Switching antidepressant medications in adults

AUTHORS: Michael Hirsch, MD, Robert J Birnbaum, MD, PhD
SECTION EDITOR: Peter P Roy-Byrne, MD
DEPUTY EDITOR: David Solomon, MD

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INTRODUCTION

When patients respond poorly to an antidepressant medication or exhibit intolerable side effects, and switching to another antidepressant is indicated, clinicians should be familiar with the pharmacology of each drug, the potential for drug-drug interactions and discontinuation symptoms, and the time to onset of effectiveness of the new medication.

Switches from one antidepressant to another are common. A study of an administrative claims database found that among patients (n >130,000) who started antidepressant monotherapy for a new episode of depression, switching occurred in 9 percent [1].

This topic discusses switching from one antidepressant drug to another. Discontinuing antidepressants without switching to another drug and choosing a specific antidepressant regimen for the initial treatment of depression or for treatment-resistant depression are discussed separately, as are the pharmacology, administration, and side effects of different antidepressant classes.

- (See "Discontinuing antidepressant medications in adults".)
- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

- (See "Atypical antidepressants: Pharmacology, administration, and side effects".)
- (See "Serotonin modulators: Pharmacology, administration, and side effects".)
- (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)
- (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

SWITCHING ANTIDEPRESSANT MEDICATIONS

Issues to consider when switching antidepressants include preventing:

- Drug-drug interactions
- Discontinuation symptoms (see "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome')
- Relapse of depression

Standard approach and alternatives — Factors that are involved in choosing a strategy for switching antidepressants include the risk of discontinuation symptoms, potential for drug interactions, other antidepressant properties such as elimination half-life, adverse effects, and pharmacodynamics, and the how quickly symptoms need to be controlled.

The standard technique for many drug switches is cross-tapering [2]. This approach can minimize the risk of drug-drug interactions, while at the same time prevent both discontinuation and depressive symptoms that may occur from abrupt drug withdrawal. In a cross-taper, the dose of the current antidepressant is gradually reduced to zero, while simultaneously the new antidepressant is started and titrated up to the therapeutic range. Cross-tapering typically occurs over one or two weeks, but for patients who have previously demonstrated sensitivity to side effects or discontinuation symptoms, cross-tapering is extended over three to four weeks. In tapering and discontinuing the current medication, clinicians can reduce the dose by the same number of milligrams (amount) each time the dose is decreased, or by the same percent (eg, 50 percent) each time. In titrating up the new medication, one generally increases the dose by the same amount each time the dose is increased. Cross-tapering is consistent with multiple treatment guidelines [3-7].

However, cross-tapering is contraindicated if patients are switched to or from a monoamine oxidase inhibitor (MAOI). (See 'Switching to or from MAOIs' below.)

In certain situations, another alternative to cross-tapering is directly (immediately) switching from one antidepressant to another. In a direct switch, the current antidepressant is abruptly

stopped and the new drug is started the next day at the equivalent dose (table 1 and table 2) (see 'Dose equivalents' below). It may be appropriate to directly switch between antidepressants that share pharmacodynamic profiles, including antidepressants within the same drug class, such as selective serotonin reuptake inhibitors (SSRIs), or antidepressants in similar classes, such as SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) [8]. Direct switches may also be reasonable if the antidepressant to be discontinued has been used for a relatively short period of time (eg, less than one or two weeks).

Switching antidepressants may also involve abruptly discontinuing the current antidepressant if it causes a severe adverse reaction. We generally wait a few days (eg, two to three) before starting the new antidepressant.

When switching antidepressants, discontinuation symptoms that occur as a result of stopping the current drug may be mistaken as adverse side effects of the new drug that is started. Discontinuation symptoms are discussed separately. (See "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

Specific switches — Each section below describes switches between antidepressant classes and aspects that may vary from the standard approach of cross-tapering. The specific antidepressants that constitute each drug class are listed in the table (table 2), and general information about cross-tapering is discussed elsewhere in this topic. (See 'Standard approach and alternatives' above.)

Between SSRIs — Directly (immediately) switching to a new SSRI at the equivalent dose of the current SSRI is typically well-tolerated (table 1 and table 2) [9]. Nevertheless, starting the new SSRI at a lower dose is a reasonable alternative because patients occasionally have idiosyncratic side effects to particular SSRIs. Switching between SSRIs is generally the simplest antidepressant switch because SSRIs overlap in their mechanism of action, and the new SSRI usually prevents discontinuation symptoms that may otherwise occur when the current SSRI is stopped. (See "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

Additional information about administering SSRIs is discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

SSRI to SNRI — Switching directly (immediately) from most SSRIs to the equivalent dose of an SNRI (table 1 and table 2) is typically well-tolerated because SSRIs and SNRIs both enhance serotonergic neurotransmission [9-11]. However, if patients switch from a high dose of an SSRI, cross-tapering is preferable [10]. We generally taper the SSRI by the same amount for each dose decrease; at the same time, we titrate up the SNRI by the same amount for each dose

increase. As an example, sertraline 200 mg/day is decreased by 50 mg/day, every two to seven days; concurrently, venlafaxine extended release is started at 37.5 mg/day and after four to seven days is titrated up to 75 mg/day. Thereafter, the dose of venlafaxine extended release is increased every two to four weeks by increments of 75 mg per day, depending upon response and tolerability. In clinically urgent situations such as inpatient treatment, dose increases can occur as quickly as every two to four days if tolerated. The usual target dose is 75 to 225 mg/day; however, doses up to 375 mg/can be used.

Additional information about cross-tapering drugs and administering venlafaxine is discussed separately. (See 'Standard approach and alternatives' above and "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Venlafaxine'.)

Patients switching from fluoxetine or paroxetine to duloxetine or venlafaxine should start the SNRI at low doses. Fluoxetine and paroxetine strongly inhibit the hepatic enzyme CYP2D6, which metabolizes duloxetine and venlafaxine; inhibition of the enzyme thus increases the SNRI serum concentrations. In addition, inhibition of CYP2D6 may affect the efficacy of venlafaxine, which is a prodrug that is converted to desvenlafaxine by 2D6.

Inhibition of CYP2D6 is present to some degree until the SSRI is completely cleared; most SSRIs are cleared in approximately five days, but fluoxetine persists in the system for up to five weeks due to its long half-life. Completely tapering off the SSRI prior to starting an SNRI can prevent problems caused by drug-enzyme interactions, but is usually impractical because doing so risks exacerbating the patient's psychiatric illness.

SSRI to atypical antidepressants — Switching from an SSRI to atypical antidepressants is usually accomplished by cross-tapering (see 'Standard approach and alternatives' above) [10].

We generally taper the SSRI by the same amount for each dose decrease; at the same time, we titrate up the atypical antidepressant by the same amount for each dose increase. As an example, sertraline 200 mg/day is decreased by 50 mg/day, every five to seven days, while at the same time, bupropion extended release is typically started at 150 mg once daily. For patients who do not respond after two to four weeks, the dose of bupropion extended release is increased to 300 mg once daily. For patients who remain unresponsive after two to four weeks, the dose is increased to 450 mg daily. In clinically urgent situations such as inpatient treatment, each dose increase can occur after three days. The maximum single dose in the United States is 450 mg and in Europe is 300 mg per day.

Additional information about cross-tapering drugs and administering bupropion is discussed separately. (See 'Standard approach and alternatives' above and "Atypical antidepressants:

Pharmacology, administration, and side effects", section on 'Administration, dose, and discontinuation'.)

SSRI to tricyclic — SSRIs and tricyclic antidepressants are listed in the table (table 2).

The most common method used to switch from an SSRI to a tricyclic antidepressant is a cross-taper (see 'Standard approach and alternatives' above). Tricyclics should be started at low doses when cross-tapering them with an SSRI, particularly with fluoxetine, fluvoxamine, and paroxetine [10]. Fluoxetine and paroxetine strongly inhibit the hepatic enzyme CYP2D6 and fluvoxamine potently inhibits CYP1A2. These enzymes are involved in the metabolism of many tricyclics and inhibition increases tricyclic serum concentrations (several-fold higher in some cases), which can result in toxicity. Tricyclic serum levels can be checked during cross-tapering for added safety, but this is not standard practice.

Inhibition of CYP2D6 is present to some degree until the SSRI is completely cleared; most SSRIs are cleared in approximately five days, but fluoxetine persists in the system for up to five weeks due to its long half-life. Completely tapering off the SSRI prior to starting a tricyclic can prevent problems caused by drug-enzyme interactions, but is usually impractical because doing so risks exacerbating the patient's psychiatric illness.

SSRI to other antidepressants — Switching from an SSRI to serotonin modulators (table 2) is usually accomplished by cross-tapering [10]. (See 'Standard approach and alternatives' above.)

Switches between SSRIs and MAOIs are discussed elsewhere in this topic. (See 'Switching to or from MAOIs' below.)

Between SNRIs — At low doses (eg, less than 150 mg of venlafaxine or less than 60 mg of duloxetine), immediately switching from one SNRI to another is usually well-tolerated because SNRIs share many pharmacologic properties with each other [10]. However, at higher doses, cross-tapering is preferred. (See 'Standard approach and alternatives' above.)

Additional information about administering SNRIs is discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

SNRI to other antidepressants — In switching from an SNRI to antidepressants other than MAOIs, we recommend cross-tapering the SNRI with the new antidepressant over a one- to four-week period (see 'Standard approach and alternatives' above) [10]. We generally taper the SNRI by the same amount for each dose decrease; at the same time, we titrate up the new antidepressant by the same amount for each dose increase. As an example, venlafaxine

extended release 225 mg/day is decreased by 37.5 or 75 mg per day each week, while at the same time, bupropion extended release is typically started at 150 mg once daily. For patients who do not respond to bupropion extended release after two to four weeks, the dose is increased to 300 mg once daily. For patients who remain unresponsive after two to four weeks, the dose is increased to 450 mg daily. In clinically urgent situations such as inpatient treatment, each dose increase can occur after three days. The maximum single dose in the United States is 450 mg and in Europe is 300 mg per day.

Additional information about cross-tapering drugs and administering bupropion is discussed separately. (See 'Standard approach and alternatives' above and "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Administration, dose, and discontinuation'.)

SNRIs (eg, duloxetine and venlafaxine) can cause uncomfortable discontinuation symptoms upon sudden cessation. Switching to an antidepressant (such as an SSRI) that shares some neurotransmitter effects may mitigate these symptoms. (See "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

Duloxetine inhibits the liver enzyme CYP2D6 and may thus increase serum concentrations of medications (eg, tricyclics) that are metabolized by this enzyme.

Switches between SNRIs and MAOIs are discussed elsewhere in this topic. (See 'Switching to or from MAOIs' below.)

Switching to or from atypical antidepressants — Atypical antidepressants include drugs that are not related to each other or to other drug classes.

- **Agomelatine** – We suggest a cross-taper when switching between agomelatine and SSRIs, SNRIs, other atypical antidepressants, serotonin modulators, or tricyclics. (See 'Standard approach and alternatives' above.)

- **Bupropion** – In switching between bupropion and antidepressants other than MAOIs, we suggest the following:

  - When switching to bupropion from SSRIs, SNRIs, other atypical antidepressants, serotonin modulators, or tricyclics, we recommend cross-tapering over a one- to three-week period; a minimum of two weeks is suggested for drugs with prominent discontinuation syndromes such as SSRIs other than fluoxetine, as well as duloxetine and venlafaxine [10] (see 'Standard approach and alternatives' above). Bupropion does not have significant serotonergic properties and would not be expected to mitigate

discontinuation symptoms that result from stopping medications that are strongly serotonergic. (See "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

- When switching from bupropion to SSRIs, SNRIs, other atypical antidepressants, or tricyclics, we recommend cross-tapering over a one- to three-week period. Bupropion is not often associated with discontinuation symptoms and can usually be tapered and discontinued over one week while initiating a new antidepressant medication at its typical dosing schedule. However, bupropion inhibits the liver enzyme CYP2D6 and may increase the serum concentrations of medications that are metabolized by this enzyme.

- It is prudent to carefully monitor patients when prescribing bupropion concomitantly with other medications that can lower seizure threshold (table 3); the additive effects may increase the risk for drug-induced seizures.

- **Mirtazapine** – We suggest a cross-taper in switching between mirtazapine and SSRIs, SNRIs, other atypical antidepressants, serotonin modulators, or tricyclics [10]. (See 'Standard approach and alternatives' above.)

Switches between atypical antidepressants and MAOIs are discussed elsewhere in this topic. (See 'Switching to or from MAOIs' below.)

Additional information about administering atypical antidepressants is discussed separately. (See "Atypical antidepressants: Pharmacology, administration, and side effects".)

Switching to or from serotonin modulators — In switching between serotonin modulators (eg, trazodone, vilazodone, or vortioxetine) and antidepressants other than MAOIs, we recommend cross-tapering over a one- to two-week period. (See 'Standard approach and alternatives' above.)

Switches between serotonin modulators and MAOIs are discussed elsewhere in this topic. (See 'Switching to or from MAOIs' below.)

Additional information about administering serotonin modulators is discussed separately. (See "Serotonin modulators: Pharmacology, administration, and side effects".)

Switching to or from tricyclics — In switching between a tricyclic and antidepressants other than MAOIs, we recommend cross-tapering over a one- to two-week period. (See 'Standard approach and alternatives' above and 'SSRI to tricyclic' above.)

Switches between tricyclics and MAOIs are discussed elsewhere in this topic. (See 'Switching to or from MAOIs' below.)

Additional information about administering tricyclics is discussed separately. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

Switching to or from MAOIs — Clinicians must cautiously switch patients to or from an MAOI because drug-drug interactions can cause severe toxicity, including hypertensive crisis or serotonin syndrome [10]. (See "Evaluation and treatment of hypertensive emergencies in adults" and "Serotonin syndrome (serotonin toxicity)".)

Switching to an MAOI is accomplished by first tapering and discontinuing the current antidepressant over two to four weeks [10] (see "Discontinuing antidepressant medications in adults", section on 'General approach to discontinuing antidepressants'). Next, to avoid drug-drug interactions, clinicians need to allow enough time to elapse between the last dose of the discontinued antidepressant and the first dose of the MAOI. The amount of time to wait depends upon the half-life of the discontinued antidepressant and existence of active metabolites:

- **Fluoxetine** – Five weeks should elapse between stopping fluoxetine and starting an MAOI because fluoxetine has a relatively long half-life and an active metabolite (norfluoxetine).
- **Vortioxetine** – At least three weeks should elapse between stopping vortioxetine and starting an MAOI because vortioxetine also has a relatively long half-life. In addition, patients who are obese should wait at least 32 days for vortioxetine to washout before initiating an MAOI because vortioxetine accumulates in adipose tissue [12].
- **Other antidepressants** – For antidepressants other than fluoxetine and vortioxetine, two weeks should elapse between the last dose of the discontinued antidepressant and the first dose of the MAOI. However, it is reasonable to wait less than two weeks in specific urgent situations. As an example, clinicians can initiate an MAOI after five days have elapsed in hospitalized patients who are monitored daily and have discontinued duloxetine, which has a half-life elimination of approximately 12 hours and no active metabolites. The half-life of antidepressants and existence of any active metabolites are described in the Pharmacodynamics/Kinetics section of the Lexicomp drug monographs included in UpToDate.

For patients who are switching from an MAOI to an antidepressant from another class, we recommended first tapering and discontinuing the MAOI (see "Discontinuing antidepressant medications in adults", section on 'MAOIs'). Next, two weeks should elapse between the last

dose of the MAOI and the first dose of the new antidepressant; this is the length of time required for cells to reconstitute the enzyme monoamine oxidase. During the two weeks following the last dose of the MAOI, patients should continue to follow the dietary and medication restrictions (table 4 and table 5) that are required during treatment with an MAOI.

When switching between MAOIs, we recommend first tapering and discontinuing the current MAOI, and then waiting two weeks before starting the new MAOI.

Additional information about administering MAOIs is discussed separately. (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

DOSE EQUIVALENTS

One method for determining dose equivalents for different antidepressants is to use data from randomized trials that compared a standard antidepressant with other antidepressants as monotherapy for unipolar depression, and calculate the mean dose of each antidepressant that was as efficacious as the standard comparator [13]. This approach was adopted by a study that used data from 83 randomized antidepressant trials (n >14,000 patients); the trials were flexible-dose studies that allowed the blinded (masked) clinicians to adjust the dose to optimize clinical response [13]. The study found that fluoxetine 40 mg/day, as the standard comparator, was approximately equivalent to venlafaxine 150 mg/day, bupropion 350 mg/day, and mirtazapine 50 mg/day (table 1).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Coping with high drug prices (The Basics)")
- Beyond the Basics topics (see "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Depression treatment options for adults (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

SUMMARY

- **Choosing a strategy for switching** – Factors that are involved in choosing a strategy for switching antidepressants include the risk of discontinuation symptoms, potential for drug interactions, other antidepressant properties such as elimination half-life, adverse effects, and pharmacodynamics, and how quickly symptoms need to be controlled. (See 'Standard approach and alternatives' above.)
- **Standard technique** – The standard technique for many drug switches is cross-tapering, in which the dose of the current antidepressant is gradually reduced to zero, while simultaneously the new antidepressant is started and titrated up to the therapeutic range. Cross-tapering typically occurs over one to two weeks. However, cross-tapering is contraindicated if the two antidepressants can cause moderate to severe drug-drug interactions. In these situations, the current antidepressant is tapered and stopped, and the new drug is then started, either immediately or after a washout period. (See 'Standard approach and alternatives' above.)
- **Switches between specific antidepressant classes** (table 2)
  - **Between selective serotonin reuptake inhibitors (SSRIs)** – To switch between SSRIs, we generally switch directly (immediately) from the current SSRI to the new one. In a direct switch, the current antidepressant is abruptly stopped and the new drug is started the next day at the equivalent dose (table 1 and table 2). A reasonable alternative is to start the new SSRI at a lower dose. (See 'Between SSRIs' above.)

- **SSRI to a serotonin-norepinephrine reuptake inhibitor (SNRI)** – To switch from an SSRI to an SNRI, we generally switch directly to the equivalent dose of the SNRI (table 1 and table 2). However, if patients switch from a high dose of an SSRI, cross-tapering is preferable. In addition, patients switching from fluoxetine or paroxetine to duloxetine or venlafaxine should start the SNRI at low doses. (See 'SSRI to SNRI' above.)

- **SNRI to antidepressants other than monoamine oxidase inhibitors (MAOIs)** – To switch from SNRIs to antidepressants other than MAOIs, we generally cross-taper over a two- to three-week period. (See 'SNRI to other antidepressants' above.)

- **To or from an atypical antidepressant** – To switch to or from an atypical antidepressant (eg, bupropion or mirtazapine), we generally cross-taper. (See 'Switching to or from atypical antidepressants' above.)

- **To or from a serotonin modulator** – To switch to or from a serotonin modulator, we generally cross-taper. (See 'Switching to or from serotonin modulators' above.)

- **To or from a tricyclic antidepressant** – To switch to or from a tricyclic antidepressant, we generally cross-taper. (See 'SSRI to tricyclic' above and 'Switching to or from tricyclics' above.)

- **To or from an MAOI** – Generally, a two-week washout period should elapse between discontinuing any antidepressant (other than fluoxetine or vortioxetine) and starting an MAOI; however, it is reasonable to wait less than two weeks in specific urgent situations. Five weeks should elapse between discontinuing fluoxetine and starting an MAOI; at least three weeks should elapse between stopping vortioxetine and starting an MAOI. In addition, we wait two weeks between discontinuing an MAOI and starting a different antidepressant; during the two weeks, patients should continue to follow the dietary and medication restrictions (table 4 and table 5) that are required during treatment with an MAOI. (See 'Switching to or from MAOIs' above.)

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