

New Investigators

Tips to manage and prevent discontinuation syndromes

Informed tapering can protect patients when you stop a medication

Sriram Ramaswamy, MD

Instructor, department of psychiatry
Creighton University
Omaha, NE

Shruti Malik, MBBS, MHSA

Foreign medical graduate

Vijay Dewan, MD

Assistant professor
Department of psychiatry
University of Nebraska Medical Center
Omaha, NE

Abruptly stopping common psychotropics—particularly antidepressants, benzodiazepines, or atypical antipsychotics—can trigger a discontinuation syndrome, with:

- rebound or relapse of original symptoms
- uncomfortable new physical and psychological symptoms
- physiologic withdrawal at times.

To increase health professionals' awareness of the risk of these adverse effects,¹ this article describes discontinuation syndromes associated with various psychotropics and offers strategies to anticipate, recognize, and manage them.

ANTIDEPRESSANTS

Discontinuation syndromes can occur with tricyclic and tetracyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin

New insights on psychotropic drug safety and side effects

This paper was among those entered in the 2005 Promising New Investigators competition sponsored by the Neuroleptic Malignant Syndrome Information Service (NMSIS). The theme of this year's competition was "New insights on psychotropic drug safety and side effects."

CURRENT PSYCHIATRY is honored to publish this peer-reviewed, evidence-based article on a clinically important topic for practicing psychiatrists.

NMSIS is dedicated to reducing morbidity and mortality of NMS by improving medical and psychiatric care of patients with heat-related disorders; providing support information for medical professionals, patients and families; and improving scientific understanding of these conditions through research.

Table 1

Discontinuation symptoms seen with TCAs

Physical symptoms	Lethargy, headache, tremor, sweating, anorexia, insomnia, nausea, vomiting, diarrhea, akathisia (rare), parkinsonism (rare)
Psychological symptoms	Irritability, anxiety/agitation, low mood, excessive dreaming, nightmares, paradoxical activation resulting in manic/hypomanic symptoms (rare)

TCA: Tricyclic antidepressants
Source: Reference 2

Table 2

Discontinuation symptoms seen with SSRIs

Type	Symptoms
Disequilibrium	Lightheadedness/dizziness, vertigo, ataxia
Sensory symptoms	Paraesthesia, numbness, electric shock-like sensations
General somatic symptoms	Lethargy, headache, tremor, sweating, anorexia
Sleep disturbance	Insomnia, nightmares, excessive dreaming
GI symptoms	Nausea, vomiting, diarrhea
Affective symptoms	Irritability, anxiety/agitation, low mood

SSRIs: Selective serotonin reuptake inhibitors
Source: Reference 5

reuptake inhibitors (SSRIs), and other newer antidepressants. Symptoms usually start within a few days of stopping a drug—or less commonly, reducing its dosage—and are usually mild and self-limited. Serious outcomes have been reported.

Distinguishing antidepressant discontinuation symptoms from depression recurrence is important. Discontinuation symptoms emerge within 1 to 3 days, whereas depressive symptoms usually occur 2 to 3 weeks after an antidepressant is stopped. Discontinuation reactions remit within a few days, especially if the antidepressant is re-instituted.

TCAs block serotonin and norepinephrine reuptake, increasing the availability of these biogenic amines at receptor sites in the brain and other tissues. Abrupt discontinuation can cause physical symptoms—such as lethargy, headache, and tremor—and psychological symptoms including irritability, anxiety, agitation, and low mood (Table 1).²

Long-term use of TCAs with potent anticholinergic properties leads to up-regulation of postsynaptic muscarinic receptors, creating a “supersensitive” state. Abrupt discontinuation can cause cholinergic rebound, with symptoms emerging as soon as 12 hours—but typically 24 to 48 hours—after the last dose.

MAOIs such as phenelzine and tranylcypromine inhibit the enzyme monoamine oxidase, which is responsible for monoamine degradation and increases synaptic monoamine concentrations. Discontinuation syndromes may include acute confusional states, paranoid delusions, hallucinations, or worsening of depressive symptoms.³ These problems rarely occur in clinical practice, however, because MAOIs’ serious side effects discourage doctors

from prescribing them.

SSRIs and other agents. SSRIs block synaptic reuptake of serotonin. Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine inhibit both serotonin and norepinephrine reuptake. Mirtazapine—an alpha2-adrenergic and heteroreceptor antagonist—increases serotonin and norepinephrine at the synapse. Bupropion increases dopamine and norepinephrine turnover in the CNS and also blocks serotonin.

Up to 30% of patients who stop taking SSRIs develop discontinuation symptoms.⁴ Six symptom

continued on page 37

continued from page 30

clusters—disequilibrium, sensory symptoms, general somatic symptoms, sleep disturbance, GI symptoms, and affective symptoms—characterize the SSRI discontinuation syndrome (*Table 2, page 30*).⁵ The four most common symptoms—in decreasing order of frequency—are dizziness, nausea, lethargy, and headache.⁶ Ataxia, sensory abnormalities, and possibly aggressive and impulsive behavior differentiate this discontinuation syndrome from that of the TCAs.

Risk factors. Risk factors for SSRI discontinuation syndrome have been identified (*Table 3*).⁷ Symptoms usually begin 1 to 3 days after an SSRI is abruptly stopped and are usually mild. However, some patients report falls, inability to work, and difficulty walking and driving. Untreated symptoms are short-lived and remit within 1 to 2 weeks. They also remit if the original antidepressant is reintroduced or a pharmacologically similar agent is substituted.

Discontinuation syndrome risk among SSRIs is highest for paroxetine, intermediate for sertraline and fluvoxamine, and lowest for fluoxetine.⁴ Citalopram may cause a mild and transient discontinuation syndrome.⁸ Citalopram's long elimination half-life (30 to 35 hours) and fewer and much less-potent active metabolites⁹ may explain its relatively low risk of discontinuation symptoms.

Discontinuation reactions have been reported to occur 100 times more frequently with paroxetine than with fluoxetine.¹⁰ Fluoxetine's lower rate could be explained by its 2- to 3-day half-life, compared with half-lives of 33 hours or less for paroxetine, sertraline, citalopram, and fluvoxamine. A longer half-life might protect against a discontinuation syndrome.

Among other newer antidepressants:

- venlafaxine's discontinuation syndrome is similar to the SSRI syndrome¹¹
- no discontinuation symptoms have been reported with mirtazapine, bupropion, or duloxetine.

Table 3

SSRI discontinuation syndrome: The patient at risk . . .

Is taking an SSRI with a relatively short half-life

Has received antidepressant treatment > 4 weeks

Has history of treatment-emergent anxiety, discontinuation symptoms, nonadherence

SSRI: Selective serotonin reuptake inhibitor

Source: Reference 7

Causes. Theories to explain SSRI discontinuation syndrome include cholinergic rebound,¹² as described with TCAs, or a decrease in available synaptic serotonin coinciding with down-regulated serotonin receptors.¹³ Paroxetine's pharmacologic properties—cholinergic effects, short half-life, and high potency of serotonin reuptake blockade—may explain its relatively high frequency of discontinuation symptoms.

ATYPICAL ANTIPSYCHOTICS

Except for aripiprazole—which is a partial dopamine receptor agonist—most atypical antipsychotics are serotonin-dopamine antagonists. Discontinuation syndrome occurs most commonly with clozapine.

Clozapine. Abruptly stopping clozapine can exacerbate psychosis or cause delirium, agitation, confusion, and diaphoresis. Less-common symptoms may include extrapyramidal effects, nausea, diarrhea, headache, or restlessness.¹⁴ Clozapine is a weak dopamine D2 antagonist and a potent antagonist at the serotonin 5HT₂, alpha adrenergic, histaminergic, and anticholinergic receptors. Thus, rebound from cholinergic, serotonin, dopamine and/or adrenergic receptor supersensitivity is thought to cause its discontinuation syndrome.¹⁵

Other atypicals. Case reports describe tics and withdrawal-emergent dyskinesia with risperidone¹⁶ and supersensitivity psychosis and a cholinergic/sero-

tonergic syndrome with olanzapine.^{17,18} Anecdotal reports suggest that abruptly discontinuing quetiapine can cause nausea, emesis, lightheadedness, diaphoresis, orthostasis, tachycardia, and nervousness.^{19,20} Although discontinuation syndromes have not been reported with ziprasidone or aripiprazole, tapering any atypical antipsychotic during discontinuation is prudent.

BENZODIAZEPINES

Benzodiazepines modulate the neurotransmitter activity of gamma-aminobutyric acid (GABA). They differ in their pharmacokinetic properties and have varying half-lives:

- chlordiazepoxide and diazepam have long half-lives (≥ 48 hours)
- clonazepam has an intermediate half-life (10 to 24 hours)
- alprazolam, lorazepam, and oxazepam have short half-lives (≤ 10 hours).

Abruptly discontinuing benzodiazepines can cause relapse or rebound of pretreatment symptoms. Rebound—with symptoms exceeding pretreatment levels—sometimes occurs after 4 weeks of therapy. The syndrome may last 1 to 3 weeks and is more common with agents having relatively short half-lives.²¹

Withdrawal. During benzodiazepine withdrawal, new symptoms emerge and pre-existing symptoms worsen. An autonomic component differentiates withdrawal from relapse or rebound. Prominent symptoms include excess sensitivity to light and sound, insomnia, tachycardia, mild systolic hypertension, anxiety, nausea, irritability, tremors, sweating, and abdominal distress. Less-common but serious symptoms include confusion, paranoid delusions, hallucinations, and seizures.²²

Withdrawal symptoms are more likely to occur after 6 months of benzodiazepine therapy,

when physical dependence also can develop. More-severe benzodiazepine discontinuation syndrome is associated with higher dosages, longer duration of therapy, shorter half-lives, and rapid tapers. Patient factors associated with withdrawal symptoms include:

- personality traits such as dependency and neuroticism
- high pretreatment anxious and depressive symptoms
- history of substance abuse or dependence.²³

PREVENTING DISCONTINUATION SYNDROMES

Antidepressants. For TCAs, no discontinuation protocols exist, although some experts suggest tapering regimens over 4 weeks to 3 months. For MAOIs, reducing dosages 10% per week has been suggested.²⁴ The SSRI taper rate depends on the drug's pharmacologic profile, how long the patient has been taking the SSRI, and the dosage.²⁵

With paroxetine, for example, a gradual reduction of 10 mg/d per week is recommended, based on clinical trial experience. When you reach 20 mg/d, continue this dosage for 1 week before stopping treatment. If reducing a dosage or discontinuing paroxetine causes intolerable symptoms, consider resuming the previously prescribed dosage and then taper more gradually.²⁶

Also gradually taper other SSRIs with short half-lives. Suggested taper regimens for sertraline and fluvoxamine call for weekly reductions of 50 mg/d until you reach 25 to 50 mg. It is not unusual for this final dosage to be lower than the starting dosage.²⁵ Substituting fluoxetine—with its longer half-life—for other SSRIs at the end of treatment has been suggested to suppress withdrawal symptoms,²⁷ although the safety and efficacy of this approach is unknown.⁵ With venlafaxine, taper over a minimum of 2 to 4 weeks.²⁸

Abruptly stopping a benzodiazepine after only 4 weeks of therapy may cause rebound

Antipsychotics. To prevent psychotic relapse when discontinuing clozapine, some experts advocate starting a new antipsychotic in a therapeutic dosage before stopping clozapine. When high-dose clozapine must be withdrawn immediately, hospitalize the patient and consider using cholinergics to prevent cholinergic rebound.¹⁵

Data on managing discontinuation syndromes associated with risperidone, olanzapine, or quetiapine are limited. In some cases, reinstating the original drug, gradually tapering the antipsychotic,^{18,19} or using prochlorperazine²⁰ have been useful.

Benzodiazepines. Taper oral benzodiazepines if a patient has taken them >4 to 6 weeks. Also taper IV midazolam used >7 days to sedate a critically ill patient. For the elderly, an 8- to 10-week taper may be required to discontinue benzodiazepines used >3 months for insomnia.

The American Psychiatric Association practice guideline for patients with panic disorder²⁹ recommends tapering benzodiazepines across 2 to 4 months, reducing dosages not more than 10% weekly. Another option is to reduce the daily dosage by 25% per week, but close monitoring and flexibility are required during this taper.

Outcomes when tapering benzodiazepines, according to Rickels et al,²³ depend less on pharmacologic adjuvant treatment than on benzodiazepine dosage before the taper, initial psychopathology severity, and patient personality traits (such as passivity/dependency). Before tapering, those authors recommend that you:

- establish a stable patient-physician relationship
- aggressively treat clinically significant anxiety and depression symptoms with medication or other means while the patient continues the established benzodiazepine dosage.

When the taper is nearly complete, maintain the reduced benzodiazepine dosage several

Table 4

Common conditions requiring abrupt psychotropic discontinuation

- Preoperative management of elective/emergency surgery
- Delirium
- Unknown medication history
- Acute pancreatitis
- Emergent abdominal surgery
- Acute intoxication
- Pregnancy and breast feeding

months before the final taper.²³ Carbamazepine, imipramine, valproate, or trazodone may help alleviate benzodiazepine discontinuation symptoms in select patients.²¹

WHEN DISCONTINUATION OCCURS

Medical comorbidity. Common medical conditions, including pregnancy or acute surgical procedures, may necessitate abrupt psychotropic discontinuation (*Table 4*).

Because up to 30% of medical patients have a psychiatric disorder,³⁰ primary care physicians often start psychotropics to manage anxiety and depressive symptoms and may seek psychiatric advice when switching or stopping medications. Moreover, 10% to 15% of hospitalized medically ill patients require dosage reduction or discontinuation of psychotropics that are contributing to the clinical presentation.³¹

Switching. When switching psychotropics, effects from the first psychotropic may appear to be adverse effects of the new psychotropic. Thus, unrecognized discontinuation syndromes may lead to unnecessary treatment changes.

In our experience, a general rule is to cross-taper and decrease the psychotropic being discontinued

continued on page 43

continued from page 39

by 10% every 1 to 2 weeks. Prescribe adequate dosages of the new psychotropic, closely monitor vital signs, and watch for emerging discontinuation symptoms.

Pregnancy. For women who become pregnant while taking psychotropics, consider the patient's psychiatric stability, week of pregnancy, psychotropic agent, and treatment preferences when adjusting the treatment plan. In one study of 34 women who stopped psychotropics abruptly for fear of harming the fetus:

- 26 (70%) reported physical and psychological adverse effects
- 11 (30%) reported suicidal ideation, and 4 were hospitalized.³²

Patient education. In the study described above, some of the pregnant women's physicians were unaware of the risks associated with abrupt psychotropic discontinuation and others were aware but failed to inform their patients.³² Thus, patient and family/caregiver education is important. When stopping psychotropics, discuss their risks/benefits, address unrealistic expectations, and individualize therapy by tapering and providing adequate dosing. Watch for suicidality; a weekly telephone call might be useful.

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Related resource

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DRUG BRAND NAMES

Alprazolam • Xanax	Lorazepam • Ativan
Aripiprazole • Abilify	Mirtazapine • Remeron
Bupropion • Wellbutrin	Oxazepam • Serax
Carbamazepine • Equetro, Tegretol	Paroxetine • Paxil
Chlordiazepoxide • Librium	Phenelzine • Nardil
Citalopram • Celexa	Quetiapine • Seroquel
Clonazepam • Klonopin	Risperidone • Risperdal
Clozapine • Clozaril	Tranylcypromine • Parnate
Diazepam • Valium	Trazodone • Desyrel
Duloxetine • Cymbalta	Sertraline • Zoloft
Fluoxetine • Prozac	Valproate • Depakene
Fluvoxamine • Luvox	Venlafaxine • Effexor
Imipramine • Tofranil	Ziprasidone • Geodon

DISCLOSURE

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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Discontinuation symptoms can occur when patients abruptly stop taking antidepressants, benzodiazepines, or antipsychotics. To prevent rebound, relapse, and withdrawal, follow tapering regimens when possible. When switching agents, a general rule is to cross-taper and gradually decrease the drug being discontinued.

BottomLine

continued on page 44

continued from page 43

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