

Practice Guideline for the Treatment of Patients With Major Depressive Disorder: American Psychiatric Association

Our clinical advisor adds updated advice on electroconvulsive therapy, transcranial magnetic stimulation, lithium, light therapy, sleep hygiene, and more

Summary Recommendation Created by
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First of all, here are the major changes since the last time this guideline was published:

- Use clinician- or patient-administered rating scales: Rating scales can assess the type, frequency, and magnitude of psychiatric symptoms to tailor the treatment plan to individual patient needs
- Strengthening of maintenance treatment recommendation: After the continuation phase of depression, maintenance treatment should be considered, especially for patients with risk factors for recurrence
- Aerobic exercise or resistance training: Mood symptoms may improve with aerobic exercise or resistance training, particularly in older adults and patients with co-occurring medical problems
- Electroconvulsive therapy (ECT) for treatment-resistant depression: Options for treatment-resistant depression include ECT, monoamine oxidase inhibitors, transcranial magnetic stimulation (TMS), and vagus nerve stimulation

In our clinical advisor's view, ECT is appropriate for using in these special cases:

- o Severe psychotic depression with severe suicidality, catatonia, or not eating — so that remission can occur as soon as possible
- o TMS now has much stronger evidence of effectiveness for treatment-resistant depression, including catatonia

Acute-Phase Treatment

For acute phase treatment, focus on remission of the depressive episode, achieving full return to baseline functioning, addressing co-occurring psychiatric disorders, such as substance abuse, and base treatment on MDD severity.

Our clinical advisor believes it is also crucial to address other medical comorbidities

Treatments Based on Severity

MDD Severity	Treatments			
	Pharmacotherapy	Psychotherapy (depression-focused)	Combination pharmacotherapy + psychotherapy	ECT
Mild to moderate	✓	✓	May be useful for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring Axis II disorder	✓ for certain patients
Severe without psychotic symptoms	✓	✗	✓	✓
Severe with psychotic symptoms	✓ Use both antidepressant and antipsychotic medication	✗	✓ Use both antidepressant and antipsychotic medication	✓

ECT = electroconvulsive therapy
Source: APA

When assessing suicide risk, look for:

- Presence of suicidal or homicidal ideation, intent, or plans
- History and seriousness of previous attempts
- Access to means for suicide and lethality potential
- 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

According to our clinical advisor, for patients with suicidal tendencies, lithium is the best option. Consider it when the patient has a strong family history of suicide, history of persistent suicidal ideation, or multiple attempts at suicide.

Selecting Antidepressants

Generally, antidepressants are similar between and within drug classes in terms of effectiveness. Consider patient factors relative to antidepressant characteristics. Patient factors include patient preference, prior response, and comorbidities. Antidepressant characteristics include efficacy, safety, potential drug interactions, duration of effect, and cost.

The best first-choice treatment for most patients are selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and bupropion.

Two complementary and alternative agents—S-adenosylmethionine (SAM-e) and St John's wort (SJW)—have modest evidence for efficacy. Note, however, that SJW causes frequent drug interactions.

Additionally, aerobic exercise or resistance training may improve mood symptoms, especially in older adults with comorbidities. Regular exercise may also reduce the prevalence of depressive symptoms in the general population.

Our clinical advisor believes that light therapy can also be considered.

Treatments to Avoid

Avoid first-line treatment with nonselective monoamine oxidase inhibitors (MAOIs). Dietary restrictions and potential drug interactions relegate which medications to use in patients unresponsive to other treatments. Also avoid using tricyclic antidepressants (TCAs). Most antidepressants are better tolerated than are TCAs.

SUMMARY OF RECOMMENDATION

Optimal antidepressants**SSRI**

(selective serotonin reuptake inhibitor)

Citalopram (Celexa)
 Escitalopram (Lexapro)
 Fluoxetine (Prozac, Sarafem, Prozac Weekly)
 Paroxetine (Paxil, Paxil CR)
 Sertraline (Zoloft)

DNRI

(dopamine-norepinephrine reuptake inhibitor)

Bupropion (Wellbutrin, Wellbutrin
 XL, Wellbutrin SR, Forfivo XL, Aplenzin)

SNRI

(serotonin-norepinephrine reuptake inhibitor)

Desvenlafaxine (Pristiq, Khedezla)
 Duloxetine (Cymbalta)
 Venlafaxine (Effexor, Effexor XL)

Norepinephrine-serotonin modulator

Mirtazapine (Remeron, Remeron SolTab)

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Keep in mind that the following antidepressants were approved and marketed after guideline publication:

- Vilazodone (Viibryd): SSRI/partial serotonin 5-HT_{1A} receptor agonist
- Vortioxetine (Trintellix): SSRI/serotonin 5-HT₃ receptor antagonist/serotonin 5-HT_{1A} receptor agonist
- Levomilnacipran (Fetzima): Isomer of milnacipran (SNRI)

Treatment Monitoring

Titrate antidepressants based on the patient's age, treatment setting, comorbidities, concurrent pharmacotherapy, and adverse events. When adverse events occur, lower the dose or switch treatments. Additionally, assess psychiatric symptoms for type, frequency, and magnitude.

The following charts provide an in-depth look at managing potential adverse reactions:

SUMMARY OF RECOMMENDATION		
Managing cardiovascular side effects		
Side effect	Associated antidepressant	Management ¹
Arrhythmias	TCAs	Avoid in patients with cardiac instability or ischemia; monitor for 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 (eg, labetalol, sodium nitroprusside) may be required
Increase in cholesterol	Mirtazapine	Add a statin
Orthostatic hypotension	TCAs, trazodone, nefazodone, MAOIs	Add fludrocortisone; add salt to diet

¹First try decreasing or discontinuing medication or switching to another antidepressant with a different side effect profile. These management suggestions are for situations in which medication is continued.
Source APA

SUMMARY OF RECOMMENDATION

Managing anticholinergic side effects

Side effect	Associated antidepressant	Management ¹
Constipation	TCAs	Encourage adequate hydration; add bulk laxative
Delirium	TCAs	Evaluate for other possible contributors to delirium
Dry mouth	TCAs	Suggest sugarless gum or candy
Urinary hesitancy	TCAs, SNRIs, bupropion	Add bethanechol
Visual changes	TCAs	Add pilocarpine eye drops

¹First try decreasing or discontinuing medication or switching to another antidepressant with a different side effect profile. These management suggestions are for situations in which medication is continued.
Source: APA

In Dr. Knight's experience, dry mouth can also result from taking SSRIs

SUMMARY OF RECOMMENDATION

Managing neurologic side effects

Side effect	Associated antidepressant	Management ¹
Headaches	SSRIs, SNRIs, bupropion	Assess for other etiologies (eg, caffeineism, bruxism, migraine, tension headache)
Myoclonus	TCAs, MAOIs	Add clonazepam
Seizures	Bupropion, TCAs, amoxapine	Assess for other etiologies; add anticonvulsant medication, if clinically indicated

¹First try decreasing or discontinuing medication or switching to another antidepressant with a different side effect profile. These management suggestions are for situations in which medication is continued.
Source : APA

According to Dr. Knight, seizures are more common with generic bupropion because the time to peak is very short

SUMMARY OF RECOMMENDATION

Managing sexual side effects

Side effect	Associated antidepressant	Management ¹
Arousal, erectile dysfunction	TCAs, SSRIs, SNRIs	Add phosphodiesterase-5 (PDE5) inhibitor (eg, sildenafil), buspirone, or bupropion
Orgasm dysfunction	TCAs, SSRIs, venlafaxine, desvenlafaxine, MAOIs	Add phosphodiesterase-5 (PDE5) inhibitor (eg, sildenafil), buspirone, or bupropion
Priapism	Trazodone	Obtain emergency urological evaluation

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Source: APA

SUMMARY OF RECOMMENDATION

Managing other side effects

Side effect	Associated antidepressant	Management ¹
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 (eg, terazosin), central α 2-adrenergic agonist (eg, clonidine), or anticholinergic agent (eg, 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

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Source: APA

According to Dr. Knight, many also need low dose benzodiazepine (especially with newer branded SNRIs and special SSRIs)

SUMMARY OF RECOMMENDATION

Managing other side effects

Side effect	Associated antidepressant	Management ¹
Gastrointestinal (GI) bleeding	SSRIs	Identify whether concomitant medications may affect clotting
Hepatotoxicity	Nefazodone	Provide education about symptoms and monitor for hepatic dysfunction; obtain liver function tests if clinically indicated
Insomnia	SSRIs, SNRIs, bupropion	Use morning dosing; add a sedative-hypnotic at bedtime; add melatonin; provide cognitive behavioral therapy <i>and</i> sleep hygiene education
Nausea, vomiting	SSRIs, SNRIs, bupropion	Administer after food or in divided doses

¹First try decreasing or discontinuing medication or switching to another antidepressant with a different side effect profile. These management suggestions are for situations in which medication is continued.

Source: APA

According to Dr. Knight, do not underestimate the importance of sleep hygiene education – it is a MUST!

SUMMARY OF RECOMMENDATION

Managing other side effects

Side effect	Associated antidepressant	Management ¹
Osteopenia	SSRIs	If clinically indicated, obtain bone density monitoring and add specific treatment to reduce bone loss (eg, 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 (SS)	MAOIs (SS may occur with SSRIs and SNRIs)	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 (eg, bupropion)

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Source: APA

According to Dr. Knight, watching for weight gain is essential. It is often treated by adding metformin. Some consider adding the herb gymnema 500 to 750 mg. Liraglutide can be added if metformin alone isn't successful

Treatment Response

Incomplete response is associated with poor functional outcomes. If improvement does not occur in 4 to 8 weeks, reconsider diagnosis, assess adverse effects and adherence to treatment, review comorbidities and psychosocial factors, adjust treatment plan, and consider consultation.

Continuation Phase

The continuation phase takes place in the 4 to 9 months after acute-phase treatment, usually with the same dose of antidepressant. During this phase, use a clinician- or patient-administered rating scale to assess treatment and tailor the treatment plan. It is essential to assess symptoms, side effects, adherence, and functional status. Depression-focused psychotherapy is recommended. Evidence suggests that cognitive behavioral therapy (CBT) is the best option. Continue pharmacotherapy in patients who respond to an acute course of ECT. Best evidence is to use lithium and nortriptyline. Alternatively, continue ECT in patients who responded to an acute ECT course, particularly if medication or psychotherapy does not maintain remission.

Maintenance Phase

Maintenance phase treatment should progress from continuation phase treatment in patients with 3 or more prior major depressive episodes or chronic depressive disorder.

Consider maintenance treatment in patients with additional risk factors for recurrence, including presence of residual symptoms, ongoing psychosocial stressors, early age at onset, and family history of mood disorders. Continue medication at full therapeutic dosage. If necessary, continue psychotherapy with less frequent sessions.

According to our clinical advisor:

- *Often psychotherapy sessions and other psychosocial interventions (such as yoga, exercise, and participation in support groups) are increased as medication is tapered*
- *CBT should include problem-solving therapy, behavioral activation therapy, and interpersonal therapy to, among other things, address social support issues*

Maintenance phase treatment may be required indefinitely, particularly in patients with chronic and recurrent MDD. Factors that play into duration are:

- Patient preference
- Type of treatment used
- Adverse effects
- Comorbid conditions
- Frequency and severity of previous depressive episodes, including psychosis and suicide risk
- Persistence of depressive symptoms after recovery

Discontinuing Treatment

Antidepressants should be tapered. Taper should occur over at least several weeks. Advise patients not to stop medications abruptly. To reduce the risk of discontinuation syndrome, taper slowly and temporarily switch to a longer half-life antidepressant. Warn patients about possibility of relapse and monitor for several months after discontinuation.

About the authors

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