Psychological intervention, antipsychotic medication or a combined treatment for adolescents with a first episode of psychosis: the MAPS feasibility three-arm RCT

Anthony P Morrison,[1,2*] Melissa Pyle,[1,2] Rory Byrne,[1,2] Matthew Broome,[3,4,5,6] Daniel Freeman,[4,6] Louise Johns,[4,6] Anthony James,[4,6] Nusrat Husain,[2,7] Richard Whale,[8] Graeme MacLennan,[9] John Norrie,[10] Jemma Hudson,[9] Sarah Peters,[2] Linda Davies,[2] Samantha Bowe,[1] Jo Smith,[11] David Shiers,[1,2] Emmeline Joyce,[1] Wendy Jones,[1,2] Chris Hollis[12] and Daniel Maughan[6]

[1]Psychosis Research Unit, Greater Manchester Mental Health NHS Foundation Trust, Manchester, UK
[2]Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
[3]Institute for Mental Health, School of Psychology, University of Birmingham, Birmingham, UK
[4]Department of Psychiatry, Medical Sciences Division, University of Oxford, Oxford, UK
[5]Centre for Human Brain Health, School of Psychology, University of Birmingham, Birmingham, UK
[6]Warneford Hospital, Oxford Health NHS Foundation Trust, Oxford, UK
[7]Early Intervention in Psychosis Service, Lancashire and South Cumbria NHS Foundation Trust, Chorley, UK
[8]Brighton and Sussex Medical School, University of Sussex, Brighton, UK
[9]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[10]Clinical Trials Unit, University of Edinburgh, Edinburgh, UK
[11]School of Allied Health and Community, University of Worcester, Worcester, UK
[12]National Institute for Health Research MindTech MedTech Co-operative, Division of Psychiatry and Applied Psychology, Institute of Mental Health, University of Nottingham, Nottingham, UK

*Corresponding author anthony.p.morrison@manchester.ac.uk

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Scientific summary

The MAPS feasibility three-arm RCT

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Scientific summary

Background

The first episode of psychosis usually occurs at an age between 15 and 35 years, during adolescence or young adulthood. Developing psychosis during this period can lead to significant personal, social and economic costs. Research indicates that functional outcomes can be worse for psychosis developed during adolescence than for psychosis developed in adulthood (especially when there have been premorbid difficulties), with higher rates of suicide and suicide attempts, and greater economic costs than other mental health conditions in adolescence. Providing access to evidence-based treatments for young people with psychosis is paramount. However, the evidence base for antipsychotic medication is limited to a small number of studies that suggest only a small benefit of antipsychotic medication over placebo, and a greater risk of metabolic side effects for adolescents than for adults. There is sparse evidence for psychological intervention, with only one small feasibility study of psychological intervention in under-18-year-olds. The treatment recommendations in the National Institute for Health and Care Excellence clinical guideline (CG155) for the treatment of psychosis and schizophrenia in children and young people were drawn primarily from the larger adult psychosis evidence base, which was considered sufficiently strong to make the current recommendations. However, in the light of the limited evidence base for children and young people, the National Institute for Care Excellence made a specific research recommendation for an evaluation of the clinical effectiveness and cost-effectiveness of antipsychotic medication versus psychological intervention (cognitive–behavioural therapy and family intervention) versus both treatments combined for an adolescent first episode of psychosis.

Objectives

The broad objective of Managing Adolescent first-episode Psychosis: a feasibility Study (MAPS) was to produce quantitative and qualitative data to answer the question of how feasible it is to conduct a study to examine the effectiveness of psychological intervention, antipsychotic medication or a combined treatment in young people with a first episode of psychosis. Our specific objectives were (1) to identify the willingness of clinicians to refer to the trial and the proportion of young people who consented to take part and subsequently adhered to their treatment allocation; (2) to assess retention at follow-up of the proposed primary outcome, the Positive and Negative Syndrome Scale, at the end of treatment; (3) to determine the acceptability and feasibility of the three treatment options to participants, their parents or carers and prescribing clinicians; (4) to determine the relevance and validity of the candidate outcomes in preparation for a definitive trial; and (5) to test our randomisation and blinding procedures.

Methods

Our trial design was a prospective randomised open-blinded evaluation feasibility trial. The trial was conducted in early intervention in psychosis services and child and adolescent mental health services across seven UK sites: Manchester, Oxford, Lancashire, Sussex, Birmingham, Norfolk and Suffolk, and Northumberland, Tyne and Wear. Trial participants were randomised in a 1 : 1 : 1 ratio to psychological intervention, antipsychotic medication or a combined treatment, and were stratified by centre and family contact. Randomisation was via a web-based platform hosted by the Centre for Healthcare Randomised Trials unit. All assessors were blind to allocation until all participants' outcome measures were completed.

Participants were eligible if they were aged 14–18 years; were experiencing their first episode of psychosis with current delusions or hallucinations; met either the *International Classification of Diseases*, Tenth Revision, criteria for a schizophrenia spectrum diagnosis or the entry criteria for early intervention in psychosis; were under the care of early intervention in psychosis services and/or child and adolescent mental health services; and were able to provide written informed consent. Participants were not eligible if they had an *International Classification of Diseases*, Tenth Revision, diagnosis of organic psychosis; had a moderate to severe learning disability; had a primary diagnosis of alcohol or substance dependency; had insufficient command of English to provide written informed consent; scored ≥ 5 points on the Positive and Negative Syndrome Scale on conceptual disorganisation; presented with immediate risk to self or others at the time of referral; and/or had received antipsychotic medication or psychological intervention in the 3 months prior to referral.

Interventions were antipsychotic medication psychological intervention or a combined treatment. Antipsychotic medications were prescribed by the participant's usual care team psychiatrist. The psychiatrist was asked to commence antipsychotic medication as soon as possible after randomisation, and was free to make the decision about the type and dose of antipsychotic medication as well as the change of antipsychotic in line with their usual practice.

Psychological intervention was a combination of cognitive–behavioural therapy and family intervention. Up to 26 hours of cognitive–behavioural therapy was offered over a 6-month treatment window, with an additional four booster sessions over the subsequent 6 months. Cognitive–behavioural therapy was based on an integrative cognitive model of psychosis and was manualised with four phases of engagement, assessment, formulation and change strategies. Family intervention was delivered by the same cognitive–behavioural therapy therapist, with up to six sessions available over the 6-month treatment window. Family intervention was optional; therefore, participants and families could decide to decline this component of psychological intervention if they wished. The combined treatment was a combination of antipsychotic medication and psychological intervention, as described.

Our primary outcome was feasibility data pertaining to recruitment rates, psychological intervention and antipsychotic medication adherence, and retention to follow-up of the proposed primary outcome for a definitive trial at the end of treatment. To evaluate the success of these feasibility criteria we adopted a three-stage progression criterion that was approved by our independent Data Monitoring and Ethics Committee, the Trial Steering Committee and the funder. Adherence to therapy was determined via cognitive–behavioural therapy session records, and adherence to antipsychotic medication was determined via screening of the participant's medical records.

Our secondary outcomes were psychosis symptoms and dimensions of psychosis; service user-defined recovery; anxiety and depression; social and occupational functioning; substance and alcohol use; adverse effects of medication and metabolic side effects; potential adverse effects of trial participation; (serious) adverse events; and health economics data. At baseline, we recorded the duration of untreated psychosis and the Autism Spectrum Quotient.

Participants were followed up at 3, 6 and 12 months (those who were recruited after the first 16 months did not receive a 12-month follow-up assessment). We conducted a qualitative study nested within MAPS to explore both the acceptability and the feasibility of the trial and the three treatment options. Interviews were conducted with trial participants, their parents or carers and their prescribing clinicians. The qualitative interviews and analyses were conducted with leadership from people with personal or parental experience of psychosis spectrum difficulties. Data were thematically analysed with inductive coding of the data at the manifest level to produce thematic representations of the participants' perspectives.

Results

For our three-stage progression criterion, the green zone was achieved for 50% of the criterion and the amber zone for 50% of the criterion. In total, 61 participants (aged 14–18 years; mean age range 16.2–16.4 years; standard deviation 1.3–1.4 years) were enrolled into the study: 18 were assigned to psychological intervention, 22 to antipsychotic medication and 21 to the combination treatment. The study referral to randomisation ratio was low, and overall recruitment was 67.8% of the target (amber zone). We had low rates of attrition (< 20%) and high rates of retention (> 80%) at the 3- and 6-month follow-ups, with a rate of retention to follow-up at the end of treatment of 83.6% (green zone). Retention was lower at longer-term follow-up. In the psychological intervention and combined arms, 82.1% received six or more sessions of cognitive–behavioural therapy (green zone) and the median number of sessions of cognitive–behavioural therapy was 14 for those in the psychological intervention arm and 15 for those in the combined arm. In the antipsychotic arm and the combined arm, 65.1% received antipsychotic medication for 6 consecutive weeks (amber zone). The mean duration of antipsychotic prescription was 31.5 weeks (standard deviation 14.6 weeks, minimum 8.7 weeks and maximum 52 weeks).

Some participants crossed over from their allocated treatment arm. In the psychological intervention arm, 8 out of 18 (44%) participants crossed over. One participant met the deterioration criteria (1/18, 6%), three (3/18, 17%) had an antipsychotic medication added to their treatment, two (2/18, 11%) participants did not receive an adherent dose of therapy and had an antipsychotic medication added to their treatment and two (2/18, 11%) participants did not receive an adherent dose of therapy. In the antipsychotic arm, eight (8/22, 36%) participants crossed over. In six cases (6/22, 27%), this was because the participant was not prescribed an antipsychotic. In addition, two (2/22, 9%) participants met the deterioration criteria. In the combined arm, 10 (10/21, 48%) participants crossed over: nine (9/21, 42%) because they were not prescribed an antipsychotic medicine and one (1/21, 5%) because they did not receive an adherent dose of therapy. There were no serious adverse events related to the trial and one related adverse event.

We conducted a repeated-measures analysis of the proposed primary outcome (Positive and Negative Syndrome Scale) and the secondary outcome (Questionnaire about the Process of Recovery) using a mixed-effects model to account for the discrete timing of the follow-up assessments and adjust for site and/or therapist. Safety outcomes were reported on the basis of as-treated status, defined as any one session of cognitive–behavioural therapy or any one dose of antipsychotic medication descriptive statistics are reported for safety outcomes. There were no significant differences in the Positive and Negative Syndrome Scale total at 6 months between the three treatment arms. For the comparison of the psychological intervention arm with the antipsychotic arm at 6 months, the Positive and Negative Syndrome Scale total was lower in the psychological intervention arm, with a mean difference of −7.79 points (95% confidence interval −16.02 to 0.45 points; $p = 0.064$). For comparisons between the combined arm and monotherapies, the Positive and Negative Syndrome Scale total was lower in the psychological intervention arm (mean difference −1.31, 95% confidence interval −9.92 to 7.30 points; $p = 0.766$), but higher in the antipsychotic arm (mean difference 6.44, 95% confidence interval −2.44 to 15.32 points; $p = 0.155$). The completion rate of health economics data was low across the three treatment arms.

Treatment beliefs varied within the group of prescribers interviewed, with both positive and negative aspects of each main treatment type identified. However, there was a strong, clear consensus for the perceived value of antipsychotic medication as a primary treatment for first episode of psychosis, with cognitive–behavioural therapy and/or family intervention considered valuable adjuncts or secondary treatment options. Although prescribers valued antipsychotic medication owing to its perceived function of alleviating acute distress, symptomatology or risk more quickly than other treatments, the potential harms to children and young people were also frequently highlighted as an important factor in treatment decision-making and willingness to refer a young person to a randomised treatment trial. Referring young people to the treatment trial was perceived by prescribers to be a clinical decision,

whereby skilled clinical judgement was required to determine individually appropriate treatments for what was a complex and emerging experience, and they were hesitant to relinquish clinical control. Prescribers balanced the value of careful assessment and accurate diagnosis with the need for immediate treatment to reduce risk and distress. Professional and organisational influences, such as duty of care and prescribers' own treatment beliefs, underpinned this decision-making process. Trial procedures also influenced the acceptability of referring patients; clinicians perceived the trial as addressing an important question for which evidence was lacking and for a population with clinical need for whom psychological services were not routinely available. Close communication with the trial team, which included experienced clinicians, and scope to retain clinical control over treatment choices were highly valued.

Young people perceived both antipsychotic medication and psychological interventions to be acceptable treatment approaches. However, the specific benefits and mechanisms of action were viewed as potentially different. Antipsychotic medications were perceived to have the potential to address symptoms, often quickly, such as reducing cognitive intrusions and anxiety, but concerns were expressed around sedative side effects. Cognitive–behavioural therapy was viewed as a more interactive treatment approach, hard to access in routine care. Moreover, young people perceived benefits to functioning and improved understanding of their experiences. Combining treatment was seen to have added benefits, with a perceived interaction whereby antipsychotic medication enabled participants to engage with psychological interventions. Young people were central to determining whether or not to take part in the trial, with support by family members. Family members played an important role in monitoring engagement in treatment and outcomes.

Conclusions

This is the first trial to demonstrate that it is feasible to conduct a clinical trial to compare the clinical effectiveness and cost-effectiveness of a psychological intervention with antipsychotic medication and the combination of both in young people with a first episode of psychosis. However, adaptations are required to ensure that a full-scale effectiveness trial is viable. Careful site selection with one or more site leads being a psychiatrist employed by the local early intervention in psychosis service, with prescribing responsibility for young people with first episode of psychosis, will (1) ensure swift access to antipsychotic medication for those allocated to an antipsychotic arm; (2) minimise crossover into 'no-treatment' for those in the antipsychotic monotherapy arm or into psychological intervention only for those in the combined arm; and (3) ensure that consideration of prescribers' opinions is incorporated into the design of a definitive trial and ensure effective communication about trial participants. Crossover may be further reduced by the removal of the 3-month deterioration criteria. Adaptations are required and suggested for health economic data collection to ensure that a definitive trial determines cost-effectiveness. Qualitative data speak to the importance of retaining a combined treatment arm for both recruitment and retention of trial participants. Currently the World Health Organization defines adolescence as up to the age of 25 years and consideration should be given to increasing the upper age limit for a definitive trial, which would facilitate recruitment and ensure value for money. An adequately powered effectiveness trial is required to provide robust evidence.

Trial registration

This trial is registered as ISRCTN80567433.

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This report

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