

# The benefit of minocycline on negative symptoms in schizophrenia

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		<input type="checkbox"/> Protocol
<b>Registration date</b> 12/12/2016	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan
		<input checked="" type="checkbox"/> Results
<b>Last Edited</b> 20/01/2023	<b>Condition category</b> Mental and Behavioural Disorders	<input type="checkbox"/> 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

### ORCID ID

<http://orcid.org/0000-0002-2750-962X>

### Contact details

G907 Stopford Bldg  
University of Manchester  
Oxford Road  
Manchester  
United Kingdom  
M13 9PT

## 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 erythematosus (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  
Edmonton  
London  
United Kingdom  
N9 0PD

**Study participating centre**  
**University of Cambridge**  
NHS Department of Psychiatry  
Herchel Smith Building,  
Robinson Way  
Cambridge  
United Kingdom  
CB2 0SZ

**Study participating centre**  
**University of Manchester**  
Neuroscience and Psychiatry Unit,  
Dept of Psychiatry  
Stopford Building  
Oxford Road  
Manchester  
United Kingdom  
M13 9PL

**Study participating centre****Kings College NHS**

Institute of Psychiatry  
Box P089  
De Crespigny Park  
London  
United Kingdom  
SE5 8AF

**Study participating centre****Birmingham And Solihull Mental Health NHS Foundation Trust**

Unit 1  
50 Summer Hill Road  
Birmingham  
United Kingdom  
B1 3RB

**Study participating centre****University College London NHS Institute of Neurology**

Queen Square  
London  
United Kingdom  
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 publicly 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?
<a href="#">Results article</a>	results	01/11/2018		Yes	No
<a href="#">Results article</a>	NIHR journal	01/08/2019	20/01/2023	Yes	No