Cognitive behavioural therapy in clozapine-resistant schizophrenia (FOCUS): an assessor-blinded, randomised controlled trial

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Summary

Background Although clozapine is the treatment of choice for treatment-refractory schizophrenia, 30–40% of patients have an insufficient response, and others are unable to tolerate it. Evidence for any augmentation strategies is scarce. We aimed to determine whether cognitive behavioural therapy (CBT) is an effective treatment for clozapine-resistant schizophrenia.

Methods We did a pragmatic, parallel group, assessor-blinded, randomised controlled trial in community-based and inpatient mental health services in five sites in the UK. Patients with schizophrenia who were unable to tolerate clozapine, or whose symptoms did not respond to the drug, were randomly assigned 1:1 by use of randomised-permuted blocks of size four or six, stratified by centre, to either CBT plus treatment as usual or treatment as usual alone. Research assistants were masked to allocation to protect against rater bias and allegiance bias. The primary outcome was the Positive and Negative Syndrome Scale (PANSS) total score at 21 months, which provides a continuous measure of symptoms of schizophrenia; PANSS total was also assessed at the end of treatment (9 months). The primary analysis was by randomised treatment based on intention to treat, for all patients for whom data were available. This study was prospectively registered, number ISRCTN99672552. The trial is closed to accrual.

Findings From Jan 1, 2013, to May 31, 2015, we randomly assigned 487 participants to either CBT and treatment as usual (n=242) or treatment as usual alone (n=245). Analysis included 209 in the CBT group and 216 in the treatment as usual group. No difference occurred in the primary outcome (PANSS total at 21 months, mean difference –0·89, 95% CI –3·32 to 1·55; p=0·48), although the CBT group improved at the end of treatment (PANSS total at 9 months, mean difference –2·40, –4·79 to –0·02; p=0·049). During the trial, 107 (44%) of 242 participants in the CBT arm and 104 (42%) of 245 in the treatment as usual arm had at least one adverse event (odds ratio 1·09, 95% CI 0·81 to 1·46; p=0·58). Only two (1%) of 242 participants in the CBT arm and one (<1%) of 245 in the treatment as usual arm had a trial-related serious adverse event.

Interpretation At 21-month follow-up, CBT did not have a lasting effect on total symptoms of schizophrenia compared with treatment as usual; however, CBT produced statistically, though not clinically, significant improvements on total symptoms by the end of treatment. There was no indication that the addition of CBT to treatment as usual caused adverse effects. The results of this trial do not support a recommendation to routinely offer CBT to all people who meet criteria for clozapine-resistant schizophrenia; however, a pragmatic individual trial might be indicated for some.

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Introduction

Schizophrenia is associated with significant personal, social, and economic costs. The mortality risk associated with schizophrenia is also a major concern—eg, a recent systematic review and meta-analysis found that people with a diagnosis of schizophrenia die an average of 14·5 years earlier than those without diagnosed schizophrenia.[1] About a third of people with a diagnosis of schizophrenia respond poorly to standard treatment with antipsychotic medication. Treatment-resistant schizophrenia is defined as schizophrenia treated over two periods with different antipsychotics at an adequate dose for at least 4 weeks, and symptoms are not reduced by at least 20%.[2] 8 million people are estimated to have treatment-resistant schizophrenia.[3] For people meeting diagnostic criteria for treatment-resistant schizophrenia, economic costs are greater because of longer-term residential and intensive community treatment,[4] quality of life is 20% lower,[5] and community functioning is poorer than those individuals with a diagnosis of schizophrenia that is not resistant to treatment with antipsychotic medication.[6]

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Research in context

Evidence before this study

For people with a diagnosis of schizophrenia who respond poorly to standard treatment with antipsychotic medication, the antipsychotic clozapine is generally considered to be the treatment of choice. However, 30–40% of people who trial clozapine can have a poor response to the medication and the range of adverse effects can prevent the optimal dose being reached or tolerated long term. We searched PubMed from inception to Feb 28, 2018, for publications in English, using the terms "clozapine resistant schizophrenia" and "treatment". Our search yielded 24 publications, of which four were small randomised controlled trials (RCTs) of pharmacological or biological treatments for people with clozapine-resistant schizophrenia and four were systematic reviews and meta-analyses of pharmacological or biological augmentation strategies. No RCTs of psychological treatments for clozapine-resistant schizophrenia were found. Evidence for pharmacological and psychological treatments for people who meet criteria for clozapine-resistant schizophrenia is limited by small studies providing low-quality evidence.

Added value of this study

The reduction in psychiatric symptoms observed at the end of treatment with cognitive behavioural therapy is of a similar magnitude to that reported for pharmacological augmentation. However, there appear to be fewer side-effects associated with cognitive behavioural therapy, and the evidence for symptom reduction at end of treatment is of higher quality than that for pharmacological augmentation.

Implications of all the available evidence

There is insufficient evidence to support offering cognitive behavioural therapy to all patients with clozapine-resistant schizophrenia. A pragmatic individual trial might be indicated for some individuals, particularly when the person prefers talking therapy to pharmacological augmentation as their treatment choice.

Clozapine is generally considered the treatment of choice for people with treatment-resistant schizophrenia,[7] which is reflected in recommendations in clinical guidelines. However, 30–40% of patients show an inadequate response to clozapine.[8] Debate exists about the superiority of clozapine for treatment-resistant schizophrenia, with one network meta-analysis finding clozapine to be equivalent to many other antipsychotics for treatment-resistant schizophrenia.[9] However, another meta-analysis found clozapine to be superior to all other antipsychotics for positive symptoms.[10]

Some people cannot tolerate clozapine; serious side-effects include seizures and agranulocytosis. Poor response to clozapine, termed clozapine-resistant schizophrenia, is defined as inadequate response to treatment for at least 12 weeks at a stable dose of 400 mg or more per day, unless limited by side-effects. The most common treatment of clozapine-resistant schizophrenia is augmentation with another antipsychotic medication.[11] Although meta-analyses have found some evidence of small benefits of such augmentation,[12–14] this evidence is limited by few, small, low-quality studies. A small study examined the effects of augmentation with electroconvulsive therapy in 39 participants, but this was of short duration (8 weeks).[15]

Several meta-analyses of cognitive behavioural therapy (CBT) have found small to moderate effects on psychotic symptoms when delivered in combination with antipsychotic medications.[16–18] However, conclusions regarding the efficacy of CBT are claimed to be mistaken, since most large, well conducted trials have not shown a significant effect at the end of treatment and the effect sizes are reduced overall if meta-analyses are limited to studies of high quality.[17] The efficacy of augmentation of clozapine with CBT for clozapine-resistant schizophrenia is unknown, since only one small unrandomised trial has investigated this.[19]

The Focusing On Clozapine Unresponsive Symptoms (FOCUS) trial aimed to determine whether CBT is clinically effective for people with clozapine-resistant schizophrenia. We hypothesised that CBT plus treatment as usual would reduce the psychiatric symptoms of schizophrenia, improve quality of life, and improve user-defined recovery over a 21-month follow-up period compared with treatment as usual alone.

Methods

Study design and participants

FOCUS was a pragmatic, parallel group, prospective, randomised, open trial with masked evaluation of outcomes, comparing CBT plus treatment as usual with treatment as usual alone in individuals unable to tolerate clozapine, or whose symptoms did not respond to the drug. We recruited participants through referrals from community-based and inpatient mental health services in five sites in the UK. The National Research Ethics Committee approved the FOCUS trial. Full details of the protocol are provided elsewhere.[20]

The inclusion criteria were: (1) persistent symptoms despite an adequate trial of clozapine in terms of dose, duration, and adherence,[11] defined as treatment with clozapine at a stable dose of 400 mg or more (unless limited by tolerability) for at least 12 weeks, or if currently augmented with a second antipsychotic that had been given for at least 12 weeks, without remission of psychotic symptoms, or discontinuation of clozapine because of adverse reactions or inefficacy in the past 24 months; (2) presence of at least one psychotic symptom with a severity of 4 or more (for hallucinations or delusions) or 5 or more (for suspiciousness or grandiosity) on the

Positive and Negative Syndrome Scale (PANSS), plus a PANSS total score of at least 58, which is equivalent to a clinical global impression of being at least mildly ill;[21] (3) in contact with mental health services and have a care coordinator; (4) meet either ICD-10 criteria for schizophrenia, schizoaffective disorder, or delusional disorder, or criteria for an Early Intervention for Psychosis service to allow for diagnostic uncertainty in early phases; (5) aged 16 years or older; and (6) competent and willing to provide written, informed consent.

Our exclusion criteria were primary diagnosis of alcohol or substance dependence, developmental disability, non-English speaking, and having received CBT within the past 12 months.

Potential participants were given an information sheet and, if willing to participate and provide written informed consent, they were offered an assessment.

Randomisation and masking

Randomisation was 1:1 by use of randomised-permuted blocks of random size (block sizes of four or six), stratified by centre and administered via a study-specific web-based portal. Allocation was notified to the trial manager, trial administrator, and trial therapists by email and to the participant by letter. Research assistants assessing outcomes were masked to allocation to protect against rater bias and allegiance bias. Masking was maintained with a wide range of measures, described in detail in our protocol.[20] If a blind break occurred, where possible, a new research assistant masked to allocation was identified for subsequent follow-up assessments.

Procedures

CBT was delivered by appropriately qualified psychological therapists on an individual basis over a period of 9 months and included up to 26 h of treatment on an approximately weekly basis over the 9-month treatment window with up to four additional booster sessions in the following year. CBT was based on a specific cognitive model[22] and used a manualised approach based on an individualised formulation:[23] the chief investigator developed the model and manualised approach. CBT is a collaborative therapy that is problem orientated, working towards shared goals. Thus, treatment targets often included positive symptoms, but also included social issues (eg, improvement of relationships or development of meaningful roles) and emotional difficulties (eg, anxiety and depression). Fidelity to the treatment protocol was ensured by a combination of an initial week of training on the use of the specific model and manual, weekly supervision sessions, and quarterly training days, and was assessed by rating audio recordings of therapy sessions by use of the Cognitive Therapy Scale–Revised.[24] Further details regarding establishing and monitoring adherence are provided elsewhere.[20]

The comparator was treatment as usual, which included care coordination from secondary care mental health services, including community mental health teams, early intervention in psychosis, or inpatient settings. All patients received follow-up from a multidisciplinary team within secondary mental health services. We did not ask services to withhold any treatment. All treatments in both conditions were monitored by use of an Economic Patient Questionnaire.

Outcomes

The primary outcome was total PANSS score at 21 months. The PANSS is a 30 item rating scale designed to provide a comprehensive assessment of psychiatric symptoms in adult patients with schizophrenia. Five components have been reported: positive, negative, depression-anxiety, agitation-excitement, and disorganisation.[25] The PANSS was completed at baseline assessment, end of treatment (9 months), and 1-year follow-up (21 months). PANSS total score at 21 months was selected as the primary outcome because the durability of any treatment effect observed at the end of treatment was considered the most important criterion.

We collected secondary outcome measures at the timepoints mentioned earlier: the Psychotic Symptom Rating Scales (PSYRATS)[26] to assess dimensions of auditory hallucinations and delusional beliefs; the Personal and Social Performance Scale to assess social functioning;[27] the Calgary Depression Rating Scale for Schizophrenia to assess depression;[28] and the Clinical Global Impression Scale (CGI)[29] and a participant version (CGI-P) to obtain clinician and participant perception of global illness severity. Self-report questionnaires were used to assess self-rated recovery (the brief, 15 item Questionnaire about the Process of Recovery),[30] health status and health-related utility (EQ-5D-5L),[31] anxiety (meta-worry subscale of the Anxious Thoughts Inventory),[32] alcohol use (Alcohol Use Disorder Test),[33] and drug use (Drug Abuse Screening Test).[34] An economic evaluation was also done, which will be reported elsewhere. The measure of health benefit was the quality-adjusted life-years derived from the health status and health-related utility questionnaire.

We recorded all events that met UK National Research Ethics Committee criteria for a serious adverse event—ie, serious negative events that are unexpected and deemed to be associated with the trial protocol or procedures. Additional unwanted effects of trial participation were defined as more than a 25% increase on PANSS total score or scoring 6+ on the CGI-Improvement Scale. We also developed a bespoke measure of potential unwanted effects of trial participation.

Statistical analysis

We calculated our sample to detect a difference in means between groups using a standardised effect size of 0·33 for 90% power and two-sided α of 5%. We required outcome data on 194 participants per group, using our modelling approach to increase precision rather than potentially

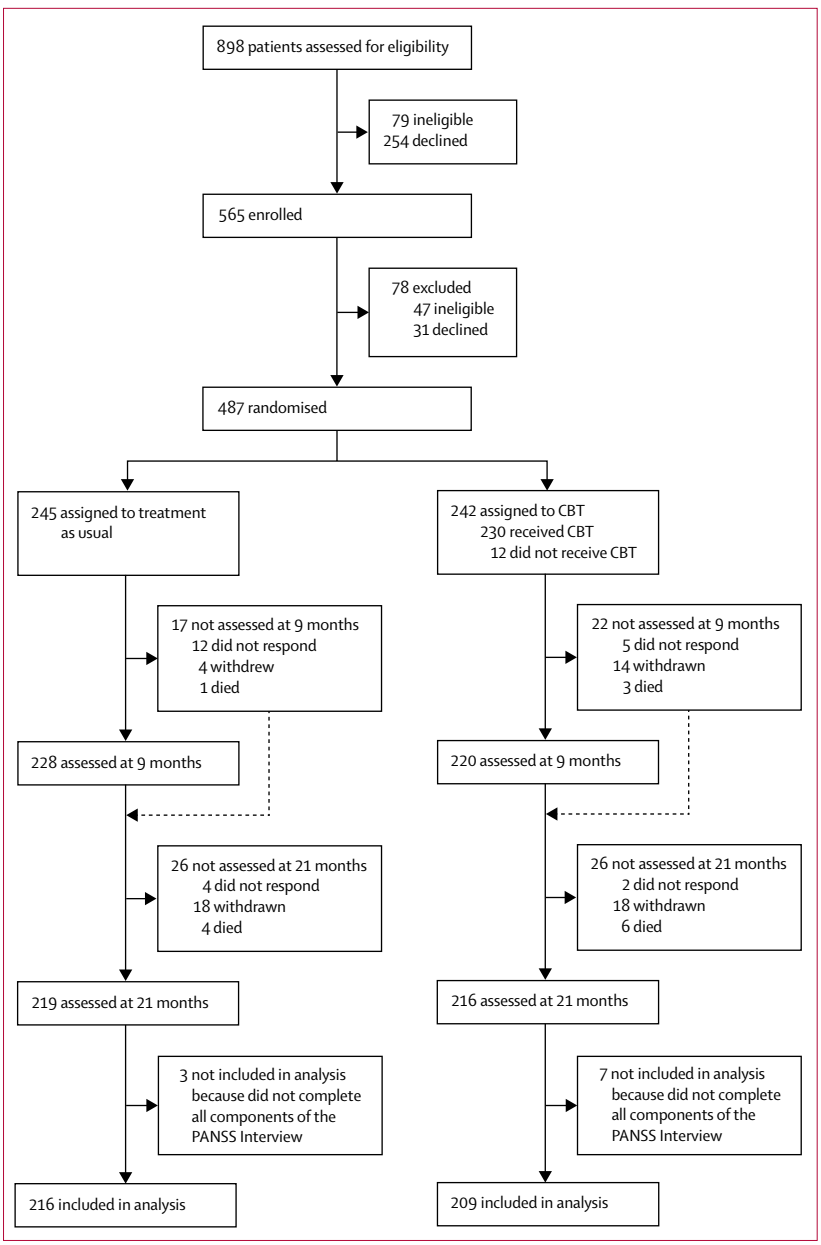

Figure: **Trial profile**
CBT=cognitive behaviour therapy. PANSS=Positive and Negative Syndrome Scale.

reduce sample size. To account for 20% missing data, we inflated the sample size to 485. Statistical analysis was done after all participants completed 21 months of follow-up. This analysis followed a prespecified plan. Continuous variables were summarised using mean (SD) or median (IQR), and discrete variables were reported as absolute number and percentage. The primary outcome was analysed with repeated measures from linear mixed models that adjusted for prespecified baseline covariates (baseline PANSS, sex, and age) and included a random effect for site. Treatment effects are presented with 95% CIs for each timepoint. Additionally, the results of the primary analysis are expressed in the standardised mean difference scale to assist in the interpretation of our results compared with our hypothesised effect. The primary analysis was by randomised treatment based on intention to treat for all patients for whom data were available. To estimate treatment efficacy, we estimated complier average casual effects using instrumental variable methods. Secondary outcomes were analysed with linear mixed models, and adverse events were analysed with a χ^2 test or logistic regression. We made no adjustments to secondary outcome CIs for multiple testing. Use of these linear mixed models allowed for the analysis of all available data, on the assumption that data were missing at random,[35] conditional on covariates. Sensitivity analysis by use of multiple imputation on the primary outcome was done as well as the removal of participants who discontinued clozapine because of side-effects. We used estimated treatment effects adjusted for non-attendance at CBT with Complier Average Causal Effect models using two-stage least squares. We report the primary outcome showing improvement from baseline using 20%, 25%, 50%, and 75% thresholds, and the corresponding number needed to treat to aid interpretation. Additionally, we report the PANSS outcomes by severity based on inclusion criteria (delusions or hallucinatory behaviour with a score of 4 or greater and grandiosity or suspiciousness persecution with a score of 5 or greater). All analyses used Stata version 14·0. The Independent Data Monitoring Committee monitored accumulating unblinded data throughout the trial.

This study was prospectively registered, number ISRCTN99672552.

See Online for appendix

Role of the funding source

The funder 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 and had final responsibility to submit for publication.

Results

We identified 898 potentially eligible participants, of whom 565 (63%) met criteria for further assessment between Jan 1, 2013, and May 31, 2015. We randomly assigned 487 (86%) of 565 participants who met inclusion criteria and agreed to take part in either CBT plus treatment as usual (n=242) or treatment as usual alone (n=245; figure). Participants recruited via Early Intervention in Psychosis services (n=8) all met criteria for an ICD-10 schizophrenia spectrum diagnosis. Details of ineligibility are shown in the appendix. Analysis included 209 in the CBT group and 216 in the treatment as usual group. Baseline clinical and demographic data are shown in table 1; the groups were balanced across characteristics. Participants assigned to CBT plus treatment as usual received a median of 21 CBT sessions (IQR 12–25) within the 9-month treatment window; 213 (88%) of 242 attended six or more sessions, with only 12 (5%) participants attending no sessions (appendix).

	Treatment as usual (n=245)	Cognitive behavioural therapy plus treatment as usual (n=242)
Age, years	42·8 (10·4)	42·2 (10·7)
Sex		
Male	173 (71%)	176 (73%)
Female	72 (29%)	66 (27%)
Ethnicity		
White	222 (91%)	222 (92%)
Asian	4 (2%)	9 (4%)
Black	3 (1%)	5 (2%)
Mixed	12 (5%)	4 (2%)
Other	3 (1%)	2 (1%)
Refused to answer	1 (<1%)	..
Employment		
Paid, full or part time	10 (4%)	10 (4%)
Voluntary	16 (7%)	14 (6%)
Education or training	5 (2%)	9 (4%)
Other unpaid activity	8 (3%)	6 (3%)
Unemployed	204 (83%)	203 (84%)
Missing	2 (1%)	..
Residential status		
Inpatient	16 (7%)	17 (7%)
Rehabilitation ward	8 (3%)	13 (5%)
Supported accommodation	45 (18%)	39 (16%)
Independent living	174 (71%)	172 (71%)
Missing	2 (1%)	1 (<1%)
Full-time education, years	12 (11–14); 229	12 (11–14); 223
Untreated psychosis, months	18 (2–48); 203	8 (1–24); 195
Illness, months	240 (144–300); 231	216 (132–300); 227
(Continued from previous column)		
Diagnosis at baseline		
Schizophrenia	218 (89%)	209 (86%)
Schizoaffective	20 (8%)	28 (12%)
Delusional disorder	5 (2%)	2 (1%)
Unspecified psychosis*	1 (<1%)	2 (1%)
Missing	1 (<1%)	1 (<1%)
Prescribed clozapine	221 (90%)	223 (92%)
Time on clozapine, months	60 (24–120); 216	60 (24–120); 218
Clozapine dose, mg	400 (300–500); 221	400 (300–525); 221
Discontinued clozapine	24 (10%)	19 (8%)
Time discontinued, months	13 (3–20); 24	9 (5–13); 19
Reasons for discontinuing clozapine		
Side-effects	23 (96%)	16 (84%)
Lack of efficacy	1 (4%)	3 (16%)
Taking other antipsychotic medication		
None	142 (58%)	136 (56%)
One	95 (39%)	99 (41%)
Two	7 (3%)	7 (3%)
Three	1 (<1%)	..
Other medication		
Antidepressants	129 (53%)	113 (47%)
Other mental health medication	35 (14%)	52 (22%)
Benzodiazepines	30 (12%)	27 (11%)
Medication for antipsychotic side-effects	24 (10%)	27 (11%)

Data are mean (SD), n (%), or median (IQR); N. *Not due to a substance or known physiological condition.

Table 1: **Baseline characteristics**

At 9 months, 51 blind breaks had occurred (23 of these patients were transferred to a new assessor, so 28 remained unblinded). By 21 months, there were 55 blind breaks (35 patients were transferred to a new assessor, so 20 remained unblinded). PANSS outcome at baseline by severity based on inclusion criteria showed no difference between the groups (appendix).

Mean PANSS scores improved in both randomised groups over time from a mean of 83 at baseline (table 2). At 21 months, no difference occurred between the groups on PANSS total score (–0·89, 95% CI –3·32 to 1·55; p=0·48), although at 9 months, a small difference occurred between the groups in favour of CBT on PANSS total (–2·40, –4·79 to –0·02; p=0·049). This difference is equivalent to an effect size of –0·16 (95% CI –0·32 to –0·001) at 9 months and –0·06 (95% CI –0·21 to 0·10) at 21 months using the standardised mean difference scale. Multiple imputation sensitivity analysis gave similar results (appendix). Removal of participants who discontinued clozapine because of side-effects at baseline overall gave similar results (appendix). The adjustment for receiving at least six sessions of CBT had little effect on treatment effect estimates due to high compliance proportions: at 9 months, the Complier Average Causal Effect estimate was –2·50 (95% CI –5·10 to 0·11; p=0·060) and –0·87 (–3·69 to 1·96; p=0·55) at 21 months (appendix). We also estimated that the effect of each extra treatment session resulted in a change in PANSS total score of –0·12 (95% CI –0·24 to 0·00, p=0·059). Treatment effect estimates followed a similar pattern for other PANSS outcomes (tables 2 and 3). At 21 months, 28 (13%) of 209 participants in the CBT plus treatment as usual group and 14 (7%) of 216 in the treatment as usual alone group had more than 50% improvement in PANSS (number needed to treat 15, 95% CI 8 [number needed to treat, benefit] to 81 [number needed to treat, benefit]).

The difference between groups on health-related quality of life was 0·028 (95% CI –0·012 to 0·068; p=0·17) at 21 months, and for the Questionnaire about the Process of Recovery, the difference was 2·03 (0·04 to 4·01; p=0·045).

	Treatment as usual (n=245)	Cognitive behavioural therapy plus treatment as usual (n=242)	Mean difference (95% CI)	p value
PANSS total				
Baseline	83·3 (14·0); 245	82·8 (13·7); 242	..	..
9 months	77·8 (14·6); 224	75·2 (15·5); 218	−2·40 (−4·79 to −0·02)	0·049
21 months	74·1 (14·8); 216	73·0 (16·7); 209	−0·89 (−3·32 to 1·55)	0·48
PANSS positive				
Baseline	25·2 (5·7); 245	24·7 (5·9); 242	..	..
9 months	23·6 (6·2; 225	21·7 (6·6); 218	−1·56 (−2·53 to −0·59)	0·002
21 months	22·5 (6·1); 216	21·3 (7·0); 209	−0·85 (−1·84 to 0·15)	0·095
PANSS negative				
Baseline	19·4 (6·4); 245	19·3 (6·1); 242	..	..
9 months	18·6 (6·7); 227	18·1 (7·0); 220	−0·49 (−1·48 to 0·49)	0·33
21 months	17·5 (6·1); 216	17·8 (6·8); 211	0·29 (−0·72 to 1·29)	0·58
PANSS disorganised				
Baseline	24·8 (6·6); 245	24·7 (6·5); 242	..	..
9 months	23·1 (6·0); 225	23·2 (6·4); 218	−0·01 (−0·91 to 0·88)	0·98
21 months	22·4 (6·2); 216	22·7 (6·6); 210	0·14 (−0·78 to 1·05)	0·77
PANSS excitement				
Baseline	17·9 (4·3); 245	18·0 (4·5); 242	..	..
9 months	17·4 (4·2); 228	16·2 (4·1); 220	−1·18 (−1·85 to −0·50)	0·0006
21 months	15·9 (4·0); 216	15·4 (3·9); 210	−0·57 (−1·26 to 0·12)	0·11
PANSS emotional distress				
Baseline	27·4 (5·6); 245	27·0 (5·6); 242	..	..
9 months	25·4 (6·3); 228	24·1 (6·2); 220	−1·08 (−2·02 to −0·13)	0·025
21 months	24·0 (6·0); 216	23·4 (6·6); 210	−0·27 (−1·24 to 0·70)	0·58

Data are mean (SD); N, unless otherwise stated. PANSS=Positive and Negative Syndrome Scale.

***Table 2*: PANSS outcomes**

	Treatment as usual (n=245)	Cognitive behavioural therapy plus treatment as usual (n=242)	Number needed to treat (95% CI*)
More than 20%			
9 months	98/216 (45%)	96/209 (46%)	178 (−11 to 10)
21 months	74/224 (33%)	82/218 (38%)	22 (−23 to 8)
More than 25%			
9 months	57/224 (25%)	68/218 (31%)	18 (37 to 8)
21 months	82/216 (38%)	80/209 (38%)	318 (11 to 11)
More than 50%			
9 months	11/224 (5%)	16/218 (7%)	42 (48 to 15)
21 months	14/216 (7%)	28/209 (13%)	15 (8 to 81†)
More than 75%			
9 months	2/224 (1%)	2/218 (1%)	4070 (57 to 56)
21 months	2/216 (1%)	4/209 (2%)	102 (78 to 31)

Data are n/N (%), unless otherwise stated. The Positive and Negative Syndrome Scale (PANSS) is rescaled. *Number needed to treat (harm) to number needed to treat (benefit). †Number needed to treat (benefit) to number needed to treat (benefit).

***Table 3*: Improvement in PANSS outcomes**

Effect estimates for the complete set of secondary outcomes from the linear mixed models are provided in table 4. The direction of effect favours CBT for all outcomes, but with considerable uncertainty for all but a few outcomes at the end of treatment (positive symptoms, emotional distress, excitement, and voices) and at follow-up (self-rated recovery, emotional distress related to delusions, and CGI improvement).

Few serious adverse events occurred and few were attributable to trial participation (table 5). The total number of adverse events was higher in the group receiving CBT than in the treatment as usual alone group, but this was driven by one participant who had 22 self-harm events. Slightly more participants in the CBT group had an adverse event (107 [44%] of 242 *vs* 104 [42%] of 245, odds ratio 1·09 (95% CI 0·81–1·46; p=0·58). Fewer suicidal crises and symptom exacerbation or outcome deterioration threshold events occurred in the CBT group than in the treatment as usual group, and no differences in reports of potential unwanted effects of trial participation occurred (appendix). Participants receiving CBT had weekly contact with trial staff tasked with reporting adverse effects (the trial therapists), whereas participants receiving treatment as usual alone had less frequent contact with trial staff (the trial research assistants) resulting in a maximum of 37 opportunities for such events to be detected in patients receiving CBT and treatment as usual versus seven opportunities for the group receiving treatment as usual alone. This might result in surveillance bias, favouring treatment as usual.

Discussion

In our study assessing whether CBT is an effective treatment for clozapine-resistant schizophrenia, we found no effect of CBT on our primary outcome (21-month PANSS total), although there was a small effect on PANSS total by the end of treatment. The number needed to treat for a good outcome at 21 months, defined using the commonly accepted more than 50% PANSS improvement threshold,[36] was 15, which suggests that CBT can produce worthwhile, lasting outcomes for a proportion of people with clozapine-resistant schizophrenia. However, the threshold for improvement recommended for use with treatment-resistant schizophrenia by an international working group in their consensus guidelines is 20%;[37] the analysis of good outcomes at 21 months using this threshold suggests that little difference exists between CBT and treatment as usual. The high retention and adherence to treatment clearly show that CBT was highly acceptable to participants. Several other small effects on secondary outcomes that are considered to be important occurred at the end of treatment (PANSS positive symptoms, PANSS emotional distress, PANSS excitement, and PSYRATS hallucinations) and at follow-up (self-rated recovery, emotional distress related to delusions, and CGI improvement), although these average effects are unlikely to be clinically significant. The change observed at 21 months on the measure of recovery is encouraging given the debate about the most meaningful outcomes (clinicians tend to prioritise symptom change, whereas service users tend to prioritise improvements in recovery,

	Treatment as usual (n=245)	Cognitive behavioural therapy plus treatment as usual (n=242)	Mean difference (95% CI)	p value
PSYRATS: auditory hallucinations				
Baseline	24·9 (12·6); 200	21·1 (14·1); 214	..	..
9 months	22·4 (13·4); 192	17·8 (14·2); 185	−2·56 (−4·87 to −0·26)	0·029
21 months	20·3 (14·4); 182	17·1 (14·2); 179	−1·38 (−3·75 to 0·99)	0·26
PSYRATS: delusion				
Baseline	14·9 (5·3); 236	14·3 (5·7); 218	..	..
9 months	13·2 (6·7); 216	12·2 (6·8); 200	−0·42 (−1·61 to 0·77)	0·49
21 months	12·7 (6·8); 203	11·4 (7·1); 193	−0·76 (−1·98 to 0·46)	0·22
PSYRATS unusual beliefs: cognitive				
Baseline	9·9 (3·5); 240	9·6 (3·8); 221	..	..
9 months	8·8 (4·3); 216	8·2 (4·5); 201	−0·24 (−1·01 to 0·54)	0·55
21 months	8·5 (4·4); 205	7·8 (4·7); 194	−0·35 (−1·14 to 0·44)	0·39
PSYRATS unusual beliefs: emotional				
Baseline	5·0 (2·4); 238	4·7 (2·6); 227	..	..
9 months	4·4 (2·9); 219	3·9 (2·9); 206	−0·29 (−0·79 to 0·22)	0·27
21 months	4·3 (2·9); 206	3·6 (3·0); 199	−0·53 (−1·05 to −0·00)	0·049
PSYRATS voices: cognitive				
Baseline	4·5 (2·5); 213	3·9 (2·8); 224	..	..
9 months	4·0 (2·7); 204	3·4 (2·8); 193	−0·32 (−0·82 to 0·17)	0·19
21 months	3·8 (2·8); 187	3·3 (2·9); 187	−0·17 (−0·68 to 0·34)	0·51
PSYRATS voices: emotional				
Baseline	5·4 (2·8); 222	4·7 (3·1); 232	..	..
9 months	5·0 (3·0); 208	4·2 (3·3); 202	−0·43 (−0·95 to 0·08)	0·10
21 months	4·6 (3·3); 197	4·1 (3·3); 199	−0·03 (−0·55 to 0·50)	0·91
PSYRATS voices: physical				
Baseline	6·2 (3·4); 223	5·5 (3·8); 232	..	..
9 months	5·7 (3·6); 209	4·7 (3·8); 208	−0·58 (−1·11 to −0·04)	0·034
21 months	5·1(3·8); 198	4·4 (3·6); 201	−0·30 (−0·85 to 0·24)	0·28
PSYRATS voices: loudness				
Baseline	2·6 (1·4); 239	2·5 (1·5); 229	..	..
9 months	2·3 (1·6); 219	2·0 (1·6); 206	−0·22 (−0·50 to 0·06)	0·12
21 months	2·3 (1·6); 206	1·9 (1·7); 199	−0·28 (−0·57 to 0·01)	0·056
CDSS				
Baseline	7·4 (4·7); 238	7·1 (4·8); 233	..	..
9 months	6·8 (4·8); 215	6·3 (4·5); 210	−0·54 (−1·31 to 0·23)	0·17
21 months	6·6 (5·1); 205	6·0 (4·4); 202	−0·50 (−1·28 to 0·29)	0·21
ATI				
Baseline	18·9 (4·9); 236	18·2 (4·8); 226	..	..
9 months	18·0 (5·0); 206	17·5 (5·2); 189	−0·07 (−0·88 to 0·73)	0·86
21 months	18·1 (5·0); 193	16·9 (5·1); 180	−0·60 (−1·44 to 0·24)	0·16
PSP				
Baseline	48·3 (13·5); 245	49·2 (15·5); 242	..	..
9 months	50·9 (13·9); 224	53·2 (14·6); 213	1·90 (−0·31 to 4·11)	0·093
21 months	51·4 (14·7); 214	51·5 (15·2); 206	0·18 (−2·07 to 2·44)	0·87
QPR				
Baseline	47·4 (11·1); 228	48·5 (11·4); 216	..	..
9 months	48·7 (11·1); 194	50·9 (11·6); 181	1·88 (−0·03 to 3·79)	0·053
21 months	49·1 (11·7); 185	52·0 (9·6); 165	2·03 (0·04 to 4·01)	0·045
AUDIT				
Baseline	3·5 (5·4); 234	4·3 (6·0); 230	..	..
9 months	3·5 (5·7); 209	4·4 (6·0); 194	0·69 (−0·17 to 1·56)	0·12
21 months	3·2 (5·0); 193	4·6 (6·5); 190	0·80 (−0·09 to 1·69)	0·078

(Table 4 continues on next page)

	Treatment as usual (n=245)	Cognitive behavioural therapy plus treatment as usual (n=242)	Mean difference (95% CI)	p value
(Continued from previous page)				
DAST				
Baseline	0·7 (1·5); 231	0·7 (1·4); 224	..	..
9 months	0·9 (1·7); 173	0·7 (1·7); 153	−0·13 (−0·43 to 0·18)	0·41
21 months	0·6 (1·3); 181	0·6 (1·3); 170	0·12 (−0·17 to 0·41)	0·42
Condition improvement CGI*				
9 months	3·3 (1·1); 157	3·3 (1·1); 141	−0·04 (−0·50 to 0·42)	0·82
21 months	3·5 (1·0); 147	3·2 (0·9); 131	−0·33 (−0·54 to −0·11)	0·013
Severity CGI				
Baseline	4·8 (0·8); 162	4·8 (0·9); 158	..	..
9 months	4·3 (1·1); 213	4·2 (1·0); 207	−0·09 (−0·30 to 0·12)	0·40
21 months	4·2 (1·0); 212	4·1 (1·0); 208	−0·03 (−0·24 to 0·18)	0·77
Participant severity CGI				
Baseline	4·0 (1·6); 157	3·9 (1·4); 152	..	..
9 months	3·7 (1·5); 186	3·6 (1·7); 197	0·06 (−0·27 to 0·39)	0·73
21 months	3·7 (1·6); 210	3·7 (1·5); 193	0·12 (−0·22 to 0·46)	0·48
EQ-5D-5L				
Baseline	0·703 (0·225); 230	0·740 (0·201); 223	..	..
9 months	0·721 (0·254); 205	0·760 (0·223); 187	0·035 (−0·004 to 0·073)	0·079
21 months	0·730 (0·223); 189	0·773 (0·204); 180	0·028 (−0·012 to 0·068)	0·17

Data are mean (SD); N, unless otherwise stated. PSYRATS=Psychotic Symptom Rating Scales. CDSS=Calgary Depression Rating Scale for Schizophrenia. ATI=Anxious Thoughts Inventory. PSP=Personal and Social Performance Scale. QPR=Questionnaire about the Process of Recovery. AUDIT=Alcohol Use Disorder Test. DAST=Drug Abuse Screening Test. CGI=Clinical Global Impression Scale. EQ-5D-5L=health status and health-related utility. *Analysed separately at 9 and 21 months because baseline score was not collected.

Table 4: **Secondary outcomes**

functioning, and emotion). The absence of association between psychiatric symptoms and recovery is consistent with research showing the indirect effects of symptoms on recovery. There was no suggestion that the addition of CBT to treatment as usual caused more adverse effects. Fewer suicidal crises, symptom exacerbations, and deteriorations occurred in those allocated to CBT. This finding is noteworthy given the increased surveillance and opportunity for these events to be observed in the CBT arm.

Although the benefit of CBT was significant at the end of the treatment (9 months), CBT had no lasting effect on total psychiatric symptoms in clozapine-resistant schizophrenia (at 21 months). This is similar to the observed effects of medications for people with psychosis, which also diminish when treatment ends.[38] The observed average reductions in PANSS total score were lower than the 15 points estimated to be equivalent to a rating of minimal improvement on the CGI scale.[39] The effects on PANSS positive symptoms, PANSS emotional distress, and auditory hallucinations (PSYRATS total) by the end of the treatment show that CBT can change psychotic symptoms, as well as negative emotions, in a large, well conducted, assessor-blind clinical trial. This finding suggests that claims that such effects cannot be replicated under these conditions[17] are unfounded. The effect sizes observed in the FOCUS trial are similar to those found across all heterogeneous but rigorous CBT trials when meta-analysed.[17] The effect sizes are also similar to those found for pharmacological augmentation of clozapine with a second antipsychotic. However, our trial provides stronger evidence, with less risk of bias than the few, small, short-duration, high risk of bias trials in meta-analyses of augmentation with antipsychotics. The adverse effect profile for CBT is also likely to be favourable when compared with the cardiovascular risks associated with multiple antipsychotic medications.[40] Some small lasting effects were observed at 21 months, including on self-rated recovery, which is important to service users; however, these effects are unlikely to reach a threshold of clinically important change.

Despite our trial being methodologically rigorous, several limitations exist. The comparator was treatment as usual, which meant that concealment of allocation from participants was not possible. Additionally, the lack of an active comparator means we are unable to control for non-specific effects such as contact time and a therapeutic relationship. We did not correct for multiple comparisons; therefore, multiple hypothesis testing could have led to type one error. The 26 h of therapy might have been an insufficient length for patients with clozapine-resistant schizophrenia, who have problems with memory, negative symptoms, and side-effects of polypharmacy, which would be consistent with other trials of CBT for similar populations.[41] A small number of participants met criteria for

diagnoses other than schizophrenia (eg, delusional disorder), which might have reduced the homogeneity of the sample. Arguably, participants who were unable to tolerate clozapine due to side-effects could meet criteria for treatment-resistant schizophrenia rather than clozapine-resistant schizophrenia; however, alternatives to clozapine are still required for such a population, and the sensitivity analysis excluding those who discontinued clozapine found a similar pattern of results. Similarly, we did not routinely assess clozapine blood levels, nor did we assess response to placebo before randomisation therefore, some of our participants might not have been truly clozapine resistant. The mean baseline PANSS total score of 83 suggests that, on average, our participants were moderately ill; however, our entry criteria were also modified to include those who were at least mildly ill (ie, at least 58), whereas Honer's trial[11] had a minimum of 80 for inclusion. Although attempts were made to minimise the likelihood of allegiance bias (eg, masking of assessors), this possibility remains.

Some might argue that, since positive symptoms are the target of clozapine, and are often considered the primary target of CBT for psychosis, they would have been a more appropriate primary outcome for this trial. We chose severity of total symptoms of schizophrenia because the FOCUS trial was a pragmatic effectiveness trial. A similar pattern was seen with PANSS positive symptoms and PSYRATS hallucinations showing significant effects at the end of treatment but not at follow-up. Therefore, a similar overall conclusion is likely to have been reached if the trial had chosen to use a specific measure of positive symptoms as the primary outcome. The choice regarding the timing of the primary outcome is more likely to have influenced the overall conclusion. If end of treatment had been selected, the conclusion would probably have been that CBT is of benefit to people with clozapine-resistant psychosis, but the effect does not persist.

Our results do not support a recommendation to routinely offer CBT for clozapine-resistant schizophrenia. Offering it as a pragmatic individual trial might be worthwhile, particularly in cases where distressing positive symptoms exist or where service users are reluctant to consider pharmacological augmentation because of probable side-effect burden. CBT should probably be offered earlier in the course of psychosis, since individuals with a long history of mental health problems and a lack of response to pharmacological interventions might also be less likely to benefit from psychological interventions than those with psychoses who are more responsive to antipsychotic medications.

Given that more people with clozapine-resistant schizophrenia showed a good clinical outcome to CBT with treatment as usual than those to treatment as usual alone, it is important to be able to identify factors that might predict who is going to benefit. Identification of responders to CBT might be possible by use of trajectory analysis, risk modelling, or methods such as cluster analysis. Future research should examine how intensive psychological treatment needs to be after 9 months to maintain the effects observed at the end of treatment. Further consideration should also be given to the most

	Treatment as usual (n=245)	Cognitive behavioural therapy plus treatment as usual (n=242)	OR (95% CI)	P value
Serious adverse events				
Participants who had a trial-related SAE	1 (<1%)	2 (1%)	..	..
Life threatening or results in self-harm	1	..	..	..
Involuntary hospitalisation	..	1	..	..
Self-harm requiring treatment at accident and emergency	..	1	..	..
Adverse events or effects				
Participants who had at least one adverse event or effect	104 (42%)	107 (44%)	1·09 (0·81–1·46)	0·58
Total adverse events or effects*	120	143	..	..
Death	4	6	..	..
Voluntary hospitalisation	24	33	..	..
Involuntary hospitalisation	14	10	..	..
Prolongation of hospitalisation	2	4	..	..
Risk to others	0	2	..	..
Self-harm	6	27	..	..
Suicide attempt	3	2	..	..
Suicidal crisis (CDSS item 8, rating 2)				
9 months	14/224 (6%)	12/215 (6%)	0·90 (0·40–1·10)	0·79
21 months	7/214 (3%)	9/209 (4%)	1·35 (0·49–3·73)	0·56
Severe symptomatic exacerbation: CGI severity of 6 or more				
9 months	25/213 (12%)	18/207 (9%)	0·69 (0·36–1·33)	0·27
21 months	17/212 (8%)	19/208 (9%)	1·16 (0·57–2·33)	0·69
Severe symptomatic exacerbation: CGI improvement of 6 or more†				
9 months‡	5/147 (3%)	0/131	NA	0·062
21 months	6/157 (4%)	3/141 (2%)	0·45 (0·10–2·02)	0·30
More than 25% deterioration in PANSS total				
9 months	28/224 (13%)	22/218 (10%)	0·75 (0·41–1·38)	0·35
21 months	21/216 (10%)	15/209 (7%)	0·68 (0·33–1·37)	0·28
More than 50% deterioration in PANSS total				
9 months	7/224 (3%)	6/218 (3%)	0·77 (0·25–2·43)	0·66
21 months	8/216 (4%)	8/209 (4%)	0·90 (0·32–2·55)	0·84
More than 75% deterioration in PANSS total				
9 months	1/224 (>1%)	2/218 (1%)	1·78 (0·15–20·95)	0·65
21 months	3/216 (1%)	1/209 (1%)	0·26 (0·03–2·73)	0·26

Data are n, n (%), or n/N (%), unless otherwise stated. SAE=serious adverse event. CDSS=Calgary Depression Rating Scale for Schizophrenia. CGI=Clinical Global Impression Scale. NA=not applicable. PANSS=Positive and Negative Syndrome Scale. *Two participants had two involuntary hospitalisations, one participant had 22 self-harm events, one participant had two self-harm events, and nine participants had two voluntary hospitalisations. †High scores indicate deterioration. ‡χ^2 test.

Table 5: **Adverse events and effects**

appropriate and valued outcomes for this population. For individuals who do not respond to clozapine or CBT, attempting to increase wellbeing, subjective recovery, and social functioning might be more successful than attempting to reduce symptoms, and might be more important to service users and their families.

In conclusion, there was no lasting effect of CBT for clozapine-resistant schizophrenia on our primary outcome of psychiatric symptoms at 21 months. However, CBT was highly acceptable, produced small but significant improvements in psychiatric symptoms at the end of treatment (9 months) and a lasting improvement on self-rated recovery (21 months), with little evidence of adverse effects. Entrenched symptoms might need a longer period of continuing psychological intervention, similar to the use of medication.

Contributors

APM wrote the first draft of the manuscript, planned the study, made substantial contribution to the design of the statistical analysis plan, and led the trial as Chief Investigator. APM, AG, MS, DT, JN, PF, RB, SS, TREB, LD, and DK contributed to the application for funding. AG, MS, DT, JN, PF, RB, SS, TREB, LD, DK, GM, JH, SEB, HJM, and HG substantially contributed to the design of the trial. APM, AG, MS, DT, JN, PF, RB, SS, RD, TREB, LD, and DK substantially contributed to the design of the protocol. MP, GM, JH, SEB, HJM, and HG substantially contributed to the development of the protocol. JN and PF substantially contributed to the design of the statistical analysis plan. GM and JH substantially contributed to the development of the statistical analysis plan. LD substantially contributed to the design of the health economic analysis plan. MP managed the trial and data. GM and JH conducted the analysis. AG, MS, DT, GM, JN, JH, SEB, PF, RB, SS, RD, HJM, HG, LD, and DK critically read the manuscript. All authors read and approved the final manuscript.

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Declaration of interests

APM reports delivering training workshops and has written textbooks about CBT for psychosis, for which he has received fees, and reports delivering CBT in the National Health Service (NHS). AG, MS, and HJM provide training to NHS Scotland staff in CBT for psychosis, outside the submitted work. DT reports personal fees and non-financial support from Insight-CBT partnership, Institutt Aktiv Psycoterapi (Norway), non-financial support from Anding Hospital, Beijing, China, outside the submitted work. GM reports grants from the UK National Institute for Health Research Health Technology Assessment, during the conduct of the study. JN is the Deputy Chair of the National Institute for Health Research Health Technology Assessment General Board and is an Editor on the National Institute for Health Research Journals Library. SEB reports personal fees from private practice delivering CBT, and personal fees from the CBT Training Centre, outside the submitted work. RD reports payment for providing workshops on the topic of CBT and receives royalties for books and book chapters on the topic of CBT. HG reports teaching, training, and supervision in CBT and CBT for psychosis as a regular employment activity. TREB reports personal fees from Janssen, Sunovion, Otsuka and Lundbeck, and Newron Pharmaceuticals, outside the submitted work. LD reports grants from National Institute for Health Research Health Technology Assessment, during the conduct of the study. All other authors declare no competing interests.

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