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# Antipsychotic medication versus psychological intervention versus a combination of both in adolescents with first-episode psychosis (MAPS): a multicentre, three-arm, randomised controlled pilot and feasibility study



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See [Comment](#) page 726

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## Summary

**Background** Evidence for the effectiveness of treatments in early-onset psychosis is sparse. Current guidance for the treatment of early-onset psychosis is mostly extrapolated from trials in adult populations. The UK National Institute for Health and Care Excellence has recommended evaluation of the clinical effectiveness and cost-effectiveness of antipsychotic drugs versus psychological intervention (cognitive behavioural therapy [CBT] and family intervention) versus the combination of these treatments for early-onset psychosis. The aim of this study was to establish the feasibility of a randomised controlled trial of antipsychotic monotherapy, psychological intervention monotherapy, and antipsychotics plus psychological intervention in adolescents with first-episode psychosis.

**Methods** We did a multicentre pilot and feasibility trial according to a randomised, single-blind, three-arm, controlled design. We recruited participants from seven UK National Health Service Trust sites. Participants were aged 14–18 years; help-seeking; had presented with first-episode psychosis in the past year; were under the care of a psychiatrist; were showing current psychotic symptoms; and met ICD-10 criteria for schizophrenia, schizoaffective disorder, or delusional disorder, or met the entry criteria for an early intervention for psychosis service. Participants were assigned (1:1:1) to antipsychotics, psychological intervention (CBT with optional family intervention), or antipsychotics plus psychological intervention. Randomisation was via a web-based randomisation system, with permuted blocks of random size, stratified by centre and family contact. CBT incorporated up to 26 sessions over 6 months plus up to four booster sessions, and family intervention incorporated up to six sessions over 6 months. Choice and dose of antipsychotic were at the discretion of the treating consultant psychiatrist. Participants were followed up for a maximum of 12 months. The primary outcome was feasibility (ie, data on trial referral and recruitment, session attendance or medication adherence, retention, and treatment acceptability) and the proposed primary efficacy outcome was total score on the Positive and Negative Syndrome Scale (PANSS) at 6 months. Primary outcomes were analysed by intention to treat. Safety outcomes were reported according to as-treated status, for all patients who had received at least one session of CBT or family intervention, or at least one dose of antipsychotics. The study was prospectively registered with ISRCTN, ISRCTN80567433.

**Findings** Of 101 patients referred to the study, 61 patients (mean age 16.3 years [SD 1.3]) were recruited from April 10, 2017, to Oct 31, 2018, 18 of whom were randomly assigned to psychological intervention, 22 to antipsychotics, and 21 to antipsychotics plus psychological intervention. The trial recruitment rate was 68% of our target sample size of 90 participants. The study had a low referral to recruitment ratio (around 2:1), a high rate of retention (51 [84%] participants retained at the 6-month primary endpoint), a high rate of adherence to psychological intervention (defined as six or more sessions of CBT; in 32 [82%] of 39 participants in the monotherapy and combined groups), and a moderate rate of adherence to antipsychotic medication (defined as at least 6 consecutive weeks of exposure to antipsychotics; in 28 [65%] of 43 participants in the monotherapy and combined groups). Mean scores for PANSS total at the 6-month primary endpoint were 68.6 (SD 17.3) for antipsychotic monotherapy (6.2 points lower than at randomisation), 59.8 (13.7) for psychological intervention (13.1 points lower than at randomisation), and 62.0 (15.9) for antipsychotics plus psychological intervention (13.9 points lower than at randomisation). A good clinical response at 6 months (defined as  $\geq 50\%$  improvement in PANSS total score) was achieved in four (22%) of 18 patients receiving antipsychotic monotherapy, five (31%) of 16 receiving psychological intervention, and five (29%) of 17 receiving antipsychotics plus psychological intervention. In as-treated groups, serious adverse events occurred in eight [35%] of 23 patients in the combined group, two [13%] of 15 in the antipsychotics group, four [24%] of 17 in the psychological intervention group, and four [80%] of five who did not receive any treatment. No serious adverse events were considered to be related to participation in the trial.

**Interpretation** This trial is the first to show that a head-to-head clinical trial comparing psychological intervention, antipsychotics, and their combination is safe in young people with first-episode psychosis. However, the feasibility of

a larger trial is unclear because of site-specific recruitment challenges, and amendments to trial design would be needed for an adequately powered clinical and cost-effectiveness trial that provides robust evidence.

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## Introduction

Early-onset psychosis refers to the development of a first episode of psychosis before the age of 18 years, with estimates in the UK suggesting an incidence rate of 5.9 per 100 000 people.<sup>1</sup> Adolescence is a period of substantial change in biological, social, and psychological development, and those with early-onset psychosis face additional challenges. Compared with psychosis in adults, the long-term prognosis of early-onset psychosis can be poor, particularly in relation to functional outcomes, worse overall outcomes, and greater numbers of hospitalisations and relapses.<sup>2</sup> The risk of poor long-term outcomes appears to be increased by premorbid difficulties, a long duration of untreated psychosis, and severe symptoms at baseline assessment.<sup>3</sup> The risk of suicidal behaviour has been shown to be greater in young

people with psychosis than in those with other mental health problems.<sup>4</sup> In addition to personal costs, early-onset psychosis also accounts for a considerable proportion of inpatient admissions and economic costs.<sup>5</sup>

In 2015, a systematic literature review indicated that for young people with psychosis the mainstay of treatment is antipsychotic drugs.<sup>6</sup> However, the evidence base for the effectiveness of antipsychotics in early-onset psychosis is sparse compared with in adult psychosis. Although a previous meta-analysis indicated that antipsychotics have a small but significant benefit over placebo treatment on total, positive, and negative symptoms (Positive and Negative Syndrome Scale [PANSS]), social functioning, and a significant effect on improvement in global state (Clinical Global Impression Scale), this evidence comes from a small number of

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## Research in context

### Evidence before this study

We searched PubMed for articles published from database inception up to Dec 10, 2019, with the terms "schizophrenia", "psychosis", "psychological therapy", "psychosocial intervention", "CBT", "family intervention", "antipsychotic", "neuroleptic", "child\*", "adolescent", "young person", and "first episode psychosis", without language restrictions. One systematic review identified seven placebo-controlled trials of antipsychotic medication for young people with psychosis (aged <18 years), and the subsequent meta-analysis indicated small but significant effects of antipsychotics on psychotic symptoms and a moderate and significant adverse effect on weight gain. We identified no trials of psychological intervention in a population strictly younger than 18 years. A systematic review and network meta-analysis of antipsychotics identified 28 randomised controlled trials (RCTs) of antipsychotics for children or adolescents (aged 7–18 years) with psychosis. Results of the pairwise meta-analyses indicated a benefit of a number of antipsychotics over placebo treatment for overall psychotic symptoms, and the network meta-analysis indicated that clozapine was superior to all other antipsychotics for total, positive, and negative symptoms. However, network meta-analysis relies on the use of indirect as well as direct evidence, and, with regard to clozapine, only two studies were available that directly compared clozapine to another antipsychotic. Since publication of these systematic reviews, two further trials of antipsychotics and one feasibility RCT of psychological intervention in young populations (<18 years) have been published. No head-to-head trials have compared

the clinical or cost-effectiveness of pharmacological, psychological, and combined pharmacological and psychological treatment in adolescents with psychosis.

### Added value of this study

The present trial showed that a methodologically rigorous clinical trial that randomly assigns young people with psychosis to psychological treatment, pharmacological treatment, or their combination, is possible. Our study suggests that antipsychotic medication, psychological intervention (cognitive behavioural therapy plus family intervention), and a combination of the two are acceptable, safe, and helpful treatments for young people with first-episode psychosis, with all three treatments seeming to provide benefit in terms of symptoms (Positive and Negative Syndrome Scale total score) and recovery (Questionnaire about the Process of Recovery total). No findings suggested that psychological interventions in the absence of antipsychotic medication were detrimental.

### Implications of all the available evidence

An adequately powered efficacy and effectiveness trial is now required. Such a trial could test hypotheses regarding superiority (eg, combined treatment being superior to monotherapies for effectiveness) and non-inferiority (eg, between monotherapies). Our preliminary findings appear consistent with current UK National Institute for Health and Care Excellence guidelines (CG155) that recommend informed choices and shared decision making regarding treatment options for early-onset psychosis on the basis of cost-benefit profiles.

For the **trial protocol** see <https://www.journalslibrary.nihr.ac.uk/programmes/hta/153104/#>  
See Online for appendix

low-quality studies and the placebo groups also showed improvement, on average, to a clinically significant extent in psychiatric symptoms.<sup>6</sup> Additionally, concern has been expressed over the increased risk of adverse metabolic side-effects of antipsychotics in young people, with weight gain being particularly problematic.<sup>7,8</sup>

With regard to psychological interventions for psychosis, a systematic review of the literature found no studies of either cognitive behavioural therapy (CBT) or family intervention in people younger than 18 years.<sup>6</sup> Eight low-quality studies of CBT and family intervention in people younger than 25 years showed a small but significant effect of combination therapy with CBT and family intervention on the number of days to relapse.<sup>6</sup> Since 2015, when Stafford and colleagues<sup>6</sup> did their systematic review search, one small ( $n=30$ ), non-randomised feasibility study of CBT versus family intervention versus treatment as usual has been done in a psychosis population younger than 18 years, which showed the feasibility of recruiting people with early-onset psychosis to a trial comparing psychological interventions.<sup>9</sup>

At present, the evidence for the effectiveness of treatments for early-onset psychosis is scarce and treatment recommendations of the UK National Institute for Health and Care Excellence (NICE) for psychological interventions (clinical guideline CG155)<sup>10</sup> are extrapolated from the larger adult psychosis evidence base, which was considered sufficiently strong to make the current recommendations of antipsychotics, CBT, and family intervention. The paucity of evidence specific to young people is recognised in the NICE clinical guideline CG155, on psychosis and schizophrenia management in children and young people, and led to a research recommendation for an evaluation of the clinical effectiveness and cost-effectiveness of antipsychotics versus psychological intervention versus a combination of both in adolescents with early-onset psychosis.<sup>10</sup> To inform a definitive trial, in the present study we investigated the feasibility of a randomised controlled trial of antipsychotic monotherapy, psychological intervention monotherapy, and antipsychotics plus psychological intervention in adolescents with first-episode psychosis.

## Methods

### Study design

We did a multicentre pilot and feasibility trial according to a randomised, single-blind, three-arm, controlled design, recruiting individuals at UK National Health Service (NHS) Trusts located at seven sites (Birmingham, Greater Manchester, Lancashire, Oxfordshire and Buckinghamshire, Northumberland Tyne and Wear, Norfolk and Suffolk, and Sussex). This trial, named the Managing Adolescent first episode Psychosis: a feasibility Study (MAPS), was approved by the North West–Greater Manchester East Research Ethics Committee on Feb 6, 2017 (reference 16/NW/0893). The protocol, approved by an independent data monitoring committee

and independent trial steering committee, is available online and provided in the appendix (p 29). Six substantial protocol amendments were submitted to and approved by the research ethics committee, which are described in full in the appendix (pp 5–7).

### Participants

Eligible participants were aged 14–18 years; help-seeking; presented with first-episode psychosis (defined as being within 1 year of presentation to mental health services with psychosis symptoms); under the care of a psychiatrist within an Early Intervention in Psychosis (EIP) service or Child and Adolescent Mental Health Service (CAMHS); symptomatic at the time of randomisation (baseline), defined by a score of 4 or higher on the PANSS delusions or hallucinations subscales for at least 7 consecutive days; and met either the ICD-10 criteria for schizophrenia, schizoaffective disorder, or delusional disorder, or the entry criteria for an EIP service for first-episode psychosis at baseline. All participants had to have the capacity to provide informed, written consent to enter the trial. Participants aged 14–15 years also needed to have a parent or guardian willing to provide initial written consent for the research team to contact their child.

Individuals who met any of the following criteria were excluded: receipt of antipsychotics or structured psychological intervention within the past 3 months; non-English speaking; scored 5 or higher on the PANSS conceptual disorganisation item (to maximise the likelihood that those allocated to talking therapies would be able to engage in conversation with the therapist); were deemed an immediate risk to themselves or others by their psychiatrist or care coordinator; diagnoses of moderate-to-severe learning disabilities, ICD-10 organic psychosis, or primary alcohol or substance dependence.

Participants were referred to the study by mental health staff (primarily psychiatrists and care coordinators) within EIP or CAMHS teams across the seven sites. Research assistants completed baseline assessments including the PANSS to determine eligibility. Assessments generally took place within participants' homes, schools or colleges, or within clinical services. All baseline PANSS assessments were reviewed by a qualified clinician working on the trial to confirm eligibility before randomisation.

All participants provided written informed consent before their participation in the trial.

### Randomisation and masking

Participants were randomly allocated in a 1:1:1 ratio to receive either antipsychotic medication, psychological intervention, which comprised CBT plus optional family intervention at the participant's discretion, or a combination of both antipsychotics and psychological intervention. Research assistants randomly assigned participants using a secure web-based randomisation system developed by the University of Aberdeen Centre for Healthcare Randomised Trials (CHaRT; Aberdeen,

UK), a UK Clinical Research Collaboration clinical trials unit. Randomisation was done in permuted blocks of random size, stratified by centre and family contact (to account for participants allocated to receive psychological intervention who did not have regular family contact). Randomisation was independent and concealed at the individual level, with outcome assessors masked to treatment. The trial manager (MP), chief investigator (APM), therapists, and administrator were informed of participants' allocations by email. Participants and their care teams received their allocation details via letter, and participants and psychiatrists were offered telephone calls to provide further details. A standard operating procedure for allocation concealment, reviewed and approved by the data monitoring and trial steering committees, was provided to all research staff, which highlighted the importance of allocation concealment and outlined potential sources of non-adherence to masking, and methods to maintain masking, including arrangements for separate offices and telephone numbers for research assistants and therapists and verbal reminders to participants, family members, and care team clinicians about the importance of masking. All research staff were required to sign a declaration to confirm that they would abide by the standard operating procedure while working on the trial. Breaks in allocation concealment were reported to the trial manager and chief investigator, with learning points disseminated to the study team, and to the independent data monitoring and independent trial steering committees for monitoring.

### Procedures

Participants allocated to receive psychological intervention were offered up to 26 h of individual CBT and up to six optional sessions of family intervention (plus regular communication with family members following CBT sessions for individuals who consented to the sharing of information) by appropriately trained therapists over a 6-month treatment period, and up to 4 booster sessions of CBT following the treatment period. CBT sessions were typically once a week and family intervention once a month, and were generally delivered by the same therapist. Both interventions were informed by an integrative cognitive model.<sup>11</sup> In the initial phase of CBT, patients and therapists collaboratively identified problems and agreed on goals to work on in CBT and an individualised maintenance formulation was developed. Subsequent phases focused on change strategies with interventions described in a published manual,<sup>12</sup> historical formulations (ie, factors leading to the development of first-episode psychosis), and a final consolidation phase focusing on relapse prevention. Family intervention was based on the behavioural family therapy approach.<sup>13</sup> After an initial session involving assessment, formulation sharing, and agreeing goals and problems to be worked on, family intervention involved aspects such as psychoeducational work, provision of

normalising information and recovery-oriented information, problem solving, and relapse prevention planning. Therapy session records were completed by therapists throughout the delivery of psychological interventions, and therapists received supervision once a week from two MAPS group members (APM and SB). Audio-recorded CBT sessions, taped with the patient's consent, were rated regularly via rotational sampling of tapes with the Cognitive Therapy Scale-Revised (by APM and SB) to ensure fidelity to the protocol.

For participants allocated to receive drug intervention, antipsychotics were prescribed by the treating psychiatrist in their care team. Psychiatrists were asked to prescribe in line with NICE guideline CG155. They were encouraged to commence treatment as soon as possible following randomisation and to maintain treatment for at least 3 months, but preferably for 6 months or longer. Psychiatrists made decisions about the type and dose of antipsychotic consistent with their usual practice, and could change antipsychotic and dose as clinically required in response to monitoring of efficacy and adverse effects. The psychiatrists within the MAPS team (DM, MRB, NH, AJ, PMH, RW, RU, and FP) were available by phone or email to discuss antipsychotic prescribing with the participant's psychiatrist.

Participants allocated to receive antipsychotics plus psychological intervention were offered all treatments as described for the monotherapy groups. All participants in the trial were able to receive any other concomitant therapies throughout the trial including mental health medications (this could include antipsychotics in the psychological intervention group), and psychological therapies (this could include CBT or family intervention in the antipsychotics group). We collected data on concomitant therapies via self-report and medical record screening at follow-up visits at 3 months, 6 months, and 12 months.

To address concerns about the safety of withholding antipsychotic medication to participants in the psychological intervention monotherapy arm, at 3 months after the start of intervention we assessed for any deterioration in rescaled PANSS total scores from the baseline assessment at randomisation. Any participant allocated to receive monotherapy (ie, antipsychotics only or psychological intervention only) with an increase of more than 12·5% in PANSS, selected as a conservative threshold to prioritise safety, was offered the combination therapy, as were any with a compulsory hospital admission and those deemed to be an immediate suicide risk. Such patients remained as participants in the trial and took part in follow-up assessments.

### Outcomes

As MAPS is a feasibility study, our primary outcomes were trial referral and recruitment rates, participant attendance at CBT sessions, medication adherence, acceptability of treatments (determined by assessing

discontinuation rates, and by a nested qualitative study of participants being published in parallel<sup>14</sup>) and completion of follow-up appointments including PANSS interviews. To determine the feasibility of progression to a definitive trial, we applied a three-stage progression criteria relating to recruitment, retention to follow-up at the primary endpoint (6 months), and adherence to psychological intervention and to antipsychotics. The progression criteria were agreed with our independent trial steering committee, independent data monitoring committee, and funder. The specific progression criteria for each outcome were: recruitment of at least 80% of the planned population (green zone for progression), recruitment within 60–79% of the planned population (amber), or recruitment less than 60% of the planned population (red); retention of participants within the study with baseline and outcome assessments at the primary endpoint (6 months, end of treatment) with at least 80% having completed a PANSS interview (green), 60–79% having completed a PANSS interview (amber), or less than 60% having completed a PANSS interview (red); satisfactory delivery of adherent therapy to at least 80% of groups receiving psychological intervention (green), 60–79% of groups receiving psychological intervention (amber), or less than 60% of groups receiving psychological intervention (red); and satisfactory delivery of antipsychotic medication to at least 80% of groups receiving antipsychotics (green), 60–79% of groups receiving antipsychotics (amber), or less than 60% of groups receiving antipsychotics (red). Satisfactory delivery of adherent psychological therapy was operationalised as attending six or more sessions of CBT. Satisfactory delivery of adherent antipsychotic medication was operationalised as any exposure to antipsychotics for at least 6 consecutive weeks (this could include a dose lower than the British National Formulary lower limits given this is a frequent clinical practice for people of this age, and the drugs are licensed for adults). As a further feasibility assessment, we intended to assess the proportion of eligible people whom clinicians were willing to refer, but we were unable to capture these data systematically.

We collected data on a number of secondary outcomes to assess their acceptability and usefulness for inclusion in a definitive trial. Secondary outcome measures were collected at baseline and at the follow-up visits at 3 months, 6 months, and 12 months. We designed a variable length follow-up. Participants recruited in the first 16 months were followed-up for the full 12 months, and those recruited thereafter were offered assessments up to the end of treatment (6 months). Our prespecified proposed primary outcome measure for a definitive trial was total score on PANSS—a 30-item rating scale designed to assess psychopathology in people with a diagnosis of schizophrenia<sup>15</sup>—with an endpoint of 6 months. We assessed difference in PANSS from baseline, and categorised improvement according to 25% (minimal improvement), 50% (good clinical response), and 75% thresholds at each

follow-up visit. Thresholds were selected and defined for the purposes of our study on the basis of previous recommendations regarding reporting of PANSS assessments.<sup>16</sup> We also assessed social and educational or occupational functioning (First Episode Social Functioning Scale), subjective recovery (Questionnaire about the Process of Recovery [QPR]), dimensions of paranoia, hallucinations, cognitive disorganisation, grandiosity, and anhedonia (Specific Psychotic Experiences Questionnaire), anxiety and depression (Hospital Anxiety and Depression Scale), and alcohol and drug use (Alcohol Use Disorder Identification Test and Drug Abuse Screening Test). At baseline, we measured diagnostic symptoms for autism spectrum conditions using the NICE-recommended 10-item version of the Autism Spectrum Quotient. Health economics data were measured with an economic patient questionnaire adapted from our previous study,<sup>17</sup> to assess NHS resource use, and the EuroQol five-dimension, five-level scale health status questionnaire. Further details regarding secondary outcomes are provided in the appendix (pp 2–3, 42–44).

At each follow-up visit, we also measured non-neurological adverse effects with the Antipsychotic Non-neurological Side-Effects Rating Scale<sup>18</sup> and completed a cardiovascular screening comprising height, weight, blood pressure, waist circumference, and blood tests (total cholesterol, low-density lipoproteins, high-density lipoproteins, triglycerides, prolactin concentrations, glycated haemoglobin concentrations, and fasting plasma glucose). We recorded all serious adverse events and adverse events, including potential adverse effects of trial participation and deteriorations in PANSS score according to 12.5%, 25%, and 50% thresholds. Medical records were screened for details of adverse events at follow-up by a member of the research team who was not masked to allocation at each site, and self-reported adverse events were noted at follow-up or by therapists to the chief investigator and trial manager. Potential adverse effects associated with psychological intervention were monitored via a self-report measure developed in our previous trial (appendix pp 23–24).<sup>17</sup> Full definitions of adverse events are provided in the appendix (p 2).

Diagnosis and antipsychotic prescribing were recorded via review of medical record case notes. The type, dose, and duration of each antipsychotic prescribed were recorded for each participant for the full 12-month trial period (or for 6 months for those recruited during the second stage of the variable follow-up).

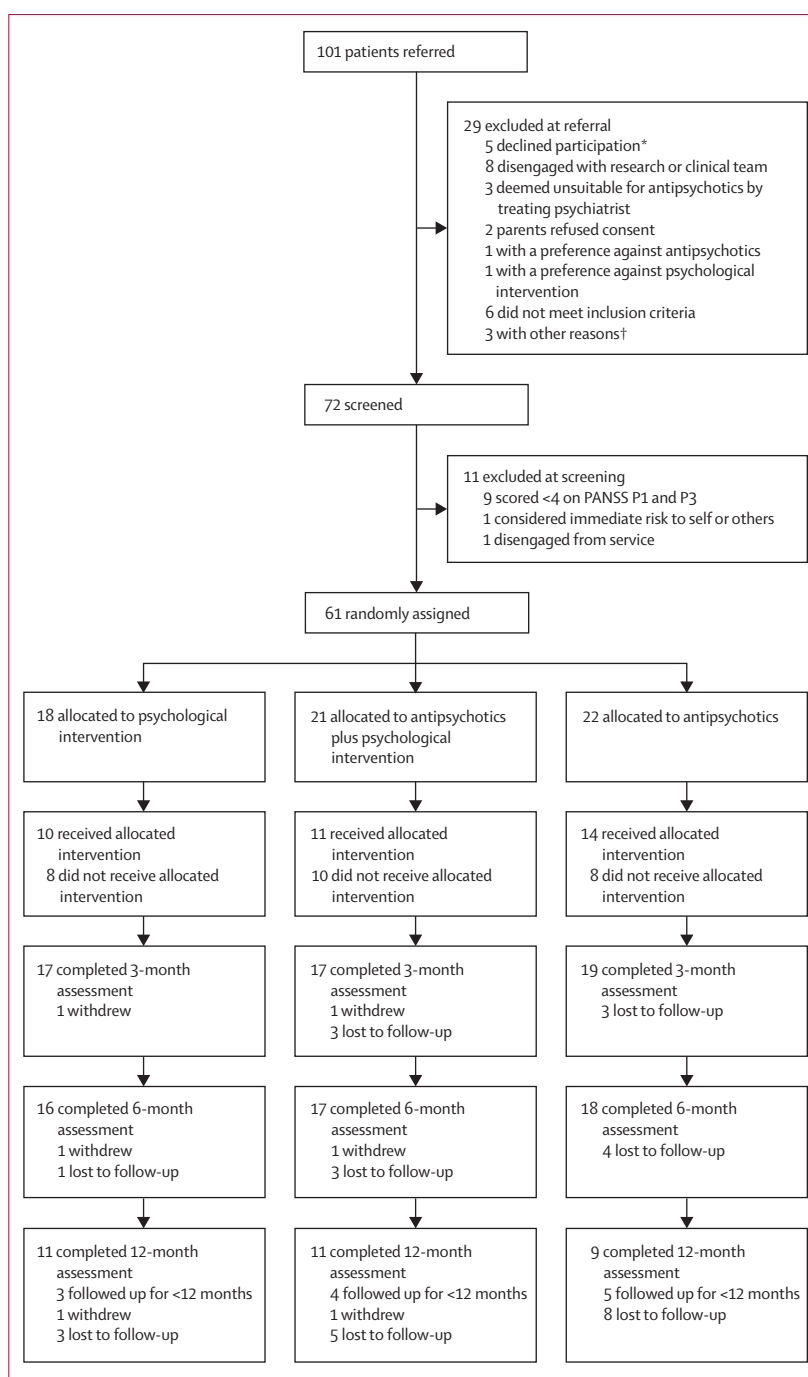
### Statistical analysis

A proposed sample size of 90 participants (30 per treatment arm) was considered sufficient to gain reliable information to inform sample size estimates for a larger trial<sup>19</sup> and feasibility information about trial procedures. We did not do a formal power calculation to detect treatment differences, given that the focus of analysis was not hypothesis testing. The analysis

followed a prespecified statistical analysis plan agreed by the chief investigator and the data monitoring committee. All main analyses were according to the intention-to-treat principle and done at the participant level. Safety and unwanted effects were analysed on the basis of treatment received (as-treated) rather than as-randomised, with psychological intervention defined as any session of CBT or family intervention from the trial therapist and antipsychotic treatment defined as any dose of an antipsychotic prescribed by the participant's psychiatrist. We summarised progression criteria using descriptive statistics, regarding the number of participants referred, the number of eligible referrals the number of consenting individuals and recruited individuals to each group, drop-out from the allocated intervention; withdrawal of consent, and absence of follow-up outcome data. We also report descriptive statistics for the components of psychological intervention received, including number of sessions and milestones achieved, and completion of between-session tasks. Additionally, we calculated the proportion of participants who received the allocated intervention versus the proportion that did not, and the proportion who moved to the combined arm due to deterioration. A repeated-measures analysis was done of the proposed primary outcome (total PANSS score) and the secondary outcome of subjective recovery (QPR; prioritised to assess recovery defined by service users), with a mixed-effects model to account for the discrete timing of the follow-up assessments and adjust for site and baseline score. We used all available data from each timepoint, and treatment effects were estimated at each timepoint with a treatment-by-time interaction. Missing baseline data was imputed with a centre-specific mean. Due to low response rates or low number of events, analyses for other variables were descriptive, but outcomes are reported in full. All analyses were done in Stata (version 15)<sup>20</sup> at CHaRT. The focus of the analysis was on point estimates and associated 95% CIs rather than statistical significance (p values); however, we have reported p values for completeness in the appendix (p 10), but all analyses were underpowered and not based on a power calculation. The percentage change in total PANSS score was calculated with adjusted PANSS methodology.<sup>21</sup> Descriptive data from baseline and follow-up visits were summarised as the mean (SD) or medians (IQR) for continuous data and frequencies and percentages for categorical variables. Full details of our statistical analyses are provided in the appendix (p 4). The study was prospectively registered on Feb 27, 2017, on the ISRCTN registry, ISRCTN80567433.

#### Role of the funding source

MAPS was funded by the UK National Institute for Health Research under its Health Technology Assessment Programme following a commissioned call (project number 15/31/04). The call specified the interventions,



**Figure: Trial profile**

PANSS=Positive and Negative Syndrome Scale. P1=delusions. P3=Hallucinatory behaviour. \*Reasons unknown. †Reasons are unknown; randomisation closed; and moved out of area.

population, setting, study design, and main outcomes. The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

For the statistical analysis plan see <https://www.abdn.ac.uk/hsrc/what-we-do/trials-unit/statistical-analysis-plans-611.php>

## Results

Between April 1, 2017, and Oct 31, 2018, 101 patients were referred to the study. The first patient was recruited on April 10, 2017 and the last on Oct 31, 2018. We recruited 61 participants (mean age 16·3 years [SD 1·3]): 18 to

psychological intervention, 22 to antipsychotics, and 21 to antipsychotics plus psychological intervention (figure). Baseline characteristics are summarised in table 1 and the appendix (p 8). Follow-up assessments were done between July 1, 2017 and April 30, 2019.

Regarding our feasibility criteria, our recruitment rate was 68% of the target sample size of 90 participants (amber progression zone); 51 (84%) participants were retained at the 6-month primary endpoint (green); and, as measures of satisfactory treatment delivery, 32 (82%) of 39 assigned to psychological intervention (as monotherapy or in combination with antipsychotics) received six or more sessions of CBT (green), and 28 (65%) of 43 assigned to antipsychotics (as monotherapy or in combination with psychological intervention) were exposed to antipsychotics for 6 or more consecutive weeks (amber).

The referral to recruitment rate was about 2:1, with five (5%) of 101 referred patients declining to take part and only two (2%) parents declining consent to contact their child. The most common referring service type was the EIP, which referred 83 (82%) patients. Of the 61 participants randomly assigned across UK NHS Trusts, most randomisations were done at the Oxford (25 [41%]) and Manchester (21 [34%]) sites. The number of participants with an ICD-10 diagnosis of a psychotic disorder in their medical records at baseline was 41 (67%), among whom the most commonly recorded diagnosis was unspecified non-organic psychosis (ICD-10 code F29; 40 [98%] participants). At the primary endpoint assessment at 6 months, only two patients had been withdrawn from the primary analyses (retained in assessments of safety) and attrition was low (figure). 51 (84%) participants had been retained in the trial at the primary endpoint and had completed the PANSS total assessment (green progression zone). Retention at the 12-month follow-up was lower: of 49 participants who were eligible for a 12-month assessment, 31 (63%) completed the follow-up (figure). The number of full blind breaks (ie, randomly assigned group revealed) was three, with two in the psychological intervention group and one in the antipsychotics group, all of which occurred before the 3-month follow-up visit. Seven partial blind breaks (ie, one treatment revealed to assessor) occurred at 3 months, seven at 6 months, and four at 12 months (four in the antipsychotics group, two in the psychological intervention group, and one in the combined group). Of the 135 follow-up assessments, seven (5%) were completed by an assessor with whom a full blind break had occurred and 12 (9%) were completed by an assessor with whom a partial blind break had occurred. The remaining breaks (full and partial) were transferred to a new and independent assessor.

32 participants in the psychological intervention groups (monotherapy or combined group) received six or more sessions of CBT, as our predefined feasibility criteria for adherent delivery. Of the seven participants assigned to psychological intervention who did not receive six sessions,

|   | Antipsychotics<br>(n=22) | Psychological<br>intervention<br>(n=18) | Antipsychotics plus<br>psychological<br>intervention (n=21) |
|---|--------------------------|---|---|
| Age, years                              | 16·4 (1·3)               | 16·3 (1·4)                              | 16·2 (1·3)  |
| Gender                                  |                          |   |   |
| Male                                    | 12 (55%)                 | 8 (44%)                                 | 10 (48%)  |
| Female                                  | 9 (41%)                  | 10 (56%)                                | 10 (48%)  |
| Non-binary                              | 1 (5%)                   | 0                                       | 1 (5%)  |
| Duration of untreated psychosis, months | 15; 9 (3–14)             | 13; 12 (7–18)                           | 16; 8 (2–18)  |
| Highest level of education              |                          |   |   |
| Secondary                               | 11 (50%)                 | 9 (50%)                                 | 11 (52%)  |
| Tertiary                                | 11 (50%)                 | 9 (50%)                                 | 10 (48%)  |
| Employment status                       |                          |   |   |
| College student                         | 9 (41%)                  | 7 (39%)                                 | 8 (38%)   |
| Secondary school student                | 7 (32%)                  | 5 (28%)                                 | 8 (38%)   |
| Unemployed                              | 2 (9%)                   | 4 (22%)                                 | 2 (10%)   |
| Full-time                               | 3 (14%)                  | 1 (6%)                                  | 1 (5%)  |
| Part-time                               | 1 (5%)                   | 1 (6%)                                  | 1 (5%)  |
| Voluntary                               | 0                        | 0                                       | 1 (5%)  |
| Marital status, single                  | 22 (100%)                | 18 (100%)                               | 21 (100%)   |
| Living arrangements                     |                          |   |   |
| Parents and siblings                    | 20 (91%)                 | 15 (83%)                                | 18 (86%)  |
| Supported accommodation                 | 1 (5%)                   | 2 (11%)                                 | 1 (5%)  |
| Other family members                    | 0                        | 1 (6%)                                  | 2 (10%)   |
| Alone                                   | 1 (5%)                   | 0                                       | 0   |
| Ethnicity                               |                          |   |   |
| White British                           | 17 (77%)                 | 14 (78%)                                | 18 (86%)  |
| Indian                                  | 0                        | 1 (6%)                                  | 0   |
| Pakistani                               | 2 (9%)                   | 0                                       | 1 (5%)  |
| White Asian                             | 0                        | 0                                       | 1 (5%)  |
| Black African                           | 1 (5%)                   | 1 (6%)                                  | 0   |
| Black Caribbean                         | 1 (5%)                   | 0                                       | 1 (5%)  |
| White Irish                             | 1 (5%)                   | 0                                       | 0   |
| Other                                   | 0                        | 2 (11%)                                 | 0   |
| Religion                                |                          |   |   |
| Atheism                                 | 12 (55%)                 | 7 (39%)                                 | 10 (48%)  |
| Christianity                            | 4 (18%)                  | 4 (22%)                                 | 4 (19%)   |
| None                                    | 2 (9%)                   | 6 (33%)                                 | 3 (14%)   |
| Islam                                   | 2 (9%)                   | 0                                       | 1 (5%)  |
| Buddhism                                | 0                        | 0                                       | 1 (5%)  |
| Other                                   | 2 (9%)                   | 1 (6%)                                  | 2 (10%)   |
| PANSS score                             |                          |   |   |
| Total                                   | 74·8 (12·2)              | 72·9 (9·7)                              | 75·9 (14·8)   |
| Positive                                | 22·9 (6·0)               | 21·2 (3·8)                              | 21·2 (5·8)  |
| Negative                                | 17·9 (5·6)               | 15·8 (3·3)                              | 18·5 (6·6)  |
| Disorganised                            | 19·9 (4·6)               | 20·1 (4·5)                              | 21·0 (5·4)  |
| Excitement                              | 19·3 (4·1)               | 17·1 (3·7)                              | 17·9 (4·9)  |
| Emotional distress                      | 24·7 (6·7)               | 25·2 (4·5)                              | 24·8 (5·8)  |

(Table 1 continues on page)



the reasons were participant disengagement after commencing CBT (four), participants declining therapy before commencing CBT (two), and participant withdrawal before six sessions (one). Three patients switched to antipsychotic monotherapy (two from the psychological intervention group and one from the combined group). The 18 participants assigned to psychological intervention monotherapy received a median of 14 sessions (IQR 9–23) of CBT and a median of three sessions (2–5) of family intervention, with nine participants receiving at least one session of family intervention. Only one participant received no sessions of CBT or family intervention. The 21 participants assigned to combined treatment received a median of 15 sessions (IQR 9–17) of CBT and a median of four sessions (2–5) of family intervention, with 12 participants receiving at least one session of family intervention. Only one participant received no sessions. For all patients allocated to receive psychological intervention (monotherapy and combined groups), the median time to the first recorded CBT session was 15 days (IQR 6–44).

28 participants in the antipsychotic groups (monotherapy or combined group) were exposed to antipsychotics for 6 consecutive weeks, as our predefined feasibility criteria for satisfactory exposure. Of the 15 participants assigned to antipsychotics who did not reach 6 weeks of exposure, the reasons were participants declining antipsychotics before prescription (three), clinicians not prescribing antipsychotics (three), both participant and family declining medication before prescription (one), and data that were unable to be extrapolated from medical records (eight). Seven patients switched to psychological intervention monotherapy from the combined group. Of those with adequate exposure to antipsychotics, the median duration of treatment was 23 weeks (IQR 13–36) in the monotherapy group and 43 weeks (32–51) in the combined group (overall median 32 weeks [20–44]). For all patients allocated to receive antipsychotics (monotherapy and combined groups), the median time to prescription was 18 days (IQR 10–42). 14 (33%) of the 43 participants assigned to antipsychotics switched from one antipsychotic drug to another during their involvement in the study. Of the 43 prescriptions made, the most commonly prescribed was aripiprazole (21 prescriptions), risperidone (ten), and quetiapine (nine). Full details regarding the drugs prescribed, durations, and doses are given in the appendix (p 9).

Overall, the proportion of participants who received their allocated intervention was similar across groups, with a slightly higher proportion observed in the antipsychotics monotherapy group (table 2), and the majority of participants received treatment as allocated. Ten (56%) of 18 participants in the psychological intervention group, 14 (64%) of 22 in the antipsychotics group, and 11 (52%) of 21 in the combined group received an adherent dose of their allocated treatment (at least six sessions of CBT or 6 consecutive weeks of

|   | Antipsychotics<br>(n=22) | Psychological<br>intervention<br>(n=18) | Antipsychotics plus<br>psychological<br>intervention (n=21) |
|---|--------------------------|---|---|
| (Continued from previous page)  |                          |   |   |
| PANSS symptom profiles  |                          |   |   |
| At least moderate hallucinations<br>(PANSS P3 score $\geq$ 4)   | 21                       | 15                                      | 18  |
| At least moderate delusions (PANSS P1<br>score $\geq$ 4, PANSS P6 score $\geq$ 5 and<br>PANSS P5 score $\geq$ 5)  | 14                       | 13                                      | 14  |
| At least moderate for both  | 13                       | 10                                      | 11  |
| Questionnaire about Process of Recovery   | 15; 42.1 (10.0)          | 12; 46.1 (9.3)                          | 18; 42.6 (10.1)   |
| AQ-10   | 11; 5.2 (1.8)            | 8; 4.8 (2.1)                            | 10; 5.4 (2.1)   |
| Participants with AQ-10 score greater<br>than the clinical threshold ( $\geq$ 6)  | 6 (55%)                  | 2 (25%)                                 | 4 (40%)   |
| Hospital Anxiety and Depression Scale   |                          |   |   |
| Anxiety   | 15; 12.7 (4.0)           | 10; 11.2 (2.6)                          | 13; 14.2 (2.5)  |
| Score greater than the case threshold<br>( $\geq$ 11)   | 9 (60%)                  | 5 (50%)                                 | 12 (92%)  |
| Depression  | 15; 9.7 (5.1)            | 10; 9.2 (3.8)                           | 13; 10.2 (4.4)  |
| Score greater than the case threshold<br>( $\geq$ 11)   | 5 (33%)                  | 3 (30%)                                 | 6 (46%)   |
| Antipsychotic Non-neurological Side Effects Rating Scale  |                          |   |   |
| Total score   | 12; 15.9 (6.4)           | 8; 17.5 (10.4)                          | 11; 17.2 (7.1)  |
| Number of side effects  | 12; 11.2 (5.2)           | 8; 10.6 (4.8)                           | 11; 11.5 (3.8)  |
| Data are n, n (%), mean (SD), n; mean (SD), or n; median (IQR). Percentages do not always add up to 100% due to rounding. PANSS=Positive and Negative Syndrome Scale. P1=delusions. P3=hallucinatory behaviour. P5=grandiosity. P6=suspiciousness or persecution. AQ-10=10-item Autism Spectrum Quotient. |                          |   |   |

Table 1: Baseline characteristics

|  | Antipsychotics<br>(n=22) | Psychological<br>intervention<br>(n=18) | Antipsychotics plus<br>psychological<br>intervention (n=21) |
|--|--------------------------|---|---|
| <b>Treatment received*</b>   |                          |   |   |
| Psychological<br>intervention  | 0                        | 10 (56%)                                | 7 (33%)   |
| Antipsychotics   | 14 (64%)                 | 2 (11%)                                 | 1 (5%)  |
| Antipsychotics<br>plus<br>psychological<br>intervention  | 2 (9%)                   | 4 (22%)                                 | 11 (52%)  |
| None†  | 6 (27%)                  | 2 (11%)                                 | 2 (10%)   |
| <b>Adherence*</b>  |                          |   |   |
| Overall  | 16 (73%)‡                | 14 (78%)‡                               | 11 (52%)  |
| *Six or more cognitive behavioural therapy sessions or 6 weeks of antipsychotic exposure. †Including the two participants who withdrew from the trial. ‡Including participants who received their assigned treatment in addition to an unassigned treatment. |                          |   |   |

Table 2: Randomly assigned treatment vs treatment received

antipsychotics) as randomly assigned. As indicated in table 2, some participants received no treatment due to non-engagement with treatment or non-adherence (10 [16%] of 61), and a minority received an unassigned treatment (eight [13%]).

In our intention-to-treat analysis of efficacy, we assessed adjusted PANSS total scores at 6 months,

|           | Antipsychotics  | Psychological intervention | Antipsychotics plus psychological intervention |
|-----------|-----------------|----------------------------|--|
| Baseline  | 22; 74.8 (12.2) | 18; 72.9 (9.7)             | 21; 75.9 (14.8)                                |
| 3 months  | 19; 65.6 (15.4) | 17; 64.9 (9.9)             | 17; 64.2 (16.1)                                |
| 6 months  | 18; 68.6 (17.3) | 16; 59.8 (13.7)            | 17; 62.0 (15.9)                                |
| 12 months | 9; 55.4 (7.0)   | 11; 61.3 (12.4)            | 11; 56.2 (12.3)                                |

Data are n; mean (SD) for patients retained at each follow-up assessment (figure). PANSS subscale scores are provided in the appendix (pp 10–11). PANSS=Positive and Negative Syndrome Scale.

**Table 3: PANSS total scores (intention-to-treat groups)**

|           | Antipsychotics  | Psychological intervention | Antipsychotics plus psychological intervention |
|-----------|-----------------|----------------------------|--|
| Baseline  | 15; 42.1 (10.0) | 12; 46.1 (9.3)             | 18; 42.6 (10.1)                                |
| 3 months  | 13; 44.6 (12.3) | 11; 47.1 (10.5)            | 10; 51.8 (8.6)                                 |
| 6 months  | 15; 49.9 (13.4) | 8; 49.4 (7.8)              | 12; 51.3 (10.7)                                |
| 12 months | 6; 52.7 (12.0)  | 7; 54.1 (6.9)              | 9; 59.6 (7.8)                                  |

Data are n; mean (SD). Data were missing when participant engagement and Positive and Negative Syndrome Scale interviews were prioritised.

**Table 5: Questionnaire about Process of Recovery scores (intention-to-treat groups)**

|             | Antipsychotics | Psychological intervention | Antipsychotics plus psychological intervention |
|-------------|----------------|----------------------------|--|
| <b>≥25%</b> |                |                            |  |
| 3 months    | 8/19 (42%)     | 7/17 (41%)                 | 8/17 (47%)                                     |
| 6 months    | 5/18 (28%)     | 10/16 (63%)                | 11/17 (65%)                                    |
| 12 months   | 6/9 (67%)      | 6/11 (55%)                 | 8/11 (73%)                                     |
| <b>≥50%</b> |                |                            |  |
| 3 months    | 3/19 (16%)     | 2/17 (12%)                 | 2/17 (12%)                                     |
| 6 months    | 4/18 (22%)     | 5/16 (31%)                 | 5/17 (29%)                                     |
| 12 months   | 3/9 (33%)      | 3/11 (27%)                 | 3/11 (27%)                                     |
| <b>≥75%</b> |                |                            |  |
| 3 months    | 0/19           | 0/17                       | 1/17 (6%)                                      |
| 6 months    | 0/18           | 1/16 (6%)                  | 1/17 (6%)                                      |
| 12 months   | 0/9            | 1/11 (9%)                  | 1/11 (9%)                                      |

Sample sizes represent number of patients retained at each follow-up assessment (figure). ≥25% was considered minimal improvement and ≥50% was considered a good clinical response. Patients are represented more than once if consecutive thresholds were met, and for each timepoint.

**Table 4: Improvement in Positive and Negative Syndrome Scale total score (intention-to-treat groups)**

among those participants retained for this primary endpoint. Mean scores for PANSS total at the 6-month primary endpoint were 68.6 (SD 17.3) for antipsychotic monotherapy (6.2 points lower than at baseline), 59.8 (13.7) for psychological intervention (13.1 points lower than at baseline), and 62.0 (15.9) for antipsychotics plus psychological intervention (13.9 points lower than at baseline) (table 3). PANSS score was improved by at least 25% (minimal clinical improvement) in ten (63%) of 16 participants in the psychological intervention group, five (28%) of 18 in the antipsychotics group, and 11 (65%) of 17 in the combined group (table 4). A good clinical response at 6 months (≥50% improvement in PANSS total score) was achieved in four (22%) of 18 patients receiving antipsychotic monotherapy, five (31%) of 16 receiving psychological intervention, and five (29%) of 17 receiving antipsychotics plus psychological intervention. Mean QPR scores at 3–12 months are summarised in table 5. Compared with baseline, mean QPR score at the 6-month primary endpoint was increased by 7.8 points in the antipsychotics group, 3.3 points in the

psychological intervention group, and 8.7 points in the combined group. All other secondary outcomes and results of statistical tests of PANSS and QPR scores are reported in the appendix (pp 9–20).

In our as-treated assessment of safety in participants who received at least one dose or session, more patients experienced serious adverse events in the combined group (eight [35%] of 23 participants) than in the antipsychotics group (two [13%] of 15) and psychological intervention group (four [24%] of 17). The greatest proportion of patients with serious adverse events was in the no-treatment group (four [80%] of five). Table 6 summarises adverse events and deteriorations in PANSS. No serious adverse events were deemed to be related to the trial regimens. Other adverse events were experienced in greater proportions in the antipsychotics group (13 [87%] patients) and combined group (16 [70%]) than in the psychological intervention group (five [29%]) and no-treatment group (three [60%]). The most commonly occurring adverse event in participants receiving antipsychotics was medication side-effects. One adverse event in the psychological intervention group was related to trial participation (distress about allocation to psychological intervention reported immediately after randomisation). Between baseline and 3 months, nine of 53 participants with an available PANSS assessment had deteriorations of 12.5% or more in PANSS total score (five had deteriorations of 25% or more): four in the psychological intervention group, three in the antipsychotics group, one in the combined group, and one who did not receive any treatment. At 6 months, PANSS had deteriorated by at least 25% in four patients and by at least 50% in two patients. At 12 months, one patient had a 25% or more deterioration in PANSS (table 6). At 3 months, two participants receiving antipsychotics were switched to combined treatment after 27.5% and 14.3% deteriorations in PANSS, and one participant receiving psychological intervention was switched to combined treatment after a 24.3% deterioration in PANSS. Adverse effects including non-neurological side-effects, metabolic effects, and weight gain are summarised in the appendix (pp 21–22). Potential unwanted effects of trial participation are also included in the appendix (pp 23–24).

## Discussion

The MAPS trial has shown that a study comparing antipsychotics with psychological therapies and a combined treatment in adolescents with first-episode psychosis is possible, although recruitment challenges at some sites indicate that changes might be required. This pragmatic pilot and feasibility trial had low attrition (<20% up to 6 months), similar attrition across the study groups, and a considerable proportion of participants adhered to the therapy that they were allocated. However, a notable minority of participants did not receive the allocated treatment, and recruitment proved challenging, particularly at some sites. Therefore, revisions to the design and implementation of the trial would be needed for a definitive trial. Our recommendations are given in the appendix (pp 25–28).

All three regimens were broadly safe and acceptable, with no involuntary hospital admissions and no suggestions that psychological interventions in the absence of antipsychotic medication were detrimental. All three regimens also seemed to provide benefit, with mean PANSS scores improving from baseline by approximately 6–14 points at 6 months, and 12–20 points at 12 months, most of which are within the range recognised as clinically important differences; for example, the minimal clinically important difference thresholds for patient-rated PANSS (11 points)<sup>22</sup> and clinician-rated PANSS (15 points).<sup>16</sup> Participants receiving combined treatment had the highest rate of serious adverse effects, which is a logical outcome given that more treatments being delivered increases the potential for unwanted effects. However, combined treatment was associated with fewer deteriorations in PANSS total. In addition, participants receiving antipsychotics had fewer serious adverse events (n=2) than those receiving psychological intervention, but more adverse events than the psychological intervention and combined groups. No serious adverse events were considered related to the study treatments. As such, a reasonable conclusion is that all treatments confer benefit and each treatment has its own adverse effect profile. A definitive test of effectiveness is now required.

The delivery of interventions within the trial seemed competent. Antipsychotics were administered quickly (median of 18 days from randomisation), for a reasonable duration (median of 32 weeks), with the majority of participants exposed for 6 or more consecutive weeks (28 [65%] of 43), and attempts were made to maximise benefit for a third of participants allocated to antipsychotics by switching to a different antipsychotic. The three most commonly prescribed antipsychotics were aripiprazole, risperidone, and quetiapine, which reflects the clinical practice of UK child and adolescent psychiatrists and is consistent with findings of an international study of antipsychotic prescribing for children and young people with early-onset psychosis.<sup>23</sup> Detailed information on dosages prescribed in this trial are given in the

|  | Antipsychotics<br>(n=15)† | Psychological<br>intervention<br>(n=17)† | Antipsychotics<br>plus psychological<br>intervention<br>(n=23)† | No<br>treatment<br>(n=5)† |
|--|---------------------------|--|---|---------------------------|
| <b>Serious adverse events</b>  |                           |  |   |                           |
| Participants   | 2 (13%)                   | 4 (24%)                                  | 8 (35%)   | 4 (80%)                   |
| Total events   | 2                         | 5  | 11  | 5                         |
| Participants with more than one event                                  | 0                         | 1 (25%)                                  | 2 (25%)   | 1 (25%)                   |
| Type of event  |                           |  |   |                           |
| Voluntary psychiatric admission  | 0                         | 0  | 3   | 0                         |
| Life threatening (suicide attempt)                                     | 0                         | 1  | 1   | 1                         |
| Serious violent incident   | 2                         | 2  | 1   | 2                         |
| Admission to a general medical ward for physical condition (voluntary) | 0                         | 2  | 1   | 2                         |
| Otherwise considered medically significant: overdose of medication     | 0                         | 0  | 4   | 0                         |
| Otherwise considered medically significant: overdose of painkillers‡   | 0                         | 0  | 1†  | 0                         |
| <b>Adverse events</b>  |                           |  |   |                           |
| Participants   | 13 (87%)                  | 5 (29%)                                  | 16 (70%)  | 3 (60%)                   |
| Total events   | 41                        | 10                                       | 35  | 3                         |
| Participants with more than one event                                  | 9 (69%)                   | 3 (60%)                                  | 9 (56%)   | 0                         |
| Type of event  |                           |  |   |                           |
| Self-harm  | 7                         | 6  | 12  | 3                         |
| Medication side-effect   | 28                        | 0  | 17  | 0                         |
| Other adverse event  | 6                         | 4  | 5   | 0                         |
| Distress reported regarding allocation                                 | 0                         | 0  | 1   | 0                         |
| <b>Deterioration in PANSS total§</b>                                   |                           |  |   |                           |
| 3 months   |                           |  |   |                           |
| ≥12.5%   | 0/13                      | 3/17 (18%)                               | 6/20 (30%)  | 0/3                       |
| ≥25%   | 0/13                      | 3/17 (18%)                               | 2/20 (10%)  | 0/3                       |
| ≥50%   | 0/13                      | 0/17                                     | 0/20  | 0/3                       |
| 6 months   |                           |  |   |                           |
| ≥12.5%   | 1/13 (8%)                 | 3/16 (19%)                               | 4/19 (21%)  | 1/3 (33%)                 |
| ≥25%   | 1/13 (8%)                 | 2/16 (13%)                               | 2/19 (11%)  | 1/3 (33%)                 |
| ≥50%   | 0/13                      | 1/16 (6%)                                | 1/19 (5%)   | 0/3                       |
| 12 months  |                           |  |   |                           |
| ≥12.5%   | 1/6 (17%)                 | 2/10 (20%)                               | 2/13 (15%)  | 0/2                       |
| ≥25%   | 0/6                       | 0/10                                     | 1/13 (8%)   | 0/2                       |
| ≥50%   | 0/6                       | 0/10                                     | 0/13  | 0/2                       |

Data are n or n (%) for as-treated groups according to treatment received for at least one dose or session. PANSS=Positive and Negative Syndrome Scale. \*Data could not be retrieved on one participant who withdrew from the trial before medical record screening had commenced. †Discrepancies between as-treated (safety) groups here and as-treated (treatment received) groups in table 2 result from operationalisation of the criteria. For example, a participant taking antipsychotics was classified as receiving antipsychotic monotherapy in table 2 if they received less than 6 sessions of psychological intervention, but would be antipsychotics plus psychological intervention in the safety assessment if they had received at least one session but less than six. ‡Ingested five painkillers. §In those patients who had a PANSS assessment at each timepoint; patients are represented more than once if consecutive thresholds were met, and for each assessment time.

**Table 6: Adverse events and deterioration in PANSS total score (as-treated groups)\***

appendix (p 8). Psychiatrists prescribed the antipsychotics, as per normal practice, to achieve control of psychotic symptoms within the British National Formulary recommended dosages. The NICE guidance for management of psychosis and schizophrenia in adolescents (CG155)<sup>10</sup> recommends starting with a low dose of an antipsychotic and gradually increasing. The doses in this trial were generally low, except for the highest mean dose of risperidone, which was greater than the 2 mg normally recommended for first-episode psychosis. Olanzapine was an unusual choice for first-episode psychosis, as it is no longer recommended as a first-line treatment due to concerns about its effects on metabolism and weight gain.<sup>10</sup> The provision of psychological therapies was also consistent with good practice, with first appointments being offered quickly (median time from randomisation of approximately 2 weeks), and most participants receiving 6 or more sessions (32 [82%] of 39 participants in the monotherapy and combined groups). With regard to those allocated to receive an offer of family intervention, 21 (54%) of 39 received at least one session, with the mean number being 3–4 sessions. These findings are reflective of family intervention being offered to all of our participants, but the choice regarding uptake residing with the young person themselves, as some adolescents will not consent to family involvement, and again is a pragmatic reflection of real-world complexities in evaluating multiple psychosocial interventions; however, our findings do suggest that family intervention might be less acceptable than CBT to adolescents with first-episode psychosis.

Our trial had several limitations. The feasibility trial design and small sample size means that caution must be taken in interpreting any statistical tests and significance values. With regard to the integrity of treatment allocation, the proportions of patients receiving interventions as allocated ranged between 52% and 64%, although the proportion receiving an additional, unallocated intervention was only 13%. These proportions reflect real-world behaviours, in that many people frequently do not adhere with treatment regimens exactly as prescribed; similar rates of non-adherence are commonly observed in trials of antipsychotic medication, and psychological therapy trials are often confounded by participants receiving additional medications and other psychosocial interventions. In this trial, we were unable to mask participants to allocation, which might represent a source of bias. All participants met the entry criteria, including presentation to services with psychosis symptoms, being under the care of a psychiatrist within an EIP service or CAMHS, and scoring 4 or higher on the PANSS delusions and hallucinations subscales for at least 7 days. However, hallucinations can be prevalent in the general population of adolescents, with a median of 7.5% of adolescents (aged 13–18 years) reporting such experiences in a meta-analysis of 19 population-based studies.<sup>24</sup> Although our sample was fairly homogeneous in terms of age and

experience of early-onset psychosis and need for psychiatric care, only 67% had a diagnosis of a psychotic disorder recorded in their notes at baseline, with the most common entry being first-episode psychosis and the most common formal ICD-10 diagnosis being unspecified non-organic psychosis (code F29). Comorbidities were also frequent in our sample, including high rates of caseness for anxiety, depression, and autistic spectrum disorders, and high levels of drug and alcohol use. The heterogeneity of our population reflects the reality of both early intervention services that embrace diagnostic uncertainty, and the complexity of an emerging clinical picture in adolescents presenting with distressing psychotic experiences, often with clinically significant complexities. However, this diagnostic heterogeneity might result in heterogeneity in patient responses to both psychological interventions and antipsychotics, which might affect the appropriateness and cost to benefit ratio of each treatment relative to adverse effects. For example, people with psychotic symptoms in the context of depression or post-traumatic stress disorder might be more likely to benefit from psychological intervention, and those with psychotic symptoms in the context of autism spectrum disorder might be more likely to show treatment resistance to antipsychotics.<sup>25</sup>

The clinical heterogeneity of a help-seeking adolescent population might require a tailored and personalised treatment approach delivered via an adaptive trial design. In a future definitive trial, a baseline adolescent diagnostic assessment with a validated structured tool such as the Development and Wellbeing Assessment<sup>26</sup> might provide a detailed picture of the range of adolescent psychopathology and predictors of treatment response.

Our trial also had limitations with regard to the initiation and delivery of medication. Although we recommended that prescribing psychiatrists followed NICE guidelines, we did not systematically monitor fidelity to NICE prescribing guidance, and we did not assess drug plasma concentrations, which might be required to identify a potential cause of non-response;<sup>27</sup> a definitive trial should consider these options. Our more rigorous monitoring of fidelity to the delivery of psychological interventions compared with antipsychotics might have resulted in a bias that favoured psychological intervention; the proportion of patients showing a good response to antipsychotics ( $\geq 50\%$  improvement in PANSS; 4 [22%] of 18 participants at 6 months) was low compared with a 2018 trial showing remission in 287 (64%) of 446 adult patient receiving antipsychotics for first-episode psychosis.<sup>28</sup> Low response in our trial could be the result of non-adherence, or could be specifically related to specific characteristics of an adolescent population, including common comorbidities, or the long duration of untreated psychosis that was observed in our sample. A placebo condition would have been helpful in interpreting treatment efficacy (and was used in a 2020 study of CBT with and without

antipsychotics<sup>29</sup>), particularly in relation to the effects of antipsychotics; however, a placebo condition might not be needed to investigate the pragmatic effectiveness of interventions in NHS settings, and was unnecessary for a feasibility study that was not designed to investigate efficacy. Because all participants were receiving care from an EIP service or CAMHS, we cannot exclude the possibility that any benefits observed are attributable to factors such as effective care coordination, engagement, and crisis management, rather than the specific active treatments provided by the trial. The diagnostic heterogeneity of our sample, although reflecting clinical realities of early intervention provision, also represents a limitation, given that different diagnostic groups might exhibit differential treatment responses. The omission of a diagnostic interview at the point of entry to the study is also a limitation. Some of the less prioritised secondary outcome measures (ie, self-report scales) had large amounts of missing data (as a result of minimising the effect of participant burden on attrition) and a high number of blood test results were missing because many young people were reluctant to consent to these. As such, a future trial should reduce the number of secondary assessments. The duration of follow-up should be at least 12 months to allow for evaluation of the longevity of treatment effects. Our trial had several challenges in recruitment, including lower incidence in rural areas, polarised opinions regarding treatment options in potential referrers and prescribers (as addressed in our related MAPS trial paper<sup>30</sup>), and integration between the research and clinical teams; therefore, site selection for a definitive trial should be based on prevalence of adolescent first-episode psychosis, and willingness of clinicians to recognise clinical equipoise and the need for a trial, and, thus, to randomly allocate treatments. In addition, the upper age limit could be increased from 18 to 25 years, as definitions of adolescence often extend to 25 years of age (eg, the WHO definition of youth), which would widen the potential pool of participants. More extensive recommendations for a clinical trial are considered in the appendix (pp 25–28).

The main implication of this trial is that an adequately powered effectiveness trial is now required to provide evidence regarding the relative effectiveness of antipsychotic medication and psychological therapies (CBT and family intervention) in adolescents with early-onset psychosis. On the basis of our trial, it seems reasonable to support young people with early-onset psychosis and their families (in the absence of immediate risk to themselves or others) to make informed treatment choices as outlined in the NICE guidelines.

#### Contributors

APM planned the study, contributed to the trial design, trial protocol, statistical analysis plan, and manuscript writing, managed the trial as chief investigator, and critically revised the manuscript. APM, MP, DFr, DfO, MRB, JN, DS, and CH applied for funding. MP developed the trial protocol and contributed to trial and data management. DM, LJ, DFr, DfO, MRB, NH, JH, GM, JN, DS, CH, and AJ developed the trial design

and protocol and critically revised the manuscript. JH, GM, and JN developed the statistical analysis plan. JH and GM analysed the data. All authors read the final manuscript.

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#### Declaration of interests

APM reports personal fees from training workshops in cognitive behavioural therapy (CBT) for psychosis and royalties from books on the topic, outside of the submitted work. MP reports personal fees and fees paid to the Psychosis Research Unit of Greater Manchester Mental Health NHS Foundation Trust for CBT training outside of the submitted work. LJ reports personal fees from New Harbinger Publications, outside of the submitted work. DFr reports grants from the National Institute for Health Research (NIHR) and the UK Medical Research Council outside of the submitted work. MRB reports royalties from Oxford University Press and personal fees from the UK Medical Defence Union, outside of the submitted work. NH is the chair of the board of trustees of the Manchester Global Foundation, a Charitable Incorporated Organisation registered in England and Wales; is a past trustee of Lancashire Mind, the Pakistan Institute of Living and Learning, and the Abaseen Foundation; established an independent general hospital (Remedial Centre) in Karachi, Pakistan, which is now owned and operated by his sibling with a pharmacy attached; and received honoraria and travel grants from Eli Lilly, Bristol Myers Squibb, Lundbeck, AstraZeneca, and Janssen Pharmaceuticals outside of the submitted work. GM reports grants from the NIHR Health Technology Assessment (HTA) Programme during the conduct of the study. JN reports membership in the NIHR boards: Efficacy and Mechanisms Evaluation Board (2019–present), Commissioning Priority Review Decision-Making Committee (2015), HTA Commissioning Board (2010–16), HTA Commissioning Sub-Board (Expression of Interest; 2014), HTA Funding Boards Policy Group (2016–19), HTA General Board (2016–19), HTA Post-Board Funding Teleconference (2016–19), NIHR Clinical Trials Unit Standing Advisory Committee (2018–present), NIHR HTA and Efficacy and Mechanism Evaluation Editorial Board (2014–19), and Pre-exposure Prophylaxis Impact Review Panel (2017); outside of the submitted work. DS reports personal fees from the National Clinical Audit of Psychosis of the Royal College of Psychiatrists, royalties from Wiley Blackwell publication for the book *Promoting Recovery in Early Psychosis*, membership in the current National Institute for Health and Care Excellence (NICE) guideline development group for rehabilitation in adults with complex psychosis and related severe mental health conditions, and current board membership at the UK National Collaborating Centre for Mental Health, outside of the submitted work. CH was chair of the NICE guideline development group for schizophrenia in children and young people (2011–13) and was chair of the NICE psychosis and schizophrenia in children evidence update (2014–15), outside of the submitted work. All other authors declare no competing interests.

#### Data sharing

Anonymised data will be made available upon reasonable request, which must include a protocol and statistical analysis plan and not be in conflict with our prespecified publication plan, consistent with our data sharing policy (available on request from APM). Requests for data

sharing will be considered by APM and the independent trial steering and data monitoring committees.

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