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Antipsychotic discontinuation and reduction in people with schizophrenia and multiple-episode psychosis: the RADAR mixed-methods research programme including RCT

Joanna Moncrieff, Maria Long, Stefan Priebe, Johura Akther-Robertson, Thomas Barnes, George Bray, Ruth Cooper, Nadia Crellin, Katherine Darton, Nick Freemantle, Robert Freudenthal, Vasiliki Gkofa, Lisa Grünwald, Zoe Haime, Nadia Haynes, Robert Horne, Mark Horowitz, Rachael Hunter, Sonia Johnson, Lyn Kent, Glyn Lewis, Louise Marston, Nicola Morant, Vanessa Pinfold, Georgina Ramsay, Ruth Smith, Jacki Stansfeld, Tom Stockmann and Victoria Vickerstaff





Extended Research Article

Antipsychotic discontinuation and reduction in people with schizophrenia and multiple-episode psychosis: the RADAR mixed-methods research programme including RCT

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This article

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Abstract

Background: Antipsychotic medication is beneficial for people with psychosis or schizophrenia in the short term, but the balance of risks and benefits in the long term is less clear. Many patients remain functionally impaired, experience significant and distressing side effects and physical health problems. Evidence in people with first episode psychosis suggests that social functioning may be improved for some patients following a gradual reduction or discontinuation of antipsychotics, but there is no evidence in people with recurrent conditions.

Objectives:

1. To assess patients' attitudes to long-term use of antipsychotic medication (work package 1a).
2. To develop a gradual strategy of antipsychotic reduction and discontinuation and to design a trial to assess its benefits and harms (work packages 1a and 1b).
3. To evaluate the antipsychotic reduction strategy in a randomised pilot trial (work package 2).
4. To conduct a full randomised trial (work package 3a) of the antipsychotic reduction strategy in patients with multiple episode psychosis.
5. To explore the experiences of people enrolled in the antipsychotic reduction strategy (work package 3b).

Methods

Design: Objective 1: A mixed-methods survey of attitudes to long-term treatment and (work package 1a). Objective 2: Survey of attitudes to participation in a randomised trial, expert consultation, lived experience consultation, literature review, including a systematic review of definitions of relapse in previous trials of antipsychotics, focus groups (work packages 1a and 1b). Objectives 3 and 4: Multicentre, pragmatic, open, parallel group randomised controlled trial (with blinded assessors) (work packages 2 and 3a). Objective 5: qualitative study using semistructured interviews (work package 3b).

Participants: Patients with schizophrenia or recurrent, non-affective psychotic episodes, taking antipsychotics.

Setting: English community mental health services.

Interventions: A gradual strategy of antipsychotic reduction, with discontinuation where possible (evaluated in work packages 2 and 3, developed during work package 1).

Main outcome measures: In work package 1a: Patients' views of antipsychotic medication and participation in a randomised trial of antipsychotic reduction. In work package 2: Recruitment rates and adherence to trial procedures. In work package 3a: Primary outcome was the Social Functioning Scale. The principal secondary outcome was severe relapse (admission to mental health inpatient care). Other outcomes included any relapse, symptoms, and a full economic analysis was performed.

Results: Work package 1a – 269 participants were interviewed. Only 33% were content with taking antipsychotic medication for long term, and 31% and 45% wished to try and stop or reduce it, respectively, with clinical support. Seventy-nine per cent indicated that they would or might be interested in taking part in a future trial.

Work package 1b – Trial recruitment strategy and intervention protocol, procedures and adherence protocols were developed, along with definitions and procedures for determining relapse. The systematic review failed to identify a previous definition of relapse that was reliable, clinically relevant and feasibly to apply.

Work package 2 – Recruitment was 65% of the projected target and the trial was approved to continue to a full trial.

Work package 3a – 253 participants were randomised, 126 to supported reduction, 127 to maintenance antipsychotic treatment. At 24 months, there was no statistically significant difference between groups in change on the Social Functioning Scale (b : 0.19, 95% confidence interval -1.94 to 2.33 , $p = 0.859$). The rate of severe relapse was significantly higher in the intervention group (25%) compared to the maintenance group (13%) (odds ratio, b : 2.39, 95% confidence interval 1.25 to 4.56). The risk of any relapse was also higher, but there was no difference in other outcomes. There were 93 serious adverse events in 49 individuals in the reduction arm (mostly admissions to hospital

for a mental health relapse) and there were 64 in 29 individuals in the maintenance arm. In the economic analysis, at 24 months, there was no significant difference between the two arms in costs (£5619; 95% confidence interval –£386 to £11,625) or quality-adjusted life-years (–0.035, 95% confidence interval –0.125 to 0.054). There were significantly fewer years of full capability in the supported reduction arm (–0.103, 95% confidence interval –0.191 to –0.015).

Work package 3b – 26 patients were interviewed. Analysis indicated that patients experienced improvements in adverse effects, social functioning and sense of self. However, some experienced increased symptoms, challenging emotional intensity and relapse. For some patients, supported medication reduction provided an opportunity for learning and empowerment.

Work package 3c – 15 clinicians provided feedback on their experiences. They felt that antipsychotic reduction had been beneficial for some but had led to negative outcomes for other patients. Some reported that the trial enabled more collaborative relationships with patients.

Limitations: Recruitment was challenging, and some participants did not adhere to their randomised treatment programme. The number recruited was a small proportion of the number screened, which means the sample may differ from the general population of people considered likely to be suitable to take part in a trial of this sort. The COVID pandemic affected the social functioning measure.

Conclusions: Quantitative analysis showed that antipsychotic reduction and discontinuation over a period of months does not improve social functioning at 24 months, and increases the risk of severe relapse. There is a low probability that supported reduction is cost-effective compared to maintenance. In qualitative findings, patients and clinicians noted positive and negative effects of antipsychotic reduction.

Future work: Future work should include long-term follow-up of the trial cohort and investigation of more gradual reduction strategies.

Trial registration: The trial is registered as ISRCTN90298520 on 7 February 2017 and at ClinicalTrials.gov on 18 June 2018.

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- Report Supplementary Material 2** Antipsychotic Reduction and Discontinuation Manual
- Report Supplementary Material 3** Maintenance Treatment Manual
- Report Supplementary Material 4** Wellbeing booklet – reduction
- Report Supplementary Material 5** Wellbeing booklet – maintenance
- Report Supplementary Material 6** Patient self-report relapse questionnaire
- Report Supplementary Material 7** Relapse Criteria
- Report Supplementary Material 8** Two monthly Medical Notes Review Form
- Report Supplementary Material 9** End-point Committee Charter
- Report Supplementary Material 10** Trial Protocol
- Report Supplementary Material 11** Consolidated Standards of Reporting Trials checklist
- Report Supplementary Material 12** Case report form (CRF)
- Report Supplementary Material 13** Statistical analysis plan
- Report Supplementary Material 14** Consolidated Standards of Reporting Trials checklist for Abstracts
- Report Supplementary Material 15** Clinician interview study summary

Supplementary material can be found on the NIHR Journals Library report page (<https://doi.org/10.3310/GJJM0506>).

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List of abbreviations

ASEX	Arizona Sexual Experiences Scale	NELFT	North East London Foundation Trust
CCA	complete case analysis	NICE	National Institute for Health and Care Excellence
CMHT	Community Mental Health Team	NIHR	National Institute for Health and Care Research
CONSORT	Consolidated Standards of Reporting Trials	PANSS	Positive and Negative Syndrome Scale
CSQ	Client Satisfaction Questionnaire	PMG	Programme Management Group
CSRI	Client Service Receipt Inventory	PPI	patient and public involvement
DAI	Drug Attitude Inventory	PRIMENT	Registered Clinical Trial Unit
ELFT	East London Foundation Trust	PSC	Programme Steering Committee
EQ-5D-3L	EuroQol-5 Dimensions, three-level version	QALY	quality-adjusted life-year
EQ-5D-5L	EuroQol-5 Dimensions, five-level version	QPR	Questionnaire about the Process of Recovery
GASS	Glasgow Antipsychotic Side-Effect Scale	RADAR	Research into Antipsychotic Discontinuation and Reduction trial
GSDS	Groningen Social Disability Scale	RCT	randomised controlled trial
ICECAP-A	ICEpop CAPability Measure for Adults	REC	Research Ethics Committee
IMP	investigational medicinal product	SFS	Social Functioning Scale
LEAP	Lived Experience Advisory Panel	SIX	Objective Social Outcomes Index
MANSA	Manchester Short Assessment of quality of life	UCL	University College London
MARS-5	Medication Adherence Report Scale	WP	work package
		YFC	year of full capability

Plain language summary

Schizophrenia and other psychotic conditions are common and can cause considerable suffering. The widely established treatment is long-term antipsychotic medication, but this can cause harmful and unpleasant side effects. In this programme, we designed a 'clinical trial' to test the benefits and harms of helping people to gradually reduce and stop their antipsychotic medication. In the trial, people were randomly assigned to have their antipsychotic medication dose reduced or to continue on their current dose. We followed up people and assessed their ability to live their daily lives (social functioning) and other outcomes. In the first part of the research, we interviewed 269 patients and found that almost a third (31%) would welcome an opportunity to try to stop their antipsychotic medication with support from their psychiatrist. Just under half (45%) would like to reduce it. We enrolled 253 participants in the clinical trial and followed up 190 people 2 years later. At 2 years, there were no differences in social functioning between people who were assigned to antipsychotic reduction and those assigned to continue their antipsychotic treatment. People assigned to antipsychotic reduction were approximately twice as likely to have a severe relapse of their condition. At 2 years, there were no differences in the levels of symptoms or side effects. Antipsychotic reduction was more costly and did not lead to financial savings. In-depth interviews showed that people experienced some beneficial effects from reducing antipsychotics, including reduced side effects and increased empowerment, and some negative effects, including intense emotions, worsening of symptoms and relapse. Psychiatrists felt that antipsychotic reduction had been beneficial for some patients but had led to negative outcomes for others. Psychiatrists felt that the reduction process had enabled them to develop a more equal partnership with some patients.

Scientific summary

Background

Antipsychotic medication suppresses acute symptoms and prevents relapse in the short term, but the balance of risks and benefits in the long term is less clear. Many patients remain functionally impaired, experience significant and distressing side effects and physical health problems, leading to dissatisfaction with treatment and non-adherence. Evidence in people with first episode psychosis suggests that social functioning may be improved for some patients following a gradual and supported reduction and discontinuation, but there is no evidence in people with recurrent psychotic conditions.

Work package 1a

Objective

To explore patients' attitudes to long-term use of antipsychotic medication and to reduction and discontinuation of antipsychotics.

Methods

Design

A mixed-methods survey of attitudes to long-term treatment and willingness to participate in a randomised controlled trial (RCT) of an antipsychotic reduction programme.

Participants

Patients with schizophrenia or recurrent, non-affective psychosis, taking antipsychotics, aged ≥ 18 years with sufficient English to complete assessments, who have capacity to consent and are not legally compelled to take medication recruited from community mental health services in four London-based mental health trusts and general practices.

Setting

Community mental health services in four mental health Trusts in London and London-based general practices.

Interventions

A survey of attitudes to antipsychotics and antipsychotic reduction and discontinuation.

Main outcomes

Views about use of long-term antipsychotic medication, reduction and discontinuation of antipsychotic medication. Views about participation in a randomised trial of a clinically supported antipsychotic reduction strategy.

Results

A total of 269 participants with psychosis were interviewed. Of these, 31% wished to try and stop their antipsychotic with professional support, and 45% tried to reduce it. Only 33% were content with taking antipsychotic medication for long term. People who wanted to discontinue had more negative attitudes towards the medication but were otherwise similar to other participants. Wanting to stop or reduce medication was motivated mainly by adverse effects and health concerns. Professional support was identified as potentially helpful to achieve reduction. Seventy-nine per cent indicated that they would or might be interested in taking part in a future trial. Altruistic reasons were most commonly given for wanting to take part and concern about randomisation for not wanting to.

Limitations

The survey sample was influenced by clinician's decisions to put people forward and patients' interest and consent. The majority of participants had used antipsychotics for many years, so the sample does not necessarily reflect the views of shorter-term users.

Conclusions

A substantial proportion of people using long-term antipsychotics would like support to try to reduce their dose or discontinue treatment, mainly due to adverse effects. The survey was a useful recruitment strategy for the main trial even though fewer people eventually enrolled in the trial than had indicated they would be interested.

Work package 1b

Objectives

To explore how antipsychotics should be reduced in clinical practise and how a trial could be designed to evaluate such a process.

Methods

Methods consisted of: expert consultation with national and international experts, lived experience consultation with the programme's Lived Experience Advisory Committee members, literature review and focus groups with staff members from two London-based mental health trusts. These were conducted to inform trial design, recruitment and outcomes. A systematic review of relapse definitions in antipsychotic discontinuation trials was conducted.

Results

The systematic review failed to identify a previous definition of relapse that was reliable, clinically relevant and feasibly to apply. The trial recruitment strategy, the intervention protocol, procedures and monitoring protocols were developed. Eligibility criteria were determined and definitions and procedures for determining relapse were developed, including terms of reference for an end-point committee to assess non-severe relapses.

Conclusions

Procedures to conduct a randomised trial comparing gradual antipsychotic reduction and discontinuation with maintenance treatment were developed.

Work package 2

Objective

To ascertain whether a trial of a supported antipsychotic reduction programme is feasible.

Methods

Design

Pilot trial of a multicentre, pragmatic, open, parallel group RCT of antipsychotic reduction in people with schizophrenia and recurrent psychotic conditions.

Participants

Patients with schizophrenia or recurrent, non-affective psychosis, aged ≥ 18 years, taking antipsychotics, with sufficient English to complete assessments, who have capacity to consent and are not legally compelled to take medication recruited from community mental health services in two London-based mental health trusts.

Setting

Two London-based mental health trusts.

Intervention

Evaluation of a strategy of gradual antipsychotic reduction and discontinuation overseen by a clinician.

Outcomes

Recruitment rate and feasibility of monitoring.

Results

The recruitment during the 4 months of the pilot trial was 65% of the projected target. Intervention monitoring was judged to be feasible.

Conclusions

The trial was approved to continue to a full trial.

Work package 3a

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Objectives

To evaluate the benefits and harms of an antipsychotic reduction programme compared to maintenance treatment in patients with multiepisode psychosis.

Methods

Design

A full RCT of antipsychotic reduction in people with schizophrenia and recurrent psychotic conditions.

Participants

Patients with schizophrenia or recurrent, non-affective psychosis, taking antipsychotics, with sufficient English to complete assessments, who have capacity to consent and are not legally compelled to take medication recruited from community mental health services in 19 mental health trusts in England.

Setting

Community mental health services in 19 mental health trusts in England.

Interventions

A strategy of gradual antipsychotic reduction and discontinuation overseen by a clinician.

Outcomes

The primary outcome was social functioning at 24-month follow-up, measured using the Social Functioning Scale (SFS). The principal secondary outcome was severe relapse, which was defined as hospital admission for psychiatric inpatient treatment. An expert end-point committee was convened to assess the presence or absence of relapse more broadly, which was based on blinded information from clinical case-notes, using predefined criteria and guidance. Other secondary outcomes were mental state, measured by the Positive and Negative Syndrome Scale, quality of

life, measured by the Manchester Short Assessment of quality of life, and the Objective Social Outcomes Index (SIX), which is derived from it. Adverse effects of antipsychotics were measured using a modified version of the Glasgow Antipsychotic Side-Effect Scale, body weight and sexual dysfunction using the Arizona Sexual Experiences Scale. Other assessments included the Questionnaire about the Process of Recovery, the Client Satisfaction Questionnaire and the Medication Adherence Report Scale. Neuropsychological function was measured using a brief battery of tests designed for this trial. Health economics outcome measures included the EuroQol-5 Dimensions, five-level version and the ICEpop CAPability measure for Adults.

Results

A total of 253 participants were randomised: 126 were assigned to antipsychotic dose reduction and 127 to maintenance. One hundred and ninety participants were interviewed at a 24-month follow-up. The difference between the groups on the primary outcome, the SFS, was small and not statistically significant (0.19, -1.9 to 2.3: [Table a](#)). Sensitivity analyses, including the degree of COVID-19 lockdown and predictors of missingness, did not change this. The time to severe relapse was shorter in the reduction group compared with the maintenance group [hazard ratio 2.2, 95% confidence interval (CI) 1.2 to 4.0, $p = 0.007$]. At 24 months, 32 participants (25.4%) in the reduction group had had at least 1 severe relapse compared with 17 (13.4%) of the maintenance group (odds ratio 2.2, 95% CI 1.2 to 4.2). Rates of non-severe and overall relapse were also higher in the reduction group. There was no difference in median bed-days between groups.

TABLE a Baseline demographic and clinical characteristics of randomised trial participants

Characteristic	Antipsychotic dose reduction/ discontinuation, maximum, N = 126		Antipsychotic maintenance treatment, maximum, N = 127	
	N	n (%) or mean (SD) or median (IQR)	N	n (%) or mean (SD) or median (IQR)
Male	126	85 (67.4%)	127	83 (65.3%)
Female	126	40 (31.7%)	127	42 (33.1%)
Transgender	126	1 (0.79%)	127	2 (1.6%)
Age	126	Mean 46.6 (SD 12.2)	127	Mean 46.0 (SD 11.5)
Marital status				
Single, separated, divorced, widowed	126	106 (84.1%)	127	110 (86.6%)
Married, cohabiting, civil partnership	126	20 (15.9%)	127	17 (13.4%)
Ethnicity				
White	126	89 (70.6%)	125	82 (65.6%)
Black	126	25 (19.8%)	125	27 (21.6%)
Asian	126	8 (6.3%)	125	8 (6.4%)
Other	126	4 (3.2%)	125	8 (6.4%)
First language English	126	107 (84.9%)	127	114 (89.8%)
Highest educational achievement				
Primary and secondary education to age 16 years	125	49 (39.2%)	126	36 (28.6%)
Primary and secondary education to age 18 years	125	22 (17.6%)	126	27 (21.4%)
Tertiary or further education	125	40 (32.0%)	126	56 (44.4%)
Other general education	125	14 (11.2%)	126	7 (5.6%)
Years of completed education	121	Mean 14 (SD 3.3)	125	Mean 14 (SD 3.9)

continued

TABLE a Baseline demographic and clinical characteristics of randomised trial participants (*continued*)

Characteristic	Antipsychotic dose reduction/ discontinuation, maximum, N = 126		Antipsychotic maintenance treatment, maximum, N = 127	
	N	n (%) or mean (SD) or median (IQR)	N	n (%) or mean (SD) or median (IQR)
Employment				
Employed, voluntary or in education	126	38 (30.2%)	125	36 (28.8%)
Not working or in education	126	88 (69.8%)	125	89 (71.2%)
Length of time in contact with mental health services				
0–3 years	126	11 (8.7%)	127	6 (4.7%)
4–10 years	126	34 (27.0%)	127	28 (22.0%)
11–15 years	126	20 (15.9%)	127	23 (18.1%)
16–20 years	126	20 (15.9%)	127	22 (17.3%)
> 20 years	126	41 (32.5%)	127	48 (37.8%)
Age when first referred to mental health services				
< 20 years	126	26 (20.6%)	127	27 (21.3%)
20–30 years	126	57 (45.2%)	127	67 (52.7%)
31–40 years	126	25 (19.8%)	127	22 (17.3%)
≥ 41 years	126	18 (14.3%)	127	11 (8.7%)
Number of previous mental health admissions		Median 3 (IQR 1–5)		Median 3 (IQR 1–5)
Recreational drugs used in the last month	126	11 (8.7%)	126	14 (11.1%)
Alcohol use over the past month				
Once a month or less	126	80 (63.5%)	126	82 (65.1%)
Two to four times a month	126	24 (19.0%)	126	20 (15.9%)
Two or more times a week	126	22 (17.5%)	126	19 (19.0%)
Antipsychotic medication dose in chlorpromazine equivalents	126	Median 300 (IQR 200–450)	127	Median 300 (IQR 200–400)
Outcome measures at baseline				
SFS overall	123	Mean 107.7 (SD 8.6)	120	Mean 108.2 (SD 10.2)
PANSS positive symptom subscale	124	Median 10 (IQR 8–14)	127	Median 11 (8–16)
PANSS negative symptom subscale	124	Median 11 (IQR 9–15)	124	Median 11 (8–15)
PANSS total	122	Median 48 (IQR 41–59)	123	Median 48 (IQR 40–61)
MANSA	126	Mean 4.7 (SD 0.82)	127	Mean 4.6 (SD 0.83)
SIX	125	Mean 3.4 (SD 1.3)	127	Mean 3.4 (SD 1.3)
Modified GASS	105	Mean 27.6 (SD 15.2)	104	Mean 29.0 (SD 17.1)
Body weight in kg	114	Mean 90.9 (SD 20.2)	116	Mean 89.7 (SD 19.1)
CSQ-8	125	Median 20 (IQR 20–21)	122	Median 20 (IQR 19–21)
MARS-5	124	Median 24 (IQR 22–25)	124	Median 25 (IQR 23–25)
QPR-15	123	Mean 55.7 (SD 9.9)	122	Mean 56.6 (SD 10.0)
ASEX	42	Mean 16.3 (SD 6.1)	39	Mean 15.5 (SD 5.0)

TABLE a Baseline demographic and clinical characteristics of randomised trial participants (*continued*)

Characteristic	Antipsychotic dose reduction/ discontinuation, maximum, N = 126		Antipsychotic maintenance treatment, maximum, N = 127	
	N	n (%) or mean (SD) or median (IQR)	N	n (%) or mean (SD) or median (IQR)
Cognitive tests				
Digit span	124	Mean 14.8 (SD 4.5)	126	Mean 14.7 (SD 4.7)
Digit symbol substitution	117	Mean 47.2 (SD 17.4)	121	Mean 47.3 (SD 18.2)
Rey Auditory Verbal Learning	121	Mean 35.7 (SD 12.0)	120	Mean 36.1 (SD 12.4)
Trail making	121	Median 45 (IQR 35–62)	121	Median 50 (IQR 36–64)
Verbal fluency	124	Mean 16.5 (SD 4.9)	126	Mean 16.6 (SD 5.2)
ASEX, Arizona Sexual Experience Scale; CSQ, Client Satisfaction Questionnaire; GASS, Glasgow Antipsychotic Side-Effect Scale; IQR, interquartile range; MANSA, Manchester Short Assessment of quality of life; MARS, Medication Adherence Report Scale; PANSS, Positive and Negative Syndrome Scale; QPR, Questionnaire about the Process of Recovery; SD, standard deviation.				

Other secondary outcomes showed no difference between the groups at 24 months, including measures of symptoms, quality of life, adverse effects scales, body weight and employment.

The median dose reduction at any point during the trial was 67% in the reduction arm and 0% in the maintenance arm. At 24 months, it was 33% versus 0%. Thirty-four people (27.0%) randomised to reduction stopped their antipsychotic medication completely at some time during the 24-month follow-up period, and 13 (10.2%) of those randomised to maintenance treatment did so. Eighty-eight (69.8%) participants in the reduction group reduced their antipsychotic dose by 50% or more when compared with 21 (16.5%) of the maintenance participants. Serious adverse events were more common in the reduction group, largely due to a higher number of hospitalisations for relapse.

There were no significant differences between arms in total costs for any perspectives. There were no significant difference in quality-adjusted life-years (–0.035, 95% CI –0.123 to 0.052), whereas years of full capability were significantly lower in the reduction arm compared to the maintenance arm (baseline-adjusted difference: –0.103, 95% CI –0.192 to –0.014). The reduction strategy was dominated by maintenance and was not likely to be cost-effective for all perspectives taken and outcomes employed.

Limitations

Recruitment was challenging, and some participants did not adhere to their randomised treatment programme. The COVID pandemic affected the social functioning measure.

Conclusions

The current trial provides data on the pros and cons of a gradual strategy of antipsychotic reduction and discontinuation in people with recurrent psychotic disorders. The findings demonstrate that a strategy of reducing and stopping antipsychotic medication over several months increases the risk of relapse compared with maintenance treatment but does not measurably improve social functioning or affect other clinical and social outcomes after 2 years. Further follow-up data will provide information about longer-term outcomes.

Trial registration

The trial is registered as ISRCTN90298520 on 7 February 2017 and at ClinicalTrials.gov on 18 June 2018.

Work package 3b

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Objectives

To explore the experiences of people enrolled in an antipsychotic reduction programme in a clinical trial.

Methods

Design

Qualitative study using semistructured interviews.

Participants

Participants in the full trial in work package 3a who were randomised to the antipsychotic reduction arm.

Setting

Community mental health services involved in the randomised trial.

Outcomes

Qualitative data on patients' experiences of antipsychotic reduction within the randomised trial.

Results

Twenty-six participants from the antipsychotic reduction arm of the trial were interviewed. Most reported reduced adverse effects of antipsychotics with dose reductions, primarily in mental clouding, emotional blunting and sedation, and some positive impacts on social functioning and sense of self. Over half experienced deteriorations in mental health, including psychotic symptoms and intolerable levels of emotional intensity. Nine had a psychotic relapse. The trial context in which medication reduction was explicitly part of clinical care provided various learning opportunities. Some participants were highly engaged with reduction processes, and despite difficulties, including relapses, they developed novel perspectives on medication, dose optimisation and how to manage their mental health. Others were more ambivalent about reduction or experienced less overall impact. Experiences of antipsychotic reductions over 2 years were dynamic and diverse, shaped by variations in dose reduction profiles, reduction effects, personal motivation and engagement levels, and relationships with prescribers. Relapse risks and challenges were apparent, but some people experienced medication reduction done with clinical guidance as empowering.

Limitations

The sample may have excluded people with more negative experiences.

Conclusions

Participants described both positive and negative effects of reducing antipsychotics. Some gained a deeper understanding of their condition and felt empowered to take a more active role in managing their medication.

Work package 3c

Objectives

To explore clinician's experiences of being involved in a trial of supported antipsychotic reduction.

Methods

Design

Qualitative study using semistructured interviews.

Outcomes

Clinician's experiences of taking part in a randomised trial of antipsychotic reduction.

Results

Fifteen psychiatrists were interviewed. They described the positive and negative effects of antipsychotic reduction. Some felt that the trial had enabled them to establish more collaborative relationships with patients.

Limitations

The sample may have excluded clinicians with more negative experiences.

Conclusions

Clinicians have mixed views about antipsychotic reduction.

Trial registration

The trial is registered as ISRCTN90298520 on 7 February 2017 and at ClinicalTrials.gov on 18 June 2018.

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Synopsis

Introduction

Schizophrenia spectrum disorders affect up to 1% of the population and are associated with a range of poor long-term health outcomes, including early death and physical illness as well as significant disability and distress.^{1,2} Antipsychotic drugs are the main form of treatment. They are effective in reducing symptoms³ and are also recommended to be taken on a long-term basis for relapse prevention. Long-term treatment recommendations are based on evidence from trials of maintenance treatment,⁴ but such trials involve the discontinuation of antipsychotics in people randomised to placebo treatment and discontinuation is usually done abruptly, leading to potential withdrawal effects that may inflate the chance of relapse.⁵ Most such trials also have short follow-up and focus only on relapse, ignoring other outcomes that may be of importance to patients.⁶

By contrast, some other evidence suggests that long-term antipsychotic treatment may be associated with detrimental effects for at least some people. Several naturalistic studies find that people who take continuous, long-term antipsychotic medication have worse outcomes than those who do not.⁷⁻⁹ One of these studies controlled for premorbid predictors of poor outcome and still found a medication-related effect.⁷ On the other hand, some naturalistic studies find worse outcomes in people who do not take or who stop antipsychotic medication.^{10,11}

A randomised controlled trial (RCT) in people with a first episode of psychosis found that, at 7-year follow-up, those randomised to maintenance treatment were less than twice as likely to have achieved a social recovery, and although they had a lower chance of relapse initially, rates of relapse equalising over time between the groups.^{12,13} However, another recent long-term follow-up of participants from a randomised trial of quetiapine maintenance did not find superior outcomes for people originally randomised to antipsychotic discontinuation and placebo substitution.¹⁴

Antipsychotics are associated with a number of potentially serious adverse health effects, including tardive dyskinesia, diabetes and cardiovascular disease.¹⁵⁻¹⁷ Moreover, they are associated with a reduction in brain volume over the course of treatment.¹⁸ The subjective experience of taking antipsychotics is also reported to be highly unpleasant for some people, with patients reporting emotional numbing, sexual dysfunction and sedation.^{19,20}

For these reasons, it is suggested that exposure to antipsychotic treatment should be minimised and only employed where benefits clearly outweigh risks.²¹ Further trials of antipsychotic reduction and discontinuation in people with a first episode of psychosis are underway, but,²² as our preliminary patient and public involvement (PPI) work found, and our research confirmed, people with recurrent episodes also want more treatment options.²³ The Research into Antipsychotic Discontinuation and Reduction trial (RADAR) programme was set up to produce evidence of the benefits and harms of a gradual process of antipsychotic reduction and discontinuation in people with schizophrenia, or another non-affective psychotic disorder with more than one episode.

Research pathway diagram

The research pathway diagram is presented in [Figure 1](#).

Aims

The overall aim of the research programme ([Figure 1](#)) was to provide evidence on the outcomes of a gradual antipsychotic reduction and discontinuation strategy. The specific objectives were:

1. to explore patients' attitudes to long-term antipsychotic treatment and to clinically supported antipsychotic reduction and discontinuation

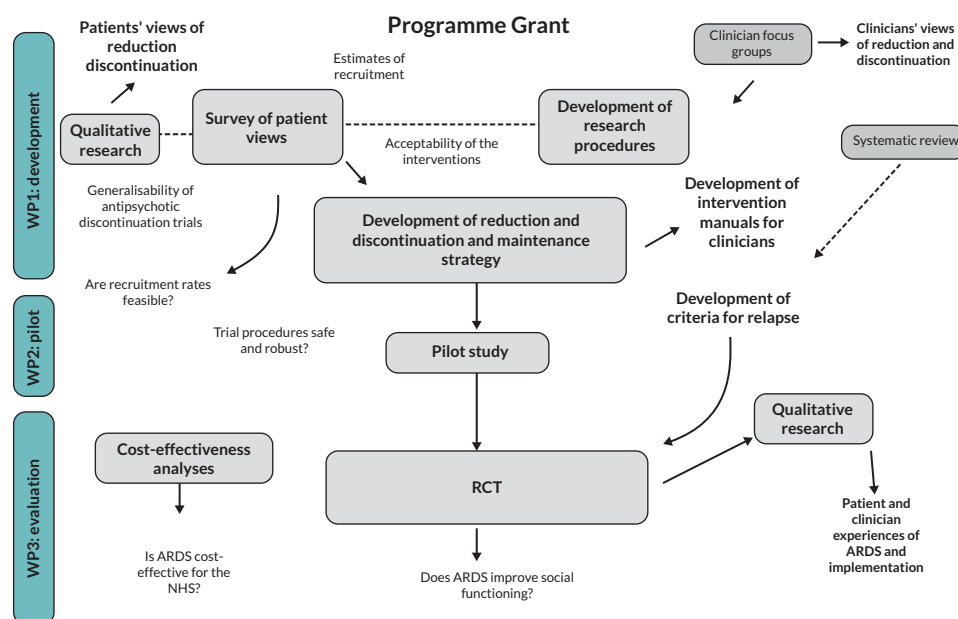


FIGURE 1 Research pathway diagram. ARDS, acute respiratory distress syndrome.

2. to develop a protocol for a gradual strategy of antipsychotic reduction and discontinuation to be implemented by clinicians
3. to design a trial to evaluate this strategy in people with schizophrenia or recurrent psychotic conditions
4. to assess recruitment for the planned trial in order to maximise and facilitate recruitment
5. to compare the antipsychotic reduction and discontinuation strategy with maintenance antipsychotic treatment in an internal pilot trial
6. to conduct a full, randomised, multicentre, pragmatic trial with social functioning as the primary outcome and relapse, symptoms, side effects and costs among further outcomes.

Research summary: changes to original programme aims/design

The research aims and objectives remained the same; however, the design and timeline of the programme was revised in the following ways.

Outcomes

National Institute for Health and Care Research (NIHR) approved a change to the primary outcome for the trial (via a Variation to Contract request). Initially, the Groningen Social Disability Scale (GSDS) was chosen, as this had been used in a similar trial in the Netherlands.¹² However, during piloting of trial outcome measures, it became apparent that the GSDS is very long, requires intense and lengthy training and does not cover relevant areas of social functioning for the intended population. The Social Functioning Scale (SFS) was used instead,²⁴ which has been widely used, has good psychometric properties and is easy and quick to administer with low training needs. The sample size calculation was repeated in line with the change of measures, and it was found that the agreed sample size was more than sufficient to detect a minimum clinically relevant difference between the groups using the SFS.

The RCT sample size was planned at 402, which was powered at 90% to detect a 10% difference in the primary safety outcome 'severe relapse' (hospitalisation for a psychotic relapse). However, due to recruitment difficulties, the target sample size was revised to that required to detect a minimum clinically significant effect on the primary outcome (SFS). An options appraisal was conducted, and in April 2019, the NIHR approved an extension to recruitment and the reduction in minimum recruitment target to 218.

The Objective Social Outcomes Index (SIX)²⁵ was added to the outcome measures to evaluate social outcomes. This is computed using data that were already collected as part of the Manchester Short Assessment of quality of life (MANSA).²⁶ No new data were collected from participants.

Recruitment arrangements

The recruitment study recruitment period was extended from February 2017 to August 2017 to enable recruitment of larger numbers and to maintain engagement of the study sites in preparation for the RCT. Initial planning included the initiation of six sites to recruit for the RCT. An additional 13 sites were opened to improve recruitment rates and to reach the recruitment target.

COVID-19 adaptations

After national restrictions were introduced in March 2020, changes were made to data collection procedures across the programme. Research Ethics Committee (REC) were notified of a Category C non-substantial amendment. To mitigate the risk from COVID-19 to both researchers and participants, consent and data collection for RCT follow-up assessments and qualitative interviews were conducted remotely, either by telephone or on an internet-based video platform. Procedures for the administration of some of the cognitive measures were amended in order for them to be completed during a remote assessment. Where follow-up assessments were completed remotely, researchers posted these measures to participants in advance of the assessment and administered them over the communication platform. Researchers either collected these measures or they were sent by secure electronic means to the research team.

Overview of work packages

Work package 1a: mixed-methods recruitment study

Using a pre-designed interview schedule, we conducted a survey and brief qualitative interview to explore patients' views of antipsychotic medication reduction and discontinuation and willingness to take part in the proposed trial of a supported reduction. We investigated factors associated with wishing to reduce and discontinue medication. We analysed the proportion of participants who subsequently enrolled in the RCT, and we explored predictors of enrolment.

Work package 1b: development of intervention methods and procedures

Through an iterative process of discussion and presentation, members of the various trial management committees and groups developed the intervention strategy, intervention adherence criteria, recruitment procedures and trial eligibility criteria. Focus groups explored clinicians' views of reduction/discontinuation of antipsychotics, and this informed the development of the intervention and recruitment strategies. A systematic review explored definitions and measures of relapse in antipsychotic trials.

Work package 2: pilot randomised controlled trial

An internal pilot was conducted in two NHS Trusts in London to assess recruitment and trial processes. Twenty-six people were recruited in 3.5 months, which represented just under 70% of the recruitment target. Based on pre-specified stop-go criteria, the Trial Steering Committee authorised that the pilot should proceed to the main trial.

Work package 3a: randomised controlled trial

One hundred and forty-nine participants were randomly allocated to the antipsychotic reduction and discontinuation strategy, and 150 to the maintenance strategy, where they were asked to remain on their baseline dose of antipsychotic medication. Measures were administered to capture change across a number of outcomes across 24 months, including social functioning, positive and negative symptoms of psychosis, neuropsychological functioning, quality of life, recovery and sexual functioning. Relapse and health economics data were extracted from medical records. Participants were recruited from secondary care mental health services in 19 trusts across England.

Work package 3b: qualitative substudy of participants

Twenty-six participants who were allocated to the antipsychotic reduction and discontinuation strategy were interviewed. Service users were asked questions on a range of topics, including their experiences of antipsychotic reduction, impact on mental health and their views on the programme and support offered.

Work package 3c: qualitative substudy of clinicians

Fifteen clinicians who delivered the intervention across participating trusts were interviewed about their experiences in delivering the discontinuation strategy, support from the research team, and if relevant, their experiences of managing mental health impacts and relapse.

Work package 1: development and feasibility phase of the Research into Antipsychotic Discontinuation and Reduction trial intervention, feasibility and acceptability of the intervention

Introduction

The development phase of RADAR consisted of one work package (WP) with two parts which ran in parallel:

- Work package 1a: Mixed-methods recruitment study
- Work package 1b: Development of trial intervention protocols and procedures.

Ethics approval

The recruitment study (WP1a) and focus group study (included in WP1b) were approved by the East of Scotland Research Ethics Service (REC reference: 15/ES/0163).

Work package 1a: mixed-methods survey

Work package 1a: aim

To conduct a survey and interviews with patients to (1) explore views of antipsychotic reduction and discontinuation and their predictors; (2) explore the acceptability of the planned trial intervention; (3) inform the recruitment strategy for the trial by providing more precise estimates of recruitment; (4) investigate the feasibility of recruitment in primary care and (5) facilitate recruitment to the trial by establishing links with services and identifying a pool of potential participants to be approached for the RCT. This study contributed to the development of trial and intervention protocols and helped to determine recruitment pathways. Some text in this section has been reproduced with permission from Crellin *et al.*²³ and Ramsay *et al.*²⁷ These are Open Access articles distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The text below includes minor additions and formatting changes to the original text.

Methods

Setting and participants Eligible participants were identified by clinical staff from community mental health services in four NHS Trusts and primary care practices across areas of London. In mental health services, clinical staff screened their caseloads for eligible service users to whom they briefly introduced the study before seeking consent for researchers to make contact. In primary care, practice managers organised mail-outs to patients with eligible diagnoses with study information and instructions for contact with the research team enclosed.

Eligibility criteria were designed to be as close as possible to those intended to be used in the trial. Eligible individuals involved those taking antipsychotics with a clinical diagnosis of non-affective psychosis, a history of more than one episode and not having required acute care in the last 3 months. Those who were legally compelled to take antipsychotics or were considered as a risk by a clinician were excluded. Further details can be read in Crellin *et al.*²³

Procedure

Eligible participants were approached by researchers, and those willing to participate were invited to take part in a structured interview. A pre-designed interview schedule of open and closed questions was used to elicit attitudes to reduction/discontinuation (see [Report Supplementary Material 1](#)). Attitudes to taking antipsychotic medication were measured using the Drug Attitude Inventory (DAI). Information on the nature and design of the proposed trial were presented to participants, who were asked to indicate their willingness to participate using pre-worded options. Opportunity to provide alternative reasons was also offered.

Data analysis

Descriptive statistics were used to present participants' views about long-term antipsychotic treatment, options to reduce or discontinue this treatment and views about enrolling in the planned trial. Analyses were conducted to explore the factors associated with wanting to stop or reduce antipsychotic medication by using univariate tests and multivariable logistic regression. Potential predictors of enrolment in the subsequent trial were also explored. Participants recruited from primary care were excluded from these analyses as the RCT recruited in secondary mental health services only.

Qualitative data (open-ended questions) exploring reasons for wanting to reduce, discontinue or maintain antipsychotic medication were analysed using content analysis, taking the 'directed approach', in which knowledge from previous research was used to guide the initial formulation of categories.²⁸ Seven members of the research team listened to five randomly selected interview recordings to develop an initial set of categories. These were reviewed by the research team, refined and then a further five interviews were analysed using these refined categories. Categories were subsequently reviewed again and collapsed, divided or further refined in order to produce a set of categories that were conceptually clear, distinct from each other and were named appropriately to reflect content. These finalised categories were used to analyse the complete data set. Analysis was reviewed for accuracy by two researchers. Any discrepancies or disagreements were reviewed by the research team before finalising the category structure. Data were analysed using NVivo version 10 (QSR International, Warrington, UK).

Results

Potential participants were screened for the study from a total of 29 clinical teams across 4 mental health organisations. Forty-one participants were also recruited from 18 primary care practices. A total of 269 patients consented to take part. Participant characteristics can be viewed in [Table 1](#).

Views of reducing or discontinuing antipsychotic

Answers to closed questions revealed that one-third [87/265; 33%, 95% confidence interval (CI) 27 to 39] were content to take antipsychotic medication on a long-term basis. A further 19% (51/265; 95% CI 15 to 25) accepted it reluctantly. Eighteen per cent (47/265; 95% CI 13 to 23) of participants reported that they were not satisfied with taking antipsychotic medication for long term and another 24% (64/265; 95% CI 19 to 30) accepted taking it for the present but not necessarily forever.

When asked their views about the possibility of discontinuing antipsychotic medication with professional support and supervision, almost a third of patients (82/266; 31%, 95% CI 25 to 37) reported that they would definitely like to do this, with a further 21% (55/266; 95% CI 16 to 26) reporting that they had some concerns but would be willing to try. Twenty-one per cent (57/266; 95% CI 17 to 27) wanted to try to discontinue medication in the future, but not at the present moment. Twenty-five per cent (66/266; 95% CI 20 to 31) of patients reported that they did not want to stop their antipsychotic medication.

When asked how they would feel about the possibility of reducing antipsychotic medication with professional support, almost half the participants (118/262; 45%, 95% CI 39 to 51) reported that they would definitely like to reduce their medication and 13% (35/262; 95% CI 10 to 18) reported that they would be willing to try to reduce. Fourteen per cent (36/262; 95% CI 10 to 19) wanted to reduce medication in the future but not at present. Twenty-one per cent (59/262; 95% CI 18 to 28) reported that they would not want to reduce their antipsychotic medication now or in the future.

Potential predictors of wanting to discontinue antipsychotic medication

Only DAI score showed a statistically significant association, with people with more negative attitudes towards taking medication being more likely to want to discontinue. Notably, no demographic factors, illness or treatment characteristics were associated with wanting to discontinue medication and neither was coming from primary or secondary care services. Multivariable analysis confirmed that DAI was the only statistically significant predictor of wanting to discontinue medication ([Table 2](#)).

TABLE 1 Mixed-methods survey: participants' characteristics

Characteristics	Total, N = 269 (%)
Gender, N (%)	
Male	175 (65%)
Female	94 (35%)
Age in years, M (SD) range	46.2 (11.50) 21–76
Diagnosis,^a N (%)	
Schizophrenia	188 (70.4%)
Schizoaffective disorder	47 (17.6%)
Delusional disorder	6 (2.2%)
Drug-induced psychosis	1 (0.4%)
Psychosis/psychotic episodes	17 (6.4%)
Bipolar disorder	5 (1.9%)
Other	3 (1.1%)
Time in contact with mental health services, N (%)	
< 1 year	2 (0.7%)
1–3 years	14 (5.2%)
4–10 years	67 (25.1%)
11–15 years	45 (16.9%)
16–20 years	44 (16.5%)
> 20 years	95 (35.6%)
Type of antipsychotic medication, N (%)	
First generation only	82 (30.9%)
Second generation only (excluding clozapine)	128 (48.3%)
Clozapine only	34 (12.8%)
First and second generations (excluding clozapine)	14 (5.3%)
Clozapine plus other antipsychotic	7 (2.6%)
Services recruited through, N (%)	
Primary care	41 (15%)
Secondary care	228 (85%)
Time taking antipsychotic medication, M years (SD) range	16.5 (10.3) 1–49
Antipsychotic dose (chlorpromazine equivalent)	353.1 mg (269.4)
M (SD) range	25–1333 mg
Number of antipsychotic medications taken, N (%)	
1 antipsychotic	222 (84.1%)
2 or more antipsychotics	42 (15.9%)

TABLE 1 Mixed-methods survey: participants' characteristics (*continued*)

Characteristics	Total, N = 269 (%)
Form of medication, N (%)	
Oral only	131 (49.6%)
Depot only	111 (42.0%)
Both oral and depot	22 (8.3%)
DAI, M (SD) range	2.6 (5.1) –8 to 10
Relationship status, N (%)	
Single	176 (66.7%)
Married/civil partnership/in a long-term relationship	53 (20.1%)
Separated/divorced/widow/widower	30 (11.4%)
Other	5 (1.9%)
Ethnicity, N (%)	
White British/Irish/other White background	137 (51.5%)
Black or Black British	69 (25.9%)
Mixed	15 (5.6%)
Asian or Asian British	36 (13.5%)
Other	9 (3.4%)
Employment status, N (%)	
Employed	27 (10.2%)
Unemployed	187 (70.3%)
Student	12 (4.5%)
Retired	24 (9.0%)
Voluntary work	16 (6.0%)
Living situation, N (%)	
Living alone	174 (66.4%)
Living with husband/wife/partner	39 (14.9%)
Living with parents	20 (7.6%)
Living with other relatives/friends/supported living	29 (11.1%)

M, mean; SD, standard deviation.

a Diagnoses are listed according to those given by participants, which may not have agreed with diagnoses established during screening.

Therefore, some people are included, who described their condition as 'bipolar disorder' even though this was not an inclusion diagnosis.

Source

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TABLE 2 Potential predictors of wanting to discontinue antipsychotic medication

Potential predictor variable	% (SD) or value in people who want to stop antipsychotics	% (SD) or value in people who do not want to stop antipsychotics	Mean difference/odds ratio (95% CI)	p-value of difference ^a
Marital status	73.2% single/unmarried	63.7% single/unmarried	1.55 (0.87 to 2.76)	0.173
Ethnicity	50% White British or other	52.2% White British or other	0.92 (0.55 to 1.54)	0.846
Employment	85.3% unemployed	83.2% unemployed	0.85 (0.40 to 1.82)	0.824
Time taking antipsychotics	14.68 (9.57) (n = 65)	17.32 (10.57) (n = 142)	-2.64 (-5.67 to 0.391)	0.087
Antipsychotic preparation	44.4% oral only	51.4% oral only	0.76 (0.45 to 1.28)	0.366
Dose of antipsychotics (in chlorpromazine equivalents)	328.91 (275.46) (n = 64)	365.01 (268.04) (n = 152)	-36.10 (-115.48 to 43.27)	0.371
DAI total	-0.86 (5.16) (n = 74)	4.32 (4.11) (n = 165)	-5.18 (-6.53 to -3.83)	< 0.001

DAI, Drug Attitude Inventory; SD, standard deviation.

^a p-values are derived from t-tests for continuous variables and Chi-squared tests for categorical variables.

Content analysis

Reasons for wishing to reduce or discontinue antipsychotics

A total of 90 of the 121 participants (74%) cited concerns about the adverse effects of antipsychotic medication and/or its actual and potential impacts on their physical health. The most commonly cited specific adverse effects included sedative effects, weight gain and neurological effects (such as shaking, twitching, stiffness, etc.). Impairment of general functioning, cognitive and emotional capacities and sexual functioning were also mentioned. Some respondents felt that they no longer needed medication, and others simply disliked the idea of taking medication for long term ([Table 3](#)).

Reasons for wanting to continue antipsychotics

Among those who did not want to discontinue medication, the most common reason was fear of relapse, with 70% of the 132 participants citing this. Other common reasons included the view that antipsychotic medication helps to maintain stability or produce a general improvement, that it reduces positive symptoms, particularly hallucinations, the sedative or calming effects of antipsychotics, and the reduction of other symptoms such as agitation and suicidal thoughts. A total of 24% of the 132 participants said that they took antipsychotics because doctors told them to take it.

Views on support when reducing or discontinuing

A total of 61 participants provided responses that described what they thought would be helpful if they were to consider reducing or discontinuing antipsychotics. Support from psychiatrists and other professionals was most commonly mentioned. Reducing medication gradually and being in a stable situation or having a 'healthy lifestyle' at the time of reduction (e.g. being in employment or having a good diet) were considered to be important by 40% of participants. Several people (16%) reported that the aspiration to be independent or obtain employment was a significant motivation for trying to reduce or stop antipsychotics and might help them to reduce or discontinue medication successfully. Access to a supply of medication to take 'as required', family support, psychological therapy and alternative therapies were mentioned as being potentially useful by some participants (16%; 10 out of 61).

Acceptability of the supported reduction

See also Ramsay *et al.*²⁷

Following presentation of the design of the RCT of supported reduction by a researcher, 151 (71.9%) participants indicated they would be interested in taking part, 16 (7.6%) said they might and 43 (20.5%) indicated they would not. The most common reasons given for wanting to take part were altruistic, followed by the opportunity to reduce or stop medication and reduce the side effects of medication ([Table 4](#)). At least 57 people, representing 27.1% of all those who took part in the acceptability study, ultimately enrolled in the randomised trial. Of those who said they would like to

TABLE 3 Content analysis of participant views about taking antipsychotics on a long-term basis and attitudes towards reducing or stopping

Category	N (%) ^a	Example or quotes
Reasons for valuing or accepting long-term antipsychotic medication (n = 132)		
Wanting to avoid relapse	93 (70%)	<i>I relapse much less when I'm on it, so in that sense I'm happy to take it</i>
General feelings of stability or improvement	48 (36%)	<i>Helps me stay on an even keel</i>
Doctor tells me to take them	32 (24%)	<i>I have to take it because I'm told by my doctors, I have to listen to them, I know that</i>
Positive symptom reduction	20 (15%)	<i>The voices are much worse when I don't take the medication</i>
Sedative and calming effects	21 (16%)	<i>Medication keeps me calm and out of trouble</i>
Indifference, passivity, uncertainty, ambivalence	18 (14%)	<i>I know that I have to take it, it kind of, doesn't mean nothing no more, y'know ... I just take it</i>
Other symptom reduction (including depression, agitation, suicidal ideation)	16 (12%)	<i>My antipsychotic medication is the reason why I'm alive, because I've had suicidal thoughts before</i>
Improved functioning	11 (8%)	<i>I'm just pleased to be able to function, do normal things</i>
Other reasons	13 (10%)	<i>For example to please family members, habit, to receive welfare benefits, to 'not feel different'</i>
Concerns about long term use of antipsychotics and reasons for wanting to reduce or stop (n = 121)		
Unspecified adverse effects	40 (33%)	<i>Side effects are the main problem ... the more you take them, the more you get the side effects</i>
Sedative effects	36 (30%)	<i>I feel so relentlessly tired and can't get out of bed like everyone else</i>
Weight gain	33 (27%)	<i>Olanzapine made me put on a huge amount of weight, 3 stones in 3 months without really changing anything</i>
Neurological effects	31 (26%)	<i>Makes me weaker, takes my power away. Can't do as much as I used to, in the gym and things</i>
Concern about long-term health effects	25 (21%)	<i>I am scared of the unseen damage that it may do to my makings ... my chemistry ... my makings</i>
Impact on functioning	20 (17%)	<i>I seem to function better when I'm not on tablets ... if I wasn't on the tablets I'd hear more voices, but I had a job, I'd cook, clean, have my own place, when I'm on the tablets I don't seem to be doing anything</i>
Dislike the idea of taking long-term medication	20 (17%)	<i>The idea of having to take drugs just to not go crazy doesn't sit well with me, it makes me feel like I'm not capable of handling life</i>
Cognitive and emotional side effects	15 (12%)	<i>Lose your feelings, like you're a dead person. Want to feel life a bit more</i>
Doubtful of need for medication	13 (11%)	<i>I really want to come off it now, because I feel that I am well</i>
Sexual dysfunction	6 (5%)	<i>I don't have interest in sex</i>
Other adverse effects	5 (4%)	<i>Sometimes I don't like it, sometimes it makes me feel a bit bloated and sometimes I get a funny taste in my mouth</i>
Other reasons	14 (12%)	<i>For example Dislike of injections, embarrassment, fear of addiction, inconvenience, doesn't resolve symptoms, wanting a 'holistic approach'</i>
Factors that might facilitate antipsychotic reduction or discontinuation (n = 61)		
Support from psychiatrists, other health-care professionals and services	29 (48%)	<i>I believe that true collaborative work with the medication staff and myself about reducing my antipsychotic medication is the best way for me to go</i>
Gradual reduction	15 (25%)	<i>Not too quick, I don't think you should drop it too quick. Maybe slowly do it</i>
Wanting to be independent	10 (16%)	<i>If I did that [discontinued medication] I'd be on the road to much more independence</i>

continued

TABLE 3 Content analysis of participant views about taking antipsychotics on a long-term basis and attitudes towards reducing or stopping (continued)

Category	N (%) ^a	Example or quotes
Stable circumstances and healthy lifestyle (e.g. employment, career, diet)	9 (15%)	<i>I'd need a healthy lifestyle [to reduce]</i>
Other	10 (16%)	<i>For example as required medication, family support, alternative therapies ('natural remedies'), therapy or counselling.</i>

a Responses categories are not mutually exclusive, so percentages do not add up to 100.

Source

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TABLE 4 Reasons for wanting to and not wanting to take part in the trial

	All participants N (%) (N = 210) ^a
Reasons for wanting to take part	
Improve treatment for others	110 (52.3)
Help with research	104 (49.5)
Opportunity to reduce or stop medication	85 (40.5)
Reduce side effects of medication	84 (40.0)
More psychiatrist appointments	44 (21.0)
Reasons for not wanting to take part	
Do not want to reduce or stop medication	34 (16.2)
Concern about randomisation	32 (15.2)
Inconvenience	19 (9.1)
Want to reduce or stop medication	10 (4.8)
Other reasons: concern about relapse, loss of benefits	10 (4.8)

a People could give more than one reason, therefore percentages do not add up to 100.

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take part, 51 (33.7%) enrolled in the trial. Five people who said they might like to take part were enrolled (31.3%) and one person who said they did not want to participate changed their mind and enrolled (Figure 2).

Of the 85 in the acceptability study who said they would like to enrol but did not end up taking part, 31 (38.3%) changed their minds and declined participation, and 50 (61.7%) did not meet eligibility criteria at the time of recruitment. Changes to eligibility were likely to do with changes to clinical stability or clinicians' appraisal of risk. There were no differences between those who subsequently took part in the RADAR trial and those who did not participate in demographic and clinical characteristics. However, logistic regression, including gender and ethnicity as potential predictors, revealed that both had a statistically significant effect on the likelihood of being enrolled in the trial, with women being twice as likely to take part as men, and people from a White background were 1.9 times more likely to enrol than those from a non-White background (Table 5).

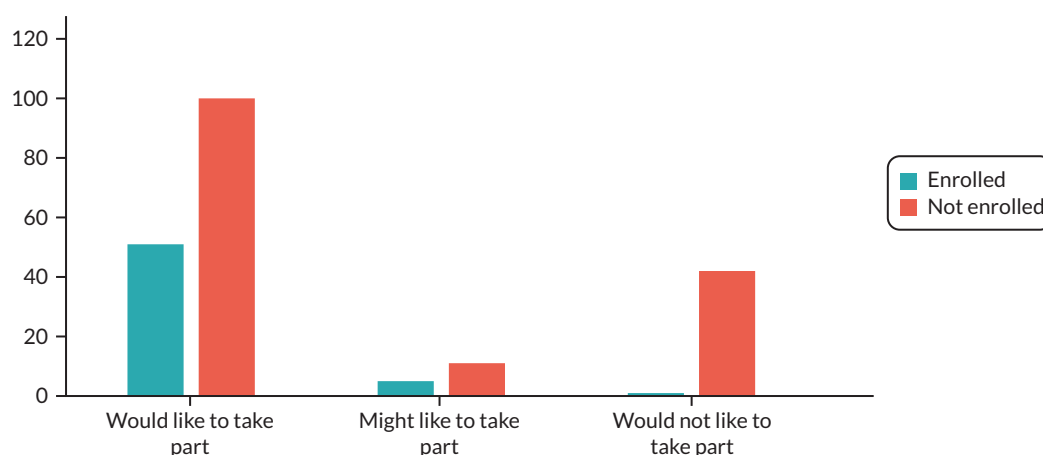


FIGURE 2 Bar chart of numbers eventually enrolled in the randomised trial by stated willingness in the acceptability study. Reproduced with permission from Ramsay *et al.*²⁷ This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The figure includes minor additions and formatting changes to the original text.

TABLE 5 Logistic regression of predictors of enrolling in the randomised trial

	B	Standard error	Wald	Degrees of freedom	p-value	Exp (B)	95% CI for exp (B)
Gender (male vs. female)	0.68	0.32	4.4	1	0.037	0.51	0.27 to 0.96
Ethnicity (White vs. non-White)	0.62	0.33	4.1	1	0.042	1.94	1.0 to 3.7
Constant	0.94	0.31	9.5	1	0.002	0.39	

Forty-one patients were recruited from primary care. Eighteen (43.9%) indicated potential interest in being involved in the planned trial, which was lower than the proportion of patients in secondary care (71.0%), and 19 (46.3%) said they would not be willing to participate. Meetings with general practitioners suggested that they would be reluctant to participate in the trial, therefore it was decided that recruitment for the RCT in primary care would not be feasible. In secondary care services, barriers to recruitment reflected some organisational-level barriers, including challenges with accessing busy clinicians for referrals. Clinicians also expressed concerns about managing deterioration or relapse in services in the context of antipsychotic reduction and discontinuation alongside existing workforce and workload challenges. Difficulties with recruitment informed the decision to approach more sites for the RCT, and informed effective presentation of the study to clinicians, including the rationale and discussion of risk mitigation strategies, as well as facilitating patients' choice.

Limitations

The sample was recruited from clinical services, but responses are not necessarily generalisable to the general population of patients who fulfil the eligibility criteria. Clinical staff may have influenced who was put forward and were aware of the association with a future randomised trial of antipsychotic reduction. People who consent to take part in research may be more adherent and accepting of treatment than other patients. People with long histories of medication use and service contact made up the majority of the sample, which may also have biased responses towards more acceptance of medication. Some interviewers were connected to the planned trial, and this may have influenced the manner in which questions were presented. The analysis of associations with wanting to discontinue medication could potentially have involved many explanatory variables and could have been subject to false-positive findings. Patient enrolment in the trial required psychiatrists to make a decision about one of the eligibility criteria (presenting a risk of harm to self or others), and although the eligibility criteria in this study were designed to match those of the trial, it is likely that this criterion was applied differently, resulting in a lower proportion of people being considered for the trial than anticipated.

Key findings

- Around a third of participants wished to reduce or discontinue their medication, and experiencing adverse effects was the most common reason for wishing to reduce or discontinue antipsychotics.
- General attitudes to antipsychotic treatment predicted wanting to reduce or discontinue medication, but no clinical or demographic variables were associated with this.
- Participants would value support from professionals or psychiatrists when reducing or discontinuing their antipsychotics.
- Around two-thirds of participants indicated that they would like to participate in a trial of reduction and discontinuation.
- Twenty-seven per cent of those who indicated that they would like to participate actually enrolled in the main trial.
- The feasibility study facilitated enrolment to the main trial by raising the profile of the study in clinical teams and enabling researchers to build relationships with staff, but overestimated recruitment rates.

Work package 1b: development of research procedures and outcomes for the randomised controlled trial

Findings from WP1a suggested that a clinician-supported reduction and discontinuation intervention would be acceptable to patients with schizophrenia spectrum disorders in secondary care services.

Work package 1b: aim

To design the supported reduction programme for patients with schizophrenia spectrum disorders to be delivered by psychiatrists within existing mental health services. To develop intervention protocols and trial methods and to review outcomes to be used during the RCT. Information obtained in WP1a was also assimilated into this process.

Objectives

- To design and develop a strategy for the gradual reduction and discontinuation of antipsychotics (the intervention strategy) and manuals for treating clinicians to guide them in implementing it.
- To develop methods to assess and monitor adherence to the interventions.
- To develop valid criteria and procedures to assess relapse.
- To develop appropriate inclusion/exclusion criteria.
- To explore clinicians' views on intervention procedures, suitability of patients, detection and definition of relapse and barriers and facilitators of antipsychotic reduction and discontinuation in secondary care services.

Methods

The design of the treatment strategies, manuals and the trial procedures were developed by assimilating the findings and outcomes from WP1a along with additional research activities that were conducted in parallel, including: (1) an iterative process of presentation and discussion with members of the Programme Management Group (PMG), Programme Steering Committee (PSC), Trial Management and Methodology Group [which included members of PRIMENT (Registered Clinical Trial Unit) at University College London (UCL), the Sponsor] and the Lived Experience Advisory Panel (LEAP). Members across these groups had expertise in conducting clinical trials, of designing complex interventions for people with psychosis and lived experience of reducing and discontinuing antipsychotics. (2) Expert consultation and consultation of the service user and voluntary sector literature; (3) focus groups with clinicians and (4) a systematic review of definitions of relapse used in discontinuation trials. These activities were grounded within principles elaborated in the Medical Research Council framework for complex interventions.

Focus groups

Focus groups were conducted with a range of multidisciplinary team clinicians from two trusts [North East London Foundation Trust (NELFT) and East London Foundation Trust (ELFT)] to explore the views on best practice, barriers and facilitators to reduction and discontinuation of antipsychotics, patient suitability, judgement of relapse, trial inclusion/exclusion criteria and sources of support for antipsychotic reduction and discontinuation. Besides collecting data for designing the intervention and trial procedures, the focus groups provided a means of introducing RADAR to Community Mental Health Teams (CMHTs) in preparation for WP2 and WP3.

Procedure

Recruitment and data collection methods are detailed in Cooper *et al.*²⁹ Focus groups were audio-recorded and transcribed verbatim.

Data analysis

Thematic analysis was conducted using NVivo software version 11. Patterns of similarity and difference were identified and critically discussed within the research team. Codes, subthemes and themes were developed from the data in an iterative process until a plausible account of the data was produced see (see [Report Supplementary Material 15, Table 1](#))

Systematic review of relapse definitions

To explore existing criteria for relapse and to supplement committee discussion, a systematic review was conducted of relapse definitions used in trials of maintenance antipsychotic treatment compared with discontinuation, intermittent treatment or dose reduction in people with schizophrenia spectrum disorders (see Moncrieff *et al.* 2020³⁰ for further details). Trials were identified from two Cochrane reviews and a new search. Relapse definitions were extracted and assigned a quality rating in terms of reliability and clinical relevance. Definition was considered to be reliable if objective criteria were used, such as hospitalisation, resumption of antipsychotics or precisely specified rating scale changes or other methods, such as would be easily replicable. Clinical relevance was based on clinicians' understandings of relapse as suggested by previous research, which includes the presence of positive symptoms and changes in functioning or behaviour.^{31,32}

Results

Between 2016 and 2017, there were three PMG meetings, two PSC meetings and three LEAP meetings. The committees discussed and refined the eligibility criteria, trial outcomes, Antipsychotic reduction and Discontinuation and Maintenance Treatment intervention programmes, intervention adherence procedures and criteria for relapse. Key supporting documents were produced and further discussed and reviewed by each group across the development phase. These documents are included in the supplementary materials. These included:

- Antipsychotic Reduction and Discontinuation Manual ([Report Supplementary Material 2](#))
- Maintenance Treatment Manual ([Report Supplementary Material 3](#))
- 'wellbeing' booklets for patients ([Report Supplementary Materials 4](#) and [5](#))
- Patient self-report relapse questionnaire ([Report Supplementary Material 6](#))
- Relapse Criteria ([Report Supplementary Material 7](#))
- Two Monthly Medical Notes Review Form ([Report Supplementary Material 8](#)).

The following experts were personally consulted for their views about the process of antipsychotic reduction, professional barriers to conducting antipsychotic reduction, patient experiences and potential concerns, how to define relapse and implementation and monitoring of the reduction process within a trial: Dr Peter Hadad (psychiatrist, Manchester); Professor Lex Wunderink (psychiatrist, University of Groningen); Professor Tom Craig (retired psychiatrist, London), Will Hall (patient advocate and author of Harm Reduction Guide to Withdrawal from Psychiatric Drugs). There are no official guidelines on reducing and stopping antipsychotic medication; therefore, literature on reduction of psychiatric drug treatment from the voluntary sector was consulted, including the Harm Reduction Guide to Withdrawal from Psychiatric Drugs and the Ashton Manual on benzodiazepine withdrawal.^{33,34}

Development of trial eligibility criteria

Eligibility criteria were designed to ensure that the trial was as generalisable as possible to routine clinical care while minimising the risks of antipsychotic reduction in those with a history of posing a serious risk to self or others. Risk was minimised by an inclusion criterion that required psychiatrists to consider participant's history of serious risk of harm to self or others when identifying patients for referral. Decisions about risk were primarily a clinical decision. To minimise risk and to avoid including people who were experiencing acute symptoms or a mental health crisis, patients were required to not have accessed acute or crisis services in the month before enrolment. This period was shorter than that used in the preliminary recruitment survey because the survey clarified that many potential participants have ongoing symptom fluctuations that may entail referral to a crisis team for a short period. There was in-depth discussion about whether or not to include people taking clozapine in view of the fact that such patients are likely to have had

more prolonged and severe symptoms or episodes of psychosis in the past. However, it was noted that criteria for starting clozapine vary between clinicians and services and that some people who have been stable on clozapine for several years may reasonably wish to try to reduce it with clinical support. In view of the exclusion criteria for people considered to be at high risk, it was agreed that patients on clozapine were eligible to enrol, but it was acknowledged that numbers were likely to be low. In cases where it was unclear if patients had experienced multiple episodes, evidence was sought from electronic medical records in ambiguous cases, and where patients had experienced ongoing chronic symptoms since illness onset, with discrete episode less clear-cut, a year of symptom duration was required. Electronic medical records were used to determine if participants had eligible diagnoses, and a widely used and reliable computerised diagnostic system was used to confirm diagnosis in a subgroup of patients.^{35,36} Those with a confirmed pregnancy were not eligible to participate due to guidelines which recommend clinical decision-making based on individual clinical profiles. Involvement in another investigational medicinal product (IMP) trial was included as an exclusion criterion to minimise risk to patients and to protect the integrity of the trial. The final eligibility criteria that were settled on are displayed in [Table 6](#).

Discussions with the LEAP and findings from the focus groups) suggested that patients may value accessing other psychosocial treatment available as part of routine care. Focus group clinicians expressed challenges around the availability of treatment alternatives. Therefore, a Wellbeing booklet was devised to signpost participating patients to other support such as local third-sector and online support fora (see [Report Supplementary Materials 4](#) and [5](#)). These were adapted locally at each site and were distributed to participants in both arms.

Development of the intervention

Both the Antipsychotic Reduction and Discontinuation strategy and Maintenance Treatment were designed to be delivered by psychiatrists within mental health services, with monitoring from care teams according to usual practice. Both interventions were formalised in twin manuals, which were distributed to psychiatrists upon patient randomisation of individual participants. Relapse prevention plans were included in the manuals, and psychiatrists were asked to complete these with patients in both arms to facilitate discussion of early warning signs and identify strategies and steps for engaging with support, including from mental health services.

Development of the Antipsychotic Reduction and Discontinuation strategy and manual development

The Antipsychotic Reduction and Discontinuation Strategy manual can be viewed in [Report Supplementary Material 2](#). Treating psychiatrists were asked to monitor patients’ mental state and review antipsychotic medication dosage every 2 months, with the aim to discontinue antipsychotics within a period of 12–18 months for most, with variation allowed

TABLE 6 Trial eligibility criteria

Inclusion	Exclusion
Aged ≥ 18 years	Lack of capacity to consent to the trial
Clinical and/or ICD-10 revision, diagnosis of schizophrenia, schizoaffective disorder, delusional disorder or other non-affective psychosis	Insufficient command of spoken English to understand trial procedures
More than one previous episode or psychotic exacerbation, or a single episode lasting longer than a year	Subject to a section of the Mental Health Act that includes a requirement to take antipsychotic medication
Prescribed continuing antipsychotic medication	Clinician considers that there will be a serious risk of harm to self or others
	Admitted to hospital or treated by a Home Treatment or Crisis Team within the last month
	Women who have a confirmed pregnancy
	Women who are breastfeeding
	Involvement in another IMP trial

ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision.

according to baseline antipsychotic dose and patient's and clinician's preference. Guidance emphasised the need to deliver the strategy flexibly and according to individual patient's need and preference. The strategy drew on the model used in the Dutch first episode study of supported reduction of antipsychotics.^{12,13} In addition to the manual, individualised reduction schedules were devised by the research team based on clinical judgement and were adjusted according to baseline antipsychotic medication regimes. Schedules included both the option for discontinuation as well as reduction to a low dose, defined as the equivalent of 2 mg haloperidol a day or less, twice the dose defined as 'low dose' in the Dutch first episode study, due to guidelines recommending that first episode antipsychotic treatment dose should be maintained at around half that of patients with long-term psychosis.^{37,38} For both the treatment and maintenance arms, manuals provided a hierarchy of interventions and guidance on monitoring and managing withdrawal symptoms and signs of relapse. New research on psychiatric drug withdrawal became available during the course of the study, suggesting slow tapering at lower doses, tapering schedules reflected this.³⁹

Development of the maintenance treatment and manual development

Since National Institute for Health and Care Excellence (NICE) does not provide specific guidance on long-term antipsychotic treatment, the maintenance treatment manual development was informed by the World Federation of Societies of Biological Psychiatry guidelines on the long-term treatment of schizophrenia. To ensure meaningful differences in antipsychotic dosage between the Antipsychotic Reduction and Discontinuation and Maintenance Treatment, psychiatrists were asked to regard the participant's baseline dose as the minimum dose in the trial for those randomised to Maintenance Treatment where possible. Small reductions of antipsychotic medication in response to side effects were permitted as well as any increases in dosage according to clinical need. An antipsychotic equivalence guide was developed to guide prescription in the event of patient wish or clinical need to change administration or type of antipsychotics. The Maintenance Treatment manual can be viewed in [Report Supplementary Material 3](#).

Work package 1a findings indicated that some patients preferred to be offered further support during the process of supported reduction. Drugs other than antipsychotics could be prescribed as indicated by treating psychiatrists to patients in both groups as well as social or psychological interventions. The Wellbeing booklets were produced and sent to all participants, which included details of online, local community and third-sector groups and resources (see [Report Supplementary Materials 4](#) and [5](#)).

Participant intervention and wellbeing booklets

'Wellbeing' booklets (see [Report Supplementary Materials 4](#) and [5](#)) were developed in consultation with the LEAP and were provided to all participants upon randomisation. Booklets were tailored to each randomised arm and contained information on the intervention and what to expect, as well as evidenced-based information on maintaining wellbeing, and relevant local services, including community mental health and crisis care contact details, national services, including Mind, and online services, including community groups and peer support.

Intervention adherence protocols

Patient notes were scrutinised on a 2-monthly basis by research staff at all sites to monitor use of antipsychotics in both intervention arms to ensure that they were being implemented as planned, including ongoing calculation of adequate differentiation in dose between the arms. Prompt liaison with treating psychiatrists by the chief investigator and other medical staff supporting the programme upon identification of deviations from protocols ensured that, where possible, interventions were followed.

Focus groups

Seven focus groups, including 35 participants from various professional backgrounds, were conducted between July and October 2016 to explore clinicians' views of antipsychotic reduction and discontinuation (see also Cooper *et al.*²⁹). Details of participant characteristics are presented in [Table 7](#).

Attitudes to antipsychotics and reduction

Participants acknowledged that antipsychotics can have severe adverse effects, and some were critical of what they viewed as an over-reliance on medication in services, including polypharmacy and rapid dose escalation to quickly stabilise patients for discharge from acute services. However, a small number of psychiatrists expressed strong views

TABLE 7 Focus groups: characteristics of study participants

Characteristics	N (%)
Gender	
Female	22 (63%)
Male	13 (37%)
Age, mean (standard deviation)	43 (8.3)
Ethnicity	
White British	12 (34%)
African	10 (28%)
White other	5 (14%)
Bangladeshi	2 (6%)
Indian	2 (6%)
Black other	1 (3%)
Not given	3 (9%)
Profession	
Consultant psychiatrists	18 (52%)
Speciality doctor	1 (3%)
Mental health nurse	13 (37%)
Social workers	2 (6%)
Community recovery service manager	1 (3%)

that when weighing up the benefits and drawbacks, long-term antipsychotic medication was the best treatment for the vast majority.

Reduction and discontinuation in practice

All psychiatrists described the importance of reducing antipsychotics in some circumstances and some described trying to attain a 'minimally effective dose' with the aim to prevent relapse while maximising the quality of life. The minority of positive experiences of antipsychotic reduction were often reported by staff working in Early Intervention in psychosis services, where reduction is supported by clearer guidelines. The most common experience of reduction seemed to be that it resulted in relapse and other adverse outcomes, and therefore maintenance treatment was preferred. Drawing on their clinical experience, participants linked both supported and unsupported discontinuation to adverse outcomes, with the possibility of increased treatment resistance to antipsychotics following relapse. Participants often felt professionally accountable for such events and described a gap in experience in judging who might benefit from discontinuation as well as managing adverse events.

Organisational and knowledge-based barriers

Participants described significant organisational barriers to reducing and discontinuing antipsychotics, including lack of resources to provide effective care and monitoring during tapering, lack of psychological therapies or alternate treatment options, pressure to discharge to primary care, which can lead to overmedicalisation to rapidly stabilise patients, and poor continuity of care which results in psychiatrist reluctance to make changes to medication. Knowledge barriers to antipsychotic reduction and discontinuation included a lack of evidence that it is safe, achievable and worthwhile. A lack of professional guidelines and evidence and uncertainty around who may be suitable for reduction meant that psychiatrists often relied on intuition.

Across participants, relationships with patients' close others were perceived as helpful for providing important information or support during the reduction process, spotting early signs of relapse and were often tasked with managing emerging symptoms.

Systematic review and development of valid criteria for relapse of psychosis

Fifty-four definitions of relapse were identified from 81 trials, which compared maintenance treatment with intermittent (see also Moncrieff *et al.*³⁰), withdrawal and reductions in antipsychotics. Definitions have become increasingly complex over time, with trials conducted since 2000 frequently employing four or five definitions of relapse simultaneously. No trials distinguished between relapses in those with chronic and remitted symptoms at baseline; only 19% of identified trials indicated a duration of relapse, and of these, 1–2 days was most commonly specified. Seven per cent of trials ($n = 6$) included definitions, which were both reliable and clinically relevant. No one definition was identified which could be applied reliably, was clinically relevant, distinguished between relapse and mild fluctuations in symptoms, and was practical and ethical to administer within a trial context.

Subsequently, hospitalisation was chosen as the most robust measure of severe relapse. To determine if less-severe relapse had occurred, a blinded end-point committee was convened based on a consensus method developed by Bebbington *et al.*⁴⁰ (see [Report Supplementary Material 9](#) for the committee charter). The committee included a consultant psychiatrist, a research psychiatrist and LEAP member who applied predefined criteria to summaries of changes in mental state extracted from electronic records covering the follow-up period of 24 months (using Medical Notes Review form – see [Report Supplementary Material 8](#)). Committee members reached a consensus or voted where agreement could not be reached, with judgements given for all participants, except those whom had been hospitalised. Details that might unblind committee members were removed. Information included the presence or absence of chronic symptoms at baseline to inform judgement of relapse based on the individual clinical picture. Notes were supplemented with a patient self-report relapse questionnaire that had been administered at follow-up time points (see [Report Supplementary Material 6](#)). Predefined criteria included clinically relevant presence of positive symptoms and changes to functioning, risk or behaviour, continuing for 14 days or longer. The process was piloted in July 2018 where the predefined criteria were applied to the notes of the first 20 participants. Following the pilot, the criterion on the duration of positive symptoms was amended from 7 to 14 days because of the fluctuating nature of symptoms in many participants who had chronic symptoms. In order to improve accuracy and facilitate judgements in ambiguous cases, it was decided that baseline information on symptomology and functioning should be included for each patient. Two additional meetings were held in June 2022 and March 2022, where the committee provided judgements on all participants. Consensus was reached for all except two participants, where a vote was taken. The integrity of the blinding to group allocation was maintained with the exception of two participants.

Review of trial outcomes

After review of the literature and consultation with trial committees, a measure of sexual functioning [Arizona Sexual Experiences Scale (ASEX),^{40,41} McGahuey *et al.*] was added to the data collection schedule to ensure that the impact of antipsychotics on sexual dysfunction was captured. A questionnaire about 'recovery' [Questionnaire about the Process of Recovery (QPR),⁴² Neil *et al.*] was also added to the data collection schedule at the suggestion of LEAP members to ensure that all outcomes relevant to patients were included. After review of numerous side effects rating scales, the Glasgow Antipsychotic Side-Effect Scale (GASS)⁴³ was selected. It was modified by adding 11 items to it from other scales to capture the full spectrum of antipsychotic side effects, including subjective experiences such as sedation, metabolic effects and extrapyramidal side effects.

Key findings

- The RCT design and methods were published in the protocol paper.⁴⁴
- Manuals for both the antipsychotic reduction and maintenance treatment strategies were produced.
- Clinicians were generally supportive of reducing to lowest effective dose, though discontinuation was viewed as less acceptable.
- Clinicians approached reduction/discontinuation of antipsychotics with caution due to past experiences of adverse effects and organisational and knowledge-based barriers.
- Severe relapse was defined as hospitalisation due to relapse in mental state, as this was deemed as the most objective and practical measure of significant deterioration.

- To evaluate other, less severe relapses, a blinded relapse end-point committee was convened, including clinicians and a lay member for whom patient clinical notes were summarised on changes to mental state. Relapse criteria were developed following Bebbington *et al.*⁴⁰ (see [Report Supplementary Materials 7](#) and [9](#)).
- Outcomes for the trial were finalised.
- Information on the likely barriers to trial recruitment and developing links with local services enabled trial recruitment to be optimised.

Work package 2: pilot randomised controlled trial

Background

Following the development of trial procedures and intervention protocols in WP1b, participants who were identified in WP1a as interested in participating in the proposed supported reduction and discontinuation trial were approached along with their psychiatrist to determine their suitability for the RCT. The full protocol of the RCT has been previously published.⁴⁴ Ethical approval was obtained from Brent REC for the pilot trial, the full trial and the qualitative substudies (reference is 16/LO/1507).

Work package 2: aim

The aim of WP2 was to conduct an internal pilot trial preceding the main trial, comparing the antipsychotic reduction and discontinuation strategy to maintenance treatment. The pilot evaluated the recruitment strategy, intervention implementation and adherence, effectiveness of monitoring procedures and retention rates with a view to move forward into WP3, the main trial, if predefined stop/go criteria were met.

Methods

Setting and participants

Participants were recruited between March and August 2017 at two London sites, Northeast London NHS Foundation Trust and East London NHS Foundation Trust, which were chosen due to their close proximity to maximise the efficiency of the study. Planned recruitment targets were 20 participants per group within 4 months. The participants were recruited from secondary care mental health services that provide care for people with a diagnosis of psychosis, including CMHTs, Brief Intervention teams, Older Adults and Early Intervention in Psychosis teams, in the London boroughs of Havering, Waltham Forest, Redbridge, Barking and Dagenham, Newham, City and Hackney and Tower Hamlets. The caseloads of participating clinicians were screened to identify eligible participants, and clinicians were asked to confirm eligibility as per below.

Participants were eligible if they were aged over 18 years, had a clinical and/or *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision diagnosis of non-affective psychosis, had more than one episode or an episode of psychosis lasting longer than a year and were taking antipsychotic medication at the time of enrolment. Exclusion criteria included being subject to any section that includes a requirement to take antipsychotic medication, and the clinician considered considering there to be a risk of serious harm to self or others. Full eligibility criteria are listed in [Table 6](#). All participants consented to randomisation to either treatment strategy.

Randomisation and masking

Randomisation was conducted through an independent internet-based system (Sealed Envelope) with 1 : 1 allocation using permuted block sizes of 4, 6 and 8. Researchers collecting outcome data were masked to participant allocation. Assigned unmasked researchers liaised with participants, clinicians and the central team to avoid unmasking of the researchers performing the follow-up assessments. Researchers sent details of each participant's baseline antipsychotic medication. Participants were randomised by the central team with allocation 1 : 1 using a remote computerised system managed by PRIMENT Clinical Trials Unit at UCL.

Procedure

After randomisation, participants and clinicians were contacted with details on the allocated treatment arm. Unmasked researchers added details of the allocation to the electronic medical records. Clinicians were sent the Antipsychotic

Reduction and Discontinuation or Maintenance Treatment strategy manuals and a link to an online version, and for clinicians with participants allocated to the reduction treatment, a suggested reduction schedule based on baseline antipsychotic medication regime was also provided. 'Wellbeing booklets' (see [Report Supplementary Materials 4](#) and [5](#)) were posted to participants in both arms, followed by a phone call to discuss the intervention and explore any concerns. For participants allocated to the Antipsychotic Reduction and Discontinuation strategy, clinicians were advised to schedule the first appointment within a month of randomisation. For participants allocated to the Maintenance Treatment strategy, clinicians were advised to try and avoid reducing antipsychotic doses, though small changes were permitted to manage adverse effects from antipsychotic medication. Clinicians were advised to complete a relapse prevention plan with participants in both arms.

Outcomes

The principal outcome of the pilot trial was the recruitment rate. Randomisation procedures, the implementation of the interventions, monitoring procedures, assessment processes and retention rates were also assessed.

Stop/go criteria

Stop/go criteria were developed to review recruitment rates based on similar trials, and progress was reviewed by the study team and PSC. Permission to expand recruitment to other sites was dependent on recruitment of at least 70% of the target participants ($n = 28$). Lower recruitment rates of 50–70% would require review and consultation by the PSC.

Results

Progress was reviewed at the PSC in July 2017 and the committee recommended proceeding to the main trial and extending recruitment to other sites. Twenty-six people were recruited in 4 months, which was just below 70% of the projected target of 40. Randomisation procedures, intervention monitoring procedures and intervention implementation were all satisfactory. Assessments were feasible and were well tolerated by participants, and retention rates were high as far as they could be assessed in a short period. There were no safety concerns and no changes were recommended.

Key findings

- Recruitment, data collection and randomisation procedures were feasible and conducted within specified time frames.
- Protocols for monitoring intervention adherence were adequate in identifying deviations from the randomised treatment strategy.

Work package 3a: randomised controlled trial

Work package 3a: aim

The aim was to compare the 24-month outcomes of a supported and gradual strategy of antipsychotic reduction with maintenance treatment in people with recurrent psychotic conditions or schizophrenia spectrum disorders [see Consolidated Standards of Reporting Trials (CONSORT) checklist, see [Report Supplementary Material 11](#)].

Methods

The trial was an open, parallel group trial with individual randomisation to the intervention: antipsychotic reduction and discontinuation; and the control condition: antipsychotic maintenance treatment, delivered in routine mental health services.

Setting and participants

A total of 19 recruiting sites across England enrolled participants in the main trial.

Participating trusts The NELFT, ELFT; Kent and Medway NHS Partnership Trust; Lincoln Partnership NHS Trust; Barnet, Enfield and Haringey Mental Health Trust; Camden and Islington NHS Foundation Trust; Oxford Health NHS Foundation Trust; Central North West London NHS Foundation Trust; Avon and Wiltshire Mental Health Partnership

NHS Trust; Dorset Healthcare University NHS Foundation Trust; Sussex Partnership NHS Foundation Trust; Cornwall Partnership NHS Foundation Trust; Somerset NHS Foundation Trust; Norfolk and Suffolk NHS Foundation Trust; Lancashire Care NHS Foundation Trust; Southern Health NHS Foundation Trust; Livewell Southwest NHS Trust; Gloucestershire Health and Care NHS Foundation Trust; Coventry and Warwickshire Partnership NHS Trust.

Participants were recruited from secondary care mental health services who provide care to people with schizophrenia spectrum disorders.

Data collection

Patient outcomes were assessed at baseline, 6 months, 12 months and 24 months, and for each, they received a £20 reimbursement for their time. The case report form can be viewed in [Report Supplementary Material 12](#). Data were collected from patient notes every 2 months for some outcomes (e.g. severe relapse/readmission and adverse events) and intervention monitoring.

Outcome measures

The SFS, measuring social activity over the past 3 months, was collected as the primary outcome at 24 months.²⁴ Secondary outcomes included: (1) rates of severe relapse defined as hospitalisation in a mental health inpatient unit; (2) observer-rated symptoms of psychosis measured using the Positive and Negative Syndrome Scale (PANSS);⁴⁵ (3) neuropsychological function as measured by testing including Digit Span (cite), Digit Symbol Coding (cite), trail making A (cite), Verbal Fluency (cite), Rey Auditory Verbal Memory (cite); (4) subjective quality of life measured by the MANSA²⁶(cite); (5) satisfaction with services as measured by the Client Satisfaction Questionnaire (CSQ) 8 (cite);⁴⁶ (6) patient-reported side effects as measured by a modified version of the Glasgow Antipsychotics Side Effects Scales (cite);⁴³ (7) patient-reported adherence to antipsychotic medication as measured by the Medication Adherence Report Scale (MARS-5); (8) patient-reported assessment of relapse from a patient perspective as measured by a questionnaire developed as part of the programme; (9) subjective health-related quality of life as measured by the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) and ICEpop CAPability measure for Adults (ICECAP-A);^{47,48} (10) use and cost of services as measured by the Client Service Receipt Inventory (CSRI) and an economic schedule; (11) objective social situation as measured by the SIX;²⁵ (12) patient-reported impairment in paid and unpaid work as measured by the Work Productivity and Activity Questionnaire;⁴⁹ (13) patient-reported recovery as measured by the QPR;⁴² (14) sexual function as measured by the ASEX;⁴¹ and (15) patient-reported deterioration and relapse using a short questionnaire developed as part of the Programme (see [Report Supplementary Material 6](#)), demographics including weight and substance use. Data were extracted from patient records every 2 months on the use of antipsychotics for purposes of monitoring the application of the antipsychotic reduction and maintenance protocols. Adverse events were also monitored by reviewing patient records using a pre-designed schedule. The schedule for assessments is displayed in the trial protocol (see [Report Supplementary Material 10](#)).

Power calculation

Assuming an attrition rate of 15%, sample size calculations revealed a sample size of 134 participants were required to be enrolled to achieve 90% power with an alpha of 0.05 to detect a five-point difference on the SFS by using a standard deviation (SD) of 8.8 derived from the literature.⁵⁰ A sample of 206 was required to detect a four-point difference in the SFS.²⁴ Assuming an attrition rate of 15%, a secondary sample size calculation for the principal secondary safety outcome revealed 402 participants were required to be enrolled to achieve 90% power to detect a 10% margin of difference in hospitalisation. The event rate for hospitalisation in the maintenance group was assumed to be 10%, as derived from a meta-analysis of antipsychotic discontinuation studies.⁴ An increased risk of relapse of up to 10% was assumed to be acceptable to clinicians if balanced with improvements in social functioning and a reduction in side effects. The target sample size was therefore 402 participants.

Statistical analysis

Statistical analyses were conducted in accordance with the statistical analysis plan agreed upon and were finalised prior to database lock and extraction ([Report Supplementary Material 13](#)) and were conducted using Stata® version 17 (StataCorp LP, College Station, TX, USA). The plan for the primary outcome (SFS score at 24 months) involved using a linear mixed model, with the randomisation variable and baseline SFS score included as fixed effects and trust as a random effect, if the model fitted well. If not, then it was specified that a similar modelling strategy would be

used without random effects, using robust standard errors. The principal analysis used all available data. Sensitivity analyses were conducted, including predictors of missingness of the outcome and a variable reflecting the degree of COVID-related lockdown.

Time to severe relapse (readmission) was analysed with survival analysis using a Cox proportional hazards model with robust standard errors. The extent to which there was a departure from constant proportional hazards was assessed statistically using Schoenfeld residuals. Logistic models with robust standard errors on the occurrence of severe relapse within 24 months and the combination of severe and less severe relapse were conducted as supportive analyses.

Other secondary outcomes were analysed in the same way as the primary outcome, using linear regression models, with the score at 24 months as the outcome. The number of psychiatric inpatient days was analysed using zero inflated negative binomial regression with robust standard errors, controlling for number of psychiatric inpatient days in the 6 months to baseline, and the natural log of the number of days of follow-up as an offset. Employment status was analysed using logistic regression with robust standard errors.

Health economics analysis

For the cost-effectiveness analysis, the primary analysis calculated the incremental cost per quality-adjusted life-year (QALY) gained from a mental health services cost perspective, using the EQ-5D-5L to EuroQol-5 Dimensions, three-level version (EQ-5D-3L) mapping algorithm to calculate QALYs,⁵¹ as recommended by NICE.⁵² This was an update to the algorithm specified in the SAP, in line with changes in the NICE position statement on the reference case. A secondary analysis used the ICECAP-A to calculate the cost per year of full capability (YFC) gained of the antipsychotic reduction strategy compared to maintenance treatment over 24 months.⁵³ Additional sensitivity analyses explored the impact of severe relapse and COVID-19 restrictions on costs and effects. Data on wider health service use, unpaid care and employment costs were obtained from an adapted CSRI and the Work Productivity and Activity Impairment – General Health questionnaires.⁴⁹ Costs for antipsychotics, health services and other interventions were derived from nationally published sources.^{54–56}

Secondary analyses were conducted from a wider NHS and Personal Social Services, as well as from a societal perspective, to capture the impact on employment, criminal justice, benefits, family and close others. All costs and outcomes were discounted in line with NICE guidance at 3.5% per year.⁵⁶ Linear regression with two-stage bootstrapping that adjusted for baseline costs or effects was used to calculate incremental costs and incremental effects. Bootstrapping was used to construct CIs for total mean costs, QALYs and YFCs and to construct cost-effectiveness acceptability curves and cost-effectiveness planes. Complete case analysis (CCA) was conducted as the primary analysis, with multiple imputation as a sensitivity analysis.

The manuscript, including the Abstract, was prepared according to the CONSORT guidelines (see [Report Supplementary Materials 11](#) and [14](#)).

Efficacy results

Results are detailed in Moncrieff *et al.*⁵⁷ Four thousand one hundred and fifty-seven people were screened by the research team, of whom 253 were randomised, 126 to the reduction arm and 127 to the maintenance arm ([Figure 3](#)). Recruitment lasted from March 2017 to March 2020 and the last follow-up was conducted in March 2022. The demographic and clinical characteristics of the participants at baseline are shown in [Table 8](#).

One hundred and ninety participants were interviewed at 24-month follow-up. Assessors guessed or were inadvertently unblinded to group allocation in 13 cases. The primary outcome, the SFS, was analysed using multiple linear regression with robust standard errors, since the model that included trust as a random effect did not fit well due to some trusts having few recruits. The difference in SFS scores between the groups was small and not statistically significant (0.19, –1.9 to 2.3: [Table 9](#)). The sensitivity analyses, including the degree of COVID-19 lockdown and predictors of missingness, did not change this (see Moncrieff *et al.*, 2023, supplementary information, tables 2S–4S⁵⁷).

Time to severe relapse was shorter in the reduction group compared with the maintenance group (hazard ratio 2.2, 95% CI 1.2 to 4.0, $p = 0.007$). [Figure 4](#) presents the Kaplan–Meier curve for severe relapse.

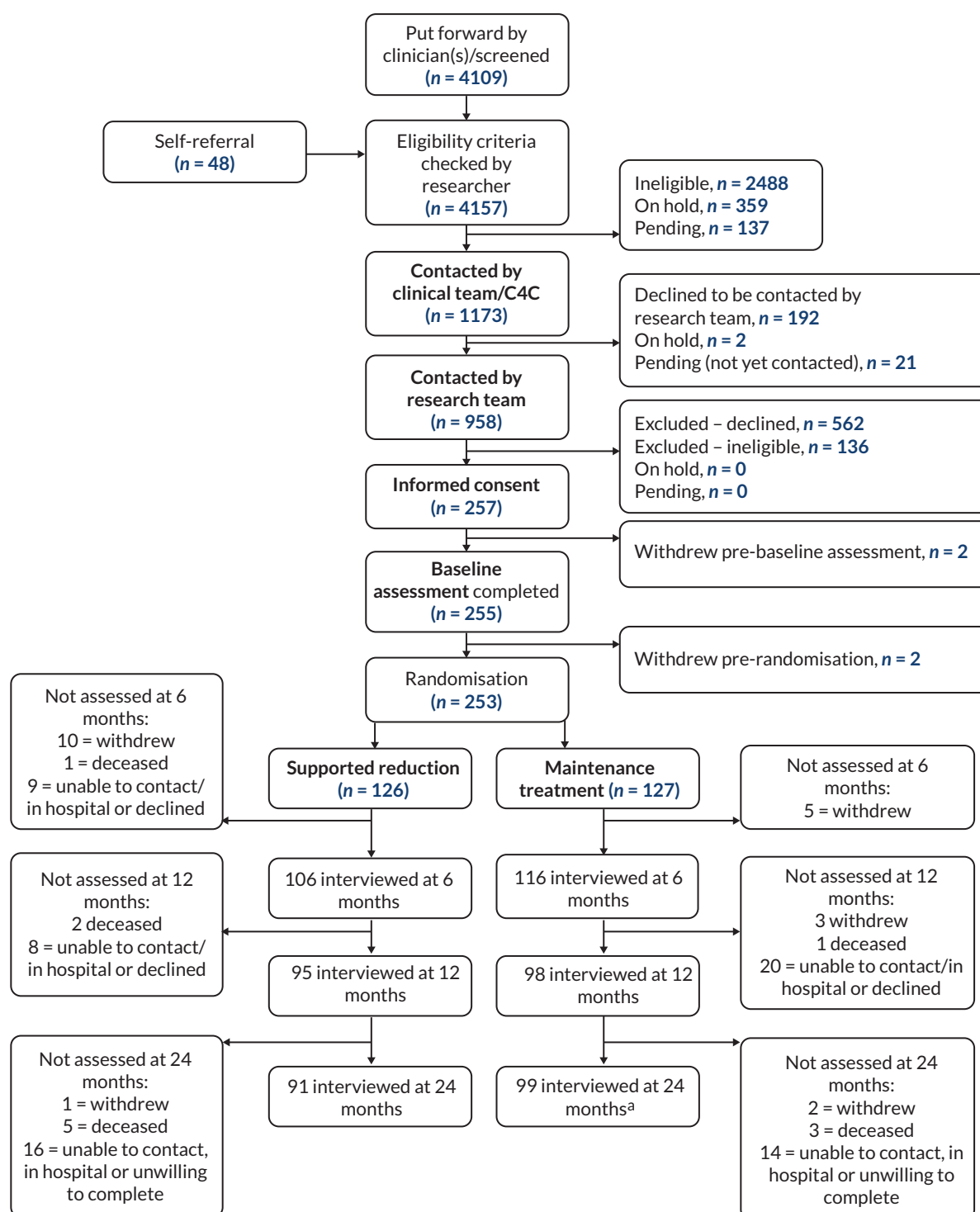


FIGURE 3 Trial CONSORT. a, Continued attempts were made to follow-up participants, including those who did not participate in earlier follow-up data collection.

At 24 months, 32 participants (25.4%) in the reduction group had at least 1 severe relapse compared with 17 (13.4%) of the maintenance group (odds ratio 2.2, 95% CI 1.2 to 4.2). By the end of follow-up (which was longer for some participants), 34 participants (27.0%) in the reduction arm had at least 1 severe relapse compared with 17 (13.4%) in the maintenance arm. Rates of non-severe and overall relapse were also higher in the reduction group (see [Table 9](#)). There was no difference in the median bed-days between groups.

TABLE 8 Baseline demographic and clinical characteristics of randomised trial participants

Characteristic	Antipsychotic dose reduction/ discontinuation, maximum, N = 126		Antipsychotic maintenance treatment, maximum, N = 127	
	N	n (%) or mean (SD) or median (IQR)	N	n (%) or mean (SD) or median (IQR)
Male	126	85 (67.4%)	127	83 (65.3%)
Female	126	40 (31.7%)	127	42 (33.1%)
Transgender	126	1 (0.79%)	127	2 (1.6%)
Age	126	Mean 46.6 (SD 12.2)	127	Mean 46.0 (SD 11.5)
Marital status				
Single, separated, divorced, widowed	126	106 (84.1%)	127	110 (86.6%)
Married, cohabiting, civil partnership	126	20 (15.9%)	127	17 (13.4%)
Ethnicity				
White	126	89 (70.6%)	125	82 (65.6%)
Black	126	25 (19.8%)	125	27 (21.6%)
Asian	126	8 (6.3%)	125	8 (6.4%)
Other	126	4 (3.2%)	125	8 (6.4%)
First language English	126	107 (84.9%)	127	114 (89.8%)
Highest educational achievement				
Primary and secondary education to age 16 years	125	49 (39.2%)	126	36 (28.6%)
Primary and secondary education to age 18 years	125	22 (17.6%)	126	27 (21.4%)
Tertiary or further education	125	40 (32.0%)	126	56 (44.4%)
Other general education	125	14 (11.2%)	126	7 (5.6%)
Years of completed education	121	Mean 14 (SD 3.3)	125	Mean 14 (SD 3.9)
Employment				
Employed, voluntary or in education	126	38 (30.2%)	125	36 (28.8%)
Not working or in education	126	88 (69.8%)	125	89 (71.2%)
Length of time in contact with mental health services				
0–3 years	126	11 (8.7%)	127	6 (4.7%)
4–10 years	126	34 (27.0%)	127	28 (22.0%)
11–15 years	126	20 (15.9%)	127	23 (18.1%)
16–20 years	126	20 (15.9%)	127	22 (17.3%)
> 20 years	126	41 (32.5%)	127	48 (37.8%)
Age when first referred to mental health services				
< 20 years	126	26 (20.6%)	127	27 (21.3%)
20–30 years	126	57 (45.2%)	127	67 (52.7%)
31–40 years	126	25 (19.8%)	127	22 (17.3%)
≥ 41 years	126	18 (14.3%)	127	11 (8.7%)
Number of previous mental health admissions		Median 3 (IQR 1–5)		Median 3 (IQR 1–5)

continued

TABLE 8 Baseline demographic and clinical characteristics of randomised trial participants (*continued*)

Characteristic	Antipsychotic dose reduction/ discontinuation, maximum, N = 126		Antipsychotic maintenance treatment, maximum, N = 127	
	N	n (%) or mean (SD) or median (IQR)	N	n (%) or mean (SD) or median (IQR)
Recreational drugs used in the last month	126	11 (8.7%)	126	14 (11.1%)
Alcohol use over the past month				
Once a month or less	126	80 (63.5%)	126	82 (65.1%)
Two to four times a month	126	24 (19.0%)	126	20 (15.9%)
Two or more times a week	126	22 (17.5%)	126	19 (19.0%)
Antipsychotic medication dose in chlorpromazine equivalents	126	Median 300 (IQR 200–450)	127	Median 300 (IQR 200–400)
Outcome measures at baseline				
SFS overall	123	Mean 107.7 (SD 8.6)	120	Mean 108.2 (SD 10.2)
PANSS positive symptom subscale	124	Median 10 (IQR 8–14)	127	Median 11 (8–16)
PANSS negative symptom subscale	124	Median 11 (IQR 9–15)	124	Median 11 (8–15)
PANSS total	122	Median 48 (IQR 41–59)	123	Median 48 (IQR 40–61)
MANSA	126	Mean 4.7 (SD 0.82)	127	Mean 4.6 (SD 0.83)
SIX	125	Mean 3.4 (SD 1.3)	127	Mean 3.4 (SD 1.3)
Modified GASS	105	Mean 27.6 (SD 15.2)	104	Mean 29.0 (SD 17.1)
Body weight in kg	114	Mean 90.9 (SD 20.2)	116	Mean 89.7 (SD 19.1)
CSQ-8	125	Median 20 (IQR 20–21)	122	Median 20 (IQR 19–21)
MARS-5	124	Median 24 (IQR 22–25)	124	Median 25 (IQR 23–25)
QPR-15	123	Mean 55.7 (SD 9.9)	122	Mean 56.6 (SD 10.0)
ASEX	42	Mean 16.3 (SD 6.1)	39	Mean 15.5 (SD 5.0)
Cognitive tests				
Digit span	124	Mean 14.8 (SD 4.5)	126	Mean 14.7 (SD 4.7)
Digit symbol substitution	117	Mean 47.2 (SD 17.4)	121	Mean 47.3 (SD 18.2)
Rey Auditory Verbal Learning	121	Mean 35.7 (SD 12.0)	120	Mean 36.1 (SD 12.4)
Trail making	121	Median 45 (IQR 35–62)	121	Median 50 (IQR 36–64)
Verbal fluency	124	Mean 16.5 (SD 4.9)	126	Mean 16.6 (SD 5.2)

ASEX, Arizona Sexual Experience Scale; IQR, interquartile range.

Other secondary outcomes showed no difference between the groups at 24 months, including measures of symptoms, quality of life, adverse effects scales, body weight and employment (see [Table 9](#)).

Process measures showed that participants randomised to antipsychotic dose reduction achieved a median 67% reduction (IQR –100% to –40%) of their baseline dose at some point during the trial. Their median dose at 24 months was 33% less than at baseline ([Table 10](#)). The median change among maintenance participants was zero. Thirty-four people (27.0%) randomised to reduction stopped their antipsychotic medication completely at some time during the 24-month follow-up period, and 13 (10.2%) of those randomised to maintenance treatment did so. Eighty-eight (69.8%) participants in the reduction group reduced their antipsychotic dose by 50% or more when compared with 21 (16.5%) of the maintenance participants.

TABLE 9 Randomised trial: 24-month outcomes

	24-month outcomes				
	Antipsychotic dose reduction		Antipsychotic maintenance treatment		Treatment effect
	N	Number (%); mean (SD) or median (IQR)	N	Number (%); mean (SD) or median (IQR)	Estimate: B coefficient (if not otherwise specified), HR, OR IRR (95% CI)
SFS (overall score)	90	Mean 105.7 (SD 10.5)	94	Mean 106.7 (SD 9.7)	0.19 (-1.9 to 2.3)*
Time to severe relapse	126		127		2.2 (1.2 to 4.0) (HR)**
Severe relapse at any time over 24 months	126	32 (25.4)	127	17 (13.4)	2.2 (1.2 to 4.2) (OR)
Severe relapse at any time to the end of follow-up	126	34 (27.0%)	127	17 (13.4%)	2.4 (1.3 to 4.6) (OR)
Non-severe relapse at any time over 24 months	126	20 (15.9%)	127	11 (8.7%)	2.0 (0.9 to 4.4) (OR)
Any relapse at any time over 24 months	126	52 (41.3%)	127	28 (22.0%)	2.5 (1.4 to 4.3) (OR)
Psychiatric bed-days	117	Median 0 (IQR 0–31)	121	Median 0 (IQR 0–0)	0.95 (0.53 to 1.70) (IRR)
PANSS positive symptoms subscale	82	Median 10 (IQR 8–14)	91	Median 10 (IQR 8–14)	0.33 (-0.91 to 1.6)
PANSS negative symptoms subscale	77	Median 9 (IQR 8–13)	88	Median 10 (IQR 8–14)	-0.82 (-2.0 to 0.32)
PANSS total score	52	Median 43 (IQR 36–54)	59	Median 48 (IQR 38–63)	-2.10 (-6.2 to 2.0)
MANSA	86	Mean 4.6 (SD 0.95)	89	Mean 4.7 (SD 0.70)	-0.05 (-0.24 to 0.14)
SIX	86	Mean 3.34 (SD 1.2)	90	Mean 3.3 (SD 1.1)	0.01 (-0.25 to 0.26)
GASS	70	Mean 21.9 (SD 15.5)	68	Mean 25.3 (SD 16.0)	-3.98 (-8.8 to 0.81)
CSQ-8	83	Median 25 (IQR 19–28)	84	Median 25 (IQR 22–29)	-1.3 (-3.5 to 0.85)
MARS-5	81	Median 25 (IQR 23–25)	85	Median 25 (IQR 23–25)	0.47 (-0.26 to 1.2)
QPR-15	78	Mean 41.5 (SD 9.5)	83	Mean 41.1 (SD 9.5)	-0.04 (-2.4 to 2.3)
ASEX	10	Mean 14.6 (SD 4.2)	18	Mean 17.4 (SD 6.7)	-0.02 (-3.1 to 3.0)
Body weight (kg)	63	Mean 89.6 (SD 25.0)	71	Mean 85.5 (SD 18.4)	2.8 (-2.3 to 7.8)
Cognitive tests					
Digit span	83	Mean 14.7 (SD 4.9)	88	Mean 15.4 (SD 4.7)	-0.89 (-2.1 to 0.34)
Digit symbol substitution	62	Mean 47.2 (SD 20.8)	66	Mean 47.7 (SD 20.9)	-1.9 (-6.1 to 2.3)
Rey Auditory Verbal Learning	76	Mean 37.0 (SD 16.1)	85	Mean 38.2 (SD 12.6)	-0.91 (-4.4 to 2.6)
Trail making median (IQR)	63	Median 48 (IQR 35–61)	69	Median 44 (IQR 34–67)	2.9 (-4.7 to 10.5)
Verbal fluency	82	Mean 17.4 (SD 6.8)	83	Mean 17.3 (SD 5.5)	-0.06 (-1.7 to 1.6)
Employment					
Employed, voluntary work or in education	91	18 (19.8%)	99	20 (20.2%)	Reference
Not working or in education	91	73 (80.2%)	99	79 (79.8%)	1.0 (0.50 to 2.1) (OR)

p* = 0.859; *p* = 0.007.

HR, hazards ratio; IQR, interquartile range; IRR, incidence rate ratio; OR, odds ratio.

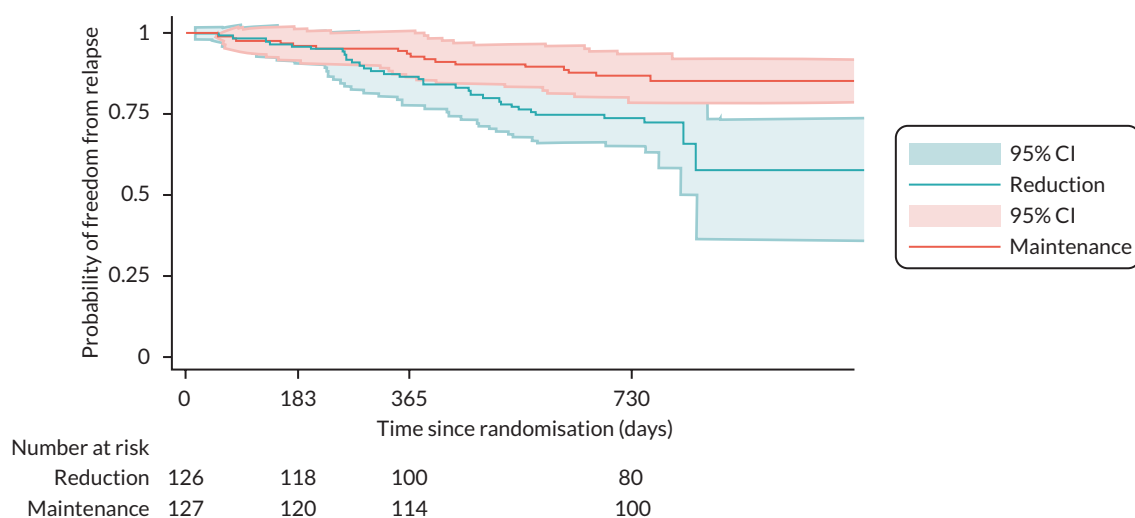


FIGURE 4 Kaplan-Meier curve.

TABLE 10 Randomised trial: antipsychotic medication changes during the trial

	Antipsychotic dosage reduction		Antipsychotic maintenance treatment	
	Median (IQR) or n/N (%)	(IQR or %)	Median or n/N	(IQR or %)
Medication dose at baseline: chlorpromazine equivalents (median, IQR)	300 mg	(200 to 450 mg)	300 mg	(200 to 400 mg)
Medication dose at 24 months: chlorpromazine equivalents (median, IQR)	200 mg	(75 to 400 mg)	300 mg	(150 to 425 mg)
Maximum change in dose during the course of the study: chlorpromazine equivalents (median, IQR)	-200 mg	(-300 to -100 mg)	0 mg	(-67 to 0 mg)
Change in dose by 24-month follow-up: chlorpromazine equivalents (median, IQR)	-100 mg	(-200 to 0 mg)	0 mg	(-25 to 0 mg)
Maximum change in dose during the course of the study: percentage of baseline dose (median, IQR)	-67%	(-100% to -40%)	0%	(-22% to 0%)
Change in dose at the end of the study: percentage of baseline dose (median, IQR)	-33%	(-67% to 0%)	0%	(-15% to 0%)
Antipsychotic medication stopped at some point during 24-months follow-up	34/126	27.0%	13/127	10.2%
Antipsychotic dose reduced by more than 50% at some point during the 24-month follow-up	88/126	69.8%	21/127	16.5%

Nine of the 34 participants (26.5%) in the reduction group who stopped their antipsychotic medication completely during the 24-month follow-up had a severe relapse requiring hospitalisation when compared with 4 of the 13 (30.8%) who stopped in the maintenance group ([Figure 5](#)).

Similar proportions of participants who reduced their antipsychotics by at least 50% had a severe relapse ([Figure 6](#)).

Serious adverse events were more common in the reduction group, largely due to a higher number of hospitalisations for relapse ([Table 11](#)). There were eight deaths in the reduction group during the study and four in the maintenance group. Seven were due to natural causes. Two deaths, one in the maintenance arm and one in the reduction arm, were due to accidental drug overdoses, and one was the suicide of a participant in the maintenance arm (as determined

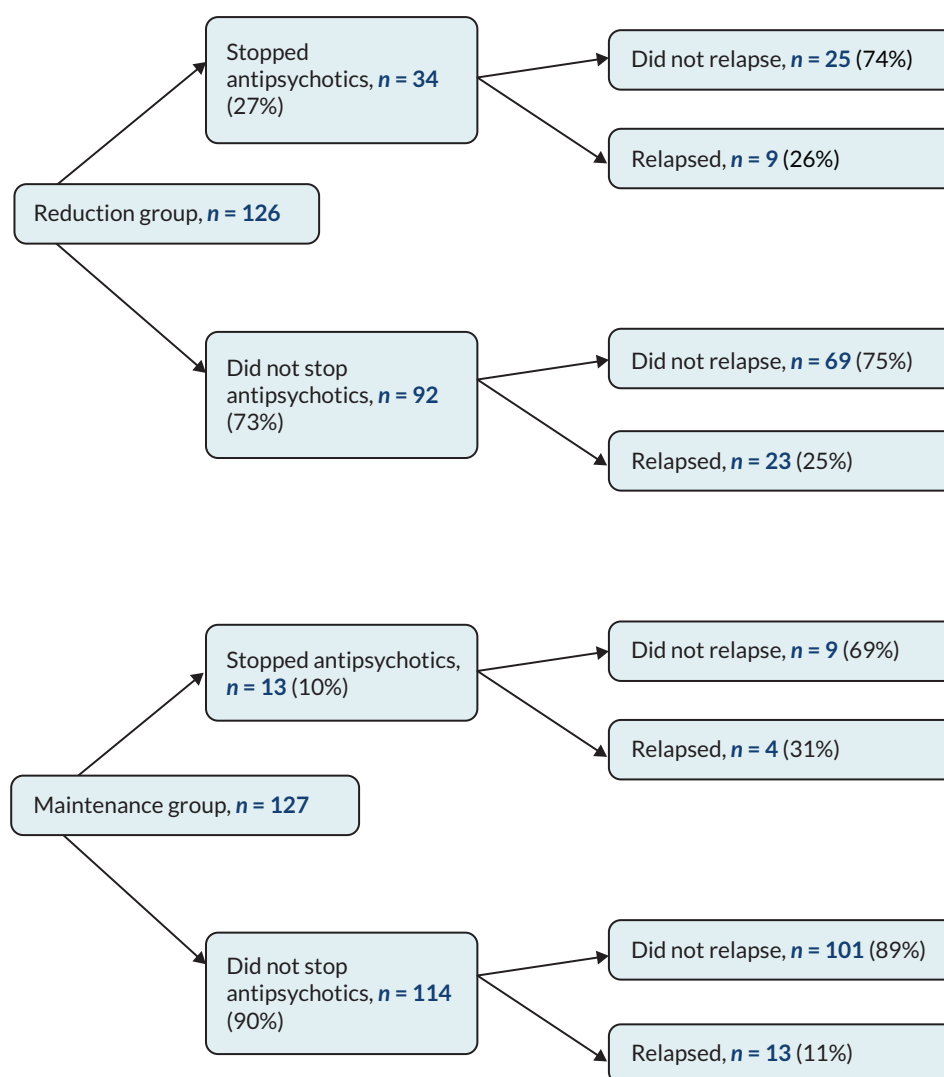


FIGURE 5 Tree diagram showing whether participants stopped taking antipsychotics at some point during the trial and relapse status at 24 months by randomised group.

by the coroner's investigation). One death of a participant in the reduction arm was attributed to the effects of antipsychotic medication, and the cause of another remains unknown at the time of writing, but there were no suspicious circumstances.

Key findings

- A gradual process of antipsychotic reduction did not produce improvements in social functioning over 24 months compared with maintenance treatment.
- A gradual process of antipsychotic reduction increased the risk of severe relapse and any relapse compared with maintenance treatment.
- There were no differences between the groups in any other outcomes at 24 months, including symptoms.

Health economics results

Costs and outcomes

Mean costs for groups of services comprising the mental health services perspective are reported in [Table 12](#). The reduction arm had significantly lower antipsychotic medication costs at all follow-up time points and in total (baseline-adjusted difference: -£630, 95% CI -£895 to -£365). There was no significant difference in acute care costs, although there was a trend towards higher costs among the antipsychotic reduction group (baseline-adjusted difference: £5490, 95% CI -£7 to £10,987) (see also [Bray et al. 58](#)).

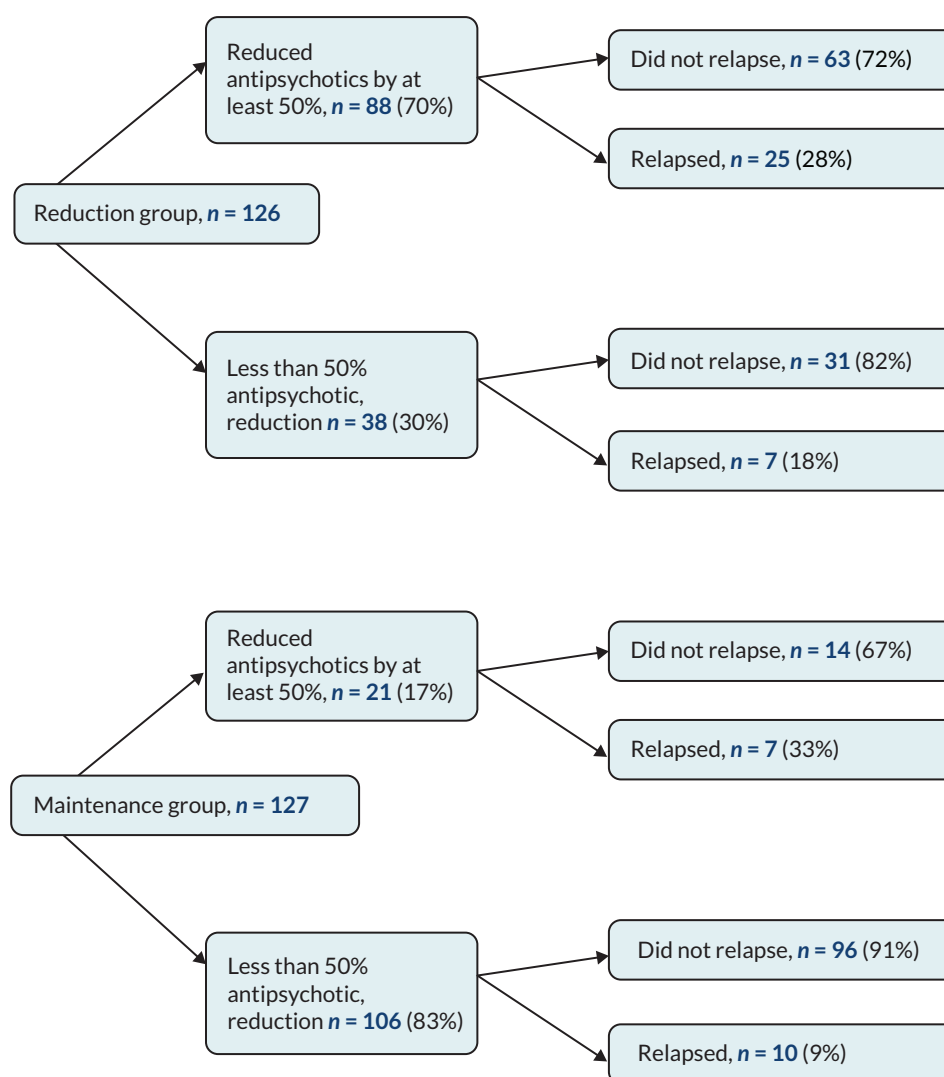


FIGURE 6 Tree diagram showing whether participants reduced antipsychotics by at least 50% at some point during the trial and relapse status at 24 months by randomised group.

TABLE 11 Randomised trial: adverse events

	Antipsychotic dosage reduction N (% of events or participants)	Antipsychotic maintenance treatment N (% of events or participants)
Number of SAEs	93	63
Death	8 (8.6% of events)	4 (6.3% of events)
Life-threatening event	1 (1.1% of events)	1 (1.6% of events)
Mental health hospitalisation	53 (57.0% of events)	30 (47.6% of events)
Physical health hospitalisation	16 (17.2% of events)	20 (31.7% of events)
Other	15 (16.1% of events)	8 (12.7% of events)
Participants experiencing a SAE	48 (38.1% of participants)	32 (25.2% of participants)
Number of non-serious AEs	691	476
Participants experiencing any non-serious AE	88 (69.8% of participants)	97 (76.4% of participants)

AE, adverse event; SAE, serious adverse event.

TABLE 12 Unadjusted and baseline-adjusted mean mental health-related costs from medical records, by randomised group and time point, with unadjusted or baseline-adjusted differences using bias-corrected and accelerated bootstrapped regressions (CCA)

		Reduction		Maintenance		Adjusted difference (95% CI) (£)
		N	Mean (SE) (£)	N	Mean (SE) (£)	
Antipsychotic medication	Baseline ^a	126	338 (49)	127	300 (44)	38 (–92 to 169)
	12 months	125	347 (46)	126	657 (53)	–310 (–446 to –174)
	24 months	119	303 (47)	121	628 (62)	–325 (–476 to –174)
	24 months (discounted)	119	293 (45)	121	606 (60)	–314 (–460 to –167)
	Total unadjusted cost ^a	119	700 (110)	121	1241 (177)	–541 (–939 to –143)
	Total adjusted cost	119	655 (81)	121	1285 (109)	–630 (–895 to –365)
Acute care	Baseline ^a	126	138 (145)	127	298 (153)	–160 (–582 to 262)
	12 months	119	4920 (3674)	121	3178 (3810)	1742 (–1868 to 5352)
	24 months	118	7649 (1962)	119	2405 (1027)	5243 (1083 to 9404)
	24 months (discounted)	118	7381 (1893)	119	2321 (991)	5060 (1045 to 9075)
	Total unadjusted cost ^a	117	11,023 (1990)	119	5540 (2028)	5483 (18 to 10,947)
	Total adjusted cost	117	11,026 (2673)	119	5536 (2639)	5490 (–7 to 10,987)
Community and outpatient	Baseline ^a	126	1667 (128)	127	1766 (171)	–99 (–517 to 319)
	12 months	119	3383 (220)	121	3483 (310)	–100 (–839 to 640)
	24 months	118	3689 (270)	119	3082 (251)	607 (–125 to 1338)
	24 months (discounted)	118	3560 (261)	119	2974 (242)	585 (–120 to 1291)
	Total unadjusted cost ^a	117	6949 (448)	119	6498 (531)	452 (–927 to 1831)
	Total adjusted cost	117	6976 (403)	119	6472 (480)	504 (–720 to 1727)

a Adjustment for baseline differences in costs not applicable.

Note

Unadjusted and baseline-adjusted total costs include discounted 24-month costs.

Source

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Mean utility scores for the EQ-5D-5L to EQ-5D-3L cross-walk and ICECAP-A and their associated outcome measures are reported in [Table 13](#). There was no significant difference in EQ-5D-5L utility scores at any time point or QALYs between arms (baseline-adjusted difference: –0.035, 95% CI –0.124 to 0.054), with no changes to conclusions when deaths were excluded in a sensitivity analysis.

Baseline-adjusted YFCs were significantly lower in the reduction arm (baseline-adjusted difference: –0.103, 95% CI –0.191 to –0.015) in the CCA. Multiple imputation did not change the direction of difference or conclusions on significance for any of the utility or outcome measures.⁵⁸

Cost–utility analysis

[Table 14](#) reports the results of the cost–utility analysis for both CCA and multiple imputation. For the primary analysis, over the course of the 24 months, participants in the reduction arm had a greater mean point estimate for costs (£5619, 95% CI –£386 to £11,625) and a negative mean point estimate for QALYs (–0.035, 95% CI –0.125 to 0.054), meaning

TABLE 13 Unadjusted and baseline-adjusted mean utilities and outcomes for the EQ-5D-5L to EQ-5D-3L cross-walk and ICECAP-A, by randomised group and time point, with unadjusted or baseline-adjusted differences using bias-corrected and accelerated bootstrapped regressions (CCA)

		Reduction		Maintenance		Adjusted difference (95% CI)
		N	Mean (SE)	N	Mean (SE)	
EQ-5D-3L cross-walk	Baseline ^a	125	0.703 (0.022)	124	0.719 (0.025)	−0.017 (−0.081 to 0.047)
	6 months	99	0.750 (0.019)	108	0.717 (0.018)	0.033 (−0.019 to 0.085)
	12 months	90	0.706 (0.023)	92	0.720 (0.019)	−0.014 (−0.073 to 0.045)
	24 months	93	0.683 (0.033)	90	0.689 (0.027)	−0.006 (−0.089 to 0.077)
	Total unadjusted QALY ^a	75	1.388 (0.047)	73	1.469 (0.044)	−0.082 (−0.211 to 0.048)
	Total adjusted QALY	75	1.411 (0.035)	73	1.446 (0.029)	−0.035 (−0.124 to 0.054)
ICECAP-A	Baseline ^a	124	0.508 (0.023)	121	0.482 (0.024)	0.026 (−0.038 to 0.090)
	6 months	96	0.460 (0.020)	104	0.495 (0.020)	−0.035 (−0.089 to 0.019)
	12 months	86	0.445 (0.021)	88	0.476 (0.022)	−0.030 (−0.090 to 0.030)
	24 months	87	0.384 (0.024)	84	0.496 (0.021)	−0.112 (−0.173 to −0.051)
	Total unadjusted YFC ^a	66	0.853 (0.058)	67	0.932 (0.051)	−0.080 (−0.235 to 0.076)
	Total adjusted YFC	66	0.841 (0.034)	67	0.944 (0.030)	−0.103 (−0.191 to −0.015)

SE, standard error.

a Adjustment for baseline differences in utilities or outcomes not applicable.

Source

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reduction was dominated by the maintenance strategy. The probability of cost-effectiveness was 1.03% and 0.89% at £20,000 and £30,000 thresholds, respectively (Figure 7). The results for the secondary and sensitivity analyses are published elsewhere and also find a low probability that reduction is cost-effective for a range of decision thresholds.⁵⁸

Key findings

- The antipsychotic reduction strategy is unlikely to be cost-effective.
- There was no difference in QALYs between the randomised groups, but YFCs favoured the maintenance arm.

Work package 3b: qualitative evaluation patients

Aim

The aim of WP3b was to explore experiences and implementation of the Antipsychotic Reduction and Discontinuation strategy and trial processes from a participant's perspective. Parts of this section have been reproduced with permission from Morant *et al.*⁵⁹ This is an Open Access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. The text below includes minor additions and formatting changes to the original text.

TABLE 14 Mean incremental costs, QALYs, YFCs, ICERs and probabilities of the reduction arm being cost-effective at the standard £20,000 and £30,000 per QALY gained thresholds commonly used by NICE (CCA and Multiple imputation analysis)

				Cost-effectiveness probability (%)	
Cost perspective	Incremental cost (£)	Incremental QALY	ICER	£20,000	£30,000
QALYs (CCA)					
Mental health services	5622 (−378 to 11,622)	−0.035 (−0.123 to 0.053)	Maintenance dominates reduction	0.88	0.90
NHS	11,649 (−4688 to 27,987)	−0.035 (−0.124 to 0.053)	Maintenance dominates reduction	8.32	7.68
Societal	12,647 (−7303 to 32,596)	−0.035 (−0.124 to 0.054)	Maintenance dominates reduction	15.70	14.82
YFCs (CCA)					
Mental health services	5622 (263 to 10,981)	−0.103 (−0.192 to −0.015)	Maintenance dominates reduction	1.23	0.64
NHS	11,649 (−3793 to 27,092)	−0.103 (−0.191 to −0.015)	Maintenance dominates reduction	4.47	3.43
Societal	12,647 (−6480 to 31,774)	−0.103 (−0.191 to −0.016)	Maintenance dominates reduction	7.53	6.07
QALYs (multiple imputation)					
Mental health services	4222 (−1769 to 10,214)	−0.027 (−0.106 to 0.052)	Maintenance dominates reduction	6.3	6.04
NHS	8879 (−6132 to 23,890)	−0.027 (−0.106 to 0.052)	Maintenance dominates reduction	9.47	8.99
Societal	891 (−17,675 to 19,457)	−0.027 (−0.106 to 0.052)	Maintenance dominates reduction	42.52	41.52
YFCs (multiple imputation)					
Mental health services	4222 (−1769 to 10,214)	−0.079 (−0.157 to −0.002)	Maintenance dominates reduction	3.71	2.58
NHS	8879 (−6132 to 23,890)	−0.079 (−0.157 to −0.002)	Maintenance dominates reduction	8.58	7.25
Societal	891 (−17,675 to 19,457)	−0.079 (−0.157 to −0.002)	Maintenance dominates reduction	38.28	35.37
ICER, incremental cost-effectiveness ratio.					

Methods

Subjects and sampling

From December 2019 onwards, all participants who were randomised to the Antipsychotic Reduction and Discontinuation strategy were screened for inclusion following their final quantitative data collection visit. Purposive sampling was used to obtain variation in clinical profile, experience of reduction, completion of the antipsychotic reduction protocol and experience of relapse. Participants who successfully reduced or discontinued antipsychotics, those who have not managed to do this and those who reduced or discontinued but had to increase or restart antipsychotics were included.

Procedure

Patients were systematically screened when completing the final follow-up, and potential participants were approached by the research team. Those willing to participate took part in semistructured interviews either face to face or using video or audio communication platforms. Paired interviews were conducted with lived experience researchers for most participants. Timelines charting antipsychotic medication trajectory during the trial were devised to aid researcher and participant recall and were shared with participants prior to the interview. Participants answered questions around experiences of the acute respiratory distress syndrome strategy and impacts on daily life, negative experiences and changes in mental health, the process of reduction and views on support and attitudes to the use of antipsychotics in the future.

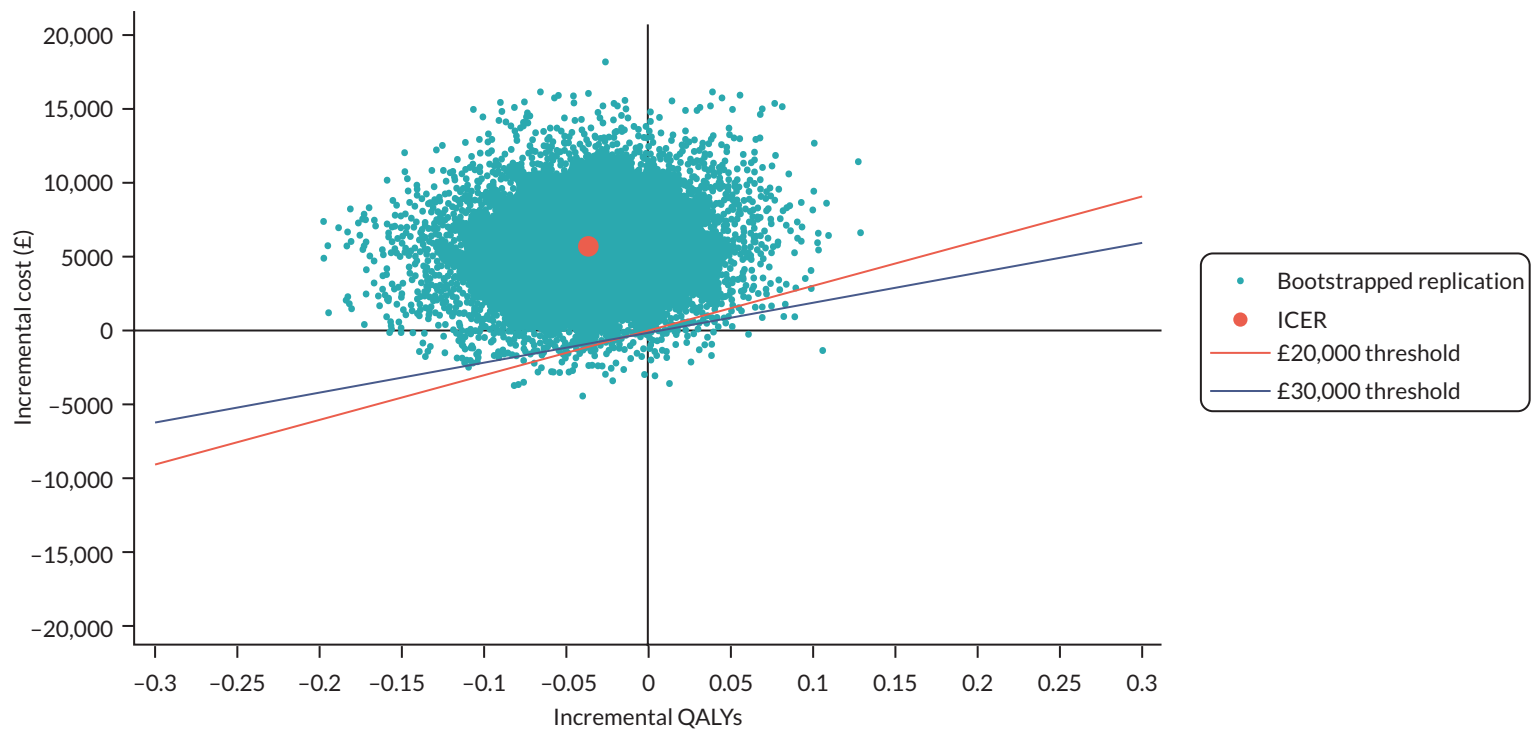


FIGURE 7 Cost-effectiveness acceptability curves for a mental health services' perspective using QALYs. This figure has been reproduced with permission from Bray *et al.*⁵⁸ This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The figure includes minor additions and formatting changes to the original text.

Data analysis

The interview data were analysed using Thematic Analysis conducted within NVivo software (version 12).⁶⁰ A series of meetings between members of the team who collected and analysed these data were held to discuss data, generate an initial coding frame and iteratively refine this. A lived experience researcher who had also conducted interviews contributed to this process by reading four transcripts representative of the variation in experiences and suggesting revisions to the coding frame accordingly.

Results

Between December 2019 and December 2021, 26 people were interviewed. Interviews lasted for 30–90 minutes. [Table 15](#) shows participants' sociodemographic and clinical characteristics and antipsychotic reductions at trial end. Reduction profiles during the trial varied – dose reductions were often followed by increases or periods of stabilisation as negotiated with prescribers (and permitted within the trial protocol). These varying profiles form the context of interview narratives.

Details of the thematic analysis with illustrative quotes are presented in Morant *et al.*⁵⁹ The following themes and subthemes emerged:

- Effects of antipsychotic reduction/discontinuation
- Reduction of negative effects

Most participants ($n = 21$) described reduced adverse effects with dose reductions. Reductions in sedative effects and increased energy levels were most common, alongside cognitive changes, including improvements in concentration, alertness, mental clarity, fluency of speech and reductions in emotional blunting. Some described more specific impacts, including reductions in increased appetite and hypersalivation, and less commonly, improvements in sleep, agitation and anxiety.

- Returning aspects of self and social functioning

Some participants described a broader return of psychological and social aspects of the self that they felt had been suppressed by antipsychotics. This manifested in various ways, including improved self-confidence, more authentic connections with others, better social integration and functioning and a return of creativity or sense of humour. Some experienced a substantial shift in self-identity linked to a forgotten enthusiasm for life and a sense of optimism for a more active and normal future.

- Challenges with emotional intensity

Although reductions in overall numbing or mental clouding brought benefits for many, often the intensity, rawness or 'realness' of emotions as antipsychotic levels reduced were challenging or experienced as a mixed blessing (e.g. 'when you stop taking it you feel too much' P06004). Reducing antipsychotics was described by some as losing an emotional buffer to cushion life stressors or difficult events. Low mood, increased anxiety and strong feelings of anger or regret were described.

- Mental health deteriorations and relapse

Over half of participants described negative impacts of antipsychotic reduction on their mental health, consisting of the return of specific psychotic symptoms, increases in emotional intensity or other symptoms and relapse. Nine people experienced a psychotic relapse (as defined by the trial end-point committee). Five were defined as severe relapses (requiring hospitalisation), four were non-severe (managed in the community). Many described negative impacts of mental health deteriorations on social functioning or family relationships. Often antipsychotic doses were increased, or reductions paused at this point.

TABLE 15 Participant demographic and clinical characteristics, antipsychotic reductions and relapses (N = 26)

Characteristic	N
Primary diagnosis	
Schizophrenia	18
Other psychosis	8
Age (years)	
< 30	3
30–39	3
40–49	11
50–59	6
> 60	3
Ethnicity	
White	20
Black	6
Employment status	
Unemployed	18
Employed	8
Clozapine	
Yes	3
No	23
Antipsychotic polypharmacy	
Yes	6
No	20
Antipsychotic administration	
Oral	19
Depot	7
Mental health service contact (years)	
< 4	3
4–10	8
11–15	3
16–20	4
20 +	8
Change in antipsychotic dose at trial end compared to baseline (CPZ equivalents)^a	
No change or increase	5
Slight reduction	2
Reduction	6
Significant reduction	9
Discontinuation	4

TABLE 15 Participant demographic and clinical characteristics, antipsychotic reductions and relapses (*N* = 26) (*continued*)

Characteristic	<i>N</i>
Relapse during trial^b	
No relapse	17
Non-severe relapse	4
Severe relapse	5

a CPZ = chlorpromazine equivalent; slight reduction = 1–20% CPZ; reduction = 21–50% CPZ; significant reduction = 51–99% CPZ.

b Relapse as defined by RADAR trial expert end-point committee: Severe relapse = requiring acute psychiatric hospitalisation; non-severe relapse = managed by community services.

- Short-term difficulties/withdrawal effects

Some participants described short-term physical or mental effects following dose reductions that resolved after a few weeks, indicative of possible withdrawal effects. These included shakiness, sweating, skin crawling, dizziness, poor sleep, low mood, anxiety, emotional intensity and psychotic-like symptoms, and these were reported most by those who made the largest reductions or discontinued entirely.

- Making sense of reduction experiences: the RADAR trial as a novel potential learning context

Participants made sense of antipsychotic reduction/discontinuation experiences over the 24-month period by weighing up benefits and challenges across the broad domains described above. This was shaped by each person's profile of medication reduction and was embedded within social circumstances, personal priorities, relationships with services and existing beliefs about health, mental health and medication.

- Medication: learning about the implications of reduction

For many participants, experiencing lower medication doses helped them to understand the role, impacts, and value of medication for them personally or ascertain a personally optimum dose. Several thought that, without the trial, their psychiatrist would not have supported this. Some extended these insights into differentiating between medication effects, their illness and their underlying self-concept. A sense of having more options about medication was significant or empowering for some, and many were highly engaged with reduction processes and detailed reflections about dose levels.

Other participants – some of whom valued antipsychotics for symptom management and framed their mental health problems in biomedical terms – found reductions difficult to tolerate as psychotic symptoms returned or increased, but they often appeared less engaged in further reflections.

- Self-management

New perspectives on self-management and the interaction of medication with other support for mental health were also apparent. Here again, there was diversity. Some described their symptoms as unpredictable or appeared to struggle to understand their condition, conveying a passive stance towards their illness and its management. Other interviews featured detailed personal understandings of mental health problems and their management (which sometimes pre-dated trial participation).

- Relationships with clinicians: partnership possibilities

Some participants described interactions with psychiatrists as differing from those they had experienced previously when they had not been offered options to reduce medication. For many, open discussions with prescribers about medication reduction and its impacts had enabled new dynamics that felt more partnership-like, equal or trusting

and were experienced as confidence-building or empowering. Others described few changes and a more traditional care model in which they deferred to clinical expertise. Views about future relationships with clinicians were similarly diverse. Some felt more confident to ask about future medication changes than previously. Most said they would not go against medical advice, although a few expressed wanting to stop medication even if their psychiatrist did not support this.

In summary, the analysis revealed that experiences of antipsychotic reductions over 2 years were dynamic and diverse, shaped by variations in dose reduction profiles, reduction effects, personal motivation and engagement levels and relationships with prescribers. Most participants reported reduced adverse effects of antipsychotics with dose reductions, primarily in mental clouding, emotional blunting and sedation and reported some positive impacts on social functioning and sense of self. Over half experienced deteriorations in mental health, including psychotic symptoms and intolerable levels of emotional intensity. Nine had a psychotic relapse. The trial context in which medication reduction was explicitly part of clinical care provided various learning opportunities. Some participants were highly engaged with reduction processes, and despite difficulties, including relapses, they developed novel perspectives on medication, dose optimisation and how to manage their mental health and experienced medication reduction done with clinical guidance as empowering. Others were more ambivalent about reduction or experienced less overall impact.

Key findings

- Many participants in the dose reduction arm of the trial experienced relief from some adverse effects of antipsychotics.
- Some also experienced negative effects on their mental health with antipsychotic dose reductions, including exacerbation of psychotic symptoms and relapse.
- For some participants, the experience of undertaking antipsychotic reduction with a clinician provided an opportunity to develop a deeper understanding of their condition and its treatment.
- For some participants, the experience of being in the trial enabled them to adopt a more assertive role in management of their mental health condition.

Work package 3c: qualitative evaluation clinicians

Aim

To explore experiences of the antipsychotic reduction strategy and its results from a clinician perspective (for more details, see [Report Supplementary Material 15](#)).

Methods

Subjects and sampling

Clinicians who had been involved in administering the antipsychotic reduction strategy were sampled. Sampling was purposive and aimed to identify clinicians from a range of trusts, both within and outside London, and to include some who had been principal or coinvestigators for the study and some who had not been.

Procedure

A semistructured interview was conducted either in person or on the telephone (according to clinician's preference) using an interview schedule developed by the core team. Questions covered the clinician's experience of implementing the antipsychotic reduction strategy, how it had impacted them and their patients and how it had influenced the nature of their relationships with patients. Interviews were recorded with participants' consent.

Data analysis

The interview data were analysed using Thematic Analysis (Braun and Clarke, 2021)⁶¹ conducted within NVivo software (version 12). Analysis was conducted in an iterative manner, involving meetings and discussions between team members. An initial coding frame was generated and iteratively refined through this process.

Results

Fifteen clinicians were interviewed (for more details, see [Report Supplementary Material 15](#)). All were psychiatrists who had been involved in supporting the treatment of trial participants. The sample comprised 12 men and 3 women. Eleven worked in London-based services and four worked outside London. Twelve worked in CMHTs, and three in assessment teams. For each psychiatrist, between one and eight of their patients were enrolled in the trial. Patients could have been allocated to the antipsychotic reduction arm, the maintenance arm or both.

Seven themes were identified with some themes encompassing several subthemes ([Table 16](#)). Theme 1 covered psychiatrist's views about the RADAR trial. Most felt they had received good support during the trial, but some had concerns about the speed of tapering – either feeling it was too fast or too slow. Some felt that more intensive monitoring of participants by other team members would have been useful. Theme 2 reflected psychiatrists' views of how participants had experienced the trial. Several mentioned that some participants had been highly motivated to reduce their antipsychotics, and some who were randomised to maintenance treatment were disappointed. Some participants in both groups had stopped their medication abruptly without following the planned reduction strategy because of their strong desire to be off medication. Theme 3 related to psychiatrists' view about the impact of implementing the antipsychotic reduction intervention on themselves. They described feeling pleased when participants had done well with the dose reduction, but they were disappointed and concerned when the process had not gone well. In theme 4, clinicians described their views of the effects of the antipsychotic reduction intervention on their patients. They felt that it had been a successful process for some, leading to reductions in side effects and a more positive view of treatment, even for some who experienced relapse (in line with the views expressed in the qualitative analysis of participant views). However, for others, they felt the process had been more challenging. Theme 5 explored the impact of the trial on the doctor–patient relationship. Some psychiatrists felt that the trial had provided an opportunity to develop more collaborative relationships with patients concerning the management of their medication. Theme 6 explored psychiatrists' views about their future practise. Some said their practise would not change and that they had already been committed to finding the minimum effective dose for patients. Some felt that they had become more open to considering reductions of antipsychotic medication. Finally, theme 7 concerned psychiatrists' views of the various barriers to reducing antipsychotics in clinical practise. They mentioned the lack of resources to support and monitor patients, the effects of the fragmentation of services, pressure to discharge patients from mental health services back to primary care and the lack of national guidance.

TABLE 16 Clinician interview analysis: themes

Theme	Subthemes
1. Psychiatrists' views of RADAR trial	1.1 Adequate support 1.2 Speed of reduction
2. Participants' reaction to RADAR trial	2.1 Motivation to reduce 2.2 Abrupt discontinuation
3. Effects of the intervention on psychiatrists	3.1 Positive experiences 3.2 Disappointment 3.3 Stress
4. Effects of the intervention on patients	4.1 Improvements 4.2 Negative experience 4.3 Relapse 4.4 Withdrawal symptoms
5. Psychiatrist–patient relationship	5.1 Building trust and openness around medication 5.2 Sharing power within their clinical encounters
6. Psychiatrists' views around future practice	6.1 Continuing as before 6.2 Being more open to antipsychotic reduction
7. Barriers to reducing medication in mental health services	7.1 Resources and services 7.2 Knowledge and guidance 7.3 Priorities

Key findings

- Psychiatrists welcomed the antipsychotic reduction intervention for the benefits it had for some of their patients, but they expressed concern about its effects on others.
- For some psychiatrists, the trial had provided an opportunity to develop more collaborative ways of working with patients

Limitations related to the method or execution

Recruitment

Achieving recruitment rates in line with the target of 402 was challenged by difficulties in accessing psychiatrists for service user referrals and then with accessing other members of the clinical team through whom contact with potential participants was established. As identified in the focus groups, factors, including understaffing and clinician commitment to antipsychotic treatment, challenged recruitment to the study in some mental health services. Attending and presenting the scientific rationale of the study at clinical team meetings helped to convey evidence for clinical equipoise, foster relationships with staff and provide a forum to discuss the risk reduction strategies employed as part of the study. Despite the success of these strategies in some services, some clinicians nevertheless held negative attitudes towards reduction and discontinuation. Acceptability of randomisation challenged the recruitment of some service users who had a strong preference for either discontinuation or maintenance. For all these reasons, the number recruited was a small proportion of the number screened, which means that the sample may differ from the general population of people who were considered likely to be suitable to take part in a trial of this sort. Unfortunately, reasons for non-participation could not be collected because non-participants had not consented to data collection.

Although the final sample was smaller than the target sample, the power to detect a difference in the primary outcome was maintained because the target sample size was based on power calculations for the outcome of severe relapse. The difference in severe relapse was large enough to be detected with the final sample size even though this was smaller than the target. However, the trial may have been underpowered to detect differences in other secondary outcomes.

A small number of carers and close others raised concerns about the risk of relapse and highlighted the importance of their role in supporting their close others with treatment. In response to this, research procedures were adapted to facilitate the inclusion of carers and close others in service users' decision-making around participation, where this was agreed with the service user. A separate information sheet, oriented towards common carer concerns, was created for this purpose.

Retention

Keeping participants with long-term psychosis and other comorbidities engaged in follow-up for 2 years posed many challenges. Discharge to primary care, pressure to discharge during COVID and other factors added additional burden. Strategies for increasing engagement were developed in discussion with the LEAP and included sending postcards, Christmas cards and regular newsletters with updates on the study. Participants were offered various options for participating in follow-up, including face to face, over the phone or online communication platforms.

Primary outcome

We had planned to use the GSDS, as chosen by Wunderink *et al.*,^{12,13} but this measure required up to 2 days of training and up to an hour to administer. It also focuses primarily on relationships; therefore, it is likely to have a limited ability to detect changes in functioning in a broader sense. After a review of the literature, the SFS was selected, as it has been validated in schizophrenia, has good psychometric properties and has been used in RCTs. There is no evidence that the change in the measure of the primary outcome, which was made before the trial commenced, affected the results.

Definitions of relapse

Defining relapse was challenging. No existing definition of relapse exists, which is both reliable and clinically relevant. Hospitalisation was chosen as the criterion for severe relapse, and a committee blind to participant allocation was

convened to make judgements by consensus on relapse outcomes for all patients who were not hospitalised (see [Report Supplementary Material 9](#) for the committee charter). The committee reviewed summaries of electronic medical records as well as participant's self-report questionnaires on relapse, which were administered during at the main data collection points.

Participant characteristics

The trial sample mostly comprised people with a long history of contact with secondary mental health services, and as such, the results may not be applicable to people with a shorter history or to people who are stable enough to have been discharged to primary care.

Implementation of the randomised treatment strategies

The trial was a naturalistic trial, involving a deliberately flexible intervention. Moreover, participants could change their minds about whether they were prepared to accept their randomised treatment strategy at any point. Therefore, the treatment strategies in the two groups were not rigidly demarcated. Some participants who were randomised to antipsychotic reduction did not make any reductions and some, who were allocated to maintenance treatment, reduced or stopped their medication nevertheless. However, recorded medication use throughout the trial demonstrated that there was a reasonable separation between the groups in terms of their antipsychotic use (see [Table 10](#)).

Qualitative substudies

Despite attempts to recruit participants who reflected the range of experiences of the trial, those with the most negative trial experiences or conflictual relationships with services, are less likely to have consented to take part. Similarly, clinicians who had negative views of the trial objectives and conduct may have been less willing to participate in the qualitative evaluation.

Coronavirus pandemic

In the wake of the spread of the novel coronavirus, national restrictions on movement were imposed in England in March 2020. While recruitment had concluded, both follow-up data collection and intervention delivery were impacted by the restrictions. Provision of care between trusts varied, but some service users had less in-person contact with clinicians during the early pandemic period. Some participants in the supported reduction arm chose to pause the intervention at this stage due to anxieties around receiving remote care, the pandemic and social isolation. The primary outcome was also impacted by national restrictions as most social activities were prohibited or limited, with limitations or closures on community groups and activity centres between March 2020 and July 2021.

Programme conclusions

In the current programme, we found that many people with schizophrenia and related conditions are not content with taking antipsychotics on a long-term basis and would like an opportunity to try and reduce or stop this medication. We designed a trial that compared a gradual process of clinically supported antipsychotic reduction with maintenance treatment. We were able to implement the trial with reasonable fidelity to the randomised interventions, which meant that the groups were clearly differentiated in terms of their dose of antipsychotic medication and likelihood of discontinuation of antipsychotics. However, recruitment was more difficult than predicted, so the originally intended numbers were not achieved.

In our sample, we found that our method of gradual reduction of antipsychotics was not associated with benefits in social functioning at a 24-month follow-up and yet increased the risk of relapse, including severe relapse and admission to hospital. However, the majority of people who reduced their antipsychotics by more than half or discontinued completely did not relapse and there was no impact on other outcomes, including symptoms at 24 months. The fact that social functioning in the reduction group was not worse than that in the maintenance group at follow-up, despite the increased rate of relapse, reflects the fact that these were not measured contemporaneously. It implies that overall, people who relapsed recovered to their previous level of social functioning within 24 months.

The findings provide the first information about the outcome of a gradual process of reduction in people with multiple episodes of psychosis or a diagnosis of schizophrenia. They provide evidence that may enable clinicians and patients to make better informed decisions about whether they want to embark on or continue long-term antipsychotic treatment.

In the qualitative substudy with patients, participants identified the positive and negative effects of antipsychotic reduction. The benefits reported contrast with the quantitative findings, suggesting that quantitative measures, such as the SFS and quality-of-life measures, may average out interesting variations or may not comprehensively reflect participants' perceptions.

Patient and public involvement in the Research into Antipsychotic Discontinuation and Reduction trial Programme

Aim

Patient and public involvement work in RADAR has been central, co-ordinated by the McPin Foundation. The whole study emerged from research and conversations that several coinvestigators had been having over many years with service users and carers concerned about the adverse effects of antipsychotic medication.

Patient and public involvement in RADAR was designed to be embedded across the research programme, providing lived experience expertise in crucial decision-making, as well as a resource to draw upon at key points in the study. It was developed as a layered approach, supported by the four coinvestigators. Crucially, we worked with people with diverse experiences of medication use and discontinuation and from both a service user's and a carer's perspective.

Methods

The PPI was structured as follows:

- There were four PPI coinvestigators all with different expertise: one service user, a carer, an expert in public information, a PPI involvement co-ordinator. They shaped the original application, attended the programme management committee and worked closely with the LEAP. The service user and carer coinvestigators shared the chairing of LEAP meetings.
- We developed a LEAP by recruiting people with direct experience of antipsychotic medication use and discontinuation. The LEAP met twice a year and also supported the RADAR qualitative research programme. Members of the LEAP were also invited to join the end-point committee and to advise on aspects of the study such as interview schedules.
- There were PPI representation on the Data Monitoring and Ethics Committee and PSC committees.

Study results

We recruited eight people to the LEAP. Over the study, 3 LEAP members left and 1 person joined us, leaving 6 at the end plus the 4 PPI coinvestigators (10 members in total). The tasks undertaken by this group varied and we kept an impact log of recommendations against actions taken in practice by the study team to track progress. Examples of key tasks included supporting the selection of trial outcome measures; advice on definitions of relapse; intervention design and set-up, such as conversations about the role of peer support and information to support withdrawal from medication; development of newsletter design and content, including writing articles; creating videos for the RADAR website to support recruitment by providing personal testimony of the importance of the research in enabling patient choice around antipsychotics; speaking at RADAR annual workshops to share findings and maintain momentum in this long study by championing the importance of the research. For the dissemination stage, LEAP members were involved in writing the main paper. One LEAP member was involved in writing the qualitative paper. Another wrote a 'Lived Experience' commentary which was published alongside the two main publications (the trial and the qualitative study). The LEAP also led a two-part pod-cast series featuring four narratives but drawing upon the expertise of eight LEAP members.

Members of the LEAP advised on interview schedules and one member worked as a peer researcher alongside the team, designing the study, carrying out interviews, analysis and writing peer review papers.

Two LEAP members joined the end-point committee that reviewed all research participants who had a 'relapse' during the trial to assess if the incident was a relapse or related to medication withdrawal. This brought lived experience expertise into the conversation alongside clinical perspectives and expertise, as the other members were psychiatrists.

Discussion and conclusions

Lived Experience Advisory Panel involvement assisted with RADAR throughout, from editing materials for the REC to planning dissemination events and writing a lived experience commentary alongside the main trial data peer reviewed paper. The service users and carers all had personal reasons for joining the study as coinvestigators or advisors, keen to learn about the best practice in discontinuation of antipsychotic medication. They had expertise to share, and their lived experiences grew during the study period as some had admissions to hospital or struggles with their medication.

Lived Experience Advisory Panel members also reported that being in a PPI group had significant benefits for individual members, including increased confidence and improved knowledge as well as new supportive friendships.

People opening up and talking about their experience with medication. Gave me confidence to talk about my experience. They were giving me time ahead to help me think what my next step was going to be in my journey. I was getting advice and information that I would not have had if not part of RADAR. We were keeping each other alive. That might sounds dramatic but we need others who can help us, and RADAR group helped me.

From my service user's perspective, participation in research into antipsychotic reduction study and joining a panel of experts by experience has broadened my knowledge.

I have gained much from being part of the RADAR LEAP group, especially hearing about the many problems that others have experienced, particularly with their own attempts at withdrawal. The group bring so much more into the Study, due to their individual lived experience which is shared openly. Helping to make the Videos for the RADAR website gave me insight into the issue of the massive impairment to Quality of Life.

Reflections/critical perspective

What worked well?

We did not formally audit our LEAP members for demographic information, but they were a diverse group in terms of gender, ethnicity and disability. This 10-person group quickly formed a team ethos, and peer support among members emerged particularly during the pandemic (2020–2). A key benefit was learning about medication withdrawal from leading experts and each other. The LEAP invited doctors supporting the programme and key research staff to every LEAP meeting; this led to an exchange of views and information generally as well as specifically about RADAR. LEAP members learnt from each other and that is one reason for stable membership in the LEAP across 6 years. The LEAP also looked for opportunities for service users and carers to take on leadership roles within the parameters of what was possible in RADAR. This included speaking at webinars and planning the user-led podcast project.

In the qualitative study, having a peer researcher in the team was very useful. A peer conducting interviews with service users about their experiences improved rapport in interviews and lead to important insights during data collection and analysis.

What was challenging?

The budget for PPI was small compared to the overall grant, and service user researchers were not employed in substantive positions. Everyone in PPI roles did ad hoc work on the programme. That was clear from the outset and we had transparency throughout on the limitations and opportunities for PPI in RADAR. There were some difficult conversations early on, as most LEAP members wanted to be able to make more substantive contributions and make changes to the research design. It would have been better to have had the LEAP in place prior to the grant application rather than not until after the funding was agreed.

Equality, diversity and inclusion

Language and terminology

As discussed in greater length in the previous section on PPI, patient and public participation and inclusivity was central to this study. The LEAP consisting of individuals from the community with diverse lived experience of antipsychotic medication use and discontinuation. The panel advised and participated in various aspects of the study, including considering the development and dissemination of materials such as newsletters and videos to support recruitment. A shorter brief summary of the RCT participant information sheet was provided to participants alongside the longer version, and researchers were trained to discuss the study using an accessible visual representation (flow chart) of the study design.

Consideration of the disease burden, epidemiology, presentation and outcomes of the population groups and any differences in the application of existing preventative, screening or diagnostic strategies and treatments

Diagnoses of schizophrenia and other psychotic disorders are more common in non-White ethnic groups and people of lower socioeconomic status. However, demographics are not known to have any significant difference in response to treatment. The data were looked at in order to investigate any potential difference between ethnic groups in response to reduction or discontinuing antipsychotic medication.

Generalisability and transferability of evidence

The RADAR trial was designed to be a pragmatic study that could produce results which may be generalisable to mental healthcare settings. No extra resources were used that were not usually present in community mental healthcare settings within the NHS in the UK. The reduction and/or discontinuation of antipsychotics dependent on clinical need and patient preference should be accessible for all. The number of participants recruited represented only a small fraction of those screened, which raises the possibility that the study sample may differ from the broader population initially considered to be suitable for participation in this type of trial.

Participant representation

In line with other research, there was a statistically significant under-representation of patients from a non-White background. While eligibility criteria were designed to be as generalisable as possible, trial recruitment was dependent on referral from psychiatrists. The population area included areas of high ethnic diversity, and the lack of provision of funding for interpreters likely limited the enrolment of non-English speakers, impacting the diversity of the sample. Future study designs should include provision for the use of interpreters to ensure that a more diverse sample is achieved.

Enrolling and retaining diverse participants

All participant materials were reviewed by the LEAP designed to be as accessible and inclusive as possible, with the aim of not discouraging under-represented groups. Adaptations were made to recruitment materials in order to boost accessibility. Advertisements for the trial were placed within community settings. Participants were offered various options for participating in follow-up. LEAP were involved in designing the interview schedule, selecting the trial outcome measures and in the intervention design and set-up. LEAP helped to maintain momentum to keep participants engaged in the study through methods such as speaking at annual workshops, producing videos detailing their personal experiences, sending postcards and Christmas cards and developing a series of podcasts at the dissemination stage.

Participant data

To explore clinical relevance of the trial, a subsample ($n = 69$) of participants who were enrolled in the RCT were compared to the wider population of patients with similar diagnoses receiving treatment in the same service ($n = 3067$) (full details published in Freudenthal *et al.*, 2021).⁶² Comparison of clinical indicators revealed that trial participants were similar to the wider population in terms of number of previous acute admissions and legal detentions. Level of risk was slightly lower for participants, as would be expected, given the eligibility criteria aimed to exclude people who posed high risks.

Data disaggregation was attempted to investigate any differences in response to reduction of antipsychotics in relation to demographics, but unfortunately, numbers were too low for meaningful interpretation for most variables, aside from the sex of participants.

Reflections on the research team and wider involvement

The research team was comprised mainly (though not exclusively) of White, middle-class women and reflected the difficulties in recruiting individuals from diverse socioeconomic and minority ethnic backgrounds to roles in research. There was a range of experience and expertise across the research team, including psychology, psychiatry and research management and administration. Various members of the team had experience of using or supporting family members to access mental health services. Training and development opportunities were provided to junior members of the team to develop their research skills for data collection in WP1a, WP2/3 and WP3. Junior members of the team were supported to present research findings from various WPs from the programme at national conferences.

Regular consultation and involvement from the LEAP ensured that the voice of service users and carers was embedded throughout the programme, with members contributing to research design, recruitment and retention materials, data collection, analysis and dissemination. This is described in more detail elsewhere (see [Work package 1: development and feasibility phase of the Research into Antipsychotic Discontinuation and Reduction trial intervention, feasibility and acceptability of the intervention](#)). LEAP members reflected the diversity of the participant pool in terms of various demographic and clinical indicators, including histories of schizophrenia spectrum disorders, age, gender and ethnicity. Diverse socioeconomic backgrounds were less represented, reflecting established difficulties with diversity in public involvement. Talents and energy of the LEAP group were engaged and developed wherever possible. Members of the LEAP comprised part of the core interviewing team for WP3b and were trained in qualitative interviewing.

Recommendations for future research

1. Long-term follow-up of RADAR trial cohort.
2. Evaluation of more gradual reduction of antipsychotics (over years, rather than months).
3. Evaluation of effects of psychosocial support on outcomes of gradual antipsychotic reduction.
4. Evaluation of outcomes of gradual antipsychotic reduction in clinically stable patients from primary care.
5. Analysis of predictors of relapse within the RADAR trial data.
6. Qualitative exploration of how patients view the risks and benefits of antipsychotic reduction.

Although the current trial had a relatively long follow-up by current standards, this may not have been long enough to mitigate withdrawal-related adverse effects. These would be expected to occur concurrent with and shortly following medication withdrawal, but some evidence suggests that the onset of withdrawal effects may occur later following antidepressants withdrawal and that the risk of relapse may be raised for months after discontinuation of antipsychotics.^{5,63} Moreover, many participants were still in the process of a slow withdrawal at the end of the current trial follow-up, therefore withdrawal-related effects would continue to be relevant. The trial of antipsychotic reduction in first-episode psychosis patients in the Netherlands found an increased rate of relapse in the first 18 months of follow-up in the group randomised to antipsychotic reduction, for example, but by the 7-year follow-up, relapse had equalised with the group randomised to maintenance treatment.^{12,13} A longer-term follow-up is necessary therefore to evaluate the effects of antipsychotic reduction and discontinuation after withdrawal-related adverse effects have dissipated. This has been funded by the NIHR and is currently underway. The results of this will be critical in evaluating the ultimate outcome of antipsychotic reduction and discontinuation.

Future research also needs to evaluate whether more gradual reduction of antipsychotics over years rather than months can reduce the increased risk of relapse that we identified. Recent evidence suggests that psychiatric medication that has been used for long periods, including antipsychotics, needs to be reduced more slowly than was previously appreciated.³⁹ Further research is also merited into whether the addition of specific psychosocial support would reduce the increased risk of relapse. This was not done in the current programme partly because of the cost implications and partly in order to ensure that the intervention strategies were easily generalisable within usual clinical care. Research

with a more stable clinical population is also merited, such as that might be located in primary care. Being drawn from secondary care, the sample population had severe and ongoing mental instability, which may influence the outcome of antipsychotic reduction.

Further analysis of the RADAR trial data would be useful to explore whether there is a relationship between relapse and social functioning and other outcome measures across groups. Analysis of whether it is possible to predict who is likely to relapse following antipsychotic reduction or discontinuation, would also be useful, and whether characteristics of dose reduction, such as the rate and amount of reduction, influence outcomes. The extent to which baseline treatment characteristics, such as the use of clozapine or depot preparations, influenced outcomes, including relapse, will also be evaluated.

Research to explore how patients interpret the trial findings and how they value particular risks and benefits would be useful and could be explored using qualitative methods or health economic strategies such as discrete choice experiments.

Further research will benefit from the robust process for the assessment of relapse in people with schizophrenia and long-term psychotic conditions that were developed during the programme.

Implications for practice and lessons learnt

The RADAR programme was conducted to provide people with schizophrenia and long-term psychosis with more treatment options and better information about those options. It was important to do due to the increasing evidence of harmful effects of long-term antipsychotic treatment and due to the recognition of the importance of patient choice and quality of life. The study provides data that can inform discussions about antipsychotic use between patients and their doctors, which helps to address the desire expressed by patients to try to reduce long-term medication. Patients can be informed that a moderately gradual reduction increases risk of relapse, including severe relapse requiring inpatient admission. Social functioning is not improved at 2 years, and symptoms, adverse effects and neuropsychological functioning are not affected. Relapse is not inevitable, however. Patients can weigh up this information on the pros and cons of antipsychotic reduction with their doctors, which will facilitate shared decision-making and empower patients.

The qualitative research suggested that patients themselves experience both positive and negative effects when they reduce or discontinue antipsychotic medication. Clinicians similarly welcomed the process of antipsychotic reduction for the benefits it had for some patients, but they expressed concerns about its effects on others.

Additional information

CRediT contribution statement

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Lived Experience Advisory Group members

Karl Willetts, Jonny Benjamin, Sandra Jayacodi and Martina Pavlikova.

Programme Steering Committee members

Tom Craig, Lex Wunderink, Nils Mulder, Richard Emsley and Maurice Arbuthnot.

Independent Data Safety Monitoring Board

Victoria Cornelius, Derek Tracey, Fiona Gaughran and Prisha Shah.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.

Data-sharing statement

Deidentified participant data and a data dictionary will be made publicly available after publication through University College London's data repository (www.ucl.ac.uk/library/open-science-research-support/research-data-management/ucl-research-data-repository) according to NIHR policy. All data requests should be submitted to the corresponding author for consideration.

Ethics statement

The recruitment study (WP1a) and focus group study included in WP1b were approved by the East of Scotland Research Ethics Service (REC reference: 15/ES/0163) on 24 September 2015.

The trial and qualitative substudies (WP2 and WP3) received ethical approval from Brent Research Ethics Committee on 27 October 2016 (reference is 16/LO/1507). It was registered with the International Standard Randomised Controlled Trials register on 7 February 2017 (registration number: ISRCTN90298520) and with ClinicalTrials.gov on 18 June 2018.

Work package	Ethics committee	Reference
WP1a	East of Scotland Research Ethics Service	15/ES/0163
WP1b (Focus group study)	East of Scotland Research Ethics Service	15/ES/0163
WP2	Brent Research Ethics Committee	16/LO/1507
WP3a	Brent Research Ethics Committee	16/LO/1507
WP3b	Brent Research Ethics Committee	16/LO/1507
WP3c	Brent Research Ethics Committee	16/LO/1507

Information governance statement

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at <https://doi.org/10.3310/GJJM0506>.

Primary conflicts of interest: Joanna Moncrieff has grants from NIHR (NIHR203294; RP-PG-1214-20004) and is a co-applicant on grants from the Medical Research Future Fund (MRFF) in Australia. She receives royalties from six books about psychiatric drugs; she has received lecture fees from Alberta Psychiatric Association, British Psychological Association, Universite de Sherbrooke, Case Western Reserve University and University of Basel. She is cochair person of the Critical Psychiatry Network and a board member of the Council for Evidence-based Psychiatry (both unpaid roles). Stefan Priebe has grants from NIHR (NIHR203294; NIHR 201680; NIHR 201707) and was a member of the HTA MPOH panel from 1 January 2014 to 31 May 2018. Thomas Barnes is joint head of the Prescribing Observatory for Mental Health, Royal College of Psychiatrists. Ruth Cooper has undertaken paid consultancy work for the All Party Parliamentary Group for Prescribed Drug Dependence, is a member of the Advisory Board for the PARTANE Study (Participatory Design of a Systematic Review on Tapering Neuroleptics in People with Schizophrenia-related disorders) (a paid role) and is an unpaid Board Member of the International Institute for Psychiatric Drug Withdrawal (IIPDW). Nick Freemantle has grants from NIHR (CTU-56), Medical Research Council, Cure Parkinson's Trust and the EU. He has received consulting fees from ALK, Sanofi Avantis, Gedeo Richter, Abbott, Galderma, Astra Zeneca, Ipsen, Vertex, Thea, Novo Nordisk, Aimmune, speaker fees from Abbott Singapore and had been paid to sit on a data safety monitoring or advisory board by Orion. Mark Horowitz is co-applicant on grants from the Medical Research Future Fund (MRFF) in Australia; he has received consulting fees from Outro Health, a digital clinic aimed to support people to stop unnecessary antidepressants, lecture fees from NHS Trusts for grand rounds presentations, Salomon's University and University of Washington. He sits on the DSMB of the RELEASE trial in Australia and is a cofounder of

Outro Health. He is a member of the Critical Psychiatry Network and is an associate of the International Institute of Psychiatric Drug Withdrawal (both unpaid roles). Sonia Johnson has grants from NIHR (PR-PRU-0916-22003; RP-PG-0615-20021; NIHR206807) and UKRI. She is chair of programme advisory committees for two studies funded through NIHR Programme Grants and has acted as a paid reviewer of grant applications for programmes on social interventions for Austrian foundation – Wiener Wissenschafts-, Forschungs- und Technologiefonds (WWTF) | Vienna Science and Technology Fund. Glyn Lewis has grants from NIHR (NIHR134074; NIHR153131; RP-PG-1214-20004) and is chair of an NIHR funded trial steering committee. All other authors declare no competing interests.

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Publications

Cooper RE, Hanratty É, Morant N, Moncrieff J. Mental health professionals' views and experiences of antipsychotic reduction and discontinuation. *PLOS ONE* 2019;**14**:e0218711. <https://doi.org/10.1371/journal.pone.0218711>

Moncrieff J, Lewis G, Freemantle N, Johnson S, Barnes TRE, Morant N, *et al.* Randomised controlled trial of gradual antipsychotic reduction and discontinuation in people with schizophrenia and related disorders: the RADAR trial (Research into Antipsychotic Discontinuation and Reduction). *BMJ Open* 2019;**9**:e030912. <https://doi.org/10.1136/bmjopen-2019-030912>

Moncrieff J, Crellin NE, Long MA, Cooper RE, Stockmann T. Definitions of relapse in trials comparing antipsychotic maintenance with discontinuation or reduction for schizophrenia spectrum disorders: a systematic review. *Schizophr Res* 2020;**225**:47–54. <https://doi.org/10.1016/j.schres.2019.08.035>

Freudenthal R, Marston L, Stansfeld JL, Priebe S, Moncrieff J. How do participants in clinical trials compare with other patients with schizophrenia? *Contemp Clin Trials Commun* 2021;**22**:100803. <https://doi.org/10.1016/j.conctc.2021.100803>

Crellin NE, Priebe S, Morant N, Lewis G, Freemantle N, Johnson S, *et al.* An analysis of views about supported reduction or discontinuation of antipsychotic treatment among people with schizophrenia and other psychotic disorders. *BMC Psychiatry* 2022;**22**:185. <https://doi.org/10.1186/s12888-022-03822-5>

Ramsay G, Haime Z, Crellin NE, Stansfeld JL, Priebe S, Long M, Moncrieff J. Recruitment to a trial of antipsychotic reduction: impact of an acceptability study. *BMC Med Res Methodol* 2023;**23**:78. <https://doi.org/10.1186/s12874-023-01881-0>

Moncrieff J, Crellin N, Stansfeld J, Cooper R, Marston L, Freemantle N, *et al.* Randomised controlled trial of antipsychotic dose reduction and discontinuation versus maintenance treatment in people with schizophrenia and other recurrent psychotic disorders in England (the RADAR trial). *Lancet Psychiatry* 2023;**10**:848–59. [https://doi.org/10.1016/S2215-0366\(23\)00258-4](https://doi.org/10.1016/S2215-0366(23)00258-4)

Morant N, Long M, Jayacodi S, Cooper R, Akther-Robertson J, Stansfeld J, *et al.* Experiences of reduction and discontinuation of antipsychotics: a qualitative investigation within the 'RADAR' trial. *eClinicalMedicine* 2023;**64**:102135. <https://doi.org/10.1016/j.eclinm.2023.102135>

Bray G, Moncrieff J, Priebe S, Marston L, Lewis G, Haynes N, *et al.* Cost-utility analysis of antipsychotic discontinuation and reduction in patients with long-term schizophrenia and psychosis in English Mental Health Trusts: the RADAR Study. *Value Health* 2025;**28**:358–67. <https://doi.org/10.1016/j.jval.2024.07.017>

References

1. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev* 2008;**30**:67–76. <https://doi.org/10.1093/epirev/mxn001>
2. McCrone P, Dhanasiri S, Patel A, Knapp M, Lawton-Smith S. *Paying the Price: The Cost of Mental Health Care in England to 2026*. London: King's Fund; 2008.
3. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, *et al*. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Focus (Am Psychiatr Publ)* 2020;**18**:443–55. <https://doi.org/10.1176/appi.focus.18306>
4. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, Davis JM. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012;**379**:2063–71. [https://doi.org/10.1016/S0140-6736\(12\)60239-6](https://doi.org/10.1016/S0140-6736(12)60239-6)
5. Baldessarini RJ, Tondo L. Effects of treatment discontinuation in clinical psychopharmacology. *Psychother Psychosom* 2019;**88**:65–70. <https://doi.org/10.1159/000497334>
6. Moncrieff J. Antipsychotic maintenance treatment: time to rethink? *PLOS Med* 2015;**12**:e1001861. <https://doi.org/10.1371/journal.pmed.1001861>
7. Harrow M, Jobe TH, Faull RN. Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study. *Psychol Med* 2012;**42**:2145–55. <https://doi.org/10.1017/S0033291712000220>
8. Wils RS, Gotfredsen DR, Hjorthoj C, Austin SF, Albert N, Secher RG, *et al*. Antipsychotic medication and remission of psychotic symptoms 10 years after a first-episode psychosis. *Schizophr Res* 2017;**182**:42–8. <https://doi.org/10.1016/j.schres.2016.10.030>
9. Moilanen JM, Haapea M, Jääskeläinen E, Veijola JM, Isohanni MK, Koponen HJ, Miettunen J. Long-term antipsychotic use and its association with outcomes in schizophrenia: the Northern Finland birth cohort 1966. *Eur Psychiatry* 2016;**36**:7–14. <https://doi.org/10.1016/j.eurpsy.2016.03.002>
10. Tiihonen J, Tanskanen A, Taipale H. 20-year nationwide follow-up study on discontinuation of antipsychotic treatment in first-episode schizophrenia. *Am J Psychiatry* 2018;**175**:765–73. <https://doi.org/10.1176/appi.ajp.2018.17091001>
11. Ran MS, Weng X, Chan CL, Chen EY, Tang CP, Lin FR, *et al*. Different outcomes of never-treated and treated patients with schizophrenia: 14-year follow-up study in rural China. *Br J Psychiatry* 2015;**207**:495–500. <https://doi.org/10.1192/bjp.bp.114.157685>
12. Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *J Clin Psychiatry* 2007;**68**:654–61. <https://doi.org/10.4088/jcp.v68n0502>
13. Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry* 2013;**70**:913–20. <https://doi.org/10.1001/jamapsychiatry.2013.19>
14. Hui CLM, Honer WG, Lee EHM, Chang WC, Chan SKW, Chen ESM, *et al*. Long-term effects of discontinuation from antipsychotic maintenance following first-episode schizophrenia and related disorders: a 10 year follow-up of a randomised, double-blind trial. *Lancet Psychiatry* 2018;**5**:432–42. [https://doi.org/10.1016/S2215-0366\(18\)30090-7](https://doi.org/10.1016/S2215-0366(18)30090-7)

15. Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. *Arch Gen Psychiatry* 2007;**64**:242–9. <https://doi.org/10.1001/archpsyc.64.2.242>
16. Yood MU, DeLorenze G, Quesenberry CP Jr, Oliveria SA, Tsai AL, Willey VJ, *et al.* The incidence of diabetes in atypical antipsychotic users differs according to agent: results from a multisite epidemiologic study. *Pharmacoepidemiol Drug Saf* 2009;**18**:791–9. <https://doi.org/10.1002/pds.1781>
17. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. *Curr Opin Psychiatry* 2008;**21**:151–6. <https://doi.org/10.1097/YCO.0b013e3282f531>
18. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev* 2013;**37**:1680–91. <https://doi.org/10.1016/j.neubiorev.2013.06.001>
19. Hatano M, Kamei H, Kato A, Takeuchi I, Hanya M, Uno J, *et al.* Assessment of the latent adverse events of antipsychotic treatment using a subjective questionnaire in Japanese patients with schizophrenia. *Clin Psychopharmacol Neurosci* 2017;**15**:132–7. <https://doi.org/10.9758/cpn.2017.15.2.132>
20. Moncrieff J, Cohen D, Mason JP. The subjective experience of taking antipsychotic medication: a content analysis of Internet data. *Acta Psychiatr Scand* 2009;**120**:102–11. <https://doi.org/10.1111/j.1600-0447.2009.01356.x>
21. Murray RM, Quattrone D, Natesan S, van Os J, Nordentoft M, Howes O, *et al.* Should psychiatrists be more cautious about the long-term use of antipsychotics? *Br J Psychiatry* 2016;**209**:361–5. <https://doi.org/10.1192/bjp.bp.116.182683>
22. Begemann MJH, Thompson IA, Veling W, Gangadin SS, Geraets CNW, van 't Hag E, *et al.* To continue or not to continue? Antipsychotic medication maintenance versus dose-reduction/discontinuation in first episode psychosis: HAMLETT, a pragmatic multicenter single-blind randomized controlled trial. *Trials* 2020;**21**:147. <https://doi.org/10.1186/s13063-019-3822-5>
23. Crellin NE, Priebe S, Morant N, Lewis G, Freemantle N, Johnson S, *et al.* An analysis of views about supported reduction or discontinuation of antipsychotic treatment among people with schizophrenia and other psychotic disorders. *BMC Psychiatry* 2022;**22**:185. <https://doi.org/10.1186/s12888-022-03822-5>
24. Birchwood M, Smith J, Cochrane R, Wetton S, Copestake S. The Social Functioning Scale: The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *Br J Psychiatr* 1990;**157**:853–9. <https://doi.org/10.1192/bjp.157.6.853>
25. Priebe S, Watzke S, Hansson L, Burns T. Objective social outcomes index (SIX): a method to summarise objective indicators of social outcomes in mental health care. *Acta Psychiatr Scand* 2008;**118**:57–63. <https://doi.org/10.1111/j.1600-0447.2008.01217.x>
26. Priebe S, Huxley P, Knight S, Evans S. Application and results of the Manchester Short Assessment of Quality of Life (MANSA). *Int J Soc Psychiatry* 1999;**45**:7–12. <https://doi.org/10.1177/002076409904500102>
27. Ramsay G, Haime Z, Crellin NE, Stansfeld JL, Priebe S, Long M, Moncrieff J. Recruitment to a trial of antipsychotic reduction: impact of an acceptability study. *BMC Med Res Methodol* 2023;**23**:78. <https://doi.org/10.1186/s12874-023-01881-0>
28. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res* 2005;**15**:1277–88. <https://doi.org/10.1177/1049732305276687>
29. Cooper RE, Hanratty E, Morant N, Moncrieff J. Mental health professionals' views and experiences of antipsychotic reduction and discontinuation. *PLOS ONE* 2019;**14**:e0218711. <https://doi.org/10.1371/journal.pone.0218711>
30. Moncrieff J, Crellin NE, Long MA, Cooper RE, Stockmann T. Definitions of relapse in trials comparing antipsychotic maintenance with discontinuation or reduction for schizophrenia spectrum disorders: a systematic review. *Schizophr Res* 2020;**225**:47–54. <https://doi.org/10.1016/j.schres.2019.08.035>

31. Burns T, Fiander M, Audini B. A Delphi approach to characterising 'relapse' as used in UK clinical practice. *Int J Soc Psychiatry* 2000;**46**:220–30. <https://doi.org/10.1177/002076400004600308>
32. San L, Serrano M, Canas F, Romero SL, Sánchez-Cabezudo A, Villar M. Towards a pragmatic and operational definition of relapse in schizophrenia: a Delphi consensus approach. *Int J Psychiatry Clin Pract* 2015;**19**:90–8. <https://doi.org/10.3109/13651501.2014.1002501>
33. Hall W. *Harm Reduction Guide to Coming Off Psychiatric Drugs and Withdrawal*. 2nd edn. New York: The Icarus Project and Freedom Centre; 2013.
34. Ashton H. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiatry* 2005;**18**:249–55. <https://doi.org/10.1097/01.yco.0000165594.60434.84>
35. Cardno AG, Jones LA, Murphy KC, Asherson P, Scott LC, Williams J, et al. Factor analysis of schizophrenic symptoms using the OPCRIT checklist. *Schizophr Res* 1996;**22**:233–9. [https://doi.org/10.1016/s0920-9964\(96\)00060-6](https://doi.org/10.1016/s0920-9964(96)00060-6)
36. Williams J, Farmer AE, Ackenheil M, Kaufmann CA, McGuffin P. A multicentre inter-rater reliability study using the OPCRIT computerized diagnostic system. *Psychol Med* 1996;**26**:775–83. <https://doi.org/10.1017/s003329170003779x>
37. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia: a controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry* 1991;**48**:739–45. <https://doi.org/10.1001/archpsyc.1991.01810320063009>
38. Oosthuizen P, Emsley RA, Turner J, Keyter N. Determining the optimal dose of haloperidol in first-episode psychosis. *J Psychopharmacol* 2001;**15**:251–5. <https://doi.org/10.1177/026988110101500403>
39. Horowitz MA, Jauhar S, Natesan S, Murray RM, Taylor D. A Method for tapering antipsychotic treatment that may minimize the risk of relapse. *Schizophr Bull* 2021;**47**:1116–29. <https://doi.org/10.1093/schbul/sbab017>
40. Bebbington PE, Craig T, Garety P, Fowler D, Dunn G, Colbert S, et al. Remission and relapse in psychosis: operational definitions based on case-note data. *Psychol Med* 2006;**36**:1551–62. <https://doi.org/10.1017/S0033291706008579>
41. McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, Manber R. The Arizona Sexual Experience Scale (ASEX): reliability and validity. *J Sex Marital Ther* 2000;**26**:25–40. <https://doi.org/10.1080/009262300278623>
42. Neil ST, Kilbride M, Pitt L, Nothard S, Welford M, Sellwood W, Morrison AP. The questionnaire about the process of recovery (QPR): a measurement tool developed in collaboration with service users. *Psychosis* 2009;**1**:145–55. <https://doi.org/10.1080/17522430902913450>
43. Waddell L, Taylor M. A new self-rating scale for detecting atypical or second-generation antipsychotic side effects. *J Psychopharmacol* 2008;**22**:238–43. <https://doi.org/10.1177/0269881107087976>
44. Moncrieff J, Lewis G, Freemantle N, Johnson S, Barnes TRE, Morant N, et al. Randomised controlled trial of gradual antipsychotic reduction and discontinuation in people with schizophrenia and related disorders: the RADAR trial (Research into Antipsychotic Discontinuation and Reduction). *BMJ Open* 2019;**9**:e030912. <https://doi.org/10.1136/bmjopen-2019-030912>
45. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;**13**:261–76. <https://doi.org/10.1093/schbul/13.2.261>
46. Atkisson CC, Zwick R. The Client Satisfaction Questionnaire: psychometric properties and correlations with service utilisation and psychotherapy outcome. *Eval Program Plann* 1982;**5**:233–37. [https://doi.org/10.1016/0149-7189\(82\)90074-x](https://doi.org/10.1016/0149-7189(82)90074-x)
47. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;**20**:1727–36. <https://doi.org/10.1007/s11136-011-9903-x>

48. Al-Janabi H, Flynn TN, Coast J. Development of a self-report measure of capability wellbeing for adults: the ICECAP-A. *Qual Life Res* 2012;**21**:167–76. <https://doi.org/10.1007/s11136-011-9927-2>
49. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics* 1993;**4**:353–65. <https://doi.org/10.2165/00019053-199304050-00006>
50. Slupczynska-Kossobudzka E, Boguszezewska L. Effects of community mobile team intervention in the Drewnica Hospital catchment area: 1 – patient outcome. *Int J Soc Psychiatry* 1999;**45**:207–15. <https://doi.org/10.1177/002076409904500308>
51. Hernández-Alava M, Pudney S. EQ5Dmap: a command for mapping between EQ-5D-3L and EQ-5D-5L. *Stata J* 2018;**18**:395–415. <https://doi.org/10.1177/1536867X1801800207>
52. National Institute for Health and Care Excellence. *Economic Evaluation. NICE Health Technology Evaluations: The Manual*. London: NICE; 2022.
53. Flynn TN, Huynh E, Peters TJ, Al-Janabi H, Clemens S, Moody A, Coast J. Scoring the ICECAP-A capability instrument: estimation of a UK general population tariff. *Health Econ* 2015;**24**:258–69. <https://doi.org/10.1002/hec.3014>
54. NHS Improvement. *NHS Reference Costs*. London: NHS England; 2023.
55. Joint Formulary Committee. *British National Formulary*. London: BMJ Group and Pharmaceutical Press; 2023.
56. Curtis L, Burns A. *Unit Costs of Health and Social Care 2020*. London: Personal Social Service Research Unit; 2020.
57. Moncrieff J, Crellin N, Stansfeld J, Cooper R, Marston L, Freemantle N, *et al*. Randomised controlled trial of antipsychotic dose reduction and discontinuation versus maintenance treatment in people with schizophrenia and other recurrent psychotic disorders in England (the RADAR trial). *Lancet Psychiatry* 2023;**10**:848–59. [https://doi.org/10.1016/S2215-0366\(23\)00258-4](https://doi.org/10.1016/S2215-0366(23)00258-4)
58. Bray G, Moncrieff J, Priebe S, Marston L, Lewis G, Haynes N, *et al*. Cost-utility analysis of antipsychotic reduction and discontinuation in patients with long-term schizophrenia and psychosis in English mental health trusts: the RADAR study. *Value Health* 2025;**28**:358–67. <https://doi.org/10.1016/j.jval.2024.07.017>
59. Morant N, Long M, Jayacodi S, Cooper R, Akther-Robertson J, Stansfeld J, *et al*. Experiences of reduction and discontinuation of antipsychotics: a qualitative investigation within the 'RADAR' trial. *eClinicalMedicine* 2023;**64**:102135. <https://doi.org/10.1016/j.eclinm.2023.102135>
60. Braun V, Clark V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;**3**:77–101. <https://doi.org/10.1191/1478088706qp063oa>
61. Braun V, Clarke V. *Thematic analysis: a practical guide*. London: Sage; 2021.
62. Freudenthal R, Marston L, Stansfeld JL, Priebe S, Moncrieff J. How do participants in clinical trials compare with other patients with schizophrenia? *Contemp Clin Trials Commun* 2021;**22**:100803. <https://doi.org/10.1016/j.conctc.2021.100803>
63. Stockmann T, Odegaro D, Timimi S, Moncrieff J. SSRI and SNRI withdrawal symptoms reported on an internet forum. *Int J Risk Saf Med* 2018;**29**:175–80. <https://doi.org/10.3233/JRS-180018>

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