

Clinical Practice Guideline: Treatment for Patients with Major Depressive Disorder¹	
Section: Care Management	Total Number of Pages: 7
Original Date Adopted: 3/21/03	Review / Revision Date: 8/19/2011

INTRODUCTION

This guideline is not intended to be construed or to serve as a standard of medical care. These parameters of practice should be considered guidelines only. 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 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 (*Practice Guideline for the Treatment of Patients with Major Depressive Disorder*).

A. PSYCHIATRIC MANAGEMENT

Psychiatric management consists of interventions and activities that should be initiated and provided during all phases of treatment. (Acute, Continuation, Maintenance Phase)

1. Establish and maintain a therapeutic alliance.
2. Complete the psychiatric assessment.
3. Evaluate the safety of the patient.
4. Establish the appropriate treatment setting.
5. Evaluate and address functional impairments and quality of life.
6. Coordinate the patient's care with other clinicians.
7. Monitor the patient's psychiatric status.
8. Integrate measurements into psychiatric management.
9. Enhance treatment adherence.
10. Provide education to the patient and, when appropriate, to the family.

B. ACUTE PHASE

Choose an initial treatment. 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

Recommended Modalities for Acute Phase Treatment of Major Depressive Disorder

Severity of Illness	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

1. 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

Table 2 provides the starting and usual doses of medications that have been shown to be effective for treating major depressive disorder. In general, the use of MAOIs should be restricted to patients who do not respond to other treatments. 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^a

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

TABLE 2. DOSING OF MEDICATIONS SHOWN TO BE EFFECTIVE IN TREATING MAJOR DEPRESSIVE DISORDER^a

Generic Name	Starting Dose (mg/day)^b	Usual Dose (mg/day)^c
Doxepin	25-50	100-300
Imipramine	25-50	100-300
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 (MAIOs)		
Irreversible, nonselective inhibitors		
Phenelzine	15	45-90
Tranylcypromine	10	30-60
Isocarboxazid	10-20	30-60
Irreversible, MAO B selective inhibitors		
Selegiline transdermal ^h	6	6-12
Reversible MAO A selective inhibitor		
Moclobemide	150	300-600

^a 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.

^b Lower starting doses are recommended for elderly patients and for patients with panic disorder, significant anxiety of hepatic disease, and co-occurring general medical conditions.

^c For some of these medications (e.g., TCAs), the upper dosing limits 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.

^d 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.

^e Dose varies with diagnosis; see text for specific guidelines.

^f Has been used at doses up to 400 mg/day, although doses above 50 mg/day may not provide additional benefit.

^g This medication is not typically used for this indication.

^h 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.

TABLE 3. POTENTIAL TREATMENTS FOR SIDE EFFECTS OF ANTIDEPRESSANT MEDICATIONS

Side Effect	Antidepressant Associated With Effect	Treatment ^a
Cardiovascular		
Arrhythmias	TCAs	Avoid inpatients with cardiac instability or ischemia. Attend to interactions with antiarrhythmics.
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	TCAs, trazodone, nefazodone, MAOIs	Add fludrocortisones. Add salt to diet.
Anticholinergic		
Constipation	TCAs	Encourage adequate hydration. Add bulk laxative.
Delirium	TCAs	Evaluate for other possible contributors to delirium.
Dry mouth	TCAs, SNRIs, bupropion	Suggest use of sugarless gum or candy.
Urinary hesitancy	TCAs	Add bethanechol.
Visual changes	TCAs	Add pilocarpine eye drops.
Neurologic		
Headaches	SSRIs, SNRIs, bupropion	Assess for other etiologies (e.g., caffeineism, bruxism, migraine, tension headache). Add clonazepam.
Myoclonus	TCAs, MAOIs	Assess for other etiologies, and add anticonvulsant medication, if clinically indicated.
Seizures	Bupropion, TCAs, amoxapine	
Sexual		
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.
Other		
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
Diaphoresis	TCAs, some SSRIs, SNRIs	Add an α_1 -adrenergic antagonist (e.g., terazosin) central α_2 -adrenergic agonist (e.g., clonidine), or anticholinergic agent (e.g., benztropine).
Fall risk	TCAs, 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.
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	TCA, trazodone, nefazodone, mirtazapine	Use bedtime dosing. Add modafinil or methylphenidate.

TABLE 3. POTENTIAL TREATMENTS FOR SIDE EFFECTS OF ANTIDEPRESSANT MEDICATIONS

Side Effect	Antidepressant Associated With Effect	Treatment ^a
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).

^aInitial 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 a MAOI, a washout period is essential (Table 4) to prevent a potentially lethal interaction: 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.

2. 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.

3. Psychotherapy

- a. Depression-focused psychotherapies include cognitive-behavioral therapy (CBT), interpersonal psychotherapy, and problem-solving therapy. Psychodynamic psychotherapy is an alternative option.
- b. Considerations in the choice of a specific type of psychotherapy include the following:
 - i. Goals of treatment (in addition to resolving major depressive symptoms)
 - ii. Prior Positive response to a specific type of psychotherapy
 - iii. Patient preference
 - iv. Availability of clinicians skilled in the specific psychotherapeutic approach

4. Evaluate Response

- a. 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.
- b. No treatment should continue unmodified if there has been no symptomatic improvement after 1 month.
- c. For full response, proceed to the continuation phase of treatment
- d. For less than moderate response, assess and modify the treatment plan, as needed

5. Address inadequate response

- a. Maximizing the Initial Treatment
 - i. 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.
 - 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.
 - ii. Patients treated with Psychotherapy
 - Increase the frequency of psychotherapy sessions;
 - Appropriateness of the type of psychotherapy used and the quality of the therapeutic alliance should be reviewed.

6. Changing to Other Treatments

- a. Patients treated with psychotherapy, may be switched to an antidepressant medication.
- b. 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).
- c. For patients who can adhere to dietary and medication restrictions, a nonselective MAOI after sufficient washout period (Table 4) is an option.
- d. Transdermal selegiline could be considered.
- e. Recent evidence supports the efficacy of quetiapine monotherapy, but potential side effects need to be taken into consideration.

7. Augmenting and Combining Treatments

- a. Pharmacotherapy combined with psychotherapy may offer advantages over either modality alone, particularly for patients with chronic, severe, or complex illness.
- b. 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

8. Treatment-Resistant Depression

- a. ECT is the most effective form of therapy for patients with treatment-resistance symptoms.

C. CONTINUATION PHASE

1. To reduce the high risk of relapse, continue treatment.
 - a. 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.
 - b. Continued treatment with a depression-focused psychotherapy is also recommended.
 - c. 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).
2. Monitor for signs of relapse
 - a. Given the significant risk of relapse during the continuation phase, systematic assessment of depressive symptoms, functional status, and quality of life is essential.

D. MAINTENANCE PHASE

1. Determine if the patient requires maintenance treatment.
 - a. 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.
 - b. Risk factors should also be considered.
 - c. Patients who had three or more prior major depressive episodes or who have chronic major depressive disorder should receive maintenance treatment.
 - d. 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.
 - e. Provide maintenance treatment as needed.
 - f. Continue to monitor the patient.

E. DISCONTINUATION OF TREATMENT

1. For stable patients, consider discontinuation of treatment.
 - a. In general, psychotherapy has a longer lasting treatment effect and carries a lower risk of relapse following discontinuation than pharmacotherapy.
2. If pharmacotherapy is discontinued, taper the medication over at least several weeks
 - a. Tapering allows for the detection of recurring symptoms and facilitates a return to full treatment if needed.
 - b. In addition, tapering can minimize discontinuation syndromes, particularly with antidepressants with short half-lives, such as paroxetine and venlafaxine.
3. Continue to monitor the patient.
 - a. Risk of relapses is highest in the first 2 months following discontinuation of treatment. Hence, it is important to schedule a follow up visit during this period.
 - b. Systematic assessment is strongly recommended.
 - c. The patient should be informed about the potential for relapse, and a plan for resuming treatment if symptoms return should be established.

References: *American Psychiatric Association: Treating Major Depression Disorder, A Quick Reference Guide*, based on *Practice Guideline for the Treatment of patients with Major Depressive Disorder, Third Edition*, published in October 2010.
