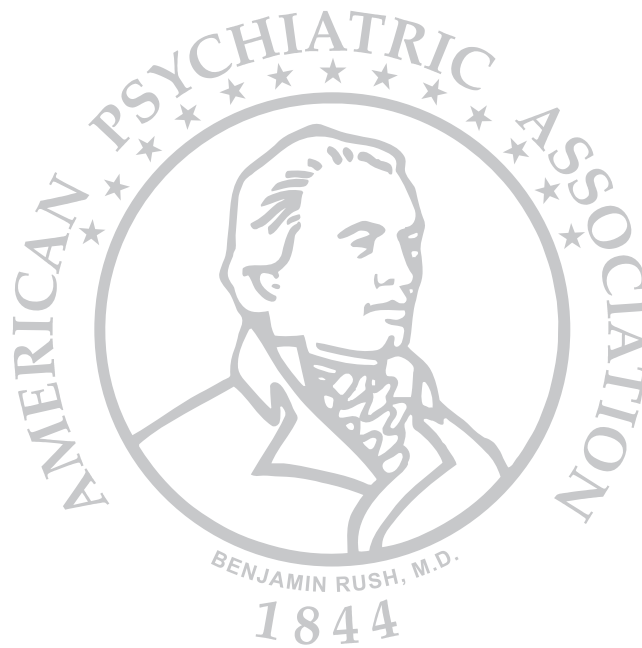


# Treating Major Depressive Disorder

A Quick Reference Guide



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Based on *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*, Third Edition, originally published in October 2010. A guideline watch, summarizing significant developments in the scientific literature since publication of this guideline, may be available.

## **INTRODUCTION**

*Treating Major Depressive Disorder: A Quick Reference Guide* is a synopsis of the American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*, Third Edition, Part A of which was originally published in *The American Journal of Psychiatry* in October 2010 and is available through American Psychiatric Publishing, Inc. The psychiatrist using this Quick Reference Guide (QRG) should be familiar with the full-text practice guideline on which it is based. The QRG is not designed to stand on its own and should be used in conjunction with the full-text practice guideline. For clarification of a recommendation or for a review of the evidence supporting a particular strategy, the psychiatrist will find it helpful to return to the full-text practice guideline.

## **STATEMENT OF INTENT**

The Practice Guidelines and the Quick Reference Guides are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available. The development of the APA Practice Guidelines and Quick Reference Guides has not been financially supported by any commercial organization.

## **A. PSYCHIATRIC MANAGEMENT**

Psychiatric management consists of interventions and activities that should be initiated and provided during all phases of treatment.

### **Establish and maintain a therapeutic alliance.**

- Collaborate with the patient in decision making and attend to the patient's preferences and concerns about treatment.
- Be aware of transference and countertransference issues.
- Depressive symptoms may make it harder to develop an alliance.

### **Complete the psychiatric assessment.**

For general principles and components of a psychiatric evaluation, refer to the American Psychiatric Association's *Practice Guideline for the Psychiatric Evaluation of Adults*. A complete diagnosis of depression should address the following:

- History of the present illness and current symptoms
- Psychiatric history, including symptoms of mania, current and past treatments (including duration and dosages), and responses to treatment
- General medical history
- Medications, including prescribed and over-the-counter agents and supplements
- History of substance use and treatment for substance use disorders
- Personal history (e.g., psychological development, response to life transitions, major life events)
- Social, occupational, and family histories

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- Review of the patient's prescribed and over-the-counter medications
- Review of systems
- Mental status examination
- Physical examination (by psychiatrist or by other health care professional)
- Diagnostic tests as indicated to rule out general medical causes of depressive symptoms

#### **Evaluate the safety of the patient.**

- Assessment of suicide risk is essential (Table 1). Note, however, that the ability to predict attempted or completed suicide is poor.
- If the patient demonstrates suicidal or homicidal ideation, intention, or plans, close monitoring is required.
- Hospitalization should be considered if risk is significant.

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**TABLE 1. FACTORS TO CONSIDER IN ASSESSING SUICIDE RISK**

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Presence of suicidal or homicidal ideation, intent, or plans
History and seriousness of previous attempts
Access to means for suicide and the lethality of those means
Presence of severe anxiety, panic attacks, agitation, and/or impulsivity
Presence of psychotic symptoms, such as command hallucinations or poor reality testing
Presence of alcohol or other substance use
Family history of or recent exposure to suicide
Absence of protective factors

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### **Establish the appropriate treatment setting.**

- Determine the least restrictive setting that will be most likely to address safety and promote improvement in the patient's condition.
- Consider the patient's
  - clinical condition, including symptom severity, co-occurring psychiatric or general medical conditions, and level of functioning;
  - available support systems; and
  - ability to adequately care for self, provide reliable feedback to the psychiatrist, and cooperate with treatment.
- Reevaluate optimal setting on an ongoing basis.
- Consider hospitalization if the patient
  - poses serious threat of harm to self or others (involuntary hospitalization may be necessary if patient refuses);
  - is severely ill and lacks adequate social supports (alternatively, intensive day treatment may be appropriate);
  - has certain co-occurring psychiatric or general medical conditions; or
  - has not responded adequately to outpatient treatment.

### **Evaluate and address functional impairments and quality of life.**

- Identify impairments in domains such as work, school, family, social relationships, leisure activities, and maintenance of health and hygiene.
- Provide interventions to maximize the patient's level of functioning and quality of life.

- Help the patient to set goals appropriate to his or her level of functioning and symptom severity.

### **Coordinate the patient's care with other clinicians.**

All clinicians involved in the patient's care should have sufficient ongoing contact with the patient and with one another to ensure that care is coordinated, relevant information is available to guide treatment decisions, and treatments are synchronized.

### **Monitor the patient's psychiatric status.**

- Carefully monitor the patient's response to treatment, including
  - symptomatic status, including functional status and quality of life;
  - degree of danger to self and others;
  - signs of "switch" to mania;
  - other mental disorders, including alcohol and other substance use disorders;
  - general medical conditions;
  - side effects of treatment; and
  - adherence to treatment plan.
- If symptoms change significantly or if new symptoms emerge, consider diagnostic reevaluation.
- Often family members or caregivers notice changes in the status of the patient first and are therefore able to provide valuable input.

### **Integrate measurements into psychiatric management.**

- Match the treatment plan to the needs of the patient by systematically assessing symptoms of the illness and effects of treatment.

- Consider facilitating this matching by integrating clinician- and/or patient-administered rating scale measurements into initial and ongoing evaluation. (The full guideline provides more discussion of available scales.)

### **Enhance treatment adherence.**

- Assess potential barriers to treatment adherence—for example, lack of motivation or excessive pessimism due to depression; side effects of treatment; problems in the therapeutic relationship; and logistical, economic, or cultural barriers to treatment.
- Collaborate with the patient (and, if possible, the family) to minimize barriers.
- Encourage the patient to articulate concerns about treatment or its side effects, and consider the patient's preferences when developing or modifying the treatment plan.
- Recognize that during the acute phase, depressed patients may be poorly motivated and unduly pessimistic and may suffer deficits of memory. During the maintenance phase, euthymic patients may undervalue the benefits and focus on the burdens of treatment.

### **Provide education to the patient and, when appropriate, to the family.**

- Use language that is readably understandable to the patient.
- Clarify common misperceptions about the illness (e.g., depression is not a real illness) and about treatment (e.g., antidepressants are addictive).
- Educate about the need for a full course of treatment, the risk of relapse, early recognition of recurrent symptoms, and the importance of obtaining treatment early.

- Emphasize
  - when and how often to take medication;
  - the typical 2- to 4-week lag for beneficial effects to be noticed;
  - the need to continue medication even after feeling better;
  - the need to consult with the prescribing doctor before medication discontinuation;
  - what to do if problems arise; and
  - the need to taper antidepressants when discontinuing them.
- Promote healthy behaviors such as exercise, good sleep hygiene, good nutrition, and decreased use of tobacco, alcohol, and other potentially deleterious substances.

## **B. ACUTE PHASE TREATMENT**

### **Choose an initial treatment.**

- Aim to induce remission of the major depressive episode and achieve a full return to the patient's baseline level of functioning. Remission is defined as at least 3 weeks of the absence of both sad mood and reduced interest and no more than three remaining symptoms of the major depressive episode.
- When selecting an initial treatment modality, consider the following:
  - Severity of symptoms
  - Presence of co-occurring disorders or psychosocial stressors
  - Biological, psychological, and environmental factors contributing to the current episode of depression
  - Patient preference
  - Prior treatment experiences



Severity of Illness	Modality			
	Pharmacotherapy	Depression-Focused Psychotherapy	Pharmacotherapy in Combination With Depression-Focused Psychotherapy	ECT
Mild to Moderate	Yes	Yes	May be useful for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring Axis II disorder	Yes, for certain patients
Severe Without Psychotic Features	Yes	No	Yes	Yes
Severe With Psychotic Features	Yes, provide both antidepressant and antipsychotic medication	No	Yes, provide both antidepressant and antipsychotic medication	Yes

**FIGURE 1–1. Recommended Modalities for Acute Phase Treatment of Major Depressive Disorder**

- Integrate treatment with psychiatric management and any other treatments provided for other co-occurring psychiatric disorders and general medical conditions.

**Recommended Modalities**

- Figure 1 describes recommended modalities according to the patient’s severity of illness.
- Clinical features that may suggest that medications are the preferred treatment include the following:

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- Prior positive response to an antidepressant
- Moderate to severe symptomatology
- Significant sleep or appetite disturbances or agitation
- Anticipation of need for maintenance therapy
- Patient preference
- Clinical features that may suggest the use of a depression-focused psychotherapy include the following:
  - Availability of clinicians with appropriate training and expertise
  - Prior positive response to psychotherapy
  - Significant psychological factors, psychosocial stressors, or interpersonal difficulties
  - Co-occurring Axis II disorders
  - Mild to moderate severity of illness
  - Patient preference
- In addition to the above, in women who are pregnant or wish to become pregnant or are breastfeeding, a depression-focused psychotherapy alone is recommended and, depending on the severity of symptoms, should be considered as an initial option.
- In patients who prefer complementary and alternative therapies, *S*-adenosyl methionine (SAMe) or St. John's wort might be considered, although evidence for their efficacy is modest, and careful attention to drug-drug interactions is needed with St. John's wort.
- Bright light therapy may be considered to treat seasonal affective disorder as well as nonseasonal depression.

## Pharmacotherapy

- The effectiveness of antidepressant medications is generally comparable between and within classes of medications, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Therefore, choose a medication largely based on the following:
  - Patient preference
  - Nature of prior response to medication
  - Safety, tolerability, and anticipated side effects
  - Co-occurring psychiatric or general medical conditions
  - Pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions; consult the full guideline or a current drug database)
  - Cost
- For most patients, a SSRI, a SNRI, mirtazapine, or bupropion is optimal.
- In general, the use of MAOIs should be restricted to patients who do not respond to other treatments.
- Table 2 provides the starting and usual doses of medications that have been shown to be effective for treating major depressive disorder.
- If side effects occur, lowering the dose or changing to a different antidepressant should be considered. If these approaches are not effective, other strategies can be considered, as shown in Table 3.

**TABLE 2. DOSING OF MEDICATIONS SHOWN TO BE EFFECTIVE IN TREATING MAJOR DEPRESSIVE DISORDER<sup>a</sup>**

Generic Name	Starting Dose (mg/day) <sup>b</sup>	Usual Dose (mg/day) <sup>c</sup>
Selective serotonin reuptake inhibitors <sup>d</sup>		
Citalopram	20	20–60 <sup>e</sup>
Escitalopram	10	10–20
Fluoxetine	20	20–60 <sup>e</sup>
Paroxetine	20	20–60 <sup>e</sup>
Paroxetine, extended release	12.5	25–75
Sertraline	50	50–200 <sup>e</sup>
Dopamine norepinephrine reuptake inhibitor <sup>d</sup>		
Bupropion, immediate release	150	300–450
Bupropion, sustained release	150	300–400
Bupropion, extended release	150	300–450
Serotonin norepinephrine reuptake inhibitors <sup>d</sup>		
Venlafaxine, immediate release	37.5	75–375
Venlafaxine, extended release	37.5	75–375
Desvenlafaxine	50	50 <sup>f</sup>
Duloxetine	60	60–120
Serotonin modulators		
Nefazodone	50	150–300
Trazodone <sup>g</sup>	150	150–600
Norepinephrine-serotonin modulator		
Mirtazapine <sup>d</sup>	15	15–45
Tricyclics and tetracyclics		
Amitriptyline	25–50	100–300
Doxepin	25–50	100–300
Imipramine	25–50	100–300

**TABLE 2. DOSING OF MEDICATIONS SHOWN TO BE EFFECTIVE IN TREATING MAJOR DEPRESSIVE DISORDER<sup>a</sup> (continued)**

Generic Name	Starting Dose (mg/day) <sup>b</sup>	Usual Dose (mg/day) <sup>c</sup>
Tricyclics and tetracyclics (continued)		
Desipramine	25–50	100–300
Nortriptyline	25	50–200
Trimipramine	25–50	75–300
Protriptyline	10–20	20–60
Maprotiline	75	100–225
Monoamine oxidase inhibitors (MAOIs)		
Irreversible, nonselective inhibitors		
Phenelzine	15	45–90
Tranylcypromine	10	30–60
Isocarboxazid	10–20	30–60
Irreversible, MAO B selective inhibitor		
Selegiline transdermal <sup>h</sup>	6	6–12
Reversible MAO A selective inhibitor		
Moclobemide	150	300–600

<sup>a</sup>For convenience, medications other than TCAs have been classified by their presumptive mechanism of action. However, the exact mechanism of action of several medications has yet to be determined or varies by dose. <sup>b</sup>Lower starting doses are recommended for elderly patients and for patients with panic disorder, significant anxiety or hepatic disease, and co-occurring general medical conditions. <sup>c</sup>For some of these medications (e.g., TCAs), the upper dosing limit reflects risk of toxicity or need for plasma level assessment, whereas for other medications (e.g., SSRIs), higher doses can be used safely but without evidence for overall superior efficacy. <sup>d</sup>These medications are likely to be optimal medications in terms of safety, the patient's acceptance of side effects, and the quantity and quality of clinical trial data. <sup>e</sup>Dose varies with diagnosis; see text for specific guidelines. <sup>f</sup>Has been used at doses up to 400 mg/day, although doses above 50 mg/day may not provide additional benefit. <sup>g</sup>This medication is not typically used for this indication. <sup>h</sup>Selegiline selectively inhibits MAO B at low doses but inhibits both MAO A and MAO B at the higher doses that are typically required for antidepressant activity.

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**TABLE 3. POTENTIAL TREATMENTS FOR SIDE EFFECTS OF ANTIDEPRESSANT MEDICATIONS**


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<b>Side Effect</b>	<b>Antidepressant Associated With Effect</b>	<b>Treatment<sup>a</sup></b>
<b>Cardiovascular</b>		
Arrhythmias	TCA's	Avoid in patients with cardiac instability or ischemia. Attend to interactions with anti-arrhythmics.
Hypertension	SNRIs, bupropion	Monitor blood pressure. Keep dose as low as possible. Add antihypertensive.
Hypertensive crisis	MAOIs	Seek emergency treatment. If hypertension is severe, intravenous antihypertensive agents (e.g., labetalol, sodium nitroprusside) may be required.
Increase in cholesterol	Mirtazapine	Add a statin.
Orthostatic hypotension	TCA's, trazodone, nefazodone, MAOIs	Add fludrocortisone. Add salt to diet.
<b>Anticholinergic</b>		
Constipation	TCA's	Encourage adequate hydration. Add bulk laxative.
Delirium	TCA's	Evaluate for other possible contributors to delirium.
Dry mouth	TCA's, SNRIs, bupropion	Suggest use of sugarless gum or candy.
Urinary hesitancy	TCA's	Add bethanechol.
Visual changes	TCA's	Add pilocarpine eye drops.

**TABLE 3. POTENTIAL TREATMENTS FOR SIDE EFFECTS OF ANTIDEPRESSANT MEDICATIONS (*continued*)**

<b>Side Effect</b>	<b>Antidepressant Associated With Effect</b>	<b>Treatment<sup>a</sup></b>
<b>Neurologic</b>		
Headaches	SSRIs, SNRIs, bupropion	Assess for other etiologies (e.g., caffeineism, bruxism, migraine, tension headache).
Myoclonus	TCA, MAOIs	Add clonazepam.
Seizures	Bupropion, TCAs, amoxapine	Assess for other etiologies, and add anticonvulsant medication, if clinically indicated.
<b>Sexual</b>		
Arousal, erectile dysfunction	TCAs, SSRIs, SNRIs	Add sildenafil, tadalafil, buspirone, or bupropion.
Orgasm dysfunction	TCAs, SSRIs, venlafaxine, desvenlafaxine, MAOIs	Add sildenafil, tadalafil, buspirone, or bupropion.
Priapism	Trazodone	Obtain emergency urological evaluation.
<b>Other</b>		
Activation	SSRIs, SNRIs, bupropion	Administer in the morning.
Akathisia	SSRIs, SNRIs	Add a beta-blocker or benzodiazepine.
Bruxism	SSRIs	Obtain dental consultation, if clinically indicated.

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**TABLE 3. POTENTIAL TREATMENTS FOR SIDE EFFECTS OF ANTIDEPRESSANT MEDICATIONS (continued)**


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Side Effect	Antidepressant Associated With Effect	Treatment <sup>a</sup>
<b>Other (continued)</b>		
Diaphoresis	TCAAs, some SSRIs, SNRIs	Add an $\alpha_1$ -adrenergic antagonist (e.g., terazosin), central $\alpha_2$ -adrenergic agonist (e.g., clonidine), or anticholinergic agent (e.g., benztropine).
Fall risk	TCAAs, SSRIs	Monitor blood pressure for evidence of hypotension or orthostasis; assess for sedation, blurred vision, or confusion; modify environment to reduce risk.
Gastrointestinal (GI) bleeding	SSRIs	Identify whether concomitant medications may affect clotting.
Hepatotoxicity	Nefazodone	Provide education about and monitor for clinical evidence of hepatic dysfunction. Obtain hepatic function tests if clinically indicated.
Insomnia	SSRIs, SNRIs, bupropion	Use morning dosing. Add a sedative-hypnotic at bedtime. Add melatonin. Provide CBT or education in sleep hygiene.
Nausea, vomiting	SSRIs, SNRIs, bupropion	Administer after food or in divided doses.



**TABLE 3. POTENTIAL TREATMENTS FOR SIDE EFFECTS OF ANTIDEPRESSANT MEDICATIONS (*continued*)**

Side Effect	Antidepressant Associated With Effect	Treatment <sup>a</sup>
<b>Other (<i>continued</i>)</b>		
Osteopenia	SSRIs	If clinically indicated, obtain bone density monitoring and add specific treatment to reduce bone loss (e.g., calcium and vitamin D supplements, bisphosphonates, selective estrogen receptor agents).
Sedation	TCAs, trazodone, nefazodone, mirtazapine	Use bedtime dosing. Add modafinil or methylphenidate.
Severe serotonin syndrome	MAOIs	Obtain emergency evaluation. Consider admission to a critical care unit.
Weight gain	SSRIs, mirtazapine, TCAs, MAOIs	Encourage exercise. Obtain input from dietician. If changing antidepressants, consider a secondary amine (if a TCA is required) or other antidepressant with fewer weight issues (e.g., bupropion).

<sup>a</sup>Initial approaches to treatment-emergent side effects include decreasing or discontinuing the medication and changing to another antidepressant with a different side effect profile. Treatments included here are additional measures.

**TABLE 4. REQUIRED WASHOUT TIMES BETWEEN ANTIDEPRESSANT TRIALS**

To	From	Minimum Washout Period (weeks)
MAOI	Drug with long-half-life metabolites (e.g., fluoxetine)	5–6
	Drug without long-half-life metabolites (e.g., TCAs, paroxetine, fluvoxamine, venlafaxine)	2
	MAOI	2
Non-MAOI	MAOI	2

- When the medication is being changed to or from an MAOI, a washout period is essential (Table 4) to prevent a potentially lethal interaction: the serotonin syndrome.
- The initial dose should be raised incrementally as tolerated until a therapeutic dose is reached or the patient achieves remission. Titration generally can be accomplished over initial weeks, but more time may be needed depending on development of side effects, the patient's age, and the presence of co-occurring medical and psychiatric conditions.
- Improvement may be observed as early as the first 1–2 weeks and continue for up to 12 weeks. Remind patients who achieve some improvement during initial weeks that full benefit at a given dose may not be achieved until 4–8 weeks.
- Some antidepressants can be lethal in overdose (e.g., ingestion of a 10-day supply of a tricyclic agent administered at a dose of 200 mg/day). Early on in treatment, it is prudent to dispense only small quantities of such medications and to keep in mind

the possibility of hoarding. In patients who are suicidal, it may be preferable to employ an agent that is safer in overdose, such as an SSRI.

### **Electroconvulsive Therapy (ECT)**

- ECT has the highest rates of response and remission of any form of antidepressant treatment, with 70%–90% of patients treated showing improvement.
- Evaluation for ECT should identify potential indications for caution or modifications in ECT technique or anesthesia, such as recent myocardial infarction, cardiac arrhythmias, or intracranial space-occupying lesions.
- ECT may have cardiovascular side effects, which can be managed by optimizing blood pressure control prior to ECT and administering antihypertensive agents (e.g., short-acting beta-blockers or calcium channel blockers) at the time of ECT. Arrhythmias, which are usually transient, can also occur in conjunction with ECT and can be managed with usual antiarrhythmic therapies if they do not resolve spontaneously.
- Patients may experience cognitive effects after ECT. The most common of these effects is confusion that generally lasts 30–60 minutes after treatment. Retrograde amnesia may also occur but typically resolves.
- Treatments are usually administered two or three times per week. An acute course of ECT typically consists of 6–12 treatments, until symptoms have remitted or clearly reached a plateau.

### **Psychotherapy**

- Depression-focused psychotherapies include cognitive-behavioral therapy (CBT), interpersonal psychotherapy, and problem-solving therapy. Psychodynamic psychotherapy is an alternative option.

- Individual or group formats may be used.
- Marital and family problems are common in the course of major depressive disorder and can be addressed by marital or family therapy.
- Considerations in the choice of a specific type of psychotherapy include the following:
  - Goals of treatment (in addition to resolving major depressive symptoms)
  - Prior positive response to a specific type of psychotherapy
  - Patient preference
  - Availability of clinicians skilled in the specific psychotherapeutic approach

### **Evaluate response.**

- Ensure that the treatment has been administered for a sufficient duration and at a sufficient frequency or dose. Generally, 4–8 weeks are needed before it can be concluded that a patient is partially responsive or unresponsive to a specific intervention.
- No treatment should continue unmodified if there has been no symptomatic improvement after 1 month.
- For full response, proceed to the continuation phase of treatment.
- For less than moderate response, assess the following and modify the treatment plan as needed:
  - Diagnosis
  - Side effects
  - Complicating co-occurring conditions
  - Psychosocial factors

- Quality of therapeutic alliance
- Treatment adherence
- For patients receiving psychotherapy, frequency of sessions and whether the specific approach to psychotherapy is adequately addressing the patient's needs
- For patients receiving pharmacotherapy, medication dose adjustments to take into account pharmacokinetic or pharmacodynamic factors
- After an additional 4–8 weeks, if the patient continues to show minimal or no improvement, conduct another thorough review and make additional changes. Consider consultation.

### **Address inadequate response.**

#### **Maximizing the Initial Treatment**

##### *Patients Treated With an Antidepressant*

- Optimizing (i.e., raising) the dose is a reasonable first step if side-effect burden is tolerable, especially if the upper dosage limit has not yet been reached.
- Some patients may require doses higher than those approved by the Food and Drug Administration.
- In patients who have shown a partial response, particularly those who have features of personality disorders and prominent psychosocial stressors, extending the antidepressant medication trial (e.g., by 4–8 weeks, but not indefinitely) can be considered.

##### *Patients Treated With Psychotherapy*

- As for patients treated with an antidepressant, an initial strategy is to increase the intensity of treatment (i.e., increase the frequency of psychotherapy sessions).

- The appropriateness of the type of psychotherapy used and the quality of the therapeutic alliance should be reviewed.

### **Changing to Other Treatments**

- For patients treated with psychotherapy, switching to an antidepressant medication can be considered. (Another option is to combine treatments, as described in the section that follows.)
- For patients who do not show at least a partial response to an initial antidepressant, a common strategy is to change to a different non-MAOI antidepressant in the same class (e.g., from one SSRI to another SSRI) or in a different class (e.g., from a SSRI to a TCA).
- For patients who can adhere to dietary and medication restrictions, a nonselective MAOI after sufficient washout period (Table 4) is an option.
- Transdermal selegiline could be considered.
- Recent evidence supports the efficacy of quetiapine monotherapy, but potential side effects need to be taken into consideration.

### **Augmenting and Combining Treatments**

- Pharmacotherapy combined with psychotherapy may offer advantages over either modality alone, particularly for patients with chronic, severe, or complex illness. For patients with less severe symptoms, advantages may be modest.
- For patients treated with an antidepressant, augmentation strategies with a modest evidence base include the following:
  - Adding another non-MAOI antidepressant, generally from a different class
  - Adding lithium

- Adding thyroid hormone
- Adding a second-generation antipsychotic
- Strategies with less supporting evidence include the following:
  - Adding an anticonvulsant
  - Adding omega-3 fatty acids
  - Adding folate
  - Adding a psychostimulant medication (e.g., modafinil)
  - If anxiety or insomnia is prominent, adding an anxiolytic or sedative-hypnotic medication, including buspirone, a benzodiazepine, or a selective gamma-aminobutyric acid (GABA) agonist hypnotic (e.g., zolpidem, eszopiclone)

#### **Treatment-Resistant Depression**

- ECT is the most effective form of therapy for patients with treatment-resistant symptoms.
- Another option to consider, with less supporting evidence, is transcranial magnetic stimulation.
- Vagus nerve stimulation (VNS) may be an option for patients who have not responded to at least four adequate trials of antidepressant treatment, including ECT.

### **C. CONTINUATION PHASE**

**To reduce the high risk of relapse, continue treatment.**

- For patients receiving an antidepressant, continue the medication for 4–9 months, generally at the same dose used during the acute phase to achieve remission.

- Continued treatment with a depression-focused psychotherapy is also recommended.
- For patients who respond to an acute course of ECT, provide pharmacotherapy and/or continuation ECT (particularly if medication or psychotherapy has been ineffective in maintaining remission).

### **Monitor for signs of relapse.**

- Given the significant risk of relapse during the continuation phase, systematic assessment of depressive symptoms, functional status, and quality of life is essential.
- Assessment may be facilitated by the use of standardized measures.
- Patients and families may help identify individual signs that harbingers a potential relapse.

## **D. MAINTENANCE PHASE**

### **Determine if the patient requires maintenance treatment.**

- Recurrence is common, occurring in 20% of patients within 6 months following remission. Between 50% and 85% of patients will experience at least one lifetime recurrence. Risk factors include the following:
  - Persistence of subthreshold depressive symptoms
  - Prior history of multiple episodes of major depressive disorder
  - Severity of initial and any subsequent episodes
  - Earlier age at onset



- Presence of an additional nonaffective psychiatric diagnosis
- Presence of a chronic general medical disorder
- Family history of psychiatric illness, particularly mood disorder
- Ongoing psychosocial stressors or impairment
- Negative cognitive style
- Persistent sleep disturbances
- Patients who have had three or more prior major depressive episodes or who have chronic major depressive disorder should receive maintenance treatment.
- Maintenance therapy should be considered for patients with other risk factors.
- For many patients, particularly those with chronic and recurrent illness or co-occurring medical and/or psychiatric disorders, some form of maintenance treatment will be required indefinitely.

### **Provide maintenance treatment as needed.**

- In general, the same treatment that was effective in the acute and continuation phases should be used for the maintenance phase. Antidepressants should generally be continued at a full therapeutic dose. Reduced frequency of psychotherapy sessions may be considered.
- When ECT or VNS has been effective, maintenance treatment with these modalities may be appropriate.

### **Continue to monitor the patient.**

- As in the acute and continuation phases, the patient should be monitored systematically and at regular intervals.

- Use of standardized measures can aid in the early detection of recurrence.

## **E. DISCONTINUATION OF TREATMENT**

**For stable patients, consider discontinuation of treatment.**

- How and when to discontinue treatment has not been systematically studied. Factors to consider include the following:
  - Risk of recurrence
  - Frequency and severity of past episodes
  - Persistence of depressive symptoms after remission
  - Presence of co-occurring disorders
  - Patient preference
- In general, psychotherapy has a longer lasting treatment effect and carries a lower risk of relapse following discontinuation than pharmacotherapy.
- Patients should be advised not to discontinue medications before stressful events (e.g., holidays, weddings).

**If pharmacotherapy is discontinued, taper the medication over at least several weeks.**

- Tapering allows for the detection of recurring symptoms and facilitates a return to full treatment if needed.
- In addition, tapering can minimize discontinuation syndromes, particularly with antidepressants with short half-lives, such as paroxetine and venlafaxine. Symptoms of discontinuation syndromes include both flu-like experiences such as nausea, headache, light-headedness, chills, and body aches, and neu-

rological symptoms such as paresthesias, insomnia, and “electric shock-like” phenomena.

**Continue to monitor the patient.**

- The patient should be informed about the potential for relapse, and a plan for resuming treatment if symptoms return should be established.
- Risk of relapse is highest in the first 2 months following discontinuation of treatment. Hence, it is important to schedule a follow-up visit during this period.
- Systematic assessment is strongly recommended.

