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Focusing on clozapine unresponsive symptoms trial

Submission date
28/11/2012

Recruitment status
No longer recruiting

Registration date
29/11/2012

Overall study status
Completed

Last Edited
27/02/2019

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Psychosis is a mental health problem usually starting in late adolescence or early adulthood, which can often last many years affecting behaviour, thinking and perception, as well as a person's ability to socialise, work and carry out the tasks of daily life. Common symptoms of schizophrenia are unusual beliefs ('delusions') and hallucinations (most often, hearing voices). The standard medication ('antipsychotics') for these problems is often helpful. There is also evidence that having a talking therapy ('cognitive behaviour therapy' or 'CBT') as well as medication can help reduce such symptoms further. However, for up to one in three people with schizophrenia, their difficulties do not show much improvement with antipsychotic medication. For people whose psychotic experiences are unresponsive, one particular antipsychotic called clozapine can be beneficial, although the possibility of severe side effects from taking it means that regular blood testing is necessary. If a person's response to clozapine treatment is disappointing, there is some evidence that also having the talking therapy CBT can sometimes produce more improvement. However, the evidence for this CBT-related improvement is limited, coming mainly from research studies that have involved small numbers of participants or have included other types of treatment-resistant patients on different medications. Therefore, with our research trial, we plan to test the possible benefits of CBT added to clozapine for 9 months with people whose difficulties have not been helped much by any antipsychotic medication on its own, and who are now taking clozapine, but again without much improvement. We expect that adding CBT will be more likely to bring improvements in symptoms, user-defined recovery, quality of life and emotional well-being. We hope to gain a greater understanding of the possible benefits of adding CBT to clozapine treatment in relation to particular symptoms, and a person's recovery and ability to live and work in the community, as well as identifying who is most likely to respond to the addition of CBT.

Who can participate?
People aged 16 plus who have a schizophrenia diagnosis and who continue to experience psychotic symptoms despite an adequate trial of clozapine.

What does the study involve?
Participants will be randomly allocated into one of two groups. One group will receive treatment as usual, while the other group will be provided with up to 30 hours of CBT in addition to

treatment as usual. All participants will meet with a research assistant on three occasions, once for a baseline assessment to determine whether they are eligible to take part and twice for a follow-up appointment at 9 months and 21 months, and all assessments will be carried out at a location that is convenient for the participant.

What are the possible benefits and risks of participating?
It is hoped that both the treatment and follow-up appointments will be helpful to participants. It is possible that they will improve any mental health difficulties that a participant is experiencing. However, it is also possible that talking about some of these issues may be upsetting.

Where is the study run from?
We will conduct this research across five areas in the UK (Manchester, Edinburgh, Glasgow, Newcastle and Southampton).

When is the study starting and how long is it expected to run for?
The study commenced in December 2012 and the recruitment phase begins in January 2013. The study is funded until July 2017.

Who is funding the study?
The study is funded through the National Institute for Health Research (NIHR) Health Technology Assessment (HTA). The trial is sponsored by Greater Manchester West Mental Health NHS Foundation Trust.

Who is the main contact?
Prof. Anthony P Morrison
0161 772 4642
Melissa Pyle (Trial Manager)
0161 772 4642

Contact information

Type(s)
Scientific

Contact name
Dr Melissa Pyle

Contact details
Psychology Department
Prestwich Hospital
Bury New Road Prestwich
Manchester
United Kingdom
M25 3BL
-
melissa.pyle@gmw.nhs.uk

Additional identifiers

Protocol serial number

HTA 10/101/02, 13294

Study information

Scientific Title
Focusing on Clozapine Unresponsive Symptoms (FOCUS) trial: a randomised controlled trial

Acronym
FOCUS

Study objectives
Our study is a parallel group randomised outcome blinded evaluation (PROBE) to compare the addition of a standardised Cognitive behavioral therapy (CBT) intervention to treatment for individuals who are unable to tolerate or have an inadequate response to clozapine.Our trial will be a definitive, pragmatic clinical and cost effectiveness trial lasting 4 years. The comparator group will receive treatment as usual. Randomisation (at the individual level) will be independent and concealed, using randomised-permuted blocks of random size and will be stratified by site. Assessors will be masked to allocated treatment.

We will test the hypotheses that:
1. In people with a diagnosis of a schizophrenia spectrum disorder who have an inadequate response to or are unable to tolerate clozapine, Cognitive Behavioural Therapy (CBT) plus Treatment As Usual (TAU) will lead to improvement in psychotic symptoms, measured using a psychiatric interview (PANSS), over a 21-month follow-up period compared with TAU alone.
2. CBT plus TAU will lead to improved quality of life and user-defined recovery compared to TAU alone
3. CBT plus TAU will lead to a reduction in affective symptoms and negative symptoms compared to TAU alone
4. CBT plus TAU will be cost effective compared to TAU alone
5. It will be possible to develop a risk model that identifies baseline factors that predict good outcome to CBT

The target recruitment is 485 participants (97 per site). Participants will be people aged 16-65 years with a schizophrenic illness that has been unresponsive, at a criterion level of persistent symptom severity, to an adequate trial of clozapine in terms of dosage, duration and adherence.

More details can be found at: http://www.nets.nihr.ac.uk/projects/hta/1010102
Protocol can be found at: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0008/81719/PRO-10-101-02.pdf
Statistical analysis plan can be found at: http://w3.abdn.ac.uk/hsru/CHaRT/public/content/ShowPage.aspx?page=statistical-analysis-plans

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. NRES Committee North West - Lancaster, 13/08/2012, 12/NW/0520
2. Substantial amendment four approved by the Research Ethics Committee (REC) on 02/09/2013
3. Substantial amendment six approved by the Research Ethics Committee (REC) on 29/05/2015

Study design

Randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Mental Health / Psychosis

Interventions
1. Cognitive Behavioural Therapy, CBT will be delivered by a qualified psychological therapist on an individual basis over 9-months and will include up to 30 treatment sessions on an approximately weekly basis.
2. Treatment as Usual (TAU)
Follow Up Length: 12 months

Intervention Type
Behavioural

Primary outcome(s)
Positive and Negative Syndrome Scale (PANSS) total score at Baseline, 9 months (end of treatment) and 21 months (12 month follow up)

Key secondary outcome(s))
1. Alcohol Use Disorder Test (AUDIT) at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
2. Anxious Thoughts Inventory - Meta worry subscale at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
3. Calgary Depression Rating Scale for Schizophrenia at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
4. Common Responses Questionnaire at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
5. Drug Abuse Screening Test (DAST) at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
6. Economic Patient Questionnaire at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
7. PANSS scores at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
8. Personal and Social Performance Scale at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
9. Psychotic Symptoms Rating Scale (PSYRATS) at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
10. The Beliefs about Paranoia Scale at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
11. The Brief Core Schema Scale at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
12. The Childhood Trauma Scale at 9 months (end of treatment)
13. The Internalised Stigma of Mental Illness Scale at baseline, 9 months (end of treatment) and 21 months (12 month follow up)
14. The Interpretation of Voices Inventory at baseline, 9 months (end of treatment) and 21

months (12 month follow up)
15. The Psychosis Attachment Measure at baseline; 9 months (end of treatment) and 21 months (12 month follow up)

Added 06/03/2014:
16. The Economic Patient Questionnaire (EPQ), completed at baseline, 3 months, 6 months, 9 months, 13 months, 17 months and 21 months.
17. The Euroqol EQ-5D, completed at baseline, 9 months and 21 months.

Added 17/08/2015 (approved by the REC on 02/09/2013):
18. The Clinical Global Impression Scale (the CGI-S severity and the CGI-S Improvement scales) at baseline, 9 months (end of treatment) and 21 months (12 months follow-up)
19. Participant version of the Clinical Global Impression Scale (CGI-P) at baseline, 9 months (end of treatment) and 21 months (12 months follow-up)
20. Working memory-letter-number (LN) span at baseline and 9 months (end of treatment)
21. Self-report measure of adverse effects from involvement in the trial. Administered at 21 months for those who complete the trial and offered on withdrawal to those who withdraw from the trial

Removed 17/08/2015 (approved by the REC on 29/05/2015):
Heinrichs Quality of Life Scale at baseline, 9 months (end of treatment) and 21 months (12 months follow up). When the battery of assessments was initially collated, the Heinrich's was taken from the appendix of the original publication, which only contained four instead of 21 items. This mistake was not identified and, therefore, only four items have been administered to FOCUS participants. Additionally, when the measure was copied from the appendix it was done as exactly as it appeared in the paper, which resulted in one of the items (Social Initiatives) having a 0-4 scale instead of 0-6. For the purpose of transparency of trial conduct and avoidance of unnecessary participant burden, we have stopped administering this incomplete measure altogether.

Completion date
31/07/2017

Eligibility

Key inclusion criteria
Current inclusion criteria from 04/12/2012 (trial record updated 07/03/2014):
1. A criterion level of persistent symptom severity despite an adequate trial of clozapine in terms of dosage, duration and adherence (as used by Honer et al 2006):
1.1. Treatment of clozapine at a stable dose of 400mg or more (unless limited by tolerability) for at least 12 weeks, or if currently augmented with a second antipsychotic that this has been given for at least 12 weeks, without remission of psychotic symptoms, or have discontinued clozapine due to adverse reactions (including agranulocytosis) or lack of efficacy in the past 24 months
1.2. Presence of at least one psychotic symptom with severity ≥4 (for hallucinations/delusions) or ≥5 (for suspiciousness/grandiosity) on the PANSS in addition to a PANSS total score of at least 58, which is equivalent to a clinical global impression (CGI) of being at least mildly ill 51
2. Be in contact with mental health services and have a care coordinator
3. Either meet ICD-10 criteria for schizophrenia, schizoaffective disorder or delusional disorder or meet entry criteria for an Early Intervention for Psychosis service (operationally defined using

PANSS) in order to allow for diagnostic uncertainty in early phases of psychosis
4. Aged at least 16 years old
5. Competent and willing to provide written, informed consent.

Original inclusion criteria:
1. A criterion level of persistent symptom severity despite an adequate trial of clozapine monotherapy in terms of dosage, duration and adherence (as used by Honer et al. 2006): Treatment for at least 24 weeks at a stable dose of 400 mg or more of clozapine a day, unless the size of the dose was limited by side effects, without remission of psychotic symptoms, or have discontinued clozapine due to adverse reactions (including agranulocytosis) or lack of efficacy in the past 24 months.
2. Presence of at least one psychotic symptom with severity 4 (for hallucinations/delusions) or 5 (for suspiciousness/grandiosity) on the Positive and Negative Syndrome Scale (PANSS) in addition to a PANSS total score of at least 58, which is equivalent to a Clinical Global Impression (CGI) of being at least mildly ill.
3. Be in contact with mental health services and have a care coordinator
4. Either meet ICD-10 criteria for schizophrenia, schizoaffective disorder or delusional disorder or meet entry criteria for an Early Intervention for Psychosis service (operationally defined using PANSS) in order to allow for diagnostic uncertainty in early phases of psychosis
5. Male & female aged at least 16 years old
6. Competent and willing to provide written, informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Primary diagnosis of alcohol/substance dependence, where this is clearly the cause of their psychotic symptoms
2. Developmental disability
3. Non-English speaking
4. Current receipt (or within the last 12 months) of structured CBT from a qualified psychological therapist in accordance with NICE guideline recommendations (as opposed to more generic psychosocial interventions)

Date of first enrolment
01/01/2013

Date of final enrolment
31/05/2015

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Prestwich Hospital
Manchester
United Kingdom
M25 3BL

Sponsor information

Organisation
Greater Manchester West Mental Health NHS Foundation Trust (UK)

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme, Grant Codes: 10/101/02

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2019		Yes	No
Protocol article	protocol	05/08/2016		Yes	No