Antidepressant Discontinuation

In Need of Scientific Evidence

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Abstract:

Background: The topic of patients' discontinuing use of antidepressants has received increasing attention. Patients and physicians can encounter challenges regarding the three major questions in the field of antidepressant discontinuation: who can discontinue, what is the best time to discontinue; and what is the best method to discontinue.

Methods: This commentary summarizes the current state of the evidence related to antidepressant discontinuation.

Results: There is limited evidence underlying the extremely relevant clinical topic of antidepressant discontinuation. It is poorly understood which patients, after response to antidepressants, benefit (most) from discontinuation. Moreover, established and validated markers of an individual's risk of relapse after antidepressant cessation are lacking, and non-sponsored discontinuation studies are rare. Many discontinuation studies do not distinguish between relapse and antidepressant discontinuation symptoms, and very few studies compared different discontinuation strategies, with none of the compared strategies exceeding 2 weeks of tapering. Finally, blinding of discontinuation strategies is often insufficient to properly address placebo and nocebo aspects, whereas the pharmacological characteristics of different antidepressants in relation to discontinuation have hardly been studied.

Conclusions: Antidepressant discontinuation is a clinically relevant topic. There is a strong need for more robust evidence to indicate *who* can discontinue antidepressants, *when* and in which manner (*how*). Blinded randomized controlled trials are pivotal to optimally advise physicians, patients and policy-makers. This scientific knowledge can guide evidence-based decision making in clinical practice.

Key Words: Antidepressant discontinuation, tapering strips, dose reduction, stopping antidepressants, dose reduction

In recent decades, several systematic reviews and meta-analyses have shown that continuation or maintenance of antidepressant medication (mostly SSRIs and SNRIs) in depressed patients who responded to acute treatment significantly reduces the risk of relapse or recurrence.[1–4] Prolonged used of antidepressants is therefore an effective and important treatment modality for a large group of patients. In Western countries, an estimated 7-13% of the total population have used antidepressants in the past year, of whom over half for depression. Long-term use of antidepressants (>2 years) is generally growing, and although this can be beneficial,[5] most patients discontinue antidepressants at some point. This may be either because of long-term remission, adverse effects (e.g. sexual dysfunction, emotional flattening, or weight gain), but also beliefs that antidepressant use prevents full recovery.[6] Instead, if antidepressants are inefficacious, discontinuing such an ineffective drug in favor of alternative interventions is relevant, for which several strategies exist.[7–9]

Treatment guidelines agree on continuation of antidepressants for some period after remission (and better functional recovery), but vary in their recommended period of continuation which depends on the specific country and the type and history of the psychiatric disorder.[10,11] This heterogeneity is caused by

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lack of evidence, leaving patients, clinicians, and policy-makers uncertain about rational antidepressant discontinuation strategies. Nevertheless, many patients discontinue their antidepressant each year.

When faced with the possibility of discontinuation, patients, their family members and physicians fear recurrence of the disorder, and might also fear antidepressant discontinuation symptoms (ADS). ADS can occur in the process of stopping an antidepressant, but there is a large variation in its estimated prevalence (27-86% of patients), often based on cross-sectional or biased samples.[12,13] ADS consist of somatic and psychological symptoms (e.g. dizziness, nausea, anxiety, and shock-like sensations), potentially distinct from symptoms seen during recurrence of MDD. Nevertheless, in clinical practice, distinguishing ADS from recurrence of depressive/anxiety disorder can be challenging. The quick emergence after dose-reductions, disappearance after reintroduction of the dose used before symptoms occurred, and resolution of discontinuation symptoms over time as the body readjusts (vs. continuation or even worsening when a new episode occurs) point to ADS.[14,15]

Nevertheless, it is estimated that up to 50% of patients experience problems with antidepressant discontinuation, either due to ADS or due to relapse or recurrence. The importance and prevalence of antidepressant discontinuation contrast largely with the limited scientific evidence and clinical attention for this topic. Evidence for antidepressant discontinuation revolves around three central questions: *who* can discontinue (in *which* patients is discontinuation possible without increased recurrence risk), *when* is the best time to discontinue, and *how* should antidepressants should best be discontinued to prevent ADS?

WHO CAN DISCONTINUE AND WHEN TO DISCONTINUE?

Patients are often reluctant to discontinue antidepressants that helped them to regain control over their psychiatric symptoms. Should a patient aim to discontinue antidepressants after stable remission (e.g. 6 months)? Or is it better not to discontinue, or to wait longer, as antidepressants reduce recurrence risk as long as they are used. Sometimes, continuation of antidepressants for a longer period seems the most rational choice, particularly with a history of multiple and severe episodes of an anxiety or depressive disorder. Most knowledge comes from discontinuation studies - compulsory for antidepressant registration- generally showing that maintenance treatment after remission generally halves relapse and recurrence risk compared to placebo.[2,5] These blinded studies have the advantage of reducing possible nocebo effects (i.e. knowing that antidepressants are stopped), but have been criticized for being industry-funded, focusing on more severe and chronic patient populations, and incorrectly labeling ADS as relapse/recurrence.[2] Particularly, these short-term studies most often abruptly replaced antidepressants by placebo rather than using gradual tapering strategies, which, combined with misclassification of ADS as relapse/recurrence, might overestimate recurrence-rates.[2] Moreover, studies where remitted patients are randomized to varying durations of continued antidepressants before discontinuation are lacking, and it is still unclear how long the minimum time period necessary for adequate relapse/recurrence prevention with antidepressants should be.

With regard to the question who can discontinue antidepressants, a systematic review aimed to identify predictors of individual relapse (or recurrence) risk after antidepressant discontinuation.[16] This review showed that i. it is still poorly understood which patients benefit (most) from discontinuation after response to antidepressant, and ii. that evidence was too weak to identify established, validated markers of an individual's risk of relapse after antidepressant cessation. Obviously, residual symptoms and the number of prior episodes seem plausible risk indicators, but have not been firmly proven to differentially predict relapses/recurrences after continuation versus discontinuation. This is likely to be due to the scarcity of studies that analysed the impact of these factors, or to their lack of sufficient power to establish a significant effect.

HOW TO DISCONTINUE ANTIDEPRESSANTS?

The important question *how* to discontinue antidepressants is currently based on (expert) opinion, as was demonstrated by a recent Cochrane review, where the authors concluded that "relatively few studies have focused on approaches to discontinue long-term antidepressants", and that "we cannot make any firm conclusions about effects and safety of the approaches studied to date" while all studies were at high risk of bias.[17] Van Leeuwen et al. mention that "across studies, relapse of depression and anxiety might be confounded by withdrawal symptoms, and most discontinuation regimens were limited to four weeks or less. In clinical practice, abrupt antidepressant discontinuation is generally not advised as it may induce ADS. However, evidence about the effects of abrupt discontinuation on ADS is very uncertain".[17] Interestingly, ADS also occur in blinded arms when antidepressants were *continued;* which underscores that randomized and *blinded* studies are essential to acknowledge nocebo-effects, while the placebo-effect of a special intervention aimed to reduce ADS need and will be acknowledged at the same time.

Despite meta-analyses contrasting (variably) tapered discontinuation (with or without co-intervention) versus continuation in this Cochrane review, it did not report on comparisons between different discontinuation strategies.[17] After systematically reviewing PubMed and the Cochrane Trial Register (last search February 2020, details available on request), we identified three RCTs comparing different discontinuation strategies in patients with MDD,[18,19] or in women using desvenlafaxine for vasomotor symptoms associated with menopause.[20] All three clinical trials investigated a maximum of two steps of tapering over a period of maximally two weeks. More ADS occurred after abrupt decreases of daily 50 mg and 100 mg of desvenlafaxine compared to placebo, although other reductions of desvenlafaxine doses and short (3 days) versus long (2 week) discontinuation steps were statistically comparable (Fig. 1). In general, a numerical lower frequency of ADS-symptoms

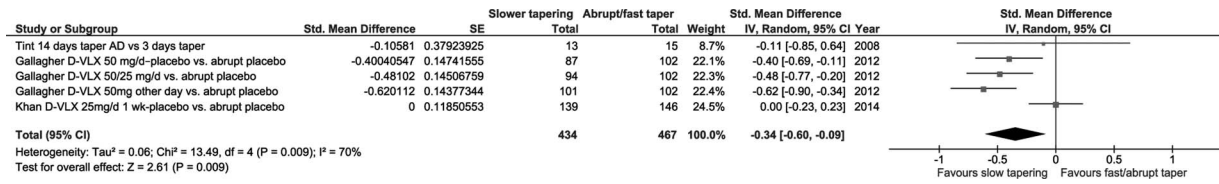

FIGURE 1. ADS occurring after various tapering strategies (all within 2 weeks) vs. abrupt discontinuation. Pooled results of 5 comparison-arms from 3 studies comparing different antidepressant discontinuation strategies. Outcome of interest is the standardized mean difference (Hedge's *g*) for severity of antidepressant discontinuation symptoms (ADS) measured 1 week after last active drug was given, compared to before discontinuation. D-VLX = des-venlafaxine.

in the slower and more gradual tapering groups was reported. These studies thus clearly demonstrate no differentiation of short term tapering strategies compared to abrupt discontinuation during the first weeks. However, these studies also suggest that a gradual tapering of antidepressants could be beneficial to reduce ADS, especially if the time to taper would be longer than 2 weeks and, possibly, when dose-reducing steps would not be limited to 50% dose reductions. Given this limited and uncertain evidence, the optimal method and duration of discontinuation, particularly for tapering beyond a couple of weeks, remains currently unknown.

Furthermore, despite suggestions for risk factors for ADS across narrative reviews,[21–25] consistent empirical evidence for a relation between patient characteristics (e.g. duration of antidepressant treatment, initial severity of adverse effects when starting the antidepressant, dose needed to achieve remission, fear for relapse/recurrence and ADS, CYP P450 metabolism) and ADS occurrence is lacking.

Finally, although incidence and severity of ADS appear to differ between antidepressants,[13] little facts are known about how pharmacological characteristics (e.g. elimination half-life and receptor affinities) influence ADS. Generally, antidepressants with shorter elimination half-lives (e.g. paroxetine and venlafaxine) appear to have more severe ADS, particularly in the lower dosage-ranges when the largest reductions in serotonin transporter (SERT) occupancy occur.[26] This has led to the hypothesis that *hyperbolic* decreases of antidepressant dosages over the course of several months could reduce ADS, although the back-translation to applicable dosage steps remains tentative.[14,27] Moreover, *in-vivo* studies show that antidepressant elimination from the brain might follow different and much slower kinetics compared to blood, suggestive of the pharmacological concept of hysteresis.[28]

WHERE SHOULD WE GO?

Antidepressant discontinuation is an important topic for millions of patients discontinuing their antidepressant each year and the physicians who want to guide these patients. However, robust scientific evidence is largely lacking, and this entails that the discussions on this topic are particularly driven by opinions or personal experiences rather than evidence. It remains unclear i) at what time after remission antidepressant discontinuation should be initiated, ii) which individual patient characteristics determine the occurrence of ADS and/or risk of relapse/recurrence, iii) how anticipation/nocebo effects impacts the discontinuation process, iv) whether and for which types of antidepressants (and dosages) more gradual tapering – rather than relatively quick discontinuation - prevents ADS and later relapse/recurrence (and is cost-effective), and v) whether the results in remitted depression can be generalized to patients with remitted anxiety disorders and obsessive-compulsive-disorders who take antidepressants.[29]

To provide pieces of evidence to solve the antidepressant discontinuation puzzle, it is vital to better understand not only the prevalence of relapse/recurrence and ADS after discontinuation but also its underlying mechanisms. We are in direct need to obtain this knowledge so that patients who want to discontinue their antidepressant can do so as safely and rationally as possible. Therefore, randomized and blinded studies are critical to learn more about *when*, in *which patients* and *how* discontinuation of antidepressants can be successfully endorsed. Specifically, there is an urgent need for trials that adequately address ADS, confounding biases, and carefully distinguish relapse/recurrence from ADS.

In the Netherlands, two large-scale randomized national randomized clinical trials (non-industry sponsored) are on the way to provide answers to the discontinuation puzzle: the OPERA study and the TEMPO study. Both studies are co-created and carried out in a multidisciplinary team of psychiatrists, general physicians, pharmacists, and patients with lived experience. The OPERA study (www.opera-project.nl) is a placebo-controlled randomized trial in Dutch depressed patients who reach a 6-month stable remission of depression during optimal antidepressant treatment with citalopram or sertraline by comparing an early discontinuation with a later discontinuation group on a broad spectrum of outcomes. This RCT will also provide insights which clinical characteristics determine successful discontinuation (i.e. previous treatments, psychiatric history, required dosing of the antidepressants, sociodemographic or biological indicators). The independent TEMPO study is a double-blind randomized RCT that compares conventional antidepressant discontinuation (halving dosages with available dosage-units which is has been treatment as usual for years) with more gradual reduction of progressively smaller dosage-units (hyperbolic tapering) for paroxetine and venlafaxine (having the highest ADS-rates). The TEMPO study can determine whether antidepressant discontinuation strategies related to 'free-fall' vs. linear decreases of SERT-occupancies influence successful discontinuation. In both the OPERA and the TEMPO study, ADS and symptomatic relapse/recurrence are prospectively and carefully monitored for at least 8 months.

In conclusion, robust clinical trials of sufficient methodological quality are essential to achieve progress the field of discontinuation of antidepressants. Hopefully, this will help guidance in clinical practice and provide evidence for tailored advice to patients who want to discontinue their antidepressant.

AUTHOR DISCLOSURE INFORMATION

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REFERENCES

1. Baldessarini RJ, Lau WK, Sim J, et al. Duration of initial antidepressant treatment and subsequent relapse of major depression. *J Clin Psychopharmacol*. 2015;35:75–76.
2. Borges S, Chen YF, Laughren TP, et al. Review of maintenance trials for major depressive disorder: a 25-year perspective from the US Food and Drug Administration. *J Clin Psychiatry*. 2014;75:205–214.
3. Geddes JR, Carney SM, Daview C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet*. 2003;361:653–661.
4. Williams N, Simpson AN, Simpson K, et al. Relapse rates with long-term antidepressant drug therapy: a meta-analysis. *Hum Psychopharmacol*. 2009;24:401–408.
5. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet*. 2003;361:653–661.
6. Ambresin G, Palmer V, Densley K, et al. What factors influence long-term antidepressant use in primary care? Findings from the Australian diamond cohort study. *J Affect Disord*. 2015;176:125–132.
7. Zhou X, Ravindran AV, Qin B, et al. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. *J Clin Psychiatry*. 2015;76:e487–e498.
8. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry*. 2008;63:699–704.

9. Ruhe HG, Huyser J, Swinkels JA, et al. Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. *J Clin Psychiatry*. 2006;67:1836–1855.
10. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol*. 2015;29:459–525.
11. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Can J Psychiatr*. 2016;61:540–560.
12. Jauhar S, Hayes J. The war on antidepressants: What we can, and can't conclude, from the systematic review of antidepressant withdrawal effects by Davies and Read. *Addict Behav*. 2019;97:122–125.
13. Davies J, Read J. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? *Addict Behav*. 2019;97:111–121.
14. Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry*. 2019;6:538–546.
15. Renoir T. Selective serotonin reuptake inhibitor antidepressant treatment discontinuation syndrome: a review of the clinical evidence and the possible mechanisms involved. *Front Pharmacol*. 2013;4:45.
16. Berwian IM, Walter H, Seifritz E, et al. Predicting relapse after antidepressant withdrawal - a systematic review. *Psychol Med*. 2017;47: 426–437.
17. Van Leeuwen E, van Driel ML, Horowitz MA, et al. Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults. *Cochrane Database Syst Rev*. 2021;4:CD013495.
18. Tint A, Haddad PM, Anderson IM. The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study. *J Psychopharmacol*. 2008;22:330–332.
19. Khan A, Musgnung J, Ramey T, et al. Abrupt discontinuation compared with a 1-week taper regimen in depressed outpatients treated for 24 weeks with desvenlafaxine 50 mg/d. *J Clin Psychopharmacol*. 2014;34: 365–368.
20. Gallagher JC, Strzinek RA, Cheng RF, et al. The effect of dose titration and dose tapering on the tolerability of desvenlafaxine in women with vasomotor symptoms associated with menopause. *J Women's Health*. 2012; 21:188–198.
21. Harvey BH, Slabbert FN. New insights on the antidepressant discontinuation syndrome. *Hum Psychopharmacol*. 2014;29:503–516.
22. Hosenbocus S, Chahal R. SSRIs and SNRIs: A review of the Discontinuation Syndrome in Children and Adolescents. *J Can Acad Child Adolesc Psychiatry*. 2011;20:60–67.
23. Lejoyeux M, Ades J. Antidepressant discontinuation: a review of the literature. *J Clin Psychiatry*. 1997;58(suppl 7):11–15; discussion 16.
24. Ogle NR, Akkerman SR. Guidance for the discontinuation or switching of antidepressant therapies in adults. *J Pharm Pract*. 2013;26:389–396.
25. Himei A, Okamura T. Discontinuation syndrome associated with paroxetine in depressed patients: a retrospective analysis of factors involved in the occurrence of the syndrome. *CNS Drugs*. 2006;20:665–672.
26. Meyer JH, Wilson AA, Sagrati S, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. *Am J Psychiatry*. 2004;161:826–835.
27. Ruhe HG, Horikx A, van Avendonk MJP, et al. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry*. 2019;6:561–562.
28. Takano A, Suzuki K, Kosaka J, et al. A dose-finding study of duloxetine based on serotonin transporter occupancy. *Psychopharmacology*. 2006; 185:395–399.
29. 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.