A pilot and feasibility randomised controlled trial comparing antipsychotic medication to cognitive behavioural therapy to a combination of both in people with psychosis

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Abstract

Background: There is very little evidence regarding head to head comparisons of psychosocial interventions and pharmacological interventions for psychosis. We aimed to determine whether it is feasible to conduct a randomised controlled trial comparing Cognitive Behaviour Therapy (CBT) with antipsychotic medication and a combination of both in people with psychosis.

Methods: A single-site, single-blind pilot randomised controlled trial comparing CBT with antipsychotics with the combination recruited 75 participants with psychosis (aged 16-43 years; mean 23.61; SD 6.06), largely from early intervention services in NHS Trusts across Greater Manchester. 26 were assigned to CBT, 24 to antipsychotics and 25 to the combination. Participants were followed-up over 12 months. CBT incorporated up to 26 sessions over 6 months (mean sessions 14.39) plus up to four booster sessions. Choice and dose of antipsychotics were at the discretion of the treating consultant (median duration of total antipsychotic treatment was 44.5 weeks, SD 16.1, range 2-52). The primary outcome was feasibility data (recruitment, retention, acceptability) and the main effectiveness outcome was the Positive and Negative Syndrome Scale (PANSS) total score, which provides a continuous measure of psychiatric symptoms associated with psychotic disorders on the basis of a structured psychiatric interview (assessed at baseline, 6, 12, 24 and 52 weeks). The study was prospectively registered as International Standard Randomised Controlled Trial number ISRCTN06022197.

Outcomes: The trial recruited to target with a low referral:randomisation rate (138:75), had low rates of attrition (<20%), high rates of retention (>80%) and low rates of participants receiving interventions they were not allocated to (12%). The

majority of participants (73/75) were experiencing first episode psychosis (FEP) and recruited from Early Intervention Teams. The majority of participants allocated to CBT (n=40 out of 51, 78%) attended 6 or more sessions, with only one participant (2%) attending no sessions, and 404 of 557 homework tasks were completed (73%). Of the 49 participants randomised to antipsychotics, 11 (22%) were not prescribed a regular antipsychotic; the median duration of total antipsychotic treatment was 44.5 weeks (SD 16.1, range 2-52) and mean self-rated adherence was 77% (range 0 - 100%, SD 29.19). Changes in effectiveness outcomes were analysed following the intention-to-treat principle, using random effects models, adjusted for age, gender and baseline symptoms. Safety outcomes were analysed on an as treated basis. Psychiatric symptoms, measured by PANSS Total, were significantly reduced over time across all conditions. The combined intervention was more effective than CBT monotherapy, but not antipsychotic monotherapy (PANSS Total: comparison of combined to antipsychotics = -4.52; SD = 2.44; 95% CI -9.30 to 0.26; p = 0.064; comparison of combined to CBT = -5.65; SD = 2.41; 95% CI -10.37 to -0.93; p = 0.019). There was no difference between the monotherapies (PANSS Total: comparison of CBT with antipsychotics = -1.13; SD = 2.39; 95% CI -5.81 to 3.55; p = 0.637). CBT monotherapy had less side effects than the two treatments that included antipsychotics (ANNSERS number of side effects: comparison of CBT with antipsychotics = 3.22; SD = 1.35; 95% CI 0.58 to 5.87; p = 0.017; comparison of CBT with combined = 3.99; SD = 1.35; 95% CI 1.36 to 6.64; p = 0.003). Only one Serious Adverse Event was considered related to the trial (an overdose of 3 paracetamol in the CBT as treated group).

Interpretation: This is the first trial to show it is feasible and safe to conduct a head-to-head clinical trial comparing CBT with antipsychotics and the combination in

people with FEP. An adequately powered efficacy and effectiveness trial is required to provide robust evidence.

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Key words: Schizophrenia; Cognitive therapy; Psychosis; antipsychotic medication

Declaration of interest: APM, PF and SB deliver training workshops and have written textbooks on the topic of CBT for psychosis, for which they receive fees. All authors have conducted funded research on CBT for psychosis and LD, RE, PMH, ARY have conducted funded research on antipsychotics. APM, PF, SEB, EKM, AS, NH, JPC and VB deliver CBT in the NHS. DS is an expert adviser for the National Institute of Health and Care Excellence (NICE) Centre for Guidelines and a board member of the National Collaborating Centre of Mental Health (NCCMH); these are my personal views and not those of NICE or NCCMH. PMH has received honoraria for lecturing and/or consultancy work from Allergan, Galen, Janssen, Lundbeck, NewBridge Pharmaceuticals, Otsuka, Sunovion and Teva plus conference support from Janssen, Lundbeck and Sunovion. ARY has received honoraria from Janssen Cilag and Sunovion in the last 5 years.

Research in Context:

Evidence before this study: We searched PubMed up to January 30, 2018, with the terms “schizophrenia”, “psychosis”, “psychological therapy”, “psychosocial intervention”, “CBT”, “antipsychotic” and “neuroleptic”. We did not apply any language restrictions. Although several systematic reviews and meta-analyses have found that there is robust evidence that antipsychotics are superior to placebo (1, 2) and that CBT for psychosis in addition to antipsychotics is superior to treatment as usual (3), there are no randomised controlled trials that provide head to head evidence comparing CBT and antipsychotics. A recent Cochrane review concluded that there was no usable data to answer the question of relative efficacy of antipsychotic medication and psychosocial interventions in early episode psychosis (4) .

Added value of this study: It is possible to conduct a methodologically rigorous clinical trial that randomises participants with psychosis to psychological treatment, pharmacological treatment or the combination. Our study suggests that antipsychotic medication, CBT and the combined intervention are acceptable, safe and helpful treatments for people with early psychosis, but provides some indications that the treatments may have different cost-benefit profiles.

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. CG178) that recommend

informed choices and shared decision making regarding treatment options for early psychosis on the basis of cost-benefit profiles.

Introduction

Schizophrenia and psychosis are associated with significant personal, social and economic costs. There is high quality evidence from clinical trials that both antipsychotic medication and Cognitive Behaviour Therapy (CBT) can be helpful to adults with a diagnosis of schizophrenia and other psychoses. Many clinical guidelines, therefore, suggest that people with psychosis should be offered both antipsychotic medication and CBT (as well as family intervention) and should be involved in collaborative decisions regarding the treatment options they choose (5). However, neither antipsychotics nor CBT are effective for everyone and the individual cost-benefit ratios of such treatments will vary considerably, both between and within individuals.

The cost-benefit ratio of such treatments is a balance between efficacy and adverse effects (or wanted and unwanted effects). Recent meta-analyses of Randomised Controlled Trials (RCTs) of CBT, added to antipsychotics, for psychosis (3, 6, 7) have found 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 this reduces when lower quality trials are excluded). Recent meta-analyses of antipsychotic medication relative to placebo also show modest benefits on total and positive symptoms (1, 8), with the most comprehensive meta-analysis in chronic schizophrenia reporting a standardised effect size for total symptoms of 0.47 (9). However, while CBT and antipsychotics demonstrate superiority over comparators (treatment as usual and placebo respectively) to a statistically significant level, the proportion of individuals who achieve a clinically meaningful benefit is modest. The figure will depend largely on subject characteristics and how one defines clinical improvement. For example, a recent meta-analysis (9) showed that 51% of multi-

episode patients had at least a minimal response (≥20% reduction in PANSS/BPRS) reducing to 23% when the more stringent criterion of a good response was applied (≥50% reduction PANSS/BPRS). Comparative rates with antipsychotic treatment in first episode psychosis were 81% for a minimal response and 52% for a good response (10). It has also been claimed that conclusions regarding the efficacy of CBT are exaggerated, since most large, well-conducted trials have failed to demonstrate a significant effect at end of treatment and the effect sizes are reduced overall if meta-analyses are limited to studies of high quality (3).

Antipsychotics are associated with a wide range of adverse effects though the risks vary significantly between individual drugs (1). Side effects can impair quality of life, cause stigma, reduce adherence with medication and cause physical morbidity and mortality (11). Metabolic effects (weight gain and elevation of blood lipids and glucose) are a particular concern given the increased cardiovascular mortality seen in people with psychosis (12). Other adverse effects include sedation, sexual dysfunction, extrapyramidal symptoms, hyperprolactinemia, anticholinergic effects, cardiac arrhythmias and sudden cardiac death (11).

Adverse effects for CBT for psychosis have not been well studied (3) and it is clear that research trials of psychological therapies need to improve their measurement of adverse effects. However, side effects that have been suggested to be likely, such as stigma and deterioration of mental state (13), have not been found when they have been measured in clinical trials of CBT for people with psychotic experiences; in fact, CBT can result in significant reductions of these factors (14, 15). However, there is some evidence that CBT delivered in the context of a poor therapeutic relationship may be harmful (16).

While most evidence for efficacy of CBT for psychosis is from randomised controlled trials where CBT is provided as an adjunct to antipsychotic medication (i.e. a combination of both is compared to antipsychotics alone), there is some preliminary evidence to suggest that CBT may be helpful for people with psychosis who are not taking antipsychotic medication. A recent RCT (n=74) established the safety and acceptability of using CBT as an alternative to antipsychotics in people who had chosen not to take them (15). This trial also found that participants allocated to CBT improved significantly on overall psychiatric symptoms (PANSS total), dimensions of psychotic symptoms and social functioning over 18 months.. There is currently no evidence regarding the relative head-to-head efficacy or acceptability of CBT and antipsychotics in schizophrenia. Indeed, a Cochrane review identified only 5 controlled trials in early episode schizophrenia comparing antipsychotic medication to either placebo (3 trials) or a psychosocial intervention of any sort (one trial of individual psychotherapy and one of milieu therapy) (4). The authors concluded it was not possible to reach any definitive conclusions about relative efficacy.

The COMPARE trial (ISRCTN06022197) is a single-site, three-arm pilot and feasibility RCT comparing CBT with antipsychotics with a combined treatment in people with psychosis. The primary aim is to assess the feasibility of such a trial, including analysis of recruitment rates (including willingness to be randomised), quality of data collection and follow–up (attrition), and the safety and acceptability of the interventions (in particular, the CBT monotherapy). Secondary aims include a preliminary examination of the effects on clinical, personal and social outcomes and adverse effects in order to inform the design of a definitive trial.

Method

Study design and participants

The study was a single-blind, randomised, controlled pragmatic pilot and feasibility trial that was conducted between April 2014 and June 2017 in Manchester, UK. It was prospectively registered in March 2014 (ISRCTN06022197). The recruitment target was set at 75 (see previously published protocol paper for sample size justification (17)), and this was achieved between May 2014 and August 2016.

Inclusion criteria required that participants either met International Classification of Diseases–tenth revision (ICD-10) criteria for schizophrenia, schizoaffective disorder, or delusional disorder, or met entry criteria for an early intervention for psychosis service (operationally defined with the Positive and Negative Syndrome Scale [PANSS]) as the majority of individuals experiencing their first episode of psychosis will receive their services from specialist teams, as recommended by NICE guidelines. All participants were aged at least 16 and were in contact with mental health services, under the care of a consultant psychiatrist. Participants scored at least 4 on PANSS delusions or hallucinations, or at least 5 on suspiciousness, persecution or grandiosity and participants had to have the capacity to consent and also had to be help-seeking. Individuals were identified via care coordinators, consultant psychiatrists and other mental health staff within participating mental health trusts. Exclusion criteria were receipt of antipsychotic medication or structured CBT with a qualified therapist within the last 3 months; moderate to severe learning disability; organic impairment; a score of 5+ on PANSS conceptual disorganisation; primary diagnosis of alcohol/substance dependence; immediate risk to self or others and non-English speaking.

The PANSS was administered by a research assistant in the participant's home or a suitable clinical service, and eligibility was confirmed by a qualified clinician. Participants provided written informed consent. Our protocol was approved by National Research Ethics Service of the UK's National Health Service (reference = 14/NW/0041).

Randomisation and masking

Participants were randomly assigned to the three treatment arms (1:1:1) using a secure web based randomisation system (Sealed Envelope) with randomised permuted blocks of 4 and 6, stratified by gender and first episode status. Randomisation at the individual level was independent and concealed with all assessors masked to group allocation. Allocation was made known to the trial manager, trial administrator and therapists. Participants and their care team were informed of the allocation by letter. Nine partial blind breaks (where only one treatment was revealed), representing 12% of participants, and five full blind breaks (where actual randomisation arm was revealed), representing 7% of participants, were reported by research assistants. Four of the full blind breaks were in the AP arm, 1 was in the combined arm and none were in the CBT arm. Only 3 (1.17%) out of 256 follow-up assessments were conducted by an unmasked assessor (where the blind was broken during the assessment) and all of these assessments were then scored by a masked rater and consensus was reached on ratings. This procedure ensured that none of the 256 assessments were scored without rater-masking.

Interventions

CBT: Participants allocated to CBT were offered up to 25 sessions of therapy based on a specific cognitive model (18) over the 6 month treatment window. Therapy was

individualised and problem focussed, and the range of permissible interventions are described in the manualised treatment protocol (19). Therapy sessions were usually offered on a weekly basis and were delivered by appropriately qualified psychological therapists. Fidelity to protocol was ensured by weekly supervision and regular rating of recorded sessions using the Cognitive Therapy Scale-Revised (CTSR) (20).

Antipsychotic medication: Participants allocated to antipsychotics were prescribed this medication by their responsible psychiatrist and their treatment was initiated as soon as possible post randomisation. Antipsychotic prescribing mirrored that which would be seen in normal clinical practice which meant that there were no restrictions on the antipsychotics that could be selected or their doses, and clinicians were able to switch antipsychotics and adjust dose as clinically indicated. Clinicians were encouraged to continue antipsychotic treatment for a minimum of 12 weeks, and preferably for at least 26 weeks.

Combined treatment: Participants allocated to the combined treatment were offered both CBT and antipsychotic medication as described above.

Clinicians were free to prescribe medication other than antipsychotics including antidepressants, anxiolytics and hypnotics for all participants regardless of treatment allocation.

All participants were offered monitoring assessments at 6 weeks, 12 weeks, 24 weeks and 52 weeks. In order to allay any concerns around safety of withholding antipsychotic medication for CBT monotherapy participants, trial procedures included monitoring for deterioration with the option to move to the combined treatment arm for anyone who was randomised to CBT or AP's alone, and who experienced a

decline in mental state during the trial. This procedure was detailed in the standard operating procedures for the study and was presented to the Research Ethics Committee, as well as clinicians who referred to the study. Participants experiencing evidenced deterioration remained in the RCT and the assessment schedule was maintained. Participants were given the option to move into the combined treatment arm if deterioration in mental state led to involuntary hospitalisation or if there was a >25% deterioration in PANSS scores at the 6-week assessment or a >12.5% deterioration in PANSS scores at the 12-week assessment.

Outcomes

The primary outcome was feasibility operationalised in terms of referral rates, recruitment, retention/attrition, acceptability of treatment, attendance at sessions, adherence to homework, compliance with medication. The primary effectiveness outcome measure was total score on the Positive and Negative Syndrome Scale (PANSS) (21) assessed at baseline, 6 weeks, 12 weeks, 24 weeks and 52 weeks. The PANSS is a thirty item, semi-structured interview assessing dimensions of psychosis symptoms rated on a seven-point scale between 1 (absent) and 7 (severe). Reliability and validity of the PANSS has been demonstrated in numerous studies (22). Measures were administered by research assistants trained in the use of all the instruments to achieve a good level of inter-rater reliability (ICC = 0.902).

Secondary clinical outcomes included depression and anxiety assessed using the Hospital Anxiety and Depression Scale HADS:(23)), as well as quality of life (WHOQOL (24)) and social functioning assessed using the Personal and Social Performance scale (PSP: (25)). We also included a user-defined measure of recovery (QPR: (26)) and the clinical impressions of symptom severity and

improvement (CGI) scale (27). Service use, diagnosis and antipsychotic prescribing were recorded via review of case notes. Non-neurological side effects were systemically assessed using the antipsychotic non-neurological side effects scale (ANNSERS: (28)). Additional assessments of physical health included weight, blood pressure and blood tests for HbA1C, fasting glucose, fasting lipids (total cholesterol, LDL, HDL, triglycerides and prolactin levels). At 6 months self-report data on antipsychotic adherence in the last month was obtained using a visual analogue scale. At the 52 week follow-up, we also surveyed participant's opinions on their preferences and views of measures used in the study to inform choice of measures for a definitive trial.

We report on all outcomes that were specified in our prospectively registered and recently published protocol (17) and statistical analysis plan, which was agreed with the data monitoring and ethics committee, and a-priori published on the trial registry entry.

Changes to trial protocol following commencement: After the original ethical approval for the trial in February 2014, a substantial amendment was made (approved June 2014): the lower age limit was changed from 18 to 16; 'inpatient status' was removed as an exclusion criteria and replaced by 'immediate risk to self or others'; and the randomisation time-frame was amended to 5 working days from 2 working days. Other minor amendments were made including the addition of service user and clinician surveys to gather further information on feasibility of recruitment. We had originally proposed that the recruitment window would be variable, with participants recruited in the first 22 months receiving the full 6–month follow up, whereas participants recruited thereafter would be offered assessments up to the end of treatment; however, we agreed a no-cost extension with the funder and were able to

complete 12-month follow-up of all participants. We had also originally proposed that economic analyses would explore the costs of health and social care and quality adjusted life years (QALYs) from a broadly societal perspective; however, the EQ5D was omitted from our assessment battery in error, meaning this was not possible.

Statistical analysis

The primary outcome for the trial is feasibility, including the number of participants referred and the number of consenting individuals and recruited individuals to each arm, as well as retention and the proportion of participants receiving the allocated intervention versus those who did not. Analyses were undertaken in Stata version 14 (29) after completion of all endpoint assessments; primary analysis was by intention-to-treat (ITT). Outcomes were analysed using Stata's xtreg command to fit random intercept models with summed scores as dependent variables, allowing for attrition and the variable follow-up times introduced by the design of the trial. Covariates included gender, age, time and the baseline value of the relevant outcome measure (first episode status, as a stratification factor, should have been included, but with only 2 of 75 participants not being first episode, age was a more appropriate covariate). The use of these models allowed for the analysis of all available data, on the assumption that data were Missing at Random (MAR) (30), conditional upon covariates. We report estimated treatment effects, with their standard errors, significance levels and confidence intervals. All treatment effects reported here are estimates of the effects common to all follow-up times (essentially, repeated measures ANCOVAs). Since safety and unwanted effects should be analysed on the basis of the most accurate information, these results are reported using an as treated approach rather than ITT. As treated was defined using our pre-defined minimum dose criteria for both antipsychotics (at least 6 weeks at a therapeutic

dose) and CBT (at least 6 sessions); on this basis, participants were classified as having received antipsychotics, CBT, combined or neither.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report or in the decision to submit for publication.

Data sharing

Anonymised data will be made available upon reasonable request, which must include a protocol and statistical analysis plan and not be in conflict with our pre-specified publication plan, consistent with our data sharing policy (available on request from the Chief Investigator). Requests for data sharing will be considered by the Chief Investigator and the independent Trial Steering and Data Monitoring Committee.

Results

Figure 1 shows the CONSORT diagram for the trial and Table 1 shows the baseline data for each group. The planned recruitment target of 75 was achieved, indicating it is feasible to recruit individuals to such a trial. The referral to recruitment rate was 2:1, with only 22 out 138 referrals (16%) declining to participate suggesting willingness to be randomised and consider each of the treatment options. It is clear that recruiting eligible participants was easier in EITs, with those experiencing FEP (73/75 of participants), compared to recruiting multi-episode patients from CMHTs. We randomised participants from 10 of 22 participating clinical teams (Web Appendix Table 1). 75 individuals were randomised and allocated to Cognitive Behaviour Therapy (n= 26), antipsychotics (n=24) or a combination of both (n=25).

Retention to the trial was reasonable (see figure 1), with only four withdrawals and relatively low rates of attrition (e.g. 63 of the 75 12-month assessments (84%) were completed). Rates of attrition were very similar across each arm (see Figure 1).

Participants who were randomised to CBT (in either the CBT or combined arm) received a mean of 14.39 sessions (SD 9.12, range 0-26) within the 6 month treatment window, with each session lasting around an hour (additional booster sessions were also offered as appropriate). The majority of participants (n=40 out of 51, 78%) attended 6 or more sessions, with only one participant (2%) attending no sessions. Homework compliance was good for both participants (404 of 557 participant between session tasks were completed (73%)) and therapists (396 of 445 therapist between session tasks were competed (89%)).

Of the 49 participants randomised to antipsychotic monotherapy or combined treatment, 11 (22%) were not prescribed a regular antipsychotic; reasons varied but included some participants declining to take an antipsychotic despite consenting to enter the trial. The modal dose for each participant was the most frequent daily dose of the primary antipsychotic i.e. the antipsychotic prescribed for the longest period during the study. The three most common primary antipsychotics prescribed were aripiprazole (n=14), olanzapine (n=10) and quetiapine (n=10), as chosen by the treating psychiatrist in the participants clinical care team (Table 2).The mean modal dose for each antipsychotic was defined as the mean of the modal doses for patients prescribed that drug (Table 2). Duration of antipsychotic treatment for each participant was based on all regular antipsychotics prescribed and was not restricted to the primary antipsychotic; 12 of the 38 participants (32%) treated with an antipsychotic, switched antipsychotics at least once during the study. Nearly all participants who commenced antipsychotic treatment were prescribed their primary

antipsychotic for 6 weeks or more (34/37, 92%; duration was not captured for 1 participant), and the median duration of total antipsychotic treatment was 44.5 weeks (SD 16.1, range 2-52).. 28/36 (78%) of participants with accurate duration data were continuing antipsychotic medication at the end of the study.

Self-reported data on medication adherence was available at 6 months for 42 of the 49 participants (86%) randomised to antipsychotic monotherapy or combined treatment. 29 of the 42 participants (69%) reported being prescribed an antipsychotic at that time point. Among these 29 participants, mean adherence (rated on a scale of 0% to 100%, with 100% indicating they had taken every dose over the last month) was 77% (range 0 -100%, SD 29.19).

The proportion of patients receiving allocated interventions was similar across groups (Table 3); 15/26 in the CBT alone arm (58%) received the exact allocated intervention (i.e. CBT without antipsychotics) as compared to 15/24 (62%) in the anti-psychotic group and 14/25 in the combined group (56%). Only 9 participants (12%) received an intervention that they were not allocated to.

Psychiatric symptoms, measured by PANSS Total, were significantly reduced over time across all conditions (see Web Appendix Figure 1). Tables 4 and 5 show the ITT results of the primary effectiveness outcome (PANSS) and the secondary outcome measures at each assessment point, along with treatment effect estimates and confidence intervals as well as p values for pairwise comparisons. Web Appendix Table 2 shows the PANSS analyses without covarying for age.
We report numbers of participants in each group (completer-only data i.e. observed cases) achieving a 25% and 50% improvement (ITT) and deterioration (as treated)

on adjusted PANSS total scores (31) at both 6 months and 12 months (Table 6), as has been recommended for trials using the PANSS (32).

Table 7 shows the results, on an as treated basis, of the measures of adverse effects at each assessment point, along with treatment effect estimates and confidence intervals as well as p values for pairwise comparisons. We also examined compulsory and voluntary hospital admissions during the trial; the data regarding type, number and length of stay for psychiatric hospital admissions is provided in table 8. Using an as treated analysis (rather than ITT) there were no admissions among those treated with antipsychotic monotherapy or among those who received no intervention. 2 participants treated with CBT were admitted and 4 who received combined treated were admitted.

We also recorded another 10 potential serious adverse events relating to 9 participants (2 adverse events were related to 1 participant). The 9 participants were randomised to the following treatment arms: APs n=1, CBT n=4, combined n=4. In terms of the interventions these 9 participants actually received, one received neither intervention, 2 received CBT and 6 received the combined treatment. The additional 10 potential SAEs included: two admissions related to physical health (one participant in the combined as treated group experienced seizures which led to a head injury and admission to medical ward, one participant who received neither intervention from the trial was admitted to a medical ward due to pneumonia); and one admission following an overdose (participant was in the combined as treated group). There was also one event involving aggression to others whilst in hospital (participant was in the combined as treated group), four attempted overdoses of five

or less paracetamol or eight sleeping tablets (these four events related to three participants, one in the combined as treated group and two in the CBT as treated group), one report of self-harm in the form of superficial cutting (combined as treated group) and one A&E attendance following reports of suicidal thoughts and self-harm by punching objects (combined as treated group).

These SAEs were reviewed by the chair of the independent trial steering committee, resulting in six reports being sent to the Research Ethics Committee. These related to 5 different participants: two in the CBT as treated group (events were section 3 hospitalisation and overdose of 3 paracetamol tablets); and 4 in the combined as treated group (events were superficial cutting; physical health hospital admission following seizures and head injury; informal admission due to risk to self and one hospital admission following an overdose). Only one SAE was considered related to the trial (the overdose of 3 paracetamol tablets in the CBT participant).

Regarding participants who met our deterioration criteria at 6 or 12 weeks, which triggered an offer to move into the combined arm, only 3 participants met this threshold (2 from antipsychotics only, one from CBT only).

Discussion

The COMPARE trial has demonstrated that it is possible to conduct a study comparing antipsychotics with CBT and a combined treatment in people with psychosis. This pragmatic pilot and feasibility trial had low attrition (<20% at each time point), comparable attrition across each trial arm, high retention of participants, low rates of unblinding, successful concealed and independent randomisation and only a small proportion of participants who received an intervention that they were

not allocated to receive. All 3 treatments were broadly safe and acceptable. The mean baseline PANSS total scores for our total sample was 70.4 which is similar to the baseline PANSS score of 73.8 seen in the CAFÉ study (33), but lower than the 88.5 seen in EUFEST (34) (both are large, 1-year RCTs of antipsychotics in early psychosis). The average changes in PANSS total we observed from baseline to 52 weeks (antipsychotics: 13.3; CBT: 12.3; combined: 13.4) fall within the range seen with the 3 antipsychotics in CAFÉ (olanzapine = 18.4, quetiapine = 15.6 and risperidone = 8.4), but are lower than the changes seen in EUFEST (approximately 35 points with all five antipsychotics assessed). The average PANSS reductions we observed are less than the 15 points estimated to be equivalent to a rating of 'minimal improvement' on the Clinical Global Impressions (CGI) scale (35), although it is suggested the latter value is lower for patients with less severe symptoms at baseline (35). These reductions were larger than estimates for minimal clinically important difference (MCID) in PANSS Total associated with obtaining employment as an objective measure of functioning (8.3 points) (36) and similar to the MCID associated with patient-rated improvement (11.2 points) (37). We observed improvement across measures of symptoms and personal and social recovery, functioning and quality of life, regardless of intervention condition.

There is a signal that the combined group may be superior to both monotherapies, with some significant differences in comparison to CBT alone (including PANSS total, p=0.019) and trends in comparison to antipsychotics alone (including PANSS total, p=0.06). It would appear that these differences are most pronounced at 24 weeks, but the effects of treatments seemed to converge at 52 weeks. However, since this is a pilot and feasibility study, it was not powered to reliably detect differences between groups and any such differences should be treated with

considerable caution. There was little to signal that there were any significant differences in efficacy between the two monotherapies, which is interesting given CBT finished after 24 weeks whereas antipsychotic treatment could last 52 weeks (the median duration among those who received APs was 44.5 weeks). It is also interesting that there appears to be no difference between the 3 groups after 6 weeks (see Web Appendix Figure 1), given this is a common length for drug trials. The number of participants with PANSS rated deterioration was low across all groups at each time point, with no indication that CBT was worse than antipsychotics or combined. . Notably, there were only 3 early deteriorations (at 6 or 12 weeks), with 2 from the antipsychotics only arm and 1 from the CBT only arm.

Data regarding side effects provide a signal that CBT monotherapy may be superior to antipsychotic monotherapy and the combined intervention, since there were significant differences on both ANNSERS total score and number of side effects reported. However, close inspection shows this is more accounted for by a reduction in these in CBT monotherapy, rather than an increase in the antipsychotic arms; this could be related to many ANSSERS items being non-specific (for example, sleep problems, memory and attention, loss of libido, loss of energy and autonomic symptoms). Such symptoms could represent symptoms of a psychotic disorder, a comorbid illness or be 'true' antipsychotic side effects. There was also a signal that serious adverse events (SAEs), including hospital admissions, may be more common in the arms involving CBT, since there were no such admissions for antipsychotic monotherapy (although CBT monotherapy was associated with fewer admissions than the combined arm). Similarly, there were no SAEs reported to the ethics committee for antipsychotic monotherapy, with two for CBT monotherapy and four for combined intervention, although only one SAE was considered related to the

trial. However, this should be interpreted cautiously given that this pilot trial was under-powered. It is also worth considering that there is increased surveillance and opportunity for SAEs to be observed in the CBT arms, since CBT had weekly contact with trial staff tasked with reporting adverse effects (the trial therapists), whereas antipsychotic monotherapy participants had much less frequent contact with trial staff (the trial RAs), resulting in a maximum of 35 opportunities for such events to be detected for CBT arms versus 5 opportunities for antipsychotic monotherapy.

The number of sessions attended and compliance with homework tasks suggests that CBT was delivered successfully to the majority of participants. Selection of antipsychotic medication was on an individual patient basis, consistent with NICE guidance. The four antipsychotics used most frequently (aripiprazole, olanzapine, quetiapine, risperidone) correspond to the four antipsychotics most commonly initiated in routine clinical practice in first episode services as reported in a recent cohort study (38) of 510 FEP participants across seven sites in the UK. Antipsychotic dose and duration of treatment were not limited by the protocol and were entirely at the discretion of the treating clinician and patient wishes. One patient's primary antipsychotic was promazine, a drug approved to treat agitation and not psychosis, and the dose was very low and insufficient to be regarded as an effective antipsychotic dose (table 2). The mean modal doses of the remaining primary antipsychotics were at the lower end of the dose ranges recommended to treat psychosis, but this is consistent with participants being recruited almost exclusively from early intervention services. People with first-episode psychosis respond to lower doses of antipsychotic medication than those required to treat multi-episode schizophrenia (33) and are more sensitive to side effects. As such, expert pharmacological guidelines recommend commencing antipsychotic treatment with

low doses in first episode of psychosis and that an adequate trial of an antipsychotic is up to 4 weeks at optimum dosage (39). The International Consensus Study of Antipsychotic Dosing recommended 30% lower doses were used in first episode patients compared to chronic patients (40). Nevertheless, the doses of some of the antipsychotics, especially quetiapine, were lower than the comparable doses used in the CAFÉ and EUFEST trials in first episode psychosis. In most cases, where duration of antipsychotic treatment was known (34/37, 92%), the primary antipsychotic was continued for 6 weeks or longer suggesting that treatment duration was sufficient to determine effectiveness. 12 of the 38 (32%) participants who started antipsychotic treatment switched antipsychotic at least once implying perseverance to identify an effective medication. In summary, the use of antipsychotic medication was pragmatic and seems broadly consistent with clinical practice in EI services and treatment guidelines; therefore, results should generalise to this context. However, a question remains as to whether higher doses would have improved outcomes (although they would increase side effects which may also lead to discontinuation).

There are several limitations for this trial. The pilot and feasibility trial design and small sample size means that we cannot emphasise the statistical tests and significance values and need to exercise caution in interpreting these. With regard to integrity of treatment allocation, although only 12% received an intervention they were not allocated to receive, a reasonable proportion did not take up the offer of allocated interventions (31% of those allocated to an antipsychotic did not take one for at least 6 weeks and 22% of those allocated to CBT did not attend at least 6 sessions). However, this reflects the real world in which many people do not comply with medication regimes and some do not engage with talking therapies, and such rates of non-adherence are commonly observed in drug trials and psychological

therapy trials. Indeed, a recent cohort study of 510 FEP participants found that 73% discontinued their first prescribed antipsychotic over 52 weeks (38).

The dose and duration of the antipsychotic treatment has already been referred to. It could be argued that operationalising antipsychotic treatment in terms of target doses, minimal duration of trials and encouraging switching if treatment was unsatisfactory may have enhanced the effectiveness of drug treatment. However higher doses may have led to more side effects and greater dropout rates. COMPARE relied on medication being prescribed and dispensed in accordance with normal clinical practice in the participating teams. In contrast, drug trials often deliver medication to patients and incorporate regular pill counts, both of which may enhance adherence. The lack of an effect on weight gain in the antipsychotic monotherapy group may cast doubt on adherence; however, the total number of side effects and total side effects score (ANNSERS) were significantly higher for the antipsychotic monotherapy and the combination group versus the CBT group (analysed on an as treated basis), although this was accounted for by a reduction in the CBT group rather than increases in the antipsychotic arms. We did not have a standardised operating procedure for measuring weight that emphasised consistency of flooring and many assessments were conducted in participants homes; therefore, it is also possible that the weight data contained errors. Another limitation is that we did not systematically record use of other medications such as antidepressants or anxiolytics or measure substance and alcohol use.

Our response rates on the PANSS (table 6) and the degree of improvement on the CGI were lower than those observed in 52-week RCTs of antipsychotic medication in FEP (33, 34). However, data analytic strategies and high attrition in these studies may have increased risk of bias, which could inflate effects. For example, EUFEST

used data obtained before treatment discontinuation for analysis of PANSS outcomes, which is likely to introduce bias given the high rates of discontinuation (ranging from 33-72% depending on the specific drug). CAFÉ had very high attrition at 52 weeks (ranging from 67% to 73% depending on drug), which is also likely to introduce bias given the majority of data is missing at this time point. Response is also dependent on patient and illness characteristics and these vary between studies; for example, COMPARE mostly involved participants who met PANSS-defined criteria for acceptance into EITs, whereas EUFEST and CAFÉ only included participants with schizophrenia spectrum diagnoses.

Our sample was diagnostically heterogeneous, since we recruited 73/75 of our participants from EITs, which operationally define FEP using the PANSS. Most participants did not have diagnoses in the medical records 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. Therefore, it is likely that our findings are only generalisable to early intervention services, at least in the UK. The results should not be generalised to those with chronic schizophrenia spectrum diagnoses including those seen within adult community mental health teams (CMHTs), and it is possible that a more homogenous schizophrenia spectrum sample may have responded differently to the treatments.

The design of our study (3 active treatment arms), alongside the majority of participants receiving care from early intervention services, means we cannot rule out the possibility that the benefits observed are attributable to more generic factors such as good care-coordination, engagement, assertive outreach and crisis management, rather than the specific active treatments. The failure to include the

EQ5D meant we were unable to examine quality adjusted life years and any signals regarding cost-effectiveness.

Given that the safety and feasibility of such a trial has been demonstrated, a large, efficacy and effectiveness randomised controlled trial is now required to answer the questions regarding the relative clinical and cost-effectiveness of CBT and antipsychotics in a head-to-head comparison. This trial demonstrated that the randomised participants were almost exclusively experiencing a first episode of psychosis, so a definitive trial should target this population specifically and recruit via early intervention services, which seemed to support treatment choice and view the question of which treatments are required with greater equipoise than the more generic community mental health teams. It does not appear feasible to conduct such a trial in people with multiple episode psychotic disorders in generic community mental health teams (mostly because potential participants are already prescribed antipsychotics). Given the possibility of non-adherence and variation in the quality of antipsychotic treatment between clinical teams, for example in terms of dose, duration of treatment before switching, and information given, it may be worth an efficacy and effectiveness trial employing research psychiatrists to help standardise the quality of antipsychotic treatment; however, this may jeopardise support from clinical teams and local Consultant Psychiatrists. It may also be worth considering the introduction of: a diagnostic interview to allow accurate reporting of diagnoses; a measure of substance misuse to allow characterisation of the population; and a placebo condition to facilitate meaningful comparisons of response rates (although this could raise ethical issues). On the basis of our data, it would seem reasonable to suggest that an efficacy and effectiveness trial should evaluate the following hypotheses: i) CBT will be equivalent to antipsychotics on efficacy; ii) CBT will be

superior to antipsychotics on side effects; iii) the combined intervention will be superior in efficacy to both monotherapies. Further consideration, including consultation of stakeholders such as service users and clinicians, is required to inform the selection of the most appropriate outcome measure an efficacy and effectiveness trial (for example, symptom change, quality of life or subjective recovery).

The main implication of this trial is that we need an adequately powered efficacy and effectiveness trial to provide evidence regarding relative effectiveness of antipsychotic medication and CBT. At present, in the absence of definitive evidence, and the fact that evidence supporting antipsychotic monotherapy is notably stronger than that supporting CBT monotherapy, it seems reasonable to support people with psychosis (who do not present immediate risk to self or others) to make informed choices as outlined the NICE guidelines, which recommend advising people who want to try psychological interventions alone that these are more effective when delivered in conjunction with antipsychotic medication, but allowing them to to try family intervention and CBT without antipsychotics while agreeing a time to review treatment options, including introducing antipsychotics (5).

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Contributors: All authors were involved in the design of the study and the ongoing management and delivery of the trial, and contributed to drafts of this manuscript. AM, the chief investigator, conceived of the study, prepared the protocol, contributed to the training and supervision of the therapists and supervision of the researchers, had overall responsibility for the day to day running of the study, interpreted the data, and took the lead on writing this report. He is the guarantor for the study. AM, SEB, PF, EKM, NH, AS and JPC participated in preparation of the treatment protocol and the training and supervision of the therapists. AM, HL, PMH and MP trained the researchers in the psychiatric interviews, supervised and monitored standards of psychiatric interviewing and assessment throughout the trial. In addition, AM, PMH, ARY and PF advised on diagnostic ratings and inclusion/exclusion criteria. PMH, DS and ARY advised on medical and pharmacological issues and liaised with prescribers. HL was the trial manager. She supervised and coordinated recruitment, contributed to training of research staff, and was responsible for staff management

and overall coordination of the study. HL, MP, LC and RS were responsible for maintaining reliability of assessment procedures and data collection. RE was the trial statistician. He advised on randomisation and all statistical aspects of the trial, developed the analysis plan, and performed the statistical analyses and is guarantor in this respect. LD was the health economist. RB was a service user consultant involved in all aspects of the study.

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Figure 1: Consort diagram

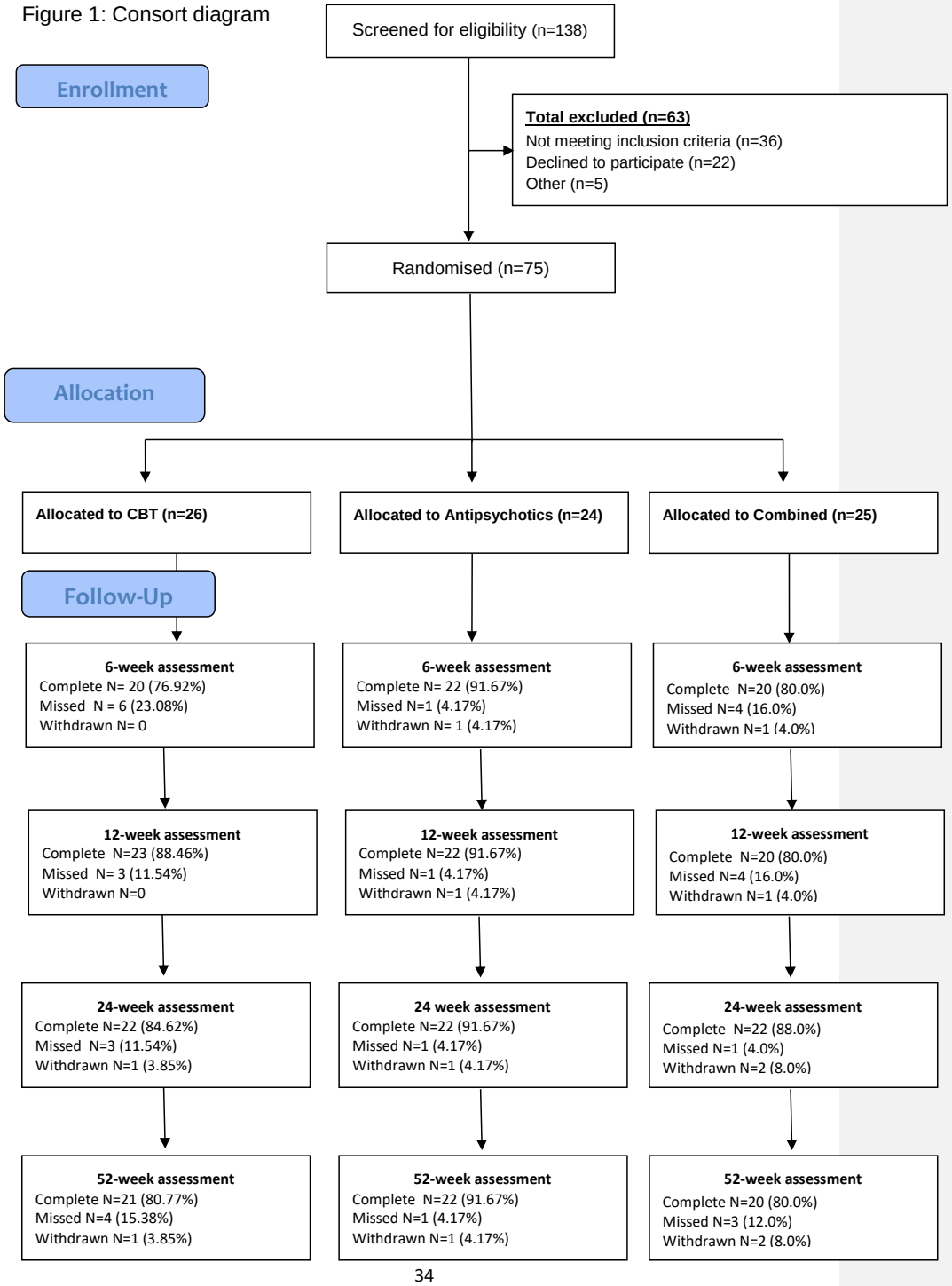

TABLE 1: Baseline characteristics, means and standard deviations

Variable	**Antipsychotics (N=24)**	**CBT (N=26)**	**Combination (N=25)**
Age (years)	23.21 (4.97)	23.19 (6.32)	24.44 (6.86)
Male	13 (54%)	16 (62%)	14 (56%)
FEP: Multiple episode	24:0	24:2	25:0
DUP (weeks)	37.33 (44.41)	44.48 (52.30)	39.43 (35.76)
PANSS total	70.17 (10.12)	70.50 (8.12)	70.76 (8.45)
PANSS Positive	23.04 (4.60)	23.15 (4.63)	21.92 (3.63)
PANSS Negative	16.17 (5.72)	15.5 (4.10)	15.24 (5.17)
PANSS disorganised	16.25 (2.60)	17.15 (3.65)	17.8 (4.27)
PANSS Excitement	18.25 (4.35)	17.85 (3.86)	17.4 (4.14)
PANSS Emotional Distress	25.46 (5.00)	25.31 (3.83)	26.28 (3.47)
QPR total	38.71 (9.23)	40.13 (9.33) (n=25)	41.8 (11.79)
HADS Total	41.05 (5.49) (n=23)	37.54 (5.42) (n=24)	36.36 (6.76)
HADS Anxiety	21.96 (2.62) (n=23)	20.5 (3.32) (n=24)	19.36 (3.89)
HADS Depression	19.05 (4.87) (n=23)	17.38 (3.32) (n=24)	17.28 (5.55)
WHO Qol total	67.03 (14.99)	68.66 (13.41) (n=25)	70.18 (15.41) (n=24)
PSP	52.67 (13.83)	57.38 (12.04)	58.16 (11.1)
CGI participant version	4.91 (0.97) (n=22)	4.42 (0.99)	4.38 (1.54)
CGI clinician version	4.13 (0.74)	4.08 (0.63)	4.04 (0.68)
ANNSERS total number of side effects	9.96 (4.72), 24	8.88 (3.77), 26	9.16 (4.69), 25
ANNSERS Total score	13.92 (7.05), 24	12.12 (6.55), 26	12.28 (6.61), 25
Cholesterol (mmol/l)	4.54 (0.91), 20	4.08 (0.82), 15	4.45 (0.93), 16
HDL- Cholesterol (mmol/l)	1.34 (0.35), 20	1.13 (0.3), 15	1.38 (0.4), 15
Total/HDL ratio	3.57 (0.94), 20	3.5 (0.86), 15	3.35 (0.93), 15
LDL Cholesterol (mmol/l)	2.58 (0.78), 15	2.33 (0.67), 12	2.46 (0.68), 14
Triglycerides (mmol/l)	1.15 (0.39), 16	1.27 (0.64), 12	1.12 (0.45), 14
Prolactin (mU/l)	183.06 (89.71), 17	187.07 (63.33), 15	198.5 (81.78), 14
Glucose (mmol/l)	6.27 (6.96), 18	5.32 (2.41), 15	4.14 (0.55), 15

Table 2: Antipsychotic details for participants in the antipsychotic monotherapy arm and combined treatment arms

Primary antipsychotic*	Number of participants	Mean modal dose (mg per day for oral drugs)	Max dose used (mg per day for oral drugs)
Aripiprazole	14	10.6	20
Olanzapine	10	8	10
Quetiapine	10	270	700
Risperidone	2	2.5	3
Promazine	1	50	100
Haloperidol decanoate	1	50mg intramuscular injection every 2 weeks	75mg intramuscular injection every 2 weeks

Table 2:

* Primary antipsychotic = antipsychotic prescribed to each participant for longest duration during the study. (38/49[78%) participants in these two arms received a regular antipsychotic.

Table 3: Participants randomised vs as treated status

		Randomised treatment arm			
As treated		Antipsychotics	CBT	Combination	Total
	Antipsychotics	15	2	4	21
	CBT	0	15	5	20
	Combination	1	6	14	21
	Neither	8	3	2	13
	Totals	24	26	25	75

Table 4: PANSS Outcomes. Mean (SD), number of observations. Effect is common to all follow-up times (ITT).

Variable	Time (weeks)	Antipsychotics (N = 24)	CBT (N = 26)	Combination (N = 25)	Mean difference (SE); (95%CI); P-value		
					CBT vs. AP	CBT vs. combined	AP vs. combined
PANSS total	0	70.13 (10.11), 24	70.35 (8.03), 26	70.76 (8.46), 25	-1.13 (2.39); (-5.81, 3.55); 0.637	-5.65 (2.41); (-10.37, -0.93); 0.019	-4.52 (2.44); (-9.30, 0.26); 0.064
	6	64.05 (11.39), 22	64.85 (7.85), 20	64.7 (9.74), 20			
	12	60.81 (16.52), 21	63.74 (7.73), 23	58.4 (14.51), 20			
	24	61.09 (14.44), 22	60.5 (8.74), 22	53.77 (12.54), 22			
	52	56.77 (14.1), 22	58.14 (11.68), 21	57.4 (13.58), 20			
PANSS Positive	0	23.04 (4.6), 24	23.15 (4.63), 26	21.92 (3.63), 25	-1.16 (1.14); (-3.40, 1.09); 0.312	-2.02 (1.15); (-4.27, 0.24); 0.080	-0.86 (1.17); (-3.15, 1.43); 0.462
	6	19.36 (5.44), 22	21 (4.38), 20	20.1 (4.41), 20			
	12	19.19 (7.72), 21	21 (4.72), 23	17.4 (5.65), 20			
	24	17.81 (6.85), 21	18.18 (4.81), 22	15.23 (5.31), 22			
	52	18.18 (6.52), 22	17.9 (5.92), 21	16.8 (6.05), 20			
PANSS Negative	0	16.17 (5.72), 24	15.5 (4.1), 26	15.24 (5.17), 25	-1.25 (0.78); (-2.78, 0.28); 0.110	-2.31 (0.79); (-3.85, -0.77); 0.003	-1.06 (0.79); (-2.61, 0.49); 0.178
	6	14.64 (5.06), 22	15.05 (3.52), 20	13.9 (4.85), 20			
	12	14 (4.32), 21	14.83 (3.1), 23	13 (5.23), 20			
	24	14.14 (5.47), 22	14.91 (4.72), 22	12.41 (4.6), 22			
	52	12.73 (4.58), 22	14.62 (4.52), 21	12.8 (3.68), 20			
PANSS Disorganised	0	16.25 (2.59), 24	17.15 (3.65), 26	17.8 (4.27), 25	-0.19 (0.77); (-1.69, 1.32); 0.809	-0.85 (0.77); (-2.36, 0.66); 0.273	-0.66 (0.80); (-2.22, 0.90); 0.408
	6	15.77 (3.18), 22	16.8 (2.91), 20	17.5 (4.01), 20			
	12	15.19 (4.96), 21	16.39 (3.37), 23	16.25 (4.1), 20			
	24	15.1 (3.86), 21	15.5 (3.53), 22	14.5 (3.78), 22			
	52	14.82 (3.67), 22	15.67 (3.73), 21	15.8 (4.25), 20			
PANSS Excitement	0	18.25 (4.35), 24	17.85 (3.86), 26	17.4 (4.14), 25	-0.45 (0.75); (-1.91, 1.02); 0.549	-0.80 (0.75); (-2.27, 0.67); 0.286	-0.35 (0.76); (-1.84, 1.13); 0.641
	6	15.95 (4.09), 22	15.9 (3.93), 20	15.75 (4.05), 20			
	12	15.52 (4.77), 21	15.52 (3.16), 23	14.35 (4.97), 20			
	24	14.77 (3.37), 22	14.45 (3.4), 22	12.86 (4.36), 22			
	52	13.41 (4.07), 22	13.62 (2.89), 21	13.8 (4.26), 20			
PANSS Emotional Distress	0	25.46 (5), 24	25.31 (3.83), 26	26.28 (3.47), 25	0.0 (1.11); (-2.17, 2.18); 0.999	-1.93 (1.12); (-4.12, 0.26); 0.084	-1.93 (1.13); (-4.15, 0.29); 0.088
	6	22.55 (5.21), 22	21.5 (4.27), 20	23.1 (3.93), 20			
	12	21.38 (6.91), 21	22.48 (4.31), 23	19.6 (5.74), 20			

	24	21.55 (5.75), 22	20.95 (3.7), 22	17.5 (5.49), 22			
	52	19.86 (6.12), 22	19.1 (5.49), 21	20.1 (5.08), 20			

Table 5: Secondary Outcomes. Mean (SD), number of observations. Effect is common to all follow-up times (ITT).

Variable	Time (weeks)	Antipsychotics (N = 24)	CBT (N = 26)	Combination (N = 25)	Mean difference (SE); (95%CI); P-value		
					CBT vs. AP	CBT vs. combined	AP vs. combined
QPR	0	38.71 (9.23), 24	40.13 (9.33), 25	41.8 (11.79), 25	-0.93 (2.97); (-6.76, 4.90); 0.754	4.01 (3.14); (-2.15, 10.17); 0.202	4.94 (3.05); (-1.03, 10.91); 0.105
	24	44.86 (14.99), 22	47.81 (8.86), 21	52 (14.05), 18			
	52	48.55 (14.73), 22	51.62 (9.25), 21	49.88 (11.04), 17			
HADS Total	0	41.05 (5.49), 23	37.54 (5.42), 24	36.36 (6.76), 25	-0.60 (1.98); (-4.48, 3.27); 0.761	-2.93 (2.03); (-6.90, 1.04); 0.148	-2.32 (1.99); (-6.22, 1.56); 0.241
	24	35.55 (7.69), 22	35.36 (12.61), 22	30.37 (9.28), 19			
	52	34.27 (9.08), 22	32.14 (6.96), 21	30.35 (6.98), 17			
HADS Anx	0	21.96 (2.62), 23	20.5 (3.32), 24	19.36 (3.89), 25	0.62 (1.28); (-1.89, 3.14); 0.627	-1.34 (1.32); (-3.92, 1.25); 0.310	-1.96 (1.30); (-4.50, 0.58); 0.131
	24	19.36 (4.51), 22	19.18 (10.8), 22	15.65 (5.98), 20			
	52	18.73 (5.03), 22	17.29 (4.64), 21	15.67 (4.89), 18			
HADS Dep	0	19.05 (4.87), 23	17.38 (3.32), 24	17.28 (5.55), 25	-0.14 (1.20); (-2.49, 2.20); 0.905	-1.60 (1.27); (-4.08, 0.88); 0.206	-1.46 (1.20); (-3.82, 0.90); 0.226
	24	16.27 (5.84), 22	15.18 (3.81), 22	13.42 (5.83), 19			
	52	14.91 (5.52), 22	14.05 (4.2), 21	14.94 (5.36), 17			
WHO Qol	0	67.03 (14.99), 24	68.66 (13.41), 25	70.18 (15.41), 24	0.62 (3.20); (-5.65, 6.88); 0.847	5.82 (3.37); (-0.78, 12.42); 0.084	5.21 (3.39); (-1.43, 11.84); 0.124
	6	72.5 (19.84), 22	76.78 (14.79), 18	77.82 (14.06), 17			
	12	77.29 (21.31), 21	79.29 (16.59), 21	85.83 (17.59), 18			
	24	79.15 (20.95), 20	79.1 (14.03), 21	89.06 (18.87), 18			
	52	81.36 (20.02), 22	83.81 (15.23), 21	82.93 (19.17), 15			
PSP	0	52.67 (13.83), 24	57.38 (12.04), 26	58.16 (11.1), 25	3.18 (4.18); (-5.02, 11.38); 0.448	2.17 (4.27); (-6.19, 10.53); 0.611	-1.01 (4.24); (-9.32, 7.30); 0.812
	24	63.95 (18.53), 22	60.05 (10.51), 22	62.48 (17.47), 21			
	52	60.45 (17.61), 22	60.95 (12.93), 21	61 (16.47), 20			
CGI Scale (clinician)	0	4.13 (0.74), 24	4.08 (0.63), 26	4.04 (0.68), 25	-0.16 (0.28); (-0.70, 0.38); 0.569	-0.64 (0.29); (1.20, -0.08); 0.026	-0.48 (0.28); (-1.03, 0.07); 0.087
	24	3.32 (1.17), 22	3.45 (0.91), 22	2.86 (1.06), 21			
	52	3.23 (1.11), 22	3.38 (1.07), 21	3 (1.08), 20			
CGI Scale (Patients)	0	4.91 (0.97), 22	4.42 (0.99), 26	4.38 (1.54), 25	0.35 (0.41); (-0.44, 1.15); 0.385	-0.29 (0.42); (1.11, 0.52); 0.482	-0.65 (0.42); (-1.46, 0.17); 0.119
	24	4.33 (1.56), 21	3.71 (1.23), 21	3.2 (1.54), 20			
	52	3.91 (1.48), 22	3.5 (1.5), 20	3.94 (1.59), 18			
CGI clinician - improvement	0	-	-	-	0.05 (0.31); (-0.56, 0.65);	-0.53 (0.32); (-1.16, 0.10)	-0.58 (0.31); (-1.19, 0.03);
	24	2.95 (1.21), 22	2.78 (1.23), 22	2.14 (0.91), 21			

	52	2.45 (1.06), 22	2.50 (1), 20	2.25 (1.12), 20	0.876	0.097	0.064

Table 6: Participants achieving improvement/deterioration on PANSS total score at 24 and 52 weeks

ITT analysis		Deterioration (n)		Improvement (n)	
		>25%	>50%	>25%	>50%
24 weeks	CBT	0	2	8	2
	Antipsychotics	0	1	5	3
	Combination	0	0	11	7
52 weeks	CBT	0	1	8	4
	Antipsychotics	2	0	8	5
	Combination	0	0	7	6
As Treated analysis		Deterioration (n)		Improvement (n)	
		>25%	>50%	>25%	>50%
24 weeks	CBT	0	1	8	3
	Antipsychotics	0	1	3	2
	Combination	0	1	9	4
	Neither	0	0	4	3
52 weeks	CBT	0	0	6	6
	Antipsychotics	2	0	6	0
	Combination	0	1	8	4
	Neither	0	0	3	5

Table 7: Secondary Outcomes (adverse effects). Mean (SD), number of observations on as treated basis (group receiving neither CBT nor Antipsychotics is not shown)

Variable	Time (weeks)	Antipsychotics (N = 21)	CBT (N = 20)	Combination (N = 21)	Mean difference (SE); (95%CI); P-value		
					CBT vs. AP	CBT vs. combined	AP vs. combined
ANNSERS total number of side effects+	0	8.52 (3.66), 21	8.55 (3.94), 20	10.33 (4.54), 21	3.22 (1.35); (0.58, 5.87); 0.017	3.99 (1.35); (1.36, 6.64); 0.003	0.78 (1.37); (-1.91, 3.47); 0.572
	24	8.47 (5.62), 17	5.7 (3.23), 20	10.05 (5.35), 19			
	52	9.06 (5.5), 16	4.74 (3.35), 19	10.42 (5.9), 19			
ANNSERS Total score+	0	11.57 (5.48), 21	11.7 (6.21), 20	13.62 (6.18), 21	5.12 (2.05); (1.11, 9.14); 0.012	6.30 (2.03); (2.32, 10.27); 0.002	1.17 (2.07); (-2.89, 5.24); 0.571
	24	11.59 (8.4), 17	7.45 (4.99), 20	14.16 (8.42), 19			
	52	12.94 (8.77), 16	6.21 (5.07), 19	13.79 (7.63), 19			
HDL-Cholesterol(mmol/l)	0	1.37 (0.35), 16	1.21 (0.32), 12	1.37 (0.41), 13	0.07 (0.09); (-0.10, 0.24); 0.389	0.09 (0.09); (-0.09, 0.26); 0.346	0.01 (0.08); (-0.15, 0.17); 0.893
	12	1.37 (0.38), 14	1.21 (0.29), 9	1.54 (0.49), 15			
	52	1.15 (0.36), 8	1.36 (0.31), 6	1.24 (0.21), 7			
Total/HDL ratio	0	3.4 (0.85), 16	3.58 (0.66), 12	3.06 (0.81), 13	-0.08 (0.22); (-0.50, 0.35); 0.722	0.01 (0.24); (-0.45, 0.48); 0.950	0.09 (0.21); (-0.33, 0.51); 0.667
	12	3.63 (1.25), 14	3.64 (0.44), 10	3.23 (0.65), 14			
	52	4.41 (2.11), 8	3.51 (0.53), 7	3.68 (1.05), 6			
LDL Cholesterol (mmol/l)	0	2.42 (0.79), 14	2.44 (0.58), 10	2.34 (0.72), 11	-0.21 (0.28); (-0.76, 0.33); 0.449	-0.15 (0.29); (-0.72, 0.42); 0.615	0.06 (0.26); (-0.45, 0.58); 0.809
	12	2.59 (0.72), 12	2.79 (0.92), 8	2.63 (0.74), 12			
	52	3.02 (0.84), 6	2.83 (0.59), 6	2.63 (0.9), 6			
Triglycerides (mmol/l)	0	1.23 (0.45), 14	1.16 (0.56), 10	1.15 (0.58), 11	0.08 (0.19); (-0.29, 0.45); 0.659	-0.27 (0.20); (-0.66, 0.12); 0.170	-0.35 (0.18); (-0.71, 0.00); 0.051
	12	1.45 (0.75), 12	1.4 (0.63), 8	1.11 (0.63), 13			
	52	1.62 (1.11), 6	0.97 (0.28), 6	2.57 (4.08), 7			
Prolactin (mU/l)	0	162.86 (98.96), 14	188.42 (72.73), 12	221.58 (74.14), 12	23.12 (26.73); (-29.27, 75.50); 0.387	-7.39 (29.00); (-64.22, 49.44); 0.799	-30.51 (28.28); (-85.94, 24.93); 0.281
	12	206.92 (83.76), 13	196.22 (83.08), 9	180 (73.9), 10			
	52	136.71 (53.84), 7	201.83 (93.32), 6	186.13 (88.69), 8			
Glucose (mmol/l)	0	6.6 (7.63), 15	5.04 (2.68), 12	4.72 (0.95), 13	-0.56 (0.50); (-1.53, 0.42); 0.265	-0.75 (0.52); (-1.77, 0.27); 0.148	-0.19 (0.45); (-1.07, 0.68); 0.662
	12	4.76 (1.1), 11	5.2 (1.72), 7	4.55 (0.55), 14			
	52	4.63 (0.65), 8	5.32 (1.81), 6	4.11 (0.76), 7			
Weight (kg)	0	75.91 (20.31), 21	73.62 (15.72), 18	70.93 (12.97), 21	1.80 (1.40);	3.70 (1.41);	1.90 (1.36);

	6	77.06 (18.2), 16	74.84 (17.27), 15	70.82 (13.56), 18	(-0.94, 4.54); 0.198	(0.93; 6.47); 0.009	(-0.76, 4.57); 0.162
	12	72.87 (13.32), 16	73.58 (15.66), 19	73.86 (14.01), 19			
	24	78.21 (17.38), 18	72.12 (15.14), 20	75.33 (13.59), 16			
	52	74.87 (15.34), 16	75.71 (14.88), 15	75.22 (15.07), 18			
Systolic Blood Pressure (mm Hg)	0	124.12 (12.91), 20	124.05 (15.02), 14	118.98 (11.11), 19	1.36 (2.76); (-4.06, 6.78); 0.624	0.52 (2.83); (-5.04, 6.07); 0.855	-0.84 (2.44); (-5.61, 3.93); 0.730
	12	124.49 (16.53), 14	122.13 (10.16), 14	123.86 (14.13), 17			
	52	123.6 (13.28), 16	122.22 (10.67), 10	116.9 (8.47), 18			

+ ANNSERS consists of 43 non-neurological side effects each rated as absent (0), mild (1), moderate (2) or severe (3) giving a total score of 129

Table 8: Hospital admissions on an as treated basis

	Antipsychotics (N = 21)	CBT (N =20)	Combination (N =21)	Neither (N=13)
Voluntary admission				
Total number of admissions	0	2	3	0
Number (%) of participants admitted	0	1 (5%)	2 (10%)	0
Mean (SD) days in hospital	0	35 (21.2)	67 (88.4)	0
Compulsory admission				
Total number of admissions	0	2	1	0
Number (%) participants admitted	0	2 (10%)	1 (5%)	0
Mean (SD) days in hospital	0	65.5 (54.45)	18	0