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# Discontinuing Medications: When, Why, and How-to

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Most often, psychiatric medications are discontinued unilaterally by the patient, without the psychiatrist's input or consent. This creates a burden on the mental health system when discontinuation of medication results in decompensation into a psychotic, manic, or severely depressed state that leads to an emergency psychiatry visit or hospitalization.

As clinicians, our best preventive strategy is educating patients and their caregivers about why the medication is being prescribed, what the adverse effects are, how to manage the adverse effects, and the risk of relapse with abrupt medication discontinuation. Setting the stage early with a discussion about medication discontinuation is time well spent. Pregnancy, medical comorbidities, extended travel abroad, relocating geographically, change in insurance/financial status, and converting to a medication-aversive religion are just a few of the occurrences that create an immediate need to discuss the risks and benefits of medication adherence.

If discontinuation of a medication is inevitable, a planned discontinuation will optimize outcomes. **Table 1** lists many common scenarios in which a planned discontinuation occurs. The psychiatrist's role is to act as a consultant to maximize the likelihood of a successful taper and discontinuation, and minimize collateral morbidities or withdrawal complications. With some disorders, including MDD, obsessive-compulsive disorder (OCD), and panic disorder, guidelines exist with a clear recommendation of a time frame for symptom remission before a taper and discontinuation are considered.

In disorders such as bipolar I and II disorders and schizophrenia, a strong case can be made for lifelong pharmacotherapy. However, even with these serious disorders, a patient or his or her guardian may request a drug holiday or medication-free trial to see if the patient can do well without continued use of the medication, with an accompanying relief of sometimes significant adverse effects. There is evidence that a minority of patients with bipolar disorder or schizophrenia remain relapse-free indefinitely after medication discontinuation.[1]

Once a patient has made a clear decision for a medication-free trial, it is important to collaborate with him during this process. Ideally, this includes regular follow-up visits to monitor the patient for early signs of relapse and withdrawal or discontinuation symptoms. Assure the patient that you will remain active in his treatment, despite your disagreement with the decision to stop the medication, and that you will restart the medication at any time as needed.

In rare cases, when medication discontinuation creates a risk of danger to the patient or others, legal intervention may be required, including the possibility of requesting a court-appointed guardian to make the final decision. One example of this is a patient with recurrent MDD, currently symptom-

## ACTIVITY GOAL

The goal of this activity is to present information on why a patient might decide to discontinue psychotropics as well as best strategies for discontinuing, and why medication discontinuation might be necessary.

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## LEARNING OBJECTIVES

At the end of this CE activity, participants should be able to:

1. Describe the reasons a patient might decide to discontinue medication.
2. Describe the primary recommendations of practice guidelines for several psychiatric disorders.
3. Develop and use a planned discontinuation to achieve optimum outcomes.
4. Recognize when medication discontinuation is warranted.

## TARGET AUDIENCE

This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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John J. Miller, MD, was on the Speakers Bureau for Pfizer Inc, until April 26, 2012. He is currently on the Speakers Bureau for AstraZeneca, Sunovion, and Forest; is a consultant for AstraZeneca and Sunovion; and holds Pfizer stock in the amount of $3552.

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CATEGORY 1

free and receiving medication, who has a history of high suicide lethality when depressed. Another example is a patient with schizophrenia, currently with remission of positive symptoms, who experiences auditory hallucinations and delusions when decompensated and places others in serious danger.

## Current evidence-based guidelines

The American Psychiatric Association has developed guidelines to aid in the treatment of many major mental illnesses. For cases in which these guidelines are outdated, an updated "Guideline Watch" is often provided as a bridge to the next published practice guideline, although these are not considered comprehensive or complete.

*Major depressive disorder*. The practice guideline for the treatment of MDD was most recently updated in October 2010.[2] The guidelines recommend that patients who have had 3 or more episodes of major depression should remain on a regimen of maintenance pharmacotherapy. Considerations that support maintenance therapy for patients with fewer than 3 episodes include severe episodes, the presence of psychosis or suicidality, family history of affective disorders, and ongoing psychosocial stressors. A higher degree of confidence for discontinuing pharmacotherapy for MDD occurs when the patient completes a course of adequate cognitive-behavioral therapy or interpersonal psychotherapy. The antidepressant medication should be slowly tapered over several weeks at a minimum.

*Bipolar disorder*. The practice guideline for the treatment of bipolar disorder was published in November 2005.[3] The more comprehensive guideline was published in April 2002.[4] An updated comprehensive guideline is pending. There is general agreement that bipolar disorder is a lifelong illness that presents with mood episodes of all types and with significant heterogeneity from person to person. The guidelines are outdated and in dire need of an update. It is common practice to treat bipolar I disorder with lifelong maintenance pharmacotherapy, but the published literature is limited on this topic. There is consensus that maintenance pharmacotherapy should follow a single manic episode.

*Schizophrenia*. The practice guideline for the treatment of schizophrenia was published in September 2009.[5] This guideline is an update of important clinical studies (eg, Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE] and Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study [CUtLASS]) and novel agents. The last comprehensive practice guideline that provides information on maintenance treatment and discontinuation strategies was published in February 2004.[6] This guideline states that antipsychotics for maintenance treatment "substantially reduce the risk of relapse in the stable phase of illness and are strongly recommended. . . . Indefinite maintenance antipsychotic medication is recommended for patients who have had multiple prior episodes or 2 episodes within 5 years."

*Obsessive-compulsive disorder*. The practice guideline for the treatment of OCD was updated in July 2007.[7] The guidelines state: "Successful medication treatment should be continued for 1 to 2 years before considering a gradual taper by decrements of 10% to 25% every 1 to 2 months while observing for symptom return or exacerbation. Successful ERP (exposure and response prevention) should be followed by monthly booster sessions for 3 to 6 months, or more intensively if response has been only partial."

*Panic disorder*. The practice guideline for the treatment of panic disorder was updated in January 2009.[8] The guidelines recommend continuing pharmacotherapy for 1 or more years after acute symptom response to allow further symptom improvement and to minimize risk of relapse. The recommendation when using SSRIs, SNRIs, and TCAs is to lower the dosage slowly every month or two and monitor for early symptoms of relapse. The recommendation for benzodiazepines is a decrease in dosage no faster than 10% weekly. A course of cognitive-behavioral therapy before medica-

### Table 1 – Reasons for psychotropic medication discontinuation

- Medication is ineffective
- Iatrogenic mental status change (switch to mania on antidepressant)
- Intolerable adverse effects
  - Sexual dysfunction
  - Weight gain
  - Weight loss
  - Hyperglycemia
  - Hyperlipidemia
  - Extrapyramidal symptoms
  - Akathisia
  - Somnolence
  - Sedation
  - Cognitive dysfunction
  - Anticholinergic adverse effects
  - Endocrinological complications: hypothyroidism, hyperprolactinemia, insulin receptor desensitization, infertility
  - Anxiety
  - Agitation
  - Insomnia
  - Nausea
  - Amotivation
  - Apathy
  - Hypertension
- Patient's choice to discontinue medication (patient competent)
- Family/guardian's preference to discontinue medication
- Patient's choice to follow family/peer group recommendation
- Pregnancy
- Change in financial status
- Change in insurance status
- Geographical relocation
- Onset of complicating medical comorbidity
- Incarceration with limited or no correctional institution's formulary
- Surgery, emergent or elective
- Recurrent abuse of a medication that a patient has developed tolerance for
- Substance abuse/dependence
- Overdose risk

### Table 2 – Pharmacokinetic and pharmacodynamic considerations

- Cytochrome P-450 pathways (of psychiatric medication or other agent being used)
  - Substrate
  - Inhibitor
  - Inducer
- P-glycoprotein pathways (of psychiatric medication or other agent being used)
  - Substrate
  - Inhibitor
  - Inducer
- Drug half-life
- Drug's binding affinity to various receptors
- Receptor profile of medication (will determine mechanism of action and adverse effects)
- Duration patient has been receiving the medication
- Medication dosage at time of discontinuation

(Please see Discontinuing Medications, page 34)

CATEGORY 1

# Discontinuing Medications

*Continued from page 33*

tion taper and addressing any underlying psychosocial stressors is also recommended.

## Strategies and considerations during discontinuation

When meeting with a patient who is requesting medication discontinuation, the first step is to engage in a conversation aimed at having the patient reconsider his decision. Exploring all of the reasons that contributed to the patient's decision for medication discontinuation provides insight that can help address his concerns. Detailed documentation in the patient's medical record of this conversation is important. In some cases, it may be prudent to have the patient or guardian acknowledge competent understanding of the risks involved with discontinuation and sign an informed consent.

Although every medication has its common adverse effects, they can vary considerably among patients. A comprehensive discussion about adverse effects may reveal sexual dysfunction that the patient is embarrassed to talk about; switching to a different medication may address this issue.

### Table 3 – Common withdrawal symptoms with abrupt discontinuation

- Anticholinergic withdrawal symptoms[10]
  - Irritability
  - Dysphoria
  - Nausea/vomiting/diarrhea
  - Slowed thinking
  - Motor retardation
  - Lassitude
  - Bradykinesia
  - Sleep disruption/nightmares
- Antihistamine withdrawal symptoms
  - Histaminergic rebound, insomnia
- Benzodiazepine withdrawal symptoms[11]
  - Anxiety
  - Restlessness
  - Insomnia
  - Agitation
  - Irritability
  - Muscle tension
  - Tremor
  - Severe: seizures, psychosis, persistent tinnitus
- Dopamine-2 receptor withdrawal symptoms
  - Dyskinesia and/or dystonia
  - Psychosis
- Serotonin discontinuation syndrome[12]
  - Dizziness
  - Lethargy/fatigue
  - Sleep disturbance/insomnia
  - Anxiety
  - Agitation
  - Irritability
  - Poor concentration
  - Increased dreaming/vivid dreams
  - Nausea/vomiting/diarrhea
  - Headache
  - Paresthesia (electric shock sensation)
  - Tremor
  - Chills

## CASE VIGNETTE

**TC is a 35-year-old single man with a 10-year history of OCD. He has done well with high-dose sertraline for the past 6 years, with sexual dysfunction as the main adverse effect. He recently entered a serious relationship, and the sexual dysfunction has become an issue. He seeks guidance to discontinue the sertraline.**

**Because he has been receiving a high dose of an SSRI for many years, the tapering schedule should be very slow. He has completed exposure/response prevention cognitive-behavioral therapy and will likely have greater success discontinuing the sertraline. The sertraline is tapered from the current daily dose of 200 mg by 25 mg every 2 weeks, and he is monitored with monthly follow-up appointments. He is instructed to track his symptoms, and if there is any symptom relapse, he will restart the previous medication dosage.**

Dosing regimens can be tailored to each patient's experience. If the patient finds it difficult to comply with a complicated dosing regimen, offering to switch to a different medication or formulation—one that is dosed once daily or is a long-acting injectable dosed biweekly or monthly—may address the frustration. Perhaps the patient is averse to the monitoring laboratory work that is required with some medications, and switching to a different drug that does not require blood draws may be the solution.

For most patients, nefazodone is sedating, but on occasion it can be activating. Patients for whom it is activating can be directed to take nefazodone in the morning rather than at bedtime. SSRIs can be similarly unpredictable with activating or sedating effects. Explaining how the patient can change the time of dosing based on how he feels several hours after taking a medication can make the difference between adherence and nonadherence.

The effects of food on the absorption of some medications (eg, ziprasidone, lurasidone, vilazodone) can be significant. Each of these drugs requires a minimal caloric intake at the time of dosing, or the absorption is decreased by up to 50%. If the patient takes the medication with food on some occasions and without food at other times, the blood level can vary 2-fold, which affects the drug's effectiveness and adverse effects.

Occasionally, there may be serious adverse effects with the continued use of a medication. Neuroleptic malignant syndrome can occur with any dopamine-2 receptor antagonist, and leukopenia can be a consequence of clozapine treatment. Serotonergic agents can cause serotonin syndrome, which is as serious and life-threatening as neuroleptic malignant syndrome. The risk of a benign rash with use of lamotrigine for bipolar disorder and other mood disorders is as high as 10%; the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis in adults is 0.08% (higher in children).

Unplanned pregnancies present an especially difficult challenge, because the risk of relapse of the primary psychiatric disorder may cause greater harm to the developing fetus than continuing the medication. Mania, severe depression, severe anxiety, and psychosis can significantly affect fetal development. With some medications, such as lithium, divalproex, carbamazepine, and the benzodiazepines, the first trimester presents the greatest risk of teratogenesis. Exposure in the third trimester is of greater concern with other agents, including the serotonin reuptake inhibitors.

## CASE VIGNETTE

**A 32-year-old woman with a long history of bipolar I disorder, who has been euthymic and functioning well for several years, presents to a routine visit matter of factly stating that she has decided to discontinue divalproex monotherapy. A lengthy discussion ensues, in which she acknowledges that she is worried about damage to her liver, especially since her father died of complications of a liver disease. Also, she has recently become engaged and is excited about starting a family. She has heard on the news that a child born to a mother who is taking divalproex can have a lower IQ, and she is scared.**

**Her concerns are validated, and alternatives to divalproex (eg, lithium, carbamazepine, many atypical antipsychotics) are discussed. She is offered a referral to the local university medical center, where there is an expert psychiatrist who specializes in psychiatric medication options/**

**risks/benefits during pregnancy. In addition, a course of cognitive-behavioral therapy designed for individuals with bipolar disorder is suggested. She agrees to consider these options, and a follow-up visit is scheduled.**

When an immediate medication discontinuation is not required and the patient is agreeable to a planned taper, there are many pharmacokinetic and pharmacodynamic factors to consider that will maximize a successful discontinuation (**Table 2**). In general, the longer the patient has been receiving the medication and the higher the maintenance dosage, the slower the taper. This is especially true for SSRIs, SNRIs, antipsychotics, lithium, and benzodiazepines.

Abrupt discontinuation of an SSRI or SNRI, with the exception of fluoxetine (because of its long half-life), can result in serotonin discontinuation syndrome. Although not dangerous, serotonin discontinuation syndrome can cause significant distress for a patient, not uncommonly resulting in a trip to the emergency department because of the patient's fear that some serious brain insult has occurred. Often, the acute distress from serotonin discontinuation syndrome is misinterpreted by the patient as relapse of symptoms, and the patient can become fearful of tapering and discontinuing the medication.

Many antipsychotics have complex receptor binding profiles, and abrupt discontinuation of these agents can produce a wide range of withdrawal symptoms (**Table 3**). For more potent dopamine-2 antagonists, withdrawal dyskinesia can be quite unsettling, although it is rapidly reversed by restarting the antipsychotic at its previous dosage and then proceeding with a much slower taper. Other abrupt withdrawal effects include psychosis, cholinergic rebound, histaminergic rebound, and α-adrenergic rebound.

It is generally accepted that rapid discontinuation of lithium increases relapse risk compared with gradual discontinuation for a patient with bipolar disorder. Although controversial, some findings suggest that after lithium discontinuation and subsequent symptom relapse, a person is less responsive to lithium when it is restarted.[9] Acute benzodiazepine discontinuation can be life-threatening, putting the individual at risk for hypertension, cardiac complications, and seizures.

## Conclusion

The decision to discontinue a psychiatric medication involves weighing the risks versus the benefits. Abrupt discontinuation, although occasionally necessary, results in a higher incidence of withdrawal symptoms, relapse, and other complications. Once the decision has been made by a competent patient to discontinue medication, even if you disagree with the patient's decision, a thoughtful and gradual tapering strategy should be designed based on the pharmacodynamic, pharmacokinetic, and disorder-specific factors that exist.

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## POST-TEST

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**1. Which of the following statements is true?**
- A. Medication discontinuation is most often a collaborative decision between patient and psychiatrist.
- B. Medication discontinuation is most often a unilateral decision by the psychiatrist.
- C. Medication discontinuation is most often a unilateral decision by the patient.

**2. Lifelong pharmacotherapy is indicated for which of the following disorders?**
- A. MDD
- B. Borderline personality disorder
- C. Panic disorder
- D. All of the above
- E. None of the above

**3. The practice guidelines for MDD recommend maintenance pharmacotherapy for which of the following?**
- A. Patients who have had 3 or more episodes of major depression
- B. Patients who have had 5 or more episodes of major depression
- C. Patients who have had 7 or more episodes of major depression
- D. None of the above

**4. Maintenance therapy should follow a single manic episode in patients with bipolar disorder.**
- A. True
- B. False

**5. Guidelines for obsessive-compulsive disorder recommend that treatment lasts for _____ before a medication discontinuation is considered.**
- A. 1 year
- B. 1 to 2 years
- C. At least 2 years
- D. Longer than 2 years

**6. The risk of continuing medication during pregnancy puts the fetus at greater risk than would a relapse of the psychiatric disorder in the mother.**
- A. True
- B. False

**7. The longer the patient has been receiving the medication and the higher the maintenance dosage, the slower the taper, is especially true for which of the following medications?**
- A. Nefazodone
- B. Citalopram
- C. Bupropion
- D. Amitriptyline

**8. Abrupt discontinuation of which of the following is least likely to result in serotonin discontinuation syndrome?**
- A. Citalopram
- B. Duloxetine
- C. Fluoxetine
- D. Sertraline

**9. Once lithium is discontinued, there is no problem restarting it if there is a relapse of symptoms.**
- A. True
- B. False

**10. Abrupt medication discontinuation may be necessary if symptoms of which of the following develop?**
- A. Neuroleptic malignant syndrome
- B. Serotonin syndrome
- C. Stevens-Johnson syndrome
- D. All of the above

**Erratum**

In question 10 on the post-test of our June CME activity, "Epidemiology and Treatment of Substance Use and Abuse in Adolescents," answer A incorrectly was given as "Brief strategic family therapy"; it should have been "Multidimensional family therapy."