Choosing and Switching Antidepressants

- Up to 2/3 of patients don't achieve remission with the first antidepressant that's tried.[1]
- Switching is a common strategy if there is no response 4 to 8 weeks after dose optimization, or the patient cannot tolerate an adequate dose.[2]
- A patient may respond better to a drug in a different class but is equally as likely to respond to another drug in the same class.[3]
- Once a patient has failed two drugs in the same class, consider a drug from a different class.[2]
- Chart below provides practical considerations for choosing and switching antidepressants. Consult product labeling regarding switching to/from MAOIs.
- Frail elderly and those with comorbid anxiety require lower initial doses and slower titration. Initial dose may be reduced by 50%. If starting with bupropion or venlafaxine, start with immediate-release formulation then titrate to optimal dose before switching to extended-release formulation.

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; others believe an effective antidepressant will eventually resolve all symptoms.[17] Non-MAOI agents with the highest risk of drug interactions include fluoxetine, fluvoxamine, paroxetine, and sertraline.[1] Those with the lowest include citalopram, escitalopram, mirtazapine, venlafaxine, and desvenlafaxine.[1] Dose all agents cautiously in elderly.[2]

Antidepressant or Antidepressant Class	Consider for…	Avoid or use particular caution in…
SSRI • Citalopram (Celexa) • Escitalopram (Lexapro) • Fluoxetine (Prozac) • Fluvoxamine (Luvox) • Paroxetine (Paxil) • Sertraline (Zoloft) • Vilazodone (Viibryd)	Anxiety disorders (start with low dose; indications vary)[2,4,16] CV disease (sertraline)[8,9] Young adults[1,4] (Fluoxetine: Depression /OCD) Underweight (paroxetine)[17] Psychomotor slowing (fluoxetine, sertraline)[17] Insomnia (paroxetine)[17] Overweight or obese patients (fluoxetine)[2] Elderly (sertraline – fewer drug interactions/cognitive effects)	Overweight or obese patients (paroxetine)[17] QT prolongation or torsades risk (citalopram)[15] Agitation or insomnia (fluoxetine, sertraline)[17] Pregnancy (paroxetine, fluoxetine)[2] Elderly (paroxetine, citalopram – requires dose adjustment)
SNRI • Desvenlafaxine • Duloxetine • Levomilnacipran • Venlafaxine	Adults <65[4] Psychomotor slowing[4] Chronic pain[4] Anxiety disorders (start with low dose; indications vary)[2,16]	Hypertension[2] Agitation or insomnia[2]
Mirtazapine (Remeron)	Agitation[4] Insomnia[2] Sexual dysfunction concern[2,5] Underweight patients[2]	Overweight or obese patients[2] Hyperlipidemia[2]
Bupropion	Sexual dysfunction concern[2,5] Smokers[2] Psychomotor slowing[4] Fatigue or sleepiness[2] Overweight or obese patients[2] Pediatrics: Depression, refractory to SSRIs: Limited data available	Seizure disorders[2] Hypertension[15] Agitation or insomnia[17]
Vortioxetine (Brintellix)	Overweight or obese patients[24] Sexual dysfunction concern[24] Psychomotor slowing[24]	Patients in whom nausea is a particular conern[23]

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

Switching / Tapering

- Evidence-based options for a second agent, due to evidence of superiority, include sertraline, escitalopram, duloxetine, venlafaxine, mirtazapine,[1] 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]
    - Taper paroxetine over at least 4 weeks.
    - Taper other SSRIs, venlafaxine, and duloxetine over 1 to 4 weeks (e.g., sertraline or venlafaxine, by 25 to 50 mg/day every one to two weeks; paroxetine or citalopram by 5 to 10 mg/day every one to 2 weeks; escitalopram by 5 mg/day every 1 to 2 weeks).[6,17]
- There is no "one size fits all" approach. Monitor patient and adjust switching strategy (e.g., speed of taper) based on symptoms of withdrawal, side effects, or return of depressive symptoms.[2.6.10]
- 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]

Switching Scenario	Suggested Approach
SSRI (other than fluoxetine) to another SSRI	Stop SSRI.[7,10] Start new SSRI at a low dose (e.g., fluoxetine, citalopram, escitalopram 10 mg/day; sertraline 25 mg to 50 mg/day).[3,6] If patient was taking a high dose of the first agent, consider tapering to lower dose before starting the new agent.[10] Or, stop the first agent and start a dose of the new agent in the same range as the first agent (i.e., low, moderate, high).[7] Keep drug interactions / side effects in mind when choosing dose.
SSRI (other than fluoxetine) to duloxetine	Stop SSRI and start duloxetine 60 mg once daily [Evidence level B; lower quality RCT; nonrandomized clinical trial].[11,18] Or, start duloxetine 60 mg once daily and taper SSRI over two weeks.[11] Keep in mind some antidepressants (e.g., paroxetine) could inhibit duloxetine metabolism through CYP2D6 inhibition until the SSRI is cleared.[14]
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] Or cross-taper, starting with venlafaxine 37.5 mg once daily.[6] Increase very slowly.[6] If the patient was taking a high dose of an SSRI, consider tapering to a lower dose before stopping it and starting venlafaxine.[10] Keep drug interactions and side effects in mind when choosing method/dose. Some antidepressants (e.g., paroxetine) could inhibit venlafaxine metabolism through CYP2D6 inhibition until the SSRI is cleared.[7]
SSRI (other than fluoxetine) to mirtazapine	**Cross-tapering.**[6,7] 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; lower quality RCT].[20]
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., fluoxetine, citalopram, escitalopram, or paroxetine 10 mg/day; sertraline 25 mg/day).[6] Increase as tolerated.[6] 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] Keep drug interactions / side effects in mind when choosing method/dose.
Venlafaxine to duloxetine	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 to a lower dose before stopping it and starting duloxetine.[10] Keep drug interactions and side effects in mind when choosing method/dose.
Venlafaxine to mirtazapine.	Cross-tapering.[6]
Duloxetine to SSRI	Stop duloxetine and start SSRI at a therapeutic dose.[7,18] Or cross-taper, starting new antidepressant at low dose (e.g., citalopram or escitalopram 10 mg/day sertraline 25 mg/day).[6] Increase as tolerated.[6] If the patient was taking a high dose of duloxetine, consider tapering to a lower dose before stopping it and starting the new agent.[10] Keep drug interactions and side effects in mind when choosing method/dose. If switching to fluoxetine or paroxetine, cross-tapering is not recommended.[6] These agents may increase duloxetine levels through CYP2D6 inhibition.[14]

Switching Scenario	Suggested Approach
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, consider tapering to a lower dose before stopping it and starting venlafaxine.[10] Keep drug interactions and side effects in mind when choosing method/dose.
Fluoxetine (e.g., *Prozac*) to another SSRI	Stop fluoxetine (taper over two weeks if dose >20 mg/day). Start new antidepressant after a four- to seven-day washout. Start new agent at a low dose (e.g., citalopram, escitalopram, paroxetine 10 mg/day; sertraline 25 mg/day) and increase slowly.[6]
Fluoxetine (e.g., *Prozac*) to mirtazapine	Taper fluoxetine while starting mirtazapine 15 mg once daily. Increase as tolerated.[6] Or, taper fluoxetine to 20 mg once daily, then switch to mirtazapine 15 mg once daily [Evidence level B; lower quality RCT].[20]
Fluoxetine to venlafaxine	Stop fluoxetine (taper over two weeks if dose >20 mg/day).[6] Consider a four- to seven-day washout. Start venlafaxine 37.5 mg once daily and increase very slowly.[6]
Fluoxetine to duloxetine	Stop fluoxetine (taper over two weeks if dose >20 mg/day).[6] Consider a four- to seven-day washout. Start duloxetine 60 mg once daily.[6,11]
Bupropion to/from another agent	Cross-tapering.[7]
Mirtazapine to SSRI or SNRI	Cross-tapering (e.g., start with duloxetine 30 mg once daily).[6,7]
Switching to/from vilazodone (*Viibryd*) or vortioxetine (*Brintellix* [U.S.]; *Trintellix* [Canada])	Information lacking. Consider managing as for SSRIs due to serotonergic mechanism. Note 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 or patient is taking a strong CYP2D6 inhibitor.[13,23] Follow manufacturer's recommended titration schedule when starting vilazodone (*Viibryd*).
Switching to/from desvenlafaxine (e.g., *Pristiq*) or levomilnacipran (*Fetzima*)	Information lacking. Consider managing as for venlafaxine due to similar mechanism of action.

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT)
	High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial
	Nonquantitative systematic review
	Lower quality RCT
	Clinical cohort study
	Case-control study / Historical control
	Epidemiologic study
C	Consensus / Expert opinion
D	Anecdotal evidence / In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. Am Fam Physician 2002;65:251-8.

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