



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

Antidepressant Withdrawal Syndrome

Antidepressant drugs are associated with drug tolerance, dependence and a discontinuation syndrome similar to other drug classes such as the opiates and benzodiazepines. **The effects of stopping any antidepressant should be more precisely termed “withdrawal syndrome” instead of “antidepressant discontinuation syndrome.”**

What is it?

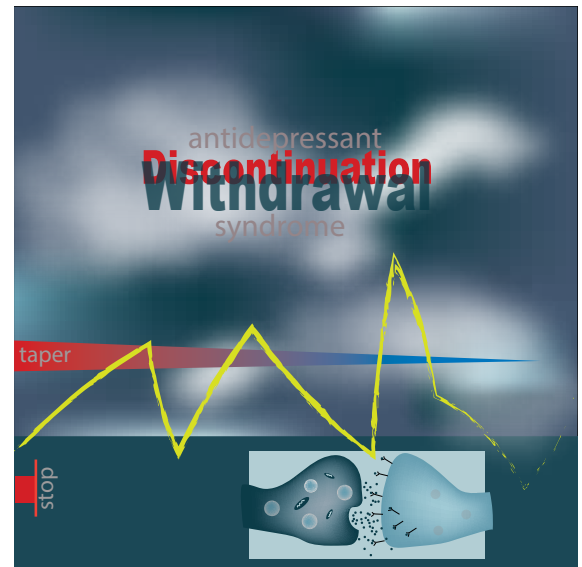
Antidepressant withdrawal syndrome refers to physical and psychological symptoms that occur when stopping, missing doses or reducing doses of any antidepressant.^{1,2} The mechanism has not been determined but various explanations have been proposed.^{3,4} Daily drug treatment can affect the availability of several neurotransmitters that can lead to many downstream physiological consequences. When drug treatment stops, the body's adaptive changes take time to recalibrate, resulting in a period of possible symptoms.⁵

Clinical Features

- Symptoms usually appear within a few days of stopping, or dose reduction.
- Symptoms include anxiety, crying, dizziness, headache, increased dreaming, insomnia, irritability, myoclonus, nausea, electric shocks (zaps), tremor, flu-like symptoms, imbalance, and sensory disturbances.¹
- Most antidepressant withdrawal symptoms resolve within 2 weeks.¹
- Severe and prolonged withdrawal symptoms have been reported lasting weeks to months.⁵ Numerous cases are reported anecdotally in great detail online.^{1,2}

Systematic Reviews

Two systematic reviews studied withdrawal reactions with selective serotonin reuptake inhibitors (SSRIs). The first review asked whether withdrawal reactions were different between benzodiazepines and SSRIs, and authors concluded the two were “very similar.” They strongly assert that SSRIs fulfill the criteria for tolerance and dependence in addition to a withdrawal syndrome.⁶ The second review



studied withdrawal symptoms associated with SSRIs. That review found 15 RCTs, 4 open trials, 4 retrospective investigations and 38 case reports. It concluded that SSRIs should be added to the list of drugs where stopping can induce withdrawal symptoms. This list includes benzodiazepines, barbiturates and other psychotropic drugs.

What proportion of patients have withdrawal symptoms?

Antidepressant withdrawal symptoms have typically been identified by post-marketing adverse drug reports. They are more frequent than suggested from early drug approval trials.⁷ The drug monograph for duloxetine (Cymbalta), for example, reports each discontinuation-related symptom experienced by 1% or more patients at a higher rate than placebo in controlled trials⁸, but doesn't provide the overall proportion of patients experiencing symptoms. A manufacturer-funded uncontrolled observational study reported that 51% of patients discontinuing duloxetine experienced one or more symptoms.⁹ In general, one to two-thirds of patients have at least one new symptom when abruptly discontinuing an antidepressant.¹⁰ When stopping is investigated in clinical trials, the Discontinuation Emergent Signs and Symptoms (DESS) checklist is often used.¹¹ The incidence of withdrawal symptoms appears higher with short half-life antidepressants (e.g. paroxetine, venlafaxine) than from long half-life antidepressants (fluoxetine and its long-lived metabolite norfluoxetine).¹⁰ A major gap in the literature surrounding the DESS checklist is that improvement in symptoms after stopping is not captured.



Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822 0700
Fax: 604 822 0701
E-mail: info@ti.ubc.ca
www.ti.ubc.ca

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Is there evidence for an optimal method of stopping antidepressants?

There are few controlled trials reporting methods for antidepressant discontinuation and resulting symptoms.^{11,13-30} Only one controlled trial directly compared a taper to an abrupt stop.^{22,23} In this, tapering reduced the rate of emerging withdrawal symptoms, but did not eliminate symptoms. One trial compared taper lengths and found a short taper may be no different than a longer taper.²⁴ The studies relied upon un-validated means to quantify symptoms, primarily focused on new or worsening symptoms, and may be biased due to loss of blinding. Populations tended to be patients with moderate depression whose depression was somewhat reduced before the antidepressants were stopped. Despite the lack of evidence most antidepressant monographs and guidelines recommend a slow taper approach.^{1,31}

When to taper or abruptly stop?

The optimal method of stopping antidepressants is currently unknown and withdrawal symptoms can happen unpredictably, despite tapering. Some considerations favouring abrupt stopping or tapering are shown in Table 1.

Other considerations

It is essential that patients are informed of the potential for antidepressant withdrawal symptoms before starting an antidepressant. For patients treated for depression, it is important they are aware of and monitored for a recurrence of depressive symptoms, or increased suicidality.²⁴

Conclusions

- **Antidepressants should be added to the list of drugs associated with tolerance, dependence and a withdrawal syndrome.**
- Withdrawal symptoms occur in at least one-third of patients who stop.
- Before starting an antidepressant, patients must be informed of the possibility of withdrawal symptoms. The requirements for informed consent are analogous to recommendations before initiating long-term opioid therapy.
- Some symptoms may improve upon stopping but this is not captured in the studies of antidepressant withdrawal.
- Any decision to abruptly stop or taper an antidepressant must consider the potential that recurrent depressive symptoms or increased suicidality may represent withdrawal or re-emergence of the original condition.

Table 1: Considerations for choosing a method of stopping antidepressants

Favours Taper	Favours Abrupt Stopping
<ul style="list-style-type: none"> • No toxicity from ongoing antidepressant therapy. • Short half-life of drug and metabolites (<24 hrs). • Previous antidepressant withdrawal symptoms. • Patient prefers autonomy of self-regulated taper. 	<ul style="list-style-type: none"> • Pregnancy and the safety of the antidepressant has not been established. • Important new drug may interact significantly with antidepressant. • Patient is experiencing troubling toxicity related to their antidepressant. • Treatment duration <6-8 weeks.^{32, 33} • Trial of tapering is prolonging the discomfort of withdrawal symptoms. • Long half-life of drug and metabolites.

EXAMPLE: Long-term paroxetine 40 mg daily is no longer indicated in a patient. A reasonable approach to discontinuation might be:

- Reduce to paroxetine 30 mg daily x 1 week, then 20 mg daily x 1 week, then 10 mg daily x 1 week, then 5 mg daily x 1 week, then stop.
- If intolerable symptoms occur, increasing back to the previously tolerated dose and reducing more slowly (e.g. every 2-4 weeks) may help.

USEFUL RESOURCES:

- medicationinfoshare.com
- rxisk.org
- switchrx.ca
- iipdw.com
- withdrawal.theinnercompass.org
- wiki.psychiatrienet.nl/index.php/SwitchAntidepressants

For the complete list of references and links to useful resources go to: www.ti.ubc.ca/letter112