TREATING MAJOR DEPRESSIVE DISORDER

A Quick Reference Guide

Based on *Practice Guideline for the Treatment of Patients With Major Depressive Disorder,* Second Edition, originally published in April 2000. A guideline watch, summarizing significant developments in the scientific literature since publication of this guideline, may be available in the Psychiatric Practice section of the APA web site at www.psych.org.

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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 interpreted 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. For more detail, see APA's "Practice Guideline Development Process," available as an appendix to the compendium of APA practice guidelines, published by APPI, and online at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.

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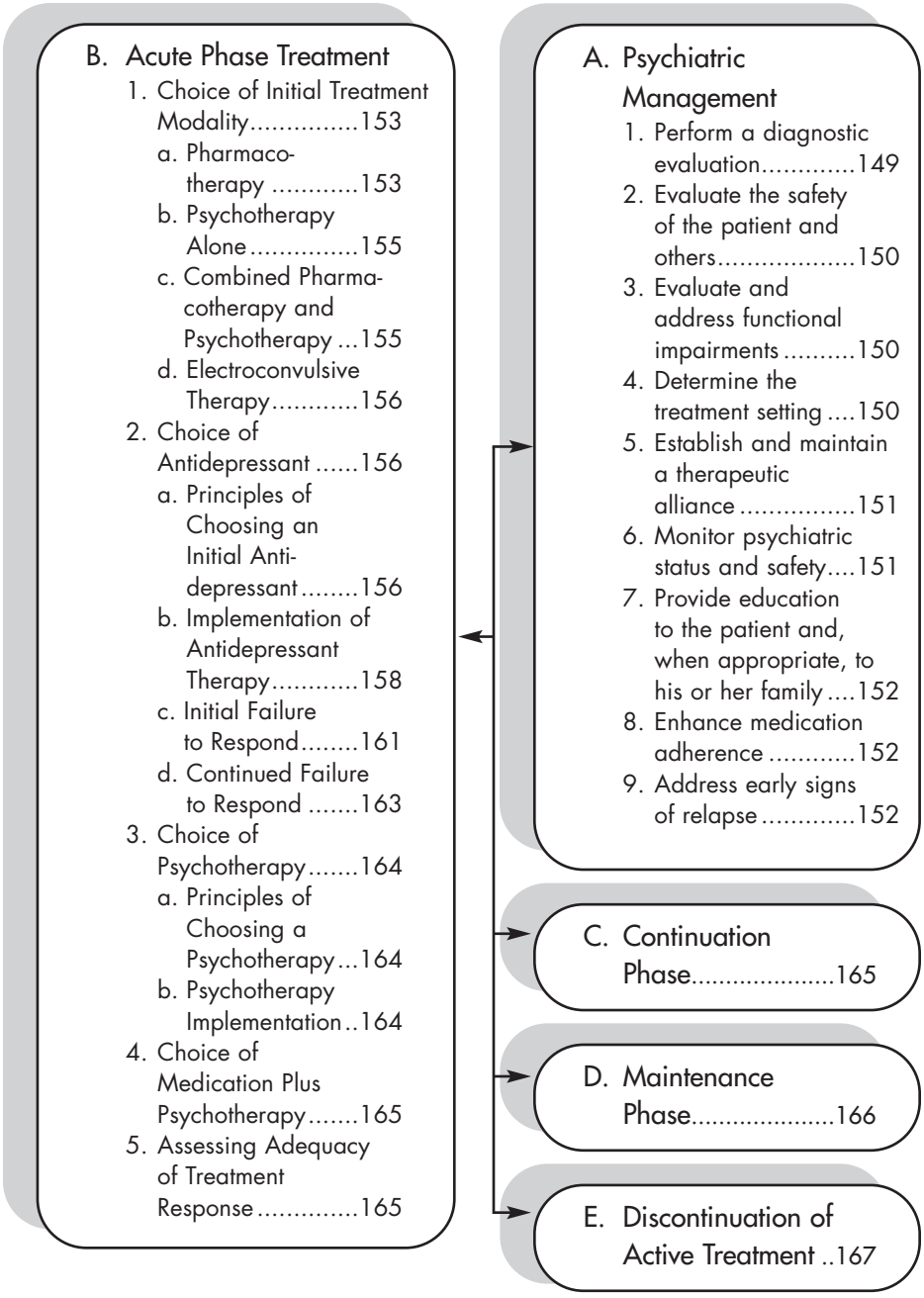
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A. Psychiatric Management

Throughout the formulation of a treatment plan and all subsequent phases of treatment, the following principles of psychiatric management should be kept in mind:

1. Perform a diagnostic evaluation.

For general principles and components of a psychiatric evaluation, refer to APA's *Practice Guideline for the Psychiatric Evaluation of Adults.*

→ **Determine whether the diagnosis is depression.**

→ **Determine whether there is psychiatric and general medical comorbidity.**

→ **Include the following in the evaluation:**

- History of the present illness and current symptoms
- Psychiatric history, including symptoms of mania
- Treatment history with current treatments and responses to previous treatments
- General medical history
- History of substance use disorders
- Personal history (e.g., psychological development, response to life transitions, major life events)
- Social, occupational, and family histories
- Review of the patient's medications
- Review of systems
- Mental status examination
- Physical examination
- Diagnostic tests as indicated

2. Evaluate the safety of the patient and others.

- Assessment of suicide risk is essential (see Table 1, p. 151).
- If the patient demonstrates suicidal or homicidal ideation, intention, or plans, close monitoring is required.
- Hospitalization should be considered if risk is significant.
- Note, however, that the ability to predict attempted or completed suicide is poor.

3. Evaluate and address functional impairments.

- Impairments include deficits in interpersonal relationships, work and living conditions, and other medical- or health-related needs.
- Address identified impairments (e.g., scheduling absences from work).

4. Determine the treatment setting.

Choose appropriate site, considering the following:

- Clinical condition (including symptom severity, comorbidity, suicidality, homicidality, and level of functioning)
- Available support systems
- Ability of the patient 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 comorbid psychiatric or general medical conditions, or
- has not responded adequately to outpatient treatment.

5. Establish and maintain a therapeutic alliance.

- It is important to pay attention to the concerns of the patient and his or her family.
- Be aware of transference and countertransference issues.

6. Monitor psychiatric status and safety.

Monitor the patient for changes in destructive impulses to self and others.

Be vigilant in monitoring changes in psychiatric status, including major depressive symptoms and symptoms of potential comorbid conditions.

Consider diagnostic reevaluation if symptoms change significantly or if new symptoms emerge.

TABLE 1. Considerations in the Evaluation for Suicide Risk

- Presence of suicidal or homicidal ideation, intent, or plans
- Access to means for suicide and the lethality of those means
- Presence of psychotic symptoms, command hallucinations, or severe anxiety
- Presence of alcohol or substance use
- History and seriousness of previous attempts
- Family history of or recent exposure to suicide

7. Provide education to the patient and, when appropriate, to his or her family.

- Emphasize that major depressive disorder is a real illness.
- Education about treatments helps patients make informed decisions, be aware of side effects, and adhere to treatment.

8. Enhance medication adherence.

To improve adherence, emphasize

- when and how often to take medication,
- the typical 2- to 4-week lag for beneficial effects to be noticed,
- need to continue medication even after feeling better,
- need to consult with the prescribing doctor before medication discontinuation, and
- what to do if problems arise.

Improve adherence in elderly patients by simplifying the medication regimen and minimizing cost.

Consider psychotherapeutic intervention for serious or persistent nonadherence.

9. Address early signs of relapse.

Inform the patient (and, when appropriate, the family) about the significant risk of relapse.

Educate the patient (and the family) about how to identify early signs and symptoms of new episodes.

Emphasize seeking help if signs of relapse appear, to prevent full-blown exacerbation.

B. Acute Phase Treatment

1. Choice of Initial Treatment Modality (see Figure 1, p. 154)

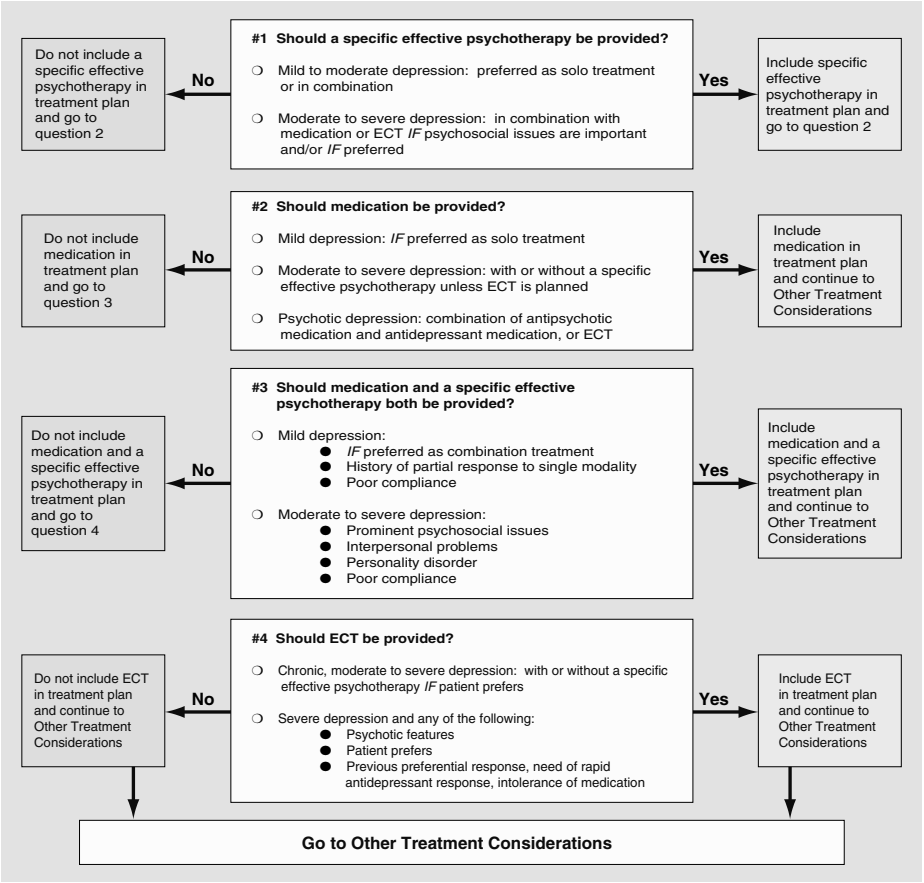
a. Pharmacotherapy

Severity of Major Depressive Episode	Pharmacotherapy
Mild	Antidepressants if preferred by patient
Moderate to severe	Antidepressants are treatment of choice (unless electroconvulsive therapy [ECT] is planned)
With psychotic features	Antidepressants plus antipsychotics or ECT

Features suggesting that medication may be the preferred treatment include the following:

- History of prior positive response
- Severe symptomatology
- Significant sleep or appetite disturbances or agitation
- Anticipation of need for maintenance therapy
- Patient preference
- Lack of available alternative treatment modalities

FIGURE 1. Choice of Treatment Modalities for Major Depressive Disorder



1. Choice of Initial Treatment Modality (see Figure 1, p. 154)
b. Psychotherapy Alone

If the severity of the major depressive episode is mild to moderate, use psychotherapy if preferred by the patient.

Features suggesting the use of psychotherapeutic interventions include the following:
- Presence of significant psychosocial stressors
- Intrapsychic conflict
- Interpersonal difficulties
- Comorbid personality disorder
- Pregnancy, lactation, or wish to become pregnant
- Patient preference

1. Choice of Initial Treatment Modality (see Figure 1, p. 154)
c. Combined Pharmacotherapy and Psychotherapy

Consider the use of combined pharmocotherapy and psychotherapy if the severity of the major depressive episode is mild to severe with clinically significant psychosocial issues, interpersonal problems, or a comorbid personality disorder.

Other features suggesting combination treatment include the following:
- History of only partial response to single treatment modalities
- Poor adherence to treatments (combine medication with a psychotherapeutic approach that focuses on treatment adherence)

1. Choice of Initial Treatment Modality (see Figure 1, p. 154)
d. Electroconvulsive Therapy

Consider ECT if any of the following features are present:
- Major depressive episode with a high degree of symptom severity and functional impairment
- Psychotic symptoms or catatonia
- Urgent need for response (e.g., suicidality or nutritional compromise in a patient refusing food)

ECT may be the preferred treatment when
- the presence of comorbid medical conditions precludes the use of antidepressant medications,
- there is a prior history of positive response to ECT, or
- the patient expresses a preference for ECT.

2. Choice of Antidepressant
a. Principles of Choosing an Initial Antidepressant

See Table 2 (p. 157) for a list of antidepressants and dosage ranges.

Because there is comparable efficacy between and within classes of medications, the initial selection is based largely on the following considerations:
- Anticipated side effects
- Safety or tolerability of side effects for individual patients
- Patient preference
- Quantity and quality of clinical trial data
- Cost

Based on these factors, the following medications are likely to be effective for most patients: selective serotonin reuptake inhibitors (SSRIs), desipramine, nortriptyline, bupropion, venlafaxine, and mirtazapine.

TABLE 2. Dosage Ranges for Antidepressant Medications

Generic Name	Starting Dosage (mg/day)	Usual Dosage (mg/day)
Tricyclics and tetracyclics		
Tertiary amine tricyclics		
Amitriptyline	25–50	100–300
Clomipramine	25	100–250
Doxepin	25–50	100–300
Imipramine	25–50	100–300
Trimipramine	25–50	100–300
Secondary amine tricyclics		
Desipramine[a]	25–50	100–300
Nortriptyline[a]	25	50–150
Protriptyline	10	15–60
Tetracyclics		
Amoxapine	50	100–400
Maprotiline	50	100–225
SSRIs		
Citalopram[a]	20	20–60
Escitalopram[a]	10	10–20
Fluoxetine[a]	20	20–60
Fluvoxamine[a]	50	50–300
Paroxetine[a]	20	20–50
Sertraline[a]	50	50–200
Dopamine-norepinephrine reuptake inhibitors		
Bupropion[a]	150	150–300
Bupropion, sustained release[a]	150	150–300
Bupropion, extended release[a]	150	150–300
Serotonin-norepinephrine reuptake inhibitors		
Duloxetine	40	40–60
Venlafaxine[a]	37.5	75–375
Venlafaxine, extended release[a]	37.5	75–225
Serotonin modulators		
Nefazodone	50	150–600
Trazodone	50	75–400
Norepinephrine-serotonin modulator		
Mirtazapine	15	15–45
MAOIs		
Irreversible, nonselective		
Phenelzine	15	15–90
Tranylcypromine	10	30–60
Isocarboxazid	20	30–60

[a]These medications are likely to be optimal medications in terms of the patient's acceptance of side effects, safety, and quantity and quality of clinical trial data.

2. Choice of Antidepressant
a. Principles of Choosing an Initial Antidepressant (continued)

Consider other features, including the following:
- History of prior response with a particular antidepressant
- Presence of comorbid psychiatric or general medical conditions (e.g., tertiary amine tricyclic antidepressants [TCAs] may not be optimal in patients with cardiovascular conditions or acute-angle glaucoma)

Use monoamine oxidase inhibitors (MAOIs) only for patients who do not respond to other treatments, because of MAOIs' dietary restrictions and potentially serious side effects.
- MAOIs may be particularly effective for major depressive episodes with atypical features (although in clinical practice, SSRIs are now commonly used for atypical depression because of their more favorable adverse effect profile).

2. Choice of Antidepressant
b. Implementation of Antidepressant Therapy

Start at the dosage levels suggested in Table 2 (p. 157).

Titrate to full therapeutic dosage, taking the following considerations into account:
- Side effects
- Patient's age
- Comorbid illnesses (e.g., starting and therapeutic doses should be reduced [generally to half] in elderly or medically frail patients)

Determine the monitoring frequency. Frequency depends on
- severity of illness,
- suicide risk,
- significant side effects or drug interactions,
- patient's cooperation with treatment,
- availability of social supports, and
- presence of comorbid general medical problems.

Determine the method of monitoring (face-to-face, phone, or e-mail contact, contact with a physician knowledgeable about the patient) according to clinical context.

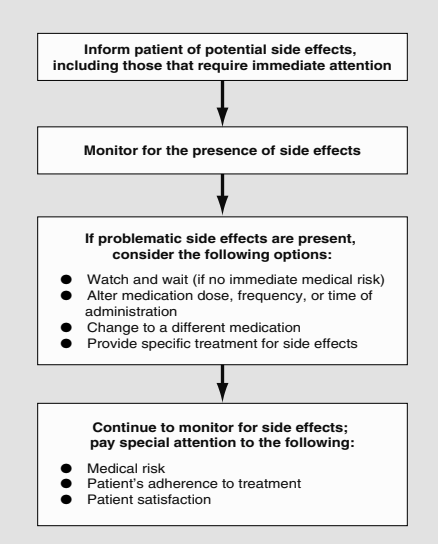
Monitor to assess the following:
- Treatment response
- Side effects (see Figure 2, p. 160)
- Clinical condition
- Safety

Monitor adults closely for worsening of depression and for increased suicidal thinking or behavior, as some evidence suggests that antidepressant treatment may increase suicidality in children and adolescents (see web sites of the FDA [http://www.fda.gov], the American Academy of Child and Adolescent Psychiatry [http://www.aacap.org], and the APA [http://www.psych.org]).

Specific monitoring may be indicated with particular drugs (e.g., life-threatening hepatic failure has been reported with nefazodone use, duloxetine is not suggested for use in individuals with chronic hepatitis or substantial alcohol use).

Serotonin syndrome can occur when SSRIs, SNRIs, or MAOIs are used alone, but it is typically seen and is of greater severity when several serotonergic drugs are given concurrently or when an MAOI is given with a serotonergic agent.

FIGURE 2. Management of Medication Side Effects



2. Choice of Antidepressant
c. Initial Failure to Respond

If the patient is not at least moderately improved after 4 to 8 weeks, reappraise the treatment regimen (see Figure 3, p. 162).

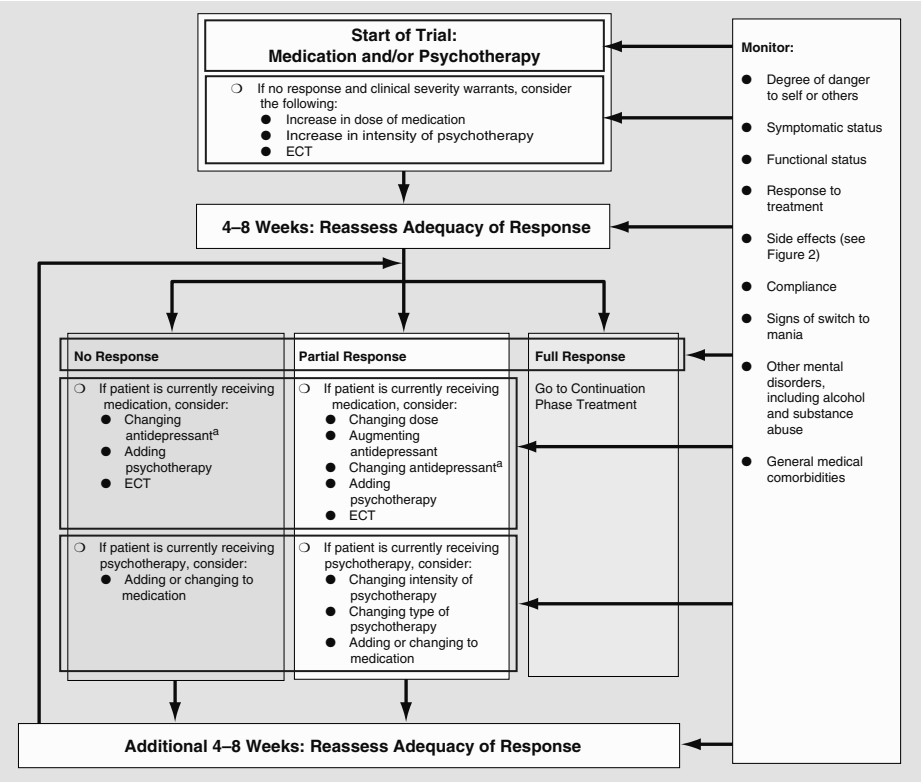
Investigate the patient's adherence to treatment.

Consider pharmacokinetic/pharmacodynamic factors (may require serum antidepressant medication levels).

Revise the treatment plan and consider the following options:

- Maximize the initial therapeutic treatment dose.
  - For partial responders, extend the trial (e.g., by 2 to 4 weeks).
  - For nonresponders on moderate doses or those with low serum levels, raise the dose and monitor for increased side effects.
- Add, change, or increase the frequency of psychotherapy.
- Switch to another non-MAOI medication (see Table 2, p. 157, and Table 3, p. 163) in either the same class or a different class, particularly if there is lack of partial response.
- Especially if there is partial response, augment with
  - a non-MAOI antidepressant from a different class (be alert to drug-drug interactions), or
  - another adjuvant medication (e.g., lithium, thyroid hormone, anticonvulsants, psychostimulants).
- Switch to an MAOI.
- Institute ECT.

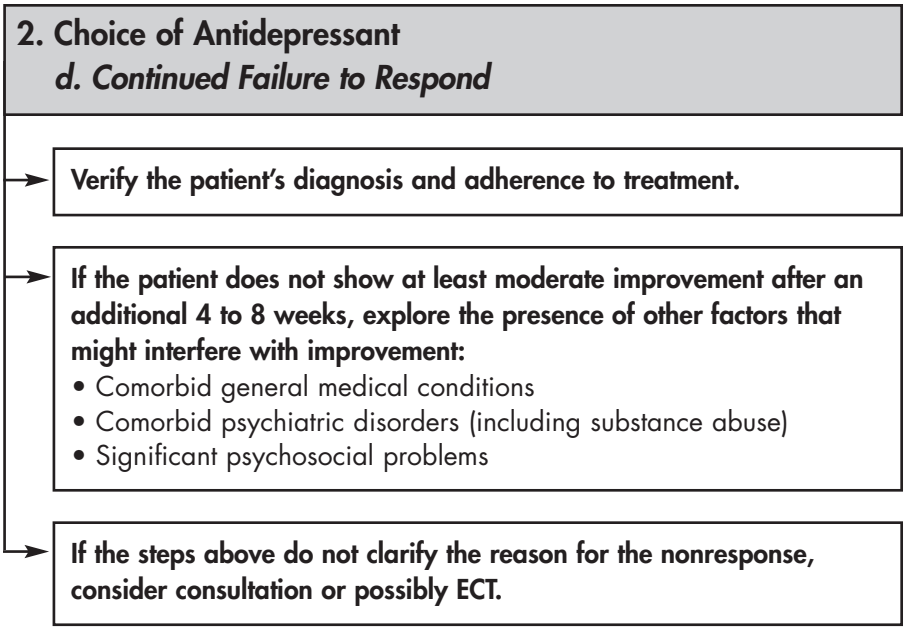
FIGURE 3. Acute Phase Treatment of Major Depressive Disorder



[a]Choose either another antidepressant from the same class or, if two previous medication trials from the same class were ineffective, an antidepressant from a different class.

TABLE 3. Required Washout Times Between Antidepressant Trials

Antidepressant Change	Minimum Washout Period
To MAOI from drug with long–half-life metabolites (e.g., fluoxetine)	5 weeks
To MAOI from drug without long–half-life metabolites (e.g., TCA, paroxetine, fluvoxamine, venlafaxine) or other MAOI	2 weeks
To non-MAOI antidepressant from MAOI	2 weeks



3. Choice of Psychotherapy
a. Principles of Choosing a Psychotherapy

Choose the modality of therapy:
- Cognitive behavior therapy and interpersonal therapy have the best research-documented efficacy.
- Psychodynamic psychotherapy, supported by broad clinical consensus, is usually oriented toward both symptomatic improvement and broader personality issues.

Consider other factors:
- Patient preference
- Availability of clinicians with appropriate training and expertise in the specific approach

3. Choice of Psychotherapy
b. Psychotherapy Implementation

Determine the frequency of psychotherapy.
Frequency generally ranges from once to several times per week in the acute phase and depends on
- specific type and goals of psychotherapy,
- need to create and maintain a therapeutic relationship,
- need to ensure treatment adherence, and
- need to monitor and address suicidality.

In situations with more than one treating clinician, maintain ongoing contact with the patient and other clinicians.

If the patient does not show at least moderate improvement after 4 to 8 weeks, conduct a thorough review and reappraisal (see Figure 3, p. 162).

4. Choice of Medication Plus Psychotherapy

Consider the same issues that influence the choice of medication (see section B.2, p. 156) and psychotherapy (see section B.3, p. 164).

If the patient does not show at least moderate improvement after 4 to 8 weeks, conduct a thorough review, including of adherence and pharmacokinetic/pharmacodynamic factors.

If the patient does not show at least moderate improvement after an additional 4 to 8 weeks following a change, conduct another thorough review and consider consultation or possibly ECT.

5. Assessing Adequacy of Treatment Response

Do not conclude acute phase treatment if the patient shows only partial response. Partial response is associated with poor functional outcome.

C. Continuation Phase

The continuation phase is defined as the 16- to 20-week period after sustained and complete remission from the acute phase.

To prevent relapse, continue antidepressant medication at the same dose used during the acute phase.

Consider the use of psychotherapy to help prevent relapse.

Consider providing ECT if medication or psychotherapy has not been effective.

Set frequency of visits depending on clinical condition and specific treatments used. Frequency can vary from once every 2 to 3 months to multiple times per week.

D. Maintenance Phase

The goal during the maintenance phase is to prevent recurrences of major depressive episodes (see Table 4, p. 167, for factors to consider).

Continue using the treatment that was effective in the acute and continuation phases.

Employ the same full antidepressant medication dosages used in prior phases of treatment.

Set the frequency of visits according to clinical condition and specific treatments used.
Frequency can range from as low as once every 2 to 3 months for stable patients to as high as multiple times per week for those in psychodynamic psychotherapy.

Consider ECT maintenance for patients who have repeated moderate or severe episodes despite adequate pharmacological treatment (or who are unable to tolerate maintenance medication).

TABLE 4. Considerations in the Decision to Use Maintenance Treatment

Factor	Component
Risk of recurrence	Number of prior episodes; presence of comorbid conditions; residual symptoms between episodes
Severity of episodes	Suicidality; psychotic features; severe functional impairments
Side effects experienced with continuous treatment	
Patient preferences	

E. Discontinuation of Active Treatment

Consider whether to discontinue treatment based on the same factors considered in the decision to initiate maintenance treatment.
For example, consider the probability of recurrence and the frequency and severity of past episodes (see Table 4, above, and Table 5, p. 168).

When discontinuing psychotherapy, the best method depends on the patient's needs and type of psychotherapy, the duration of treatment, and the intensity of treatment.

To discontinue pharmacotherapy, taper the dose over at least several weeks.
- Facilitates more rapid return to a full dose if symptoms recur.
- Minimizes the risk of antidepressant discontinuation syndromes (more likely with shorter–half-life antidepressants).

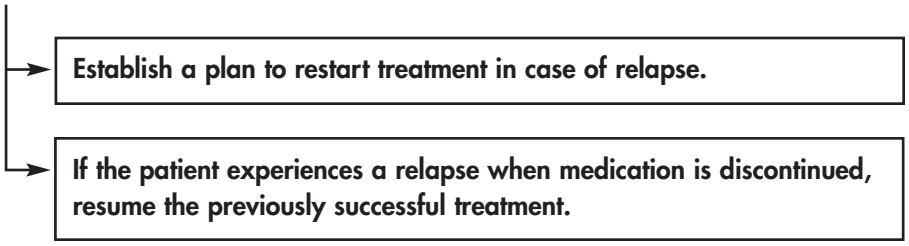


TABLE 5. Risk Factors for Recurrence of Major Depressive Disorder

- Prior history of multiple episodes of major depressive disorder
- Persistence of dysthymic symptoms after recovery from an episode of major depressive disorder
- Presence of an additional, nonaffective psychiatric diagnosis
- Presence of a chronic general medical condition