Choosing and Switching Antidepressants

(Modified April 2024)

Less than one-third of patients achieve remission with the first antidepressant tried.[23] **Switching** is a common strategy if there is no response four to six weeks after dose optimization, or the patient cannot tolerate an adequate dose.[1,5] There is no robust evidence for switching to a drug in a different class.[1,3,5,31] Other options include switching to or adding cognitive behavioral therapy, or pharmacologic combination treatment.[5,34] A pharmacologic combination treatment strategy should be considered after two antidepressant trials.[1] The chart below provides practical considerations for choosing and switching antidepressants. Consult product labeling regarding switching to/from MAOIs.

Choice of Agent (Agents not typically used as initial therapy [e.g., MAOIs, trazodone, TCAs, gepirone[e]] not included below.)

Choose an agent based on side effects, personal or family response history, drug interactions, comorbidities, and cost.[1,36] Some clinicians target specific depression symptoms (e.g., pain, fatigue, insomnia, anxiety).[17] Non-MAOIs with the highest risk of drug interactions include fluoxetine, fluvoxamine, and paroxetine.[1] Those with the lowest risk of drug interactions include citalopram, escitalopram, mirtazapine, venlafaxine, and desvenlafaxine.[1] Dose antidepressants cautiously in elderly (e.g., half the usual starting dose).[5]

Drug/Class	Consider for…		Avoid or use particular caution in…
SSRI	• anxiety disorder or anxious distress[1,2] (start with low dose;[2] indications vary) • coronary disease or CHF (sertraline)[8,9] • adolescents (fluoxetine, sertraline, escitalopram)[25,28] • constipation (sertraline)[1] • psychomotor slowing (fluoxetine)[17]	• overweight or obese patients (fluoxetine)[2] • pregnancy (sertraline)[35] • postpartum depression (citalopram, escitalopram, sertraline)[38,39]	• overweight or obese patients (paroxetine)[2] • QT prolongation or torsades risk (citalopram, escitalopram, fluoxetine, sertraline)[34] • agitation or insomnia (fluoxetine)[1,17] • elderly (paroxetine)[21]
SNRI	• psychomotor slowing (duloxetine)[1] • pain related to depression, fibromyalgia, or neuropathy[1]	• anxiety disorder or anxious distress[1,2] (indications vary)	• hypertension[2] • agitation or insomnia[2] • QT prolongation (venlafaxine)[34]
Mirtazapine	• agitation[4] • insomnia (doses ≤15 mg)[1,5]	• sexual dysfunction concern[1] • underweight patients[34]	• overweight or obese patients[5] • hyperlipidemia[2] • QT prolongation[34]
Bupropion[b]	• sexual dysfunction concern[5] • smokers[5]	• psychomotor slowing/fatigue[1] • overweight or obese patients[5]	• seizure disorders[34] • hypertension[19] • anxiety or insomnia[17]
Vilazodone[a]	• sexual dysfunction concern[34] • underweight[34]	• cognitive dysfunction[15]	• If GI side effects are of particular concern[1]
Vortioxetine	• cognitive dysfunction[1]	• overweight or obese patients[5]	• If GI side effects are of particular concern[5]

Choice of Agent, continued

Drug/Class	Consider for…	Avoid or use particular caution in…
Brexanolone (*Zulresso*) (US)	• severe and/or recalcitrant postpartum depression (due to administration complexity and cost [~$30,000[c]]) with onset up to six months after delivery (based on study inclusion criteria), alone or with another antidepressant.[40,41] o Requires a 60-hour infusion in a REMS-certified healthcare facility to monitor for sedation and oxygen desaturation. Patient/child interactions must be supervised during this time.[40] o Onset 24 to 48 hours.[41] Efficacy past 30 days is unknown.[40]	• Patients without reliable childcare during treatment[40] • Patients at risk of suicide or with a history of psychosis (based on study exclusion criteria)[41] • Pregnancy[41]
Zuranolone (*Zurzuvae*)	• Severe depression with symptom onset during the third trimester or up to four weeks after delivery, alone or with another antidepressant.[42] o Onset by third treatment day.[42] Efficacy past 45 days is unknown.[42] o 14-day course costs ~$16,000[c]	• Patients at risk of suicide or with a history of psychosis (based on study exclusion criteria)[42] • Patients who must drive or engage in hazardous activities.[42] • Pregnancy; effective contraception needed during and for one week after treatment[43]

Switching. Evidence-based options for a second agent, due to evidence of superiority, include **sertraline**, **escitalopram**, **venlafaxine**, **mirtazapine**,[1] **vortioxetine**,[24] or **bupropion**.[3] For general information of switching strategies (i.e., abruptly switching vs tapering/cross-tapering) is available in **footnote d**.

Switching Scenario	Suggested Approach Note: keep drug interactions, side effects, and illness severity in mind when choosing method/dose.[30]
SSRI (other than fluoxetine) to another SSRI	• Stop SSRI.[7,10] Start new SSRI at a low dose (e.g., citalopram, escitalopram, or paroxetine 10 mg/day; sertraline 25 mg/day; or fluoxetine 20 mg every other day).[3,27,30] **Or**, stop the first agent and start a dose of the new agent that is in the same range as the first agent (i.e., low, moderate, high).[7] • If the patient was taking a high dose of the first agent, consider tapering to a lower dose before starting the new agent.[10] • **Or**, cross-taper.[30] If cross-tapering from paroxetine, a conservative taper is 25% every four to six weeks, or for paroxetine CR, 12.5 mg weekly.[6,27] • If switching to/from fluvoxamine, cross-tapering is not recommended; taper and stop SSRI before starting new agent at a low dose (e.g., fluvoxamine 50 mg/day).[30]
SSRI (other than fluoxetine) to duloxetine	• Stop SSRI and start duloxetine 60 mg once daily [Evidence level B-1].[11,18] **Or**, start duloxetine 60 mg once daily and taper SSRI over two weeks.[11] • Keep in mind some antidepressants can inhibit duloxetine metabolism through CYP2D6 (e.g., fluoxetine, paroxetine) or CYP1A2 (e.g., fluvoxamine) inhibition until the SSRI is cleared.[14] • If switching from fluvoxamine, cross-tapering is not recommended; taper and stop fluvoxamine before starting duloxetine, at a low dose (e.g., 30 mg once daily).[19,30]

Switching Scenario	**Suggested Approach** Note: keep drug interactions, side effects, and illness severity in mind when choosing method/dose.[30]
SSRI (other than fluoxetine) to venlafaxine	• Stop SSRI and start venlafaxine at a low dose (e.g., 37.5 mg to 75 mg total daily dose).[3,7,18,19] ○ If the patient was taking a high dose of an SSRI, consider tapering to a lower dose before stopping it and starting venlafaxine.[10] • **Or**, another option is to cross-taper cautiously, starting with low dose of venlafaxine.[30] • Some antidepressants (e.g., paroxetine) can inhibit venlafaxine metabolism through CYP2D6 inhibition until the SSRI is cleared.[7] If switching from fluvoxamine, cross-tapering is not recommended; taper and stop fluvoxamine before starting venlafaxine, at a low dose (e.g., 37.5 mg to 75 mg total daily dose).[19,30]
SSRI (other than fluoxetine) to mirtazapine	• Cross-taper.[27] If cross-tapering from paroxetine, a conservative taper is 25% every four to six weeks, or for paroxetine CR, 12.5 mg weekly.[6,27] • **Or**, taper the SSRI to the minimum therapeutic dose (e.g., paroxetine 20 mg once daily, sertraline 50 mg once daily), then switch to mirtazapine 15 mg once daily [Evidence level B-1].[20] • If switching from fluvoxamine, cross-tapering is not recommended; taper and stop fluvoxamine before starting mirtazapine, at a low dose (e.g., mirtazapine 15 mg at bedtime).[19,30]
Venlafaxine to an SSRI	• Stop venlafaxine and start the SSRI at a therapeutic dose.[7,18] ○ If the patient was taking a high dose of venlafaxine, consider tapering to a lower dose before stopping it and starting the new agent.[10] • **Or**, cross-taper, starting the new SSRI at a low dose (e.g., citalopram, escitalopram, or paroxetine 10 mg/day; sertraline 25 mg/day).[27,30] • If switching to fluoxetine or fluvoxamine, cross-tapering is not recommended; taper and stop venlafaxine and start fluoxetine at 10 mg/day or fluvoxamine at 50 mg/day.[30] • A conservative taper for venlafaxine is 25% every four to six weeks,[6] or for venlafaxine ER 37.5 to 75 mg weekly.[27]
Venlafaxine to duloxetine	• If the venlafaxine dose is <150 mg/day,[27] stop venlafaxine and start duloxetine 60 mg once daily [Evidence level B; nonrandomized clinical trial].[18] • If the patient was taking a high dose of venlafaxine (e.g., ≥150 mg per day), consider tapering over four weeks before stopping it and starting duloxetine 60 mg every other day.[10,27] • **Or**, cross-taper over two to three weeks.[27,30]
Venlafaxine or duloxetine to mirtazapine	• Taper and stop SNRI, then start mirtazapine at a low dose (e.g., 15 mg at bedtime).[19,30] • **Or**, cross-taper, starting mirtazapine at a low dose (e.g., 15 mg at bedtime).[19,30]

Switching Scenario	**Suggested Approach** Note: keep drug interactions, side effects, and illness severity in mind when choosing method/dose.[30]
Duloxetine to an SSRI	• If duloxetine dose is <60 mg/day, start SSRI at a therapeutic dose.[7,18,27] • If the patient was taking duloxetine ≥60 mg/day, consider tapering to a lower dose before stopping it and starting the new agent.[10] • **Or**, cross-taper, starting SSRI at a low dose (e.g., citalopram, escitalopram, or paroxetine 10 mg/day; sertraline 25 mg/day).[27,30] • If switching to fluoxetine or fluvoxamine, cross-tapering is not recommended; taper and stop duloxetine and start fluoxetine at 10 mg/day or fluvoxamine at 50 mg/day.[30]
Duloxetine to venlafaxine	• Stop duloxetine and start venlafaxine at a therapeutic dose (e.g., 75 mg total daily dose)[7,18,19] • If the patient was taking a high dose of duloxetine (e.g., 60 mg/day), consider tapering to a lower dose before stopping it and starting venlafaxine.[10] • **Or**, cross-taper, starting venlafaxine at a low dose (e.g., 37.5 mg to 75 mg total daily dose).[19,30]
Fluoxetine to another SSRI	• Stop fluoxetine (taper if dose >40 mg/day).[30] Start new SSRI after a seven-day washout.[30] Start new agent at a low dose (e.g., citalopram, escitalopram, or paroxetine 10 mg/day; sertraline 25 mg/day).[27] • If switching to fluvoxamine, start at a dose of 50 mg/day after a 14-day washout.[30] • Cross-tapering is not recommended.[30]
Fluoxetine to mirtazapine	• Stop fluoxetine (taper if dose >40 mg/day). Start mirtazapine at a low dose (e.g., 15 mg at bedtime).[19,30] • **Or**, taper fluoxetine to 20 mg once daily, then switch to mirtazapine 15 mg once daily [Evidence level B-1].[20]
Fluoxetine to venlafaxine or duloxetine	• Taper and stop fluoxetine.[30] After a four- to seven-day washout, start SNRI at a low dose (duloxetine 60 mg/day or venlafaxine 37.5 mg/day).[11,27,30] • Cross-tapering is not recommended.[30]
Bupropion to/from another agent	• Cross-taper.[7] Consider reducing bupropion dose over one week, although withdrawal is not common.[27]
Mirtazapine to an SSRI or SNRI	• Cross-taper.[27,29] Consider reducing mirtazapine over four weeks, although withdrawal is rare.[27] If switching to duloxetine, start with 60 mg every-other day or 30 mg once daily.[27,29] • **Or**, switch abruptly to an approximately equivalent dose of an SSRI.[27] • **Or**, taper mirtazapine, then switch to an SSRI.[27]

Switching Scenario	**Suggested Approach** Note: keep drug interactions, side effects, and illness severity in mind when choosing method/dose.[30]
Switching to/from vortioxetine (*Trintellix*)	• Data are limited; use extra caution.[29] • When switching **to vortioxetine**, note that strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine) can increase vortioxetine levels.[13] Start with vortioxetine 5 mg once daily (i.e., half of the usual starting dose) when cross-tapering or switching abruptly from these agents, other SSRIs, venlafaxine, or duloxetine, or in a patient taking any strong CYP2D6 inhibitor.[13,16,23,30] • When switching **from vortioxetine**, reduce dose to ≤10 mg for one week.[13] Then, if switching to: o An SSRI, SNRI, mirtazapine, or bupropion, stop vortioxetine and add the new agent at a low dose (fluoxetine 10 mg/day, fluvoxamine 50 mg/day).[13,30] • Alternatively, consider one of the following options: ▪ cautious cross-tapering starting with a low dose of an SSRI (excluding fluoxetine and fluvoxamine), SNRI, or mirtazapine.[29,30] ▪ an abrupt switch to duloxetine 60 mg/day.[29]
Switching to/from vilazodone (*Viibryd*)	• Switching **to vilazodone**. Generally cross-taper.[37] Follow manufacturer's recommended titration schedule when starting vilazodone (*Viibryd*). • Switching **from vilazodone**. Generally cross-taper, reducing vilazodone by 10 mg/week.[37]
Switching to/from desvenlafaxine (e.g., *Pristiq*).	• Information is limited.[27] Consider management as for venlafaxine, given similarities.
Switching to/from levomilnacipran (*Fetzima*)	• Switching **from levomilnacipran**: generally cross-taper, reducing levomilnacipran dose by 20 mg/week.[37] • Switching **to levomilnacipran**: generally cross-taper.[37]

a. Vilazodone is not a first-line agent per Canadian guidelines due to lack of head-to-head or relapse data and need to titrate and take with food.[1]

b. *Auvelity* (US) contains bupropion and dextromethorphan. Dextromethorphan is an NMDA (N-methyl-D-aspartate) receptor antagonist, but its mechanism in depression is unclear.[32] Bupropion boosts dextromethorphan levels via CYP2D6 inhibition.[32] There is no proof that dextromethorphan alone is effective for depression. There is no proof that *Auvelity* is better than standard-dose bupropion (e.g., bupropion 150 mg twice or 300 mg once daily). *Auvelity* use with other dextromethorphan-containing products (e.g., cough or cold medicine) could cause neuropsychiatric adverse effects (e.g., psychosis, stupor, seizures).[32] Serotonin syndrome could result from extra dextromethorphan use, or *Auvelity* use with serotonergic drugs (e.g., linezolid, serotonergic antidepressants).[32,33]

c. Wholesale Acquisition Cost (WAC). Medication pricing by Elsevier, accessed January 2024.

d. Limited available evidence suggests that abruptly switching (i.e., direct switch) from one **short-acting** SSRI or SNRI to another SSRI or SNRI is generally well-tolerated.[3,7,10] Transient serotonergic side effects (e.g., anxiety) may occur early in the switch, but this is not usually a safety issue, and a direct switch is usually better tolerated than a washout if the first agent is short-acting. **TAPERING/CROSS-TAPERING** (i.e., gradually

increasing the new agent [often starting with a lower dose than usual] while decreasing the first agent):[22] Tapering may be more appropriate in some cases due to two concerns when switching: symptom recurrence and discontinuation syndromes.[12,30] Discontinuation syndromes are of most concern when switching from a serotonergic agent to a nonserotonergic agent, particularly when switching **from venlafaxine** or **paroxetine**.[2,7] Consider tapering any antidepressant taken for more than one week.[27] Fluoxetine and bupropion may not need tapering.[6,26,27] For others, consider tapering over several weeks unless there is a clinical reason not to.[30] Monitor patient and adjust switching strategy (e.g., speed of taper) based on symptoms of withdrawal, side effects, or return of depressive symptoms.[2,10] Consider increasing the dose of the serotonergic agent if withdrawal symptoms emerge (e.g., "GI flu"-like symptoms, paresthesias, irritability, insomnia, dizziness, vivid dreams).[10] Individual symptoms could also be treated (e.g., meclizine for dizziness).[27] A resource for switching is https://switchrx.com/antidepressants.php/switch.

e. Gepirone [*Exxua*, US] is a selective serotonin 5HT1A receptor agonist.[44] It has not been shown to be more effective than other antidepressants, and is more expensive than generic first-line agents. Long-term data is limited. Common adverse effects include dizziness, nausea, and headache.[44] It requires baseline and periodic electrocardiographic monitoring due to risk of QT prolongation, and has significant interactions with CYP3A4 inhibitors.[44] Additionally, dose adjustments are required for older adults and for patients with kidney or liver impairment.[44]

Abbreviations: CHF = congestive heart failure; GI = gastrointestinal; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. 2004 Feb 1;69(3):548-56.
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