BMJ Open

Safe discontinuation of antidepressants in individuals with clinically remitted depressive disorders: study protocol for a randomised controlled trial

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To cite: Ostuzzi G, Gastaldon C, Zaccoletti D, *et al*. Safe discontinuation of antidepressants in individuals with clinically remitted depressive disorders: study protocol for a randomised controlled trial. *BMJ Open* 2026;**16**:e119492. doi:10.1136/bmjopen-2026-119492

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2026-119492).

Received 16 March 2026
Accepted 22 June 2026

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ABSTRACT

Introduction Antidepressant overprescribing and unnecessary long-term use are common and can increase the risk of adverse effects and withdrawal symptoms on discontinuation. Although gradual tapering strategies have been proposed, empirical evidence from randomised trials is lacking. This study will compare the efficacy of two antidepressant discontinuation strategies—linear and hyperbolic tapering—in adults with remitted depressive disorders.

Methods and analysis This pragmatic, multicentre, open-label, parallel-group superiority randomised controlled trial will recruit adults (≥18 years) with remitted depressive disorders who have been taking an antidepressant for at least 6 months. During an 8-month recruitment period, participants in outpatient psychiatric and primary care settings will be randomised (1:1) to (a) linear tapering (dose reduced by 50% of the minimum effective dose every 2 weeks until cessation) or (b) hyperbolic tapering (dose reduced by 20–25% every 2 weeks until cessation). The primary outcome is the proportion of participants who fail to discontinue the antidepressant by the end of the predefined tapering schedule or who re-initiate antidepressant therapy within 16 weeks of discontinuation. Secondary outcomes include safety, tolerability (including withdrawal symptoms), acceptability, clinical effectiveness, social functioning, quality of life and cost-effectiveness. Recruiters and participants will be aware of their treatment allocation; however, outcome assessors and the biostatistician will remain blinded throughout follow-up. Validated rating scales measuring depression, anxiety, withdrawal symptoms and social functioning will be administered at baseline and at scheduled follow-up visits up to 36 weeks. Based on observational data, we aim to recruit 150 participants (75 per arm).

Ethics and dissemination The study was approved by institutional Ethics Committees and regulatory authorities. Written informed consent will be obtained from all participants and data processed in accordance with General Data Protection Regulation. Study insurance and pharmacovigilance procedures are in place. Findings will be published in open-access journals, presented at scientific meetings and communicated to policy and regulatory stakeholders.

Trial registration NCT07393919.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The pragmatic, multicentre, assessor-blinded randomised controlled design comparing two clearly specified tapering strategies (linear vs hyperbolic) increases the applicability to routine clinical practice.

⇒ Centralised concealed randomisation with stratification by centre and withdrawal risk (high vs low), along with the assessor-blinded and statistician-blinded approach, reduces selection, detection and measurement bias.

⇒ Use of validated rating scales with frequent, predefined follow-up assessments (up to 36 weeks) supports comprehensive, standardised measurement of relapse, functioning and withdrawal.

⇒ Open-label delivery (patients and recruiting clinicians unblinded) and allowance for rescue strategies reflect real-world practice but may introduce performance and reporting bias.

⇒ The use of oral-solution formulations and the need for switching drugs for some patients might add practical complexity, possibly affecting feasibility and adherence.

INTRODUCTION

Antidepressants (ADs) have been shown to be effective in the treatment of moderate-to-severe depression[1] and are recommended by national and international guidelines, although the risk of overprescribing is debated.[2–4] According to the Italian Medicines Agency (AIFA), AD consumption in Italy increased by over 10% between 2014 and 2020.[5] For people experiencing a first

depressive episode, evidence-based guidelines recommend 6–9 months of AD maintenance treatment after clinical response,[2 6] in line with meta-analytic evidence showing comparable relapse risk for maintenance periods ranging from 6 months to over 1 year.[7] Despite these recommendations, approximately one-third of patients continue AD treatment beyond 12 months,[5 8] raising concerns about long-term adverse effects, including sexual dysfunctions, weight gain, emotional numbness[9 10] and withdrawal symptoms when discontinuation is attempted.[11] The frequency of such symptoms is currently debated. According to a recent meta-analysis, about 31% of individuals will experience withdrawal symptoms (with half of them possibly attributable to a nocebo effect), while nearly 3% might experience severe and prolonged symptoms.[12] In contrast with this, a previous systematic review suggested that about 50% of individuals will experience withdrawal symptoms, half of which are severe.[11] A recent meta-analysis including 17 828 participants found that discontinuation mainly caused transient somatic symptoms (eg, dizziness, nausea) during the early weeks, without a significant increase in depressive symptoms, suggesting that these may reflect withdrawal symptoms rather than genuine relapse.[13] Risk factors might include longer treatment duration, multiple co-treatments and exposure to some high-risk ADs (ie, paroxetine, venlafaxine, duloxetine).[6 14]

There is some agreement that gradual and slow tapering approaches might help avoid or mitigate such withdrawal manifestations.[15] 'Hyperbolic' or 'proportional' tapering approaches have been proposed as alternatives to commonly employed 'linear' tapering.[16] According to the Maudsley Hospital Guidelines, hyperbolic tapering involves proportional dose reductions (typically 10–20% of the current dose) over several months to years before stopping the medication. This is in contrast with linear tapering, which involves a faster reduction of doses by a fixed amount (generally about half of the minimal effective dose).[6 16] However, no randomised controlled trials (RCTs) directly comparing such strategies have been conducted yet.[17] Several guidelines generally recommend a 'gradual' or 'slow' taper, implicitly referring to a linear approach,[14] with an important exception: the National Institute for Health and Care Excellence (NICE), which recommends a slow, stepwise reduction proportionate to the current dose.[2] Evidence from a network meta-analysis including 17 379 participants indicates that slower tapering, particularly when combined with structured psychological support, is associated with relapse rates comparable to continued AD treatment, whereas abrupt or fast tapering consistently increases relapse risk.[18] However, details on the strategies used for gradual, slower tapering were not clearly defined.

On these grounds, we designed a randomised, controlled, pragmatic, multicentre trial comparing linear and hyperbolic tapering of ADs in adults with currently remitted depression under common clinical practice.

Specifically, the primary objective is to establish whether a hyperbolic tapering strategy, compared with a linear tapering strategy, increases the proportion of adults with remitted depression who successfully discontinue their AD, defined as completing the predefined tapering schedule without re-initiating AD treatment within 16 weeks of discontinuation.

METHODS AND ANALYSIS

Patients and members of the public were not involved in the development of the trial protocol or the selection of primary outcomes prior to study start. After the completion of the primary analyses, we will convene an advisory panel of people with lived experience of depression and antidepressant discontinuation (aiming for 6–8 members with diverse backgrounds) to appraise and help interpret our findings. The panel will be invited to review draft results, comment on the clinical and lived-experience relevance of outcomes (including perceived burden of the tapering schedules and study visits) and identify outcomes or contextual factors that matter most to patients. We will ask panel members to advise on feasible, acceptable formats and timing for dissemination (plain-language summaries, infographics, webinars, and summaries for clinicians and policy audiences) and to co-produce lay materials for study participants and wider patient communities. Intellectual input will be documented and, where appropriate, acknowledged in publications. This post-analysis involvement is intended to ensure our interpretation and dissemination are grounded in patient priorities and to inform future research and implementation.

Study design

The DISContinuation of Antidepressants in Remitted Depression (DISCARD) is a multicentre, assessor-blinded, RCT aimed at comparing the efficacy of linear and hyperbolic tapering for gradually discontinuing ADs in adults with currently remitted depressive disorders. We aim to enrol 150 participants over an 8-month period. After randomisation, participants will be assessed over 36 weeks using validated scales for depressive and anxiety symptoms, withdrawal symptoms, quality of life and social adaptation. Blinding patients and clinicians to treatment allocation would have required technical procedures that could have raised feasibility issues and conflicted with the pragmatic design. However, the investigators administering the rating scales and the trial biostatistician will remain blinded throughout the study.

The recruitment will take place at four Italian University Hospitals: the University of Verona (Coordinating Centre), the University of Milan, the University of Milano-Bicocca and the University Magna Graecia of Catanzaro. Further, the University of Padua will be responsible for the methodological supervision and monitoring of the study procedures. Figure 1 provides an overview of the study's procedures and details on the tools used for data collection and the scheduled timeline.

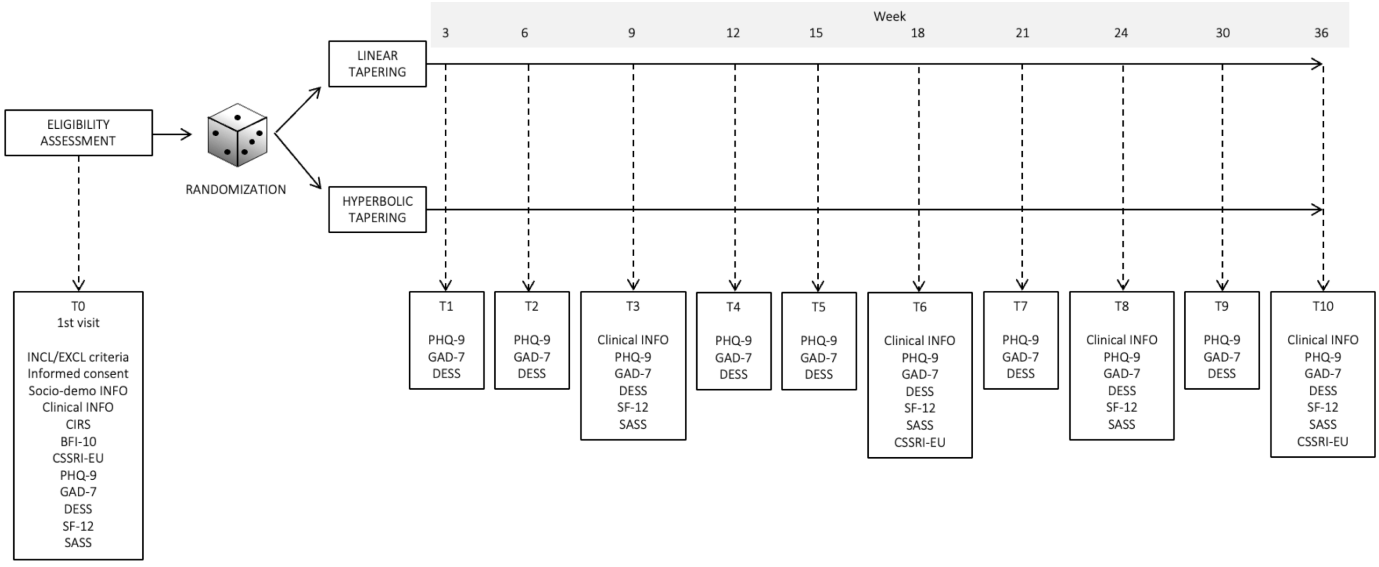

Figure 1 Overview of recruitment and follow-up procedures. BFI-10, Big Five Inventory 10 items; CIRS, Cumulative Illness Rating Scale; CSSRI-EU, Client Sociodemographic and Service Receipt Inventory; DESS, Discontinuation-Emergent Signs and Symptoms Scale; GAD-7, General Anxiety Disorder 7-item scale; PHQ-9, Patient Health Questionnaire 9-item scale; SASS, Social Adaptation Self-evaluation Scale; SF-12, Short Form 12 Health Survey.

Recruitment started on 18 February 2026, when the first participant was enrolled, and it is expected to be completed within 8 months (ie, October 2026). The last follow-up of the last enrolled participant is anticipated to be completed by July 2027.

This protocol is reported in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines,[19] and the trial results will be reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines.[20] The DISCARD trial will be conducted in accordance with the protocol, the EU Clinical Trial Regulation (CTR) 536/2014,[21] the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 Guideline for Good Clinical Practice (1 May 1996)[22] and the Declaration of Helsinki.[23] The original study protocol (available as a online supplemental appendix A; see Appendix A) has been reviewed and approved by the competent Territorial Ethics Committee (Comitato Etico Territoriale Area Sud-Ovest Veneto) and by the Italian Medicines Agency (Agenzia Italiana del Farmaco (AIFA)).

Participants

We will include individuals with the following characteristics: (a) 18 years old or above; (b) diagnosed with a depressive disorder, single episode (International Classification of Diseases, 11th Revision (ICD-11), 6A70) or recurrent (ICD-11, 6A71); (c) currently taking a selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, tricyclic antidepressant or vortioxetine for the treatment of depression; (d) the current AD has been taken for at least 6 months; (e) the current AD has been on a stable dose over the last 2 months; (f) a score ≤9 on the Patient Health Questionnaire 9-item scale (PHQ-9) and ≤5 on the General Anxiety Disorder 7-item scale (GAD-7) at study enrolment; (g) DSM-5-TR criteria for a depressive episode are not met at the time of recruitment; (h) no clinical evidence of moderate-to-severe symptoms in the last 6 months, as assessed by the recruiting clinician; (i) discontinuing the AD is clinically indicated by the recruiting clinician, and agreed to by the participant in a shared decision-making process; (j) there is uncertainty about which discontinuation strategy would be best for the participant, since it would not be ethical to randomise an individual for whom one strategy is clearly preferable (eg, individuals who have repeatedly failed previous attempts with linear tapering); (k) the participant is willing to sign the informed consent.

We will exclude individuals with (a) comorbid schizophrenia-spectrum disorders, bipolar disorder or dementia, as formally diagnosed by a psychiatrist, neurologist, geriatrician or other specialists; (b) current treatment with more than one AD at therapeutic doses; (c) current treatment with ADs of other classes (eg, mirtazapine, agomelatine, bupropion, for which the evidence on the risk of withdrawal is unclear),[6] alone or in combination with other ADs; (d) conditions or medications that contraindicate the use of any AD according to the Summary of Product Characteristics of included ADs (eg, current symptoms of mania); (e) current treatment with benzodiazepines above the dose of 2.5 mg equivalents of lorazepam per day (corresponding to clonazepam 1.2 mg/day; alprazolam 1.2 mg/day; diazepam 19 mg/day); (f) current pregnancy or the intention to become pregnant during the study period (ie, approximately the next 9–12 months), as ascertained by directly asking the participant at screening.

No exclusion criteria will be applied in terms of the number and severity of any other medical and psychiatric comorbidities or any other concomitant pharmacological and non-pharmacological treatment.

Recruitment, randomisation and blinding

Patient enrolment will be performed as part of routine clinical practice. In addition, general practitioners and other specialists (eg, neurologists and geriatricians) will actively participate in identifying potentially eligible individuals. Investigators will keep track of non-eligible individuals and reasons for exclusion. After explaining the key features of the trial to eligible patients and receiving a signed informed consent, physicians will be able to enrol participants, perform baseline assessments and randomise them.

Participants will be randomly assigned (1:1) to linear or hyperbolic tapering using a centralised web-based RedCap system according to a concealed, computer-generated randomisation list with permuted blocks, whose sizes will be concealed from site investigators. The allocation will be stratified by recruiting centre and individuals at high-risk versus low-risk of withdrawal symptoms. Those at risk of withdrawal symptoms will be defined as individuals with at least two of the following characteristics: (a) having taken the AD for 2 years or more; (b) taking ADs considered at high risk of withdrawal symptoms, namely paroxetine, duloxetine and venlafaxine; (c) taking ADs at doses twice or more of the minimal effective dose; (d) having a past history of withdrawal symptoms when discontinuing ADs or failed discontinuation attempts.[6 14] Participants will receive a unique ID, and baseline clinical and socio-demographic data will be entered in RedCap before allocation to ensure concealment.

Double-blinding of participants and recruiting psychiatrists is not feasible, but assisting investigators conducting assessments and the biostatistician will remain masked throughout the study follow-up and the statistical analysis. There will be 10 follow-up visits over 36 weeks. Follow-up assessments will be conducted in person wherever possible; otherwise, they will be conducted over the telephone. Assisting investigators will regularly instruct participants not to disclose their allocation during the assessment. Accidental breaches of masking will be recorded, and investigators' guesses at the study end will be analysed to evaluate blinding fidelity.[24]

Interventions

Eligible individuals will be randomised to one of the two following approaches:

a. Linear tapering. The AD dose will be reduced by fixed amounts (generally 50% of the minimum effective dose) every 2 weeks, according to pre-defined schedules, with the aim of reaching 50% of the minimum effective dose (as defined in the AIFA Summary of Product Characteristics) and finally discontinuing the AD after 4 to 10 weeks (depending on the initial dose) (see table 1).
b. Hyperbolic tapering. The AD dose will be reduced by 20–25% every 2 weeks, according to pre-defined schedules adapted from the Maudsley Hospital Guidelines,[6] with the aim of reaching at least 20% of the minimum effective dose (as defined in the AIFA Summary of Product Characteristics), and finally discontinuing the AD after 12–20 weeks (depending on the initial dose) (see table 2).

As hyperbolic tapering requires very low doses, which are not available as tablets, participants will be prescribed the

Table 1 Examples of linear tapering schedules for some of the most commonly prescribed antidepressants and doses. Note: as doses calculated according to this principle ('theoretical dose') might include decimals, which cannot be administered with commonly available formulations, a 'rounded dose' administrable in the form of oral solution is reported. Tapering durations might vary according to the starting dose

	Starting dose	Tapering schedule (each dose step maintained for 2 weeks)	Total tapering duration
ESCITALOPRAM oral tablet (theoretical dose reported)	20 mg	15 mg – 10 mg – 5 mg	6 weeks
ESCITALOPRAM oral solution (1 mg=1 drop) (rounded dose reported)	20 drops	15 drops – 10 drops – five drops	6 weeks
SERTRALINE oral tablet (theoretical dose reported)	100 mg	75 mg – 50 mg – 25 mg	6 weeks
SERTRALINE oral solution (25 mg=1.25 mL) (rounded dose reported)	5 mL	4 mL – 2.5 mL – 1 mL	6 weeks
VENLAFAXINE oral tablet (theoretical dose reported)	150 mg	112.5 mg – 75 mg – 37.5 mg	6 weeks
VENLAFAXINE oral solution (75 mg/mL=0.5 mL=37.5 mg) (rounded dose reported)	2 mL	1.5 mL – 1 mL – 0.5 mL	6 weeks

Table 2 Examples of hyperbolic tapering schedules for some of the most commonly prescribed antidepressants and doses. Note: as doses calculated according to this principle might include decimals, which cannot be administered with commonly available formulations, a rounded dose administrable in the form of oral solution is reported. Tapering durations might vary according to the starting dose

	Starting dose	Tapering schedule (each dose step maintained for 2 weeks)	Total tapering duration
ESCITALOPRAM oral tablet (theoretical dose reported)	20 mg	15 mg – 11.25 mg – 8.43 mg – 6.32 mg – 4.74 mg – 3.55 mg – 2.66 mg – 1.99 mg	16 weeks
ESCITALOPRAM oral solution (1 mg=1 drop) (rounded dose reported)	20 drops	15 drops – 11 drops – eight drops – six drops – five drops – four drops – three drops – two drops	16 weeks
SERTRALINE oral tablet (theoretical dose reported)	100 mg	75 mg – 56.25 mg – 42.18 mg – 31.63 mg – 23.72 mg – 17.79 mg – 13.34 mg – 10.01 mg	16 weeks
SERTRALINE oral solution (25 mg=1.25 mL) (rounded dose reported)	5 mL	4 mL – 3 mL – 2 mL – 1.6 mL – 1.2 mL – 0.9 mL – 0.6 mL – 0.5 mL	16 weeks
VENLAFAXINE oral tablet (theoretical dose reported)	150 mg	112.5 mg – 84.37 mg – 63.27 mg – 47.45 mg – 35.58 mg – 26.68 mg – 20 mg – 15 mg	16 weeks
VENLAFAXINE oral solution (75 mg/mL=0.5 mL=37.5 mg) (rounded dose reported)	2 mL	1.5 mL – 1.1 mL – 0.8 mL – 0.6 mL – 0.5 mL – 0.4 mL – 0.3 mL – 0.2 mL	16 weeks

equivalent oral solution of the current AD. If the current AD is considered inappropriate for practical reasons (eg, the corresponding oral solution is too concentrated) or clinical reasons (eg, QTc prolongation in individuals taking citalopram), the patient will be switched to another AD, according to a pre-defined schedule adapted from the Maudsley Hospital Guidelines, considering approximate AD dose equivalents.[6] The following oral solutions of ADs will be used: citalopram 40 mg/mL (2 mg=1 drop); escitalopram 20 mg/mL (1 mg=1 drop); paroxetine 33.1 mg/mL (1 mg=1 drop); sertraline 20 mg/mL (1 mL=20 mg); fluoxetine 20 mg/5 mL (1 mL=4 mg); venlafaxine 75 mg/mL (1 mL=75 mg); amitriptyline 40 mg/mL (2 mg=1 drop); vortioxetine 20 mg/mL (1 mg=1 drop). When a switch is required, it will be performed as a gradual cross-taper according to pre-defined equivalence schedules rather than an abrupt substitution, to minimise switch-related withdrawal symptoms. If withdrawal symptoms or worsening of depressive and anxiety symptoms occur during tapering or after discontinuation, clinicians may decide to adopt a 'wait and see' approach if the symptoms are mild, tolerable, and have a negligible impact on quality of life and overall functioning. In case symptoms are more severe and disabling, clinicians may adopt one or a combination of the following 'rescue strategies': (a) temporarily restoring the previous AD dose and/or reducing the speed of tapering, according to clinical judgement, and, if necessary, prolonging the tapering process beyond the tapering schedule; (b) prescribing a rescue medication (eg, benzodiazepines) to mitigate withdrawal symptoms. The Pharmacy Unit of the Coordinating Centre (University Hospital of Verona) will be responsible for purchase, label (in accordance with article 61 (5a) of the CTR), distribution and documentation, ensuring participants receive the correct doses with instructions and in compliance with EU regulations. The tapering durations specified here represent minimum planned schedules, adapted from guideline-based and observational evidence and intended to be applicable to routine clinical practice. In line with such practice, clinicians may slow or extend the taper beyond these predefined durations as a rescue strategy whenever clinically important withdrawal or relapse symptoms should emerge.

Outcome measures

The primary outcome will be the proportion of participants who fail to discontinue the AD or who re-start an AD during the 16 weeks after its discontinuation. Failure to discontinue is defined as continued AD use beyond the predefined tapering schedule, allowing a tolerance of up to 15% of the total tapering duration.

Secondary outcomes will include:

1. Proportion of participants who fail to discontinue the AD by the end of the pre-defined schedule.
2. Proportion of participants who re-start an AD for any reason during the 16 weeks after its discontinuation. No pre-defined criteria will guide the decision to re-start. In line with real-world practice, the decision to re-start the AD can be taken by the recruiting psychiatrist, another practitioner not involved in the study, or independently by the participant.
3. Proportion of participants failing to adhere to the pre-defined tapering schedule for any reason, including their own perceptions of the strategy and its feasibility,

other co-occurring conditions or treatments and various external factors.

4. Proportion of participants experiencing 'clinically relevant withdrawal symptoms' throughout the discontinuation and the 16-week follow-up period, defined as having at least one severe/extremely severe symptom or at least two moderately severe symptoms on the modified Discontinuation-Emergent Signs and Symptoms Scale (DESS)[25] online supplemental appendix B.
5. Mean of DESS highest overall scores during the tapering phase and the 16-week follow-up period.
6. Proportion of participants experiencing clinical relapse throughout the discontinuation and the 16-week follow-up period, defined as having at least moderately severe depression or anxiety symptoms, namely as PHQ-9≥15 or GAD-7≥10.
7. Proportion of participants who discontinue the study early and for whom primary outcome data cannot be collected. This includes people who do not attend follow-up visits and cannot be contacted, people who refuse to be involved in follow-up assessments or people who die during the tapering or the follow-up for reasons unrelated to withdrawal symptoms or relapse.

The study will assess exploratory outcomes including the proportion of participants requiring one or more rescue strategies to manage withdrawal symptoms during tapering and the 16-week follow-up; time to clinical relapse, defined as moderately severe depressive or anxiety symptoms (PHQ-9≥15 or GAD-7≥10), assessed at 16 weeks after discontinuation and at 36 weeks from randomisation; and the proportion of participants experiencing withdrawal-associated relapse, defined as clinical relapse occurring within 4 weeks after clinically relevant withdrawal symptoms. Additional exploratory measures include mean PHQ-9 and GAD-7 scores at 16 weeks, suicidal behaviours (including suicidal ideation, suicide attempts or death by suicide), health-related quality of life assessed using the Mental Component Summary of the Short Form-12 Health Survey (SF-12),[26] social functioning assessed with the Social Adaptation Self-Evaluation Scale (SASS)[27] and cost-effectiveness evaluated using an adapted version of the Client Sociodemographic and Service Receipt Inventory (CSSRI-EU).[28] Taken together, the quality-of-life (SF-12) and social-functioning (SASS) measures are intended to capture a patient-centred perspective on recovery after discontinuation, beyond the mere absence of relapse.

Data collection procedures

Participants will be recruited consecutively over 8 months. Baseline socio-demographic and clinical data, including previous diagnoses, treatments, hospitalisations, self-harm and AD discontinuation history. The following validated rating scales will be administered: PHQ-9; GAD-7; DESS; the Cumulative Illness Rating Scale to assess the burden of medical comorbidities[29]; the Big Five Inventory-10 (BFI-10)[30]; CSSRI-EU; SF-12; SASS. Data will be collected through electronic case report forms in REDCap.

Follow-ups will occur at 3, 6, 9, 12, 15, 18, 21, 24, 30 and 36 weeks. PHQ-9, GAD-7 and DESS will be administered at all visits, while SF-12 and SASS will be administered at 9, 18, 24 and 36 weeks, and CSSRI-EU at 18 and 36 weeks. All follow-ups will be performed by a blinded assessor. Further, at 9, 18, 24 and 36 weeks, the recruiting psychiatrist will collect clinical information, including updates on psychiatric and medical treatments, hospitalisations and adherence to the tapering schedule. Data entry checks will be performed both digitally and manually. No biological samples will be collected. Data will be stored digitally at the WHO Collaborating Centre.

All randomised participants will be followed until study completion unless they withdraw consent, die or become uncontactable. All randomised participants will be included in the analyses according to the intention-to-treat (ITT) principle, with the sole exception of participants who withdraw consent.

Discontinuation of the allocated treatment strategy will be defined as failure to adhere to the predefined tapering schedule. Reasons for non-adherence will be systematically recorded.

Safety monitoring

Adverse events (AEs), including serious adverse events (SAEs), serious adverse reactions (SARs) and suspected unexpected serious adverse reactions, will be recorded and reported in accordance with the EU Clinical Trials Regulation 536/2014.[31] As soon as a SAE occurs (not later than within 24 hours of obtaining knowledge of the event), an ad hoc form for SAEs will be filled out and forwarded to the Clinical Pharmacology Unit, University of Verona, in accordance with the EU legislation about pharmacovigilance in clinical research.[32] If the proportion of SAEs reaches 10% of participants, the Principal Investigator might plan an interim analysis to evaluate the initial safety and efficacy results. If an unfavourable risk/benefit balance emerges, the Coordinating Centre will consider protocol amendments or additional safeguards, such as more gradual tapering or the introduction of safety medications to reduce the impact of withdrawal symptoms. The clinical trial will be terminated if any of the following conditions occur: (a)≥5% of participants experience severe or life-threatening AEs, including suicidal thoughts or behaviours, considered related to the tapering strategies; (b) failure to comply with regulatory requirements at any recruiting centre; or (c) ethical violations involving informed consent or participant rights.

Sample size calculation

The primary outcome is a pragmatic indicator of withdrawal and relapse risk, based on the assumption that individuals who successfully discontinue AD treatment do not experience withdrawal or depressive symptoms severe enough to require continuation

or re-initiation of ADs. Accordingly, the sample size calculation relies on available evidence on withdrawal symptoms and clinical relapse. Importantly, the primary outcome captures the inability to complete discontinuation rather than the mere occurrence of withdrawal symptoms: transient withdrawal symptoms that do not lead to continuation or re-initiation of the AD are not counted as failures. Although data are limited, approximately 50% of patients are estimated to experience withdrawal symptoms during or shortly after AD discontinuation, with severe symptoms in up to half of cases.[6] An RCT in a comparable population reported a 56% relapse rate at 1 year among individuals discontinuing ADs using a linear tapering strategy similar to that adopted in this study.[25] Based on these data, we expect that 55% of participants allocated to linear tapering will fail to discontinue ADs. In contrast, observational evidence suggests that approximately 72% of individuals using a hyperbolic tapering approach successfully discontinue treatment[33]; therefore, we anticipate a 30% failure rate in this group, corresponding to an absolute risk reduction of 25% and a number needed to treat of 4. Assuming a two-sided alpha of 0.05, 80% power and accounting for clustering of patients within centres through a mixed-effects logistic regression model with centre as a random intercept (intra-cluster correlation of 0.05), a total of 120 participants (60 per arm) is required to detect this difference. Allowing for up to 20% of participants not providing analysable data, the target sample size is set at a minimum 150 participants (75 per arm). Power calculations were conducted using Power Analysis and Sample Size (PASS) software.[34]

Statistical analysis

The trial biostatistician, who will remain blinded to treatment identity, will perform all statistical analyses. The biostatistician will not be involved in participant eligibility assessment, intervention delivery, outcome assessment or data entry. The primary and secondary outcome analyses will follow the ITT principle, including all randomised participants, except those who withdraw consent for the use of their data in analyses. Where appropriate, secondary analyses will adjust for relevant baseline covariates to account for potential confounding due to imbalances in prognostic factors between two groups. Missing values in rating scales will be imputed following a multiple imputation approach using values from the available sociodemographic and clinical variables. Moreover, in the case of missing dichotomous time-varying outcomes, we will perform multiple imputations with chained equations through logistic regression, using the outcome values at the other timepoints as predictors, separately for each treatment arm and for each analysis. For confirmatory purposes, a per-protocol (PP) analysis will also be performed for both the primary and the secondary outcomes, including participants who completed the assessments at 16 weeks after tapering completion.

The proportion of participants failing to discontinue the AD will be compared between the two arms using a logistic regression with centre as a random intercept. Where appropriate, secondary analyses will adjust for relevant baseline covariates to account for potential confounding due to imbalances in prognostic factors between groups.[35] For the analysis of dichotomous secondary outcomes, the proportion of participants with the event will be compared between the two arms using logistic regression with centre as a random intercept. When possible, a multivariable analysis will be performed through a Poisson regression model with a robust error variance. Continuous outcomes will be compared between the two groups using analysis of covariance with baseline value as an additional covariate and robust standard errors. The same outcomes will be studied using linear mixed models with subject as a random effect and robust standard errors. The model will simultaneously estimate the treatment effect at all repeated assessments to evaluate the rate of change over time. This approach uses all available data without the need for missing-value imputation, providing unbiased treatment effect estimates under the missing-at-random assumption.

A Cox proportional hazard model will be used to investigate the effect of treatment on time to clinical relapse. The proportional hazard assumption of the treatment will be tested.

Adverse events and individual withdrawal symptoms will be tabulated.

Nominal value for statistical significance will be set at 0.05 (two-tailed).

A cost-effectiveness analysis will be performed based on an adapted version of the CSSRI-EU.[28].

Appropriate approaches will be used to adjust for multiple comparisons to control the risk of Type I errors (false positives) when assessing multiple outcomes. The False Discovery Rate approach will be applied to balance control of Type I errors while preserving statistical power across multiple endpoints.

Finally, for the primary outcome, we will analyse individuals at high- vs low-risk of withdrawal symptoms separately. All analyses will be performed using Stata, release 19 or higher.[36]

DISCUSSION

The DISCARD study aims to define the best evidence-based practice for effectively and safely discontinuing ADs, thereby reducing the risk of withdrawal symptoms and clinical relapse. In recent years, many have argued for the urgency of introducing innovative tapering approaches into routine clinical practice. [37] Routinely managing such strategies at the specialist and general practice levels is an essential step toward a more rational

use of ADs. This would reduce the risk of unneeded long-term prescriptions, long-lasting undesirable effects, and, more generally, increase awareness of over-prescription and over-medicalisation of common stress-related affective reactions.

The innovativeness of the DISCARD study lies primarily in its aim to provide clinicians with a pragmatic approach to improve person-centred outcomes and, concurrently, relieve the burden of inappropriate prescribing at the community level. Second, despite theoretical and observational knowledge on the best AD tapering practices, only experimental randomised evidence can truly promote a large-scale shift in clinical practice. Third, the DISCARD study will be conducted without any financial relationship with the pharmaceutical industry. This ultimately safeguards the intrinsic quality, transparency and applicability of this research. Fourthly, defining the comparative cost-effectiveness and feasibility of two AD tapering approaches is essential to outline whether their large-scale application is sustainable for practitioners and the healthcare system. While linear tapering is a relatively simple and time-saving approach that can be used routinely by general practitioners, hyperbolic tapering may require time and practical skills that are unlikely to fit into general practitioners' daily practice. This may imply different choices regarding evidence-based health policies, including decisions about which tapering strategy should be prioritised. Irrespective of results, the DISCARD study has the potential to support the update of national and international evidence-based guidelines, as well as regulatory and policy decisions.

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Contributors GO, CGa, CB conceived and designed the study. DZ, FB, GB, GC, SC, IAC, AD, PDF, RdF, CGo, CN, DP, IR, FT and FA participated in the study design and initiation and provided input on the study protocol. GO, CGa and DZ drafted the initial manuscript. All authors contributed to the writing and review of the final submitted manuscript. GO is responsible for the overall content as guarantor. AI-assisted language editing was used solely to review and improve the English language, grammar and clarity of the manuscript. No AI tools were used for data analysis, interpretation or content generation. All suggested revisions were carefully reviewed and approved by the authors, who take full responsibility for the final content of the manuscript.

Funding This work is supported by Ministero dell'Università e della Ricerca; Bando Prin 2022 PNRR – Settore LS5 - Decreto Direttoriale n. 1409 del 14-09-2022; project code: P2022LY3RF. The study funder has no role in study design, collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication. The study funder had no ultimate authority over any of the listed activities.

Competing interests In the last three years, RdF has received speaker fees from Angelini, Johnson & Johnson, Lundbeck, Neuraxpharm and Rovi, and travel support from Angelini, Johnson & Johnson, Lundbeck, Otsuka and Rovi; SC received consultant fees from Lundbeck, Otsuka, Angelini and Johnson & Johnson; AD received indirect honoraria for presentations and/or travel support from Johnson & Johnson, Lundbeck and Viatris. All other authors have no competing interests to disclose.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The dataset containing all de-identified individual participant data used for the analyses will be uploaded in the online repository EUDATB2SHARE under the licence 'Creative Commons Attribution-NonCommercial-NoDerivs' (CC-BY-NC-ND). Researchers interested in the analysis of such data will be asked to forward a formal request to the DISCARD Study Committee, composed of G.O., C.B., C.Ga., C.Go, D.Z. The request must include details about the research hypothesis, the variables required and the statistical methodology that will be employed. The DISCARD Study Committee will determine whether to accept the request, and if approved, a data access agreement will be created and signed by both parties.

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