Antidepressant Discontinuation Syndrome

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Antidepressant discontinuation syndrome occurs in approximately 20 percent of patients after abrupt discontinuation of an antidepressant medication that was taken for at least six weeks. Typical symptoms of antidepressant discontinuation syndrome include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal. These symptoms usually are mild, last one to two weeks, and are rapidly extinguished with reinstitution of antidepressant medication. Antidepressant discontinuation syndrome is more likely with a longer duration of treatment and a shorter half-life of the treatment drug. A high index of suspicion should be maintained for the emergence of discontinuation symptoms, which should prompt close questioning regarding accidental or purposeful self-discontinuation of medication. Before antidepressants are prescribed, patient education should include warnings about the potential problems associated with abrupt discontinuation. Education about this common and likely underrecognized clinical phenomenon will help prevent future episodes and minimize the risk of misdiagnosis. (Am Fam Physician 2006;74:449-56, 457. Copyright © 2006 American Academy of Family Physicians.)

▶ **Patient information:** A handout on antidepressant discontinuation syndrome, written by the authors of this article, is provided on page 457.

Interruption of treatment with an antidepressant medication is sometimes associated with an antidepressant discontinuation syndrome; in early reports it was referred to as a "withdrawal reaction."[1] Symptoms of antidepressant discontinuation syndrome can include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal. All approved antidepressant agents have had case reports or warnings from their manufacturers of such reactions occurring in response to either abrupt discontinuation or medication tapering.[2] These medications include selective serotonin reuptake inhibitors (SSRIs),[3] tricyclic antidepressants,[4] monoamine oxidase inhibitors (MAOIs),[5] and atypical agents such as venlafaxine (Effexor),[6] mirtazapine (Remeron),[7] trazodone (Desyrel),[8] and duloxetine (Cymbalta).[9]

The importance of understanding and recognizing antidepressant discontinuation syndrome is threefold: (1) though typically mild, antidepressant discontinuation syndrome symptoms are associated with significant discomfort, work absenteeism, other psychosocial problems, and may on rare occasions be severe enough to require hospitalization[10-12]; (2) failure to recognize antidepressant discontinuation syndrome may result in medical and psychiatric misdiagnosis, potentially exposing patients to unnecessary diagnostic investigations or potentially risky medical interventions; (3) patients may be unwilling to use psychotropic medications in the future, thereby increasing their vulnerability to future relapses of depressive or anxiety disorders.

Pathophysiology

Although several hypotheses exist, the definitive pathophysiologic explanation for antidepressant discontinuation syndrome remains unknown. Early reports of antidepressant discontinuation syndrome made heavy use of the term "withdrawal" to describe discontinuation symptoms; however, antidepressant medications are not believed to be habit forming and are not associated with drug-seeking behavior.[13] Long-term use of SSRIs increases synaptic levels of serotonin through blockade of the serotonin reuptake pump, resulting in down-regulation of postsynaptic receptors.[14]

There is speculation concerning the possibility of a temporary deficiency of synaptic

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Maintain a high index of suspicion for antidepressant discontinuation syndrome.	C	19
Be alert to times when patients may need guidance on discontinuing an antidepressant or when they are likely to discontinue an antidepressant on their own.	C	27,32
Be sure to differentiate antidepressant discontinuation syndrome from relapse of depression and other psychiatric and medical conditions.	C	19,27,28
Gradually discontinue medication using one of the suggested tapering regimens (Table 5).	C	16,17,21,22,27,28

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 363 or http://www.aafp.org/afpsort.xml.

serotonin with abrupt withdrawal of an SSRI.[15] This deficiency is compounded by the fact that down-regulated receptors will remain in their relatively hypoactive state for days to weeks.[15] This is believed to result in antidepressant discontinuation syndrome directly or indirectly via downstream effects on other neurotransmitter systems (e.g., norepinephrine, dopamine, and γ-aminobutyric acid) implicated in depressive and anxiety disorders.[15]

Because tricyclic antidepressants and MAOIs also are serotonergically active, the same mechanism is implicated for their respective antidepressant discontinuation syndromes; however, tricyclic antidepressants also affect the cholinergic system, so rapid discontinuation may cause signs of parkinsonism and problems with balance. Because MAOIs cause changes in the alpha$_2$-adrenergic and dopaminergic receptors, their discontinuation may cause agitation and psychosis.

Epidemiology and Risk Factors

Because of the varied clinical presentation, transient nature, and lack of pathognomonic clinical features, there are relatively few data on incidence, prevalence, and other estimates of burden associated with antidepressant discontinuation syndrome. One observational study[16] found that four of 45 patients (9 percent) given fluoxetine (Prozac) and 26 of 52 patients (50 percent) given paroxetine (Paxil) reported discontinuation symptoms, with a mean onset of two days and mean duration of five days. A randomized controlled trial[17] (RCT) comparing three SSRIs found a lower incidence of antidepressant discontinuation syndrome with fluoxetine (14 percent) than with paroxetine (66 percent) or sertraline (Zoloft) (60 percent). This study was limited by its open-label design and was sponsored by the manufacturer of fluoxetine. In addition, a retrospective chart review[13] of 350 patients using SSRIs showed no significant added risk associated with age, sex, or diagnosis.

Perhaps the best evidence comes from an RCT[18] that found mild to moderate antidepressant discontinuation symptoms in 35 percent of patients given paroxetine and 14 percent given placebo who were abruptly withdrawn from treatment after 12 weeks. The difference of approximately 20 percent between active treatment and placebo for one of the drugs most commonly associated with antidepressant discontinuation syndrome may provide an upper boundary for the probability of the condition.[18]

DURATION OF TREATMENT

Although unconfirmed by prospective clinical trials, case reports of antidepressant discontinuation syndrome reactions are rare

among individuals who have received less than six to eight weeks of antidepressant treatment.[19] This generalization applies to antidepressant discontinuation syndrome that occurs in the settings of both abrupt and gradual antidepressant discontinuation. Such a time frame may be required to allow the synaptic changes that occur during long-term pharmacologic antidepressant treatment.

PHARMACOLOGIC PROFILE

For SSRIs, a relatively homogenous drug class, differences among the pharmacokinetic properties such as elimination half-life and metabolism may be the most clinically relevant *(Table 1)*.[20,21] Specifically, antidepressant discontinuation syndrome is more common in patients discontinuing agents with relatively short half-lives, such as paroxetine, than in those with longer half-lives, such as fluoxetine.[13,16,17,19,22] In recent years, slow-, extended-, or controlled-release formulations of venlafaxine (Effexor XR), paroxetine (Paxil CR), and fluoxetine (Prozac Weekly) have become available. Although there are limited data concerning weekly fluoxetine, antidepressant discontinuation syndrome reactions have been reported with controlled-release paroxetine and extended-release venlafaxine.[14,23]

Clinical Manifestations and Pathophysiology

CLINICAL MANIFESTATIONS

Antidepressant discontinuation syndrome involves a large number of psychological and physiological signs and symptoms. Case reports, audits of adverse drug reaction databases, and clinical trials report certain characteristic symptoms. These symptoms depend on the class of antidepressant used *(Table 2)*.[2,13,16,17,19,22,24,25] In a recent retrospective chart review[13] of patients on antidepressants and two small, prospective, randomized controlled trials,[16,24] patients' SSRIs were replaced with placebo for five days or their antidepressant medication was abruptly discontinued. All noted that the most common symptoms of SSRI withdrawal were dizziness, gastrointestinal upset, lethargy or anxiety/hyperarousal, dysphoria, sleep problems, and headache.[13,16,24]

Antidepressant discontinuation syndrome is most often seen in the primary care office in association with SSRI discontinuation, because SSRIs are the most commonly prescribed class of antidepressant medications. In 2000, a systematic review[25] of 46 case reports of SSRI discontinuation proposed the diagnostic criteria listed in *Table 3*.[25] The FINISH mnemonic (Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances, Hyperarousal) was created to facilitate rapid recognition

TABLE 1
Pharmacologic Properties of Selected Antidepressants

Drug	*Dosage range (mg per day)*	*Half-life (hours)*	*Active metabolite?*
Selective serotonin reuptake inhibitor			
Citalopram (Celexa)	10 to 60	35	No
Escitalopram (Lexapro)	10 to 30	27 to 32	No
Fluoxetine (Prozac)	20 to 80	84 to 144	Yes
Paroxetine (Paxil)	10 to 60	21	No
Paroxetine CR (Paxil CR)	12.5 to 62.5	15 to 20	No
Sertraline (Zoloft)	50 to 200	26	Yes
Atypical antidepressant			
Bupropion (Wellbutrin)	75 to 450	12 to 30	Yes
Buproprion SR (Wellbutrin SR)	100 to 400	12 to 30	Yes
Buproprion XL (Wellbutrin XL)	150 to 450	12 to 30	Yes
Duloxetine (Cymbalta)*	40 to 60	11 to 16	Yes
Mirtazapine (Remeron)	15 to 45	20 to 40	No
Trazodone (Desyrel)	50 to 400	7.1	Yes
Venlafaxine (Effexor)	75 to 450	3 to 13	Yes
Venlafaxine XR (Effexor XR)	75 to 450	3 to 13	Yes
Monoamine oxidase inhibitors			
Phenelzine (Nardil)	15 to 90	1.2	Yes
Tricyclic antidepressant*			
Amitriptyline	25 to 300	9 to 25	Yes
Clomipramine (Anafranil)	25 to 250	22 to 84	No
Desipramine (Norpramin)	25 to 300	14.3 to 24.7	No
Doxepin (Sinequan)	25 to 300	11 to 23	No
Imipramine (Tofranil)	25 to 300	10 to 16	Yes
Nortriptyline (Pamelor)	25 to 150	18.2 to 35	No

**Dosages listed are for treatment of depression.*

Information from references 20 and 21.

TABLE 2
Signs and Symptoms of Antidepressant Discontinuation Syndrome

	SSRI	*Atypical antidepressant*	*Tricyclic antidepressant*	*MAOI*
General				
Flu-like symptoms	+	+	+	—
Headache	+	+	+	+
Lethargy	+	+	+	—
Gastrointestinal				
Abdominal cramping	+	—	+	—
Abdominal pain	+	—	+	—
Appetite disturbance	+	+	+	—
Diarrhea	+		+	—
Nausea/vomiting	+	+	+	—
Sleep				
Insomnia	+	+	+	+
Nightmares	+	+	+	+
Balance				
Ataxia	+	—	+	—
Dizziness	+	+	+	—
Lightheadedness	+	—	+	—
Vertigo	+	+	+	—
Sensory				
Blurred vision	+	—	—	—
"Electric shock" sensations	+	+	—	—
Numbness	+	—	—	—
Paresthesia	+	+	—	—
Movement				
Akathisia	+	+	+	—
Myoclonic jerks	—	—	—	+
Parkinsonism	+	—	+	—
Tremor	+	—	+	—
Affective				
Aggression/irritability	+	—	—	+
Agitation	+	—	+	+
Anxiety	+	+	+	—
Low mood	+	+	+	+
Psychosis				
Catatonia	—	—	—	+
Delirium	—	—	—	+
Delusions	—	—	—	+
Hallucinations	—	—	—	+

NOTE: *Symptom categories listed by rate of incidence.*

SSRI = selective serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor; + = occur in withdrawal from this medication; — = do not occur in withdrawal from this medication.

Information from references 2, 13, 16, 17, 19, 22, 24, and 25.

(Table 4).[26] However, neither set of criteria[25,26] has been formally validated.

Multiple case reports demonstrate that antidepressant discontinuation syndrome associated with tricyclic antidepressants closely mimics that of the SSRIs.[3,4] However, signs of parkinsonism and profound problems with balance appear to be especially characteristic of antidepressant discontinuation syndrome caused by tricyclic antidepressant discontinuation.[3,4] Additionally, case reports have noted that the antidepressant discontinuation syndrome associated with MAOIs may involve more serious symptomatology such as aggressiveness, agitation, catatonia, severe cognitive impairment, or myoclonus and psychotic symptoms and may require more intensive management.[4,5]

ONSET AND COURSE

Discontinuation symptoms typically appear within three days of stopping antidepressant medication or initiating a medication taper, though it has been reported that reactions may occur within hours of the first missed dose.[9] Untreated symptoms are usually mild and resolve spontaneously in one to two weeks.[19] In rare but more serious cases involving psychosis, catatonia, or severe cognitive impairment, immediate psychiatric consultation may be required.

Diagnostic Considerations

MAINTAIN A HIGH INDEX OF SUSPICION

Any uncomfortable symptoms reported by patients receiving antidepressants should prompt close questioning for missed doses, unreported downward adjustments in dosage, or outright medication discontinuation.

DIFFERENTIATION FROM RELAPSE

The symptoms of antidepressant discontinuation syndrome that are associated with most antidepressants share features of major depression, including dysphoria, appetite changes, sleep problems, cognitive problems, and fatigue. By focusing on symptoms that distinguish antidepressant discontinuation syndrome from depressive illness relapse (e.g., dizziness, "electric shock" sensations, "rushing" sensations in the head, headache, and

nausea) and observing for rapid (i.e., within a few days) reversal of symptoms after restarting the antidepressant or complete resolution of symptoms in one to two weeks (highly uncharacteristic of a depressive relapse), a definitive diagnosis is fairly easy to make.[19,27] Depressive relapses or recurrences typically occur after at least two to three weeks or longer after cessation of medication and are most often marked by gradual worsening of depression, insomnia, and psychomotor symptoms.[28]

DIFFERENTIATION FROM OTHER CONDITIONS

Irritability, sleeplessness, and anxiety or agitation in a patient taking antidepressants may appropriately raise suspicion of an antidepressant-associated bipolar manic episode that must be distinguished from antidepressant discontinuation syndrome. The development of these symptoms should prompt close questioning about medication adherence, as previously mentioned. If such symptoms appear shortly after discontinuation or during dose reduction, rapid symptom resolution after restoring the antidepressant medication will lead to the correct diagnosis.

Antidepressant discontinuation syndrome also may be misdiagnosed as severe conditions including stroke, other neurologic conditions, infectious diseases, and adverse effects of other medications the patient is taking.[29] Antidepressant discontinuation syndrome has been reported when switching from one antidepressant agent to another.[30] When the new agent has different pharmacologic mechanism reactions than the first agent, antidepressant discontinuation syndrome may be misinterpreted as intolerable side effects from the new medication.[29]

Prevention and Management

USE OF ANTIDEPRESSANTS

For optimal treatment of most psychiatric conditions, and especially anxiety and depressive disorders, psychosocial interventions should be recommended along with or considered as alternatives to pharmacologic therapies. The all-too-common practice of "short-term" prescriptions for off-label, non–mental health reasons (e.g., irritable bowel syndrome, weight loss, headaches,

TABLE 3
Proposed Diagnostic Criteria for SSRI Discontinuation Syndrome

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TABLE 4
FINISH Mnemonic for Recognition of Antidepressant Discontinuation Syndrome

Flu-like symptoms
Fatigue
Lethargy
General malaise
Muscle aches/headaches
Diarrhea
Insomnia
Nausea
Imbalance
Gait instability
Dizziness/lightheadedness
Vertigo
Sensory disturbances
Paresthesia
"Electric shock" sensations
Visual disturbance
Hyperarousal
Anxiety
Agitation

Information from reference 26.

insomnia) has been associated with early antidepressant discontinuation and may increase the risk of antidepressant discontinuation syndrome.[31]

PATIENTS AT RISK OF DISCONTINUATION

Patients may be tempted to discontinue their antidepressant medication after they begin to feel better, a practice that invites both early relapse of illness and antidepressant discontinuation syndrome. Women may discontinue antidepressant use after discovering that they are pregnant. Ideally, patients should be counseled regarding the risks of illness relapse, the importance of treating symptoms to remission, the need for continuation and (where appropriate) maintenance pharmacotherapy, and the need for gradual discontinuation of medications before discontinuing care.[27,32]

TABLE 5
Gradual Taper Rates for Antidepressants

Drug	*Recommended taper rate*
Monoamine oxidase inhibitor	
Phenelzine (Nardil)	Reduction of 15 mg per day every two weeks or 10 percent per week
Tricyclic antidepressant	Gradually, up to three months
Selective serotonin reuptake inhibitor	
Fluoxetine (Prozac)	Gradual taper generally unnecessary
Paroxetine (Paxil)	Reduction of 10 mg per day every five to seven days with a final dosage of 5 to 10 mg per day before discontinuation*
Sertraline (Zoloft)	Reduction of 50 mg per day every five to seven days with a final dosage of 25 to 50 mg per day before discontinuation
Atypical antidepressant	
Venlafaxine (Effexor)	Reduction of 25 mg day every five to seven days with a final dosage of 25 to 50 mg per day before discontinuation*
Venlafaxine XR (Effexor XR)	Reduction of 37.5 to 75 mg per day every week with a final dosage of 37.5 mg per day before discontinuation*

NOTE: *These recommendations are expert opinion only.*

**—Slower taper may be needed.*

Adapted with permission from Shelton RC. Steps following attainment of remission: discontinuation of antidepressant therapy. Primary Care Companion J Clin Psychiatry 2001;3:172.

DISCONTINUING MEDICATION

Although there are no clinical trials comparing abrupt discontinuation with tapered discontinuation of antidepressants, tapering is recommended by experts, based on the suspected pathophysiology of antidepressant discontinuation syndrome.[33] Patients should be forewarned of the possibility of antidepressant discontinuation syndrome if antidepressants are discontinued, and that supervised tapering of medication over six to eight weeks may be required to minimize discontinuation symptoms. Several RCTs have shown that with abrupt cessation of antidepressants, symptoms can begin within days.[16,17,22] It may be possible to discontinue medication more quickly if doses are low; discontinuation may take longer (three months or more) after maintenance therapy. It may be possible to stop fluoxetine therapy without tapering. There are no clear, validated tapering recommendations. However, *Table 5*[27] offers one expert's recommendations for tapering rates.

MANAGEMENT

If antidepressant discontinuation syndrome occurs and other serious causes of these symptoms have been ruled out, the physician should begin by providing reassurance to the patient that the condition is reversible, is not serious or life threatening, and will run its course within one to two weeks. The physician should then consider restarting the antidepressant medication with a slow dose taper or providing support if the patient desires not to restart the antidepressant. Severe symptoms should resolve in fewer than three days, and often within 24 hours. If the antidepressant discontinuation syndrome occurs during a tapering of the antidepressant, consider restarting at the original dose and then taper at a slower rate. In cases where slow tapering is poorly tolerated, a medicine with a longer half-life such as fluoxetine may be substituted for the shorter half-life agent.

GENERIC DRUGS AND SUBSTITUTIONS

Not all formulations of the same drug are bioequivalent. Generic drugs are allowed up to a 20 percent difference. This may result

in an unintended sudden reduction in drug concentration if a patient's medication is switched to a generic or alternative brand.

TRICYCLIC ANTIDEPRESSANTS

Antidepressant discontinuation syndrome symptoms caused by tricyclic antidepressants that suggest cholinergic rebound (e.g., parkinsonism and other problems with movement) may respond to short-term use of anticholinergic agents such as atropine (Atropisol) or benztropine (Cogentin). This should be considered especially for patients who are opposed to restarting their tricyclic antidepressant.[34]

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Department of Defense, the U.S. Army Medical Department, or the U.S. Army or U.S. Air Force Services at large.

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