

<b>Project Title:</b>	The Benefit of Minocycline on Negative Symptoms in Schizophrenia: Extent and Mechanisms.
<b>Project Ref:</b>	09-100-23
<b>Cost:</b>	£ 1,657,581
<b>Lead Applicant &amp; Institution:</b>	Professor Bill Deakin University of Manchester
<b>Start Date:</b>	1 July 2011
<b>Plain English Summary:</b>	<p>One of the major disabilities 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 formal clinical trials suggest that a standard antibiotic and anti-inflammatory drug called minocycline commonly used in acne and other infections, reduces negative symptoms. In both studies patients with stable symptoms took either minocycline or exactly matching dummy tablets (placebo) in addition to their routine treatment for 6 or 12 months. Negative symptoms improved twice as much in those taking additional minocycline than in those taking the dummy tablets. It also lessened the weight gain that standard treatments usually cause. Other studies suggest that minocycline may also improve positive symptoms in acute episodes of illness. The aim of this proposal is to investigate whether minocycline is especially effective given early in the course of illness and to understand how it works.</p> <p>The proposal is to compare minocycline with placebo capsules added to each person's treatment within 3 years of starting it. We will follow the effects on positive and negative symptoms over 12 months. Minocycline might work by protecting brain cells from damage possibly caused by inflammation. Brain imaging will tell us whether subtle changes in the grey matter of the brain in schizophrenia are lessened by minocycline over 12 months and whether this accounts for reduced negative symptoms. Measuring chemicals (cytokines) in the blood will tell us whether minocycline is working by blocking inflammation in the brain. Another possibility is simply that minocycline helps negative symptoms by helping brain cells work better and this can also be studied using modern brain imaging methods and by determining whether improvements are lost when the drug is stopped.</p> <p>This multicentre UK-wide study will be carried out by a group of experienced researchers in early psychosis that have worked together over several years to set up and test a secure UK research network for</p>

	<p>people in their first episode of psychosis. It is called PsyGrid (<a href="http://www.psygrid.org">www.psygrid.org</a>) and was funded by the Medical Research Council and the Department of Health. Clinical assessments from 960 patients were gathered in two years in 8 centres of the Mental Health Research Network (MHRN) in England. We have also shown that we can reliably combine brain imaging results using different brain scanners in different centres (<a href="http://www.neuropsygrid.org">www.neuropsygrid.org</a>).</p>
<p><b>Abstract:</b></p>	<p><u>AIMS:</u> To use recently developed PsyGrid infrastructure for UK-wide clinical and imaging research in first episode psychosis to: i) determine whether negative symptoms can be lessened or prevented by minocycline treatment initiated early in the course of schizophrenia and ii) collect biomarker data to test hypotheses about how minocycline improves negative symptoms.</p> <p><u>PRIMARY EFFICACY PREDICTION AND MECHANISTIC HYPOTHESES:</u> 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: a) reducing the loss of grey matter associated with early psychosis. b) interfering with inflammatory cytokine production. c) an action on glutamate systems to improve negative symptoms and cognitive function.</p> <p><u>DESIGN:</u> Multicentre, one year, double-blind randomised placebo-controlled trial of minocycline versus placebo, added to standard antipsychotic drug (APD) treatment, for patients in an early episode of schizophrenia-related psychosis.</p> <p><u>INTERVENTION:</u> Minocycline or matching placebo 300mg daily for 12 months.</p> <p><u>OUTCOMES:</u> The primary clinical outcome is negative syndrome subscale score on the Positive and Negative Syndrome Scale (PANSS). The mechanistic biomarker variables are: 1) change in medial prefrontal grey matter volume over 12 months, 2) circulating cytokine concentrations and 3) working memory performance and brain activation. These measures will be related to changes in PANSS negative symptoms at 2, and 12 months and to quality of life assessments.</p> <p><u>POPULATION AND SAMPLE SIZE:</u> 170 patients with early psychosis recruited over 22 months from 6 established PsyGrid centres.</p> <p><u>STATISTICAL ANALYSIS:</u> Group differences in outcomes and putative mediators will be evaluated using random effects models for longitudinal data (allowing for treatment centre and other baseline covariates). Tests of the mechanistic hypotheses (i.e. mediation), and their sensitivity of the results to possible hidden confounding, will use instrumental variable methods from PI Dunn's MRC Methodology Research Programme projects; see Emsley R, Dunn G &amp; White I (2009) modelling mediation and moderation of treatment effects in randomised controlled trials of complex interventions. Statistical Methods in Medical Research published online on 16/07/09.</p> <p><u>EXPERTISE:</u> The investigators are experienced in the recruitment of early psychosis patients and the confidential collection of clinical</p>

	assessments and brain imaging through their involvement in PsyGrid and NeuroPsyGrid.
<b>ISRCTN: (if applicable)</b>	To follow
<b>Project Protocol:</b>	To follow
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