Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research?

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ABSTRACT

Recent media reports have refocused attention on the syndromic manifestation experienced by some patients as they discontinue their antidepressant medication (“discontinuation syndrome”). This attention has been accompanied by criticisms that mainstream psychiatry has either ignored or minimized these symptoms and exposed patients to potentially harmful and addictive treatments. Yet, there has been very limited original research on the prevalence of discontinuation syndrome in the last decade. There is growing concern that labeling antidepressants as addictive may drive down the use of these medications and exacerbate the mental health crisis in which depression is often undiagnosed and undertreated. Hence, the onus of guiding patients through questions and concerns related to the use and discontinuation of antidepressants has fallen mainly on primary care and psychiatric clinicians. This report discusses some common decisional uncertainties relevant to antidepressant discontinuation and recommends a shared decision-making approach. Further, this report seeks to outline a roadmap for clinicians to drive research on this important yet understudied topic.

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A Brief Discussion of Selected Recent Publications

In recent years, Fava and colleagues have published 2 systematic reviews on discontinuation of SSRIs14 and SNRIs,15 with the highest rates of symptoms reported with paroxetine and venlafaxine, respectively. However, tools used to assess discontinuation symptoms have not been uniform.16 Even when the same rating scale is used,
Antidepressants (with or without psychotherapy) are usually offered as a treatment option. However, antidepressants are not the sole effective option available for these conditions. Even for MDD, alternative options include psychotherapy, exercise, neurostimulation, and nonantidepressant pharmacotherapy. Psychotherapy is recommended as first-line treatment for mild-to-moderate severity MDD. Antidepressants (with or without psychotherapy) are usually recommended as first-line treatment for MDD patients with severe depression. To inform the treatment options offered to the patient, clinicians should systematically assess prior treatment history. After inadequate improvement with 2 or more antidepressant medication courses (treatment-resistant depression [TRD]), likelihood of remission with the next medication trial is below 15%. Thus, presence of TRD should inform patients and clinicians to select TRD-specific pharmacologic (such as intranasal esketamine) or neuromodulation (such as repetitive transcranial magnetic stimulation and electroconvulsive therapy) treatments. Before making a treatment decision, clinicians should check with patients about their knowledge and comfort with making treatment decisions. In addition to their preference for a specific treatment, clinicians should also explore barriers to treatment. Such barriers may include cost, time commitment, access to trained providers, and stigma related to mental illness. With a third of the US population living with depression, antidepressants are a commonly prescribed class of medications.

### Decisional Uncertainties

**Is the use of antidepressant medication indicated?**

- Confirm diagnostic indication
- Assess prior treatment history
- Evaluate other treatment options

**Which antidepressant medication is appropriate?**

- Options available: SSRIs, SNRIs, tricyclics, atypical antidepressants
- Decision aid: cost, side effect, severity of discontinuation symptoms
- Treatment selection biomarkers

**Should antidepressant medications be discontinued?**

- Elicit patient concerns with antidepressant continuation
- Risk of relapse/recurrence vs risk of continuation
- Discuss options for alternate treatment or active surveillance

**What is the preferred discontinuation strategy?**

- Continue active surveillance till spontaneous resolution
- Resume same antidepressant, start another, or brief fluoxetine trial
- Very slow titration (hyperbolic dose reduction)

### Table 1. US Food and Drug Administration–Approved Indications (Excluding Depression) for Use of Antidepressant Medications in Adults

<table>
<thead>
<tr>
<th>Indication</th>
<th>Name of Medication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar depression</td>
<td>Fluoxetine (in combination with olanzapine)</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Chronic musculoskeletal pain</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>Duloxetine, escitalopram, paroxetine, venlafaxine</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Duloxetine, milnacipran</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Doxepin</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>Clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>Fluoxetine, paroxetine, sertraline, venlafaxine</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>Paroxetine, sertraline</td>
</tr>
<tr>
<td>Premenstrual dysphoric disorder</td>
<td>Paroxetine, sertraline</td>
</tr>
<tr>
<td>Seasonal affective disorder</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Social anxiety disorder</td>
<td>Paroxetine, sertraline, venlafaxine</td>
</tr>
</tbody>
</table>

### Shared Decision-Making Approach

Using the SDM approach, clinician(s) and patients (along with other health professional(s), friends, and family) make an optimal treatment decision when an unequivocally superior option does not exist. This process is bidirectional: the clinician shares information about available options, including the risks and benefits, while the patient conveys his or her specific preferences or values. In clinical practice, SDM can be implemented by a simple 3-step model that offers choices, discusses options, and moves patients toward making a decision. Decision aids are important tools of SDM as they facilitate sharing of knowledge and can be used outside of a clinic visit. A decision aid tool developed specifically for antidepressants was shown to improve the comfort of making decisions in both patients and clinicians. Relevant to the SDM approach for antidepressant discontinuation, this report frames decisional uncertainties as clinical questions regarding the need for, the choice among, and the necessity of continuing antidepressants, as well as potential options for managing discontinuation syndrome (Figure 1).
in an area with a shortage of mental health professionals,28 access to evidence-based psychotherapy may be limited.

**Which antidepressant medication is appropriate?** The choice of antidepressant medications (SSRIs, SNRIs, tricyclics, and atypical antidepressants) as an initial option may seem daunting to patients. Practice guidelines recommend use of subjective factors such as anticipated side effect profile and patient preference.29 In addition, clinicians should inquire about any previous history of discontinuation syndrome, as it may guide toward selection of antidepressants with a lower likelihood of these symptoms (such as fluoxetine) as compared to those with a higher likelihood (such as paroxetine and venlafaxine). A decision aid developed by Mayo Clinic and available online30 can be used to provide patients with information about cost and side effects of commonly used antidepressants as well as likelihood of discontinuation syndrome. As obesity31,32 and systemic inflammation33–35 have been associated with poor response to SSRIs (escitalopram and sertraline) in post hoc analyses from 3 separate clinical trials, their validation as treatment selection biomarkers in future clinical trials may inform antidepressant options presented to patients and potentially obviate the need for multiple trials of antidepressants and decrease the risk of discontinuation symptoms.36,37

**Should antidepressant medications be discontinued?** Common scenarios leading to this question include lack of improvement, intolerable side effects of ongoing treatment, relapse/recurrence of symptoms after initial treatment while taking the antidepressant, comorbid medical illnesses or a concomitant medication use that changes the risk vs benefit profile, planning for pregnancy or breast-feeding, and a period of sustained improvement or recovery during which the use of an antidepressant may no longer seem necessary.19 Clinicians should elicit concerns from patients about antidepressant continuation to check if one or more of the above scenarios apply and personalize the discussion of options accordingly. Further, a collaborative approach including consultations with other medical and behavioral health providers may be necessary especially in case of comorbid medical illnesses or when planning for pregnancy/ breast-feeding. Clinicians may also consider recent reports demonstrating the benefits of continuing antidepressants either alone or with evidence-based therapy in reducing the likelihood of relapse/recurrence.38,39 Data visualization tools in electronic health records that graphically present an individual patient’s changes in self-reports of symptom severity, quality of life, etc, as a function of changes in antidepressant treatment12 may be used to inform decision about antidepressant discontinuation.

**What is the preferred discontinuation strategy?** The FDA prescribing label recommends gradual reduction in dose instead of abrupt discontinuation.3 As noted by Fava et al,14 gradual taper has not been shown to help in reducing the frequency of discontinuation syndrome. However, gradual taper has been shown to reduce the likelihood of symptomatic relapse over the next year after discontinuation.40 This discrepancy might be attributed to the short periods of taper used in previous studies. Thus, Horowitz and Taylor20 recently proposed hyperbolic dose reduction, which was extended by Ruhe et al41 as a multistep dose reduction paradigm in which the initial step is to reduce the dose to half of the minimally effective dose in 1 week and then reduce very gradually and decide the time spent at each dose by SDM between clinician and the patient. If symptoms are tolerable and not burdensome, active surveillance using the MBC approach until spontaneous resolution may be an option. If the symptoms are intolerable, management strategies may include resumption of previously tolerated dose, switch to adequate dose of another SSRI/SNRI, cross-tapering—reducing the dose of current medication gradually while increasing the dose of another—or using a brief trial of fluoxetine to bridge from an SSRI/SNRI to a nonserotonergic antidepressant like bupropion.19 Clinicians should elicit the patient’s views about discontinuation and iteratively find the optimal strategy for individual patients.

**Active Surveillance With Measurement-Based Care Approach**

Finally, as mood and anxiety symptoms may occur as part of discontinuation syndrome, they need to be differentiated from those either present at baseline42,43 or worsened with treatment.44 Thus, systematic assessment of these symptoms using the MBC approach,45 prior to and during antidepressant treatment, can help in prospective assessment of their onset or worsening after antidepressant discontinuation. Using the MBC approach, regular follow-up visits should be conducted to detect symptom changes promptly prior to their worsening to intolerable levels. The side effect monitoring scale of MBC46 may also be adapted to monitor the frequency, intensity, and burden of discontinuation-emergent symptoms. Finally, the monitoring during active surveillance should include thorough review of systems and additional workup to rule out any comorbid medical condition that may account for these symptoms.19

**Roadmap for Clinicians Driving Research**

Despite SSRIs being some of the most commonly prescribed antidepressants, there has not been a single randomized placebo-controlled study assessing prevalence of discontinuation syndrome in the past decade.16 This may reflect the lack of importance placed on studying discontinuation symptom. In the second level of Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, patients were switched directly from a serotonergic antidepressant (citalopram) to either a nonserotonergic antidepressant (bupropion) or one of the two serotonergic antidepressants (sertraline and venlafaxine).47 Lack of systematic assessment of discontinuation syndrome comparing switch to a nonserotonergic vs serotonergic antidepressant may have been a missed opportunity. However, it is noteworthy that tolerability, side effect severity, and attrition rates in STAR*D were similar between switch to bupropion vs the 2 serotonergic switch arms.47

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Advances in health information technology that bring together data from multiple sources such as prescription records, progress notes, and patient-rated symptom measures offer a unique opportunity for clinicians to systematically collect data and drive research on discontinuation syndrome. The first step in this process will be to adopt a common tool for assessing symptoms in order to estimate the prevalence of discontinuation syndrome. Clinicians may then infer research into individual traits of patients that predispose to discontinuation syndrome. Finally, clinicians can drive research into efficacy of antidepressants over very long periods while considering the variability in course of symptoms. These issues are discussed briefly below.

**Describing the syndromic manifestation and estimating its prevalence.** As the range of symptoms reported following discontinuation is quite broad, clinicians may systematically collect patient reports of experiences following discontinuation of their antidepressant that include estimates of frequency, intensity, and burden of these symptoms. Further, clinicians and patients should inform definitions of clinically significant discontinuation symptoms which can then be used to estimate its prevalence. This is urgently needed due to the inconsistencies in definition of discontinuation syndrome used to date.16

**Characteristics of individual patients.** Clinicians may find it useful to know if there are specific individual patient characteristics that may predict discontinuation syndrome with any antidepressant (nonspecific predictor) or higher likelihood of discontinuation syndrome with one antidepressant vs another (moderator). Finally, tools of natural language processing paired with biological assays may be extended to identify cases of prolonged (lasting for years) and/or life-threatening discontinuation syndrome, or an inability to discontinue antidepressant once initiated, and the underlying biological mechanisms.

**Risk vs benefit of continued antidepressant treatment.** While they are often prescribed for very long periods, there is very limited information available on safety or continued benefit of antidepressants when prescribed for 3 or more years. Thus, systematic collection of information from real-world practices may reduce the decisional uncertainty for patients who improve with medication and seek options for discontinuation.

**Course of illness.** Clinicians may inform the discussion about antidepressant continuation by characterizing the different trajectories of symptoms and the variable course of illness. For example, it is not uncommon for patients to have a particular set of symptoms earlier in life (such as predominant anxiety disorder) that is distinct from those later in life (such as predominant depression). Thus, if SSRIs were used to treat anxiety disorder early on, subsequent emergence of a depressive illness may be misconstrued as medication-associated while it might be an evolution of underlying disorder. Another clinical example includes a patient who seeks psychiatric care for worsening depression and is started on pharmacotherapy but continues to get worse. In such cases, it will be important to distinguish whether treatment worsened the symptoms or whether the pharmacotherapy was ineffective and the symptoms would have worsened irrespective of the type of treatment initiated.

**CONCLUSION**

Antidepressant medications are important tools in addressing the public health crisis of inadequately treated mental illnesses. Thus, labeling antidepressants as addictive may dissuade patients from seeking this often life-saving treatment. There is an urgent need to understand the prevalence and biological underpinnings of discontinuation syndrome. Meanwhile, clinicians and patients may use a shared decision-making approach to reduce decisional uncertainties and improve treatment adherence. Finally, a systematic measurement-based care practice will help patients and clinicians in proactively managing symptoms if they occur after antidepressant discontinuation.

**REFERENCES**

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