Letters to the Editor

How Long Does Antidepressant Withdrawal Typically Last?

TO THE EDITOR: In the December 2018 issue of the *Journal*, Jha and colleagues (1) claim that antidepressant withdrawal typically resolves spontaneously over 2–3 weeks. They offer only three references in support. Two of these were case reports that included one and three patients (2, 3). In Pyke (3), the withdrawal reaction resolved in 3 weeks, whereas in the case report by Frost and Lal, withdrawal symptoms lasted between 3 and 23 weeks (2). The third reference, a small cohort study of 20 patients by Fava et al. (4), reported that a withdrawal reaction was observed in nine patients (45% of all patients examined), even though the drugs were tapered at the slowest possible pace. The withdrawal syndrome subsided within 4 weeks in six patients (67% of all patients experiencing withdrawal), whereas in three patients (33% of all patients with withdrawal), serious withdrawal symptoms persisted for several months after discontinuation.

Not only did Jha and colleagues select only three studies, representing a total of just 24 patients, but the three studies they present to readers as evidence for their 2–3 weeks claim do not actually support their claim at all. In Frost and Lal (2), the three individual withdrawal reactions described lasted between 3 and 23 weeks, and in Fava et al. (4), withdrawal effects lasted considerably longer than 4 weeks in one-third of patients. Based on this evidence, the conclusion that withdrawal reactions "typically resolve spontaneously over 2–3 weeks" is fallacious and arbitrary. Moreover, two references were merely case reports, which have very little external validity. In our view, it is problematic to quote (or, rather, misquote) such anecdotal evidence to corroborate a controversial claim that should represent the broader antidepressant user population. Although there undoubtedly is a need for more research on this important issue, systematic reviews of the existing literature conclude that withdrawal is common, is often severe, and frequently lasts much longer than merely 2–3 weeks, with and without tapering (5, 6).

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Addressing Clinical Challenges of Antidepressant Discontinuation

TO THE EDITOR: Jha and associates (1), in the December 2018 issue of the *Journal*, addressed the clinical challenges that are entailed when discontinuing selective serotonin reuptake inhibitor (SSRI) medication. The authors cited a systematic review stating that "up to 40% of patients reported new-onset symptoms after abruptly discontinuing SSRIs" (2). Actually, the review concluded that withdrawal syndromes are likely to occur with both abrupt and gradual tapering, without any significant advantage of the latter (2). The idea that by slowly tapering we can avoid withdrawal syndromes is simply not supported by the literature, both in the case of SSRIs (2) and serotonin-norepinephrine reuptake inhibitors (3).

Important clinical challenges were not sufficiently emphasized by Jha et al. (1). First, the duration of withdrawal syndromes is very variable. Symptoms typically ensue within a few days from discontinuation and last a few weeks. However, delayed occurrence and longer persistence of disturbances (months or years) may occur as well (i.e., postwithdrawal disorders) (2–4). Second, in addition to patient preference (1), there are a number of clinical situations (side effects such as gastrointestinal symptoms or bleeding; pregnancy and breastfeeding; onset of hypomania or mania; lack or loss of efficacy; improved clinical conditions) that may suggest interruption (4). Further, SSRIs interact with a number of medical drugs, such as anticoagulants and beta-blockers, and their discontinuation often requires readjustment of

medical therapies and appropriate consultations. Finally, a basic disagreement with the recommendations of Jha et al. (1) is whether we view withdrawal syndromes as isolated, self-limiting manifestations or as related to other clinical phenomena. According to the oppositional model of tolerance (4), continued drug treatment may trigger processes that oppose the initial acute effects of a drug. When drug treatment ends, oppositional processes may operate for some time, resulting in appearance of withdrawal symptoms, resistance if treatment is reinstituted, and a more malignant and treatment-unresponsive course (4), as was found to be the case in the clinical case presented (1). We should be aware that by reintroducing the antidepressant that was initially used or by switching to another antidepressant to suppress clinical manifestations of withdrawal (1), we are simply postponing, and most likely aggravating, the problem (4). Discontinuing SSRIs is far more difficult than prescribing them. We absolutely need sound research on withdrawal phenomena related to antidepressant drugs and to redefine the use and indications of these medications, including their differential likelihood of inducing behavioral toxicity (4).

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When Discontinuing SSRI Antidepressants Is a Challenge: A Response to Letters to the Editor

TO THE EDITOR: We appreciate the opportunity to respond to the letters to the editor from Fava and Cosci and Hengartner et al. in response to our article (1–3). These letters are welcome additions to the discussion regarding management of antidepressant medication discontinuation.

We fully agree with Fava and Cosci (2) that discontinuing antidepressant medication(s) may be far more challenging than prescribing such medication, which is what prompted our article. Our intent was to make note of the multitude of factors to be considered when discontinuing antidepressant medications. We also agree that it is likely that individual patients may have more persistent or troubling withdrawal symptoms, the exact rate of which is not easily discernable from the extant literature based on clinical trials. In fact, Fava et al. (4) state in the discussion section of their article that the "withdrawal syndrome typically occurs within a few days from drug discontinuation and lasts a few weeks. However, many variations are possible, including late onset and/or longer persistence of disturbances." The issue of typical duration of discontinuation symptoms was brought up by Hengartner et al. in their letter (3). We agree with them that extant literature may underestimate the duration of discontinuation symptoms owing to short periods of assessment after discontinuation of antidepressants. In fact, the Davies and Read systematic review cited by Hengartner et al. also found that most studies assessed discontinuation symptoms for only a few weeks (5).

In the first paragraph of their letter, Fava and Cosci suggest that we argue discontinuation symptoms occur only in the context of abrupt discontinuation. In fact, elsewhere in the article we do state:

> Factors not shown to predict development of discontinuation symptoms include … length of medication taper;
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> With paroxetine, discontinuation symptoms may also occur if doses are skipped for a few days;
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> Any patient who either discontinues or markedly reduces the antidepressant medication dosage is at risk of discontinuation symptoms; and
>
> Gradual taper may reduce the severity of discontinuation symptoms as compared with abrupt discontinuation.

We also included information about persistence of discontinuation symptoms beyond a few weeks: "However, some reports have documented persistence of symptoms for up to 1 year." Other clinical situations listed by Fava et al. that might warrant interruption in antidepressant treatment were also listed in our article:

> Beyond the acute phase, changes to the patient's antidepressant medication regimen may be warranted to address residual symptoms, persistent functional impairments, loss of initial therapeutic effect (antidepressant tachyphylaxis), occurrence or prevention of relapse or recurrence, side effects, affordability, or anticipated drug-drug interactions with medications for other medical conditions.

In addition, we addressed the very concerns raised by Fava and Cosci regarding the conceptualization of discontinuation symptoms as "isolated, self-limiting manifestations" (2) in the section of our article titled "What are the Best Strategies to Manage Discontinuation Symptoms?" In this section, we recommended strategies for prevention as well as treatment. Moreover, we recommend that clinicians need to enhance shared decision making by improving patient education about major depressive disorder, its treatments, and the risk of discontinuation symptoms.