

Strategies and Solutions for Switching Antidepressant Medications

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One of the most common questions regarding antidepressants involves strategies for switching medications. This is not surprising, considering that results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial drew attention to the high rates of initial treatment failure with first-line agents.¹ More specifically, up to 65% of patients fail to achieve remission, and approximately half of all patients fail to achieve an adequate response from their first antidepressant medication trial. High treatment failure rates make it critical for prescribers to know how to safely and effectively switch antidepressants to ensure patient-treatment targets are met.

Understanding drug interactions

There is limited guidance on the efficacy and tolerability of various switch strategies, which makes it essential that providers have a strong foundation in the pharmacological properties of antidepressants to understand how pharmacokinetic and pharmacodynamic drug interactions affect patients during the switch period. For example, if a patient is completing a cross-taper to transition from an antidepressant that is a potent inhibitor of the cytochrome 450 metabolizing enzyme 2D6 (CYP2D6) (eg, bupropion, fluoxetine, paroxetine) to a new antidepressant metabolized primarily by CYP2D6, the serum concentration of the new medication will be elevated by the CYP2D6 inhibitor until the first medication is eliminated. This leads to slower titration of the second antidepressant.

An example of a pharmacodynamic drug interaction is the required 2-week antidepressant-free period af-

TABLE 1. Receptor activities and symptoms of abrupt discontinuation^{3,8}

Receptor activity	Withdrawal phenomena
Serotonergic	Flu-like symptoms (eg, dizziness, headache, nausea, weakness, lethargy), insomnia, anxiety, paresthesias
Alpha- or beta-adrenergic	Tachycardia, hypertension, rebound anxiety or restlessness, sweating, tremors, headache
Cholinergic	Nausea, vomiting, sweating, headache, abdominal cramping, muscle spasms, urinary urgency
Histaminergic	Activation, insomnia, mild anticholinergic withdrawal (eg, headache, sweating, nausea)

ter stopping an MAOI because of the risk of serotonin syndrome and hypertensive crisis from accumulated synaptic monoamines. Furthermore, providers must consider the severity of their patient's mood symptoms and weigh it against the concern of adverse drug events. This may lead to a more rapid switch in the hope of realizing benefit from the new medication as quickly as possible.

Discontinuation syndrome

Discontinuation syndrome can occur upon abruptly stopping or rapidly

lowering the dose of an antidepressant. Symptoms of discontinuation syndrome associated with various neurotransmitter and receptor systems are summarized in **Table 1**. Withdrawal phenomena need to be considered based on the pharmacology of how specific antidepressant medications affect serotonergic, adrenergic, histaminergic, and cholinergic activity. For example, TCAs have significant anticholinergic properties. Therefore, rapid withdrawal of these agents may precipitate cholinergic rebound, which can be associated

with vomiting, nausea, headache, sweating, and muscle spasms. Cholinergic rebound can also apply to other antidepressants with anticholinergic properties that may be discontinued abruptly, such as paroxetine.²

Prescribers should focus on the pharmacology involved rather than on specific medication classes, as differences in pharmacology of drugs in the same class can be significant enough to induce disparate withdrawal syndromes. Another example of this might be abrupt discontinuation of SNRIs, which can result in serotonergic withdrawal in addition to increased gastrointestinal motility and urinary urgency due to loss of noradrenergic effects.

In the case of rapid discontinuation of mirtazapine, reports include hypertension, tachycardia, insomnia, and mild anticholinergic withdrawal.³ In the case of rapid discontinuation of MAOIs, potential symptoms may include flu-like symptoms, tachycardia, hypertension, restlessness, dysphoria, excitation, or psychosis.

The need to mitigate the risk of

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TABLE 2. Advantages and disadvantages of various switching strategies^{5,9}

Switching approach	Method	Advantages	Disadvantages
Direct	<ol style="list-style-type: none"> 1. Stop old antidepressant 2. Start new antidepressant the next day at therapeutic dose (equivalent to old antidepressant) 	No washout period required; may hasten response by attaining target dose more rapidly	Limited use to specific drug classes; risk of drug interactions; may precipitate discontinuation syndrome, depending on agents utilized
Cross-taper	<ol style="list-style-type: none"> 1. Gradually reduce and stop old antidepressant 2. At the same time, start new antidepressant at low dose while tapering down old antidepressant 3. Either titrate new antidepressant to therapeutic dose while old agent is being tapered or increase new antidepressant to therapeutic dose once old antidepressant is stopped 	Reduces symptom recurrence; minimizes withdrawal symptoms; no washout period required, therefore beneficial for higher-risk patients	Risk of drug interactions; may take a long time to successfully taper old antidepressant, depending on how rapidly new antidepressant is titrated
Modified cross-taper when antidepressant medications interact	<ol style="list-style-type: none"> 1. Gradually reduce and stop old antidepressant 2. May consider a drug-free washout period over 2-4 days (or 2-5 weeks for MAOIs) 3. Start new antidepressant at typical starting dose 	Low risk of drug interactions	Risk of withdrawal symptoms; washout period plus time for new antidepressant to reach efficacy increases risk of potentially life-threatening exacerbation of illness/relapse; may take a long time to successfully taper old antidepressant

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discontinuation syndrome is particularly important when directly switching antidepressants or rapidly decreasing the dose of the first antidepressant. Symptoms appear to be most common when antidepressants are taken for more than 6 weeks, especially those with short half-lives (eg, paroxetine, venlafaxine), or are discontinued abruptly.⁴ Fluoxetine has notably less propensity to cause discontinuation syndrome because of its long half-life of 4 to 16 days (when taking into consideration its active metabolite, norfluoxetine).⁵ Patients are more likely to experience discontinuation syndrome when they have had difficulty tolerating an antidepressant during the initial phase of treatment.^{5,6}

Wilson and Lader⁶ describe various management approaches to minimize discontinuation syndrome symptoms when stopping or lowering the dose of antidepressants. In the case of severe withdrawal symptoms, they recommend restarting the antidepressant at the previous dose and initiating a slower taper. Although there was no consensus on best practice, many studies recommend at least 4 weeks of tapering the dose before discontinuing the medication. However, this is not always feasible in clinical practice. Ultimately, it is important for providers to monitor tolerability of the medication changes and to adjust the titration process according to individual reactions.

Switching strategies

Switching strategies that we discuss are listed in **Table 2**. The direct switch approach can be employed if the first agent was used for a short period (< 1 week) or when switching between some SSRIs, SNRIs, and TCAs (for more details, see **Table 3**). It is best to switch to an equivalent dose when possible. If the agent was used for a long period, or the patient was taking a high dose of medication, the cross-taper method is recommended. Cross-tapering is beneficial for individuals who are at high risk for relapsing from any improvement gained with the first medication, or are prone to discontinuation symptoms. As a general strategy, it is best to taper over at least 4 weeks if the agent was previously taken for 6 weeks or longer, and reduce the dose of the first medication by 25% per week.⁷ The first med-

TABLE 3. Guide for switching antidepressants^{5-7,9}

Switching from	Switching to	Suggested approach
SSRI ^{a,b}	Other SSRI or SNRI	Direct switch to equivalent or lower dose; consider a cross-taper when higher doses of the initial SSRI/SNRI are used
SSRI or SNRI	TCA	Cross-taper over 1-2 weeks; start with lower TCA doses if switching from an agent with CYP2D6 (eg, fluoxetine, paroxetine, duloxetine) ^{a,b,c} or CYP1A2 (eg, fluvoxamine) inhibition
Any antidepressant (except MAOIs)	Mirtazapine or bupropion	Cross-taper ^b (when switching from an SSRI/SNRI, it is recommended to cross-taper over 1-4 weeks to minimize serotonin discontinuation syndrome)
Bupropion ^b	Other antidepressant	Cross-taper over 1-3 weeks
Mirtazapine	Other antidepressant	Cross-taper
TCA ^c	Other antidepressant	Cross-taper over 1-2 weeks
MAOI	A different MAOI or other antidepressant	Reduce MAOI dose gradually over 2-4 weeks and wait at least 2 weeks after discontinuation of the MAOI before initiating new medication
Any antidepressant	MAOI	Reduce agent gradually over 2 weeks, if starting at a high dose; then wait 2 weeks before MAOI initiation; a 5-week washout period is required if switching from fluoxetine to an MAOI ^a

^aWhen fluoxetine is involved, it is important to remember norfluoxetine (active metabolite) has a mean half-life of about 9 days, which indicates potential drug interactions can persist after the drug has been discontinued.

^bWhile a washout is not routinely utilized with strong CYP2D6 inhibitors (eg, fluoxetine, paroxetine, bupropion) when switching to an SSRI, an SNRI such as duloxetine or venlafaxine, a tricyclic antidepressant, or an SSRI to bupropion, clinicians must be aware of potential drug-drug interactions via CYP2D6 inhibition.

^cCYP2D6 inhibition may cause elevations of medications metabolized by this pathway (eg, TCAs, SSRIs, and SNRIs).

Cross-tapering is beneficial for individuals who are at high risk for relapsing from any improvement gained with the first medication, or are prone to discontinuation symptoms.

ication can be reduced at a slower rate if discontinuation symptoms were experienced previously, or if the patient is not tolerating the initial switching strategy.

When completing a cross-taper, it is also important to be aware of available dose formulations to avoid instructing the patient to take doses that are not feasible during the taper. Both the direct switch and cross-tapering

methods have increased risk of drug-drug interactions when compared with a conservative switch strategy that utilizes a washout period of no medication. In practice, this approach is rarely attempted, with the exception of discontinuing an MAOI. Fluoxetine also has specific recommendations because of its long half-life, as detailed in **Table 3**. Although not comprehensive, **Table 3** may be used as a general guide for switching between antidepressant medications.

Conclusion

There are many patient-specific factors that affect how rapidly an antidepressant is switched or withdrawn when medication changes are made; practitioners must treat patients on an individualized basis. Factors such as withdrawal from the old antidepressant, discontinuation syndrome, or washout periods can prolong the achievement of remission, and successful switching may take several weeks to months. This may seem overwhelming to an already at-risk population, since it leads to further protracted treatment response.

Clinicians should strongly encourage patients to closely monitor for adverse effects when switching agents. Milder adverse events will

dissipate with time, but severe, life-threatening events require immediate medical attention. Each switch strategy must be tailored to the patient and realistic expectations given to help optimize treatment success.

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