Cognitive–behavioural therapy for clozapine-resistant schizophrenia: the FOCUS RCT

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Scientific summary

The FOCUS RCT

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Scientific summary

Background

For around one-third of the people who meet the criteria for a schizophrenia diagnosis, treatment with antipsychotic medication will result in little change in symptoms and, commonly, the symptoms become progressively more unresponsive to medication, with subsequent relapses. For people who experience a poor response to treatment with standard antipsychotic medication, the antipsychotic clozapine is currently considered the mainstay of treatment for those who meet the criteria for treatment-resistant schizophrenia (TRS). However, a significant proportion of people will experience persistent symptoms after an adequate trial of clozapine. For this group of people, who meet the criteria for clozapine-resistant schizophrenia (CRS), the evidence base for treatments is limited; augmentation strategies with a second antipsychotic are a common clinical practice, but meta-analyses demonstrate small effects for this treatment strategy. There is a clear indication from cognitive–behavioural therapy (CBT) trials that people who meet the criteria for both TRS and CRS can be engaged in CBT. There is emerging evidence to suggest that, for this population, CBT can have small to moderate effects on overall symptoms and may be particularly beneficial for auditory hallucinations. However, the field has lacked a large high-quality trial of CBT for people with CRS.

Objectives

The objectives of the Focusing on Clozapine Unresponsive Symptoms (FOCUS) trial were to provide evidence of the clinical effectiveness and cost-effectiveness of CBT for people who meet the criteria for CRS and to utilise baseline data from this randomised controlled trial (RCT) to develop a risk model that identifies factors that predict a good outcome from CBT. Our objectives were to test the following hypotheses:

- In people with a diagnosis of a schizophrenia spectrum disorder, who have an inadequate response to or are unable to tolerate clozapine, CBT plus treatment as usual (TAU) will lead to an improvement in psychotic symptoms, measured using a psychiatric interview [Positive and Negative Syndrome Scale (PANSS)] over a 21-month follow-up period, compared with TAU alone.
- Cognitive–behavioural therapy plus TAU will lead to an improved quality of life and user-defined recovery compared with TAU alone.
- Cognitive–behavioural therapy plus TAU will lead to a reduction in affective symptoms and negative symptoms compared with TAU alone.
- Cognitive–behavioural therapy plus TAU will be cost-effective compared with TAU alone.

Methods

The FOCUS trial was a parallel-group, randomised, outcome-blinded evaluation (PROBE) trial, conducted to evaluate the addition of a standardised CBT intervention to TAU for individuals who are unable to tolerate or have had an inadequate response to clozapine. The comparison group received TAU only. CBT was delivered over a 9-month treatment window and participants received up to 30 hours of CBT.

The FOCUS trial was conducted over a 4-year period across five sites in the UK. Recruitment for the trial commenced on 1 January 2013 and ended on 1 June 2015. The follow-up phase of the trial ended in February 2017. Participants were recruited from a number of NHS mental health services, including community mental health teams (CMHTs), early intervention teams, recovery teams and inpatient services. People were eligible to take part in the FOCUS trial if they were considered to have had an inadequate

response to a trial of clozapine treatment. This was defined as treatment with clozapine at a stable dose of ≥ 400 mg (unless limited by tolerability) for ≥ 12 weeks, or, if currently augmented with a second antipsychotic, for ≥ 12 weeks, without remission of psychotic symptoms. Alternatively, potential participants could have discontinued clozapine in the preceding 2 years because of side effects, lack of efficacy or a problem identified during routine blood monitoring appointments. Potential participants were also required to meet the following inclusion criteria: have an *International Classification of Diseases*, Tenth Revision (ICD-10), diagnosis on the schizophrenia spectrum or meet the criteria for an Early Intervention in Psychosis (EIP) service; have a minimum total PANSS score of 58 points at baseline assessment; score ≥ 4 points on items for delusions or hallucinations or ≥ 5 points for items on suspiciousness or grandiosity on the PANSS; be aged ≥ 16 years; have an identified care co-ordinator or consultant psychiatrist; and be competent and willing to provide written informed consent to take part. Participants were excluded based on the following criteria: a primary diagnosis of substance or alcohol dependence when this could be the cause of the psychotic experiences; diagnosis of developmental disability; organic impairment; non-English speaking (in cases in which this would prevent engagement in assessment and CBT); and currently receiving or had received structured CBT for psychosis from a qualified psychological therapist within the previous 12 months.

The primary outcome was the total PANSS score at 21 months (i.e. at the 12-month follow-up). Secondary outcomes were the total PANSS score at 9 months (end of treatment), PANSS subscales, self-rated recovery, social and occupational functioning, Clinical Global Impression (CGI), depression, anxiety, adverse effects and substance use. Other measures, including measures of psychological processes, included appraisals of voices and paranoia, beliefs about self and others, working memory, attachment, childhood trauma and stigma. Health benefit data were collected using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), and data on the resources used for each participant were collected using the Economic Patient Questionnaire (EPQ). All measures were collected at baseline, 9 months and 21 months, except for the EPQ score, which was also collected at 3, 6, 13 and 17 months.

The primary outcome, total PANSS score at 21 months, was analysed using an intention-to-treat (ITT) linear model with adjustment for prespecified baseline covariates of sex, age and baseline PANSS score. The treatment effects over time were explored using repeated-measures mixed-effects models. The secondary outcomes were analysed in a similar way using an ITT linear model adjusted for prespecified baseline covariates.

Results

A total of 487 participants were recruited to the trial; of these, 242 were allocated to CBT and 245 to TAU. The median number of CBT sessions attended was 23, and 88% of participants attended at least six sessions of CBT, which was the minimum number of sessions needed to be classified as having received CBT.

At 9 months, the total PANSS score was 2.4 points lower in the CBT group (95% CI –4.79 to –0.02 points; $p = 0.049$) than in the TAU group. At 21 months, the total PANSS score was 0.89 points lower in the CBT arm, but this difference was not statistically significant (95% CI –3.32 to 1.55 points; $p = 0.475$).

Analysis of secondary outcomes at 9 months showed that the following outcomes were significantly lower in the CBT arm than in the TAU arm: PANSS positive 1.56 points lower (95% CI –4.79 to –0.02 points; $p = 0.049$), PANSS emotional distress 1.08 points lower (95% CI –2.02 to –0.13 points; $p = 0.025$) and Psychotic Symptom Rating Scale (PSYRATS) auditory hallucinations 2.56 points lower (95% CI –4.87 to –0.26 points; $p = 0.029$). At 21 months, PSYRATS delusions emotional distress was 0.53 points lower in the CBT arm (95% CI –1.05 to –0.00 points; $p = 0.049$), CGI was 0.33 points lower in the CBT arm (95% CI –0.54 to –0.11 points; $p = 0.013$) and self-rated recovery was 2.03 points higher in the CBT arm (95% CI 0.04 to 4.01 points; $p = 0.045$). Risk modelling did not reveal any subgroups of people who had a good response to CBT. There was no evidence that the treatment effect was moderated by any of the prespecified

subgroups. The number of reportable serious adverse events was two in the CBT arm and one in the TAU arm. There were 107 people with one or more adverse events in the CBT arm and 104 in the TAU arm ($p = 0.58$). However, there were no significant differences between the CBT and TAU arms on other prespecified outcomes for potential unwanted side effects of trial participation including suicidal crisis, severe symptomatic exacerbation or PANSS deterioration. CBT was associated with a net cost of £5378 (95% CI –£13,010 to £23,766) and net quality-adjusted life-year (QALY) gain of 0.052 (95% CI 0.003 to 0.103 QALYs) compared with TAU. The probability that CBT was cost-effective was 0.13.

Conclusions

The FOCUS trial is the first study to provide high-quality evidence with a low risk of bias regarding the clinical effectiveness and cost-effectiveness of CBT for people who meet the criteria for CRS. CBT for CRS was not superior to TAU on the primary outcome of total PANSS score at 21 months, but was superior on total PANSS score at 9 months (end of treatment). CBT was not found to be cost-effective compared with TAU, despite producing a net gain in overall health measured by QALYs. However, self-rated recovery did differ between the groups at 21 months (i.e. at the12-month follow-up).

Trial registration

This trial is registered as ISRCTN99672552.

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This report

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