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The benefit of minocycline on negative symptoms in schizophrenia

Submission date
22/08/2016

Recruitment status
No longer recruiting

Registration date
12/12/2016

Overall study status
Completed

Last Edited
20/01/2023

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Schizophrenia is a long-term mental health condition that causes a range of symptoms including hallucinations (seeing or hearing things that aren't there), delusions (beliefs that are not based on reality) and changes in behaviour. One of the most disabling factors affecting the quality of life of people with schizophrenia is the development of a set of so-called negative symptoms comprising social withdrawal, self-neglect, loss of motivation and mild impairment of intelligence. Standard drug treatments are effective in reducing psychotic symptoms such as paranoid delusions and hearing voices, but they have little impact on negative symptoms. Two major studies have shown that a standard antibiotic and anti-inflammatory drug called minocycline commonly used in acne and other infections, reduces negative symptoms in schizophrenia. It was also found to lessen the weight gain that standard treatments usually cause. Other studies suggest that minocycline may also improve positive symptoms (such as hallucinations and delusions) in acute (sudden) episodes of illness. The aim of this study is to investigate whether minocycline is especially effective given early in the course of illness and to understand how it works.

Who can participate?
Schizophrenic adults aged between 16 and 35 who are having an acute episode.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group are given 300mg of minocycline to take every day for 12 months. Those in the second group are given an identical looking placebo (dummy pill) to take every day for 12 months. During the study, all participants continue to receive their usual treatment. At the start of the study and then again after 2, 6, 9 12 and 15 months, participants complete a number of questionnaires to assess their symptoms. In addition at the start of the study and after 12 months, participants have a brain scan in order to find out if treatment with the study drug has caused any changes to their brain. Blood samples are also taken at the start of the study and then again after 6, 12 and 15 months to measure levels of chemicals called cytokines in the blood, which should show whether minocycline is working by blocking inflammation in the brain.

What are the possible benefits and risks of participating?
Minocycline is antibiotic that has been widely used for 50 years, for example in treating acne. The direct benefits of participating are additional clinical contacts and assessments plus any therapeutic effects of minocycline. The main side effect is that small patches of skin pigmentation may occur after several months of use, although this usually clears up if spotted early. Rare cases of liver damage have been reported at less than 1/10,000 cases. There is a small risk of pain or bruising during blood tests.

Where is the study run from?
Manchester Mental Health Social Care NHS Trust (lead site) and other mental health services in England and Scotland (UK)

When is the study starting and how long is it expected to run for?
July 2011 to June 2016

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Professor Bill Deakin
bill.deakin@manchester.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Bill Deakin

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Additional identifiers

EudraCT/CTIS number
2010-022463-35

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
10411

Study information

Scientific Title
The benefit of minocycline on negative symptoms in schizophrenia: Extent and mechanisms

Study objectives
Primary efficacy predictions:
1. Minocycline minimises later negative symptoms when administered during the acute phase of early psychosis
2. Minocycline reduces or prevents the negative symptoms of schizophrenia by:
2.1. Reducing the loss of grey matter associated with early psychosis
2.2. Interfering with inflammatory cytokine production
2.3. An action on glutamate systems to improve negative symptoms and cognitive function

Mechanistic hypotheses:
1. Minocycline works by lessening a degenerative process, which is most active in the acute phase of psychosis and is responsible for the development of negative symptoms. The hypothesis predicts that the loss of grey matter, known to occur during the early years following onset of psychosis, will be lessened by minocycline treatment and that this will correlate with and explain improved negative symptoms.
2. Minocycline works by lessening an inflammatory process in the brain which gives rise to negative symptoms, possibly but not necessarily mediated by subtle neurodegeneration (see H1 above). The hypothesis predicts that circulating pro-inflammatory cytokines will be lessened by minocycline treatment.
3. Minocycline works by reversing defective NMDA glutamate receptor function to improve negative symptoms and frontal executive cognition. The hypothesis predicts that minocycline will improve functional brain imaging and performance measures of cognitive function. It also predicts that benefits on negative symptoms wane when the drug is stopped. However, it is possible glutamate actions could also be neuroprotective (see H1 above) whether or not it enhances glutamate function in the short-term.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Greater Manchester Central Research Ethics Committee, 06/07/2011, ref: 11/NW0218

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Specialty: Mental Health, Primary sub-specialty: Psychosis

Interventions
Participants are randomised to one of two groups according to a randomised permuted blocks algorithm, after stratification by centre, as specified by the trial statistician.

Intervention group: Participants take 300mg daily minocycline for 12 months
Control group: Participants take a matched placebo daily for 12 months

Both groups continue treatment as usual from their clinical teams throughout the study period.

Follow up for all participants involves assessments at 2, 6, 9 and 12 months after randomization. All primary and secondary outcome assessments are carried out at randomization and 12 months. At 6 and 9 months all non-imaging outcome assessments are carried out and again at 15 months (3 months after stopping trial medication). The final assessments are at 15 months.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Minocycline

Primary outcome measure
Negative symptom severity is measured using the negative syndrome subscale score on the Positive and Negative Syndrome Scale (PANSS) at 2, 6, 9, 12 and 15 months

Primary mechanistic biomarker outcomes:
1. Medial prefrontal grey matter volume is measured using voxel-based morphometry at baseline and 12 months
2. Circulating IL6 cytokine concentrations are measured using Luminex arrays at baseline, 6, 12 and 15 months
3. Working memory performance and brain activation are measured using the n-back task during functional magnetic resonance imaging at baseline and 12 months

Secondary outcome measures
1. Body weight is measured using digital weighing scales at baseline and 12 months
2. Body mass index (BMI) is calculated using weight and height measurements taken at baseline

and 12 months
3. General functional outcome is measured using the Global Assessment of Function (GAF) from DSMIV at baseline, 2, 6, 9, 12 and 15 months
4. Social and occupational functioning is measured using the Social Functioning Scale (SFS) self-rating in 7 domains at baseline, 6, 12 and 15 months
5. IQ is measured using the Blyler WAISIII short form at baseline, 12 and 15 months
6. Processing speed is measured using the Digit-symbol test at baseline, 12 and 15 months
7. Verbal fluency is measured using the FAS task at baseline, 12 and 15 months
8. Verbal learning is assessed using the Auditory Verbal Learning Task at baseline, 12 and 15 months

Secondary mechanistic biomarker outcomes:
1. Total and other regional grey matter volumes are measured using voxel-based morphometry at baseline and 12 months
2. Cytokine levels are measured using Luminex arrays at baseline, 6, 12 and 15 months
3. Resting connectivity and distribution of the Hurst exponent is assessed using functional magnetic resonance imaging at baseline and 12 months

Overall study start date
01/07/2011

Completion date
09/06/2016

Eligibility

Key inclusion criteria
1. Male or female aged 16-35 years
2. Current DSM-IV diagnosis of schizophrenia, schizophreniform or schizoaffective psychosis, psychosis NOS as assessed with the clinical team
3. In an episode as defined by
3.1. An onset or exacerbation of symptoms
3.2. With continuing positive symptoms scoring at least mild (>2) on items P1, P2 or P6 of the PANSS within the last month
4. In contact with early intervention, community or inpatient services
5. Within 3 years of onset of symptoms
6. Current IQ greater than 70
7. Female patients must use effective birth control with a negative pregnancy test
8. Able to understand and willing to give written informed consent
9. Fluent in English

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants

Planned Sample Size: 170; UK Sample Size: 170

Key exclusion criteria
1. Current substance misuse diagnosis that in the opinion of the investigator may interfere with the study (urine toxicology screens will be used to monitor drug use)
2. Patients who, in the Investigator's judgment pose a current serious suicidal or violence risk
3. Prior tetracycline use within 2 months of baseline visit or history of sensitivity or intolerance
4. History of systemic lupus erythematosis (SLE) or a history of SLE in a first-degree relative
5. Use of any investigational drug within 30 days of baseline visit
6. Relevant current or past haematologic, hepatic, renal, neurological or other medical disorder that in the opinion of the investigator may interfere with the study
7. Clinically significant deviation from the reference range in clinical laboratory test results as judged by the Investigator
8. Previous randomisation in the present study
9. Pregnant or nursing

Date of first enrolment
10/12/2012

Date of final enrolment
01/05/2015

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Manchester Mental Health Social Care NHS Trust
NHS R&D Office
Rawnsley Bldg
Manchester Royal Infirmary
Hathersage Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Greater Manchester West MH NHS Foundation Trust
NHS R&D Office
Harrop House
Bury New Road
Manchester

United Kingdom
M25 3BL

Study participating centre
Camden And Islington NHS Foundation Trust
R&D Office
St Pancras Hospital
4 St Pancras Way
London
United Kingdom
NW1 0PE

Study participating centre
North West London Mental Health
London West Mental Health R&D Consortium
Uxbridge Road
London
United Kingdom
UB1 3EU

Study participating centre
West London Mental Health NHS Trust
Research and Development Directorate
Uxbridge Road
London
United Kingdom
UB1 3EU

Study participating centre
South London And Maudsley NHS Foundation Trust
NHSSLaM/IoP R&D Office
De Crespigny Park
London
United Kingdom
SE5 8AF

Study participating centre
Cambridgeshire and Peterborough NHS Foundation Trust
Research and Development Office
Fulbourn Hospital
Cambridge

United Kingdom
CB21 5EF

Study participating centre
Lancashire Care NHS Foundation Trust
NHS R&D Office
Sceptre Way
Walton Summit
Preston
United Kingdom
CB21 5EF

Study participating centre
Royal Edinburgh Hospital
NHS Lothian
NHSR&D office
Morningside Place
Edinburgh
United Kingdom
EH10 5HF

Study participating centre
Lynebank Hospital
NHS Fife
NHS R&D Dept
Halbeath Rd
Dunfirmline
United Kingdom
KY11 4UW

Study participating centre
NHS Forth Valley Royal
NHS R&D Dept
Stirling Road
Larbert
United Kingdom
FK5 4WR

Study participating centre
Borders General Hospital
NHS Borders

NHS R&D Office
Melrose
United Kingdom
TD6 9BS

Study participating centre
Salford NHS Foundation Trust
NHS R&D Office
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
Barnet, Enfield and Haringey Mental Health Trust
Community Mental Health Services
305309 Fore Street
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United Kingdom
N9 0PD

Study participating centre
University of Cambridge
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Study participating centre
University of Manchester
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Study participating centre
Kings College NHS
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Box P089
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United Kingdom
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Study participating centre
Birmingham And Solihull Mental Health NHS Foundation Trust
Unit 1
50 Summer Hill Road
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Study participating centre
University College London NHS Institute of Neurology
Queen Square
London
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WC1N 3BG

Study participating centre
Cheshire And Wirral Partnership NHS Foundation Trust
Trust Board Offices
Upton Lea Resource Centre
The Countess Of Chester Health Park
Chester
United Kingdom
CH2 1BQ

Sponsor information

Organisation
Manchester Mental Health And Social Care NHS Trust

Sponsor details
NHS Research & Development Office
Rawnsley Bldg

Manchester Royal Infirmary
Hathersage Road
Manchester
England
United Kingdom
M21 9UN

Sponsor type
Hospital/treatment centre

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Submission of main results for publication by December 2016

Intention to publish date
31/07/2017

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publically available repository not yet identified.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/11/2018		Yes	No
Results article	NIHR journal	01/08/2019	20/01/2023	Yes	No