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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A three-arm feasibility randomised controlled trial comparing antipsychotic medication to psychological intervention to a combined treatment in adolescents with first episode psychosis: The Managing Adolescent first episode Psychosis Study (MAPS)

Anthony P. Morrison*[1, 2], Melissa Pyle[1,2], Daniel Maughan[3], Louise Johns[3,4], Daniel Freeman[3,4], Matthew R. Broome[3,4,5,6], Nusrat Husain[2,7], David Fowler[8], Jemma Hudson[9], Graeme MacLennan[10] John Norrie[11], David Shiers[1], Chris Hollis[12], Anthony James[3,4] and on behalf of the MAPS Trial Group: Max Birchwood, Ravneet Bhogal, Samantha Bowe, Rory Byrne, Joe Clacey, Linda Davies, Robert Dudley, Richard Emsley, Renata Fialho, Rick Fraser, Paul French, Thomas Goodall, Emmeline Goodby, Peter Haddad, Emmeline Joyce, Negar Khozoee, Miriam Kirkham, Amy Langman, Amanda Larkin, Helena Laughton, Ashley Liew, Eleanor Longden, Ashley Louise Teale, Laura McCartney, Elizabeth Murphy, Fiona Padgett, Jasper Palmier-Claus, Sarah Peters, Catarina Sacadura, Jo Smith, Verity Smith, Ann Steele, Rachel Upthegrove, Richard Whale[8], Lauren Wilcox, Alison Yung[1]

[1] Psychosis Research Unit, Greater Manchester Mental Health NHS Foundation Trust, Prestwich, M25 3BL, UK

[2] Division of Psychology and Mental Health, University of Manchester, Zochonis Building, Manchester, M13 9PL, UK

[3] Department of Psychiatry, Medical Sciences Division, University of Oxford, Warneford Hospital, Oxford, OX3 7JX, UK.

[4] Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, OX4 7JX, UK

[5] Institute for Mental Health and Centre for Human Brain Health, School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

[6] Birmingham Women's and Children's NHS Foundation Trust, Steelhouse Lane, Birmingham, B4 6NH, UK

[7] Early Intervention in Psychosis Service, Lancashire and South Cumbria NHS Foundation Trust, Chorley, PR7 1PS UK

[8] Brighton and Sussex Medical School, University of Sussex, Brighton BN1 9PX

[9] Health Services Research Unit, University of Aberdeen, Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD, UK

[10] The Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit, University of Aberdeen, Aberdeen, UK

[11] Clinical Trials Unit, University of Edinburgh. Medical School, Teviot Place, Edinburgh, EHY8 9AG, UK

[12] NIHR MindTech MedTech Co-operative, Division of Psychiatry and Applied Psychology, Institute of Mental Health, University of Nottingham, Innovation Park, Triumph Road, Nottingham, NG7 2TU, UK

* corresponding author Professor Anthony P Morrison: anthony.p.morrison@manchester.ac.uk

Abstract

Background: The evidence base for treatments for early-onset psychosis (EOP) is limited and of low quality. Current guidance for the treatment of EOP is mostly extrapolated from trials in adult populations. NICE, in the United Kingdom (UK), make a specific research recommendation for the evaluation of clinical and cost-effectiveness of antipsychotics (AP), versus psychological intervention (cognitive behaviour therapy [CBT] and family intervention), versus combination treatment for EOP. The National Institute for Health Research (NIHR) in the UK commissioned this research to establish feasibility and acceptability of a definitive trial examining these three treatment options.

Methods: We conducted a multi-site, Prospective Randomised Open Blinded Evaluation (PROBE) design, feasibility randomised controlled trial (RCT) comparing AP monotherapy with psychological intervention monotherapy (PI) plus a combination of these treatments in 14-18-year olds with a first episode of psychosis. We recruited participants from seven United Kingdom sites. Participants were followed-up at six and 12 months. Cognitive behavioural therapy incorporated up to 26 sessions over 6 months plus up to four booster sessions. Family intervention included up to six sessions over 6 months. Choice and dose of antipsychotic were at the discretion of the treating consultant psychiatrist. The primary outcome was feasibility data (recruitment, retention, acceptability) and the main effectiveness outcome was the Positive and Negative Syndrome Scale (PANSS) total score at 6 months. We conducted a repeated-measures analysis of the proposed primary outcome (PANSS) and the secondary outcome, the Questionnaire about the Process of Recovery (QPR) using a mixed effects model to account for the discrete timing of the follow-up assessments and adjusted for site. Safety outcomes were reported on the basis of as treated status defined as any one session of CBT or any one dose of APs; descriptive statistics are reported for safety outcomes. The study was prospectively registered on 27th February 2017, http://www.isrctn.com/ISRCTN80567433.

Findings: 61 patients (aged 14-18 years; mean 16.3, SD 1.3) were recruited from 1st April 2017 to 31st October 2018, 18 were assigned to psychological intervention, 22 to antipsychotics and 21 to the combination. The feasibility of recruitment was unclear, since the trial only recruited 61 of a target of 90 participants. The study had a low referral: randomisation ratio (101:61), high rates of retention (>80%), high rates of adherence for psychological intervention (82.1%) defined as 6 or more sessions of CBT, and moderate rates of adherence for antipsychotic medication (65.1%), defined as 6 or more consecutive weeks of APs. The

median number of sessions for CBT for those in the PI arm was 14 (IQR 9, 23) and 15 in the combined arm (IQR 9, 17). Of those in receipt of APs the mean duration that the participant remained on the medication was 31·5 weeks (SD 14·6, minimum 8·7 and maximum 52). There were no serious adverse events considered to be related to the trial.

Interpretation: This is the first trial to show that it is safe to conduct a head-to-head clinical trial comparing psychological intervention with antipsychotics and the combination in people in young people with a first-episode psychosis. However, feasibility is unclear due to not meeting the recruitment progression criteria, so amendments to trial design are required in order to conduct an adequately powered clinical and cost effectiveness trial to provide robust evidence.

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Introduction

Early-onset psychosis (EOP) refers to the development of a first episode before the age of 18 and estimates suggest that the incidence rate of EOP is 5.9 per 100,000 people.[1] As adolescence is a period of significant change in biological, social and psychological development, those with EOP face significant challenges: the long-term prognosis can be poor, particularly in relation to functional outcomes, worse global outcomes and greater number of hospitalisations and relapses.[2] The risk of poor long-term outcomes appears to be inflated by premorbid difficulties, a longer duration of untreated psychosis (DUP), and greater symptom severity at baseline.[3] The risk of suicidal behaviour has been shown to be greater in young people with psychosis than those with other mental health problems.[4] In addition to the personal costs, EOP also accounts for a significant proportion of inpatient admissions and economic costs.[5]

In the United Kingdom (UK), care for those with EOP is typically provided by Early Intervention in Psychosis (EIP) and Child and Adolescent Mental Health Services (CAMHS). In Guideline CG155, the National Institute for Health and Care Excellence (NICE) make a specific recommendation that care should include a consultant psychiatrist with training in child and adolescent mental health (NICE, 2013). Communication and joined-up working across EIP and CAMHS is considered essential for effective delivery of care for EOP. However, there are indications that EIP staff do not always feel adequately trained to work with young people[6] and that CAMHS are poor at identifying EOP.[7] This may reflect challenges in the assessment and diagnosis of psychosis in children and young people[8], including distinguishing between autistic spectrum disorders (ASD) and symptoms of psychosis, ruling out organic causes[9], and the high prevalence of unusual perceptional experiences and beliefs in young people.[10] Whilst there is evidence to support the prospective validity of schizophrenia and affective psychosis, other psychotic diagnoses are considered to have low prospective validity.[11] Acceptance into EIP does not usually require a schizophrenia spectrum diagnosis, and diagnostic uncertainty in the early phases of psychosis is embraced by EIP services.[12]

Providing access to evidence-based treatments for young people with psychosis is of paramount importance. NICE Guideline CG155 [13] recommends that children and young people with psychosis should be offered oral antipsychotic (AP) medication and psychological intervention (PI), specifically Cognitive Behavior Therapy (CBT) and family intervention (FI). NICE also recommend that a young person who wishes to have PI without APs should be given this choice but advised that it can be more effective when delivered with APs; however, it is worth noting that this is extrapolated from the adult evidence-base and there is minimal age-specific data and there are reasons why the risk-benefit ratio may differ. A systematic literature

review indicated that for young people with psychosis the mainstay of treatment is APs [14] and research from the United States (US) indicates that there is an increase in the amount of prescriptions of APs for young people with psychosis over time.[15] However, the evidence base for APs in EOP is limited compared to adult psychosis. Whilst meta-analysis indicates that APs have a small but significant benefit over placebo for positive and negative symptoms and social functioning, and a large effect for improvement in global state, this evidence comes from a small number of low-quality studies and the placebo groups also improved, on average, to a clinically significantl extent on psychiatric symptoms.[14] A more recent network meta-analysis indicated benefits of a number of APs over placebo and, in particular, clozapine, olanzapine and risperidone had the greatest effect sizes. [16] However, network meta-analysis relies on indirect evidence and there is a high risk of selection and detection bias across the studies.[16] Concern has been expressed over the increased risk of adverse metabolic side-effects of AP in young people, with weight gain being particularly problematic.[17, 18]

With regards to psychological interventions, a systematic review of the literature found no studies of either CBT or FI in young people under the age of 18.[14] Eight low-quality studies of CBT and FI in young people under the age of 25 demonstrated a small but significant effect for the combination of CBT and FI on the number of days to relapse.[14] Since Stafford et al.[14] carried out their systematic review search, one small (n=30), non-randomised feasibility study of CBT vs. FI vs. treatment as usual (TAU) has been conducted in an under 18-years of age psychosis population, which concluded it is feasible to recruit people with EOP to a trial comparing psychological interventions.[19]

Currently, the evidence base for treatments for EOP is lacking and NICE Guidance treatment recommendations for psychological interventions are extrapolated from the larger adult psychosis evidence base, which was considered sufficiently strong to make the current recommendations of APs, CBT and FI. The paucity of evidence specific to young people is recognized in the NICE Guideline CG155 and led to a research recommendation for an evaluation of the clinical and cost-effectiveness of antipsychotics (AP), versus PI versus combination treatment for adolescents with EOP.[13] To inform a definitive trial, we investigated the feasibility of conducting a randomised controlled trial of PI monotherapy, AP monotherapy, and a combination of PI and APs in adolescents with a first episode of psychosis.

Methods

Study design

We conducted a feasibility Prospective Randomised Open Blinded Evaluation (PROBE) design randomised controlled trial, recruiting participants between April 1, 2017 and October 31, 2018 in National Health Service (NHS) Trusts within seven UK sites (Birmingham, Greater Manchester, Lancashire, Oxfordshire & Buckinghamshire, Northumberland Tyne & Wear, Norfolk & Suffolk, Sussex). Participants were allocated in the 1:1:1 ratio to receive either antipsychotic (AP) medication, or psychological intervention (PI), which comprised of Cognitive Behaviour Therapy (CBT) plus the option of family intervention (FI), or a combination of both AP and PI. Managing Adolescent first episode Psychosis: a feasibility Study (MAPS) was approved by the North West - Greater Manchester East Research Ethics Committee on 6th February 2017 (reference: 16/NW/0893). The current, Research Ethics Committee approved trial protocol is available at: https://www.journalslibrary.nihr.ac.uk/programmes/hta/153104/#/. All participants provided written informed consent to participate.

Participants

Eligible participants were aged between 14-18 years; help-seeking; presented with FEP (defined as being within one year of presentation to services with psychosis symptoms); under the care of a psychiatrist within EIP or CAMHS; symptomatic at baseline, defined by scoring 4+ on the PANSS delusions or hallucinations subscales for at least seven consecutive days; and met either International Classification of Diseases Version 10 (ICD-10) criteria for schizophrenia, schizoaffective disorder or delusional disorder or entry criteria for FEP within EIP. All participants had to have capacity to provide informed, written consent to enter the trial. For ethical reasons, participants aged 14-15 also needed to have a parent/guardian willing to provide initial written consent for the research team to contact their child.

People who met any of the following criteria at baseline were excluded: receipt of APs or structured PI within the last 3 months; did not speak English; scored 5+ 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); presented with immediate risk to themselves or others; diagnoses of moderate-to-severe learning disabilities, ICD-10 organic psychosis, or primary alcohol/substance dependence.

Participants were referred by mental health staff (primarily psychiatrists and care coordinators) within EIP or CAMHS teams across the seven sites. Research assistants (RAs) completed baseline assessments including the PANSS to determine eligibility. Assessments generally

took place within participants' homes, schools/colleges, or within clinical services. All baseline PANSS assessments were reviewed by a qualified clinician working on the trial to confirm eligibility prior to randomisation.

Randomisation and masking

RAs randomised participants using a secure web-based randomisation system developed by the Centre for Healthcare Randomised Trials (CHaRT). Participants were randomly assigned via a 1:1:1 ratio using randomised permuted blocks, stratified by centre and family contact (to account for participants allocated to receive PI who did not have regular family contact). Randomisation at the individual level was independent and concealed to the assessors (RAs). The trial manager, chief investigator, therapists, and administrator were informed of participants' allocations. 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 (SOP) for allocation concealment was provided to all research staff, which highlighted the importance of allocation concealment and outlined potential threats to the blind and methods to maintain the blind including arrangements for separate offices and telephone numbers for RAs and therapists and verbal reminders to participants, family members and participants' care team clinicians about the importance of the blind. All research staff were required to sign a declaration to confirm that they would abide by the SOP whilst working on the MAPS trial.

Procedures

Participants allocated to PI were offered up to 26 hours of individual CBT and up to 6 optional sessions of FI by appropriately trained therapists over a 6-month treatment window and up to four booster sessions of CBT following the treatment window. CBT sessions were generally weekly and FI monthly and delivered by the same therapist. Both interventions were informed by an integrative cognitive model.[20] Clients and therapists collaboratively agreed on goals and problems to work on in CBT, using interventions described in a published manual [21] and informed by clients' individualised formulations. FI was based on the Behavioural Family Therapy (BFT) approach.[22] After an initial session involving assessment, formulation-sharing and agreeing goals and problems to be worked on, FI involved facets such as psychoeducational work, provision of normalizing information and recovery-oriented information, problem-solving and relapse-prevention planning. Therapists completed therapy session records and

received weekly supervision and regular rating of audio-recorded CBT sessions with the Cognitive Therapy Scale – Revised (CTS-R) to ensure fidelity to the protocol.

Participants allocated to APs were prescribed for 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 12 weeks, but preferably for 26 or more weeks. Psychiatrists made decisions about the type and dose of antipsychotic for participants consistent with their usual practice, and could change antipsychotic and dose as clinically required. The study team psychiatrists (DM, MRB, NH, AJ, PMH, RW, RU and FP) were available to discuss antipsychotic prescribing with the participant's psychiatrist.

Participants allocated to PI plus AP were offered all treatments as described for the monotherapy groups. All participants were able to receive any concomitant therapies throughout the trial including mental health medications (this could include antipsychotics), and psychological therapies (this could include CBT or FI). We collected data on concomitant therapies via self-report data and medical record screening.

To address concerns about the safety of withholding antipsychotic medication to participants in the CBT-only arm, at the 3-month follow-up we assessed for any deterioration in re-scaled PANSS scores from the baseline assessment. Any monotherapy participant (i.e. AP only or PI only) with an increase of more than 12.5% was offered the combination therapy, as were any with a compulsory hospital admission. They remained able to participate in the trial and take part in follow-up assessments.

Outcomes

As MAPS is a feasibility study, our primary outcomes were referral and recruitment rates, attendance at therapy sessions, medication adherence, acceptability of treatments (determined through assessing discontinuation rates, and through a nested qualitative study with participants) and completion of follow-up appointments. To determine feasibility, we applied 3-stage progression criteria relating to recruitment, retention to follow-up at the primary end point (6-months), adherence to PI and to AP. The progression criteria were agreed with our trial steering committee (TSC), independent data monitoring committee (iDMC) and funder. The specific criteria for meeting each outcome were as follows:

Recruitment ≥80% of planned (green), recruitment within 79–60% of planned (amber), recruitment < 60% of planned (red).

Retention of participants within the study with baseline and outcome assessments at primary end point (6-months, end of treatment) ≥80% of primary outcome completed (green), 79–60% of primary outcome completed (amber), < 60% of primary outcome completed (red).

Satisfactory delivery of adherent therapy to ≥80% of groups receiving PI (green), 79–60% of groups receiving PI (amber), < 60% of groups receiving PI (red). Satisfactory delivery of adherent therapy is operationalised as attending 6 or more sessions of CBT.

Satisfactory delivery of antipsychotic medication to ≥80% of groups receiving AP (green), 79-60% of groups receiving AP (amber), < 60% of groups receiving AP (red). Satisfactory delivery of antipsychotic medication is operationalised as any exposure of AP for six consecutive weeks (this would include a dose below British National Formulary [BNF] lower limits given this is a frequent clinical practice for people of this age, and the drugs are licensed for adults).

We collected a number of secondary outcomes to assess the acceptability and usefulness of the measures for inclusion in a definitive trial. Secondary outcome measures were collected at baseline, 3-months, 6-months and 12-months post-baseline. We designed a variable length follow-up period. Participants recruited in the first 16 months were followed-up for the full 12 months, those recruited thereafter were offered assessments up to the end of treatment (6-months). Our pre-specified provisional choice of primary outcome measure for a definitive trial is total PANSS score and the primary end-point was 6 months. The PANSS is a 30-item rating scale designed to assess psychopathology in people with a diagnosis of schizophrenia.[23] The PANSS assessment was carried out and scored by a trained Research Assistant (RA). Prior to being signed off to carry out and score PANSS assessments, each RA was required to achieve a minimum of 70% percent agreement, and a deviation of no more than 20% on the PANSS total score, between their submitted PANSS scores and a gold standard rating across three PANSS training films produced by the research team. An annual inter-rater reliability event was held for RAs across the sites in 2017 and 2018. The mean PANSS inter-class correlation coefficient (ICC) across the two events was 0.87. We also assessed social and educational/occupational functioning (First Episode Social Functioning Scale; FESFS),[24] subjective recovery (Process of Recovery a questionnaire),[25] dimensions of paranoia, hallucinations, cognitive disorganisation, grandiosity, and anhedonia (Psychotic Experiences

Questionnaire),[26] anxiety and depression (the Hospital Anxiety and Depression Scale),[27] alcohol and drug use (Alcohol Use Disorder Identification Test and Drug Abuse Screening Test)[28]. At baseline, we measured diagnostic symptoms for autism spectrum conditions using the NICE-recommended 10-item version of the Autism Spectrum Quotient (AQ-10).[29]

We also measured non-neurological side effects with the ANNSERS[30] 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, HbA1c concentrations, and fasting plasma glucose). We recorded all of the following as Serious Adverse Events (SAEs): death; life-threatening events; hospitalisation or prolongation of existing hospitalisation; an event that results in persistent or significant disability or incapacity or is otherwise considered medically significant; serious violent incidents; and formal complaints about treatment. In addition to SAEs, we also recorded adverse events (AEs) as determined as any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the treatment e.g. self-harm. SAE and AEs were obtained via self-report from the participant, report from the care team and via medical record note screening. At the final assessment we also assessed for potential adverse effects of trial participation using a measure.

Health economics data were measured using an economic patient questionnaire adapted from previous studies conducted by the authors (Morrison et al., 2018) and the EuroQol five-dimension, five level scale (EQ-5D-5L) health status questionnaire.[31] Diagnosis and antipsychotic prescribing were recorded via review of medical record case notes. The type, dose and duration of each AP prescribed were recorded for each participant for the full 12-month period of involvement in the trial (or 6-months for those who were on a variable follow-up rate).

Minor editorial changes were made to the assessments as follows: space to record an answer to the prompt question on sections 2, 6 and 7 of the Health Economics Questionnaire, removal of the full title of the measure at the top of the AQ-10 and the instructions below the questionnaire to avoid confusion about the purpose of using the measure i.e. we were not using it for the purpose of screening of autism for referral to relevant services, amendment to the language of the ANNSERS to ensure it was understandable in lay terms and that the questions did not break the single blind (REC approval date 11/05/2017) and addition of the category ‘transgender’ on the participant demographic form (REC approval date 19/10/2017).

Statistical analysis

The 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[32] and feasibility information about trial procedures. We did not perform a formal power calculation to detect treatment differences, since the focus of analysis was not hypothesis testing. The analysis followed a pre-specified Statistical Analysis Plan (SAP) agreed by the CI and the iDMC, and published on the Clinical Trials Unit (CTU) website here: https://www.abdn.ac.uk/hsru/what-we-do/trials-unit/statistical-analysis-plans-611.php . All main analyses were based on the Intention-To-Treat (ITT) principle and all analysis was at the participant level. Safety and unwanted effects were analysed based on treatment received rather than as-randomised, with PI defined as any dose of CBT or FI from the trial therapist and AP defined as any dose of an antipsychotic prescribed by the participant's psychiatrist. The analysis took place after full recruitment and follow-up with no interim analyses for efficacy, although the iDMC monitored the trial progress and safety throughout the trial. All analyses were done in Stata version 15.[33] The progression criteria were summarized using descriptive statistics, including: the number of participants referred; number of eligible referrals; number of consenting individuals and recruited individuals to each arm; numbers for drop-out from the allocated interventions; withdrawal of consent; and failure to provide follow-up outcome data. We have provided summary data for treatment adherence and treatment received in each arm, to describe withdrawal from the allocated intervention. We operationalised satisfactory delivery of therapy as attendance at six or more sessions of CBT, which is consistent with our previous trials. Satisfactory delivery of APs was operationalised as uptake of an AP for at least six consecutive weeks (including doses below British National Formulary lower limits, as this is a frequent clinical practice for CYP, and APs are licensed for adults) as assessed by examination of the participants medical records. We have reported descriptive statistics for the components of PI received including number of sessions and milestones achieved, and completion of between-session tasks. We also calculated the proportion of participants who received allocated intervention vs not, and the proportion who moved to the combined arm due to deterioration. Appropriate descriptive statistics were used to summarise baseline and follow-up data with mean (SD) or medians for continuous data and frequencies and percentages for categorical variables. We conducted a repeated-measures analysis of the proposed primary outcome (PANSS) and the secondary outcome (QPR) using 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 time point, and treatment effects were estimated at each time point using a treatment-by-time interaction. For the analysis, missing baseline data was imputed using centre-specific mean. The focus of the analysis was on point estimates and associated 95% confidence intervals rather than statistical significance (p-values); however, we have reported p-values for completeness in the appendix, but all analyses were under-powered and not based on a power calculation. The percentage change on the PANSS was calculated using adjusted PANSS methodology.[34] Due to low response rates or low number of events, analyses for other variables were descriptive, but these outcomes are reported in full. As MAPS was a feasibility study, there was no formal analysis to account for missing data and no attempt was made to adjust for multiple testing. The study was prospectively registered on 27th February 2017, http://www.isrctn.com/ISRCTN80567433.

Role of the funding source

MAPS (both main trial and qualitative studies) was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme following a commissioned call (15/31/04). The call specified the interventions, population, setting, comparator, study design, and important 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.

Changes to the Protocol

Six substantial amendments were submitted to, and approved by the Research Ethics Committee (REC) with full details in the appendix. Important changes to the protocol included: further clarity regarding the feasibility objectives (protocol version 2 22/02/2017; REC approval date 03/03/2017), inclusion criteria change from ‘within one year of onset of psychosis’ to ‘within one year of presentation to services with psychosis’ (protocol version 3 29/03/2017, REC approval date 29/03/2017), following advice from our independent Data Monitoring and Ethics Committee (DMC) and Trial Steering Committee we operationalized the success criteria for AP and PI adherence (protocol v4 12/03/2018; REC approval

12/06/2018) and provided stop/refine/go parameters (protocol v5 17/07/2018; REC approval 21/08/2018).

Results

Between April 1st, 2017 and 31st, October 2018, 101 patients were identified. The first patient was recruited on April 10, 2017.We recruited 61 participants, 18 to PI, 22 to AP and 21 to the combined treatment (Figure 1; Table 1). Follow-up assessments were conducted between July, 2017 and April, 2019.

In summary, regarding our feasibility criteria, our recruitment was 68% of the target (amber progression zone), our retention was 84% at primary end point (green), and for treatment receipt, 82% received six or more sessions of CBT (green) and 65% were exposed to AP for 6 consecutive weeks (amber). Further details follow.

The referral to recruitment rate was 1·6:1 with seven (7%) referred patients declining to take part and only two (2%) parents declining consent to contact their child. At 83 (82·2%) referrals, the Early Intervention in Psychosis services were the most commonly referring service type. The majority of the randomisations were made at the Oxford and Manchester sites with 25 and 21 participants randomised respectively. The number of participants with a psychosis diagnosis at baseline was 41 (67%) and the most commonly recorded diagnosis was F29 unspecified non-organic psychosis (98%). In addition, participants' diagnoses were considered by Consultant Psychiatrists from our research team (AJ, DM, MRB, RW) on the basis of vignettes based on information extracted from PANSS interviews and reviews of medical records. This suggests the vast majority of our sample (at least 57/61) met criteria for a schizophrenia spectrum diagnosis (F20-F29) at point of entry to the trial (see Appendix). Retention at the primary end point (6-months assessment) was high with only two withdrawals from the trial and low attrition. The number of participants retained in the trial at primary end point (6-months assessment) was 51 (84%; green progression zone). Retention at the 12-month follow-up was lower, of the 49 participants who were eligible for a 12-month assessment, a total of 31 (63%) completed the follow-up. See Figure 1 for the flow of participants through the trial. Across all follow-up points, the number of full blind breaks (i.e. actual randomly assigned group was revealed) was three, with two in PI and one in AP. At 3- and 6-months follow-up, the number of partial breaks (i.e. only one treatment was revealed) was seven and at 12 months was four. Of the 135-follow-up assessments, seven assessments (for three participants) (5%) were completed by an assessor with whom a full break had occurred and 12 (9%) completed by an

assessor with whom a partial break had occurred. The remaining breaks (full or partial) were transferred to a new and independent assessor. We intended to assess the proportion of eligible people clinicians were willing to refer, but we were unable to capture this data systematically.

Of the 39 participants assigned to a PI arm, 32 (82%) received six or more sessions of CBT meeting the green zone for progression. Participants who were assigned to PI monotherapy received a median of 14 sessions of CBT (IQR 9, 23) and a median of 3 sessions of FI (IQR 2, 5), only one participant attended zero sessions. Participants who were assigned to the combined treatment received a median of 15 sessions of CBT (IQR 9, 17) and a median of 4 sessions of FI (IQR 2, 5) only one participant attended zero sessions.

Of the 43 participants assigned to an AP arm, 28 (65%) were exposed to AP for 6 consecutive weeks meeting the amber zone for progression. Of the 15 participants who did not meet the AP success criteria, the reasons why success was not met included: participants declined APs (n=3), clinician did not prescribe APs (n=3), both participant and family jointly decided to decline (n=1), and data were unable to be extrapolated from the medical records (n=8). Of those who were in receipt of APs, the mean duration that the participant remained on the medication was 31.5 weeks (SD 14·6, minimum 8·7 and maximum 52). Fourteen participants switched from one AP to another during their involvement in the study. Of the 43 AP prescriptions made, the most commonly prescribed was aripiprazole (n=21), risperidone (n=10) and quetiapine (n=9). For full details regarding medication types, durations and doses see Appendix.

Although slightly higher in the AP arm, overall the proportion of participants who received their allocated intervention was similar across groups (table 2), with the majority of participants receiving treatment as allocated. 10 participants (56%) in the PI arm, 14 participants (64%) in the AP arm and 11 participants (52%) in the combined arm received an adherent dose of their treatment as randomised. As indicated in Table 2, some participants received no treatment due to non-engagement or non-adherence (10 of 61, 16%) and only a small minority received a treatment that they were not allocated to (8 of 61, 13%).

In the intention-to-treat analysis, the numbers of participants in each group achieving ≥25% improvements on adjusted PANSS total scores at 6 months were 16/16 (100%) in the PI arm, 9/18 (50%) in the AP arm 17/17 (100%) in the combined arm (table 3). In the as-treated analysis, few deteriorations were noted across the arms at 6 or 12 months (Table 4). All PANSS and QPR outcomes for 3, 6 and 12 months are summarized in Table 5. All other secondary

outcomes are reported in the Appendix, along with statistical tests of significance for PANSS and QPR.

The as-treated analysis indicated a greater number of serious adverse events (SAE) in the combined arm (n=11) in comparison with the PI arm (n=5), the AP arm (n=2) and the no treatment group (n=5); see Table 4 for a summary of adverse events and PANSS deteriorations. There were no SAEs deemed to be related to trial proceedings. There was a greater number of adverse events (AE) in the AP arm (n=41) and the combined arm (n=35) in comparison to the PI (n=10) and the no treatment group (n=3). The most commonly occurring AE was medication side effects, as noted in the medical records by the participant's clinician. One adverse event in the PI arm (distress about allocation to PI reported immediately post randomisation) was deemed to be related to trial proceedings. Overall, there were nine deteriorations of 125% or greater in PANSS total score: four in the PI arm, one in the combined arm, three in the AP arm, and one where a participant did not receive any treatment. Adverse effects including non-neurological side effects, metabolic effects and weight gain are summarized in the appendix. Potential unwanted effects of trial participation are also included in the Appendix.

Discussion

The MAPS trial has shown that it could be possible to conduct a study comparing antipsychotics with psychological therapies and a combined treatment in adolescents with first-episode psychosis, although the recruitment challenges would indicate that some changes might be required. This pragmatic pilot and feasibility trial had low attrition (<20% at each time point), comparable attrition across each trial arm, and a sizable proportion of participants adhered to the intervention that they were allocated to receive. However, while the majority received exactly what was allocated, a sizable minority of participants did not, and recruitment proved challenging, particularly in certain sites. Therefore, revisions would be required to the trial design and implementation in order to conduct a definitive trial (see Appendix for recommendations).]

All 3 treatments 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 3 treatments also seemed to provide benefit, with average PANSS changes ranging between approximately 13 and 16 points improvement at 6 months and 11 and

10 points at 12 months, all of which fall within the range recognized as clinically important differences; for example, all of these meet the threshold for a patient-rated Minimal Clinical Important Difference (MCID) on the PANSS (11 points)[35] and most are within the threshold for clinician-rated MCID for the PANSS (15 points).[36] Participants receiving the combined treatments experienced more adverse effects; this makes sense given that there are more treatments being delivered that have the potential to cause unwanted effects. However, combined treatment was associated with fewer deteriorations. In addition, participants receiving APs experienced fewer SAEs (n=2) than those receiving PI (n=2) or combined (n=11), but more adverse events (n=41) than PI (n=10) or combined (n=35). However, no SAEs were considered related to the trial treatments. Therefore, it seems reasonable to conclude that all treatments confer benefit and that the different treatments have different adverse effect profiles. However, a definitive test of effectiveness is now required.

The delivery of interventions within the trial seemed competent. APs were administered relatively quickly (average approximately 25 days from randomisation), for a reasonable duration (average approximately 8 months) and attempts were made to maximize benefit for one third of participants allocated to antipsychotics by switching antipsychotic. The three most commonly prescribed antipsychotics were aripiprazole, risperidone and quetiapine, which reflects clinical practice by UK Child and Adolescent Psychiatrists and is consistent with findings of an international study of antipsychotic prescribing for CYP with EOP.[37] For more detailed information regarding dosages, see appendix. Psychiatrists prescribed, as per normal practice, to achieve control of psychotic symptoms within BNF (British National Formulary) recommended dosages. The NICE guidance for Psychosis and Schizophrenia recommends starting with a low dose of an antipsychotic and gradually increasing. The doses in the trial were generally low, except for the higher mean dose of risperidone, which was higher than the 2mg normally recommended for FEP. Olanzapine was an unusual choice for FEP, as it is no longer recommended as a first line treatment due to concerns about its metabolic and weight gaining properties [13]. The provision of the psychological therapies was also consistent with good practice, with first appointment being offered quickly (average of approximately 2 weeks), and the majority of participants receiving over 6 sessions (32 of 39, 82%). With regard to those allocated to receive the offer of family intervention, 21 of 39 (54%) received at least one session, with the average number being 3-4 sessions. This is consistent with FI being offered to all, 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, this suggests FI may be less acceptable to adolescents with FEP than CBT.

Our clinical trial had several limitations. The feasibility trial design and small sample size means that we must exercise caution in interpreting any statistical tests and significance values. With regard to integrity of treatment allocation, the proportions receiving the interventions exactly as allocated ranged between 52% and 64%, although the proportion receiving an additional intervention they were not allocated to receive was only 13% (8 of 61). However, this reflects the real world in which 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 ensure participants were blind to allocation, which may represent a source of bias. All participants met entry criteria including presenting to services with psychosis symptoms; under the care of a psychiatrist within EIP or CAMHS; scoring 4+ on the PANSS delusions or hallucinations subscales for $\geq$7 days. However, it is worth noting that hallucinations can be prevalent in the general population of adolescents, with a median of 7.5% reporting such experiences [38]. While our sample was fairly homogenous 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 F29 unspecified non-organic psychosis. There were also frequent comorbidities in our sample, including high rates of caseness for anxiety, depression and Autistic Spectrum Disorders (ASD) 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 experiencing distressing psychotic experiences, often with significant complexities as mentioned. However, this diagnostic heterogeneity may result in heterogeneity of treatment response to both PI and AP, which may affect the appropriateness and cost:benefit ratio of each treatment relative to adverse effects. For example, psychotic symptoms in the context of depression or PTSD may be more likely to benefit from PI, whereas psychotic symptoms in the context of ASD may be more likely to demonstrate treatment resistance to APs [39].

The clinical heterogeneity of this help-seeking adolescent population may require a more tailored and personalised treatment approach delivered through an adaptive trial design. In a

future definitive trial, a baseline adolescent diagnostic assessment using a validated structured tool such as the Development and Wellbeing Assessment (DAWBA)[40] may provide a more detailed picture of the range of adolescent psychopathology and predictors of treatment response.

There were several limitations with regard to the initiation and delivery of medication within the trial. While we recommended that prescribing psychiatrists followed NICE guidelines, we did not systematically monitor fidelity to NICE prescribing guidance and we did not assess drug levels, which may be required to identify a potential cause of non-response [41]; a definitive trial should consider these options. It is possible that the more rigorous monitoring of fidelity for delivery of PI relative to APs may have resulted in bias that favoured PI; the proportion demonstrating a good response to APs (>50% improvement) observed in our trial was relatively low compared to the response rate of 65% in the recent OPTIMISE trial of antipsychotics in adult FEP [42], which could be the result on non-concordance or could be more specific to the nature of an adolescent population or the relatively long duration of untreated psychosis that was observed in our sample. A placebo condition would have been helpful in interpreting treatment efficacy (and is currently being used in an ongoing study of PI with and without APs[43]), particularly in relation to the effects of APs; however, it may not be necessary to investigate pragmatic effectiveness of interventions in NHS settings and is unnecessary for a feasibility study that is not designed to investigate efficacy. Since all participants were receiving care from EIP and/or CAMHS, it is impossible to exclude the possibility that any benefits observed are attributable to factors such as good care-coordination, engagement and crisis management, rather than the specific active treatments provided by the trial. The diagnostic heterogeneity mentioned above, while reflecting clinical realities of EIS provision, also represents a limitation, since different diagnostic groups may exhibit differential treatment responses. The omission of a diagnostic interview at point of entry to the study is also a limitation. Some of the less prioritised secondary outcome measures (self-report scales) had large amounts of missing data (as a result of minimising the impact of participant burden on attrition) and there were high rates of missing data from blood test results since many young people were reluctant to consent to these, so the size of assessment battery should be limited. Duration of follow-up should be at least 12 months to allow for evaluation of the longevity of treatment effects. Given the extensive recruitment challenges faced by our trial, site selection for a definitive trial should be based on prevalence of adolescent FEP, willingness of clinicians to recognise clinical equipoise and the need for a trial and, therefore, to randomly allocate

treatments. In addition, the upper age limit could be increased from 18 to 25 years, since definitions of adolescence often extend to 25 years of age (e.g. World Health Organisation's definition of youth) and this would widen the potential pool of participants. More extensive recommendations for a clinical trial are considered in the Appendix.

The main implication of this trial is that there is a need for an adequately powered effectiveness trial to provide evidence regarding relative effectiveness of antipsychotic medication and psychological therapies (CBT and family intervention) for adolescents with EOP. On the basis of our trial, it seems reasonable to support young people with EOP and their families (in the absence of immediate risk to self or others) to make informed treatment choices as outlined in the NICE guideline CG155.[13]

Research in Context:

Evidence before this study: We searched PubMed up to December 10, 2019, with the terms "schizophrenia", "psychosis", "psychological therapy", "psychosocial intervention", "CBT", "family intervention", "antipsychotic", "neuroleptic", "child*", "adolescent", "young person", "first episode psychosis". We did not apply any language restrictions. One systematic review identified seven placebo-controlled trials of antipsychotic medication for young people with psychosis who were under the age of 18 and meta-analysis indicated small but significant effects of antipsychotics on psychotic symptoms and a medium and significant adverse effect on weight gain. There were no trials of psychological intervention in a strictly under 18 years of age population. A systematic review and network meta-analysis of antipsychotics identified 28 randomised controlled trials (RCTs) of APs for children or adolescents with psychosis. Results of the pairwise meta-analyses indicated a benefit of number of antipsychotics over placebo for overall symptoms and 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 regards to clozapine the majority of the evidence was indirect. Since publication of these systematic reviews there have been two further trials of AP and one feasibility RCT of psychological intervention in an under 18 population. There are no head-to-head trials comparing the clinical or cost effectiveness of pharmacological, psychological and a combined treatment for adolescents with psychosis.

Added value of this study: It is possible to conduct a methodologically rigorous clinical trial that randomises young people with psychosis to psychological treatment, pharmacological treatment or the combination. Our study suggests that antipsychotic medication, psychological intervention (CBT plus family intervention) and the combined intervention are acceptable, safe and helpful treatments for young people with early psychosis, with all three treatments seeming to provide benefit in terms of symptoms (total PANSS score) and recovery (QPR total). There was no suggestion 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 (e.g. combined treatment being superiority to monotherapies for effectiveness) and non-inferiority (e.g. between monotherapies). Our preliminary findings appear consistent with current guidelines (e.g. CG155) that recommend informed choices and shared decision making regarding treatment options for early psychosis on the basis of cost-benefit profiles.

Contributors

The MAPS Group

Max Birchwood

Ravneet Bhogal

Samantha Bowe

Rory Byrne

Joe Clacey

Linda Davies

Robert Dudley

Richard Emsley

Renata Fialho

Rick Fraser

Paul French

Thomas Goodall

Emmeline Goodby

Peter Haddad

Emmeline Joyce

Negar Khozoee

Miriam Kirkham

Amy Langman

Amanda Larkin

Helena Laughton

Ashley Liew

Eleanor Longden

Ashley Louise Teale

Laura McCartney

Elizabeth Murphy

Fiona Padgett

Jasper Palmier-Claus

Sarah Peters

Catarina Sacadura

Jo Smith

Verity Smith

Ann Steele

Rachel Upthegrove

Richard Whale

Lauren Wilcox

Alison Yung

Contributors

APM planned the study, contributed to the application for funding, made substantial contribution to the design of the trial protocol, the statistical analysis plan, managed the trial as Chief Investigator, contributed to writing, and critically read the manuscript. MP contributed to the application for funding, made substantial contribution to the development of the trial protocol, as well as providing overall management of the trial and data management. DM made substantial contribution to the development of the trial design and protocol, and critically read the manuscript. LJ made substantial contribution to the development of the trial design and protocol, and critically read the manuscript. DF contributed to the application for funding, made substantial contribution to the design of the trial and protocol, and critically read the manuscript. MRB contributed to the application for funding, made substantial contribution to the design of the trial and protocol, and critically read the manuscript. NH made substantial

contribution to the development of the trial design and protocol, and critically read the manuscript. DF contributed to the application for funding, made substantial contribution to the design of the trial and protocol, and critically read the manuscript. JH made substantial contribution to the development of the trial design and protocol, as well as the statistical analysis plan, conducted the analysis and critically read the manuscript. GM made substantial contribution to the development of the trial design and protocol, as well as the statistical analysis plan, conducted the analysis and critically read the manuscript. JN contributed to the application for funding, made substantial contribution to the design of the trial and protocol, the statistical analysis plan, and critically read the manuscript. DS contributed to the application for funding, made substantial contribution to the design of the trial and protocol, and critically read the manuscript. CH contributed to the application for funding, made substantial contribution to the development of the trial design and protocol, and critically read the manuscript. AJ made substantial contribution to the development of the trial design and protocol, and critically read the manuscript. All authors read the final manuscript.

Declaration of interests

APM reports personal fees from the provision of training workshops in cognitive behaviour 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 from CBT Training at Greater Manchester Mental Health NHS Foundation Trust. MRB reports royalties from Oxford University Press and personal fees from Medical Defence Union, outside the submitted work. DF reports grants from the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) during the conduct of the study, outside the submitted work. LJ reports personal fees from New Harbinger Publications, outside the submitted work. NH reports that he is the chair of the board of trustees of Manchester Global Foundation, a Charitable Incorporated Organisation (CIO) registered in England and Wales; he is a past Trustee of Lancashire Mind, Pakistan Institute of Living & Learning and Abasseen Foundation. Nusrat Husain reports that he established an independent general hospital (Remedial Centre) in Karachi Pakistan, this is now owned and operated by his sibling, the hospital is also attached to a pharmacy. Nusrat Husain reports that he has received an honorarium and travel grants from various pharmaceutical industries. GM grants from NIHR HTA during the conduct of the study. JN reports membership of the following NIHR boards: CPR decision making committee; HTA Commissioning Board; HTA Commissioning sub-board (EOI); HTA Funding Boards Policy Group; HTA General Board; HTA Post-Board funding teleconference; NIHR CTU Standing

Advisory Committee; NIHR HTA & EME Editorial Board; Pre-exposure Prophylaxis Impact Review Panel. DS reports personal fees from the National Clinical Audit of Psychosis, royalties from Wiley Blackwell publication for "Promoting Recovery in Early Psychosis" 2010, ISBN 978-1-4051-4894-8 and reports membership of the current NICE guideline development group for Rehabilitation in adults with complex psychosis and related severe mental health conditions, board member of the National Collaborating Centre for Mental Health (NCCMH), outside the submitted work. CH reports that he was Chair of the NICE Guideline Development Group for Schizophrenia in Children & Young People (2011-2013) and was Chair of the NICE Psychosis and Schizophrenia in Children Evidence Update (2014-2015), outside of the submitted work.

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Tables

Table 1: Baseline characteristics

	PI N=18	PI + AP N=21	AP N=22
Age (years)	18; 16.3 (1.4)	21; 16.2 (1.3)	22; 16.4 (1.3)
Gender – n (%)			
Male	8 (44.4)	10 (47.6)	12 (54.5)
Female	10 (55.6)	10 (47.6)	9 (40.9)
Non-binary	0 (0)	1 (4.8)	1 (4.5)
Duration of untreated psychosis (months) – n; median	13; 12	16; 8	15; 9
Highest level of education – n (%)			
Secondary	9 (50.0)	11 (52.4)	11 (50.0)
Further	9 (50.0)	10 (47.6)	11 (50.0)
Employment status – n (%)			
College student	7 (38.9)	8 (38.1)	9 (40.9)
High school student	5 (27.8)	8 (38.1)	7 (31.8)
Unemployed	4 (22.2)	2 (9.5)	2 (9.1)
Full-time	1 (5.6)	1 (4.8)	3 (13.6)
Part-time	1 (5.6)	1 (4.8)	1 (4.5)
Voluntary	0 (0)	1 (4.8)	0 (0)
Marital status (single) – n (%)	18 (100.0)	21 (100.0)	22 (100.0)
Living arrangements – n (%)			
Parent(s) and/or siblings	15 (83.3)	18 (85.7)	20 (90.9)
Living in supported accommodation	2 (11.1)	1 (4.8)	1 (4.5)
Other family member(s)	1 (5.6)	2 (9.5)	0 (0)
Alone	0 (0)	0 (0)	1 (4.5)
Ethnicity – n (%)			
White British	14 (77.8)	18 (85.7)	17 (77.3)
Indian	1 (5.6)	0 (0)	0 (0)
Pakistani	0 (0)	1 (4.8)	2 (9.1)
White Asian	0 (0)	1 (4.8)	0 (0)
Black African	1 (5.6)	0 (0)	1 (4.5)
Black Caribbean	0 (0)	1 (4.8)	1 (4.5)
White Irish	0 (0)	0 (0)	1 (4.5)
Other	2 (11.1)	0 (0)	0 (0)
Religion – n (%)			
Atheism	7 (38.9)	10 (47.6)	12 (54.5)
Christianity	4 (22.2)	4 (19.0)	4 (18.2)
None	6 (33.3)	3 (14.3)	2 (9.1)
Islam	0 (0)	1 (4.8)	2 (9.1)
Buddhism	0 (0)	1 (4.8)	0 (0)
Other	1 (5.6)	2 (9.5)	2 (9.1)
PANSS total	18; 72.9 (9.7)	21; 75.9 (14.8)	22; 74.8 (12.2)
PANSS positive	18; 21.2 (3.8)	21; 21.2 (5.8)	22; 22.9 (6.0)
PANSS negative	18; 15.8 (3.3)	21; 18.5 (6.6)	22; 17.9 (5.6)
PANSS disorganised	18; 20.1 (4.5)	21; 21.0 (5.4)	22; 19.9 (4.6)
PANSS excitement	18; 17.1 (3.7)	21; 17.9 (4.9)	22; 19.3 (4.1)
PANSS emotional distress	18; 25.2 (4.5)	21; 24.8 (5.8)	22; 24.7 (6.7)
At least moderate hallucinations PANSS P3 (Hallucinatory Behaviour) ≥ 4 score	15	18	21

At least moderate delusions	13	14	14
Delusions (PANSS P1 (Delusions) ≥ 4 score, PANSS P6 (Suspiciousness/persecution) ≥5 score and PANSS P5 (Grandiosity) ≥5 score)			
At least moderate on both	10	11	13
QPR	12; 46.1 (9.3)	18; 42.6 (10.1)	15; 42.1 (10.0)
AUDIT	9; 7.7 (7.9)	11; 7.4 (8.6)	12; 6.8 (7.4)
DAST	9; 1.9 (1.8)	11; 2.5 (3.2)	12; 1.6 (2.3)
AQ-10	8; 4.8 (2.1)	10; 5.4 (2.1)	11; 5.2 (1.8)
Ratio of participants scoring over AQ-10 clinical threshold	12 (66.7)	15 (71.4)	17 (77.3)
SPEQ			
Paranoia	8; 31.5 (12.9)	13; 42.3 (14.8)	14; 41.8 (14.0)
Hallucinations	9; 23.4 (10.1)	12; 27.0 (6.6)	14; 27.4 (8.8)
Cognitive disorganisation	9; 7.3 (2.9)	12; 9.1 (1.6)	13; 9.2 (2.6)
Grandiosity	9; 6.1 (4.6)	12; 4.9 (6.5)	13; 3.9 (3.1)
Anhedonia	9; 27.2 (9.6)	11; 22.5 (8.7)	13; 18.8 (9.6)
HADS			
Anxiety	10; 11.2 (2.6)	13; 14.2 (2.5)	15; 12.7 (4.0)
Scoring over threshold for caseness – n (%)	5 (27.8)	12 (57.1)	9 (40.9)
Depression	10; 9.2 (3.8)	13; 10.2 (4.4)	15; 9.7 (5.1)
Scoring over threshold for caseness – n (%)	3 (16.7)	6 (28.6)	5 (22.7)
ANNSERS			
Total	8; 17.5 (10.4)	11; 17.2 (7.1)	12; 15.9 (6.4)
Number of side effects	8; 10.6 (4.8)	11; 11.5 (3.8)	12; 11.2 (5.2)
FESFS			
Ability			
Living skills	9; 13.3 (1.2)	10; 12.6 (1.6)	12; 11.8 (2.5)
Interacting with people	9; 10.6 (2.4)	10; 10.4 (2.6)	12; 9.2 (2.2)
Friends and activities	9; 16.3 (3.9)	10; 13.8 (2.8)	12; 16.0 (2.8)
Intimacy	9; 12.3 (2.4)	7; 13.7 (1.6)	10; 14.0 (3.7)
Family	9; 8.6 (2.6)	10; 8.5 (1.9)	10; 9.1 (1.9)
Relationships and social activities at work	6; 8.2 (1.6)	7; 8.3 (1.4)	7; 7.7 (0.8)
Work	6; 9.8 (2.0)	7; 8.6 (1.6)	7; 9.0 (1.2)
School relationships and social activities at school	6; 8.0 (1.9)	10; 8.5 (1.3)	8; 6.4 (1.9)
Educational	6; 8.3 (1.6)	10; 7.2 (1.7)	7; 7.6 (1.9)
Frequency			
Living skills	9; 12.9 (2.3)	10; 11.7 (2.4)	12; 11.9 (2.4)
Interacting with people	9; 11.0 (1.9)	10; 10.2 (2.7)	11; 9.2 (2.2)
Friends and activities	9; 13.9 (4.1)	9; 13.6 (2.5)	12; 15.1 (2.5)
Intimacy	9; 8.8 (4.1)	9; 9.2 (4.0)	11; 11.6 (5.5)
Family	9; 9.6 (2.5)	10; 8.7 (2.5)	11; 8.9 (2.3)
Relationships and social activities at work	6; 5.3 (3.4)	7; 5.9 (1.9)	7; 5.4 (1.5)

Work	6; 8.5 (4.6)	7; 8.7 (2.8)	7; 9.1 (2.4)
School relationships and social activities at school	6; 8.8 (1.7)	10; 8.4 (1.9)	8; 6.8 (2.4)
Educational	6; 8.5 (1.4)	10; 7.2 (2.4)	7; 7.6 (2.4)
BMI	10; 23.6 (4.5)	13; 22.5 (3.7)	13; 24.1 (6.4)
Blood pressure(mmHg)			
Systolic	10; 108.1 (11.0)	12; 112.2 (10.1)	10; 114.8 (11.5)
Diastolic	10; 67.8 (7.8)	12; 69.6 (9.7)	10; 67.8 (5.7)
Waist circumference	9; 80.6 (11.4)	12; 76.3 (8.0)	11; 78.3 (13.3)
FBG	5; 4.6 (0.2)	3; 5.0 (1.1)	6; 4.2 (0.4)
HbA1c	5; 30.4 (1.1)	2; 35.5 (2.1)	7; 30.7 (3.7)
Cholesterol	6; 3.5 (0.3)	3; 3.9 (0.4)	7; 3.8 (0.6)
LDL	6; 2.0 (0.2)	3; 2.1 (0.2)	6; 2.1 (0.5)
HDL	6; 1.0 (0.3)	3; 1.5 (0.6)	7; 1.1 (0.5)
Triglycerides	6; 1.0 (0.4)	3; 0.7 (0.2)	7; 1.0 (0.8)
Prolactin	6; 163.2 (79.2)	3; 170.3 (35.9)	7; 268.6 (86.6)

Values are n; mean (standard deviation) unless otherwise stated

Table 2: Treatment received (adherence)

	PI N=18	AP N=22	PI + AP N=21
Treatment received (adherence)			
PI	10 (55.6)	0 (0)	7 (33.3)
AP	2 (11.11)	14 (63.66)	1 (4.8)
PI + AP	4 (22.2)	2 (9.11)	11 (52.4)
None	2 (11.11)	6 (27.3)	2 (9.5)
Adherence			
Complied with treatment	14 (77.8)	16 (72.7)	11 (52.4)

Values are n (percent)

Table 3: PANSS improvement (ITT analyses)

		PI N=18	PI + AP N=21	AP N=22
>25%				
	3 months	7 (41.2)	8 (47.1)	8 (42.1)
	6 months	10 (62.5)	11 (64.7)	5 (27.8)
	12 months	6 (54.5)	8 (72.7)	6 (66.7)
>50%				
	3 months	2 (11.8)	2 (11.8)	3 (15.8)
	6 months	5 (31.3)	5 (29.4)	4 (22.2)
	12 months	3 (27.3)	3 (27.3)	3 (33.3)
>75%				
	3 months	0 (0)	1 (5.9)	0 (0)
	6 months	1 (6.3)	1 (5.9)	0 (0)
	12 months	1 (9.1)	1 (9.1)	0 (0)

Table 4: Adverse events and deterioration in PANSS total by treatment received (as treated)

	PI N=17	PI + AP N=23	AP N=15	None N=5	Unable to be captured N=1
Serious adverse events					
Participants with an SAE	4 (23.5)	8 (34.8)	2 (13.3)	4 (23.5)	0 (0)s
Total number of SAEs	5	11	2	5	0
Participants with more than one SAE	1 (25.0)	2 (25.0)	0 (0)	1 (25.0)	0 (0)
Details					
Voluntary psychiatric admission	0	3	0	0	0
Life threatening (suicide attempt)	1	1	0	1	0
Serious violent incident	2	1	2	2	0
Admission to a general medical ward	2	1	0	2	0
Otherwise considered medically significant (overdose of medication)	0	4	0	0	0
Otherwise considered medically significant (ingested 5 painkillers)	0	1	0	0	0
Adverse events					
	5 (29.4)	16 (69.6)	13 (86.7)	3 (60.0)	0 (0)
Participants with an AE	10	35	41	3	0
Total number of AEs	3 (60.0)	9 (56.3)	9 (69.2)	0 (0)	0 (0)
Participants with more than one AE					
Details					
Self-harm	6	12	7	3	0
Medication side-effect	0	17	28	0	0
Other adverse event	4	5	6	0	0
Distress reported regarding allocation	0	1	0	0	0
Deterioration in PANSS total					
6 months					
>25%	1 (6.3)	1 (5.3)	1 (7.7)	1 (33.3)	0 (0)
>50%	1 (6.3)	1 (5.3)	1 (14.3)	0 (0)	0 (0)
12 months					
>25%	0 (0)	1 (7.7)	0 (0)	0 (0)	0 (0)
>50%	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 5: PANSS and QPR outcome (ITT)

	PI N=18	PI + AP N=21	AP N=22
Total			
Baseline	18; 72.9 (9.7)	21; 75.9 (14.8)	22; 74.8 (12.2)
3 months	17; 64.9 (9.9)	17; 64.2 (16.1)	19; 65.6 (15.4)
6 months	16; 59.8 (13.7)	17; 62.0 (15.9)	18; 68.6 (17.3)
12 months	11; 61.3 (12.4)	11; 56.2 (12.3)	9; 55.4 (7.0)
Positive			
Baseline	18; 21.2 (3.8)	21; 21.2 (5.8)	22; 22.9 (6.0)
3 months	17; 19.7 (5.6)	17; 16.1 (5.2)	19; 18.9 (7.0)
6 months	16; 17.4 (6.9)	17; 15.3 (5.9)	18; 19.2 (6.1)
12 months	11; 18.6 (4.6)	11; 13.4 (7.0)	9; 14.0 (5.7)
Negative			
Baseline	18; 15.8 (3.3)	21; 18.5 (6.6)	22; 17.9 (5.6)
3 months	17; 14.4 (3.7)	17; 16.8 (6.8)	20; 16.5 (5.6)
6 months	16; 14.4 (5.4)	18; 16.8 (7.4)	18; 17.8 (5.3)
12 months	11; 13.7 (3.8)	11; 14.5 (5.7)	9; 15.1 (4.8)
Disorganised			
Baseline	18; 20.1 (4.5)	21; 21.0 (5.4)	22; 19.9 (4.6)
3 months	17; 18.4 (3.6)	17; 18.4 (5.3)	19; 18.2 (5.1)

6 months	16; 16.6 (3.7)	17; 17.5 (4.3)	18; 19.3 (6.7)
12 months	11; 17.8 (3.4)	11; 16.5 (3.3)	9; 15.1 (4.8)
Excitement			
Baseline	18; 17.1 (3.7)	21; 17.9 (4.9)	22; 19.3 (4.1)
3 months	17; 15.6 (3.8)	17; 15.7 (4.5)	20; 16.7 (5.2)
6 months	16; 14.8 (3.7)	18; 16.2 (5.6)	18; 16.6 (5.8)
12 months	11; 15.9 (4.8)	11; 14.5 (4.6)	9; 14.3 (3.0)
Emotional distress			
Baseline	18; 25.2 (4.5)	21; 24.8 (5.8)	22; 24.7 (6.7)
3 months	17; 21.4 (5.5)	17; 20.3 (5.6)	20; 21.5 (8.3)
6 months	16; 19.4 (5.9)	17; 19.9 (7.2)	18; 21.5 (8.4)
12 months	11; 18.9 (6.6)	11; 16.1 (6.2)	9; 17.1 (3.4)
QPR			
Baseline	12; 46.1 (9.3)	18; 42.6 (10.1)	15; 42.1 (10.0)
3 months	11; 47.1 (10.5)	10; 51.8 (8.6)	13; 44.6 (12.3)
6 months	8; 49.4 (7.8)	12; 51.3 (10.7)	15; 49.9 (13.4)
12 months	7; 54.1 (6.9)	9; 59.6 (7.8)	6; 52.7 (12.0)