram with bupropion SR or buspirone resulted in remission rates of 39 percent and 32.9 percent after means of 5.7 and 4.8 weeks, respectively. Higher percentages of subjects remitted with augmentation than by switching to a different agent, although this may reflect differences in the rates of partial response and tolerability to citalopram as monotherapy in Step 1. Augmentation of bupropion, sertraline, citalopram or venlafaxine with lithium or T_3 was an option in Steps 3 and 4. Remission rates were 14.5 percent and 25.7 percent for lithium and T_3, respectively (p>.05); the mean time to remission was 5.3 weeks for both groups. Lithium was not as well tolerated as T_3. (Rush et al., 2006b)
- A systematic review and meta-analysis of 10 randomized, double-blind, placebo-controlled clinical trials assessed the efficacy of atypical antipsychotics (olanzapine, risperidone, quetiapine, or ziprasidone) as augmentation agents to antidepressants in patients with treatment resistant depression. The pooled remission and response rates favored the augmentation of atypical antipsychotics vs. placebo, 47.4 percent vs. 22.3 percent and 57.2 percent vs. 35.4percent, with a pooled risk ratios of 1.75 (95%CI: 1.36 to 2.24, p<.0001) and 1.35 (95% CI: 1.13 to 1.63, p=.001), respectively. (Papakostas et al., 2007)
- In one retrospective chart review of 76 trials, reported augmentation with olanzapine, quetiapine, risperidone, or ziprasidone in 49 patients resulted in an overall improvement in CGI-I ratings in 65 percent of patients (32/49). Individual response rates varied by agent: olanzapine 57 percent (21/37), risperidone 50 percent (7/14), quetiapine 33percent (6/18), and ziprasidone 10 percent (1/10). Lack of response to one atypical antipsychotic medication did not predict response to another agent. (Barbee et al., 2004)
- Combination of olanzapine and fluoxetine in patients with treatment resistant major depressive disorder was not shown to provide a superior response to either drug alone or to nortriptyline after 8 weeks in a double-blind trial that randomly assigned 500 patients who had not responded to separate trials with an SSRI and nortriptyline (Shelton et al., 2005).
- Augmentation with aripiprazole was found to result in higher remission and response rates compared to placebo in an 8-week, randomized, double blind trial of 362 patients who had not had an adequate response to an antidepressant. Remission and response rates both favored

aripiprazole over placebo (18.8% and 8.7%, p=.006 and 26% and15.7%, p=.011). The number needed to treat was 10.

- Results of open-label augmentation with aripiprazole have been reported for 15 patients with major depressive disorder who had either partial response or no response to an SSRI, bupropion or venlafaxine. Nine patients achieved remission by the end of their second week taking aripiprazole and all 8 patients completing the 8-week trial achieved remission. The most common reason for discontinuing treatment was akathesia in 3 patients (Simon et al., 2005).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	Augmentation can be introduced at any time during treatment, provided the patient has demonstrated a partial response to an existing antidepressant.	Rush et al., 2006b Barbee et al., 2004	I	Fair	B
2	Consider atypical antipsychotics after other augmenting agents have failed or are contraindicated	Papakostas et al., 2007 Berman et al., 2007	I	Fair	B

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.

RATIONALE

Depression in the medically ill elderly occurs frequently and is underdetected in part because of the difficulty in diagnosing depression in this population. Older patients whose depressive symptoms are interfering with their functional capabilities or their participation in prescribed therapies to improve or restore function after a medical illness may be considered for a trial of methylphenidate.

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
	Stimulant drugs do not appear to be as effective as the conventional antidepressants in primary depression	Satel et al., 1989 (SR)	I	Fair	B
	Stimulants in apathetic or depressed geriatric patients are likely to produce positive results, but outcomes frequently consisted of partial improvement	Satel et al., 1989 (SR)	II	Poor	C
	Stimulants may be of value in refractory cases or in special cases, such as medically ill patients	Satel et al., 1989 (SR) Emptage & Semla, 1996	II	Poor	C

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

In general, psychotherapy trials find that these interventions are superior to no treatment, attention controls and pill placebo controls. Most studies do not find differences between psychotherapies and pharmacotherapy, and most do not find differences between different psychotherapies. However, relative to pharmacotherapy, the overall body of literature on psychotherapy is limited. CBT has the largest body of adequate studies, with IPT and PST having several well-designed RCTs as well. There is less data for other interventions and there is a limited body of literature available for special populations (e.g., older patients or pregnant/postpartum women).

EVIDENCE STATEMENTS

General Evidence

Recommendations are based on the NICE practice guidelines (NICE, 2004), systematic reviews (de Mello et al., 2005; Frazer et al., 2005) and RCTs (Bolton et al., 2003; DeRubeis et al., 2005; Dimidjian et al., 2006).

- *Psychotherapies vs. wait-list:* There is good evidence that individual CBT, IPT, and PST reduce symptom severity and improve remission rates at the end of treatment. There is strong evidence indicating clinically significant differences favoring CBT over wait-list controls in reducing symptoms at the end of treatment (average difference in BDI = -11.64). One study found that counseling led to improvement over general practice at the end of treatment, although not at 12-month follow-up (N = 134; NICE, 2004).
- *Comparisons between psychotherapies:* Evidence does not indicate that CBT, IPT and PST differ on outcomes.
    - One meta-analysis of three studies comparing IPT and CBT (de Mello et al., 2005) concluded that while there was not a statistically significant difference for remission, there was evidence that IPT led to significantly lower levels of depressive symptoms at the end of treatment. However, other reviews and meta-analyses have concluded there is not sufficient evidence to conclude that treatments lead to differences. A recent comparison between IPT and CBT (Luty et al., 2007) found that CBT led to better outcomes for severe depression. Recent comparisons of BT and CBT found that BT did not differ from CBT in outcomes for mild to moderate depression (Jacobson et al., 1996) and one study found that (BT) was superior to CBT for severe depression (Dimidijian et al., 2006; Jacobson et al., 1996).

    - For second line interventions (short-term psychodynamic psychotherapy [SDPP], counseling) there is little comparative data with other treatments. One study compared CBT and SDPP in adults with MDD (8 or 16 sessions depending on randomization; N=117; Shapiro et al., 1994). In general, there were no significant differences on outcomes, although there were some benefits for CBT on self-reported depression at the end of treatment. An earlier study found that CBT was superior to either relaxation or SDPP (McLean & Hakstian, 1979).

- *Psychotherapies vs. pharmacotherapy (antidepressant medication):* The current research evidence has not demonstrated that first line psychotherapies (CBT, IPT, and PST) perform better or worse than antidepressant medication. One study found that counseling was less beneficial than antidepressant medication in achieving symptom reduction and remission at both the end of treatment and at 12 months (N = 103, NICE, 2004).
- *Severe depression:* CBT and Behavior Activation (BA) have both been tested in regards to severe MDD (generally defined as a HRSD score ≥ 20). One recent RCT found CBT reduces depressive symptoms and improves remission rates in severe MDD, compared to a control group and CBT was not significantly different from pharmacotherapy (DeRubeis et al., 2005). However, one study found CBT was significantly less efficacious than either BA or antidepressant medication treatment for patients with severe MDD (Dimijidian et al., 2006). BA was at least as efficacious as pharmacotherapy, and significantly more efficacious than cognitive therapy (CT) and placebo conditions when treating severely depressed patients. One recent comparison of IPT and CBT found that CBT was superior to IPT for severe MDD (Luty et al., 2007). There are no data on longer term comparisons with placebo or no-treatment controls for severe depression.
- *Decreasing suicidality:* One RCT (N=120) found that a 10-session CBT led to 50 percent fewer suicide attempts when compared to enhanced usual care (tracking and referral) (Brown et al., 2005), without reducing rates of suicidal ideation.
- *Inpatient treatment:* One RCT (N=25; Hopko et al., 2003) compared brief BA to standard supportive psychotherapy (TAU) with severely depressed patients on an inpatient psychiatric unit (N=25) and found that BA was superior to TAU (effect size = 0.73).
- *Retention:* There is limited evidence that BT or BA may have a positive effect on retention. In Dimidjian and colleagues' study (2006), a greater percentage of patients in the BA condition completed treatment as compared to both the CT and pharmacotherapy interventions.

Group Psychotherapies

- The NICE guidelines conclude that CBT group therapy is superior for treatment of depression relative to other group therapies (4 RCTs of 4 different modalities; Gestalt, supportive, traditional, and meditation-relaxation). The effect for CBT over other groups for achieving remission was described as "strong" in the NICE guidelines (RR = .60, CI, .46 to .79).
- There is insufficient evidence to determine which treatment modality (group or individual) is preferable.

Pregnant or Postpartum Patients

- A meta-analysis found fair evidence that CBT and IPT are efficacious for treatment of postpartum depression (Bledsoe & Grote, 2006).
    - The best RCTs were home-based treatment delivery programs and were therefore not necessarily generalizable to most models.
    - Group and individual treatments were equivalent to other psychosocial treatments, and superior to control groups.
    - Combined CBT and medication had the largest effect size in this meta-analysis.
- An additional RCT (N=192) comparing treatments for postpartum MDD found that group treatments were not significantly different from each other, although they were not as effective as individual counseling (Milgrom et al., 2005).

Older patients

- Older patients appear to benefit from CBT compared to control conditions (Cuijpers et al., 2006; Frazer et al., 2005). Cuijpers and colleagues (2006) reviewed 25 RCTs of various

psychotherapies, of which 17 compared CBT to control groups. No differences were found between psychological treatments generally, but CBT specifically was superior to control (mean effect size for CBT was 0.70).

- CBT was not effective in one study of older, depressed stroke patients (Frazer et al., 2005).
- *Older adults (IPT):* Two systematic reviews (Cuijpers et al., 2006; Frazer et al., 2005) addressed acute psychotherapy treatment with older adults. Psychotherapies in general led to reductions in depressive symptoms and increased the likelihood of recovery. Psychotherapy did not differ from pharmacotherapy for reducing depression and, in three reviewed studies, there was no evidence that IPT differed from other psychotherapies. One study compared CBT and SDPP for major depression in older caregivers with MDD (20 sessions; N=66; Gallagher-Thompson & Steffen, 1994). Participants who had been caregivers for more than 3.5 years benefited more from CBT, while those who had been caregivers for less than 3 years benefited more from SDPP.
- One trial (Lynch et al., 2003) demonstrated that dialectical behavioral therapy (DBT) plus medication led to significantly better outcomes than medication alone for older patients. However, this study did not have a medication only control condition and therefore, is of limited utility in determining the additive benefit of DBT.

CBT Plus Pharmacotherapy

- Based on 6 studies (N = 724), the NICE guidelines conclude that CBT in combination with pharmacotherapy is superior to pharmacotherapy alone, although it is not clear that any benefit is maintained over time. Specifically, there is some evidence of greater symptom reduction at the end of treatment, although there is no evidence of different rates of remission or benefit at 6 months or 1 year post-treatment. There is insufficient evidence to determine if CBT plus pharmacotherapy is superior to CBT alone in treating depression.
- There are some exceptions to these findings. Combined treatment appears to lead to better outcomes for moderate to severe depression and chronic depression. One study of treatment comparing CBT alone, medication alone, and combined treatment for treatment of chronic depression found significantly better outcomes for combined treatment than either monotherapy (Keller et al., 2000). The NICE guidelines indicated that two studies found greater likelihood of remission of depression in moderate to severe depression, and six studies found that combined treatment led to better symptoms remission outcomes for moderate to very severe depression.
- *IPT Plus Antidepressant medication:* Three trials of IPT plus antidepressant medication compared with antidepressant medication alone, found higher rates of remission after 4 months of treatment (N= 35, 96 and 157), but similar rates of remission after 6 months.
- *Combined PST and antidepressant medication versus antidepressant medication alone:* There is insufficient evidence of clinically significant differences between combined problem-solving therapy and antidepressant medication alone in reducing symptom severity or achieving remission at the end of treatment or at 12 months.
    - One study compared psychodynamic therapy, behavior therapy, relaxation therapy and pharmacotherapy (10 sessions; N=178; McLean & Hakstian, 1979). Behavior therapy was superior to other treatments on 9 of 10 outcome measures at the end of treatment, although these benefits were reduced at 3 months post-treatment. Psychodynamic therapy performed most poorly on outcome measures of any treatment in this study.
    - Based on these studies, there is not sufficient evidence to determine whether psychodynamic therapy differs from CBT, BT, or pharmacotherapy for treatment response.

- *Dosage:* Most studies of CBT and IPT use a model of 16 to 24 sessions over approximately 16 weeks (DeRubeis et al., 2005; Dimidjian et al., 2006; Hollon et al., 2005; NICE, 2004, Reynolds et al., 1999), although there is significant variation (6-25 sessions; NICE, 2004). PST is briefer, 6 sessions over 3 months. DBT for older patients was 28 sessions of weekly group skills training, supplemented by weekly skills-coaching phone contacts.

Limitations of the Literature

- Comparisons with pharmacotherapy are often limited by the lack of pill placebo, although recent studies have included appropriate placebo controls (DeRubeis et al., 2005; Dimidjian et al., 2006). This may underestimate the benefit of pharmacotherapy and reduce the likelihood of finding differences between treatments.
- Magnitude of effect for psychotherapy trials may be overestimated because of study design issues that include not being blind to treatment.
- Antidepressant medication treatment in comparison trials is not always provided in a manner consistent with best clinical practices (e.g., unusual augmentation approaches, non-standard discontinuation of pharmacotherapy; DeRubeis et al., 2006).
- Some trials provide additional clinical contact in the pharmacotherapy condition. This design feature is likely to improve the benefit of the pharmacotherapy and reduce the difference with CBT.
- Some antidepressant medication trials used problematic medications (e.g., Klein et al., 2004).

Limitations of the IPT Literature

- There are a limited number of available trials, although several are large scale and well-designed.
- The magnitude of effect for psychotherapy trials may be overestimated because of study design issues, including patients not being blind to treatment.
- Antidepressant medication treatment in comparison trials is not always provided in a manner consistent with best clinical practices.

Limitations of the BT Literature

- There has been little replication of the above described results.
- BT has not been manualized, except for BA; therefore. it is not possible to know how similar or dissimilar the BT approaches were in the four studies.
- One study found that 10 weeks of psychodynamic psychotherapy combined with clomipramine was superior to clomipramine plus supportive care for reducing depressive symptoms and improving functioning in patients with severe depression (HRSD $\geq$ 20).

Limitations of the SDPP Literature

- None of the studies with SDPPs have been adequately replicated. They represent single tests of specific hypotheses; therefore, making general conclusions about the efficacy and effectiveness of SDPPs is premature.
- The magnitude of effect for psychotherapy trials may be overestimated because of study design issues, including patients not being blind to treatment.
- Some trials provide additional clinical contact in the pharmacotherapy condition. This design feature is likely to improve the benefit of the pharmacotherapy and reduce the difference with CBT.
- The antidepressant medication comparisons used medications that are no longer 1st line medications, reducing generalizability to current practice.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Benefit	SR
1	*Psychotherapy reduces depression:* CBT, IPT, PST, BT, CFT, SDPP and counseling are more effective for symptom reduction and remission than no treatment or placebo and are similarly effective to other evidence-based treatments	DeRubeis et al., 2005 Dimidjian et al., 2006 Ellis et al., 2004 McLean Hakstian, 1979 NICE, 2004	I	Good	Mod	A
	CBT, IPT, and PST have the most extensive supportive research literature	NICE, 2004	I	Good	Mod	A
	PST benefits are not maintained at 6 or 12 months post-treatment	NICE, 2004	I	Good	Mod	B
	Severe MDD: BA may be superior to CBT; CBT may be superior to IPT; results are inconsistent for symptoms reduction and remission	DeRubeis et al., 2005 Dimidjian et al., 2006 Luty et al., 2007 NICE, 2004	I	Good	Mod	B
	CBT reduces the risk of suicide attempts when compared to enhanced usual care	Brown et al., 2005	I	Good	Subst	B
	CFT did not differ from individual therapy for reducing depression and led to greater reductions in marital distress	NICE, 2004	I	Good	Mod	B
2	*Group therapies:* Group CBT is superior to other group therapies for symptom reduction and remission	NICE, 2004	I	Good	Mod	B
3	*Postpartum Depression:* Individual CBT or IPT is better than no treatment and is not different from other treatments	Bledsoe & Grote, 2006	I	Good	Mod	B
	Group CBT for postpartum depression has similar outcomes to other group interventions	Bledsoe & Grote, 2006 Milgrom et al., 2005	I	Good	Mod	B
	Group CBT for postpartum depression is less efficacious than individual psychotherapy	Milgrom et al., 2005	I	Good	Small	C
4	*Depression in older adults:*	Cuijper et al., 2006	I	Good	Mod	A

	CBT, IPT, and PST are better than no treatment, and have similar outcomes to other active treatments	Frazer et al., 2005				
	CBT was not effective with stroke patients	Frazer et al., 2005	I	Good	Small	D
	SDPP is better than CBT for older patients who have been caregivers less than 3.5 years. CBT is better than SDPP for older patients who have been caregivers for 3.5 years or more	Gallagher-Thompson & Steffen, 1994	I	Good	Mod	B
5	*Psychotherapy combined with pharmacotherapy:* Both CBT plus antidepressant medication and IPT plus antidepressant medication are superior to antidepressant medication alone for initial treatment response, but benefit does not appear to be maintained over time	NICE, 2004	I	Good	Small	B
	For specific populations (chronic MDD, recurrent MDD, severe MDD), CBT plus antidepressant medication and SDPP plus antidepressant medication treatment is superior to antidepressant medication alone	Keller et al., 2000 NICE, 2004	I	Good	Mod	A
	For older patients, DBT plus antidepressant medication was significantly better than antidepressant medication alone in reducing depressive symptoms and in achieving remission at the end of treatment and at 6 months	Lynch et al., 2003	II	Fair	Mod	C
	Brief BA is more efficacious than TAU (standard supportive psychotherapy) with severely depressed patients on an inpatient psychiatric unit	Hopko et al., 2003	I	Good	Mod	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

CBT is identified as an effective and well-researched first line short-term psychotherapeutic intervention for patients with MDD. Of the 3 identified first line agents for this condition (CBT, IPT, PST), CBT has the most extensive relevant body of research from well respected sources. CBT has been determined to be an effective option for the treatment of severe depression (HSRD $\geq$ 20 or equivalent) and is recommended for patients with a history of suicide attempts as a deterrent. In addition, CBT in combination with pharmacotherapy is recommended for patients with severe, recurrent, and chronic major depression or double depression combination.

EVIDENCE STATEMENTS

CBT Reduces Depression

- CBT is more effective for symptom reduction and remission than no treatment or placebo, and is similarly effective to other evidence-based treatments (DeRubeis et al., 2005 Dimidjian et al., 2006 Ellis et al., 2004; NICE, 2004)

- Findings for CBT in severe depression are inconsistent for symptom reduction and remission (DeRubeis et al., 2005; Dimidjian et al., 2006; NICE, 2004).

Suicide

- CBT reduces the risk of suicide attempts compared to enhanced usual care (Brown et al., 2005).

Group CBT

- CBT is superior to other group therapies for symptom reduction and remission (NICE, 2004). Individual CBT or IPT is better than no treatment and is not different from other treatments in postpartum patients (Bledsoe & Grote, 2006).

- Group CBT for postpartum depression has similar outcomes to other group interventions (Bledsoe & Grote, 2006; Milgrom et al., 2005).

- Group CBT for postpartum depression is less efficacious than individual psychotherapy (Milgrom et al., 2005).

Severe MDD

- Findings for CBT in severe depression are inconsistent for symptom reduction and remission.

- *Depression in older patients:* CBT, IPT, and PST are better than no treatment and have similar outcomes to other active treatments (Cuijper et al., 2006; Frazer et al., 2005).

- CBT was not effective with stroke patients (Frazer et al., 2005).

Severe Recurrent

- *CBT combined with pharmacotherapy:* CBT + ADM is superior to ADM alone for initial treatment response, but benefit does not appear to be maintained over time (NICE, 2004).

- For specific populations (chronic MDD, recurrent MDD, severe MDD), combined treatment is superior to ADM alone (Keller, et al., 2000; NICE, 2005).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Benefit	SR
1	CBT reduces depression	DeRubeis et al., 2005 Dimidjian et al., 2006 Ellis et al., 2004 NICE, 2004	I	Good	Mod	A
	Findings for CBT in severe depression are inconsistent for symptom reduction and remission	DeRubeis et al., 2005 Dimidjian et al., 2006 NICE, 2004	I	Good	Mod	B
	CBT reduces the risk of suicide attempts compared to enhanced usual care	Brown et al., 2005	I	Good	Subst	B
2	Group CBT is superior to other group therapies for symptom reduction and remission	NICE, 2004	I	Good	Mod	B
3	*Postpartum depression:* a. Individual CBT or IPT is better than no treatment and not different from other treatments	Bledsoe & Grote, 2006	I	Good	Mod	B
	b. Group CBT has similar outcomes to other group interventions	Bledsoe & Grote, 2006 Milgrom et al., 2005	I	Good	Mod	B
	c. Group CBT is less efficacious than individual psychotherapy	Milgrom et al., 2005	I	Good	Small	C
4	Depression in older adults: a. CBT, IPT, and PST are better than no treatment and have similar outcomes to other active treatments	Cuijper et al., 2006 Frazer et al., 2005	I	Good	Mod	A
	CBT was not effective with stroke patients for depression	Frazer et al., 2005	I	Good	Small	D
5	CBT + ADM is superior to ADM alone for initial treatment response, but benefit does not appear to be maintained over time	NICE, 2004	I	Good	Small	B
	For specific populations (chronic MDD, recurrent MDD, severe MDD), combined treatment is superior to ADM alone	Keller, et al., 2000 NICE, 2005	I	Good	Mod	A

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix 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]

RATIONALE

IPT refers to a specific manualized, brief psychotherapy intervention (usually 16 to 20 weekly sessions) originally developed by Klerman and colleagues (Klerman et al., 1984; Weissman et al., 2000). IPT, as a short-term psychological therapy, is well-researched and has been shown to be an efficacious intervention in a large number of well-designed research trials. Research findings indicate it is superior to control or placebo. IPT may be particularly useful in pregnant women who find the risks of antidepressant medication treatment to their fetus unacceptable.

EVIDENCE STATEMENTS

- One high quality clinical practice guideline (NICE, 2004), one systematic review specifically addressing IPT (de Mello et al., 2005), and one more RCT (Bolton et al., 2003) support the use of IPT for adults with mild to moderate symptoms of MDD.

- NICE (2004) found eight well-designed RCT trials that included IPT as a component, and de Mello and colleagues (2005) identified 13 (seven studies overlapped between the practice guideline and the review).

- *IPT vs. placebo:* de Mello and colleagues (2005) reported on nine studies that included IPT vs. placebo comparisons (653 patients, 337 in IPT and 316 in placebo). For acute treatment, IPT was associated with significantly greater symptom reduction at the end of treatment. IPT was also associated with higher rates of remission in most trials, but in the meta-analysis this was not statistically significant. An additional recent RCT suggests that IPT may not be superior to

12 weekly clinical management sessions lasting 20 to 25 minutes and covering education about depression and its treatment, reassurance, and encouragement to adhere to depression treatment (Lesperance et al., 2007).

- Of note, de Mello and colleagues (2005) misreported the number of patients for at least one study (reported 180 when it was in fact 80), reducing confidence in their conclusions.

- *IPT vs CBT:* Three studies compared IPT and CBT (a total of 204 patients, 102 in each condition). The meta-analysis indicated that while there was not a statistically significant difference for remission, IPT had significantly lower levels of depressive symptoms at the end of treatment.

- *IPT vs Antidepressant medication:* Nine studies compared IPT alone with pharmacotherapy (a total of 947 patients). Five trials reported acute treatment response, with IPTalone not leading to significant differences.

- IPT compared to a "usual care" placebo has effect sizes in the small to moderate range (de Mello et al., 2005; NICE, 2004). This effect size is similar to the effect size for antidepressants and other psychological therapies.

Pregnancy

- A systematic review of depression treatment during pregnancy or postpartum period identified 4 studies that tested IPT, with a total of 181 participants (three were RCTs, one was an open treatment trial). The overall effect size of 1.26 was significant and the authors conclude that IPT is a beneficial treatment for pregnant and postpartum women.

Older adults

- One RCT with 80 participants addressed acute IPT with older adults. IPT was not superior to pill placebo in this trial, but the low patient population (17 in the IPT group) suggest that the study was underpowered (Reynolds et al., 1999).

- *IPT plus Antidepressant Medication:* Three trials of IPT plus antidepressant medication compared with antidepressant medication alone found higher rates of remission after 4 months of treatment (N of 35, 96 and 157), but after 6 months, the rates of remission were all similar..

Limitations of the literature

- There are a limited number of available trials, although several are large scale and well-designed.

- Magnitude of effect for psychotherapy trials may be overestimated because of study design issues, including patients not being blind to treatment.

- Antidepressant medication treatment in comparison trials is not always provided in a manner consistent with best clinical practices.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Benefit	SR
1	IPT is more beneficial for depression symptom reduction and remission than no treatment or placebo, and provides a similar level of benefit as other evidence-based treatments	de Mello et al., 2005 Lindsayer et al., 2007 NICE, 2004	I	Good	Small	A
	IPT may be more beneficial than CBT for treatment of major depression	de Mello et al., 2005	II	Fair	Small	B
2	Pregnant/postpartum depression: Individual IPT is better than no treatment and has benefits similar to other treatments for pregnancy/postpartum depression	Bledsoe &Grote, 2006	I	Good	Mod	B
3	IPT is better than no treatment and has outcomes similar to other active treatments for depression in older adults	Cuijper et al., 2006 Reynolds et al., 1999	II	Fair	Small	C
	IPT plus antidepressant medication is superior to antidepressant alone for initial treatment response; benefit does not appear to be maintained over time	de Mello, 2005 NICE, 2004	I	Good	Small	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

Problem-solving therapy has been examined as a treatment for depression, particularly in primary care settings. There is evidence it achieves clinically significant reductions in symptom severity and increased probability of remission at the end of treatment compared to no treatment control, although this comparative benefit does not hold at 6 and 12 months. There is insufficient evidence for clinically significant differences between PST with or without antidepressant medication is compared to antidepressant alone at the end of treatment or at 12 months. There is evidence it is effective in reducing symptom severity for older adults.

EVIDENCE STATEMENTS

The following evidence for PST comes from NICE (2004) and one later study with older adults. The NICE literature search yielded 12 RCTS, 3 of which met their inclusion criteria. All three studies were in primary care settings, so there is less generalizability to specialty care settings. Study patients were adults of all ages and did not include special populations (e.g., postpartum).

- *PST versus no treatment control:* There was some evidence of clinically significant differences favoring PST in reducing depressive symptoms and achieving remission at the end of treatment. However, there is insufficient evidence of clinically significant differences between PST and no treatment control at 6 and 12 months after treatment. (NICE, 2004)

- *PST alone versus antidepressant therapy alone:* There is insufficient evidence of clinically significant differences between PST alone and antidepressant medication in reducing symptom severity or achieving remission at the end of treatment or at 12 months (NICE, 2004).

- *Combined PST and antidepressant therapy versus antidepressant therapy alone:* There is insufficient evidence of clinically significant differences between combined PST/antidepressant medication and antidepressant medication alone in reducing symptom severity or achieving remission at the end of treatment or at 12 months (NICE, 2004).

- In a systematic review of treatments of depression for older adults, Frazer et al. (2005) concluded that there was good RCT evidence for PST in reducing depressive symptom severity.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Benefit	SR
1	In uncomplicated mild to moderate MDD, PST, when compared to no treatment control conditions (Wait list, ill placebo): Reduces symptoms and improves remission rates at end of treatment, but not at 6 or 12 months	NICE, 2004	I	Good	Mod	B
	Insufficient evidence of clinically significant differences in reducing symptoms or achieving remission at end of treatment or at 12 months	NICE, 2004	I	Good	Mod	B
2	PST for older adults reduces symptoms	Frazer et al., 2005	I	Good	Subst	A

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix 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]

RATIONALE

BT alone, without a cognitive component, shows promise for treating MDD, including severe MDD and MDD in patients who do not want, or cannot tolerate, antidepressive medication.. Although it has a limited body of research, three of the four primary trials were well designed and well-powered, increasing the confidence in these findings. However, the confidence in the overall findings is lower than in CBT, IPT or ADM, as they have a much larger body of literature to date.

EVIDENCE STATEMENTS

There is evidence that BT may be an effective treatment option for mild to severe MDD. The scope of the evidence is limited, however. The literature search revealed no systematic reviews and only four RCT's that met criteria.

- Dimidjian et al. (2006) found that BA was at least as efficacious as pharmacotherapy, and significantly more efficacious than cognitive therapy and placebo conditions when treating severely depressed patients (24 sessions over 18 weeks, N=241; effect sizes for BA relative to cognitive therapy were 0.87 BDI and 0.59 HRSD).

- McLean & Hakstian (1979) compared psychodynamic therapy, BT, relaxation training, and pharmacotherapy in treating patients with MDD (10 sessions; N=178). BT was superior to other treatments on 9 of 10 outcome measures at the end of treatment, although these benefits were reduced at 3 months post-treatment.

- Jacobson et al. (1996) compared behavioral activation, standard CBT, and a combination of activation with a focus on modifying dysfunctional thoughts in treating patients with MDD (N=150, 12 to 20 sessions). The study found that BA alone was equal in efficacy to more complete versions of cognitive therapy. There were no significant differences between the two at the 6 month follow-up.

- Hopko et al. (2003) compared brief behavioral activation to standard supportive psychotherapy with severely depressed patients on an inpatient psychiatric unit (N=25; effect size 0.73). They found that BA was superior to standard supportive therapy (effect size 0.73).

- There is limited evidence that BT/BA may have a positive effect on retention. In Dimidjian and colleagues' 2006 study, a greater percentage of patients in the BA group completed treatment as compared to both the CT and pharmacotherapy groups.

- There is limited evidence that there is no difference in relapse rates between BA and CT (Jacobson et al., 1996).

- There is insufficient evidence to determine the effect of BA increasing functioning or decreasing suicidality. The studies rated symptom severity vs. functioning. Follow-up periods were too limited to detect differences in suicide rates.

Behavioral Therapy/Behavioral Activation with pregnant or postpartum patients

- There is insufficient evidence for using BT/BA with pregnant or postpartum patients specifically. However, evidence from general trials should be applicable to this population. There is no evidence that pregnant women would not benefit from BT/BA. Risks of side effects and adverse outcomes are lower than with pharmacotherapy. .

Behavioral Therapy/Behavioral Activation with older patients

- There is insufficient evidence for using BT/BA with older patients specifically. However, as in the general population the risks of side effects and adverse outcomes are lower than with pharmacotherapy.

Behavioral Therapy/Behavioral Activation plus pharmacotherapy

- There is insufficient evidence for combining BT/BA with pharmacotherapy. There is also insufficient evidence on contraindications. There have not been any RCTs studying this particular combination of treatment.

Limitations of the literature

- There has been little replication of the above described results.

- BT has not been manualized, except for BA, and therefore it is not possible to know how similar or dissimilar the behavioral therapy approaches were in the four studies.

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**Benefit**	**SR**
1	Behavioral therapy/behavioral activation (BT/BA) is efficacious in the treatment of MDD: BT/BA is more effective for symptom reduction and remission than no treatment, placebo, or relaxation training, and similarly effective to other evidence-based treatments	Dimidjian et al., 2006 Jacobson et al., 1996 McLean & Hakstian, 1979	I	Good	Mod	A
	BA is more efficacious than cognitive therapy for severely depressed patients	Dimidjian et al., 2006	I	Fair	Mod	B
	BT is more efficacious than psychodynamic therapy, although these benefits were reduced at 3 months post-treatment	McLean & Hakstian, 1979	I	Fair	Mod	B
	BT is more efficacious than relaxation training, although these benefits were reduced at 3 months post-treatment	McLean & Hakstian, 1979	I	Fair	Mod	B
	Brief BA is more efficacious than TAU (standard supportive psychotherapy) with severely depressed patients on an inpatient psychiatric unit	Hopko et al., 2003	I	Fair	Mod	B
	BT/BA has a positive effect on retention compared to both cognitive therapy and ADM	Dimidjian et al., 2006	I	Fair	Mod	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

Clinical trials indicate that CFT is superior to wait-list controls for reducing MDD and relationship distress. Of note, CFT did not differ significantly when compared to CBT for reducing MDD, and led to greater reductions in relationship distress compared to CBT. However, there is a much smaller body of literature for CFT compared to other interventions (e.g., CBT, IPT), thereby reducing the strength of recommendations.

EVIDENCE STATEMENTS

- Evidence for CFT comes from the NICE guideline (2004). Their literature review yielded no systematic reviews and 15 RCTs, 5 of which met their inclusion criteria. Studies entailed couples in which at least one of the partners met diagnostic criteria for depression and there was associated marital distress. Most of the studies looked at CBT- or IPT-based therapies tailored toward couples. Evidence was limited to short-term effects on symptoms, did not include special populations (e.g., post partum or elderly) or more specialized outcomes (suicidality, relapse rates, etc).

- There is strong evidence indicating clinically significant differences favoring CFT over wait-list controls in reducing symptoms at the end of treatment (average difference in BDI = -11.64). There is no evidence of longer term benefits. There is no evidence comparing CFT with antidepressants. There was insufficient evidence of clinically significant differences between CFT and individual therapy (mostly CBT and IPT) in reducing depressive symptom severity at the end of treatment and no evidence of long-term effects.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Benefit	SR
1	CFT is significantly better than no treatment in reducing depressive symptom severity at the end of treatment, but there is no examination of longer term efficacy	NICE, 2004	I	Good	Mod	C
2	In addition to reducing depression, CFT is significantly better than individual psychotherapies at reducing comorbid marital distress	NICE, 2004	I	Good	Mod	B
3	Insufficient evidence of clinically significant differences between CFT and individual psychotherapy in symptom severity at end of treatment	NICE, 2004	I	Good	Mod	I

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

Psychotherapy meta-analyses have demonstrated that "non-specific" therapist-patient relationship variables (the kind emphasized by client-centered counseling) are quite often the most robust factors in predicting treatment outcomes. There is evidence that counseling is significantly better than normal general practice in reducing symptom severity at the end of treatment, although differences are not apparent at 12 months. There is some evidence that there are no clinically significant differences between counseling and CBT in reducing symptom severity at the end of treatment or at 12 months. Adding counseling to general practice does not appear to lead to clinically significant improvements in symptom severity and other outcome measures. Additionally, there is evidence that adding counseling to general practice does not add to treatment efficacy with patients with chronic depression. There is evidence that antidepressant medication therapy is more effective than counseling in reducing symptom severity at the end of treatment and at 12 months.

EVIDENCE STATEMENTS

- Evidence for counseling comes from the NICE guideline (2004). Their literature review yielded no systematic reviews and nine RCTs, three of which met their inclusion criteria. All three studies examined the use of counseling in primary care settings, utilizing brief counseling intervention modalities. The evidence statements below derive from the results of these three studies. There was no specific evidence regarding special populations (e.g., postpartum, elderly) or specific, high-interest symptom outcomes (suicidality).

- *Counseling vs normal general practice:* There is some evidence (one study, n=134) of clinically significant differences favoring counseling between counseling and general practice (mean BDI difference = -5.4) at the end of treatment, but not at 12 months.

- *Counseling vs antidepressant medication:* There is some evidence (one study, n=103) that antidepressant medication achieves clinically significant better results in symptom reduction and achieving remission at both the end of treatment and at 12 months.

- *Counseling combined with general practice versus general practice alone:* There is some evidence (one study, N=145) that there are no clinically significant differences between combined counseling and general practice and general practice alone in reducing depressive symptoms below 14 on the BDI or on any other outcome measures 6 months after treatment started.

- *Chronic depression:* There is no evidence of clinically significant differences between counseling added to general practice versus general practice alone for patients who have been depressed at least 6 months

- *Counseling vs CBT:* There is some evidence (one study; n=130) that there are not clinically significant differences between counseling and CBT in reducing depressive symptoms at the end of treatment or at 12 months.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Benefit	SR
1	Counseling is more effective than general practice in reducing depressive symptoms at the end of treatment, but not at 12 months	NICE, 2004	I	Good	Mild	B
2	Some evidence that antidepressant medication achieves clinically significant greater reductions than counseling in symptom severity at the end of treatment and at 12 months	NICE, 2004	I	Good	Neg	D
3	Counseling added to general practice does not result in clinically significant better results in reducing depressive severity below 14 on BDI or other outcome measures	NICE, 2004	I	Good	Mild	C
4	No evidence of clinically significant differences between counseling and general practice for chronic depression	NICE, 2004	I	Good	Zero	C
5	No clinically significant differences between counseling and CBT in reducing symptom severity at end of treatment or at 12 months were noted	NICE, 2004	I	Good	Mild	C

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

At this point, there is limited data available on these interventions as treatments for MDD. MBCT is specifically designed as an adjunctive treatment to reduce risk of depressive relapse after initial treatment response, and is therefore reviewed in the continuation/relapse prevention recommendations. At this time, there is one RCT of DBT for depression, conducted in older adults. There are no adequate trials identified in the current review of ACT for MDD. Therefore, while these are promising interventions for the future (e.g., there is much stronger support for ACT for anxiety disorders and chronic pain), at this time first-line interventions remain CBT and IPT.

EVIDENCE STATEMENTS

- There are no adequate trials comparing MBIs alone to control conditions, medication, or other forms of psychotherapy. There are no adequate trials in pregnant or postpartum women. One trial (Lynch, et al., 2003), demonstrated that DBT plus medication, led to significantly better outcomes than medication alone for older patients. However, this study did not have a medication only control condition, and therefore is of limited utility in determining the additive benefit of DBT. There is good quality evidence that MBCT is effective as a relapse prevention intervention for patients with recurrent depression (3 or more prior episodes). This will be focused on in more detail in the annotation on psychotherapy and relapse prevention (see Section 17). There is no evidence of application of MBIs with other special populations (e.g., postpartum).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**Benefit**	**SR**
1	DBT combined with pharmacotherapy was significantly better than pharmacotherapy alone in reducing depressive symptoms and in achieving remission at the end of treatment and at 6 months	Lynch et al., 2003	II	C	Mod	C

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

Psychodynamic psychotherapy is the longest established psychotherapy, and SDPP is a more recent development. Of note, with the exception of IPT, good quality research studies of SDPP are rare, limiting the ability to determine the efficacy and effectiveness of these interventions. In addition, there is significant variability among SDPP; the interventions are frequently not manualized when used in research trials, reducing replicability, and adherence and competence ratings of the intervention are not frequently reported, reducing the ability of readers to clearly understand what the intervention entailed. Despite these limitations, the fact that it does not appear significantly inferior to other common treatments in clinical research studies may make it of value if patients prefer this kind of treatment.

EVIDENCE STATEMENTS

The evidence for SDPP was derived from the NICE guidelines (2004). The NICE guidelines found the following 4 RCTs of sufficient quality addressing SDPPs:

- There is insufficient evidence to determine if there are clinically significant differences between short-term psychodynamic psychotherapy and CBT in reducing depressive symptoms at the end of treatment, at 6 or 12 months after treatment; or of achieving remission of MDD at the end of treatment, or 3 months after the end of treatment. One study compared CBT and psychodynamic therapy for major depression in older caregivers with MDD (20 sessions; N=66; Gallagher-Thompson & Steffen, 1994). Participants who had been caregivers for more than 3.5 years benefited more from CBT, while those who had been caregivers less than 3.5years benefited more from SDPP.

- One study compared CBT and SDPP in adults with MDD (8 or 16 sessions depending on randomization; N=117; Shapiro et al., 1994). In general, there were no significant differences on outcomes, although there was some benefit for CBT on self reported depression at the end of treatment. There were no differences on treatment outcomes at 8 vs. 16 sessions except for patients with severe depression.

- One study compared psychodynamic therapy, BT, relaxation and pharmacotherapy (10 sessions; N=178; McLean & Hakstian, 1979). BT was superior to other treatments on 9 of 10 outcome measures at end of treatment, although these benefits were reduced at 3 months post-treatment. Psychodynamic therapy performed the most poorly on outcome measures of any treatment in this study.

- Based on these studies, there is not sufficient evidence to determine whether psychodynamic therapy differs from CBT, behavioral therapy or pharmacotherapy for treatment response.

- One study found that 10 weeks of psychodynamic psychotherapy combined with clomipramine was superior to clomipramine plus supportive care for reducing depressive symptoms and improving functioning in patients with severe depression (HRSD $\geq$ 20).

Limitations of the literature

- None of the studies with short-term psychodynamic psychotherapy (SDPP) have been adequately replicated. They represent single tests of specific hypotheses, and therefore making general conclusions about the efficacy and effectiveness of SDPPs is premature.

- Magnitude of effect for psychotherapy trials may be overestimated because of study design issues, including patients not being blind to treatment.

- Some trials provide additional clinical contact in the pharmacotherapy condition. This design feature is likely to improve the benefits of the pharmacotherapy and reduce differences with CBT.

- The antidepressant medication comparisons used medications that are no longer first line medications, reducing generalizability to current practice.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Benefit	SR
1	SDPP reduces depression: SDPP is more effective for symptom reduction and remission than no treatment or placebo, and similarly effective to other evidence-based treatments	NICE, 2004	I	Fair	Small	C
2	Depression in older adults: SDPP is better than CBT for older patients who have been caregivers less than 3.5 years SDPP is less efficacious than CBT for older patients who have been caregivers more than 3.5 years	Gallagher-Thompson & Steffen, 1994	I	Good	Mod	C
3	Psychodynamic therapy combined with pharmacotherapy: SDPP plus antidepressant medication is superior to antidepressant medication and supportive care for initial treatment response	NICE, 2004	I	Good	Mod	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

There is strong empirical support for CBT; however, it is not always readily accessible to many patients. CCBT may offer a viable alternative. The empirical support is on a much smaller scale relative to CBT. However, there is evidence that CCBT can achieve clinically significant differences in symptom reduction at the end of treatment and follow-up compared to waiting list control and treatment as usual. In limited head-to-head studies comparing CCBT to CBT, there is insufficient evidence for clinically significant differences in rates of remission or symptom reduction.

EVIDENCE STATEMENTS

The evidence comes from two sources, the NICE guideline (2004) and a 2006 more focused review of computerized cognitive behavior for depression and anxiety by NICE. The former reviewed 4 RCTs with a total of 499 patients. The latter focused on three well-known computerized cognitive behavioral programs for depression. Outcome measures were restricted to symptom reduction and rates of remission at the end of treatment and follow-up, and did not include measures of functioning or suicidality.

- *CCBT vs TAU:* There is strong evidence that CCBT achieves clinically significant differences than TAU in reducing depressive symptoms at the end of treatment, and 1- 3- and 6-month follow-ups, but there is insufficient evidence for clinically significant different rates of remission. The mean difference in BDI scores at the end of treatment for 273 patients was -5.95.

- *CCBT vs CBT:* There is insufficient evidence for clinically significant differences between CCBT and CBT in rates of remission at the end of treatment or at the 2-month follow-up and in symptom reduction at the end of treatment and at the 2-month follow-up.

- *CCBT vs wait list control:* In one study of 24 patients, there was insufficient evidence for clinically significant differences in rates of remission at the end of treatment, but there was some evidence for clinically significant differences in rates of remission at the 2-month follow-up. This pattern of suggested improvement after the end-of-treatment was seen in symptom reduction rates. For the BDI, there were clinically significant differences in symptom reduction at the end of treatment (-8.17 difference) and at the 2-month follow-up (-14.5). For the HRSD, these figures were -8.0 and -9.58, respectively.

- The more focused NICE study of three popular CCBTs for depression resulted in NICE recommending “Beating the Blues” as an option for delivering CCBT in the management of mild to moderate depression, but concluding that there was insufficient evidence to recommend the use of “COPE” or “Overcoming Depression” as clinically effective options. The latter conclusion resulted from lower quality studies that tended to focus on patient satisfaction. The strongest support for “Beating the Blues” came from a RCT of 274 patients randomly assigned to this CCBT or TAU, where there were clinically significant differences in depressive symptom reduction at the end of treatment as measured by the BDI (Effect Size =.65)

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Benefit	SR
1	Strong evidence for clinically significant differences between CCBT and TAU in symptom reduction at end of treatment and follow-up up to 6 months, but not in clinically significant differences in rates of remission	NICE, 2004 NICE, 2006	I	Good	Mod	B
2	Insufficient evidence for clinically significant differences between CCBT and CBT in symptom reduction or rates of remission at the end of treatment and at the 2-month follow-up	NICE, 2004	I	Good	Mod	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

Short term psychological therapy may be a useful approach of therapy in patients who are being followed in primary care, who have mild or moderate depression, and who may not be able, or willing, to consider other forms of intervention.

EVIDENCE STATEMENTS

Much of the quality evidence is derived from the 2004 NICE guideline. Their literature search yielded nine relevant RCT's, two of which were utilized most extensively:

- GSH vs. waiting list control: strong evidence in favor of GSH indicating clinically significant differences in rates of remission and symptom severity at end of treatment.

- GSH vs. group CBT: insufficient evidence demonstrating clinically significant differences in rates of remission and symptom severity at the end of treatment and at 3 and 6 month follow ups.

- GSH vs. group self-help vs. individual phone contact: insufficient evidence demonstrating clinically significant differences between groups in terms of rates of remission, symptom severity at end of treatment and up to 6 months follow up.

- GSH vs. individual or group psychotherapy: insufficient evidence for clinically significant differences in symptom severity at the end of treatment or at 10 month follow-up.

- Cuijpers' 1997 meta analysis of seven guided self-help studies yielded similar results as NICE, namely that guided self-help appears to be no less effective than individual and group psychotherapy and benefits appear to be sustained at 6 months. These results are consistent with Lewis and colleagues' 2003 systematic review which concluded that there is evidence to recommend guided self-help as long as it is CBT-based and is monitored by a mental health professional.

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	GSH is significantly better than waiting list control in remission rates and symptom severity at end of treatment	NICE, 2004	I	Good	B
2	Insufficient evidence of clinically significant differences between GSH and group CBT in rates of remission and symptom severity at end of treatment and 6 month follow-up	Cuijpers, 1997 NICE, 2004	I	Poor	I
3	Insufficient evidence of clinically significant difference between GSH and group self-help or individual telephone follow-up at rates of remission and symptom severity at end of treatment and at 6 month follow-up	NICE, 2004	I	Poor	I
4	Insufficient evidence of clinically significant differences between GSH and individual or group psychotherapy in symptom severity at end of treatment and at 10 months follow-up	Cuijpers, 1997 NICE, 2004	I	Poor	I
5	GSH should be CBT-based and entail monitoring by a mental health professional	Richards et al., 2003	I	Good	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

EVIDENCE STATEMENTS

- ECT is more efficacious than simulated ECT in patients with MDD (standardized effect size 0.91 in 6 trials involving 256 patients). ECT is more efficacious than pharmacotherapy in patients with MDD (standardized effect size 0.80 in 8 trials involving 1144 patients) (UK ECT review group, 2003).

- Different regimens of ECT may have different effects on depression symptoms:

  - Bilateral compared with unilateral electrode placement ECT improved symptoms (standardized effect size 0.32 in 22 trials involving 1137 patients)

  - High dose ECT also compared with low dose significantly improved symptoms (standardized effect size 0.58 in 6 trials, 337 patients)

  - There is no significant difference in outcomes between twice weekly and three times weekly treatment or between brief pulse waveform and sine wave (UK ECT review group, 2003).

- Symptom improvement with ECT is short-term and should be followed by maintenance treatment with antidepressants, or if antidepressants are not tolerated, repeated treatment with ECT (Kellner et al., 2006; Sackeim et al., 2001; van den Broek et al., 2006).

- ECT is effective in the acute treatment of late life depression and is generally safe. There is insufficient evidence regarding the relative efficacy of ECT over antidepressants, the long-term efficacy of ECT, morbidity and mortality related to ECT, cost-effectiveness and the efficacy of ECT in subgroups of patients (Van der Wurff et al., 2004).

- The impact of ECT on short- and long-term cognitive functioning was inconsistently assessed across studies and results reported vary across studies included in the systematic reviews. One RCT found that ECT compared to simulated ECT had a greater impact on short-term cognitive functioning, but not on cognitive function at 6 months. Compared to antidepressants, one RCT found ECT had a greater impact on short-term cognitive function and another RCT found there was no difference in short-term cognitive function (UK ECT Review Group, 2003).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	ECT is efficacious for severe MDD	Kho et al., 2003 NICE, 2003 Pagnin et al., 2004 UK ECT Review Group, 2003	I	Good	A
2	Different regimens of ECT	Kho et al., 2003 NICE, 2003 Pagnin et al., 2004 UK ECT Review Group, 2003	I	Good	A
3	ECT should be followed by maintenance antidepressants	Kellner et al., 2006 Sackeim et al., 2001 van den Broek et al., 2006	I	Good	A
4	Insufficient evidence to recommend for or against ECT in the elderly	Van der Wurff et al., 2003	II	Poor	I
5	Effect of ECT on cognitive functioning	UK ECT Review Group, 2003	II	Poor	C

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

Several important issues surround the use of VNS for treatment of depression. First, VNS is a proposed treatment for patients with "treatment resistant depression." However, the definition of treatment resistance is not clear and is highly variable even across researchers (Rush et al., 2003). This makes it extremely difficult to determine who might benefit from this treatment if it is efficacious. Of note, in FDA testimony from patients, patients who received VNS described receiving over 20 different treatments for their depression prior to VNS (Phurrough et al., 2007). This is in contrast to the definition used by NICE (2004) - "[depression] which fails to respond to two or more antidepressants given sequentially at an adequate dose for an adequate time." Second, there have been significant adverse events reported in > 5percent of implanted patients, including voice alteration, dypshagia, dyspnea, increased cough, asthenia, chest pain, headache, vocal cord paralysis, palpitations, dizziness, infection, and incision site reaction. Third, the cost of the device and surgical implantation is estimated to be $25,000. Finally, although there have been multiple calls for a second RCT of VNS for treatment resistant depression, there has been reluctance to pursue another RCT due to the manufacturer's resistance (Shuchman, 2007).

EVIDENCE STATEMENTS

There is good evidence to recommend that VNS not be used for severe treatment resistant depression except as a last resort.

- One double-blind RCT of 235 outpatients found no difference between VNS and a sham-placebo (Rush, Marangell et al., 2005). VNS was compared to a *sham* control (patients received the VNS but it was not turned on). Concomitant treatments were held stable. After 3 months, 15 percent (17/111) of patients receiving VNS had a 50 percent reduction in symptoms based on the HRSD-24 compared to 10 percent (11/110) in the sham control group. This difference was not statistically significant (p = 0.238).

- The remainder of the studies are 12-month non-blinded follow-up of study participants (Rush, Sackeim et al., 2005), comparison of intervention group patients to a non-concurrent cohort of treatment as usual patients (George et al., 2005), or observational studies (Corcoran et al., 2006; Marangell et al., 2002; Nahas et al., 2005; Sackeim et al., 2001). Of note, most VNS studies have been done by a single group of researchers.

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	VNS compared to sham control group found no difference in outcomes at 3 months	Blue Cross Blue Shield Association Technology Assessment, 2006 ICSI, 2006 Rush et al., 2005	I	Good	D
2	VNS might be considered as a treatment of last resort for patients with severe treatment resistant depression	Expert Opinion	III	Poor	I

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

Several mechanisms may explain the mood elevating effects of exercise: psychological (increased self-worth, self-efficacy, stress tolerance, hardiness, and positive reinforcement), social (increased social contact), and physiological (changes in central endorphin, serotonin, and monoamine concentrations). There are numerous other health benefits to exercise and few adverse effects.

EVIDENCE STATEMENTS

- Regarding relatively older literature, three meta-analyses (Carlson, 1991; Craft & Landers, 1998; North et al., 1990) have examined the effect of exercise and concluded it has significant benefits. For instance, Craft & Lander's (1998) meta-analysis of 30 studies showed an overall mean effect size of -0.72 for exercise in reducing clinical depression.

- A more recent systematic review and meta-regression analysis of RCTs by Lawlor & Hopker, (2001) is more critical and pessimistic regarding the efficacy of exercise. In that study, in 11 RCTs comparing exercise to no treatment controls, exercise reduced symptoms of depression slightly with a standardized mean difference in effect size of -1.1 and a weighted mean difference in Beck Depression Inventory of -7.3.

- Other studies examine exercise as an adjunct to antidepressant medication:
  - Blumenthal et al. (1999) assessed the effectiveness of a 16-week aerobic exercise program compared to standard medication alone and exercise with medication combined for 156 older adults (age 50+) with MDD. After 16 weeks, the groups did not differ on the HAM-D or BDI scores (P= .67). Regarding exercise related remission utilizing diagnostic interviews, 66 percent of patients taking antidepressant medication, 60 percent on exercise only, and 69 percent receiving both, achieved remission.

- Babyak et al (2001) assessed the longer term effectiveness of treatments for these patients at 6 months post-treatment and found that the exercise group had significantly lower relapse rates than the medication or combined groups (p = .01).

- In another study, Mather et al (2002) studied the effectiveness of exercise on patients (53 years or older) who responded poorly to antidepressant medication. Patients were randomly assigned to group exercise or a health education class, while continuing medication. A significantly greater number of patients achieved a 30 percent or greater reduction in depressive symptoms as measured by the HRSD (55% vs. 33%) for the exercise versus control group.

- Knubben et al. (2007) assessed the short-term effect of exercise on patients with presumably moderate to severe MDD. Thirty-eight consecutive inpatients with MDD on standard antidepressant treatment were randomly assigned to a 10-day aerobic exercise treatment condition (walking) or control condition. After 10 days, reduction in depression symptom severity on the CES-D was significantly larger for the exercise than the control group (41% vs. 21%). Noting these results were opposite the results of Blumenthal et al. (1999) (where medication appeared to produce more rapid effects), the authors speculated their more intensive exercise regime may have contributed to more rapid results in their protocol.

- Dunn et al. (2005) studied the dose-response relation of exercise and reduction of depressive symptoms. In a 2 x 2 factorial design, 80 subjects diagnosed with mild to moderate MDD, were randomly assigned to low dose (LD; 7.0 kcal/kg/week), public health dose (PHD; 17.5 kcal/kg/week) at 3 or 5 days/week, or control (3 days/week flexibility exercise). The main effect for energy expenditure was significant at 12 weeks. HRSD scores were reduced by 47 percent from baseline for PHD, 30 percent for LD, and 29 percent for control.

- A variety of epidemiological studies have demonstrated a significant inverse relationship between physical activity and depression in community (non-clinical) samples. With increased focus on a clinical sample Harris et al. (2006) assessed the association between physical activity, exercise coping, and depression in a sample of 424 initially depressed patients in four waves over 10 years, with a 90 percent wave-to-wave retention rate. More physical activity was associated with less concurrent depression, even after controlling for gender, age, medical problems, and adverse life events. Physical activity counteracted the effects of medical problems and negative life events on depression. Findings for exercise for coping were similar, although not as strong.

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	Exercise as an adjunct to other empirically supported treatments	Blumenthal et al., 1999 Knuebben et al., 2007 Mather et al., 2002	I	Good	A
2	Exercise as monotherapy if other evidence based treatments are contraindicated	Blumenthal et al., 1999 Craft & Landers, 1998 Dunn et al., 2005 Lawlor & Hopker, 2001	I	Fair	B

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

A systematic review of 8 trials, including 294 patients with SAD found that light therapy was effective; however, the studies were of short duration (7 - 42 days) and suffered from other methodological concerns. An additional 3 RCTs evaluated light therapy in 66 patients with non-SAD. Light therapy was more efficacious than controls, but again study duration was only 7 days. Adverse effects have not been systematically categorized but may include headache, nausea, agitation and eye strain. Additional research limitations include the challenge of establishing a true "placebo" control group and a more heterogeneous sample base of patients

EVIDENCE STATEMENTS

- Light therapy is more efficacious than control for patients with seasonal affective disorder (effect size 0.84 in 8 trials involving 294 patients) (Golden et al., 2005; Lam et al., 2006).

- Lam et al (2006), when comparing light treatment to antidepressant (fluoxetine), found that light therapy showed earlier response onset and lower rate of some adverse events relative to fluoxetine. However, no other significant differences in outcome between light therapy and antidepressant medication were demonstrated.

- There are limited RCTs suggesting that light therapy may be more efficacious than control in patients with non-seasonal affective disorder (Golden et al., 2005).
- A 2,500-Lux white light for two hours/day or treatment with 10,000-Lux for 30 minutes/day are equally efficacious and better than control treatments done with dim light .
    - There is significantly better remission when light therapy treatments are done in the early morning than later in the day (Goldon et al, 2005).
    - SAD is also responsive to dawn simulation (Golden et al., 2005).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	Light therapy is efficacious for SAD	Golden et al., 2005 Lam et al., 2006	I	Good	B
2	Light therapy may be more efficacious than control for non-SAD	Golden et al., 2005	II	Fair	C

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

The beneficial effects of St John's Wort have been demonstrated in a systematic review of studies comparing this treatment to placebo and standard antidepressant treatment in patients with mild to modrate depression. For major depression, the evidence is inconclusive. SJW should not be used in patients with moderate to severe symptoms. Caution should be exercised in patients taking medications metabolized by the CYP3A4 enzyme system, since SJW is a potent inducer of this system. In addition, patients should be cautioned that preparations of SJW vary considerably in the amounts of active compounds. SJW is contraindicated in pregnancy, can elevate TSH, cause photosensitivity, and has been reported to cause hypertensive crisis and induce mania.

EVIDENCE STATEMENTS

- A systematic review identified 12 trials comparing SJW to placebo for patients with major depression; SJW was more efficacious. However, the larger, more precise trials showed only a small benefit (ratio of SJW responders to placebo responders was 1.15, 95% CI, 1.02 to 1.29). These larger trials tended to include patients with more severe major depression (mean HAMD17 = 22) and were of higher methodological quality (Linde et al., 2005). In five subsequent short duration RCTs, SJW was more efficacious than placebo in three moderate sized studies (140 to 388 subjects) (Gastpar et al., 2006; Kasper et al., 2006; Uebelhack et al., 2004). Two smaller (n=72 to 135) three-arm studies showed no statistically significant differences (Fava et al., 2005; Moreno et al., 2006).

- A systematic review identified 6 trials comparing SJW to an SSRI in patients with major depression. Response rates did not differ (ratio of SJW responders to SSRI responders was 0.98, 95% CI 0.85 to 1.12) (Linde et al., 2005). Five subsequent trials compared SJW to SSRIs. Two studies found greater symptom reduction with SJW compared to fluoxetine (Fava et al., 2005) and paroxetine (Szegedi et al., 2005). Two studies found non-inferiority of SJW compared to citalopram (Gastpar et al., 2006) and sertraline (Gastpar et al., 2005) and one small trial showed no statistically significant differences between SJW and fluoxetine (Moreno et al., 2006).

- In trials that included a high proportion of patients with non-major depression, SJW showed substantial benefit (ratio of SJW responders to placebo responders was 1.71, 95% CI, 1.40 to 2.09) Linde et al. (2005).

- Hypericum dosages tested in RCTs range from 350 to 1,200 mg/day. Most trials are of short duration (4 - 12 weeks). The long-term efficacy of SJW is unknown (Linde et al., 2005).

- Compared to tricyclic antidepressants, SJW is associated with fewer dropouts for any reason (OR 0.65, 95% CI 0.46 to 0.92) and fewer dropouts due to adverse effects (OR 0.25, 95% CI, 0.14 to 0.45). Compared to SSRIs, there was no difference in dropout rates for any reason (OR 0.95, 95% CI, 0.65 to 1.40) and a non-significantly lower rate of dropouts due to adverse effects (OR 0.60, 95% CI, 0.31 to 1.15) (Linde et al., 2005).

- Knuppel, Geddes et al. (2004) systematic review looked at safety and adverse events from 35 double-blind randomized trials showed that dropout and adverse effects rates in patients receiving hypericum extracts were similar to placebo, lower than with older antidepressants, and slightly lower than with selective serotonin reuptake inhibitors. Dropout rates due to adverse effects in 17 observational studies including 35,562 patients ranged from 0% to 5.7%.

Serious interactions or adverse effects were not reported in any study. Published cases and cases reported to drug surveillance agencies suggest that interactions with a variety of drugs are the most relevant adverse effects of hypericum extracts.SJW is a potent inducer of CYP3A4 isoenzyme and the multi-drug resistance transporter P-glycoprotein. Approximately 40 percent of drugs are metabolized by these pathways. The enzyme induction appears to depend on two factors: 1) the amount of hyperforcin ingested per day and 2) the duration of use. Short term exposure to SJW (< 4 days) is unlikely to produce significant enzyme induction, while exposure for ≥ 7 days is associated with clinically significant enzyme induction. The duration of enzyme induction is unknown but has been shown to last for up to 27 days after SJW's discontinuation. SJW can cause important drug-drug interactions reducing the effectiveness of numerous medications including: cyclosporine, tacrolismus, indinavir, fexofenadine, simvastatin, omeprazole, warfarin, digoxin, oral contraceptives, erythromycin, alprazolam, midazolam, verapamil and imidazole antifungals. SJW can interact with other antidepressants such as MAOIs and SSRIs to cause serotonin syndrome (Wang et al., 2001; Whitten et al., 2006).

- Over-the-counter preparations of SJW have considerable variation in the amounts of active compounds (Liu et al., 2000). Hyperforin, a likely primary active constituent of SJW, acts as a serotonin uptake inhibitor (Schulte-Lobbert et al., 2004) and has been shown to vary 100-fold between brands (de los Reyes & Koda, 2002); some products vary significantly between batches. Preparations with a lower amount of hyperforin (≤ 4mg per daily dose) have not been associated with the same extent of enzyme induction as preparations with a higher amount of hyperforin (> 10 mg per daily dose) (Whitten et al., 2006; Wurglics et al., 2001).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**SR**
1	SJW may be used for patients with mild symptoms of MDD	Linde et al., 2005	I	Fair	B
2	SJW is not recommended for patients with moderate to severe symptoms of MDD	Linde et al., 2005	I	Fair	D
3	SJW should not be used by patients taking medication whose clearance is substantially dependent on the Cytochrome P450 (CYP) 3A4 isoenzyme	Whitten et al., 2006	I	Good	D
7	Patients taking SJW should be informed of potential drug-drug interactions	Wang et al., 2001 Whitten et al., 2006	III	Poor	C

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

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]

RATIONALE

Research focusing on the efficacy of acupuncture, while progressing toward western standards of research, has yielded inconclusive evidence as to its value in treating depression. Methodological variance, including varying dosages of antidepressant medication as a treatment variable, differing modes of acupuncture, and varying times of treatment, have rendered a firm conclusion impossible.

EVIDENCE STATEMENTS

Cochrane review (Smith & Hay, 2005), summarized in a meta analysis seven trials comprising 517 subjects met the inclusion criteria. Five trials (409 subjects) included a comparison between acupuncture and medication. Two other trials compared acupuncture with a wait list control or sham acupuncture. Subjects generally had mild to moderate depression. There was no evidence that medication was better than acupuncture in reducing the severity of depression (WMD 0.53, 95% CI, -1.42 to 2.47), or in improving depression, defined as remission versus no remission (RR1.2, 95% CI, 0.94 to 1.51).

Seven randomised comparative trials involving 509 patients were included in a systematic review by Mukaino et al., (2005). The evidence is inconsistent on whether manual acupuncture is superior to sham, and suggests that acupuncture was not superior to waiting list. Evidence suggests that the effect of electroacupuncture may not be significantly different from antidepressant medication, weighted mean difference -0.43(95% CI, -5.61 to 4.76).

Leo & Ligot, (2007) summarized 9 RCTs examining the effects of acupuncture treatment of depression; five studies were deemed to be of low quality, based upon Jadad criteria. The odds ratios derived from comparing acupuncture with control conditions within the RCTs suggests some evidence for the utility of acupuncture in depression. General trends suggest that acupuncture modalities were as effective as antidepressants employed for treatment of depression in the limited studies available for comparison. The authors concluded that, despite the findings, the evidence thus far is inconclusive.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	SR
1	There is insufficient evidence that acupuncture may be helpful with the management of depression, and more research is needed.	Smith & Hay, 2005 Leo & Ligot, 2006 Allen et al., 2006 Mukaino et al., 2005	I	Poor	I

QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

APPENDICES

Table of Contents

Appendix A: Guideline Development Process

Appendix B: Screening and Assessment Instruments

- B-1: Quick Guide to the Patient Health Questionnaire (PHQ)
- B-2: Example of Diagnosing MDD and Calculating PHQ-9 Depression Severity
- B-3: PHQ-9 Scores and Proposed Treatment Actions
- B-4: Nine Symptom Checklist (PHQ-9)

Appendix C: Suicidality

Appendix D: Pharmacotherapy

- D-1: Antidepressant Dosing and Monitoring
- D-2: Antidepressant Adverse Drug Effects: Receptor Affinities and Relative Comparisons
- D-3: Drug-Drug Interaction

Appendix E: Participant List

Appendix F: Acronym List

Appendix G: Bibliography

Appendix A: Guideline Development Process

The development update of the VA/DoD Clinical Practice Guideline for Management of MDD followed the steps described in "Guideline for Guidelines," an internal working document of the VA/DoD Evidence Based Practice Working Group, that requires an ongoing review of the work in progress. The Working Group of the VA/DoD was charged to update the evidence-based action recommendations whenever possible.

The Offices of Quality and Performance and Patient Care Services, in collaboration with the network Clinical Managers, the Deputy Assistant Under Secretary for Health, and the Medical Center Command of the DoD identified clinical leaders to champion the guideline development process. During a preplanning conference call, the clinical leaders defined the scope of the guideline and identified a group of clinical experts from the VA and DoD that formed the Management of MDD Working Group. Working Group members included internists, family practitioners, psychiatrists, psychologists, psychiatric nurses, and social workers, from a wide variety of specialty and primary care settings, diverse geographic regions, and both VA and DoD health care systems.

The Working Group defined a set of clinical questions within the area of the guideline. This ensured that the guideline development work outside the meeting focused on issues that practitioners considered important and produced criteria for the search and the protocol for systematic review and, where appropriate, meta-analysis.

The Working Group participated in an initial face-to-face meeting to reach consensus about the guideline algorithm and recommendations and to prepare a draft update document. The draft continued to be revised by the Working Group through numerous conference calls and individual contributions to the document. Following the initial effort, an editorial panel of the Working Group convened to further edit the draft document. Recommendations for the performance or inclusion of specific procedures or services were derived through a rigorous methodological approach that included the following:

- Determining appropriate criteria, such as effectiveness, efficacy, population benefit, or patient satisfaction
- Reviewing literature to determine the strength of the evidence in relation to these criteria
- Formulating the recommendations and grading the level of evidence supporting the recommendation

Experts from the VA and DoD reviewed the final draft and their feedback was integrated into the final draft document.

This update of the MDD Guideline is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VA, DoD, and academia, as well as guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The list of participants is included in Appendix E.

Formulation of Questions

The Working Group developed researchable questions and associated key terms after orientation to the scope of the guideline and to goals that had been identified by the Working Group. The questions specified (adapted from the Evidence-Based Medicine toolbox, Center for Evidence-Based Medicine, [http://www.cebm.net]):

- **P**opulation – Characteristics of the target patient population
- **I**ntervention – Exposure, diagnostic, or prognosis
- **C**omparison – Intervention, exposure, or control used for comparison
- **O**utcome – Outcomes of interest.

These specifications served as the preliminary criteria for selecting studies. Literature searches were conducted on all topics identified in the algorithm or recommendations of the original guidelines.

Selection of Evidence

The evidence selection was designed to identify the best available evidence to address each key question and ensure maximum coverage of studies at the top of the hierarchy of study types. Published, peer-reviewed RCTs, as well as meta-analyses and systematic reviews that included randomized controlled studies, were considered to constitute the strongest level of evidence in support of guideline recommendations. This decision was based on the judgment that RCTs provide the clearest, most scientifically sound basis for judging comparative efficacy. The Working Group made this decision while recognizing the limitations of RCTs, particularly considerations of generalizability with respect to patient selection and treatment quality. When available, the search sought out critical appraisals already performed by others that described explicit criteria for deciding what evidence was selected and how it was determined to be valid. The sources that have already undergone rigorous critical appraisal include Cochrane Reviews, Best Evidence, Technology Assessment, and AHRQ systematic evidence reports.

In addition to Medline/PubMed, the following databases were searched: Database of Abstracts of Reviews of Effectiveness (DARE) and Cochrane Central Register of Controlled Trials. For Medline/PubMed searches, limits were set for language (English), and type of research (RCT, systematic reviews and meta-analysis).

As a result of the literature reviews, articles were identified for possible inclusion. These articles formed the basis for formulating the guideline recommendations. The following inclusion criteria were used for studies:

- English language only of studies performed in United States, United Kingdom, Europe, Australia, Japan, New Zealand
- Full articles only
- Study populations age limited to adults greater than 18 years; all races, ethnicities, cultural groups
- Randomized controlled trials or prospective studies
- Key outcomes cited
- Published from July 2000 to the end of 2006.

Admissible evidence (study design and other criteria):

- Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results.

- Randomized controlled trials (RCT), systematic reviews (including EPC and HTA reviews), and meta-analyses.
- Relevant outcomes must be able to be abstracted from data presented in the articles.
- Sample sizes must be appropriate for the study question addressed in the paper. RCTs will be included only if they are initiated with 10 or more participants.

Preparation of Evidence Tables (Reports) and Evidence Rating

The results of the search were organized and evidence reports, as well as copies of the original studies, were provided to the Working Group for further analysis. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the Federal healthcare system. Recommendations were based on consensus of expert opinions and clinical experience only when scientific evidence was unavailable.

A group of research analysts read and coded each article that met inclusion criteria. The articles have been assessed for methodological rigor and clinical importance.

Recommendation and Overall Quality Rating

Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research. The Working Group received an orientation and tutorial on the USPSTF 2001 evidence rating process, reviewed the evidence and independently formulated Quality of Evidence ratings (see Table A-1), a rating of Overall Quality (see Table A-2), and a Strength of Recommendation (see Table A-3).

Table A-1: Quality of Evidence (QE)	
I	At least one properly done RCT
II-1	Well-designed controlled trial without randomization
II-2	Well-designed cohort or case-control analytic study, preferably from more than one source
II-3	Multiple time series evidence with/without intervention, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, descriptive studies, case reports, and expert committees

Table A-2: Overall Quality	
Good	High grade evidence (I or II-1) directly linked to health outcome
Fair	High grade evidence (I or II-1) linked to intermediate outcome; *or* Moderate grade evidence (II-2 or II-3) directly linked to health outcome
Poor	Level III evidence or no linkage of evidence to health outcome

Table A-3: Net Effect of the Intervention	
Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; *or* A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; *or* A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; *or* A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients; *or* No relative impact on either a frequent condition with a substantial burden of suffering, or an infrequent condition with a significant impact on the individual patient level.

Table A-4: Final Grade of Recommendation				
	The net benefit of the intervention			
Quality of Evidence	**Substantial**	**Moderate**	**Small**	**Zero or Negative**
Good	A	B	C	D
Fair	B	B	C	D
Poor	I	I	I	I

Strength of Recommendation Rating System

A	A strong recommendation that the 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.*

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.

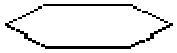
Algorithm Format

The goal in developing the guideline for management of MDD was to incorporate the information in a format which would maximally facilitate clinical decision-making. The use of the algorithm format was chosen because of evidence showing that such a format improves data collection, diagnostic and therapeutic decision-making, and changes patterns of resource use. However, few guidelines are published in such a format.

The algorithmic format allows the provider to follow a linear approach to critical information needed at the major decision points in the clinical process and includes:

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

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm (Society for Medical Decision-Making Committee, 1992). Arrows connect the numbered boxes indicating the order in which the steps should be followed.

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the guideline.

A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. Included in the annotations are brief discussions that provide the underlying rationale and specific evidence tables. Annotations indicate whether each recommendation is based on scientific data or expert opinion. A complete bibliography is included in the guideline.

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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.

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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 C: Suicidality

Suicidality – Suicidality is a topic relevant to all health care providers. It is highly prevalent, representing one of the leading causes of mortality in the United States. It is the leading cause of violent death in this country. Up to one-third of people in the general population report having had suicidal ideation during some point in their life. As many as two-thirds of patients who commit suicide visited their physician within one month of their death.

Evaluation of the Potentially Suicidal Patient consists of three main parts:

a. Eliciting suicidal ideation, intent, and/or planning

b. Gathering data on risk as well as protective factors for suicide

c. Weighing items one and two to make clinical decisions about safety.

A. Eliciting Suicidal Ideation, Intent, and/or Planning

Ideally, eliciting suicidal ideation, intent, and/or planning involves a free and honest exchange of information between the patient and clinician. Unfortunately, this is not always so. Familiarity with the existing epidemiological and demographic data concerning suicide (see below) is useful in generating an index of suspicion. From there, *direct questioning* regarding suicidal ideation/intent/planning may be initiated. There are no data demonstrating an increased rate of suicide attempts or deaths following questioning about suicide. Avoid rushing this part of the history or putting it off.

Despite the lack of reliable measures of suicide risk among individuals, a basic assessment should:

1. Determine presence/absence of depression, delirium, and/or psychosis
2. Elicit patient's statements about his/her suicidality
3. Elicit patient's own ideas concerning what would help attenuate or eliminate suicidal ideation/intent/planning
4. Attempt to gather collateral data from a third party in order to confirm the patient's story
5. A suggested sequence of suicide questions to ask is:
   - Are you discouraged about your medical condition (or social situation, etc.)?
   - Are there times when you think about your situation and feel like crying?
   - During those times, what sorts of thoughts go through your head?
   - Have you ever felt that if the situation did not change, it would not be worth living?
   - Have you reached a point that you've devised a specific plan to end your life?
   - Do you have the necessary items for completion of that plan readily available?
6. Formulate an acute and chronic management plan. Encourage active patient participation in negotiating a plan for follow-up:
   - What epidemiological risk factors are present (may have to inquire about each one individually)?
   - What other psychiatric conditions are present (besides the ones mentioned above)?
   - What is the level of psychological defense functioning?

- Has there been a will made recently?
- Is there talk of plans for the future?
- What is the makeup and condition of the patient's social support system? How can the patient be contacted?
- Is there active suicidal ideation? "How strong is (your) intent to do this?"
- "Can you resist the impulse to do this?" "Do you tend to be impulsive?"
- "Have you ever rehearsed how you would kill yourself?"
- "Have any family members or people close to you ever killed themselves?"

B. Gathering Data on Risk as Well as Protective Factors for Suicide

The causes of suicide are multifactorial. The risk for suicide increases with the accumulation of risk factors in an individual. Clinician should be alert for suicide risk in patients with a sad or depressed mood, suicidal ideation and one or more risk factors.

There is no accepted standard screening instrument for suicidal risk. Recent publications including the VA Education Module, "Prevention of Suicide: Everyone's Concern", and the article by Hirschfeld and Russell provide examples of brief, thorough screening tools (Hirschfeld & Russell, 1997).

Patients with evidence of intent for suicide should be offered mental health counseling and possibly hospitalization (U.S. PSTF, 1996).

Patients with definite intent (suicidal/homicidal ideation, intent, and/or plan) to harm self or others require voluntary or involuntary emergency psychiatric treatment (APA, 1993; DHHS pub. no. 95-3061, 1995).

The endorsement of suicidal ideation or intent represent obvious risk factors for suicide completion, especially if intent exists with an active plan for carrying it out. Other identified risk factors are listed below:

- **Presence of psychiatric illness –** Greater than 90 percent of adults who successfully complete suicide have some form of psychiatric illness. A symptom triad of mood symptoms, aggressiveness and impulsivity has been described as representing a major contribution to risk of suicide completion. The presence of hopelessness has been similarly classified.

- **Serious medical illness** – This is especially true of disorders marked by a debilitating course. Even so, suicide in this particular population rarely occurs in the absence of a psychiatric condition.

- **Means for suicide completion readily available** – Refers to immediate accessibility of firearms or other highly lethal modality. The presence of firearms in the home is believed to greatly increase the danger if other risk factors are present. Males in general tend to choose highly lethal means, such as firearms, which greatly increases the risk of death.

- **Psychosocial disruption** – Includes recent separation, divorce, loss of job, retirement, bereavement, or other perceived negative life event (including living alone).

- **History of previous suicide attempts** – One percent of suicide attempters will go on to completion each year, and 10 to 20 percent will eventually succeed at some point.

- **Active substance abuse and/or dependence -** is a contributing factor in approximately half of suicide completions, although the involvement of intoxication as a risk factor decreases in the elderly.

- **Impulsivity or history of poor adaptation to life stress.**

- **Family history** of completed suicide or suicide behavior.

- **Male sex** - though females attempt suicide three times as frequently as males, 75 percent of completed suicides are by males.

- **Advanced age** – Higher rates of suicide completed and suicide attempts are reported in patients greater than age 60. Age generally becomes a risk factor beginning at age 45. This is a gross generalization of a complex body of data.

- **Caucasian race** – Risk is highest for Caucasians.

C. Evaluating the Available Data to Make Clinical Decisions About Safety:

If suicide risk is present, a stratification system is useful in terms of formulating a strategy for intervention. One such system includes the following divisions: (1) imminent (suicide may be attempted within the next two days); (2) short-term (days to weeks); and (3) long term.

1) ***Imminent Risk*** – Suspect if patient endorses suicidal intent, an organized plan is presented, lethal means are available, signs of psychosis (especially command hallucinations) are present, extreme pessimism is expressed (despair, hopelessness, etc.), or several additional risk factors for suicide are present.

   Management suggestions:

   a. Immediate action is required. Hospitalize or commit. DO NOT leave the patient alone.

2) ***Short-Term Risk*** – Suspect if several risk factors for suicide are present, but no suicidal behaviors are present.

   Management suggestions:

   a. With patient's permission, involve family member or other person close to patient and advise them of the situation.
   b. If potentially lethal means of suicide completion are available, initiate steps to make these items inaccessible.
   c. Collaboratively generate a safety plan with the patient and/or family member (after obtaining patient consent). The plan should include emergency contact numbers for the national suicide hotline (1-800-SUICIDE) as well as information for local hospital(s) or emergency center(s).
   d. Stay in contact with the patient (telephone calls, more frequent office visits, etc.). Frequently re-evaluate risk. Document all contact and explain decision-making process for management.
   e. Treat psychiatric conditions as appropriate, including substance abuse/dependence (may require consultation from mental health

professional). Close follow-up will help to improve compliance and continue risk assessment.

f. Consider hospitalization as appropriate.

3) ***Long-Term Risk*** – The therapeutic goal is to eliminate or improve modifiable suicide risk factors. This may involve treatment of psychiatric illness (through biological means or through psychotherapy), treatment of substance abuse, etc. Frequent reassessment is still a useful guideline, and acute situations mandating psychiatric referral or hospitalization may arise. Thus, all of the aforementioned management suggestions should be considered even here.

The clinician should be reminded that the assessment of suicidal potential is far from exact, and that the above text serves only as one of many suggested approaches. In any case, the provider should adopt a systematic approach, such as the one offered above, in order to more comfortably assess and manage the potentially suicidal patient.

The clinician is also encouraged to document all aspects of the case in a thorough manner. Clinical notes should clearly indicate patient's current level of suicide ideation, intent, and/or planning and subsequent risk (none, mild, moderate, or severe). Specific risk and protective factors should be outlined. The clinician should provide a brief outline of the assessment strategies utilized (e.g., screening instrument, clinical interview, consultation with colleague, conversation with spouse) and comment on the results of the assessment. A succinct explanation should be provided to outline the sequence of decision making steps to arrive at the decision to hospitalize or not to hospitalize.

Finally, the clinician is urged to seek consultation when necessary. Research has demonstrated that a team approach to risk management is protective of both the patient and the provider.

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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	No change	10 mg	C
	Fluoxetine	20 mg once a day	20 mg 2weeks	80 mg	10 mg	Avoid	↓dose 50%	C
	Fluoxetine weekly	90 mg once a week	NA	90 mg	90 mg	10 mg	Avoid	C
	Paroxetine	20 mg once a day	20 mg weekly	50 mg	10 mg	12.5mg	10 mg	D
	Paroxetine CR	25 mg once a day	12.5 mg weekly	62.5 mg	12.5 mg	25 mg	12.5 mg	D
	Sertraline	50 mg once a day	50 mg weekly	200 mg	25 mg		↓ 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
aSSA	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 – QID	Weekly	150 mg	10-25 mg HS	No change		D
	Desipramine	25 mg three times or- 75 mg once a day	Weekly	300 mg	10-25 mg QD	No change		C
	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 D-3. Antidepressant Drug Interaction

Cytochrome P450 Effects

	Primary Metabolic Pathway	Inhibitory Effects
SSRIs		
Citalopram	3A4, 2C19 (also 2D6)	2D6 (mild)
Escitalopram	3A4, 2C19 (also 2D6)	2D6 (mild)
Fluoxetine[1]	2D6, 2C9, (also 2C19, 3A4)	2C9/10, 2D6 (substantial) 2C19 (moderate) 1A2, 2B6, 3A4 (mild to moderate)
Paroxetine	2D6 (also 3A4)	2D6, 2B6 (substantial)
Sertraline[2]	Multiple pathways	2D6 (dose-dependent) 2B6, 2C19 (moderate) 1A2, 3A4 (mild)
SNRIs		
Duloxetine	2D6, 1A2	2D6 (moderate)
Venlafaxine[3]	2D6 (also 3A4)	2D6 (mild)
SARIs		
Nefazodone[4]	3A4 (mCPP metabolite 2D6)	3A4 (substantial) 2D6 (very mild)
Trazodone[4]	3A4 (mCPP metabolite 2D6)	
NDRIs		
Bupropion[5]	2B6	2D6
NaSSAs		
Mirtazapine	2D6 (also 1A2, 3A4)	-
TCAs		
Secondary amines		
Nortriptyline	2D6	2D6 (moderate)
Desipramine	2D6	2D6 (moderate)
Tertiary amines		
Amitriptyline	2C19, 2D6 (also 1A2, 3A4)[6]	2D6 (mild), 2C19 (mild)
Imipramine	2C19, 2D6 (also 1A2, 3A4)[6]	2D6 (mild), 2C19 (mild)
Doxepin	2C19, 2D6 (also 1A2, 3A4, 2C9)[6]	2D6 (mild)
MAOIs		
Phenelzine[7]	-	-
Selegiline	2B6, 2C9, 3A4 (also 2A6)	2D6[8]
Tranylcypromine[7]	-	2A6 (substantial) 1A2, 2C19 (mild to moderate) 2E1 (mild to moderate)

[1] And its active metabolite norfluoxetine

[2] Mild 2D6 inhibition with sertraline at doses < 100 mg/day; moderate to substantial at doses > 150 mg/day; sertraline is also a potent inhibitor of uridine 5'-diphosphate. glucuronosyltransferase (UGT) 1A4, one of a family of enzymes performing phase II conjugative metabolism.

[3] Elimination of venlafaxine and its primary active metabolite is predominantly renal; minimal effect on CYP isoenzymes.

[4] Nefazodone has three major metabolites, including metachlorophenylpiperazine (mCPP), a partial serotonin agonist with acute anxiogenic properties metabolized by 2D6. mCPP is also one of the major metabolites of trazodone.

[5] Bupropion may induce drug-metabolizing enzymes.

[6] Tertiary amine TCAs undergo demethylation to secondary amine TCAs (via 1A2, 2C19, 3A4) in addition to hydroxylation by 2D6.

[7] MAOIs are substrates of monoamine oxidase A.

[8] Inhibitory effects observed at concentrations several orders of magnitude above those seen clinically.

SOURCES

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Precipitant Agent	Object Agent	Effect / Comments
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Barbiturates	Paroxetine (↓)	May decrease paroxetine levels
Carbamazepine	SSRIs (↓) (citalopram, escitalopram, sertraline)	May decrease therapeutic effect
Cimetidine	SSRIs (↑)	May inhibit first-pass SSRI metabolism; may need to adjust SSRI dose after starting, stopping, or changing cimetidine
Cyproheptadine	SSRIs (↓)	Cyproheptadine is a serotonin antagonist; may decrease or reverse antidepressant effects; combination has been used to treat fluoxetine-induced sexual dysfunction
Grapefruit	Sertraline (↑)	Elevated mean trough levels of sertraline ~47%; clinical significance unknown
Phenytoin	SSRIs (↓) (paroxetine, citalopram, escitalopram)	May reduce levels of paroxetine, citalopram, escitalopram (induction of 3A4, 2C19). Reduced paroxetine AUC by 50% and half-life by 35%.
Potent 3A4 inducers (e.g., rifamycins, carbamazepine)	SSRIs (↓) (citalopram, escitalopram, sertraline)	May decrease therapeutic effect
Potent 3A4 inhibitors (e.g., azole antifungals, erythromycin, clarithromycin, ritonavir)	SSRIs (↑) (citalopram, escitalopram, fluoxetine, sertraline)	May increase levels, therapeutic effect; caution with macrolide antibiotics; reports of delirium when clarithromycin added to fluoxetine; erythromycin may increase citalopram levels; no effect reported with ketoconazole and citalopram
Potent 2D6 inhibitors (e.g., quinidine)	SSRIs (↑) (fluoxetine, paroxetine, sertraline)	May increase levels of SSRIs
Fluoxetine	Ritonavir (↑)	Fluoxetine and ritonavir may inhibit each other's 2D6 metabolism, increasing levels of both drugs
Ritonavir	Fluoxetine (↑)	
SSRIs	Alcohol, CNS drugs	Potential for additive CNS effects

Precipitant Agent	Object Agent	Effect / Comments
SSRIs (fluoxetine, paroxetine)	Atomoxetine (↑)	May increase atomoxetine levels
SSRIs (fluoxetine, paroxetine, sertraline)	Benzodiazepines (↑) (e.g., diazepam, alprazolam, midazolam)	Fluoxetine and sertraline may increase benzodiazepine levels and decrease psychomotor performance; diazepam half-life increased. Paroxetine may increase CNS effects of oxazepam.
SSRIs (citalopram, escitalopram)	Beta blockers (↑) (e.g., metoprolol)	Citalopram, escitalopram may increase metoprolol levels
SSRIs (fluoxetine, paroxetine)	Bupropion (↑)	May inhibit 2B6 metabolism of bupropion; increased risk of seizures.
Fluoxetine	Buspirone (↑↓)	Fluoxetine may block serotonergic activity of buspirone and decrease effect; paradoxical worsening of OCD reported. Potential for serotonin syndrome.
Fluoxetine	Carbamazepine(↑)	Fluoxetine may increase carbamazepine levels, toxicity
Fluvoxamine	Bupropion (↑)	May inhibit 2B6 metabolism of bupropion; increased risk of seizures.
SSRIs (citalopram, escitalopram, fluoxetine, sertraline)	Clozapine (↑)	May inhibit clozapine metabolism; monitor and adjust dose as needed.
SSRIs (fluoxetine, paroxetine, sertraline)	Cyclosporine (↑)	May increase levels; monitor trough cyclosporine whole blood concentrations when adding or discontinuing SSRI; citalopram may be safer alternative
Fluoxetine	Dextromethorphan (↑)	Hallucinations reported
SSRIs (**paroxetine,** fluoxetine, sertraline)	**Digoxin (↑)**	Paroxetine may increase digoxin levels; suspected inhibition of renal tubular glycoprotein excretion; monitor. Fluoxetine and sertraline may increase digoxin levels; mechanism unknown.
Fluoxetine Sertraline	Drugs tightly bound to plasma proteins (↑) (e.g., warfarin, digitoxin)	May displace or be displaced by other drugs tightly bound to plasma proteins

Precipitant Agent	Object Agent	Effect / Comments
SSRIs (fluoxetine, paroxetine)	Drugs metabolized by 2D6 (↑)	SSRIs may increase levels of drugs metabolized by 2D6: e.g., atomoxetine, certain beta blockers [metoprolol], quinidine, phenothiazines, **risperidone**, TCAs, **trazodone**, type I-C antiarrhythmics [propafenone, flecainide], **thioridazine (contraindicated**).
SSRIs (fluoxetine, sertraline)	Estrogen component of oral contraceptives (↑)	May increase estrogen levels and potentially increase adverse effects; inhibition of 3A4 metabolism suspected.
Paroxetine	Galantamine (↑)	Increased oral bioavailability of galantamine (~40%)
Fluoxetine	Haloperidol (↑)	May increase haloperidol levels; severe extrapyramidal symptoms reported; closely monitor.
SSRIs (citalopram, escitalopram)	Ketoconazole (↓)	May reduce ketoconazole levels; clinical significance unknown.
SSRIs	**Linezolid (↑)**	Linezolid apparently has MAOI activity; potential for serotonin syndrome (allow 2 weeks after stopping linezolid before starting SSRI).
SSRIs	Lithium (↑↓)	May increase or decrease lithium levels; monitor. Increased potential for serotonin syndrome. Lithium may be used to potentiate antidepressant response to SSRIs.
SSRIs	**L-tryptophan (↑)**	May result in symptoms of CNS toxicity (headache, dizziness, agitation, aggressiveness, worsening OCD) and peripheral toxicity (GI symptoms); potential for serotonin syndrome; **concomitant use not recommended**
SSRIs	**MAOIs (↑)**	**Contraindicated** - potential for serotonin syndrome Wait 2 weeks after stopping MAOI before giving an SSRI Wait 2 weeks after stopping citalopram, escitalopram, paroxetine, or sertraline before giving an MAOI Wait 5 weeks after stopping fluoxetine before giving an MAOI
SSRIs	Metoclopramide	Potential for serotonin syndrome.
SSRIs	Narcotic analgesics (e.g., meperidine, oxycodone)	Potential for serotonin syndrome.

Precipitant Agent	Object Agent	Effect / Comments
Fluoxetine	Nifedipine (↑)	May increase effects of nifedipine
Fluoxetine	Olanzapine (↑)	May increase olanzapine levels
Fluoxetine	PDE-5 inhibitors (↑) (sildenafil, tadalafil, vardenafil)	May increase PDE-5 levels; use caution; consider reducing initial dose
SSRIs (**fluoxetine, paroxetine**)	**Phenothiazines** (↑)	May increase levels of **chlorpromazine**, other phenothiazines; **thioridazine contraindicated**
SSRIs (fluoxetine, paroxetine, sertraline)	Phenytoin (↑)	May increase phenytoin levels
SSRIs	**Pimozide** (↑)	**Contraindicated (all SSRIs)** – increased risk of cardiac arrhythmias Citalopram, escitalopram –- increased QTc (with citalopram) without apparent inhibition of pimozide metabolism Fluoxetine – potentially life-threatening bradycardia reported; caution with preexisting cardiac disease Sertraline, paroxetine – increase in pimozide AUC, C_{max}
Paroxetine	Procyclidine (↑)	Increased levels; reduce dose if anticholinergic effects occur
SSRIs (fluoxetine, paroxetine)	Type I-C antiarrhythmics (↑) (e.g., propafenone, flecainide)	May increase levels
SSRIs (fluoxetine, paroxetine, sertraline)	**Risperidone (↑)**	May increase levels
SSRIs	Ritonavir	Potential for serotonin syndrome.
SSRIs	SNRIs and other serotonergic antidepressants (mirtazapine, nefazodone, trazodone, St. John's wort)	Potential for serotonin syndrome
SSRIs	**Sibutramine**	**Potential for serotonin syndrome.**

Precipitant Agent	Object Agent	Effect / Comments
SSRIs	Sympathomimetics (e.g., ADHD medications, weight loss agents)	Increased sensitivity to sympathomimetic effects, potential for serotonin syndrome
Paroxetine	Theophylline (↑)	May increase theophylline levels; monitor
SSRIs (**fluoxetine, paroxetine**)	**Thioridazine** (↑)	**Contraindicated** – prolonged QTc and potential risk of life-threatening cardiac arrhythmias; avoid for 5 weeks after fluoxetine stopped
Sertraline	Tolbutamide (↑)	May increase levels; clinical significance unknown
SSRIs	**Tramadol**	Potential for serotonin syndrome.
SSRIs (fluoxetine, paroxetine)	Trazodone (↑)	May increase levels, potential for serotonin syndrome
SSRIs	TCAs (↑)	May increase TCA levels. Use of this combination to potentiate antidepressant response to SSRIs may warrant a psychiatry consult.
SSRIs	**Selective 5-HT1 receptor agonists** (e.g., sumatriptan)	Potential for serotonin syndrome.
SSRIs	**St. John's wort (↑)**	Increased sedative hypnotic effects; potential for serotonin syndrome; **avoid combination**
Fluoxetine	Valproic acid, divalproex, valproate sodium (↑)	May increase levels
SSRIs	Warfarin, heparins, NSAIDs, aspirin (↑)	SSRIs associated with anticoagulant effects, may interact with drugs that interfere with hemostasis; increased risk of GI adverse effects (UGI bleeding) with NSAIDs, aspirin. Pharmacodynamic interaction reported with warfarin (increased bleeding, no change in PT); sertraline and citalopram may increase PT; monitor.
SSRIs (fluoxetine, paroxetine, sertraline)	Zolpidem (↑)	Shortened onset of action, increased effect of zolpidem.

Precipitant Agent	Object Agent	Effect / Comments
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)		
Bupropion	Duloxetine (↑)	Bupropion may inhibit 2D6 metabolism of duloxetine.
Carbamazepine	Duloxetine (↓)	Carbamazepine may induce 1A2 metabolism of duloxetine, potential loss of therapeutic effect.
Cimetidine	SNRIs (↑) (venlafaxine, **duloxetine**)	**Avoid** cimetidine and other potent 1A2 inhibitors with duloxetine. Only slight increase in pharmacological activity expected with venlafaxine, although cimetidine may inhibit first pass metabolism (more potential in elderly, hepatic dysfunction, preexisting hypertension).
Cyproheptadine	SNRIs (↓)	Cyproheptadine is a serotonin antagonist; may decrease or reverse antidepressant effects.
Fluvoxamine	Duloxetine (↑)	May inhibit 1A2, 2D6 metabolism and increase duloxetine levels.
Potent 1A2 inhibitors (e.g,, cimetidine, fluvoxamine, ciprofloxacin)	Duloxetine (↑)	May increase duloxetine levels; substantial increases with fluvoxamine (6-fold increase in AUC). Some quinolone antibiotics expected to have similar effects; **avoid**.
Potent 2D6 inhibitors (e.g., fluoxetine, paroxetine, quinidine)	Duloxetine (↑)	May increase duloxetine levels
Potent 3A4 inhibitors (e.g., azole antifungals, erythromycin, clarithromycin ritonavir)	Venlafaxine (↑)	May increase venlafaxine levels, particularly in poor 2D6 metabolizers; closely monitor when starting or stopping potent 3A4 inhibitors
SNRIs	Alcohol, CNS drugs (↑)	Potential for additive CNS effects
Duloxetine	Alcohol (↑)	Potential liver injury with evidence of obstruction (ALT, total bilirubin elevations) has occurred; may interact to cause liver injury or duloxetine may aggravate pre-existing liver disease; duloxetine should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.
Alcohol	Duloxetine (↑)	
Venlafaxine	Clozapine (↑)	Reports of elevated clozapine levels following addition of venlafaxine, adverse events including seizures.
Venlafaxine	Desipramine (↑)	Increased desipramine AUC ~35%; 2-OH-desipramine AUC 2.5- to 4.5-fold; clinical significance unknown

Precipitant Agent	Object Agent	Effect / Comments
Duloxetine	Drugs tightly bound to plasma proteins (↑)	May displace or be displaced by other drugs tightly bound to plasma proteins (e.g., warfarin, digitoxin)
Duloxetine	Drugs metabolized by 2D6 (↑)	Duloxetine may increase levels of drugs metabolized by 2D6: e.g., atomoxetine, certain beta blockers (e.g., metoprolol), fluoxetine, quinidine, paroxetine, phenothiazines, **risperidone**, TCAs, **trazodone**, type I-C antiarrhythmics (propafenone, flecainide), **thioridazine (contraindicated**) Venlafaxine may decrease metabolism of desipramine, risperidone, indinavir (clinical significance unknown)
Venlafaxine	Haloperidol (↑)	May increase haloperidol levels; 70% increase in AUC after a single oral dose of venlafaxine
SNRIs	Linezolid (↑)	Linezolid has MAOI activity; potential for serotonin syndrome (allow 2 weeks after stopping linezolid before starting SNRI)
SNRIs	Lithium	Potential for serotonin syndrome.
SNRIs	L-tryptophan	Potential for serotonin syndrome
SNRIs	**MAOIs**	**Contraindicated**; increased potential for serotonin syndrome Wait 2 weeks after stopping MAOI before giving a SNRI Wait at least 5 days after stopping duloxetine before giving an MAOI Wait at least 1 week after stopping venlafaxine before giving an MAOI
SNRIs	SSRIs and other serotonergic antidepressants (mirtazapine, nefazodone, trazodone, **St. John's wort**)	Potential for serotonin syndrome
SNRIs	**Sibutramine**	Potential for serotonin syndrome
SNRIs	Sympathomimetics (e.g., ADHD medications, weight loss agents)	Increased sensitivity to sympathomimetic effects; **weight loss agents** not recommended with **venlafaxine**
Duloxetine	Phenothiazine antipsychotics (↑) (**thioridazine**)	Prolonged QTc; potential risk of life-threatening cardiac arrhythmias – **should not be co-administered**
SNRIs	**Tramadol**	Potential for serotonin syndrome

Precipitant Agent	Object Agent	Effect / Comments
SNRIs	TCAs (↑)	May increase TCA levels, which may result in toxicity
Venlafaxine	**Trifluoperazine (↑)**	Potential for neuroleptic malignant syndrome, including pyrexia, muscular rigidity, tremor, and labile BP; **avoid if possible,** or start low and closely monitor.
SNRIs	**Selective 5-HT1 receptor agonists** (e.g., sumatriptan)	Potential for serotonin syndrome
SNRIs	Warfarin (↑)	Venlafaxine – increases in PT, PTT, or INR reported. Duloxetine – increased anticoagulant effect; monitor anticoagulant parameters for at least 10 days when starting or stopping duloxetine; may persist for several weeks after stopping duloxetine.
Serotonin 2A Antagonist/Reuptake Inhibitors (SARIs)		
Cimetidine	Nefazodone (↑)	May inhibit first pass metabolism of nefazodone; may need to adjust dose after starting, stopping, or changing cimetidine
Cyproheptadine	Nefazodone (↓)	Serotonin antagonist; may decrease or reverse antidepressant effects
Fluoxetine	Nefazodone (↑)	Nefazodone metabolite levels increased; increase in transient adverse events (headache, light-headedness, nausea, paresthesia); allow one to several weeks washout if switching from fluoxetine to nefazodone.
Gingko biloba	**Trazodone** (↑)	Increased risk of sedation (case report of coma); **avoid**.
Potent 3A4 Inhibitors (ketoconazole, other azole antifungals, ritonavir)	Nefazodone, trazodone (↑)	May increase levels, potential for adverse effects (nausea, hypotension, syncope)
Potent 3A4 inducers (e.g., **carbamazepine**, rifamycins)	**Nefazodone**, trazodone (↓)	May induce nefazodone and trazodone metabolism and reduce therapeutic effect; **Carbamazepine contraindicated with nefazodone;** results in insufficient nefazodone concentrations for therapeutic effect.
Phenothiazines (e.g., thioridazine)	Trazodone (↑)	May increase trazodone levels; possible 2D6 inhibition; adjust trazodone dose if needed.
Protease inhibitors (e.g., fosamprenavir, ritonavir)	Trazodone (↑)	May increase trazodone levels; 3A4 inhibition suspected; adjust trazodone dose if needed.

Precipitant Agent	Object Agent	Effect / Comments
Nefazodone, trazodone	Alcohol, CNS drugs (↑)	Potential for additive CNS effects
Nefazodone	Benzodiazepines (↑) (triazolam, alprazolam)	Clinically important increases in triazolam and alprazolam levels; reduce initial dose of **triazolam** by 75% (if possible); **avoid combination in most patients**; reduce initial dose of alprazolam by 50%; lorazepam may be better alternative.
Nefazodone	Buspirone (↑)	Marked increases in buspirone levels (up to 20-fold C_{max}, 50-fold AUC) and ~50% decrease in levels of buspirone metabolite. Slight increases in AUC of nefazodone and nefazodone metabolite. Light-headedness, asthenia, dizziness, and somnolence reported; low initial dose of buspirone (e.g., 2.5 mg daily) recommended.
Buspirone	Nefazodone (↑)	
Nefazodone, trazodone	**Carbamazepine** (↑)	Nefazodone, trazodone may inhibit 3A4 metabolism of carbamazepine; carbamazepine may induce 3A4 metabolism, negating therapeutic effect of nefazodone or trazodone; combination of **nefazodone** and **carbamazepine contraindicated.**
Carbamazepine	**Nefazodone**, trazodone (↓)	
Nefazodone	Corticosteroids (↑) (e.g., dexamethasone, hydrocortisone, methylprednisolone)	May enhance pharmacologic and adverse effects; 3A4 inhibition suspected; adjust dose when nefazodone started or stopped
Nefazodone	Cyclosporine (↑)	May inhibit 3A4 metabolism of cyclosporine; monitor and adjust dose as needed.
Nefazodone, trazodone	Digoxin (↑)	Increases in digoxin levels reported with trazodone With nefazodone, Cmax, Cmin and AUC of digoxin increased by 29%, 27%, and 15%, respectively; exercise caution; monitor digoxin levels
Nefazodone	Drugs metabolized by 3A4 (↑)	Netazodone inhibits 3A4 and may increase levels of drugs metabolized by 3A4 (e.g., **pimozide – contraindicated**; estrogen [oral contraceptives]; buspirone; cyclosporine, tacrolimus; HMG CoA reductase inhibitors [atorvastatin, simvastatin, lovastatin]; triazolam, alprazolam.
Nefazodone	Drugs tightly bound to plasma proteins	May displace or be displaced by other drugs tightly bound to plasma proteins (e.g., warfarin, digitoxin)
Nefazodone	**Eplerenone** (↑)	May increase eplerenone levels (3A4); increasing risk of hyperkalemia and associated arrhythmias; **contraindicated**.

Precipitant Agent	Object Agent	Effect / Comments
Nefazodone	Estrogen component of oral contraceptives (↑)	May increase estrogen levels, potentially increasing adverse effects; 3A4 inhibition suspected.
Nefazodone	General anesthetics	Little known; discontinue for as long as clinically feasible prior to elective surgery
Nefazodone	Haloperidol (↑)	May increase haloperidol levels; clinical significance unknown
Nefazodone	HMG CoA reductase inhibitors metabolized by 3A4 (↑) (atorvastatin, lovastatin, simvastatin)	May increase levels of statins metabolized by 3A4; increased risk of myositis, rare reports of rhabdomyolysis; avoid combination if possible or monitor for symptoms. Pravastatin, fluvastatin, rosuvastatin not metabolized by 3A4.
Nefazodone, trazodone	**Linezolid** (↑)	Linezolid has MAOI activity; increased potential for serotonin syndrome (allow 2 weeks after stopping linezolid before starting nefazodone).
Nefazodone, trazodone	Lithium	Potential for serotonin syndrome
Nefazodone	Loratadine (↑)	May increase loratadine levels; modest prolongation of QTc interval. Cetirizine and fexofenadine do not appear to affect QTc interval and may be safer with nefazodone.
Nefazodone, trazodone	L-tryptophan	Potential for serotonin syndrome
Nefazodone	**MAOIs** (↑)	Contraindicated; increased potential for serotonin syndrome Wait 2 weeks after stopping MAOI before giving nefazodone Wait at least 1 week after stopping nefazodone before giving an MAOI
Trazodone	MAOIs	Unknown; caution indicated.
Nefazodone, trazodone	Narcotic analgesics (meperidine, oxycodone),	Potential for serotonin syndrome
Nefazodone	Nifedipine (↑)	May inhibit 3A4 metabolism of nifedipine and increase levels; observe response
Nefazodone, trazodone	Other serotonergic antidepressants (SSRIs, SNRIs, mirtazapine, **St. John's wort**)	Potential for serotonin syndrome

Precipitant Agent	Object Agent	Effect / Comments
Nefazodone	PDE-5 inhibitors (↑) (sildenafil, tadalafil, vardenafil)	May inhibit 3A4 metabolism of PDE-5 inhibitors and increase levels; caution, consider lower initial PDE-5 inhibitor dose
Trazodone	Phenytoin (↑)	Increases in phenytoin levels reported
Nefazodone	**Pimozide** (↑)	May inhibit 3A4 metabolism and increase pimozide levels, increased risk of cardiac arrhythmias – **contraindicated**.
Nefazodone, trazodone	Ritonavir	Potential for serotonin syndrome
Nefazodone, trazodone	**Sibutramine**	Potential for serotonin syndrome
Nefazodone	Tacrolimus (↑)	May inhibit 3A4 metabolism; monitor and adjust tacrolimus dose as needed.
Nefazodone, trazodone	**Tramadol**	Potential for serotonin syndrome
Nefazodone, trazodone	**Selective 5-HT1 receptor agonists** (e.g., sumatriptan)	Potential for serotonin syndrome
Nefazodone	Verapamil (↑)	May inhibit 3A4 metabolism and increase therapeutic and adverse effects; 3A4 inhibition; observe response when starting or stopping nefazodone.
Nefazodone	Warfarin (↔)	Warfarin dose adjustments unlikely to be necessary; monitor
Trazodone	Warfarin (↑↓)	Reports of increased and decreased prothrombin time
Noradrenergic & Specific Serotonin Antidepressant (NaSSAs)		
Diazepam	Mirtazapine (↑)	Minimal effects on levels; additive impairment of motor skills; manufacturer recommends avoiding diazepam, similar drugs
Fluvoxamine	Mirtazapine (↑)	May increase levels; observe response when fluvoxamine started or stopped and adjust dose as needed; monitoring of mirtazapine levels may be useful
Hydantoins (fosphenytoin, phenytoin)	Mirtazapine (↓)	May decrease levels and therapeutic effect of mirtazapine; monitor response when starting, stopping, or changing hydantoin dose; adjust mirtazapine dose as needed
Mirtazapine	Alcohol, CNS drugs	Potential for additive CNS effects
Mirtazapine	Clonidine (↓)	May decrease hypotensive effects; hypertensive urgency may occur; monitor BP if mirtazapine started or stopped

Precipitant Agent	Object Agent	Effect / Comments
Mirtazapine	Lithium	Potential for serotonin syndrome
Mirtazapine	L-Tryptophan	Potential for serotonin syndrome
Mirtazapine	**MAOIs** (↑)	**Combination not recommended**; potential for serotonin syndrome Wait at least 2 weeks after stopping MAOI before giving mirtazapine Wait at least 2 weeks after stopping mirtazapine before giving an MAOI
Mirtazapine	Metoclopramide	Potential for serotonin syndrome
Mirtazapine	Narcotic analgesics [meperidine, oxycodone]	Potential for serotonin syndrome
Mirtazapine	Other serotonergic antidepressants (SSRIs, SNRIs, nefazodone, trazodone, St. John's wort)	Potential for serotonin syndrome
Mirtazapine	Ritonavir	Potential for serotonin syndrome
Mirtazapine	Sibutramine	Potential for serotonin syndrome
Mirtazapine	Tramadol	Potential for serotonin syndrome
Mirtazapine	**Selective 5-HT1 receptor agonists** (e.g., sumatriptan)	Potential for serotonin syndrome
Norepinephrine Dopamine Reuptake Inhibitor (NDRI)		
Amantadine	Bupropion (↑)	Higher incidence of adverse reactions/neurotoxicity with concurrent use (possible synergistic or additive central dopamine effects)
Levodopa	Bupropion (↑)	Higher incidence of adverse reactions with concurrent use; start low and increase bupropion dose gradually
Carbamazepine	Bupropion (↓)	May induce 2B6 metabolism and reduce therapeutic effect.
Clopidogrel	Bupropion (↑)	May increase bupropion levels (2B6 inhibition suspected); adjust dose if needed, especially if clopidogrel started or stopped.
Guanfacine	Bupropion (↑)	May increase risk of toxicity (seizures reported); unknown mechanism; closely monitor and adjust dose if necessary.

Precipitant Agent	Object Agent	Effect / Comments
Inhibitors or substrates of CYP 2B6 (e.g., fluoxetine, orphenadrine, paroxetine, sertraline, thiotepa, cyclophosphamide)	Bupropion (↑)	May inhibit bupropion metabolism; little information.
Linezolid	**Bupropion** (↑)	May increase risk of hypertensive crisis; linezolid may have MAOI effect; **avoid**
MAOIs	**Bupropion (↑)**	Increased risk of hypertensive crisis – **contraindicated**; allow at least 2 weeks between stopping an MAOI and starting bupropion
Nicotine replacement	Bupropion (↑)	May cause hypertension; monitor blood pressure
Phenytoin	Bupropion (↓)	May induce 2B6 metabolism and reduce therapeutic effect
Rifampin	Bupropion (↓)	May induce 2B6 metabolism and reduce therapeutic effect
Ritonavir	**Bupropion** (↑)	Large increases in bupropion levels may occur –**contraindicated**
SSRIs (fluoxetine, paroxetine, sertraline)	Bupropion (↑)	May inhibit 2B6 metabolism of bupropion; increased risk of seizures.
Ticlopidine	Bupropion (↑)	May inhibit 2B6 metabolism of bupropion and increase seizure risk; monitor and adjust dose as needed, especially if ticlopidine started or stopped.
Bupropion	Alcohol, CNS drugs (↑)	Minimize or avoid consumption of alcohol; rare reports of adverse neuropsychiatric reactions or reduced alcohol tolerance; potential for additive CNS effects.
Bupropion	Beta-blockers (↑) (carvedilol, labetalol, metoprolol, propranolol, timolol)	May increase levels and cardiovascular effects (bradycardia) of certain beta blockers; 2D6 inhibition suspected; monitor; consider beta blocker not metabolized by 2D6 (e.g., atenolol)
Bupropion	Cyclosporine (↑)	May reduce cyclosporine levels; monitor when bupropion started or stopped.

Precipitant Agent	Object Agent	Effect / Comments
Bupropion	Drugs metabolized by 2D6 (↑)	May substantially increase **desipramine** levels; caution with other drugs metabolized by 2D6, including other antidepressants (fluoxetine, paroxetine, sertraline; duloxetine; desipramine, imipramine, nortriptyline), antipsychotics (haloperidol, risperidone, **thioridazine**), beta blockers (metoprolol), type 1-C antiarrhythmics (propafenone, flecainide). May increase risk of cardiac arrhythmias (thioridazine, mesoridazine, type 1-c antiarrhythmics). Initiate at lower end of dosage range; may need to decrease dose if bupropion added.
Bupropion	Duloxetine (↑)	Bupropion may inhibit 2D6 metabolism of duloxetine.
Bupropion	Other drugs that lower the seizure threshold (↑) (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids)	Use extreme caution.
Bupropion	Nefazodone (↑)	May increase levels of nefazodone metabolite (mCPP) via 2D6 inhibition; potential for acute dysphoric anxiety.
Bupropion	TCAs (↑)	Bupropion may inhibit 2D6 metabolism of TCAs and increase levels; increased risk of cardiac arrhythmias, anticholinergic symptoms; monitor when bupropion started or stopped.
Bupropion	Warfarin	Altered PT, INR observed; infrequently associated with hemorrhagic or thrombotic complications.
Bupropion (smoking cessation)	Warfarin, theophylline (↑)	Smoking cessation may result in increased levels of warfarin and theophylline, since hepatic enzymes are no longer being induced by smoking.
Tricyclic & Tetracyclic Antidepressants (TCAs)		
Barbiturates	TCAs (↑↓)	Barbiturates may lower TCA levels; potential for additive central and respiratory depressant effects.
Bupropion	TCAs (↑)	May increase TCA levels, therapeutic and adverse effects
Carbamazepine TCAs	TCAs (↓) Carbamazepine (↑)	May decrease TCA levels and increase carbamazepine levels; larger TCA doses required (especially imipramine); monitor for altered TCA response if carbamazepine started or discontinued

Precipitant Agent	Object Agent	Effect / Comments
Cimetidine	TCAs (↑)	May increase TCA levels; anticholinergic symptoms reported; may require lower TCA doses
Haloperidol	TCAs (↑)	May increase TCA levels
H2 antagonists	TCAs (↑)	May increase TCA levels; mild symptoms reported
MAOIs	TCAs (↑)	**Traditionally contraindicated;** potential for serious adverse reactions (e.g., hyperpyretic crisis, convulsions, coma, hyperexcitability, hyperthermia, tachycardia, tachypnea, headache, mydriasis, flushing, confusion, hypotension, disseminated intravascular coagulation, and death) Wait at least 7-10 days after stopping MAOI before giving a TCA Wait at least 7-10 days after stopping a TCA before giving an MAOI Combined therapy has been used for refractory depression; requires cautious dosing, observance of dietary restrictions, close observation; consider psychiatric consult.
Phenothiazines	TCAs	Monitor for increased toxicity and altered therapeutic response
Rifamycins	TCAs (↓)	May decrease TCA levels
Smoking	TCAs (↑)	May increase metabolic biotransformation of TCAs (induction of 1A2)
SSRIs	TCAs (↑)	May increase pharmacologic and adverse effects; allow at least 5 weeks after stopping fluoxetine before starting an MAOI
Valproic acid, divalproex, sodium valproate	TCAs (↑)	May increase TCA levels
Venlafaxine	TCAs Desipramine (↑)	Venlafaxine increased desipramine AUC, C_{max}, and C_{min} by ≈ 35%; increased 2-OH-desipramine AUC by at least 2.5- to 4.5-fold; clinical significance unknown
TCAs	Alcohol, CNS drugs (↑)	Additive CNS effects; alcohol may increase psychomotor impairment, especially during 1st week of treatment
TCAs	Anticholinergics (↑)	May enhance anticholinergic effects; paralytic ileus may occur.
TCAs	Clonidine (↓)	May antagonize hypotensive effect; dangerous BP elevations and hypertensive crises have occurred; avoid.

Precipitant Agent	Object Agent	Effect / Comments
TCAs	Guanethidine (↓)	May antagonize hypotensive effect; avoid if possible; doxepin (up to 150 mg/day) may be given with guanethidine without reducing hypotensive effect.
TCAs	Levodopa (↓)	May delay absorption and decrease bioavailability of levodopa; hypertensive episodes have occurred.
TCAs	Quinolones (↑) (gatifloxacin, moxifloxacin)	May increase risk of life-threatening cardiac arrhythmias; moxifloxacin and gatifloxacin may cause QT prolongation.

<table>
<tr><th colspan="3">Monoamine Oxidase Inhibitors (MAOIs)</th></tr>
<tr><td>Carbamazepine, oxcarbemazepine</td><td>Selegiline</td><td>May increase selegiline levels (nearly 2-fold increase with selegiline) – contraindicated.</td></tr>
<tr><td>Foods with high tyramine, dopamine, or tryptophan content</td><td>MAOIs (↑)</td><td>May cause hypertensive crisis; avoid during MAOI treatment and for 2 weeks after stopping MAOIs.
<table>
<tr><th colspan="3">Tyramine-Containing Foods*</th></tr>
<tr><td><u>Cheese/dairy</u>
American, Blue
Boursalt, Brie,
Camembert, Cheddar, Emmenthaler, Gruyere, Mozzarella, Parmesan, Romano, Roquefort, Stilton, Swiss, yogurt sour cream,

<u>Acoholic beverages</u>
Beer (imports, some non-alcoholic); red wine (especially Chianti); sherry; distilled spirits; liqueurs</td><td><u>Meat/fish</u>
Anchovies; beef or chicken liver, meats, fish (unrefrigerated, fermented, spoiled, smoked, pickled); caviar; fermented sausages (e.g., bologna, pepperoni, salami, summer sausage); dried fish (e.g., salted herring); dry sausage; game meat; meat extracts; meat prepared with tenderizer; herring, (pickled, spoiled);
shrimp paste</td><td><u>Fruit/vegetables</u>
Bananas; bean curd; dried fruits; fruit (e.g., avocados, especially overripe); figs, canned (overripe), miso soup; raspberries; sauerkraut; soy sauce; yeast extracts (e.g., Marmite)

<u>Foods containing other vasopressors</u>
broad beans (e.g., fava beans);
caffeine; chocolate; ginseng</td></tr>
<tr><td colspan="3">*tyramine contents not consistent and may vary
Bolded – high to very high amounts of tyramine</td></tr>
</table>
Dietary modifications do not appear to be required for the 6 mg/24 hour selegiline patch; recommended for the 9- and 12-mg/24 hour patches based on limited data.</td></tr>
<tr><td>Methylphenidate</td><td>MAOIs (↑)</td><td>May cause hypertensive crisis.</td></tr>
<tr><td>Oral contraceptives</td><td>Selegiline</td><td>May increase selegiline levels.</td></tr>
</table>

MAOIs	Alcohol, CNS drugs (↑)	Avoid alcohol (potentially high tyramine content). Potential for additive CNS effects.
MAOIs	Antidiabetics (↑)	May potentiate hypoglycemic response to insulin or sulfonylureas and delay recovery from hypoglycemia.
MAOIs	Barbiturates (↑)	Reduce barbiturate dose.
MAOIs	Beta blockers (↑)	Bradycardia may develop.
MAOIs	Other antidepressants (bupropion, mirtazapine, nefazodone, SSRIs, SNRIs, TCAs, St John's wort)	**Bupropion** – **contraindicated** – increased risk of hypertensive crisis; allow at least 2 weeks between stopping an MAOI and starting bupropion **Mirtazapine – combination not recommended** – potential for serotonin syndrome; allow at least 2 weeks between administration of MAOIs and mirtazapine. **Contraindicated with selegiline.** **Nefazodone – contraindicated** – potential for serotonin syndrome Wait 2 weeks after stopping an MAOI before giving nefazodone. Wait at least 1 week after stopping nefazodone before giving an MAOI. **SSRIs, SNRIs – contraindicated** – potential for serotonin syndrome Wait 2 weeks after stopping an MAOI before giving an SSRI or SNRI. After stopping the following: Citalopram, escitalopram, paroxetine, or sertraline – wait at least 2 weeks before giving an MAOI Fluoxetine – at least 5 weeks Duloxetine – at least 5 days Venlafaxine – at least 1 week **TCAs – traditionally contraindicated** (although combined therapy has been used for refractory depression) – potential for serous adverse reactions; allow at least 7-10 days between administration of an MAOI and a TCA.
MAOIs (isocarboxazid, selegiline)	Buspirone (↑)	Avoid combination; BP elevation reported; allow at least 10 days after discontinuing an MAOI before starting buspirone.

MAOIs	Carbamazepine (↑)	Hypertensive crises, severe convulsive seizures, coma, or circulatory collapse may occur.
MAOIs	Cyclobenzaprine (↑)	Cyclobenzaprine structurally related to TCAs; use caution; potential for serotonin syndrome. Contraindicated with selegiline.
MAOIs	Dextromethorphan (↑)	Potential for serotonin syndrome - combination has been associated with hyperpyrexia, abnormal muscle movement, psychosis, bizarre behavior, hypotension, coma, and death. Contraindicated with selegiline.
MAOIs	Guanethidine (↓)	May inhibit hypotensive effect of guanethidine.
MAOIs	Levodopa (↑)	Hypertensive reactions may occur.
MAOIs	Methyldopa (↑)	May cause loss of BP control or CNS toxicity (excitation, hallucinations).
MAOIs	Narcotic analgesics (↑) (meperidine)	Potential for agitation, seizures, diaphoresis, and fever progressing to coma, apnea, and death; may occur weeks after discontinuing the MAOI; avoid combination; caution with other narcotic analgesics
MAOIs	Rauwolfia alkaloids (↑)	Potential for increased serotonin, norepinephrine levels; use caution
MAOIs	Sulfonamides (↑)	May cause sulfonamide or MAOI toxicity
Sulfonamides	MAOIs (↑)	
MAOIs	Sumatriptan (↑)	May increase systemic exposure to sumatriptan
MAOIs	**Sympathomimetics (↑)**	Potentiation of indirect- or mixed-acting sympathomimetics; may result in severe headache, hypertension, high fever, hyperpyrexia, possible hypertensive crisis; **avoid** combination; warn patients about OTC cold, allergy, or weight loss medications containing sympathomimetic amines. Discontinue MAOIs at least 10 days before elective surgery; avoid cocaine or local anesthesia containing sympathomimetic vasoconstrictors.
MAOIs	Thiazide diuretics (↑)	Potential for increased hypotensive effect
MAOIs	L-Tryptophan (↑)	Potential for serotonin syndrome, serious adverse reactions.

AUC = area under the curve; BP = blood pressure; C-max = maximum plasma concentration ; C-min = minimum plasma concentration ; CNS = central nervous system; OCD = obsessive compulsive disorder; GI = gastrointestinal; PDE-5 = phosphodiesterase-5; ADHD = attention deficit hyperactivity disorder; QTc = QT interval corrected for rate; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; UGI = upper gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs; PT = prothrombin time; PTT = ; INR = international normalized ratio; mCPP = metachlorophenylpiperazine

Symptoms of serotonin syndrome include agitation, hyperreflexia, ataxia, shivering, myoclonus, and altered consciousness.

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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

Appendix G: Bibliography

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