

Project Title:	Antiglucocorticoid augmentation of antiDepressants in Depression (The ADD study)
Project Ref:	08-43-39
Cost:	£999,002
Lead Applicant & Institution:	Professor I Nicol Ferrier Institute of Neuroscience Newcastle University
Start Date:	1 May 2010
Plain English Summary:	<p>Depression is one of the most common mental health problems, with at least one in six adults suffering from this at some time in their life. It can become long-lasting and frequently recurs. Depression has a large negative impact on quality of life of people who experience it and on their carers and it has also been shown to be one of the leading causes of working age adults receiving disability payments in the UK. The need for improved treatment has been recognised by the Department of Health and others with a recent welcome plan to provide more psychological therapy.</p> <p>However many patients are unable to settle in therapy or don't fully respond to it. Improvements in drug treatments are therefore also required. There has been recent increased understanding of some of the causes of the frequent lack of complete response seen with antidepressants. The stress hormone, cortisol, is often elevated or poorly controlled in depression and there is laboratory and clinical research to show that this hormonal change reduces the benefits from antidepressants with associated poor outcome and memory problems. Recently it has been shown in small studies that giving treatments that reduce cortisol or block its harmful effects for between 1 and 3 weeks overcome these negative consequences. Our group is particularly interested and experienced in this topic and several of us run clinics where we look after people with difficult to treat depression.</p> <p>We plan to study a drug that decreases cortisol levels in people who have not recovered with standard antidepressants so that we can find out the usefulness of this treatment (compared with placebo (dummy tablet)) in day to day life as well as checking closely for side-effects (the initial studies have shown that the particular drug we wish to study (metyrapone) has few side effects). We will also measure cortisol and see if its level can tell us which people do best with this treatment. We will carry out this study in 3 centres across the UK. We will carry out some additional tests of specific sorts of memory and decision making and also do this while scanning the brain (in a painless test).</p> <p>The results of these tests, along with tests of brain wave patterns, should</p>

	<p>help us understand more fully how this new treatment is working and who responds best to it. The study will help us find out if this drug should be used more widely for people not responding to standard treatments and will also lead on to the development of other new treatments with an anti-cortisol effect to help tackle the major problem of poor outcome from depression.</p>
Abstract:	<p><u>Design:</u> Randomised, double blind, placebo controlled trial.</p> <p><u>Setting:</u> NHS primary care and specialist mental health secondary care out-patients.</p> <p><u>Target population:</u> Men and women aged 18-70 who have a DSM-IV confirmed diagnosis of a major depressive episode that has not responded adequately to at least two different antidepressant treatments. Interventions being evaluated: The study is of augmentation of ongoing antidepressant treatment. Subjects will be randomised to receive either metyrapone 500mg, or placebo, twice a day for 3 weeks, in addition to their current antidepressant medication.</p> <p><u>Measurement of outcomes and duration of follow up:</u> The primary outcome is the degree of improvement in depressive symptoms, as rated using the Montgomery Åsberg Depression Rating Scale (MADRS), 5 weeks after randomisation (2 weeks after treatment with metyrapone or placebo has ended). Secondary outcomes include MADRS at 3 weeks (i.e. the time metyrapone/placebo is discontinued) and 9 weeks after randomisation to assess the persistence of the effects. Quality of life will be assessed at weeks 3, 5 and 9 using the EQ-5D scale. Hypothalamic-pituitary-adrenal (HPA) axis function will be assessed from saliva samples on waking and every 15 minutes for one hour at weeks 0, 3 and 5. In a sub sample of patients, neuropsychological assessments, fMRI and EEG measures sensitive to serotonin and corticosteroid changes will be made at weeks 0 and 5 to study other outcome markers and the mechanism of the effects of metyrapone.</p> <p><u>Sample size:</u> The study is powered on the primary outcome measure - the change in MADRS between start of treatment and week 5. The study requires 190 patients.</p> <p><u>Project timetable</u> The study will last 24 months.</p>
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