

## Antidepressant Medications Selection

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### Antidepressant selection

Antidepressant selection requires a patient-centered needs assessment of treatment preference, personal or family history of response, individual risk of medication-specific adverse effects and drug interactions, concomitant medications and medical illnesses, cost or insurance coverage, and safety in overdose. Benefits and adverse effects of the antidepressants and therapeutic alternatives should be discussed with the patient and/or caregivers before therapy initiation to optimize adherence and prevent adverse reactions.

First-line antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, and vortioxetine, have similar efficacy in the treatment of depression (Kennedy 2016; USF 2015). These agents have better safety and tolerability than older-generation antidepressants, including TCAs and MAOIs.

Antidepressant choice may be narrowed by targeting predominant depressive symptoms and minimizing adverse effect propensity.

Patients with predominant fatigue symptoms may benefit from more stimulating antidepressants such as fluoxetine, SNRIs, or bupropion.

For many patients, anticholinergic adverse effects or weight gain may make options like the TCAs, paroxetine, or mirtazapine not preferred.

Serotonergic antidepressants interfere with platelet aggregation and may increase the risk of bleeding in patients at increased risk, such as those taking antiplatelet or anticoagulant therapy.

### Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors inhibit presynaptic serotonin reuptake and have only weak effects on norepinephrine and dopamine reuptake. Selective serotonin reuptake inhibitors can be differentiated by their pharmacokinetics and by each agent's unique pharmacodynamic characteristics.

For example, fluoxetine is a more stimulating antidepressant that is associated with weight loss.

Because of the activation a patient may have with fluoxetine, morning dosing is recommended.

Patients with comorbid anxiety may be more sensitive to the stimulating effects of fluoxetine and may require lower initial doses.

Sertraline is considered neither stimulating nor sedating, but it is associated with a greater incidence of diarrhea than other SSRIs. Lower initial doses and slower titration may help patients predisposed to this adverse effect.

Paroxetine may be more sedating and has a higher incidence of nausea, weight gain, sexual dysfunction, serotonin withdrawal syndrome, and anticholinergic effects.

The controlled-release form of paroxetine lessens the incidence of nausea but does not extend the duration of action significantly to prevent serotonin withdrawal syndrome in cases of abrupt discontinuation.

Unless the patient has comorbidities such as renal or hepatic insufficiency, anxiety, or advanced age, SSRIs may be initiated at a typical antidepressant therapeutic dose.

Common SSRI adverse effects include headache, dry mouth, nausea, diarrhea, insomnia, anxiety, and sexual dysfunction.

Rare but serious adverse effects of SSRIs include syndrome of inappropriate antidiuretic hormone and resultant hyponatremia, serotonin syndrome, increased bleeding, bruxism, and seizures.

### Serotonin-norepinephrine reuptake inhibitors

Serotonin-norepinephrine reuptake inhibitors inhibit both serotonin and norepinephrine reuptake and are weak inhibitors of dopamine reuptake.

Serotonin-norepinephrine reuptake inhibitors may be beneficial in patients with comorbid chronic pain conditions.

Unlike SSRIs, which may be initiated at typical therapeutic doses, SNRIs, with the exception of desvenlafaxine, require dose titration to improve tolerability.

Of importance, the clinician should ensure that dose increases are continually titrated to effective daily doses. Venlafaxine requires dose titration to at least 150 mg daily to show significant norepinephrine reuptake inhibition activity.

At doses of less than 150 mg daily, venlafaxine acts as an SSRI.

Common adverse effects of venlafaxine include dose-related increases in blood pressure and serotonin withdrawal symptoms with missed doses.

Desvenlafaxine, the major active metabolite of venlafaxine, has norepinephrine reuptake activity at all doses and an adverse effect profile similar to venlafaxine.

Duloxetine has SNRI activity at all doses and has FDA-approved indications for neuropathic and nociceptive pain syndromes.

Caution should be used with duloxetine in renal insufficiency, and use is not recommended for patients with a CrCl of 30 mL/minute/1.73m<sup>2</sup> or less.

Duloxetine carries a risk of hepatotoxicity and is not recommended in hepatic impairment.

Rare but serious adverse effects include increased heart rate, urinary retention, narrow-angle glaucoma, increased hepatic enzymes, bruxism, and serotonin syndrome.

### Esketamine

Esketamine nasal spray is approved for the treatment of treatment-resistant depression in adults, in conjunction with an oral antidepressant. Esketamine may meet the unmet medical need for a rapid-acting drug that can interrupt a severe major depressive episode and

decrease the risk of suicide in patients with treatment-resistant depression; safety and efficacy of esketamine are supported by 5 phase 3 clinical studies demonstrating clinically meaningful, rapid, and sustained improvement in depressive symptoms in this population. However, esketamine has a high potential for abuse and diversion, which is one of the reasons for the required REMS program. Access to this product will be limited and it must be dispensed in certified health care settings. Additional studies are needed to determine optimal duration of therapy; potential as monotherapy; most effective concomitant antidepressant options; and the safety of prolonged therapy [1].

Recommended Esketamine Dosage		
Treatment Phase	Point in Care	Adult Dose
Induction	Weeks 1 to 4: Administer twice per week	Day 1 starting dose: 56 mg
		Subsequent doses: 56 mg or 84 mg
Maintenance	Weeks 5 to 8: Administer once weekly	56 mg or 84 mg
	Weeks 9 and after: Administer every 2 weeks or once weekly	56 mg or 84 mg

**Bibliography**

1. PSAP 2018 Book 3, Neurology/Psychiatry. ISBN-13: 978-1-939862-77-8.

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