Antidepressant discontinuation and the role of the pharmacist

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Introduction

Clinical practice guidelines currently offer minimal guidance for managing antidepressant withdrawal symptoms in patients who are tapering or discontinuing these medications.[1] Although many guidelines recommend antidepressants should be tapered gradually, out of 21 guidelines studied in a recent systematic review, none suggested how doses should be reduced, how to manage symptoms of antidepressant withdrawal or how to differentiate withdrawal symptoms vs relapse.[1] Approximately half of the patients attempting a dose reduction or discontinuation of their antidepressant have withdrawal symptoms, which can be severe and ongoing for some patients.[1-3] In addition, due to the overlap between anxiety and depression symptoms and those of antidepressant discontinuation, it may be challenging to determine which is occurring.[2] Since pharmacists are a common point of contact for many patients, we have an opportunity to identify and help manage antidepressant discontinuation issues in our patients.

When to discontinue antidepressants

Although duration of treatment varies depending on the clinical situation or remission maintenance period, generally antidepressant treatment is recommended to cease after a certain length of time.[1,4] Canadian guidelines recommend that clinicians discuss discontinuation with their patients after 6 to 9 months of clinical remission, but in some patients (such as those with frequent, recurrent or severe episodes or other comorbidities), treatment may be suggested for at least 2 years.[5]

There can be significant withdrawal risks when discontinuing an antidepressant too quickly, including mania, hypomania, suicide and suicidal ideation; withdrawal symptoms of restlessness and panic may worsen suicidal ideation, and patients should be monitored closely.[4] In addition, patients are at risk of being misdiagnosed with a relapse or other psychiatric condition if antidepressant withdrawal symptoms are not recognized.[6] Despite the potential challenges when discontinuing antidepressants, long-term use may expose patients unnecessarily to known side effects and risks of treatment, including gastrointestinal upset or bleeds, insomnia, somnolence and weight gain.[5] Other reasons why an antidepressant may be discontinued include subtherapeutic response, drug interactions, changes to drug insurance coverage, pregnancy or patient choice.[1,4,7]

Withdrawal symptoms

Symptoms of antidepressant discontinuation may be described as antidepressant discontinuation syndrome (ADS), discontinuation symptoms or withdrawal symptoms.[2,4] However, the latter is now widely recognized as the most appropriate term.[2] These withdrawal symptoms may occur after taking any antidepressant for more than a few weeks, and the common occurrence of these symptoms makes discontinuing antidepressants difficult.[2,4,5] Factors such as poor coping strategies, relapse worries, social support needs and previously failed attempts at discontinuation may also result in patient hesitancy or fear of stopping an antidepressant.[1,8]

Withdrawal symptoms associated with stopping any type of antidepressant typically begin within 2 to 4 days after the medication is stopped or reduced in dose, while the duration of withdrawal symptoms can vary from weeks to months or even years.[5,6,8,9] In some patients, withdrawal symptoms may occur within hours, may be severe, may be delayed by weeks or may be of a longer duration.[2,4-6,8] Previously, the National Institute for Health and Care Excellence (NICE) guidelines noted that withdrawal symptoms in patients discontinuing antidepressants "can be mild"[8]—a perspective that is likely outdated.

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TABLE 1 FINISH: The core symptoms after stopping antidepressants[4-6,11]

Definition	Examples
F—Flu-like symptoms	Fatigue, lethargy, aches, headache, sweatiness
I—Insomnia	Vivid nightmares or dreams
N—Nausea	May include vomiting
I—Imbalance	Vertigo, light-headedness, dizziness
S—Sensory disturbance	Paresthesias, such as "brain zaps"*; tingling, burning
H—Hyperarousal	Agitation, anxiety, irritability, mania, aggression, jerkiness, mood disturbance

*Unpleasant, electric shock-like sensations that could be caused by adrenergic withdrawal.[4]

TABLE 2 The risk of antidepressant discontinuation syndrome for specific medications[4,12-14]

Class	Lower risk	Intermediate risk	High risk
SSRIs	Fluoxetine	Citalopram* Escitalopram* Sertraline	Fluvoxamine* Paroxetine
SNRIs	Levomilnacipran Milnacipran		Desvenlafaxine† Duloxetine† Venlafaxine
TCAs	Doxepin Trimipramine	Clomipramine Desipramine* Doxepin	Amitriptyline*,† Imipramine† Nortriptyline*,†
MAOIs			Isocarboxazid Moclobemide Phenelzine Tranylcypromine
Other	Bupropion XL	Trazadone* Vilazodone* Vortioxetine	Mirtazapine*

Different references cite some medications in different risk categories. Withdrawal may occur with any antidepressant, and withdrawal risk can also be influenced by other patient-specific factors.
MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.
*May also be considered lower risk.
†May also be considered intermediate risk.

NICE recently updated their recommendations in a draft standard to include gradual dose reduction in these patients in order to decrease the severity of withdrawal symptoms.[10]

The pneumonic "FINISH" can be used to quickly remember common antidepressant withdrawal symptoms (Table 1).[11] Withdrawal symptoms can also vary based on antidepressant class and specific medication.[4]

Risk factors for withdrawal symptoms

Symptoms of withdrawal from an antidepressant can occur when the drug is abruptly stopped or the dose is significantly reduced.[4,5] These withdrawal symptoms are due to physical dependence, which may occur due to the brain's adaptation to using an antidepressant long-term, which is different from addiction.[12] Proven risk factors for withdrawal symptoms include a higher dose or longer treatment duration.[4,12] In addition, younger age and previously experiencing withdrawal symptoms after doses were missed, reduced or stopped may indicate a higher risk of discontinuation symptoms.[4,12]

Medications with a higher receptor affinity and shorter half-lives are more likely to elicit withdrawal symptoms.[4,5,12] Fluvoxamine and paroxetine have the shortest half-lives of the selective serotonin reuptake inhibitors (SSRIs) and thus have the highest risk in this class, while fluoxetine has the lowest.[4,6] See Table 2 for medication risk of ADS grouped by class.[4]

Withdrawal or relapse?

It is important to distinguish withdrawal symptoms from a relapse of anxiety or depression, as misdiagnosis of relapse (rather than withdrawal) can result in patients remaining on antidepressants longer than clinically necessary.[3,6] Given the overlap between withdrawal symptoms and symptoms of anxiety or depression, the following features may help elucidate a diagnosis:

- **Timing of symptom onset:** In general, relapse symptoms take more than a few weeks to develop compared to withdrawal symptoms, which can appear within days of stopping an antidepressant or changing the dose. However, in some cases, the onset of withdrawal symptoms may also vary; for example, fluoxetine has a longer half-life, and thus withdrawal symptoms may be delayed by weeks or longer.[2]
- **Timing of symptom resolution:** In general, if symptoms resolve quickly after restarting the last effective antidepressant dose, it is unlikely to be a relapse.[2,6,15] There is limited evidence on the time frame for resolution, but one source suggests symptoms resolving within 1 to 2 weeks are more likely indicative of withdrawal than a relapse.[15]
- **Presence of physical symptoms:** In general, coinciding psychological and physical symptoms are more likely to be due to antidepressant withdrawal than a relapse.[2] The FINISH pneumonic may be helpful in identifying more common withdrawal symptoms.
- **New intensity of symptoms:** In general, if a patient has symptoms they did not experience when initially diagnosed with anxiety or depression, or symptoms are more intense than previously experienced, these are more likely due to antidepressant withdrawal than signs of a relapse.[7]

It is important to note that these features are not "rules." Patients may experience different timelines, such as delayed onset of withdrawal symptoms or longer duration of resolution. If there is ongoing diagnostic uncertainty, then clinical judgment, close attention to the patient story and seeking consultation with a specialist may be necessary.

Patient management

There are no validated tapering schedules for antidepressants, but generally slower is better.[4] Antidepressants should be tapered gradually, and if withdrawal symptoms become severe, the medication should be restarted on a slower taper.[4,6,8] To reduce the chance of antidepressant withdrawal symptoms, tapers can be performed over weeks or months.[4] Guideline tapering recommendations vary, some suggesting between 4 weeks and 6 months, while others have no duration or even mention of tapering.[1] Due to the lack of clinical evidence for specific tapering regimens, it is difficult to develop evidence-based recommendations. Until randomized controlled clinical trial data are collected, guidance for tapering may be found from retrospective and nonrandomized tapering studies, expert opinion, dose reduction regimens based on pharmacologic theory and patient experience of withdrawal.[1] Tapering is generally considered after being on a medication for more than a few weeks, and adjusting the dose every 2 to 4 weeks, switching to a fluoxetine cross-taper or compounding liquid preparations when doses become small are possible strategies.[2,4,8]

More recently, initial data from nonrandomized trials have implied that hyperbolic tapering may decrease the occurrence of withdrawal symptoms.[1] SSRIs have shown a hyperbolic dose-response relationship with serotonin transporters, with transporter inhibition dropping sharply at doses below the minimum SSRI therapeutic dose.[16] Thus, tapering in a linear fashion may

TABLE 3 Example of a possible tapering plan for citalopram[17]

Citalopram daily dose	Tablet and liquid formulation dosing	Notes
40 mg	2 × 20 mg tablets	Reduce dose every 2 to 4 weeks. This taper follows dose reductions of 50% of the previous dose. Some patients may need a slower taper.
20 mg	1 × 20 mg tablet	
10 mg	1 × 10 mg tablet	
5 mg	½ × 10 mg tablet (or liquid formulation)	
2.5 mg	Liquid formulation	
1.25 mg	Liquid formulation	
0.6 mg	Liquid formulation	
STOP MEDICATION		

This is one example of a possible tapering plan for citalopram. An example to illustrate a strict hyperbolic taper would be if the goal is a 10% decrease in occupied serotonin receptors with each dose decrease, a taper schedule for citalopram could be 20 mg, 9.1 mg, 5.4 mg, 3.4 mg, 2.3 mg, 1.5 mg, 0.8 mg and 0.37 mg.[16]

TABLE 4 Example of a possible tapering plan for paroxetine[17]

Paroxetine daily dose	Tablet and liquid formulation dosing	Notes
40 mg	1 × 40 mg tablet	Reduce dose every 2 to 4 weeks. This taper follows dose reductions of 10% of the previous dose. Some patients may need a slower taper. When a liquid formulation is being used for tapering, one may also consider just using liquid for dosing (instead of tablet + liquid).
36 mg	1 × 30 mg tablet + 3 mL of 2 mg/mL liquid formulation	
32.4 mg	1 × 30 mg tablet + 1.2 mL of 2 mg/mL liquid formulation	
29.2 mg	1 × 20 mg tablet + 4.6 mL of 2 mg/mL liquid formulation	
26.2 mg	1 × 20 mg tablet + 3.1 mL of 2 mg/mL liquid formulation	
23.6 mg	1 × 20 mg tablet + 1.8 mL of 2 mg/mL liquid formulation	
21.3 mg	1 × 20 mg tablet + 0.65 mL of 2 mg/mL liquid formulation	
19.1 mg	1 × 10 mg tablet + 4.55 mL of 2 mg/mL liquid formulation	
17.2 mg	1 × 10 mg tablet + 3.6 mL of 2 mg/mL liquid formulation	
15.5 mg	1 × 10 mg tablet + 2.75 mL of 2 mg/mL liquid formulation	
13.9 mg	1 × 10 mg tablet + 1.95 mL of 2 mg/mL liquid formulation	
12.6 mg	1 × 10 mg tablet + 1.3 mL of 2 mg/mL liquid formulation	
	[30 more steps]	
0.6 mg	0.3 mL of 2 mg/mL liquid formulation	
	STOP MEDICATION	

Many factors should be considered when creating a patient-specific tapering plan, including patient tolerance of withdrawal symptoms. As well, in this example, these doses may be difficult for patients to measure. In these cases, clinical judgment along with patient preference and expert opinion may be helpful to create patient-centred tapering plans.

elicit progressively severe withdrawal symptoms, particularly below therapeutic doses. For example, decreasing citalopram from 20 mg to 15 mg will reduce serotonin transporter inhibition by 3% (absolute decrease), whereas decreasing from 5 mg to 0 mg will reduce this inhibition by 58%. In order to have a linear decrease in *pharmacological* effect, instead of reducing the dose by set amounts, a hyperbolic reduction using a fixed interval of biologic effect has been suggested[16] (see Table 3 footnote for an example). However, a barrier to using this method is that compounding or liquid formulations may be required. Although further research is needed to develop conclusive antidepressant tapering plans, some examples of possible tapering schedules have been provided in Table 3 and Table 4.[17] Note that these are examples only; other patient factors may affect the tapering plan, and some patients may need slower tapers. When liquid formulations are unavailable, compounding may be required.

Symptom management for antidepressant withdrawal is absent in clinical practice guidelines.[1,4] If withdrawal symptoms are severe, this may be an indication to slow the taper to a more tolerable rate for the patient.[2] In the absence of clinical evidence, clinical judgment may be used to suggest

BOX 1 Tips for pharmacists

- Realistic information about antidepressant therapy is desired by patients.[8]
- Educating patients who are starting antidepressants about potential symptoms that may occur when their medication is missed or stopped abruptly will better prepare them for discontinuation in the future, and provide reassurance that these symptoms are reversible, are not life-threatening and will resolve.[4,6,8]
- Similarly, patients may be hesitant about discontinuing an antidepressant; explaining a tapering plan and symptoms to monitor for will help with patient expectations.[5,7,8]
- Inform patients that if symptoms do become problematic, they can be managed by resuming the previous dose of the antidepressant and following a slower taper.[4]
- The Royal College of Psychiatrists (UK) has an information sheet that may be helpful to patients attempting to discontinue their antidepressants (https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants).

treatment for mild symptoms such as nausea, headaches and sleep, only if appropriate. It is also important to remember that many antidepressants are cytochrome P450 inducers or inhibitors, so re-evaluating concurrent medications for drug-drug interactions is also important when discontinuing an antidepressant.[4]

Finally, it may be helpful to discuss with patients the role of nonpharmacologic management in the prevention of relapse or recurrence. Alternatives to antidepressant treatment include cognitive behavioural therapy (CBT) and mindfulness-based cognitive therapy (MBCT). In a systematic review of managing antidepressant discontinuation, these psychological interventions led to improved patient outcomes. The combination of tapering with CBT compared to tapering and clinical management alone significantly reduced the risk of relapse or recurrence, while tapering with MBCT resulted in high discontinuation rates without an increase in rates of relapse or recurrence, compared to antidepressant maintenance treatment.[18] Other nonpharmacologic options that may be considered to treat depression (depending on severity) without or with medication are discussed in the NICE guidelines and include guided self-help; group CBT or behavioural activation; individual CBT or behavioural activation; individual problem-solving; group exercise, mindfulness or meditation; interpersonal psychotherapy and counselling.[19,20]

Conclusion

As pharmacists, we have a valuable role in both educating patients as they begin antidepressant medication and supporting them through discontinuation (see Box 1 for a summary of tips). Knowing the core symptoms of antidepressant withdrawal, risk factors for withdrawal symptoms and distinguishing withdrawal from relapse can help patients comfortably and effectively taper off antidepressants. ■

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