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Choosing and Switching Antidepressants

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 not robust evidence for switching to a drug in a different class.[1,3,5,31] Patients who fail two antidepressants in the same class should try a different class (consider venlafaxine), or combination treatement.[5] The chart below provides practical considerations for choosing and switching antidepressants. Consult product labeling regarding switching to/from MAOIs.

Abbreviations: CV – cardiovascular; GAD – generalized anxiety disorder; MAOI – monoamine oxidase inhibitor; OCD – obsessive compulsive disorder; SSRI – selective serotonin reuptake inhibitor; SNRI – serotonin norepinephrine reuptake inhibitor

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

Choose an agent based on side effects, personal or family response history, drug interactions, comorbidities, and cost.[2] Some clinicians target specific depression symptoms (e.g., pain, fatigue, insomnia, anxiety).[17] Non-MAOI agents with the highest risk of drug interactions include fluoxetine, fluvoxamine, and paroxetine.[1] Those with the lowest include citalopram, escitalopram, mirtazapine, venlafaxine, and desvenlafaxine.[1] Fluoxetine is well-tolerated.[25] 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 disorders (start with low dose;[2] indications vary) • CV disease (sertraline)[8,9] • adolescents (fluoxetine, sertraline, escitalopram)[25,28] • underweight (paroxetine)[17]	• psychomotor slowing (fluoxetine)[17] • insomnia (paroxetine)[17] • overweight or obese patients (fluoxetine)[2]	• overweight or obese patients (paroxetine)[2] • QT prolongation or torsades risk • agitation or insomnia (fluoxetine)[1,17] • pregnancy • elderly (paroxetine)[21]
SNRI	• psychomotor slowing (duloxetine)[1] • pain related to depression, fibromyalgia, or neuropathy.[1]	• anxiety disorders (start with low dose;[2] indications vary)	• hypertension[2] • agitation or insomnia[2]
Mirtazapine	• agitation[4] • insomnia[5]	• sexual dysfunction concern[5] • underweight patients[5]	• overweight or obese patients[5] • hyperlipidemia[2]
Bupropion	• sexual dysfunction concern[5] • smokers[5]	• psychomotor slowing/fatigue[1] • overweight or obese patients[5]	• seizure disorders[5] • hypertension[5] • anxiety or insomnia[17]
Vilazodone[a] or Vortioxetine	• sexual dysfunction concern[15,24] • overweight or obese patients[15,24]	• cognitive dysfunction[1,15]	• if nausea is a particular concern[1]

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Switching

Evidence-based options for a second agent, due to evidence of superiority, include **sertraline**, **escitalopram**, **venlafaxine**, **mirtazapine**,[1] **vortioxetine**,[24] or **bupropion**.[3] 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 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.[7]

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.[2,12] 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] Vortioxetine can be tapered by 10 mg/day over seven days.[29] For others, consider tapering over several weeks unless there is a clinical reason not to.[1,2] A conservative taper for paroxetine or venlafaxine is 25% every four to six weeks,[6] or for venlafaxine ER 37.5 to 75 mg weekly or paroxetine CR 12.5 mg weekly.[27] 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] Could also treat individual symptoms (e.g., meclizine for dizziness).[27]

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 paroxetine10 mg/day; sertraline 25 mg/day; or fluoxetine 20 mg every-other-day).[3,27,30] 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**, 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] **Or**, cross-taper.[30] 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 could 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.[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] Cautious cross-taper, starting with low dose of venlafaxine, is another option.[30] Some antidepressants (e.g., paroxetine) could 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]

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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 mirtazapine	Cross-taper.[27] **Or**, taper 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] **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 the patient was taking a high dose of venlafaxine, consider tapering to a lower dose before stopping it and starting the new agent.[10] 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]
Venlafaxine to duloxetine	Stop venlafaxine and start duloxetine 60 mg once daily [Evidence level B; nonrandomized clinical trial][18] if venlafaxine dose is <150 mg/day.[27] 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]
Duloxetine to an SSRI	Stop duloxetine (if <60 mg/day) and start SSRI at a therapeutic dose.[7,18,27] If the patient was taking a higher dose of duloxetine, 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 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]

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Switching Scenario	**Suggested Approach** Note: keep drug interactions, side effects, and illness severity in mind when choosing method/dose.[30]
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 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 to/from vortioxetine (*Trintellix*)	Data limited; use extra caution.[30] Note that strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine) can increase vortioxetine levels. Consider starting with vortioxetine 5 mg once daily (i.e., half of the usual starting dose) when cross-tapering or switching abruptly from one of these agents, other SSRIs, venlafaxine, or duloxetine, or in patient taking a strong CYP2D6 inhibitor.[13,16,23,30] When switching **from vortioxetine** to fluoxetine or fluvoxamine, taper vortioxetine over seven days to 10 mg/day, then stop and add new agent at a low dose (fluoxetine 10 mg/day or fluvoxamine 50 mg/day).[29,30] When switching to other SSRIs, SNRIs, or mirtazapine, first taper and stop vortioxetine, or cross-taper, starting SSRI or SNRI at a low dose (e.g., duloxetine 60 mg/day).[29,30] Can switch abruptly to duloxetine 60 mg/day.[29] Cautious cross-tapering is recommended when switching to mirtazapine.[29]
Switching to/from vilazodone (*Viibryd*)	Follow manufacturer's recommended titration schedule when starting vilazodone (*Viibryd*).
Switching to/from desvenlafaxine (e.g., *Pristiq*) or levomilnacipran (*Fetzima*)	Information limited.[27] Consider managing as for venlafaxine due to similar mechanism of action.[30]

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]

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.

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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 RCT 2. 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).
RCT = randomized controlled trial; **SR** = systematic review
[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;69:548-56. http://www.aafp.org/afp/2004/0201/p548.pdf.]

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