



Changing medications usually is not complicated, but problems can arise—especially with shorter half-life agents

Discontinuing an antidepressant?

Tapering tips to ease distressing symptoms

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Most psychiatrists have encountered patients who report distressing symptoms when they have forgotten to take their antidepressant for a few days or during changes in the medication regimen. A discontinuation syndrome can occur with almost any antidepressant, highlighting the need to slowly taper these medications when discontinuation is part of a treatment plan.

This article discusses antidepressant discontinuation syndrome (ADS) in a patient who experienced substantial distress after a rapid antidepressant taper in preparation for electroconvulsive therapy (ECT). My goal is to raise awareness of ADS, promote early detection of the syndrome, and address proper prevention and management strategies.

CASE REPORT

Feeling 'worse than ever'

Mr. J, a 32-year-old tax accountant, is hospitalized for a major depressive episode (MDE) associated with deteriorating function and suicidal ideation. This second lifetime MDE started 8 months before his admission to an inpatient mood disorders unit.

Mr. J initially was treated with fluoxetine, up to 40 mg/d across 14 weeks, with good tolerability but no significant benefit. His psychiatrist switched Mr. J to bupropion but stopped it after 4 weeks because of side effects—including headaches, insomnia, and tremor—and limited antidepressant benefit. Venlafaxine XR was initiated next, at 150 mg/d within the first 2 weeks, increased to 225 mg/d at week 6, then titrated to 300 mg/d at week 10. After 10 weeks, aripiprazole, 5 mg/d, was added because Mr. J showed only partial, limited response to venlafaxine XR and this antipsychotic is indicated for adjunctive treatment of major depressive disorder.

continued



Antidepressant discontinuation

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SSRIs and SNRIs have similar ADS symptoms but generally do not cause the anticholinergic effects seen with tricyclic discontinuation

Table 1

FINISH: Symptoms of antidepressant discontinuation syndrome

Flu-like symptoms
Insomnia
Nausea
Imbalance
Sensory disturbances
Hyperarousal (anxiety/agitation)
Source: Reference 1

Mr. J reported mild, transient restlessness but otherwise he tolerated the medications well, and he claimed excellent adherence. After 6 additional weeks of treatment, however, Mr. J was hospitalized because of persistent severely depressed mood, increasing suicidal ideation, and inability to function at work.

On admission, Mr. J is evaluated and agrees to ECT. To meet the ECT service's protocol, venlafaxine XR is reduced to 150 mg/d for 2 days and then stopped when ECT is started. Aripiprazole is continued at 5 mg/d.

Mr. J tolerates the first ECT treatment well, but the morning before his second treatment he complains of feeling "worse than ever." An agitated Mr. J reports dramatically intensified suicidal ideation—much more intrusive than before he was hospitalized. He also complains of diffuse muscle aches and cramps, runny nose, nausea, headache, and burning sensations in both arms and hands. He withdraws consent for ECT and returns to the mood disorders unit for ongoing treatment.

Could this be ADS?

Yes, it could. In this case, the inpatient psychiatrist and treatment team were lulled into a false sense of security by Mr. J's history of few side effects with various treatments and medication changes. The ECT service wanted the patient off venlafaxine XR before beginning ECT, and the treatment team believed a quick taper would not cause discontinuation symptoms

because Mr. J was taking an "extended-release" medication.

Within 72 hours, Mr. J went from taking 300 mg/d of venlafaxine XR to none. Within 2 days of cessation, he complained of symptoms that could characterize a discontinuation syndrome. A potential red herring in this case is that the patient complained of feeling worse after his first ECT treatment, and one might erroneously think the myalgias, headache, and other somatic symptoms were side effects of ECT and/or anesthesia.

Typical ADS symptoms

Nearly all antidepressant classes are associated with ADS. Symptoms vary from patient to patient but typically include the "FINISH" syndrome: flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal (anxiety/agitation) (Table 1).¹

Adverse effects after stopping tricyclic antidepressants have been well documented. They may include FINISH syndrome features as well as cholinergic overdrive or "rebound" such as abdominal cramping and diarrhea.²⁻⁴ Reports of ADS after patients stopped selective serotonin reuptake inhibitors (SSRIs) emerged soon after these agents were introduced.⁵⁻⁷ Similarly, ADS has been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs), including venlafaxine,⁸⁻¹⁰ venlafaxine XR,¹¹ and duloxetine.¹² ADS symptoms are similar with SSRIs and SNRIs, generally without the anticholinergic effects associated with tricyclic antidepressant discontinuation.

Fewer reports of discontinuation syndrome exist for bupropion, mirtazapine, monoamine oxidase inhibitors (MAOIs), and nefazodone.¹³⁻¹⁷ Discontinuation-emergent syndromes with these non-SSRI/non-SNRI antidepressants tend to present differently. With MAOIs, for example, neuropsychiatric symptoms such as severe anxiety, agitation, pressured speech, sleeplessness or drowsiness, hallucinations, delirium, and paranoid psychosis can be prominent.¹⁷

The prevalence of ADS is unclear, and published estimates vary widely because

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Evidence suggests shorter half-life antidepressants carry the highest risk for ADS

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Table 2

ADS symptoms can range across a variety of system clusters

System cluster	Symptoms
Neurosensory	Vertigo, paresthesias, shock-like reactions, myalgias, numbness, sensitivity to sound, unusual visual sensations, ringing in the ears
Neuromotor	Tremor, myoclonus, ataxia/gait instability, visual changes, restless legs, problems with speech, tongue movements
Gastrointestinal	Nausea, vomiting, cramps/bloating, diarrhea, anorexia
Neuropsychiatric	Anxiety/panic, depression, mood swings, suicidal ideation, irritability, impulsivity, confusion, psychosis
Vasomotor	Diaphoresis, flushing, temperature intolerance
Other	Headache, insomnia, vivid dreams, nightmares, lethargy/fatigue, flu-like symptoms

ADS: antidepressant discontinuation syndrome

Source: Construct suggested by Shelton,²¹ with additional symptoms added from other sources, including the discontinuation symptom checklist of Rosenbaum et al²³

of the lack of large controlled studies. ADS rates with SSRIs/SNRIs have been reported from as low as 0% for fluoxetine to higher rates for shorter half-life antidepressants:

- 2.2% with sertraline
- 14% with fluvoxamine
- 20% with paroxetine
- 30.8% with clomipramine.

These rates come from a retrospective case note review of patients who discontinued antidepressants under supervision.¹⁸ In a small cohort of outpatients being treated for major depressive disorder, stopping venlafaxine XR was associated with discontinuation symptoms for the next 3 days in 7 of 9 patients (78%), compared with 2 of 9 patients (22%) stopping placebo.¹¹

Diagnostic criteria have been proposed for ADS associated with serotonin (5-HT) reuptake inhibitors.¹⁹⁻²² Proposed ADS definitions differ somewhat, but essentially 3 features guide the diagnosis:

- appearance of characteristic symptoms (*Table 2*)^{21,23}
- timing of those symptoms, which usually emerge within 1 week of abrupt cessation or marked reduction of the antidepressant
- symptoms generally are mild, short-lived, self-limiting, and/or rapidly reversed by restarting the original antidepressant.

Evidence suggests shorter half-life antidepressants may be associated with the

highest risk for ADS, but other risk factors remain presumptive (*Table 3*).

What causes ADS?

Although the exact cause of ADS is unknown, the literature proposes several theories.

Because of the central serotonin system's complex connections, acute reduction in synaptic serotonin when an SSRI or SNRI is abruptly or too quickly stopped may be the first in a cascade of steps affecting transmission of multiple monoamines. Parallels have been drawn between the phenomenon observed with rapid depletion of tryptophan—the essential amino acid precursor for the synthesis of 5-HT—and ADS seen with abrupt discontinuation of serotonergic antidepressants. This suggests that acute drops in neurotransmitter levels can precipitate neuropsychiatric and somatic manifestations of ADS.²⁴

Patients' uncomfortable symptoms likely are caused by the serotonin, norepinephrine, and cholinergic systems and their complex interactions.²⁵ Individual genetic factors may influence patients' vulnerability for ADS.

Managing ADS

Awareness and prevention. ADS can be misinterpreted as side effects of newly started treatment after an antidepressant is stopped. In Mr. J's case, the appearance of

muscle aches, headaches, and other ADS symptoms after ECT was started easily could have been perceived as adverse effects of ECT. Mr. J's agitation and increased suicidal ideation could lead a clinician to mistakenly think that MDE was worsening because the antidepressant was stopped before ECT became effective. Being aware of ADS can prevent misdiagnosis and allow you to quickly identify the condition, manage the reversible syndrome, and continue with new treatment plan—in this case, ECT.

You can help prevent ADS by educating patients about the need to adhere to antidepressant regimens and to avoid missing doses. Consider ADS risk factors—particularly medications' half-lives—before you start, change, or stop antidepressant therapy. Gradually taper all antidepressants being discontinued, with the possible exception of fluoxetine (which, including its active metabolite, has an elimination half-life of approximately 1 to 2 weeks).

Tapering antidepressants is more art than science because we have no controlled data to support any particular tapering regimen. Tailor the taper duration based on each patient's response to sequential dosage reductions. Antidepressants with shorter half-lives—such as venlafaxine or paroxetine—may need to be tapered more slowly, perhaps by reducing the dosage by 25% every 4 to 6 weeks. If you plan to switch medications, this process may be expedited during a cross-taper to another antidepressant. You still may see discontinuation symptoms, however, depending on which new agent is chosen and which is being stopped.

Treating ADS. Appropriately recognizing ADS risk and slowly tapering antidepressants as needed usually prevents clinically significant distress associated with discontinuation. For some patients, however, ADS may be particularly severe or prolonged, or may emerge at the end of a slow taper.

Challenging cases may be more likely with paroxetine or venlafaxine—even the extended-release or controlled-release preparations. The elimination half-life of parox-

Table 3

Possible patient risk factors for developing ADS*

Abrupt antidepressant discontinuation
Shorter half-life antidepressants
Intermittent nonadherence/noncompliance
Interrupted treatment or use of 'drug holiday'
Specific antidepressant properties (such as potent [5-HT] receptor antagonism, cholinergic effects)
Younger patient age (including children and adolescents)
Female gender
Pregnancy
Neonate/breast-fed infant (mother on antidepressant therapy)
History of ADS
Vulnerability to depressive relapse
Duration of treatment (possible increased risk with more than 4 to 6 weeks of antidepressant exposure)
Switches to or between generic antidepressant formulations (related to variations in bioequivalence)
History of early adverse reactions when the antidepressant was initiated
ADS: antidepressant discontinuation syndrome *Risk factors for ADS have not been rigorously studied in randomized controlled trials. Possible risk factors in this table were found in case reports

etine is 15 to 20 hours, and the half-lives of venlafaxine and venlafaxine XR are 5 to 11 hours. Desvenlafaxine's half-life is 11 hours, and product labeling of this enantiomer of racemic venlafaxine notes that discontinuation symptoms have occurred.²⁶ ADS treatment depends on the severity of the reaction and whether or not further antidepressant therapy is necessary.

For mild ADS, reassurance and treatment focused on specific symptoms—such as sedative-hypnotics for insomnia or benzodiazepines for anxiety—may be all that is needed, because ADS tends to gradually resolve over an average of 10 days.²⁷

For more severe ADS, or when ongoing antidepressant therapy is indicated, restarting the recently withdrawn antidepressant at the pre-ADS dosage typically resolves the

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For mild ADS treatment for specific symptoms may be all that is needed



Antidepressant discontinuation

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Restarting an antidepressant at the pre-ADS dosage usually resolves symptoms within 24 hours

Related Resources

- Schatzberg AF, Blier P, Delgado PL, et al. Antidepressant discontinuation syndrome: consensus panel recommendations for clinical management and additional research. *J Clin Psychiatry*. 2006;67(suppl 4):27-30.
- American Family Physician. Patient handout on antidepressant discontinuation. www.aafp.org/afp/2006/0801/p457.html.
- Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry*. 1998;44(2):77-87. See appendix for discontinuation-emergent signs and symptoms checklist.

Drug Brand Names

Aripiprazole • Abilify	Mirtazapine • Remeron
Bupropion • Wellbutrin	Nefazodone • Serzone
Clomipramine • Anafranil	Paroxetine • Paxil
Desvenlafaxine • Pristiq	Sertraline • Zoloft
Duloxetine • Cymbalta	Venlafaxine • Effexor
Fluoxetine • Prozac	Venlafaxine extended-release • Effexor XR
Fluvoxamine • Luvox	Zolpidem • Ambien
Lorazepam • Ativan	

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Dr. Muzina reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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syndrome within 24 hours. Then employ a slower, more cautious taper when next attempting to discontinue that antidepressant.

Another option. An alternate management strategy is to substitute fluoxetine to suppress ADS associated with shorter half-life SSRIs or SNRIs. Case reports^{18,20,28} suggest that fluoxetine, 5 to 20 mg/d, can be used to ameliorate venlafaxine-induced ADS. Fluoxetine can be tried as monotherapy for 1 to 2 weeks and then rapidly tapered or stopped. Others have suggested combination therapy, such as:

- restarting venlafaxine at the pre-ADS dose plus fluoxetine, 20 mg/d
- tapering venlafaxine by 50% every 5 days until stopped
- reducing fluoxetine 1 week later to 10 mg/d for 5 days
- then stopping fluoxetine.²⁸

In general, SSRIs should not be co-administered with SNRIs long-term because of potential additive adverse effects such as serotonin syndrome. Combining fluoxetine with an SNRI such as venlafaxine for the purpose of tapering off venlafaxine and reducing ADS risk probably

is safe, however, as long as the fluoxetine dose is low (5 to 20 mg) and SNRI reduction begins immediately, with a plan for complete tapering.

CASE CONTINUED

ECT treatment proceeds

Venlafaxine XR is not restarted to address Mr. J's suspected ADS because of concerns about potential increased risk for cardiac events (asystole, prolonged bradycardia) during ECT with concomitant venlafaxine use.^{29,30} Fluoxetine, which rarely may prolong ECT-induced seizures, is deemed a safer choice and is started immediately at 20 mg/d.

Because of Mr. J's other symptoms, we prescribe lorazepam, 0.5 mg bid, for anxiety for 2 days; increase aripiprazole to 5 mg bid for agitation; and add zolpidem, 10 mg at bedtime, for insomnia. The following day, Mr. J reports substantial relief from ADS symptoms, including myalgias, paresthesias, and suicidal ideation.^{21,23}

His second ECT treatment is administered the next day, followed by a successful course of 9 treatments and partial remission of the MDE within 3 weeks. Fluoxetine is reduced to 10 mg/d one week into the ECT series, then discontinued one week later. No signs of emergent ADS are seen at discharge or 2-week outpatient follow-up. Mr. J achieves full remission with maintenance ECT plus bedtime doses of mirtazapine, 30 mg, and aripiprazole, 7.5 mg, across 6 months of follow-up care.

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Clinical Point

Substituting fluoxetine for a shorter half-life antidepressant may suppress ADS symptoms

Bottom Line

With the possible exception of fluoxetine, all antidepressants may be associated with an uncomfortable multisystem syndrome if discontinued too quickly. To minimize the risk of antidepressant discontinuation syndrome (ADS), gradually taper short half-life antidepressants such as venlafaxine across several weeks. Recognizing ADS early and quickly resuming the antidepressant or substituting fluoxetine can reverse this distressing syndrome.