NIHR | National Institute for Health and Care Research

Programme Grants for Applied Research

Extended Research Article

Internet and telephone intervention to support patients discontinuing long-term antidepressants in primary care: the REDUCE research programme including RCT

Tony Kendrick,[1*†] Beth Stuart,[2] Hannah Bowers,[1] Mahboobeh Haji Sadeghi,[3] Helen Page,[4] Christopher Dowrick,[4] Michael Moore,[1] Mark Gabbay,[4] Geraldine Leydon,[1] Guiqing Lily Yao,[5] Shihua Zhu,[1] Paul Little,[1] Gareth Griffiths,[6] Glyn Lewis,[7] Carl May,[8] Joanna Moncrieff,[7] Chris F Johnson,[9] Una Macleod,[3] Simon Gilbody,[10] Rachel Dewar-Haggart,[1] Samantha Williams,[1] Wendy O'Brien,[1] Riya Tiwari,[1] Catherine Woods,[1] Tasneem Patel,[4] Naila Khan,[4] Emma Maund,[1] Nadja van Ginneken,[4] Amy Din,[1] Claire Reidy,[1] Rebecca Lucier,[1] Bryan Palmer,[11] Taeko Becque,[1] Yumna Masood,[4] Natalie Thompson,[1] Ellen van Leeuwen,[12] Marta Glowacka[13] and Adam WA Geraghty[1]

[1]Primary Care Research Centre, School of Primary Care, Population Health & Medical Education, Faculty of Medicine, University of Southampton, Aldermoor Health Centre, Southampton, UK
[2]Centre for Evaluation and Methods, Wolfson Institute of Population Health, Faculty of Medicine and Dentistry, Queen Mary University of London, London, UK
[3]Hull-York Medical School, Allam Medical Building, University of Hull, Hull, UK
[4]Department of Primary Care and Mental Health, University of Liverpool, Liverpool, UK
[5]Leicester Clinical Trials Unit, University of Leicester, Leicester, UK
[6]Southampton Clinical Trials Unit, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK
[7]Division of Psychiatry, University College London, London, UK
[8]Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK
[9]Primary Care Pharmacy Services, NHS Greater Glasgow & Clyde, Glasgow, UK
[10]Mental Health & Addiction Research Group, Department of Health Sciences, University of York, York, UK
[11]Patient and Public Contributor, Southampton, UK
[12]Clinical Pharmacology Unit & Unit General Practice, Department of Basic and Applied Medical Sciences & Department of Public Health and Primary Care, Ghent University, Ghent, Belgium
[13]Independent researcher, Poland
[†]Programme lead

[*]Corresponding author A.R.Kendrick@Southampton.ac.uk

Published July 2025
DOI: 10.3310/BTBL3945

Scientific summary

Internet and telephone intervention to support patients discontinuing long-term antidepressants in primary care: the REDUCE research programme including RCT

Programme Grants for Applied Research 2025; Vol. 13: No. 7
DOI: 10.3310/BTBL3945

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

There is significant concern about increasing long-term antidepressant use in Western countries, much of which is not evidence-based. The median duration of treatment is more than 2 years in the UK, and more than 10% of adults are taking antidepressants, risking potentially significant adverse effects, particularly for older patients. Patients may continue treatment due to fear of relapse of depression, or to experiencing withdrawal symptoms which can make discontinuation difficult. If practitioners do not broach attempting discontinuation, then patients will assume they must continue to take repeat prescriptions.

Many patients want the option of being reviewed and attempting discontinuation with appropriate support, but general practitioners (GPs) often lack experience in reducing antidepressants flexibly, and their advice to withdraw treatment may not be successful. Trials of simply prompting GPs to review patients eligible for antidepressant discontinuation have found only 6–8% of patients succeed.

Patients anxious about discontinuing treatment may have to be persuaded of the potential benefits, then actively engaged in the process and supported through withdrawal. We considered that providing self-management internet and telephone support for patients and practitioners might facilitate antidepressant withdrawal at scale, without adding to the workload of primary care or psychological therapies.

Aim and objectives

Aim

To identify feasible, safe, effective and cost-effective ways of helping patients taking long-term antidepressants to withdraw from treatment where it is appropriate for them to do so.

Objectives

1. To conduct a systematic review of quantitative and qualitative literature, to identify interventions that have been used to help patients withdraw from antidepressant treatment.
2. To identify factors that promote or inhibit the implementation of treatment withdrawal, through interviews with patients taking them long term, and focus groups with GPs, nurse practitioners (NPs) and primary care mental health workers who treat patients.
3. To develop an internet-supported cognitive–behavioural therapy-based intervention for primary care practitioners and patients to support patient withdrawal from antidepressant treatment, through a process of co-design and co-production with practitioners and patients, taking their views into account throughout its development and implementation, in an iterative process.
4. To determine the effectiveness of the intervention in helping patients stop treatment through a randomised controlled trial (RCT), and to estimate its cost-effectiveness from a health service perspective.
5. To build a translational framework describing the intervention and addressing how it should be delivered, including overcoming practitioner and patient-related barriers, to facilitate implementation of treatment cessation.

Methods

We conducted six workstreams.

In workstream 1 (WS1), two systematic reviews were completed: one of quantitative studies of interventions to facilitate antidepressant discontinuation, and one of qualitative studies of barriers and facilitators to antidepressant discontinuation identified by patients and health professionals.

In workstream 2 (WS2), qualitative interviews were carried out with people taking long-term antidepressants, and focus groups and interviews were carried out with GPs, NPs and mental health practitioners.

In workstream 3 (WS3), we developed internet-based interventions for patients ('*ADvisor*') and primary care practitioners ('*ADvisorHP*') to support antidepressant discontinuation, through co-design and co-production with patients and practitioners, taking their views into account in an iterative process. Prototype interventions were tested using 'think-aloud' interviews where participants described their opinions while using the prototypes. We also developed guidance for psychological well-being practitioners (PWPs) to provide support to people coming off antidepressants through three telephone calls, one of 30 minutes and two follow-up calls of 15 minutes.

Workstream 4 (WS4) was a feasibility RCT to assess procedures for a definitive RCT to follow, including practice and patient recruitment (from both medical record searches and opportunistically in consultations); follow-up rates; the acceptability and feasibility of our internet and PWP telephone interventions; the acceptability and feasibility of the trial procedures and outcome measures; and participants' views of involvement in the trial, through qualitative interviews with patients and practitioners.

Workstream 5 (WS5) was a definitive non-inferiority cluster RCT with health economic evaluation; and quantitative and qualitative process evaluations. Randomisation was by remote computerised sequence generation, with minimisation by practice size, urban/rural location and deprivation index. Participants and researchers could not be blinded given the pragmatic open design, but self-complete measures avoided observer rating bias, and analyses were conducted blind.

The participants were adults on antidepressant treatment for more than 1 year for a first episode of depression, or for more than 2 years for a recurrent episode, who were no longer depressed or judged to be at significant risk of relapse.

The primary outcome was depressive symptoms on the Patient Health Questionnaire-9 items (PHQ-9) questionnaire at 6 months. Secondary outcomes were depressive symptoms over 12 months; antidepressant discontinuation at 6 and 12 months; withdrawal symptoms at 3 and 6 months; and anxiety, quality of life, adverse events, mental well-being, patient enablement, patient satisfaction, health service use and costs over 12 months.

The original sample size calculation gave a target of 402 patients for 90% power with one-sided significance of 2.5% to determine non-inferiority of the intervention, within 2 points on the PHQ-9. This was reduced to 360 on finding a significant correlation between baseline and follow-up values for the PHQ-9 part-way through the trial.

Linear mixed modelling was used to determine differences in outcomes, adjusting for previous depression, baseline outcome values, baseline anxiety, sociodemographic characteristics and practice as a random effect. Primary analysis was by intention to treat, with per-protocol and complier-average sensitivity analyses. Multiple imputation was used to account for missing values.

A quantitative process evaluation looked at participants' use of the online interventions (automatically recorded), and the fidelity of the PWP calls against the guidance provided. A qualitative process evaluation involved interviewing practitioners and patients. Semistructured topic guides were used for interviews which were audio-recorded, transcribed verbatim and analysed using reflexive thematic analysis. Normalisation process theory was used as a framework to identify issues related to implementing the interventions in practice beyond the trial.

An additional workstream was requested by the Programme Grants Board, aimed at developing a prototype intervention for a major ethnic minority group. We worked with Urdu-speaking people of South Asian origin in the north-west of England to develop a culturally acceptable version of the *ADvisor* patient intervention using the methods of co-production used in WS3.

Results

Our systematic reviews, qualitative interviews and focus groups indicated that barriers to discontinuing treatment include a fear of relapse of depression and withdrawal symptoms. If practitioners do not raise possible discontinuation,

patients will usually continue treatment without questioning it. Patients wanted information on the underlying mechanisms, effects and side effects of antidepressants, withdrawal symptoms and coping strategies. Practitioners wanted guidance on initiating discontinuation, antidepressant-tapering regimens, and distinguishing withdrawal from relapse.

Practices and patients

In the feasibility trial, we successfully recruited 14 practices, 7 randomised to each arm. In the definitive trial, we recruited 131 practices, 66 randomised to the intervention arm, and 65 to the control. We recruited a total of 330 patients (178 in intervention practices and 152 in controls), of whom 275 (83%) were followed up at 6 months, and 240 (73%) at 12 months. The 330 included 52 recruited for the feasibility trial, which was approved as an internal pilot as the protocol was not changed significantly.

Clinical outcomes

The intervention proved non-inferior to the control for the development of depression. In fact, mean PHQ-9 depression symptom scores were slightly higher among controls at 6 months {5.0 vs. 4.0; adjusted difference 1.07 [95% confidence interval (CI) 0.09 to 2.06; $p = 0.033$]}. Antidepressant discontinuation rates at 6 months were slightly higher in the intervention arm, but not significantly (45.5% vs. 41.9% in the control arm).

Over 6 months antidepressant withdrawal symptoms on the Discontinuation Emergent Signs and Symptoms Scale were fewer in the intervention arm, although the difference, while statistically significant, was small [adjusted mean difference −1.56 points (95% CI −2.85 to −0.26); $p = 0.018$]. Similarly, over 12 months, mental well-being scores on the Warwick-Edinburgh Mental Wellbeing Scale were slightly better in the intervention arm [mean difference 2.17 points (95% CI 0.21 to 4.14); $p = 0.030$]. There were no significant differences in anxiety, quality of life, patient enablement, or patient satisfaction. Adverse events occurred for 15% of patients in each arm, which were mostly not serious. One serious adverse reaction to discontinuation occurred in each arm.

Health economic outcomes

The adjusted mean cost of services used was lower in the intervention arm by −£69 (95% CI −£77 to £207). The incremental cost-effectiveness ratio was a mean saving of −£2839 per quality-adjusted life-year gained (95% CI −£30,024 to £22,227). The probability of the intervention being cost-effective compared to usual care at the National Institute for Health and Care Excellence thresholds of societal willingness to pay, of £20,000 and £30,000, was > 89% for both.

Qualitative interviews

Qualitative interviews suggested successful antidepressant discontinuation was more likely if the invitation for a review came at a time when the person was feeling well and stable, and ready to try to discontinue. Advice to taper slowly, and information on the difference between relapse and withdrawal symptoms, seemed to contribute significantly to the success of the interventions.

Urdu version of ADvisor

Interviews and focus groups with Urdu-speaking patients, practitioners and community leaders informed the development of a prototype Urdu version of the *ADvisor* intervention for patients, but as a booklet and online videos, as participants did not consider an interactive online intervention would be acceptable. The prototype was optimised through think-aloud interviews and is available for future testing and implementation.

Limitations

In our WS1 qualitative evidence synthesis, coding to generate themes was performed by one researcher and discussed with two others, due to time constraints. Similarly, in the systematic review, one researcher performed study selection, data extraction and risk of bias assessment, checked by another reviewer. Ideally, coding, study selection, data extraction and bias assessment would be done independently by two reviewers.

The use of focus groups to elicit barriers and facilitators to discontinuation from health professionals in WS1 facilitated discussion and candid responses from participants. However, discussions can become polarised or influenced by dominant members in a group, and some participants' views may be less well represented.

The GPs we enrolled were interested in mental health research and may be more knowledgeable than practitioners generally, which may explain why some felt that some of the information in *ADvisorHP* was not new. Other GPs may have learnt more from the intervention, particularly trainees and GPs new to UK practice. The development work included only two NPs, which made it difficult to identify differences between GP and NP perspectives.

In the main WS5 trial, we recruited 330 patients, falling short of the (revised) target sample size of 360. We had sufficient power to address the primary outcome, as 6-month follow-up (83%) was greater than the 80% predicted. However, only 73% were followed up at 12 months which reduced the power of the sample to exclude differences in depression and discontinuation of antidepressants developing beyond 6 months. In the missing cases multiple imputation analysis, while the non-inferiority conclusion remained, the intervention no longer appeared superior to the control.

Vetting by GPs of patient lists generated by the medical records searches would have introduced selection bias, towards including people who were well and considered ready to try tapering by the GP, and excluding people who were considered to be at greater risk of relapse. This may explain why we found a high rate of discontinuation compared to the 6–8% found in previous trials of GP reviews. In the previous trials, patients identified from medical records searches were approached directly by the researchers and many were found to be unwilling to try discontinuing their antidepressants.

Finally, we had no information on the numbers of patients in each arm who did not taper their antidepressant, or embarked on tapering, but subsequently resumed the original dose. The qualitative interviews indicated some patients went quickly back on to their original dose of antidepressants when new symptoms developed, and were not supported by their GPs to try and get through them by going back up in dose temporarily, but we do not know how many did this.

Conclusions

Rates of discontinuation of long-term antidepressants of more than 40% are achievable through enabling patients who are ready to consider reducing them to get active support from primary care practitioners.

Online and telephone support appears to help protect patients against depressive and withdrawal symptoms, and conserve mental well-being, although the benefits are modest. Advice to taper slowly and information on differences between relapse and withdrawal symptoms appear to be major factors contributing to successful discontinuation.

Adverse events from attempting discontinuation are likely to be few, and usually not serious, so this is a relatively safe thing to do in primary care, where relapse of depression is likely to occur in a minority of patients, and treatment can be quickly restarted if patients are monitored. Patients may be greatly reassured by being able to ask questions through telephone support calls.

Implications for practice and future research

In the definitive RCT, only 8% of patients approached were willing to take part and only 5% could be consented and enrolled in the trial. However, uptake in routine clinical practice is likely to be higher now the interventions have been shown to be effective.

Our qualitative process evaluation suggested that implementation methods need to include:

1. Creating opportunities for discussing antidepressant discontinuation (more active reviews of people on long-term treatment and fewer routinely repeated prescriptions).
2. Flagging the electronic records of patients who qualify for considering discontinuation.
3. Delegation of medication reviews and tapering support to other professionals besides GPs.
4. Making patients more aware of how withdrawal symptoms differ from relapse, and how to cope with them.
5. Adopting tapering regimens over months rather than weeks, to reduce the occurrence and severity of withdrawal symptoms, with flexibility to go back up in dose if necessary.
6. Proactive follow-up during tapering where possible, including brief telephone calls or text messages.
7. Embedding links to alternative treatment resources in the electronic patient record.

Future research should:

1. Try to engage a greater proportion of people taking antidepressants, including younger people, unemployed people, people from deprived areas and of ethnic minority groups.
2. Follow people more closely through their attempts to taper antidepressants, record the development of depressive and withdrawal symptoms, distinguish where possible between withdrawal and relapse, and determine relationships between symptoms and progress in tapering.
3. Assess barriers and facilitators to wider implementation of support to practitioners and patients in clinical practice for antidepressant discontinuation.
4. Assess the potential for involvement in deprescribing of other healthcare professionals (HCPs) besides GPs and NPs, in particular pharmacists, and mental health professionals.
5. Compare new interventions against best practice, that is active review of medication by HCPs, rather than usual care, which currently often means no active review for many people taking long-term antidepressants.

Permissions

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research programme (NIHR award ref: RP-PG-1214-20004) and is published in full in *Programme Grants for Applied Research*; Vol. 13, No. 7. See the NIHR Funding and Awards website for further award information.

Programme Grants for Applied Research

ISSN 2050-4330 (Online)

A list of Journals Library editors can be found on the NIHR Journals Library website

Programme Grants for Applied Research (PGfAR) was launched in 2013 and is indexed by Europe PMC, NCBI Bookshelf, DOAJ, Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and Scopus® (Elsevier, Amsterdam, Netherlands).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

Criteria for inclusion in the *Programme Grants for Applied Research* journal

Manuscripts are published in *Programme Grants for Applied Research* (PGfAR) if (1) they have resulted from work for the PGfAR programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

The full PGfAR archive is freely available to view online at www.journalslibrary.nihr.ac.uk/pgfar.

Programme Grants for Applied Research programme

The Programme Grants for Applied Research (PGfAR) programme, part of the National Institute for Health and Care Research (NIHR), was established in 2006 to fund collaborative, multidisciplinary programmes of applied research to solve health and social care challenges. Findings are expected to provide evidence that lead to clear and identifiable patient benefits, in the relatively near future.

PGfAR is researcher led and does not specify topics for research; however, the research must be in an area of priority or need for the NHS and the social care sector of the Department of Health and Social Care, with particular emphasis on health and social care areas that cause significant burden, where other research funders may not be focused, or where insufficient funding is available.

The programme is managed by the NIHR Central Commissioning Facility (CCF) with strategic input from the Programme Director. For more information about the PGfAR programme please visit the website: www.nihr.ac.uk/explore-nihr/funding-programmes/programme-grants-for-applied-research.htm

This article

The research reported in this issue of the journal was funded by PGfAR as award number RP-PG-1214-20004. The contractual start date was in October 2016. The draft manuscript began editorial review in September 2023 and was accepted for publication in February 2025. As the funder, the PGfAR programme agreed the research questions and study designs in advance with the investigators. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The PGfAR editors and production house have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, CCF, PGfAR or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the PGfAR programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).