APA Releases Guideline on Treatment of Patients with Major Depressive Disorder

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Guideline source: American Psychiatric Association

Evidence rating system used? Yes

Literature search described? Yes

Available at: http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx

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The American Psychiatric Association (APA) recently updated its guideline on the treatment of major depressive disorder. The new evidence-based guideline summarizes recommendations on the use of antidepressants and other drug therapies; psychotherapy, including cognitive behavior therapy; and electroconvulsive therapy (ECT). Because many patients with major depressive disorder have co-occurring psychiatric disorders, including substance use disorders, physicians should also consider appropriate treatments for these diagnoses. Patients who have depressive symptoms in the context of another disorder but who do not meet the diagnostic criteria for major depressive disorder should be treated according to guidelines pertaining to the primary diagnosis.

Acute Phase

Treatment in the acute phase should be aimed at inducing remission of the depressive episode and achieving a full return to the baseline level of functioning. Patients with mild to moderate depression should be treated with antidepressants *(Table 1)* or psychotherapy. Combined pharmacotherapy and psychotherapy may be useful in patients with psychosocial or interpersonal problems, intrapsychic conflict, or a co-occurring axis II disorder. ECT can be used in select patients.

In patients with severe depression without psychotic features, pharmacotherapy, combined pharmacotherapy and psychotherapy, or ECT can be used; however, psychotherapy should not be used alone. In patients with severe depression with psychotic features, antidepressant and antipsychotic agents should be used, with or without psychotherapy. ECT is also an option.

Selection of an initial treatment modality should be influenced by clinical features, such as severity of symptoms and presence of co-occurring disorders, as well as other factors, such as patient preferences and prior treatment experiences. Because the effectiveness of antidepressants is generally comparable between and within drug classes, the initial selection will be based largely on anticipated adverse effects, safety and tolerability, pharmacologic properties (e.g., half-life, drug interactions), and cost. For most patients, optimal treatments include a selective serotonin reuptake inhibitor, a serotonin-norepinephrine reuptake inhibitor, mirtazapine (Remeron), or bupropion (Wellbutrin). The use of nonselective monoamine oxidase inhibitors should be restricted to patients who do not respond to other treatments. In patients who prefer complementary and alternative therapies, *S*-adenosylmethionine (SAM-e) or St. John's wort can be considered. However, patients who take St. John's wort should be monitored carefully for drug interactions.

Once an antidepressant has been selected, it should be titrated based on the patient's age, the treatment setting, and the presence of co-occurring disorders, concomitant pharmacotherapy, or adverse effects of medication. If adverse effects occur, the dosage can be lowered or the patient should be switched to a different medication. ▶

Table 1. Medications for Treatment of Major Depressive Disorder

Drug	*Starting dosage (mg per day)**	*Usual dosage (mg per day)†*
Dopamine-norepinephrine reuptake inhibitors‡		
Bupropion, immediate release (Wellbutrin)	150	300 to 450
Bupropion, sustained release (Wellbutrin SR)	150	300 to 400
Bupropion, extended release (Wellbutrin XL)	150	300 to 450
Monoamine oxidase inhibitors		
Isocarboxazid	10 to 20	30 to 60
Moclobemide (not available in the United States)	150	300 to 600
Phenelzine (Nardil)	15	45 to 90
Selegiline, transdermal (Emsam)	6	6 to 12
Tranylcypromine	10	30 to 60
Norepinephrine-serotonin modulator‡		
Mirtazapine (Remeron)	15	15 to 45
Selective serotonin reuptake inhibitors‡		
Citalopram (Celexa)	20	20 to 60§
Escitalopram (Lexapro)	10	10 to 20
Fluoxetine (Prozac)	20	20 to 60§
Paroxetine (Paxil)	20	20 to 60§
Paroxetine, extended-release (Paxil CR)	12.5	25 to 75
Sertraline (Zoloft)	50	50 to 200§
Serotonin modulators		
Nefazodone	50	150 to 300
Trazodone‖	150	150 to 600
Serotonin-norepinephrine reuptake inhibitors‡		
Desvenlafaxine (Pristiq)	50	50
Duloxetine (Cymbalta)	60	60 to 120
Venlafaxine, immediate release (Effexor)	37.5	75 to 375
Venlafaxine, extended release (Effexor XR)	37.5	75 to 375
Tricyclics and tetracyclics		
Amitriptyline	25 to 50	100 to 300
Desipramine (Norpramin)	25 to 50	100 to 300
Doxepin	25 to 50	100 to 300
Imipramine (Tofranil)	25 to 50	100 to 300
Maprotiline	75	100 to 225
Nortriptyline (Pamelor)	25	50 to 200
Protriptyline	10 to 20	20 to 60
Trimipramine (Surmontil)	25 to 50	75 to 300

**—Lower starting dosages are recommended for older patients and for patients with panic disorder, anxiety, hepatic disease, and co-occurring medical conditions.*

†—For some drugs (e.g., tricyclics), the upper dosage limit reflects the risk of toxicity or need for plasma level assessment, whereas for other drugs (e.g., selective serotonin reuptake inhibitors), higher dosages are safe but have not been proven more effective than lower dosages.

‡—These drugs are likely optimal in terms of safety, adverse effects, and quantity and quality of clinical trial data.

§—Dosage varies with diagnosis.

‖—Not typically used for this indication.

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An incomplete response to treatment is associated with poor functional outcomes; therefore, the acute phase of treatment should not be concluded prematurely in patients who do not fully respond. If a moderate improvement in symptoms does not occur within four to eight weeks after treatment initiation, the diagnosis should be reconsidered, adverse effects and adherence to therapy assessed, comorbidities and psychosocial factors reviewed, and the treatment plan adjusted. For patients who are being treated with psychotherapy, the frequency of sessions and the specific approach to psychotherapy should be reassessed. If minimal or no improvement is noted after an additional four to eight weeks, the treatment plan should be readjusted, and consultation should be considered.

Continuation Phase

In the continuation phase, management is aimed at preventing relapse. Systematic assessment of symptoms and monitoring for adverse effects of medications *(Table 2)*, adherence to therapy, and functional status are essential. To reduce the risk of relapse, patients in whom pharmacotherapy has been successful should continue treatment at the same dosage for four to nine months. Depression-focused cognitive behavior therapy is also recommended in the continuation phase.

Patients who respond to ECT should continue treatment with medication; a combination of lithium and nortriptyline (Pamelor) is recommended. Alternatively, continuation ECT can be given, especially if medication and psychotherapy have been ineffective.

Maintenance Phase

Patients who have had three or more episodes of major depression or who have chronic major depressive disorder should proceed to the maintenance phase of treatment after completing the continuation phase. Maintenance therapy should also be considered for patients with additional risk factors for recurrence (e.g., residual symptoms, ongoing psychosocial stressors, early age at onset). Additional considerations include patient preference, the type of treatment received, adverse effects, comorbid conditions, frequency and severity of previous depressive

Table 2. Treatment of Adverse Effects Associated with Antidepressants

Effect	*Associated antidepressant*	*Treatment*
Anticholinergic		
Constipation	TCAs	Adequate hydration; bulk laxative
Delirium	TCAs	Assess for other causes
Dry mouth	TCAs, SNRIs, bupropion (Wellbutrin)	Use of sugarless gum or candy
Urinary hesitancy	TCAs	Bethanechol
Visual changes	TCAs	Pilocarpine eye drops
Cardiovascular		
Arrhythmias	TCAs	Avoid TCA use in patients with cardiac instability or ischemia; attend to interactions with antiarrhythmic drugs
Hypertension	SNRIs, bupropion	Monitor blood pressure; keep dosage as low as possible; add antihypertensive drug
Hypertensive crisis	MAOIs	Seek emergency treatment; if hypertension is severe, intravenous antihypertensive agents (e.g., labetalol, nitroprusside [Nitropress]) may be needed
Increased cholesterol levels	Mirtazapine (Remeron)	Statin drugs
Orthostatic hypotension	TCAs, trazodone, nefazodone, MAOIs	Fludrocortisone; add salt to diet
Neurologic		
Headache	SSRIs, SNRIs, bupropion	Assess for other causes (e.g., caffeinism, bruxism, migraine, tension headache)
Myoclonus	TCAs, MAOIs	Clonazepam (Klonopin)
Seizures	Bupropion, TCAs, amoxapine	Assess for other causes; add anticonvulsant drug, if indicated
Sexual		
Arousal, erectile dysfunction	TCAs, SSRIs, SNRIs	Sildenafil (Viagra), tadalafil (Cialis), buspirone (Buspar), bupropion
Orgasm dysfunction	TCAs, SSRIs, venlafaxine, desvenlafaxine, MAOIs	Sildenafil, tadalafil, buspirone, bupropion
Priapism	Trazodone	Obtain emergency urologic evaluation
Other		
Activation	SSRIs, SNRIs, bupropion	Administer in morning
Akathisia	SSRIs, SNRIs	Beta blocker or benzodiazepine
Bruxism	SSRIs	Obtain dental consultation, if indicated
Diaphoresis	TCAs, some SSRIs, SNRIs	Alpha$_1$-adrenergic antagonist, central alpha$_2$-adrenergic antagonist, or anticholinergic
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 bleeding	SSRIs	Determine whether other medications may affect clotting
Hepatotoxicity	Nefazodone	Provide education about and monitor for evidence of hepatic dysfunction; order hepatic function testing, if indicated
Insomnia	SSRIs, SNRIs, bupropion	Administer in morning; add sedative-hypnotic drug at bedtime; add melatonin; provide cognitive behavior therapy or sleep hygiene education
Nausea, vomiting	SSRIs, SNRIs, bupropion	Administer after a meal or in divided doses
Osteopenia	SSRIs	Monitor bone mineral density and treat, if indicated (e.g., calcium and vitamin D supplement, bisphosphonates, selective estrogen receptor agents)
Sedation	TCAs, trazodone, nefazodone, mirtazapine	Administer at bedtime; add modafinil (Provigil) or methylphenidate (Ritalin)
Severe serotonin syndrome	MAOIs	Obtain emergency evaluation; consider admission to a critical care unit
Weight gain	SSRIs, mirtazapine, TCAs, MAOIs	Encourage exercise; consult with dietician; if changing antidepressants, consider a secondary amine (if a TCA is required) or antidepressant with less effect on weight (e.g., bupropion)

MAOI = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

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episodes (including psychosis and suicide risk), and the persistence of depressive symptoms after recovery. In many patients—particularly those with chronic and recurrent major depressive disorder or co-occurring medical or psychiatric disorders—some form of treatment will be required indefinitely. Because of the risk of recurrence, patients should be monitored at regular intervals during the maintenance phase.

The antidepressant that produced symptom remission during the acute phase should be continued at the full therapeutic dosage. If depression-focused psychotherapy was used during the acute and continuation phases, maintenance therapy should be considered, with less frequent sessions. Maintenance ECT can be considered in patients with depressive episodes that have not responded to medications or depression-focused psychotherapy, but that have responded to ECT.

Discontinuation

Pharmacotherapy should be tapered over the course of at least several weeks. Before discontinuation of active treatment, patients should be counseled about the potential for relapse, and a plan should be established for seeking treatment if symptoms recur. Patients should be monitored for several months after medications are discontinued, and they should receive another course of acute-phase treatment if symptoms recur. ■

Answers to This Issue's CME Quiz

Q1. D	**Q6.** D
Q2. A	**Q7.** C
Q3. A, B, C, D	**Q8.** A, B
Q4. B	**Q9.** A, B, D
Q5. A, C, D	**Q10.** B