Antipsychotic drugs versus cognitive behavioural therapy versus a combination of both in people with psychosis: a randomised controlled pilot and feasibility study

Anthony P Morrison, Heather Law, Lucy Carter, Rachel Sellers, Richard Emsley, Melissa Pyle, Paul French, David Shiers, Alison R Yung, Elizabeth K Murphy, Natasha Holden, Ann Steele, Samantha E Bowe, Jasper Palmier-Claus, Victoria Brooks, Rory Byrne, Linda Davies, Peter M Haddad

Summary

Background Little evidence is available for head-to-head comparisons of psychosocial interventions and pharmacological interventions in psychosis. We aimed to establish whether a randomised controlled trial of cognitive behavioural therapy (CBT) versus antipsychotic drugs versus a combination of both would be feasible in people with psychosis.

Methods We did a single-site, single-blind pilot randomised controlled trial in people with psychosis who used services in National Health Service trusts across Greater Manchester, UK. Eligible participants were aged 16 years or older; met ICD-10 criteria for schizophrenia, schizoaffective disorder, or delusional disorder, or met the entry criteria for an early intervention for psychosis service; were in contact with mental health services, under the care of a consultant psychiatrist; scored at least 4 on delusions or hallucinations items, or at least 5 on suspiciousness, persecution, or grandiosity items on the Positive and Negative Syndrome Scale (PANSS); had capacity to consent; and were help-seeking. Participants were assigned (1:1:1) to antipsychotics, CBT, or antipsychotics plus CBT. Randomisation was done via a secure web-based randomisation system (Sealed Envelope), with randomised permuted blocks of 4 and 6, stratified by gender and first episode status. CBT incorporated up to 26 sessions over 6 months plus up to four booster sessions. Choice and dose of antipsychotic were at the discretion of the treating consultant. Participants were followed up for 1 year. The primary outcome was feasibility (ie, data about recruitment, retention, and acceptability), and the primary efficacy outcome was the PANSS total score (assessed at baseline, 6, 12, 24, and 52 weeks). Non-neurological side-effects were assessed systemically with the Antipsychotic Non-neurological Side Effects Rating Scale. Primary analyses were done by intention to treat; safety analyses were done on an as-treated basis. The study was prospectively registered with ISRCTN, number ISRCTN06022197.

Findings Of 138 patients referred to the study, 75 were recruited and randomly assigned—26 to CBT, 24 to antipsychotics, and 25 to antipsychotics plus CBT. Attrition was low, and retention high, with only four withdrawals across all groups. 40 (78%) of 51 participants allocated to CBT attended six or more sessions. Of the 49 participants randomised to antipsychotics, 11 (22%) were not prescribed a regular antipsychotic. Median duration of total antipsychotic treatment was 44·5 weeks (IQR 26–51). PANSS total score was significantly reduced in the combined intervention group compared with the CBT group (–5·65 [95% CI –10·37 to –0·93]; p=0·019). PANSS total scores did not differ significantly between the combined group and the antipsychotics group (–4·52 [95% CI –9·30 to 0·26]; p=0·064) or between the antipsychotics and CBT groups (–1·13 [95% CI –5·81 to 3·55]; p=0·637). Significantly fewer side-effects, as measured with the Antipsychotic Non-neurological Side Effects Rating Scale, were noted in the CBT group than in the antipsychotics (3·22 [95% CI 0·58 to 5·87]; p=0·017) or antipsychotics plus CBT (3·99 [95% CI 1·36 to 6·64]; p=0·003) groups. Only one serious adverse event was thought to be related to the trial (an overdose of three paracetamol tablets in the CBT group).

Interpretation A head-to-head clinical trial of CBT versus antipsychotics versus the combination of the two is feasible and safe in people with first-episode psychosis.

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Division of Psychology and Mental Health (Prof A P Morrison ClinPsyD, H Law PhD, L Carter PhD, R Sellers PhD, M Pyle PhD, Prof P French PhD, D Shiers MBChB, Prof A R Yung PhD, J Palmier-Claus PhD, R Byrne PhD, Prof P M Haddad MD), **Division of Population Health, Health Services Research and Primary Care** (Prof R Emsley PhD, Prof L Davies PhD), **and Manchester Academic Health Science Centre Clinical Trials Unit** (Prof R Emsley), **University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; and Greater Manchester Mental Health NHS Foundation Trust, Manchester, UK** (Prof A P Morrison, H Law, L Carter, R Sellers, M Pyle, P French, D Shiers, Prof A R Yung, E K Murphy ClinPsyD, N Holden DClinPsy, A Steele PhD, S E Bowe DClinPsy, J Palmier-Claus, V Brooks RMN, R Byrne, Prof P M Haddad)

Correspondence to: Dr Tony Morrison, Psychosis Research Unit, Greater Manchester Mental Health NHS Foundation Trust, Manchester, M25 3BL, UK
tony.morrison@gmmh.nhs.uk

Introduction

Schizophrenia and psychosis are associated with substantial personal, social, and economic costs. High-quality evidence from clinical trials shows that both antipsychotics and cognitive behavioural (CBT) therapy can be helpful to adults with diagnoses of schizophrenia or other psychoses.[1] Many clinical guidelines, therefore, suggest that people with psychosis should be offered both antipsychotics and CBT (as well as family interventions) and should be involved in collaborative decisions about treatment options.[1] However, neither antipsychotics nor CBT are effective for everyone, and

Research in context

Evidence before this study

We searched PubMed with the terms "schizophrenia", "psychosis", "psychological therapy", "psychosocial intervention", "CBT", "antipsychotic" and "neuroleptic" for articles published in any language up to Jan 30, 2018. Although several systematic reviews and meta-analyses have shown robust evidence that antipsychotics are superior to placebo and that cognitive behavioural therapy (CBT) for psychosis in addition to antipsychotics is superior to treatment as usual, we identified no randomised controlled trials in which a head-to-head comparison of CBT and antipsychotics was done. A 2012 Cochrane review concluded that no usable data were available to establish the relative efficacy of antipsychotic medication and psychosocial interventions in early episode psychosis.

Added value of this study

Our pilot and feasibility trial showed that a methodologically rigorous clinical trial in which participants with psychosis are randomly assigned to psychological treatment or pharmacological treatment, or both, is possible. Our findings suggest that antipsychotics, CBT, and the combination of the two are acceptable, safe, and helpful treatments for people with early psychosis, but could have different cost–benefit profiles.

Implications of all the available evidence

Our preliminary findings seem consistent with guidelines that recommend informed choices and shared decision making about treatment options for early psychosis on the basis of cost–benefit profiles. An adequately powered efficacy and effectiveness trial is now needed to test hypotheses about superiority (eg, antipsychotics plus CBT *vs* antipsychotics alone or CBT alone) and non-inferiority (eg, antipsychotics *vs* CBT).

the individual cost–benefit ratios of such treatments (ie, the balance between efficacy and adverse effects) vary substantially, both between and within individuals.

Meta-analyses[2–4] of randomised controlled trials of CBT, added to antipsychotics, for psychosis have shown effect sizes for both total symptoms and positive symptoms in the small-to-moderate range (generally 0·3–0·4 relative to treatment as usual, although the effect size is smaller when lower quality trials are excluded). Meta-analyses[5,6] of antipsychotics compared with placebo also show moderate benefits in terms of total and positive symptoms. The most comprehensive meta-analysis[7] in chronic schizophrenia showed a standardised effect size for total symptoms of 0·47 (95% CI 0·42–0·51). Although CBT and antipsychotics are better than comparators (treatment as usual and placebo, respectively), the proportion of individuals who achieve a clinically meaningful benefit is moderate. For example, a meta-analysis[7] showed that 51% of multi-episode patients had at least a minimal response (≥20% reduction in symptoms as measured on the Positive and Negative Syndrome Scale [PANSS] or Brief Psychiatric Rating Scale), and 23% had a good response (≥50% reduction in symptoms), to antipsychotics. By comparison, in first-episode psychosis, 81% of patients had at least a minimal response, and 52% had a good response, to antipsychotics.[8] The authors of a meta-analysis[2] claim that conclusions about the efficacy of CBT have been exaggerated, given that most large, robust trials have not shown significant effects at end of treatment, and that effect sizes are reduced overall if only studies of high quality are included in meta-analyses.

Antipsychotics are associated with a wide range of adverse effects.[5,9] Metabolic effects are of particular concern, in view of the increased cardiovascular mortality in people with psychosis compared with the general population.[10] Adverse effects of CBT in psychosis have not been well studied.[2] Potential side-effects, such as stigma and deterioration of mental state,[11] were not detected in clinical trials of CBT for people with psychotic experiences. Rather, CBT resulted in significant reductions in the frequency of these side-effects.[12,13] However, CBT delivered in the context of a poor therapeutic relationship could be harmful.[14]

Whereas most evidence for the efficacy of CBT for psychosis is from randomised controlled trials in which CBT was provided as an adjunct to antipsychotics (ie, a combination of both *vs* antipsychotics alone), preliminary evidence suggests that CBT might be helpful for people with psychosis who are not taking antipsychotics.[13] No data for the relative head-to-head efficacy or acceptability of CBT and antipsychotics in schizophrenia are available. We investigated the feasibility of doing a three-group randomised controlled trial of CBT, antipsychotics, and a combination of CBT and antipsychotics in people with psychosis.

Methods

Study design and participants

We did a single-blind, randomised, controlled pragmatic pilot and feasibility trial between April 1, 2014, and June 30, 2017 in four specialist mental health National Health Service trusts in Greater Manchester, UK. Eligible participants were aged 16 years or older; met ICD-10 criteria for schizophrenia, schizoaffective disorder, or delusional disorder, or met the entry criteria for an early intervention for psychosis service (operationally defined with the PANSS), because most individuals with

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