Randomised controlled trial of Antiglucocorticoid augmentation (metyrapone) of antiDepressants in Depression (ADD Study)

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Scientific summary

The ADD Study

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Scientific summary

Background

Many patients (approximately 30–50%) with depression do not respond to first-line antidepressant drugs. Responses to a second antidepressant are also disappointingly low (approximately 30%). Such non-responding patients are characterised as suffering from treatment-refractory depression (TRD). Chronic psychosocial stress and dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis are both common in depression, and are associated with an attenuated clinical response to antidepressants. In preclinical studies, co-administration of corticosteroids leads to a reduction in the ability of selective serotonin reuptake inhibitors (SSRIs) to increase forebrain 5-hydroxytryptamine, whereas co-administration of antiglucocorticoids has the opposite effect. A Cochrane review suggested efficacy of antiglucocorticoid augmentation of antidepressants in patients with depression, with the largest effect size seen with metyrapone, a cortisol synthesis inhibitor that crosses the blood–brain barrier (Gallagher P, Malik N, Newham J, Young AH, Ferrier IN, Mackin P. Antiglucocorticoid treatments for mood disorders. *Cochrane Database Syst Rev* 2008;**1**:CD005168). A positive double-blind, placebo-controlled randomised trial of metyrapone was conducted in a centre in Germany, with 63 depressed inpatients.

Objectives

The Antiglucocorticoid augmentation of antiDepressants in Depression (ADD Study) was a multicentre, patient-randomised, double-blind placebo-controlled trial of metyrapone augmentation of serotonergic antidepressants in patients with TRD in the UK NHS. The primary objective was to determine whether or not metyrapone (500 mg twice a day) for 21 days is efficacious in augmenting ongoing treatment with conventional serotonergic antidepressants in TRD. The primary outcome by which this objective was assessed was the Montgomery–Åsberg Depression Rating Scale (MADRS) scored at baseline and 2 weeks post treatment (week +5 from randomisation) in a representative sample of depressed patients who had failed to respond to at least two courses of antidepressants, drawn from primary care and psychiatric outpatient clinics in the UK. Treatment with metyrapone was compared with treatment with placebo, using analysis of covariance. Secondary clinical objectives were to (1) determine the clinical effect size at 2 weeks post completion of treatment (5 weeks post randomisation) of a 3-week course of metyrapone (vs. placebo) augmentation of antidepressants; (2) assess whether or not any observed response was sustained for up to 21 weeks post cessation of metyrapone; (3) assess whether or not metyrapone augmentation improves patients' quality of life (QoL) using the self-completed EuroQol EQ-5D instrument (European Quality of Life-5 Dimensions); (4) assess the tolerability and safety of metyrapone augmentation in this study population; and (5) assess the mechanism of action of metyrapone in mechanistic substudies using neuropsychological, neuroendocrine and neuroimaging outcomes.

Assessment of additional secondary outcome measures of symptomatology [Clinical Anxiety Scale (CAS), Beck Depression Inventory (BDI), State–Trait Anxiety Inventory (STAI) and Young Mania Rating Scale (YMRS)] were conducted at the same time points as described for the MADRS.

Methods

A total of 165 patients with moderate to severe TRD, aged 18–65 years, were randomised to metyrapone 500 mg twice daily or placebo for 3 weeks, in addition to ongoing treatment with serotonergic antidepressants. Treatment occurred between weeks 0 (randomisation) and week +3 relative to randomisation. Patients were assessed on the above outcomes at –2, 0, +3, +5, +8, +16 and +24 weeks. Inclusion criteria were that the patient had (1) a major depressive episode assessed using the Structured Clinical Interview for DSM (SCID) (*Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition, DSM-IV); (2) a Hamilton Depression Rating Scale-17 item (HDRS17) score of ≥ 18 at weeks –2 and 0; (3) a Massachusetts General Hospital Treatment Resistant Depression (MGH-TRD) staging score of 2–10 at week –2 as a measure of treatment refractoriness; and (4) current treatment with a single agent or combination antidepressant treatment [which included a serotonergic drug (a SSRI), a tertiary amine tricyclic, venlafaxine, duloxetine or mirtazapine]. At the point of randomisation, patients were required to have been on their current antidepressant medication, at the current dose, for a minimum of 4 weeks, and this medication needed to be continued unchanged during the trial. Exclusion criteria included any other DSM-IV axis 1 diagnosis other than an anxiety disorder; a physical comorbidity that would make metyrapone inappropriate; pregnancy or breastfeeding; use of medication that would interfere with metyrapone; and dependence on alcohol or other drug(s) in the past 12 months and/or current harmful use of such substances. Metyrapone treatment potentially engenders hypocortisolaemia, with manifestations including a risk of postural hypotension, hyperkalaemia and hyponatraemia. Therefore, safety assessments included serum cortisol measures at week +1, as well as measuring sitting and standing blood pressure and urea and electrolytes at weeks +1 and +5. Serious adverse events (SAEs) and adverse events (AEs) were routinely enquired for and recorded. Tolerability was further assessed using the Toronto Side Effects Scale (TSES). Metyrapone administration has previously been shown to cause an increase in levels of 11-deoxycortisol, and the increase in 11-deoxycortisol between weeks –2 and +1 was to be used, when available, as a measure of adherence to medication, as this has been shown to be highly sensitive to treatment with metyrapone. The study also investigated a number of mechanistic objectives, including whether or not the patients had evidence of baseline hypercortisolaemia and, if present, whether or not this had any impact on clinical and neuropsychological outcomes. A comparator group was also recruited to support these mechanistic investigations.

Results

Overall, 877 patients were referred to the study team: 237 from primary care, 320 from secondary care and 310 as self-referrals following media exposure of the study or seeing posters. The origin of 10 patients was unclear. A total of 284 underwent detailed screening for eligibility. The remainder were either deemed to be ineligible on the basis of a brief telephone screen or did not follow up contact, and 173 were deemed to be eligible. Of the 111 who did not meet inclusion criteria, 10 did not meet the criteria for a major depressive episode using the SCID, 52 had HDRS17 item scores of <18, 17 had axis 1 disorders other than anxiety, nine were on an inappropriate antidepressant, three had MGH-TRD staging scores outside the range of 2–10, 18 had physical disorders that excluded them, and five had other miscellaneous exclusion criteria (three patients were excluded for more than one reason).

Eight patients subsequently dropped out before randomisation (i.e. between weeks –2 and 0) and so 165 patients were randomised (82 to placebo and 83 to metyrapone). Of these, 143 (86.7%) completed the primary outcome at +5 weeks (74 on placebo and 69 on metyrapone). A further 39 dropped out between week +5 and week +24, so that 104 (63%) completed the study (58 on placebo and 46 on metyrapone). The groups were well balanced at randomisation in terms of demographics and key clinical variables. The mean MADRS score for the groups indicated moderate to severe depression, with MGH scores well in the range of treatment resistance. The group showed evidence of high Beck Depression Inventory (BDI) scores. There was evidence of high scores on measures of anxiety, and comorbid anxiety conditions were frequent.

The estimated mean difference for each of our study outcomes between randomised groups 5 weeks post randomisation (adjusting for variation between centres, whether or not patients originate from primary or secondary care and baseline score) was MADRS (the primary outcome measure) –0.51 (95% CI –3.48 to 2.46); BDI –2.65 (95% CI –6.41 to 1.10); Clinical Anxiety Scale (CAS) 0.46 (95% CI –1.20 to 2.12); STAI 1.2 (95% CI –0.6 to 3.0); European Quality of Life-5 Dimensions 0.015 (95% CI –0.069 to 0.099); EuroQol visual analogue scale 5.6 (95% CI –0.7 to 12.0); Young Mania Rating Scale –0.04 (95% CI –0.52 to 0.45). The differences were not statistically significant for any measure and tended to be small in relation to the change in both groups observed at week +5. Response rates were low and almost identical in both groups (21.6% in the placebo group and 20.3% in the metyrapone group). Remission rates were similarly low and almost identical in the two groups at this time point.

Endocrinological data required for compliance assessment are not yet available. HPA axis function, similar in patients and control subjects, was not associated with differing clinical responses. A wide range of neuropsychological impairments were found, along with changes in brain structure and function, but no differential effect of metyrapone was seen on these measures.

Metyrapone was generally well tolerated. There were 14 SAEs reported for 11 of the patients randomised to study medication (five in the group randomised to metyrapone and six in the group randomised to placebo) but none was attributed to metyrapone and most occurred well after the period of active drug treatment. Non-serious AEs were more common and broadly similar in type and frequency between the two groups, but we cannot exclude the possibility that treating patients with metyrapone may increase the risk of AEs. Of particular note, however, is that metyrapone did not increase the risk of suicidal ideation or suicide attempts. Scores on the TSES were broadly similar between the two groups, with no evidence of a difference in the frequency of postural hypotension or dizziness.

Conclusions

The broad inclusion criteria led to the sample being broadly representative of patients with TRD who are treated within the NHS. The sample had high anxiety and BDI scores and frequent comorbid anxiety. No evidence was found that metyrapone augmentation of serotonergic antidepressants is efficacious for patients with moderate to severe depression – managed in NHS secondary care outpatient clinics or by general practitioners in primary care – who have failed to respond to at least two antidepressants. There was no obvious benefit to its use either on the primary outcome or over the period of follow-up, and this negative result extended to other secondary outcomes, such as the CAS, BDI and quality-of-life measures. Metyrapone was well tolerated by this group and there were no serious AEs attributable to it. AEs were as common in patients treated with placebo. Clinical outcomes have not yet been analysed with respect to the measure of adherence utilised.

A wide range of neuropsychological impairments were found along with changes in brain structure and function, but no differential effect of metyrapone was seen on these measures. This population with TRD was characterised by increased exposure to childhood adversity (compared with the control subjects) and normal HPA axis function. These findings accord with the existing literature in chronic populations; the former predicts non-response to treatment. However, baseline HPA axis function, change in cortisol awakening response in response to drug treatment or severity of childhood trauma did not predict clinical response to metyrapone.

There are very few data specifically on the neuropsychology of treatment-resistant depressed groups. Those studies that have been conducted suggest that deficits are restricted to tests of processing speed. In this TRD sample we see broad deficits in verbal and visuospatial working memory and emotion processing compared with healthy control subjects. Deficits in attention were not general and, instead, were restricted to the executive control of attention. These findings are indicative of an impairment in effortful processing in TRD. No differential effects of metyrapone were seen on these measures.

Trial registration

This study is registered as ISRCTN45338259.

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This report

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