The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

To continue or discontinue antidepressants in anxiety disorders? A dilemma for patients and clinicians

Anna Muntingh, PhD; Neeltje Batelaan, MD, PhD; Willemijn Scholten, PhD, Anton J. van Balkom, MD, PhD

A 35-year-old woman presented seeking advice on whether to discontinue antidepressants. Several years previously she had suffered from a panic disorder that was effectively treated with cognitive behavioural therapy (CBT). A few years following remission, she began having frequent panic attacks in response to a stressful job as a self-employed entrepreneur. Subsequently she also developed severe agoraphobia. Being home-bound, she felt increasingly isolated and depressed. She restarted CBT, but it did not yield the effect she had hoped for. Her primary care physician prescribed citalopram 20 mg/d. After a few months she was free of symptoms; however, she experienced bothersome adverse effects, including weight gain, vivid dreams and a loss of libido. These adverse effects fueled her wish to discontinue the medication, but she and her primary care physician feared that symptoms would recur after discontinuation.

The patient's wish to discontinue antidepressants is understandable, but her fear of relapse is justifiable as well. This is a dilemma frequently encountered by patients and their clinicians. We elaborate on the current evidence with regard to relapse risk and discontinuation in people with anxiety disorders and provide practical advice for clinicians.

Within the natural course of anxiety disorders, relapse may occur over time. High anxiety sensitivity and lower functioning increase this risk, but their predictive value for clinical practice is limited.[1] Patients who have successfully responded to antidepressants have an increased risk for relapse when discontinuing the antidepressant. It appears that more patients than previously assumed (i.e., an estimated 51% based on 6 randomized controlled trials included in a systematic review) experience withdrawal symptoms[2] that may be severe and often last longer than the 2 weeks suggested in treatment guidelines.[3] In clinical practice, however, it may be difficult to distinguish withdrawal symptoms from a re-emergence of the anxiety disorder. Frequently reported withdrawal symptoms, such as nausea, vertigo or dizziness, may be mistakenly interpreted as a relapse. The nature of the withdrawal symptoms, their resemblance to the previously experienced anxiety disorder (e.g., panic attacks, as in the example case), and the duration and severity of these symptoms might help differentiate between withdrawal symptoms and a relapse. A meta-analysis reported an increased risk (odds ratio 3.1) for relapse in patients with remitted anxiety disorder who discontinued their medication compared with those who continued their medication (36% v. 16% relapse, respectively).[4] There were no indications that the risk of relapse was related to type of anxiety disorder (e.g., panic disorder, generalized anxiety disorder or social anxiety disorder) or the mode of discontinuation (abrupt or tapered).[4] Unfortunately, research examining which patients can discontinue safely and which will relapse following discontinuation is insufficient to guide treatment decisions.[5]

Thus, in the case we presented, we can inform the patient that most people can safely discontinue antidepressants, but we are unable to specify her risk of relapse. Although there is limited evidence that a higher number of previous episodes or severity increases risk of relapse (unlike in depression research), guidelines advocate more caution regarding discontinuation in patients with recurrent anxiety disorders.[3] It may be wise to postpone discontinuation, but it is unknown whether this decreases relapse risk following discontinuation. Another option may be to seek alternative antianxiety medications, taking into account the long-term efficacy and adverse effect profile.[6,7] In the case we presented, switching the patient to another selective serotonin reuptake inhibitor (SSRI) may be considered. Although all SSRIs have a high risk for sexual dysfunction, adverse effects may differ from person to person. Alternatively, there is the option to lower the dosage to a "minimally effective dosage," which means that the adverse effects dissipate, but the drug remains effective. However, this option is not evidence-based; it carries the risk of prescribing medication at a subtherapeutic dosage to patients who may be able to fully discontinue the antidepressant. Therefore, this option should be used only if other strategies have failed.

Adding psychotherapy when discontinuing antidepressants may be worthwhile. In patients remitted from a depressive disorder, 1 RCT showed that preventive cognitive therapy while discontinuing antidepressants was equivalent to maintenance antidepressant medication.[8] An individual patient data meta-analysis showed that adding mindfulness to discontinuation may be superior to continuing antidepressants.[9] However, only 1 study in patients with remitted anxiety disorders has been conducted to date; it found no protective effect of additional CBT.[10]

An increasingly proposed strategy for discontinuation is to taper medication over months while using hyperbolic tapering (with increasingly smaller dose reductions instead of constant dose reductions) to mitigate withdrawal symptoms.[11] The advantage of this strategy is that symptom levels can be monitored, allowing timely interventions in case of a relapse. Moreover, slowly tapering

medication allows withdrawal symptoms to resolve, and the patient may regain clinical equilibrium after each step. Observational studies have found that slow tapering (ranging from > 2 weeks to 197 weeks) was associated with fewer withdrawal symptoms and may be related to a lower risk of relapse.[11]

Usually tapering is performed linearly, for example in 10 equal tapering steps. There are indications that the occupancy of the serotonin transporter follows a "hyperbolic" pattern when antidepressants are discontinued, which may induce increasingly severe withdrawal symptoms in the last linear tapering steps.[11] By tapering hyperbolically, starting with larger dose reductions and decreasing to very small dose reductions in the last steps, the receptor occupancy may decrease in a more linear way, which may induce less severe withdrawal symptoms. Fewer withdrawal symptoms will not only increase patient well-being, but also might lead to fewer problems distinguishing withdrawal symptoms from a relapse. Unfortunately, although tapering is used in many studies examining relapse after discontinuation, usually the tapering period is limited to 2 weeks.[4] Notably, although the notion of hyperbolic tapering is plausible, there is no sound empirical evidence of an actual decrease of withdrawal symptoms or risk of relapse with hyperbolic tapering compared with abrupt discontinuation or short tapering, as established in RCTs.[12] Another problem with hyperbolic tapering is that the availability and costs of tapering strips vary among countries. Further research should verify whether hyperbolic tapering is superior to abrupt discontinuation.

Because of a high relapse risk, a paucity of individual risk indicators and a lack of evidence-based strategies to prevent relapse when discontinuing antidepressants, patients and clinicians have to make decisions regarding discontinuation without clear evidence-based guidelines. We therefore advise clinicians to consider pros and cons of discontinuing antidepressants together with their patients and to decide collaboratively whether to discontinue antidepressants. When opting for discontinuation, slow tapering is advised because, in observational studies in patients with depressive disorders, this was associated with fewer withdrawal symptoms. Furthermore, it allows for careful monitoring and timely interventions in case of a relapse.

After discussing the pros and cons of continuing or discontinuing her medication, the patient in the example case chose to discontinue it. Citalopram was tapered in 9 steps over 9 weeks using hyperbolic tapering. Although she initially experienced withdrawal symptoms (dizziness, nausea, and energy loss) and an increase in anxiety symptoms (subclinical panic attacks), she successfully discontinued the medication. The patient and her primary care physician were advised to keep monitoring her psychological health on a regular basis, to consider attending sessions with a mental health professional to make a relapse prevention plan and practise CBT techniques aimed at relapse prevention, and to consider another SSRI such as sertraline as an alternative to the citalopram in case of a recurrence of the anxiety disorder.

Affiliations: From the Amsterdam UMC, VU University, Psychiatry, Amsterdam Public Health research institute, The Netherlands (Muntingh, Batelaan, Scholten, Van Balkom); and the GGZ inGeest Specialized Mental Health Care, Amsterdam, The Netherlands (Muntingh, Batelaan, Scholten, Van Balkom).

Competing interests: None declared.

DOI: 10.1503/jpn.200099

References

1. Scholten WD, Batelaan NM, van Balkom AJ, et al. Recurrence of anxiety disorders and its predictors. *J Affect Disord* 2013; 147:180-5.
2. Davies J, Read J. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? *Addict Behav* 2019;97:111-21.
3. *American Psychiatric Association practice guideline for the treatment of patients with panic disorder*. APA; 2009.
4. Batelaan NM, Bosman RC, Muntingh A, et al. Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials. *BMJ* 2017;358: j3927.
5. Berwian IM, Walter H, Seifritz E, et al. Predicting relapse after antidepressant withdrawal — a systematic review. *Psychol Med* 2017;47:426-37.
6. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163:1905-17.
7. Zugliani MM, Cabo MC, Nardi AE, et al. Pharmacological and neuromodulatory treatments for panic disorder: clinical trials from 2010 to 2018. *Psychiatry Investig* 2019;16:50-8.
8. Bockting CLH, Klein NS, Elgersma HJ, et al. Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised control. *Lancet Psychiatry* 2018;5:401-10.
9. Kuyken W, Warren FC, Taylor RS, et al. Efficacy of mindfulness-based cognitive therapy in prevention of depressive relapse. *JAMA Psychiatry* 2016;73:565-74.
10. Scholten WD, Batelaan NM, van Oppen P, et al. The efficacy of a group CBT relapse prevention program for remitted anxiety disorder patients who discontinue antidepressant medication: a randomized controlled trial. *Psychother Psychosom* 2018;87:240-2.
11. Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry* 2019;6: 538-46.
12. Fava GA, Cosci F. Understanding and managing withdrawal syndromes after discontinuation of antidepressant drugs. *J Clin Psychiatry* 2019;80: 19com12794.