FINAL REPORT

JAMES TUDOR FOUNDATION

Project: **T**reating **U**nresponsive **D**epression **O**vercoming **R**efractoriness

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INTRODUCTION

Up to 35% of those suffering from major depression do not respond to the first two or more pharmacotherapeutic efforts(1). Such patients with treatment resistant depression (TRD) are often profoundly disabled and there is a distinct lack of novel therapeutic interventions to offer. They have been severely depressed for many months or years, are often unable to work and participate in family and society life, and sometimes a carer has given up work to look after them.

Understanding the pathophysiological processes seen in TRD has suggested systems which could be targeted in the development of novel therapies. Disturbed regulation and hyperactivity of the body's stress system, the Hypothalamic-Pituitary-Adrenal (HPA) axis, is a well established biological finding in major depression (2-4) and is thought to contribute to both treatment resistance and sleep disturbances in this patient group. This hyperactivity is due in part to reduced negative feedback to endogenous corticosteriods such as cortisol(5). Both Glucocorticoid and Mineralcorticoid Receptors (GR & MR) are less sensitive in severe and chronic TRD (6). Diurnal variation in corticosterone levels has been shown to be necessary for antidepressant action in rats. This may be mediated by hippocampal neurogenesis(7).Thus it is possible that reduced variability in cortisol levels in patients with TRD may account for the resistance to treatment seen in this patient group.

There is a strong association between major depression and sleep disturbance, with 90% of depressed patients experiencing problems with sleep(8). It is one of the few proven risk factors for suicide (9) and has huge impact on quality of life in depressed patients(10). As well as the distressing symptoms of sleep disturbance experienced by patients, changes in objective sleep architecture are well-documented in depression(11). The relationship between HPA disturbance and sleep dysregulation is well established for patients with major depression(12).

An intervention which reintroduces a level of variation into the system could permit the action of antidepressants on hippocampal neurogenesis thus resulting in an anti-depressant effect. This could explain the apparent paradox that adding further corticosteriod to an already hyperactive system results in an antidepressant effect as suggested by previous studies(13-16). Evidence also suggests that targeting the HPA axis in depression may address some of the sleep disturbances commonly suffered by these patients.

The investigators in University of Bristol have expertise in the study of the HPA axis, depression and the effects of antidepressants, and the study of the effects of these on sleep.

The TUDOR study (Treating Unresponsive Depression Overcoming Refractoriness) was designed to investigate the effects of short term, high dose (7mg/kg), hydrocortisone pulses in patients with treatment resistant depression. This randomized, placebo controlled study aimed to determine the effect on depression and sleep of adding a short course of hydrocortisone IV to existing antidepressants in patients with TRD.

Method

The study was approved by Bath Research Ethics Committee, UK (06/Q2001/215), sponsored by the University Hospitals Bristol NHS Foundation Trust (2006TUDOR_01) and registered as a clinical trial on the European Union Drug Regulating Authorities Clinical Trial database (EudraCT No. 2006-006089-40). The study was conducted according to Good Clinical Practice Guidelines and the Helsinki Declaration for ethical principles in human research.

- Patients with TRD were recruited from the Psychopharmacology Clinic at the Bristol Royal Infirmary.
- Inclusion and exclusion criteria are listed in Box 1.
- Patients attended for a screening visit, and if eligible and providing written informed consent, were randomized in a double blind manner to receive either Hydrocortisone (HCORT) IV at a dose of 7mg/kg to a maximum of 500mg or placebo (0.9% Sodium Chloride) on each of the three consecutive study days.
- They had a baseline polysomnographic sleep recording performed at home
- Patients attended the research clinic on three successive days arriving at midday, cannulated at 1pm and received the infusion at 3pm.
- Montgomery-Asberg Depression Scale (MADRS), Hamilton Depression 17 item rating scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A) were completed at baseline.
- During Study day 1 patients performed regular Profile of Mood States-Short Version (POMS-SV) questionnaires, underwent regular blood samples for ACTH and cortisol assays, provided baseline saliva samples for cortisol assays and had monitoring of heart rate and blood pressure.
- On days 2 and 3 patients only completed regular POMS-SV questionnaires in addition to the infusion of either HCORT or placebo.
- On Day 3 and day 29 sleep recordings were repeated
- On day 29, eligible patients who had not reached response (defined as a reduction in MADRS scores of >50%) were offered an open label trial of HCORT undergoing the same procedures over the next 29 days.
- Current drug treatment continued unchanged throughout the study.

Inclusion and exclusion criteria and outline of study

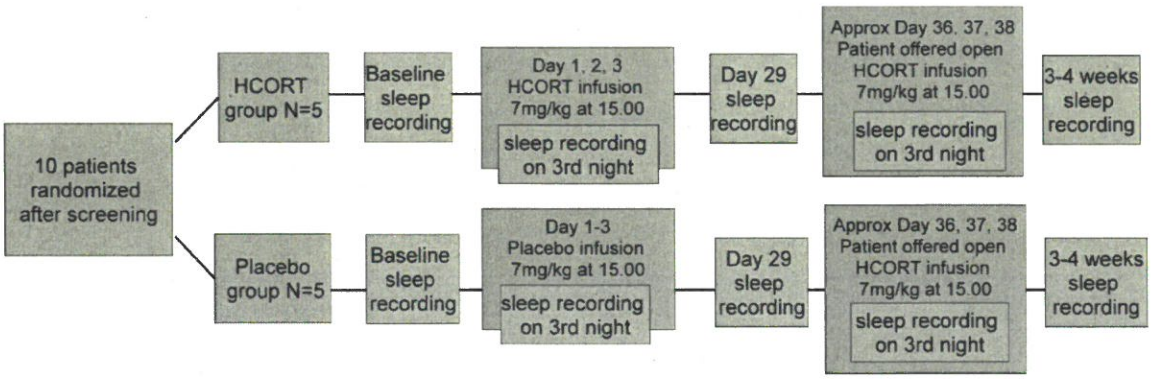
Box 1

Inclusion Criteria

- Current diagnosis of Major Depression according to DSM-IV criteria with a MADRS >20 and non-response to current antidepressant medication with a prior non-response to at least two different antidepressant medications
- Aged between 21 and 75 and able to provide informed written consent
- A satisfactory physical examination, ECG, and routine blood tests including liver, renal and thyroid function were also required.

Exclusion Criteria

- Any changes in antidepressant medication in the previous 6 weeks
- History of mania, psychosis or antisocial personality disorder determined by Mini International Neuropsychiatric Interview (MINI).
- History of drug or alcohol dependence
- History of diabetes, hypertension, BMI >40; head trauma or memory impairment; duodenal or gastric ulcers; glaucoma or cataracts.
- Pregnant or breastfeeding women



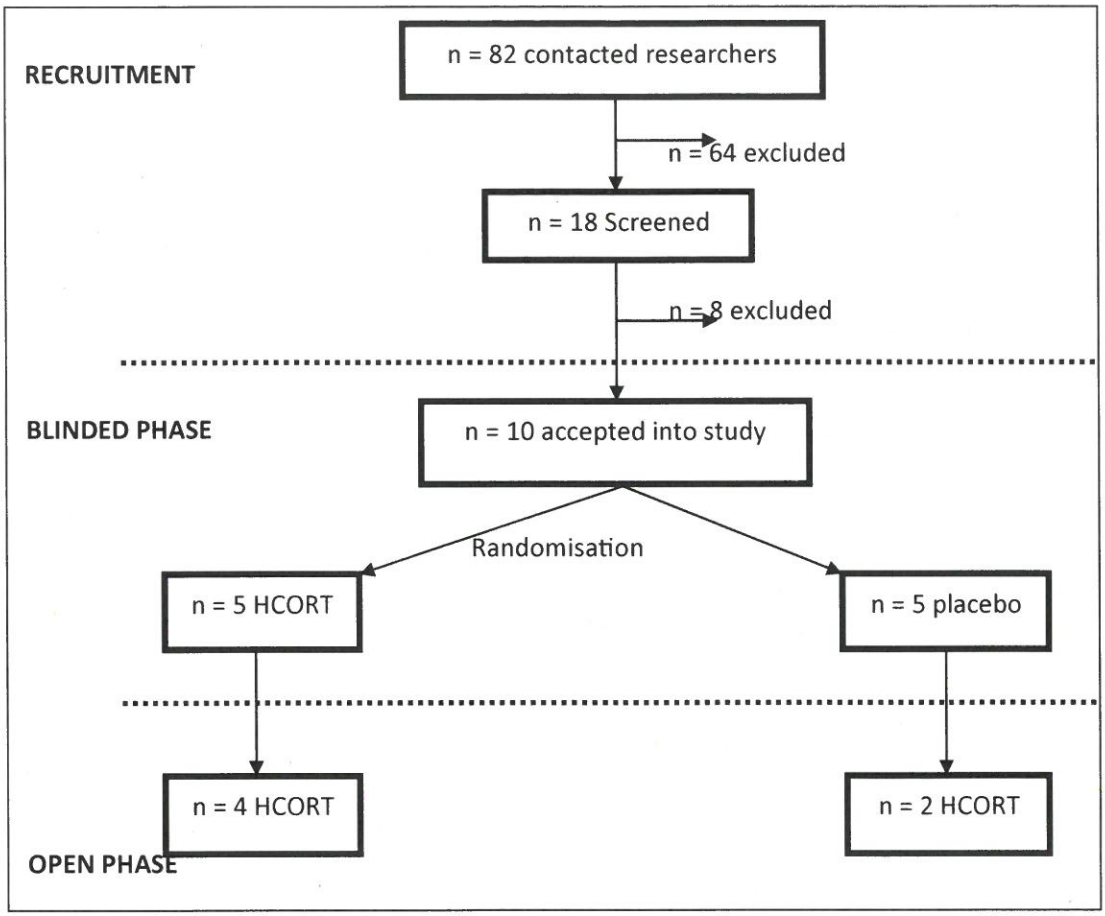
Results

Recruitment

Participant information sheets were sent to potential patients from our clinic, and we advertised to psychiatrists within Avon and Wiltshire Mental Health Partnership. When recruiting was still slow, we applied to the PCRN (primary care research network) for the project to be adopted onto their portfolio. If accepted, they offer significant help with recruitment from primary care sites (i.e. GP surgeries), exposing and promoting the study to GPs and obtaining the necessary Primary Care Trust (PCT) approvals to recruit patients from their surgeries. This was not forthcoming, mainly as ethical approval for the study was obtained before these procedures were instituted, so we sought Research and Development approval from the 4 PCTs in Bristol, North Somerset, South Gloucester and Bath and North East Somerset in order to contact GPs directly to inform them of the study and ask them to refer suitable patients to us. We also wrote articles for newsletters of patient organizations inviting potential participants to contact us.

In all 82 patients contacted us with a view to volunteering. Unfortunately, only 10 of these proved eligible and willing to participate.

Consented to telephone screening and provided phone number	61
Fulfilled eligibility criteria on telephone screening	24
Willing to consent	20
Screening visit and medical history	18
Eligible for study and consented	10

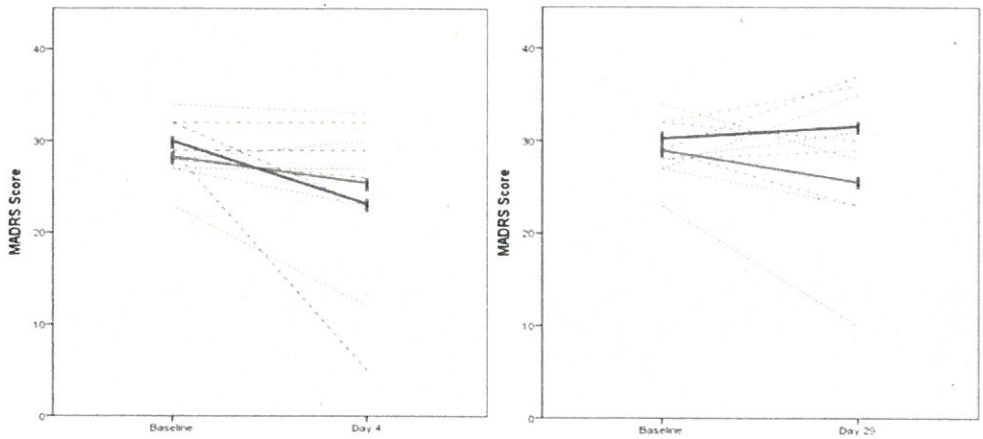


Participant progression through the TUDOR study. Dashed lines separate blinded and open phases of trial

Results: depression

There were no significant differences in gender distribution, height or weight between groups. Mean depression scores acutely (the day after the third infusion) improved in both groups, significantly more in the HCORT group. However this improvement was not maintained at day 29.

One patient in the HCORT group and none in the placebo group achieved and maintained remission at day 29.



Graphs 1 & 2: Change in MADRS scores from baseline to day 4 and day 29 between groups. GREEN = HCORT RED = Placebo Thick lines represent group mean; dashed line represent individual participants' scores

Results: sleep

There were no significant differences between baseline and day 3, or between groups on any of the sleep measures. However the baseline sleep measures showed a very wide variation, depending on whether the patients were taking a REM-suppressing antidepressant (eg SSRI, MAOI) or a drug that is known to increase slow wave sleep (eg trazodone, mirtazapine). In the 3 patients in the HCORT group not taking REM-suppressing drugs, REM sleep was reduced on the HCORT day which is similar to our healthy volunteer study differences. There were no changes in sleep latency, REM onset or slow wave sleep. Subjective sleep showed no change after the intervention in either group.

Results: adverse events

No serious adverse events were reported. 2 participants reported nausea and mild dizziness following HCORT infusion, 2 noticed a short term increase in their symptoms of anxiety, 2 felt they became more tearful, whilst feelings of flushing, itching, palpitations, chest discomfort and a metallic taste were all reported by one participant each. None of these reported effects were severe in nature and all were temporary. Side effects reported following placebo included feeling flushed, heartburn and headache.

Conclusions

Although this is a small study the fact that one patient responded to the short course of HCORT (the intervention) is significant. A response to a single intervention in patients with TRD is difficult to achieve and the results should be viewed in this context. We chose a high daily single dose administered IV on three consecutive days to ensure an effective and rapid delivery to the brain in a pulsatile manner, maximally stimulating any feedback systems remaining within the HPA axis and overwhelming the action of P-Glycoprotein to remove corticosteroids from the brain. The absence of a significant difference in POMS-SV measures between groups during the acute administration phase suggests that any effect of high dose HCORT is via relatively slow physiological processes - perhaps such as genome regulation. This is unlike the reported effects of other interventions such as ketamine and the immediate mood elevating effects of corticosteriods observed in some people. This may

support the hypothesis that diurnal variation in endogenous corticosteroids can permit the action of antidepressants possibly via encouraging neurogenesis in the hippocampus.

The patient who responded is notable by having the lowest baseline MADRS score. In addition the level of treatment resistance was at the lower end of the range. It could be that within this group of treatment resistant patients, HCORT augmentation may be best placed in those who are in the earlier stages of resistance. One patient demonstrated a marked placebo effect at days 4 and 8 which had resolved by day 15. This highlights the importance of measuring effects over a longer post-intervention period to ensure a placebo effect is excluded. 80% of those who received HCORT during the blinded phase went on to agree to the open label trial suggesting that this intervention is well tolerated and acceptable to this group of patients. Since there were no increases in anxiety symptoms, this intervention could be used without any deterioration in patients with anxiety as part of their disorder.

Recruitment into this trial was difficult due to a combination of relatively stringent exclusion criteria, the time commitment required and the use of an intravenous intervention. Previous studies have found improvements in depression symptomatology with oral corticosteroids over a slightly shorter period of assessment. This method could allow therapeutic administration without the need for outpatient facilities impacting on both the cost and location of providing such treatment as well as the acceptability to patients. Determining the most effective route and regime of administration for future larger scale investigations should be carefully considered.

Total REM sleep changes, observed in healthy volunteers, were only observed in patients who were not taking REM suppressing antidepressants.

What this study has added to the field

This is the first double-blind study to investigate the effects of short term, high dose hydrocortisone pulses in patients with treatment resistant depression. One patient got better: a response to a single intervention in patients with TRD is difficult to achieve and the results should be viewed in this context. Publications at conferences have been received favourably and this avenue of corticosteroid manipulation in depression will be pursued by other groups now.

Next steps

A future study should measure effects over a longer post-intervention period to ensure a placebo effect is excluded. Recruitment will be faster if future studies were immediately adopted onto the Trust portfolio, and thus research networks could recruit. Oral corticosteroids at high dose can be used in a larger trial, and therefore inclusion/exclusion criteria would be more pragmatic than those for an intravenous intervention. Sleep findings were interesting but not helpful in explaining or expanding results so will not be added to future studies.

Presentations

(2012) Wood B, Durant C, Scheeres K, Sinclair L, Rich A, Wilson S, Malizia AL Response to hydrocortisone infusions in patients with treatment resistant major depressive disorder: the TUDOR study. Journal of Psychopharmacology 26:8 (S) A23

(2011) Wilson SJ, Paterson LM, Durant CF, Sinclair L , Rich AS, Wood B, Lightman S, Nutt DJ, Malizia AL. Acute effects of high dose hydrocortisone on sleep in patients with treatment resistant depression: a double Blind placebo controlled study. Journal of Psychopharmacology 25:8 (S) A23

Reference List

(1) Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006 Mar 23;354(12):1243-52.

(2) Carroll BJ, Curtis GC, Mendels J. Neuroendocrine regulation in depression. II. Discrimination of depressed from nondepressed patients. Arch Gen Psychiatry 1976 Sep;33(9):1051-8.

(3) Checkley S. The neuroendocrinology of depression and chronic stress. Br Med Bull 1996 Jul;52(3):597-617.

(4) Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 2000 Nov;23(5):477-501.

(5) Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. Biol Psychiatry 2001 Mar 1;49(5):391-404.

(6) Juruena MF, Cleare AJ, Papadopoulos AS, Poon L, Lightman S, Pariante CM. The prednisolone suppression test in depression: dose-response and changes with antidepressant treatment. Psychoneuroendocrinology 2010 Nov;35(10):1486-91.

(7) Huang GJ, Herbert J. Stimulation of neurogenesis in the hippocampus of the adult rat by fluoxetine requires rhythmic change in corticosterone. Biol Psychiatry 2006 Apr 1;59(7):619-24.

(8) Jindal RD, Thase ME. Treatment of insomnia associated with clinical depression. Sleep Med Rev 2004 Feb;8(1):19-30.

(9) Agargun MY, Kara H, Solmaz M. Sleep disturbances and suicidal behavior in patients with major depression. J Clin Psychiatry 1997 Jun;58(6):249-51.

(10) Katz DA, McHorney CA. The relationship between insomnia and health-related quality of life in patients with chronic illness. J Fam Pract 2002 Mar;51(3):229-35.

(11) Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and Psychiatric Disorders: A Meta-analysis. Arch Gen Psych 1992;49:651-70.

(12) Steiger A, Holsboer F. Nocturnal secretion of prolactin and cortisol and the sleep EEG in patients with major endogenous depression during an acute episode and after full remission. Psychiatry Res 1997 Sep 19;72(2):81-8.

(13) Goodwin GM, Muir WJ, Seckl JR, Bennie J, Carroll S, Dick H, et al. The effects of cortisol infusion upon hormone secretion from the anterior pituitary and subjective mood in depressive illness and in controls. J Affect Disord 1992 Oct;26(2):73-83.

(14) Arana GW, Santos AB, Laraia MT, Leod-Bryant S, Beale MD, Rames LJ, et al. Dexamethasone for the treatment of depression: a randomized, placebo-controlled, double-blind trial. Am J Psychiatry 1995 Feb;152(2):265-7.

(15) Dinan TG, Lavelle E, Cooney J, Burnett F, Scott L, Dash A, et al. Dexamethasone augmentation in treatment-resistant depression. Acta Psychiatr Scand 1997 Jan;95(1):58-61.

(16) Bouwer C, Claassen J, Dinan TG, Nemeroff CB. Prednisone augmentation in treatment-resistant depression with fatigue and hypocortisolaemia: a case series. Depress Anxiety 2000;12(1):44-50.