questions

Afzender	Pauline Dinkelberg
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Datum	2026-07-26 18:25

Overzicht Headers Platte tekst

Dear researcher,

We feel the urge to share our thoughts about:

https://bmjopen.bmj.com/content/16/7/e119492

We are deeply concerned when we read about how this study has been designed.

One of the key pillars of safe tapering is the timely adjustment of the schedule when symptoms arise.

This principle is undermined by the application of two fixed regimens

If symptoms are ignored, there is an increased risk of long-term symptoms, which are not infrequently 'treated' – out of a sense of helplessness – with all manner of other medication unproven for this indication, marking the start of a further iatrogenic cascade of medication

Once the dose has been tapered down to 0 mg and symptoms are present, it is even more difficult than during the tapering process to distinguish between relapse and withdrawal. This is partly because, for many people, restarting the medication no longer works.

Are dose reductions calculated based on the original dose or the last dose? If the former, then the reduction percentage increases rather than decreases (hyperbolic tapering).

We find nothing in the article regarding the use of lower doses. The lowest recorded doses are not equivalent across all antidepressants. Therefore, comparison is impossible. Are lower doses self-administered by patients or is use made of tested compounded medication?

Are interactions and reverse interactions taken into account in the assessments?

Which patients are included? Does this include those taking multiple psychotropic drugs? This is essential for the findings to be representative of reality. Here in the Netherlands, for example, half of all antidepressant users also take a benzodiazepine.

It is well known that one or more failed attempts at tapering make the next attempt even less straightforward or successful. This seems to us to be a very strong reason to offer everyone the most optimal tapering method. It is not a matter of trial and error; rather, once an error has occurred, no other trial is possible.

We hope you will repond to this email and thank you in advance,

Met vriendelijke groet,kind regards

Pauline Dinkelberg, chairperson, former IC-nurse with more than 7 years experience in helping patients to come off psychotropic medication

Re: questions

Afzender
Ontvanger pauline@verenigingafbouwmedicatie.nl
Kopie
Datum 2026-08-04 08:48
Overzicht Headers Platte tekst

Dear Ms Dinkelberg,

Thank you for writing. We recognise and appreciate the long-standing work your association has done to improve safe tapering strategies, and we share your goal towards evidence-based discontinuation of psychotropic medications.

I will try to answer point by point.

1. "We are deeply concerned when we read about how this study has been designed."
The protocol was designed to reflect real-world clinical practice, and it was independently reviewed and approved by the Verona Ethics Committee and by the Italian Medicines Agency (AIFA) before it could begin. Flexibility for the individual patient and safety monitoring are an essential element of this study.

2. "One of the key pillars of safe tapering is the timely adjustment of the schedule when symptoms arise. This principle is undermined by the application of two fixed regimens."
The schedules are not intended to be rigid. Clinicians can, and are instructed to, slow the taper, prolong it, restore the previous dose, or add rescue medication whenever symptoms warrant, according to the needs of each individual. Symptoms are not ignored and, according to our primary outcome, transient symptoms that are

succesfully managed do not count as failure; only inability to stop, or restarting the medication, does. We understand that the individualisation of tapering schedules is key in common practice. Those who are randomised to linear schedules and experience difficulties tolerating them will be promptly re-assessed and, if necessary, assigned to a hyperbolic schedule. In this case, of course, the study will consider linear tapering to be ineffective for that particular patient.

3. "If symptoms are ignored, there is an increased risk of long-term symptoms... marking the start of a further iatrogenic cascade of medication."
To catch problems early, withdrawal (DESS) and depression/anxiety (PHQ-9, GAD-7) are measured separately and repeatedly throughout the study. Also, participants are instructed to contact the recruiting psychiatrist should any unexpected effect should arise. Further, there are stopping rules: we will carry out an interim analysis if serious adverse events reach 10%, and the trial halts if 5% or more have severe events related to tapering.

4. "Once the dose has been tapered down to 0 mg and symptoms are present, it is even more difficult than during the tapering process to distinguish between relapse and withdrawal. This is partly because, for many people, restarting the medication no longer works."
We do not claim to solve this, but we will attempt to make a distinction between discontinuation symptoms, proper relapse, and "withdrawal-associated relapse" by using specific tools and defintions described in the protocol. Please consider that our first rescue step is to slow or extend the taper, not simply restart. The trial will generate data on how often restarting the antidepressant is needed and whether it works.

5. "Are dose reductions calculated based on the original dose or the last dose? If the former, then the reduction percentage increases rather than decreases (hyperbolic tapering)."
On the last (current) dose. Each hyperbolic step is 20-25% of the current dose, so the absolute reduction shrinks as the dose falls (Table 3 and appendix). We acknowledge that this is an approximation of true hyperbolic tapering, chosen for feasibility with marketed oral solutions of antidepressants in Italy.

6. "The lowest recorded doses are not equivalent across all antidepressants. Therefore, comparison is impossible. Are lower doses self-administered by patients or is use made of tested compounded medication?"

We defined the lowest dose before discontinuation as 20% of the minimum effective dose in the hyperbolic tapering arm and 50% in the linear tapering arm. Participants will be provided with marketed oral antidepressant solutions (drops/mL), dispensed by the Verona University Hospital pharmacy and self-measured by patients according to written instructions, rather than as compounded tapering strips. We acknowledge that the lowest recorded doses may not be equivalent across all antidepressants. We do not claim dose equivalence between drugs; however, randomisation is expected to balance the distribution of antidepressants across the two arms, thereby preserving the fairness of the between-arm comparison. To increase the internal

validity of the study, we could have chosen to randomise only patients taking a single antidepressant, such as paroxetine. However, this would have reduced the pragmatic nature of the study and generated findings that would be less generalisable to real-world clinical practice.

7. "Are interactions and reverse interactions taken into account in the assessments?"
Concomitant medications and comorbidity (Cumulative Illness Rating Scale) are recorded and updated at every visit, and switching between antidepressants before initiating the tapering accounts for possible interactions, according to common clinical practice (for example, citalopram and other QTc-prolonging drugs). Being a pragmatic trial, we do not perform formal pharmacokinetic modelling.

8. "Which patients are included? Does this include those taking multiple psychotropic drugs?... Here in the Netherlands, for example, half of all antidepressant users also take a benzodiazepine."
Adults with remitted unipolar depression on one SSRI, SNRI, tricyclic or vortioxetine. We do include comorbidities and benzodiazepine co-users (up to 2.5 mg/day lorazepam-equivalent), but exclude multiple antidepressants, high-dose benzodiazepines, and bipolar/psychotic/dementia diagnoses. So the results will apply to single-antidepressant remitted depression with possible co-medications, but not complex polypharmacy, to reflect common practice. Further, we will stratify the randomisation by high versus low risk of withdrawal symptoms, which also fits our aim of individualising tapering schedules according to the baseline risk of withdrawal.

9. "It is well known that one or more failed attempts at tapering make the next attempt even less straightforward or successful. This seems to us to be a very strong reason to offer everyone the most optimal tapering method."
This is exactly why patients for whom one strategy is clearly better are not randomised. According to the protocol, those who have repeatedly failed linear tapering and for whom the hyperbolic tapering is clearly recommended, will not be enrolled. Randomisation applies only in genuine uncertainty, and there is as yet no randomised evidence that hyperbolic is superior, since the supporting data are merely observational. The linear arm, moreover, is current standard practice, delivered with the same flexibility and safety monitoring as the hyperbolic arm.

As an additional consideration, the roughly 72% successful-discontinuation figure that we expect to find in the hyperbolic arm (and that supported the calculation of the study sample size) comes from an observational cohort study (Groot and van Os, Ther Adv Psychopharmacol 2021). One of the aims of DISCARD is precisely to test, under randomised conditions, whether this promising result holds.

The study is independent of the pharmaceutical industry, its outcomes are patient-centred, and after the analysis we will convene a lived-experience advisory panel to help interpret the findings, to which we would warmly welcome your organisation's input.

We are aware that no study is perfect, and we are open about the limitations of this one. The DISCARD study is best seen as a comparison between a "standard"

approach commonly used in clinical practice and a more gradual strategy informed by hyperbolic principles; although the taper is not fully hyperbolic down to the lowest doses, we believe the two approaches are sufficiently distinct to detect at least a signal of differences, both in withdrawal symptoms and in medium- to long-term relapse risk. Above all, we are confident that the study was designed with respect for the patients who take part, that it can provide important information on which discontinuation strategies are genuinely useful in everyday care, and that it does not raise ethical concerns of a kind that would justify suspending it. We remain very open to continuing this conversation with you.

Kind regards,

On behalf of the DISCARD study group

Re: questions

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Datum	2026-08-05 11:24

Overzicht Headers Platte tekst

Goodmorning,

Thank you for your response;

there are many points on which we have further questions.

One of them – presumably a crucial one – in light of this ruling:

As an additional consideration, the roughly 72% successful-discontinuation figure that we expect to find in the hyperbolic arm (and that supported the calculation of the study sample size) comes from an observational cohort study (Groot and van Os, Ther Adv Psychopharmacol 2021). One of the aims of DISCARD is precisely to test, under randomised conditions, whether this promising result holds.

- this study has been done with tapering strips;

- in which doses can go down to e.g. paroxetine 0,1 mg, venlafaxine EXTENDED RELEASE to 0,5 mg

- venlafaxine can never retain extended release in a liquid

- same for duloxetine; counting beads can never be precise

- we think 'randomised conditions' are the opposite of 'personalized tapering'

- why not using compounded lower doses instead of liquids?

- Apart from differences in numeracy skills, dexterity with syringes, differences in the bioavailability of tablets versus liquids,

the fact that one drop of a medicine is not the same as another – and that this is particularly important at the end of the

tapering process – we believe that many more variables come into play than just the patient, the medicine and the dose.

We are sorry; this is not limitated. We hope to find time to comment on other things. Just because we see harmed patients everyday.

The majority get stuck right at the end of the route. Often when they practise DIY-pharmacy. No research has ever been carried out into the accuracy of these homemade liquids.

We have no financial interest whatsoever in any particular tapering method. We refuse subsidies and do everything for free to remain independent.

Kind regards,

Pauline Dinkelberg