Antidepressant augmentation with metyrapone for treatment-resistant depression (the ADD study): a double-blind, randomised, placebo-controlled trial

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Summary

Background Many patients with major depressive disorder have treatment-resistant depression, defined as no adequate response to two consecutive courses of antidepressants. Some evidence suggests that antiglucocorticoid augmentation of antidepressants might be efficacious in patients with major depressive disorder. We aimed to test the proof of concept of metyrapone for the augmentation of serotonergic antidepressants in the clinically relevant population of patients with treatment-resistant depression.

Methods This double-blind, randomised, placebo-controlled trial recruited patients from seven UK National Health Service (NHS) Mental Health Trusts from three areas (northeast England, northwest England, and the Leeds and Bradford area). Eligible patients were aged 18–65 years with treatment-resistant depression (Hamilton Depression Rating Scale 17-item score of ≥18 and a Massachusetts General Hospital Treatment-Resistant Depression staging score of 2–10) and taking a single-agent or combination antidepressant treatment that included a serotonergic drug. Patients were randomly assigned (1:1) through a centralised web-based system to metyrapone (500 mg twice daily) or placebo, in addition to their existing antidepressant regimen, for 21 days. Permuted block randomisation was done with a block size of two or four, stratified by centre and primary or secondary care setting. The primary outcome was improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) score 5 weeks after randomisation, analysed in the modified intention-to-treat population of all randomly assigned patients that completed the MADRS assessment at week 5. The study has an International Standard Randomised Controlled Trial Number (ISRCTN45338259) and is registered with the EU Clinical Trial register, number 2009-015165-31.

Findings Between Feb 8, 2011, and Dec 10, 2012, 165 patients were recruited and randomly assigned (83 to metyrapone and 82 to placebo), with 143 (87%) completing the primary outcome assessment (69 [83%] in the metyrapone and 74 [90%] in the placebo group). At 5 weeks, MADRS score did not significantly differ between groups (21·7 points [95% CI 19·2–24·4] in the metyrapone group *vs* 22·6 points [20·1–24·8] in the placebo group; adjusted mean difference of –0·51 points [95% CI –3·48 to 2·46]; p=0·74). 12 serious adverse events were reported in four (5%) of 83 patients in the metyrapone group and six (7%) of 82 patients in the placebo group, none of which were related to study treatment. 134 adverse events occurred in 58 (70%) patients in the metyrapone group compared with 95 events in 45 (55%) patients in the placebo group, of which 11 (8%) events in the metyrapone group and four (4%) in the placebo group were judged by principle investigators at the time of occurrence to be probably related to the study drug.

Interpretation Metyrapone augmentation of antidepressants is not efficacious in a broadly representative population of patients with treatment-resistant depression within the NHS and therefore is not an option for patients with treatment-resistant depression in routine clinical practice at this time. Further research is needed to clarify if such augmentation might benefit subpopulations with demonstrable hypothalamic–pituitary–adrenal axis abnormalities.

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Introduction

Clinical guidelines recommend the use of antidepressant medication for the treatment of moderate to severe major depressive disorder.[1,2] However, a substantial proportion of patients (roughly between 10% and 33%) do not obtain an optimum outcome after both first-line and second-line treatment, often described as treatment-resistant depression.[2–4] Hypothalamic–pituitary–adrenal (HPA) axis abnormalities are often reported in patients with mood disorders, and increasing evidence suggests that such dysregulation is associated with poor prognosis, defined both by non-response to antidepressants and by an increased likelihood of future relapse.[5,6] A review[7] suggested that antiglucocorticoid augmentation of antidepressants in patients with major depressive disorder is efficacious, with the largest effect size seen

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See Online for appendix

***Panel:* Research in context**

Evidence before this study

Evidence is abundant of abnormalities in hypothalamic–pituitary–adrenal (HPA) axis function in at least a proportion of patients with major depression disorder, some of whom have hypercortisolaemia. As a result, several antiglucocorticoid treatments have been investigated in patients with major depressive disorder, particularly patients with treatment-resistant depression. One such antiglucocorticoid treatment is metyrapone. We searched PubMed with the terms "depression" and "metyrapone" for articles published in English up until May 31, 2015. We found one small (n=63), double-blind, randomised controlled trial of metyrapone augmentation of serotonergic antidepressants in German inpatients. This study reported a positive difference 2 weeks after a 3 week course of metyrapone (1 g daily), compared with placebo, with an effect size of 0·63 for the reduction in Montgomery-Åsberg Depression Rating Scale score.

Added value of this study

Our study's aim was to examine whether metyrapone is efficacious in a predominantly outpatient population of patients with treatment-resistant depression, recruited using broad inclusion criteria in a larger, more naturalistic, sample than in the previous study showing efficacy of metyrapone augmentation. Furthermore, this study aimed to examine tolerability and whether any beneficial effect was sustained over the long term (6 months). As such, the study was intended to inform whether metyrapone augmentation was a realistic therapeutic option in everyday clinical practice.

Implications of all the available evidence

Contrary to the previous double-blind randomised controlled trial of metyrapone augmentation in treatment-resistant depression, results of our study did not show any beneficial effect of metyrapone augmentation. Treatment, however, was well tolerated. Our study therefore suggests that metyrapone augmentation of serotonergic antidepressants is not an option for patients with treatment-resistant depression in routine clinical practice at this time. Further research is needed to clarify the extent and longitudinal course of HPA axis abnormalities in major depressive disorder and in treatment-resistant depression, and whether this information might help to identify individuals in whom antiglucocorticoid treatments might be effective.

with metyrapone, a cortisol synthesis inhibitor. The data relating to metyrapone were taken from Jahn and colleagues' positive, double-blind, placebo-controlled randomised study[8] of metyrapone (250 mg four times daily for 3 weeks) in a small sample of 63 inpatients with depression in Germany.

The primary aim of the Antiglucocorticoid Augmentation of Anti-Depressants in Depression (ADD) study was to test the proof of concept of metyrapone for the augmentation of conventional serotonergic antidepressants, previously established by Jahn and colleagues,[8] in a clinically relevant population—ie, patients with major depressive disorder who had not responded to at least two courses of antidepressants during their current episode (ie, those with treatment-resistant depression). This is the stage in treatment sequencing (ie, non-response to antidepressant monotherapies) at which the current UK National Institute for Health and Clinical Excellence (NICE) guidelines[1] for the management of depression recommend use of antidepressant augmentation strategies. Because few patients with depression are admitted to inpatient psychiatric units in the UK,[9] we aimed to recruit a mainly outpatient (primary and secondary care) UK National Health Service (NHS) population. Until now, all published studies of the use of antiglucocorticoids in patients with treatment-resistant depression have used short treatment periods of 1–3 weeks,[7] which might seem counterintuitive in such a potentially chronic disorder. However, evidence suggests that the clinical effects of antiglucocorticoids on HPA axis function persist after their administration has ceased.[10,11] Therefore, we also aimed to study the persistence of effects on depressive symptoms and quality of life at 21 weeks after stopping metyrapone treatment, compared with 2 weeks' follow-up in Jahn and colleagues' study.[8]

Methods

Study design and participants

The ADD study was a two-arm, parallel-group, double-blind, randomised, placebo-controlled superiority trial; the hypotheses being tested and the study protocol have been published elsewhere.[12] The study was undertaken in three centres, recruiting patients from seven UK National Health Service (NHS) Mental Health Trusts and localised primary care services in the same region, in three areas: northeast England (Northumberland Tyne and Wear NHS Foundation Trust and Tees, Esk and Wear Valleys NHS Foundation Trust); northwest England (Manchester Mental Health and Social Care NHS Trust, Greater Manchester West Mental Health NHS Foundation Trust, and Pennine Care NHS Foundation Trust); and the Leeds and Bradford area (Leeds and York Partnership NHS Foundation Trust and Bradford District Care NHS Foundation Trust).

Patient identification was supported by two hubs of the UK National Institute for Health Research Mental Health Research Network (the North East and North West), a Comprehensive Local Research Network (West Yorkshire), and spanned primary and secondary care. A schedule of participant visits to study centres and assessments made on these occasions is detailed in the appendix (pp 7–8) and described elsewhere.[12]

Eligible patients were those aged 18–65 years who had a major depressive episode as defined by the DSM-IV,[13] assessed using the Structured Clinical Interview for DSM Disorders (SCID) research version.[14] They were required to have a Hamilton Depression Rating Scale 17-item (HDRS17)[15] score of 18 or more at week –2 (ie, 2 weeks before randomisation) and at week 0 (ie, time of randomisation and commencement of experimental medication), determined using the GRID-Hamilton Depression Rating Scale for improved reliability,[16] a Massachusetts General Hospital Treatment-Resistant Depression (MGH-TRD) staging score of 2–10 as a measure of treatment resistance (ie, with no response to at least two antidepressants during their current episode),[17] and to be on a single-agent or combination antidepressant treatment that included a serotonergic drug (a selective serotonin reuptake inhibitor, a tertiary amine tricyclic, venlafaxine, duloxetine, or mirtazapine). At the point of randomisation, patients had to have been taking their current antidepressant medication, at the same dose, for a minimum of 4 weeks. Exclusion criteria were: another DSM-IV axis I diagnosis (later relaxed because of initial slow recruitment, to allow enrolment of patients with an anxiety disorder regarded as secondary to a primary diagnosis of depression); physical comorbidity that would make metyrapone inappropriate, including untreated hypothyroidism, disorders of steroid production, cardiac failure, angina, myocardial infarction in the past 3 years, and renal failure; pregnancy or breastfeeding; use of medication that would interact with metyrapone; dependence on alcohol or other drugs in the previous 12 months, or current harmful use of such substances (defined as meeting SCID criteria for harmful use or dependence); and current or recent (within the previous 6 months) participation in a research study that could interfere with results.

A cohort of age-matched and sex-matched healthy volunteers was recruited to act as comparators with the patient cohort in relation to HPA axis function, and several additional investigations including neurocognitive testing, MRI, and electroencephalography, which will be reported elsewhere. Healthy volunteers were recruited by advertisements around the campus of the University of Manchester and by emails sent to the volunteer database of the Institute of Neuroscience, Newcastle University. Healthy volunteers were confirmed as having no current or past axis I disorder using DSM-IV criteria assessed with the SCID, had no first-degree family history of mental illness, and had an HDRS17 score of less than 5. Exclusion criteria were the same as for the patient cohort.

Ethical approval was granted by the Sunderland Local Research Ethics Committee (REC reference number 10/H0904/9) on April 22, 2010. Clinical trial authorisation was given by the Medicines and Healthcare products Regulatory Agency (EU Clinical Trial register number 2009-015165-31). All participants provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to metyrapone or placebo using permuted block randomisation, stratified by centre (northeast England, northwest England, or Leeds and Bradford), level of care setting (primary or secondary care) and, for the northeast and northwest England centres, by whether the patient agreed to participate in the mechanistic studies (described elsewhere[12]). The randomisation code was generated by an independent statistician in the Newcastle Clinical Trials Unit with the length of each block randomly set at two or four (with equal probability), unknown to study personnel to ensure concealment of allocation. Coded (numbered) packs of study drug and matched placebo were produced according to the randomisation schedule, by Catalent Pharma Solutions (Somerset, NJ, USA). Metyrapone capsules were over-encapsulated (using Coni-Snap capsules, Capsugel, Morristown, NJ, USA) and appeared identical to the placebo capsules, and were dispensed from the clinical trials pharmacy at Northumberland, Tyne and Wear NHS Foundation Trust, Newcastle. Randomisation was through a centralised web-based system set up by the Newcastle Clinical Trials Unit with access to the randomisation code restricted to the study pharmacist, independent statistician, and database manager to ensure concealment of allocation. Treatment allocation remained blinded until after the last participant's final 24 week visit and data locking (Aug 23, 2013). The data monitoring and ethics committee (DMEC), independently of the investigators, assessed the proportion of participants with suicidal thoughts or behaviour in the two treatment groups without unblinding, about half way through the study, and reported no difference between the groups. They repeated this analysis towards the end of the study and again reported no difference, but specifically requested this aspect of the data be analysed after unblinding.

Procedures

Participants continued their existing antidepressant regimen and received study drug (metyrapone 500 mg or placebo) twice daily, prescribed in the morning and at noon, for 21 days (matching previous studies[8]). All other treatments remained under the control of patients' usual treating clinicians, who were encouraged to avoid medication changes between enrolment (week –2) and the primary outcome timepoint (week 5) unless there was a compelling clinical reason to do so. Any such changes in treatment did not lead to the patient being excluded from the analysis.

Saliva samples to establish the cortisol awakening response (CAR)[18] were obtained at week 0 (immediately before commencement of treatment augmentation) and then at week 3 (the day after cessation of experimental medication) and week 5. Participants collected 5 mL of saliva by passive drool[19] into a plastic collecting tube on

wakening and at 15 min intervals for a further 1 h. A further sample was collected by the same method at 2300 h the night before each of the three CAR assessments. We analysed the CAR data by calculating the area under the curve (AUC) of concentration against time, calculated using the trapezoidal method with respect to zero (ie, AUC with respect to ground [AUC_G]) and with respect to the concentration on waking (ie, AUC with respect to increase [AUC_I]), as previously described.[20]

Additionally, serum samples were taken 2 weeks before randomisation (week –2) and 1 week afterwards for analysis of cortisol precursors and metabolites. The increase in 11-deoxycortisol between weeks –2 and week 1 was used as a measure of adherence to medication since 11-deoxycortisol has been shown to be highly sensitive to treatment with metyrapone.[8,21]

Outcomes

The primary outcome was measure of mood assessed by Montgomery-Åsberg Depression Rating Scale (MADRS)[22] score, 5 weeks (plus or minus 2 days) from the date medication was started, adjusted for baseline score. Secondary outcomes included the following: difference between MADRS score assessed at week 0 and at weeks 3 (end of active treatment period), 8, 16, and 24 from the date medication was started (plus or minus 2 days); treatment response (defined as an ≥50% reduction in MADRS score) and remission (defined as MADRS score of ≤10) at week 5; Clinical Anxiety Scale score;[23] Beck Depression Inventory (BDI) score;[24] State Trait Anxiety Inventory score;[25] and Young Mania Rating Scale (YMRS) score.[26] Quality of life was assessed using the self-completed EQ-5D-3L instrument[27] and tolerability using the Toronto Side Effects Scale (TSES).[28] In all scales, apart from EQ-5D-3L, a higher score suggests greater impairment. Safety assessments to assess for metyrapone-induced hypocortisolaemia included serum cortisol at week 1 and measurement of sitting and standing blood pressure and urea and electrolytes at weeks 1 and 5. A full list of secondary analyses is detailed in the appendix, pp 1–4.

Statistical analysis

The study was powered to detect a between-group difference with a standardised effect size (*d*) of 0·5 (compared with 0·63 in Jahn and colleagues' study[8]) in the change in MADRS scores between baseline and 5 weeks after randomisation, requiring 85 patients per group for 90% power with an alpha of 0·05 (to allow for 10% attrition during the trial, the original aim was to randomly assign 95 patients per group). However, as a result of slow recruitment, and with the agreement of the funder and DMEC, the power requirement was reduced to 80%, requiring a sample size of 63 per group (70 per group allowing for 10% attrition). A full detailed statistical analysis plan was agreed with the DMEC before study completion and breaking of the blind (appendix pp 1–4).

We analysed the primary outcome as an ANOVA of MADRS scores in a modified intention-to-treat population of all randomly assigned patients who completed the MADRS assessment at week 5, adjusted for baseline MADRS; we included strata (centres and whether the patient was recruited while attending primary or secondary care) and treatment groups as fixed effects. We assessed the persistence of change in MADRS score using repeated measures ANOVA using data from all timepoints. We examined secondary outcomes using the same methods. The YMRS score was analysed using the mixed models approach described above. For analysis of TSES score, we calculated the relative risk of individual symptoms in the two groups. All patients who received any dose of study drug or placebo who returned for scheduled appointments were assessed in the safety analyses. We did prespecified per-protocol analyses according to adherence to medication, based on measurements of 11-deoxycortisol before randomisation (week –2) and at week 1. To judge adherence in the metyrapone group, we used the conservative criterion that both the week 1 11-deoxycortisol concentration and the increase in 11-deoxycortisol between week –2 and week 1 had to be greater than the mean plus three times the SD of the placebo group (for patients with missing data for the week –2 concentration, week 1 11-deoxycortisol concentrations had to be more than the placebo mean plus four times the SD of the placebo group).

Salivary cortisol concentrations at 2300 h and the AUCs were non-normally distributed so were natural logarithm transformed and compared using paired (for changes over time in patients) or non-paired (comparing patients and healthy volunteers) *t* tests, with equal variance not assumed. In the event of missing data for timepoints used in the AUC analysis, we imputed the data by inserting the mean of the values immediately before and after the missing timepoint. We did not use imputation for either the first or last datapoint, and excluded patients without such data, as well as those with more than one missing datapoint.

We did the statistical analyses with IBM SPSS Statistics for Windows, version 20.0 and Stata, version 12. The study is registered with an International Standard Randomised Controlled Trial Number, ISRCTN45338259 and is registered with the EU Clinical Trial register, number 2009-015165-31.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors had full access to all the data in the study. All authors had final responsibility for the decision to submit for publication.

Results

877 potential patients were identified (figure 1), of whom 237 (27%) came from primary care, 320 (36%) from secondary care, and 310 (35%) were self-referrals

following media exposure of the study or who saw posters in their family doctors' clinic (in ten cases the source of the referral was not clear). All patients who self-referred were engaged in treatment within the NHS and were subsequently categorised and stratified on the basis of the level of care they were receiving (ie, primary or secondary care). Of the 877 potential patients, 284 (32%) were assessed for eligibility by formal face-to-face screening. Of the 111 who did not meet inclusion criteria, ten did not meet the criteria for a major depressive episode, 52 had HDRS17 item scores of less than 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 were excluded as a result of other miscellaneous criteria (three patients were excluded for more than one reason). Eight patients subsequently dropped out before randomisation (ie, between weeks –2 and 0), resulting in 165 patients being randomly assigned (82 to placebo and 83 to metyrapone) between Feb 8, 2011, and Dec 10, 2012, exceeding the revised target and providing 84% power to detect the effects postulated in the sample size determinations. Of those randomly assigned, 143 (87%) completed the primary outcome assessments at week 5. 39 (24%) dropped out between week 5 and week 24, and 104 (63%) completed the study. The last 24 week follow-up visit was on June 26, 2013, after a 7 month extension due to initial slow recruitment.

70 (42%) of 165 randomly assigned patients were recruited from primary care (47 [69%] of 68 patients from northeast England; 15 [39%] of 38 patients from Leeds and Bradford; and eight [14%] of 59 from northwest England). The placebo and the metyrapone groups were well balanced at baseline with respect to key demographic variables and clinical characteristics (table 1). Generally, very few data items were missing and only a small number of missing values needed to be imputed (appendix p 8).

Baseline MADRS scores by site and patient origin are shown in table 2. When all sites were combined, MADRS scores of patients recruited from secondary care were significantly higher than those from primary care (mean difference 3·4 points, 95% CI 1·5–5·3).

Figure 2 shows the MADRS scores of patients for whom we had data over the course of the entire study. All assessed patients (both treatment groups combined) had a significant reduction in MADRS scores of 6·0 points (95% CI 45–7·5) between baseline and week 5. However, the primary outcome of MADRS score at week 5 (21·7 points [95% CI 19·2–24·4] in 69 patients in the metyrapone group *vs* 22·6 points [20·1–24·8] in 74 patients in the placebo group) did not significantly differ after adjusting for baseline MADRS score, study centre, and primary or secondary care location of patients (adjusted MADRS score difference of 0·51 points [95% CI –3·48 to 2·46]; p=0·74). This absence of effect of metyrapone was consistent across analyses using all combinations of the three covariates (appendix p 9). Repeated measures mixed-model analyses using data from all assessment timepoints with the same covariates also showed no significant difference between treatment groups (appendix p 10). Consistent with this result, neither the proportion of patients who had a response at week 5 (14 [20%] of 69 in the metyrapone group *vs* 16 [22%] of 74 in the placebo group; adjusted [for site and

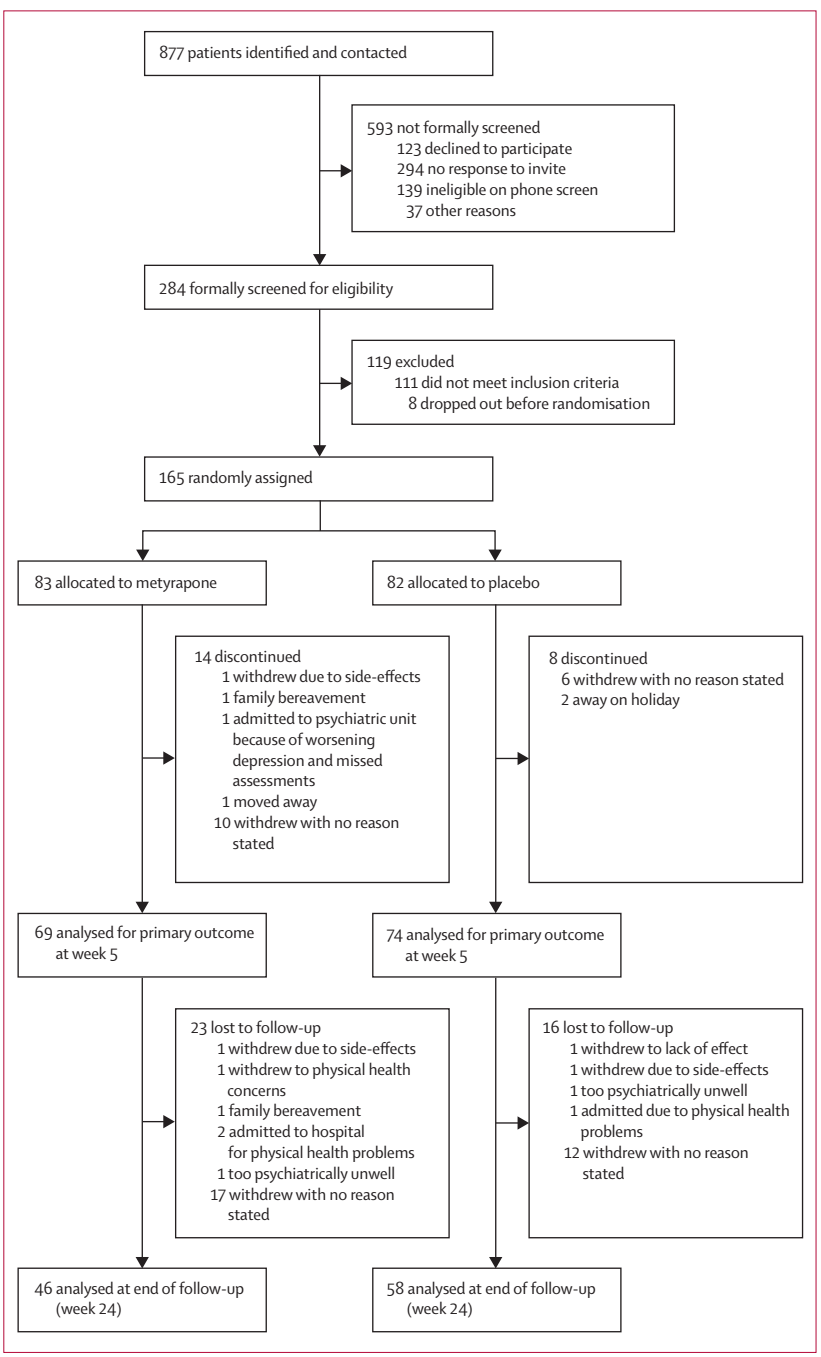

***Figure 1*: Trial profile**

origin of patient] odds ratio [OR] 0·95 [95% CI 0·41–2·20]) nor the proportion who achieved remission (11 [16%] *vs* 12 [16%]; adjusted OR 0·97 [0·40–2·55]) were significantly different between treatment groups.

Mean serum 11-deoxycortisol concentrations at week 1 were 0·9 nmol/L (SD 1·4) in the placebo group (1·6 [SD 1·7] times higher than at week 0) and 36·7 nmol/L (65·9) in the metyrapone group (65·8 [153·8] times higher than week 0). Three patients were missing 11-deoxycortisol concentration data at week –2 and hence we assessed their adherence on the basis of their week 1 measurement. All others were judged on a combination of week 1 11-deoxycortisol plasma concentration and the increase between week –2 and week 1, as described in the Methods section. 52 (75%) patients in the metyrapone group were deemed to be adherent and were compared with all 74 of the patients in the placebo group. This per-protocol analysis found no difference in week 5 MADRS scores between treatment groups, covarying for baseline MADRS score and origin of patient, with a mean difference of –1·65 points (95% CI –4·94 to 1·65). Additionally, in this per-protocol analysis, no difference was noted in the proportion of patients who had a treatment response (12 [23%] of 52 in the adherent metyrapone group *vs* 17 [22%] of 74 in the placebo group) or the proportion who achieved remission (nine [17%] *vs* 12 [16%]) at week 5. The 17 randomly assigned patients who were not adherent to metyrapone had a non-significant change in MADRS score from baseline to week 5 (–2·94 points [95% CI –6·82 to 1·18]), whereas the 52 patients who were adherent to metyrapone had a significant reduction (–7·21 points [–9·60 to –4·79]) as did the 74 patients in the placebo group (–5·77 [–7·93 to –3·66).

Of the 165 randomly assigned patients, saliva samples were obtained from 151 (92%) patients for measurement of 2300 h cortisol concentrations and CAR at week 0 (75 [90%] of 83 in the metyrapone group and 66 [80%] of 82 in the placebo group). 67 healthy volunteers who were matched to the patients with respect to age, sex, and IQ were recruited (table 1). Saliva samples for 2300 h cortisol concentrations and CAR data were available for 60 (90%) healthy volunteers. The 2300 h cortisol was greater in patients (2·48 nmol/L [SD 4·97]) than in healthy volunteers (1·38 nmol/L [1·38]; p=0·032 on transformed data; figure 3). Neither AUC_G (untransformed mean, 1·36 [SD 1·06] in patients *vs* 1·38 [0·0] in healthy volunteers; p=0·481) nor AUC_I (mean 0·0 [0·73] *vs* 0·23 [0·74]; p=0·526) differed between patients and healthy volunteers.

125 patients had baseline (week 0) and week 3 2300 h cortisol concentration data (59 [71%] of 83 in the metyrapone group and 66 [80%] of 82 in the placebo group), and 123 patients had available AUC salivary cortisol data (57 [69%] of 83 patients in the metyrapone group and 66 [80%] of 82 in the placebo group). In the

	Placebo (n=82)	Metyrapone (n=83)	Healthy volunteers (n=67)
Sex			
Male	30 (37%)	36 (43%)	29 (43%)
Female	52 (63%)	47 (57%)	38 (57%)
Race			
White	77 (94%)	80 (96%)	55 (82%)
Other	5 (6%)	3 (4%)	12 (18%)
Age, years	45·2 (10·4)	47·6 (9·9)	42·5 (9·9)
Smoking status			
Non smoker	36 (44%)	23 (28%)	40 (60%)
Ex-smoker	16 (20%)	25 (30%)	21 (31%)
Current smoker	30 (37%)	35 (42%)	6 (9%)
Alcohol consumption, units/week	6·9 (12·8)	7·0 (11·2)	5·3 (6·0)
Vital signs			
Height, cm	169·6 (10·4)	169·0 (10·4)	170·1 (10·2)
Weight, kg	90·0 (22·2)	89·4 (19·8)	73·2 (15·4)
BMI, kg/m²	31·2 (6·6)	31·5 (6·9)	25·3 (5·0)
Psychological health and quality of life			
HDRS17 (week –2)	23·0 (3·9)	23·3 (3·9)	0·5 (0·9)
HDRS17 (week 0)	22·3 (3·2)	22·2 (3·5)	..
MADRS	28·1 (5·4)	27·7 (6·7)	..
BDI	34·8 (10·3)	35·6 (10·9)	..
STAI: state anxiety	41·0 (5·8)	42·8 (6·5)	..
STAI: trait anxiety	48·3 (5·2)	48·5 (5·7)	..
CAS	10·0 (4·6)	9·5 (4·5)	..
EQ-5D	0·37 (0·3)	0·37 (0·3)	..
EQ VAS	40·9 (16·6)	42·3 (19·4)	..
Treatment history, MGH-TRD	4·6 (1·8)	4·9 (2·0)	..

Data are number (%) or mean (SD). A higher score suggests a greater impairment in all scales but EQ-5D and EQ VAS, for which a higher score suggests a less severe impairment. BMI=body-mass index. HDRS17=17 item Hamilton Depression Rating Scale. MADRS=Montgomery-Åsberg Depression Rating Scale. BDI=Beck Depressive Inventory. STAI=State Trait Anxiety Inventory. CAS=Clinical Anxiety Scale. EQ-5D=Euroquol 5 dimensions. EQ VAS=Euroquol visual analogue scale. MGH-TRD=Massachusetts General Hospital Treatment Resistant Depression staging score.

***Table 1*: Patient and healthy volunteer baseline clinical and demographic characteristics**

	Primary care			Secondary care			Total		
	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI
Total	70	25·96	24·57–27·31	95	29·36	28·19–30·59	165	27·92	27·01–28·88
Leeds and Bradford	15	24·47	21·18–27·50	23	26·35	24·18–28·59	38	25·61	23·76–27·40
Northwest England	8	28·38	25·50–32·25	51	29·67	28·36–30·97	59	29·49	28·25–30·72
Northeast England	47	26·02	24·39–27·71	21	31·90	28·73–35·53	68	27·84	26·24–29·58

***Table 2*: Patient baseline Montgomery-Åsberg Depression Rating Scale scores by site and source**

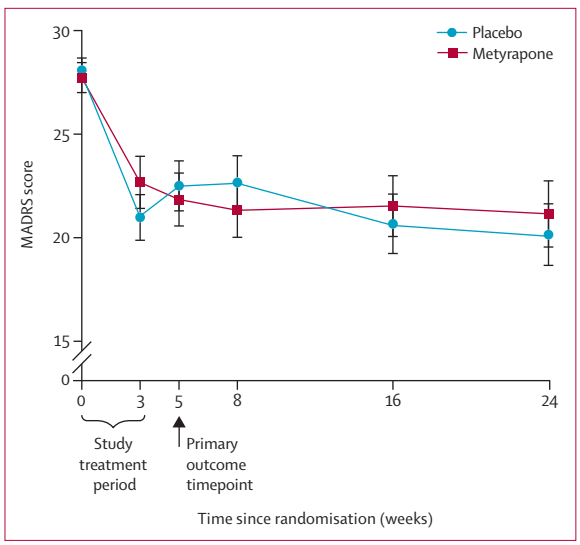

***Figure 2*: Montgomery-Åsberg Depression Rating Scale (MADRS) scores of patients randomly assigned to metyrapone or placebo over time**
Data are mean (datapoints) and SE (bars).

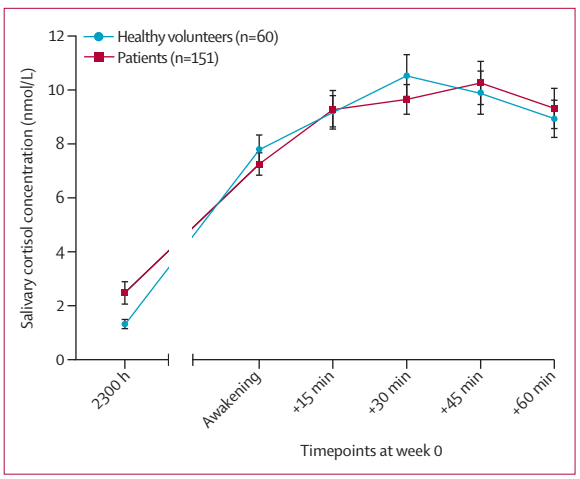

***Figure 3*: Baseline salivary cortisol concentrations of patients and matched healthy volunteers**
Salivary cortisol concentrations at 2300 h and after awakening at baseline (week 0). The data after awakening was used to calculate the area under the curve (AUC_G and AUC_I) for the cortisol awakening response (CAR). Data are mean (datapoints) and SE (bars).

patients for whom we had data, we noted no between-group difference between mean baseline and week 3 2300 h cortisol concentration (2·48 nmol/L [SD 3·31] *vs* 3·31 nmol/L [4·69]; p=0·26), AUC_G (untransformed mean, 1·39 [1·2] *vs* 1·41 [1·07]; p=0·92), or AUC_I (mean, 0·26 [0·86] *vs* 0·27 [0·65]; p=0·33).

To assess the effect of HPA axis function on response to metyrapone, we did an analysis of the effect of metyrapone on MADRS scores at week 5, covarying for baseline 2300 h salivary cortisol concentration, AUC_G, or AUC_I, or the difference in 2300 h cortisol concentrations, AUC_I, or AUC_G at week 3 compared with week 0. Our results showed an absence of effect of metyrapone in all analyses (appendix p 9).

Analysis of secondary outcomes similarly yielded estimated effects of metyrapone that were small and not statistically significant. Data regarding all clinical outcome measures are detailed in the appendix, pp 13–15.

12 serious adverse events were reported in ten patients (four in the metyrapone group and six in the placebo group; appendix p 11), none of which were judged to be related to study treatment. Most occurred well after the 3 week study treatment period or were related to pre-existing disorders (appendix pp 6–7). 229 adverse events were reported (134 events in 58 [70%] of 83 patients in the metyrapone group *vs* 95 events in 45 [55%] of 82 patients in the placebo group), of which, at the time of occurrence, 57 (43%) of 134 events in the metyrapone group and 34 (36%) of 95 events in the placebo group were judged by principle investigators to be possibly related to study drug, and 11 (8%) and four (4%) events, respectively, were judged to be probably related to the study drug. Six events (4%) in the metyrapone group and six events (6%) in the placebo group led to adjustment, interruption, or discontinuation of study medication. 58 (70%) of the 83 patients in the metyrapone group and 45 (55%) of 82 patients in the placebo group had at least one adverse event. Of those with at least one adverse event, the median number of events was two (IQR 1–3) with metyrapone and two (1–3) with placebo, and the mean was 1·7 (95% CI 1·4–2·1) with metyrapone and 2·1 (1·7–2·6) with placebo. The unadjusted estimate of the incidence rate ratio (ie, risk in the metyrapone group relative to risk in placebo group) was 1·34 (95% CI 0·90–1·98); the estimate of the incidence rate ratio adjusted for centre and origin of patient was 1·41 (0·98–2·03). After restricting the analysis to events classified as possibly or definitely related to study medication, the corresponding unadjusted incidence rate ratio estimate was 1·71 (95% CI 0·98–3·01) and adjusted estimate was 1·92 (1·14–3·24). Similar findings were made with respect to the TSES: across nearly all 32 symptoms rated by this scale, no significant difference was reported between the treatment groups in terms of incidence, except for two symptoms for which the difference in incidence between the two groups was significant at the 5% level (delayed ejaculation and weight loss were both more frequently reported in the placebo group; appendix p 11). No difference was noted between treatment groups with respect to YMRS score, consistent with an absence of risk of mania after treatment with metyrapone in this patient population (appendix p 15).

There were six instances of hypocortisolaemia during the study (in one of 82 patients in the placebo group and five of 83 patients in the metyrapone group). All of these cases were regarded as asymptomatic according to the standard operating procedure for principal investigators on the management of low cortisol, which included information about associated symptoms. As part of a

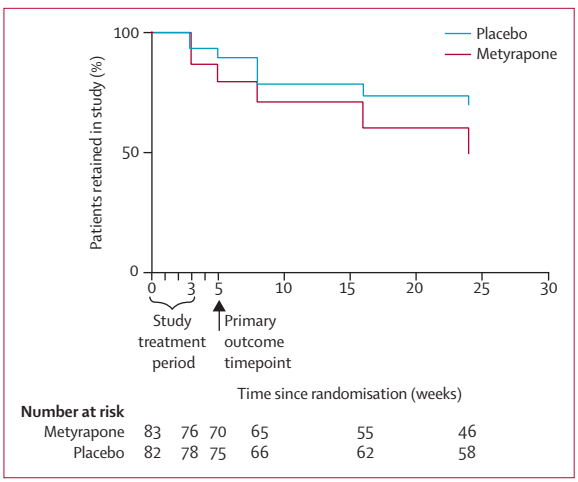

***Figure 4*: Patient retention in study over time**
Kaplan-Meier curve for patients randomly assigned to metyrapone or placebo remaining in the study.

standard operating procedure, all patients with hypocortisolaemia had their lying and standing blood pressure, and urea and electrolytes, checked, but no abnormalities were detected by these measures. Medication was continued and repeated cortisol measurements at later dates returned to normal.

The DMEC requested that the risk of events indicative of raised levels of suicidality be compared between the two trial groups. Using data from the suicide risk assessment tool (drawn from the Mini-International Neuropsychiatric Interview[29]), the incidence rate ratio (metyrapone/placebo) based on a negative binomial regression model adjusting for centre and origin of patient care was 0·47 (95% CI 0·17–1·32) suggesting no evidence of an increased risk of events associated with suicidality in the 83 patients randomly assigned to metyrapone. The estimated effect of metyrapone on suicidality score (as measured by item 10 on the MADRS) was a change of –0·15 points (95% CI –0·53 to 0·24) at week 5.

Patients randomly assigned to metyrapone were less likely to attend follow-up visits than patients randomly assigned to placebo (figure 4). Fitting a Cox proportional hazards model, the estimated hazard ratio for follow-up attendance was 0·57 (95% CI 0·35–0·93); however, most of the divergence occurred after active treatment ended (at week 3).

Discussion

The key finding of the ADD study is that in a UK NHS population of mainly outpatients with treatment-resistant depression in primary or secondary care, augmentation of serotonergic antidepressants with metyrapone is not efficacious. This result remained unchanged when only data from patients with clear evidence of adherence to study medication were included in the analysis. An absence of effect was also seen with respect to all secondary outcome measures.

The absence of a clinical response might arguably be a result of the absence of a cortisol response to metyrapone. However, in the smaller positive study by Jahn and colleagues,[8] cortisol concentrations were similarly unaffected, and results of a previous study[30] also showed no correlation between change in cortisol concentrations and improvement in mood with metyrapone. The absence of change in cortisol after metyrapone treatment might be due to homoeostatic mechanisms acting to maintain cortisol concentrations by increasing HPA axis activity. In the study by Jahn and colleagues,[8] adrenocorticotropic hormone and 11-deoxycortisol concentrations were robustly increased after metyrapone treatment. We did not measure adrenocorticotropic hormone, but 11-deoxycortisol concentrations were similarly affected by metyrapone in our study.

The normal baseline HPA axis function in our sample might have prevented a clinical response to metyrapone. Our group has previously shown that the extent of HPA axis dysregulation predicts clinical response to a different antiglucocorticoid treatment in bipolar depression.[31] However, counter to this, translational studies[32] from our group show that antiglucocorticoid strategies engender an increase in the prefrontal cortex serotonin response to a selective serotonin reuptake inhibitor, even in rats with normal HPA axis function. In our study, although patients had a small but significantly increased 2300 h cortisol concentration compared with matched healthy volunteers, no difference in CAR AUC_G or AUC_I was noted. These AUC measures have been argued to represent total cortisol output and the extent to which the HPA axis can activate,[20] and hence are a better measure of HPA axis function than one salivary cortisol concentration. Either way, change in MADRS score in patients in the metyrapone group did not correlate significantly with baseline HPA axis function, or with measures of change in HPA axis function after treatment with metyrapone. However, our study was not sufficiently powered to show whether metyrapone is efficacious in the subsample of patients with both hypercortisolaemia and treatment-resistant depression.

The ADD study is the largest randomised controlled trial of metyrapone augmentation for treatment-resistant depression done so far. A strength of our study is that, in view of the broad inclusion criteria and minimal exclusion criteria, its results can be generalised to the many patients in the NHS who have treatment-resistant depression. However, a large number (712 [81%]) of patients were excluded between referral and randomisation, so we cannot be completely confident that our sample is fully representative of the clinical disorder in the community at large.

We assessed the extent of treatment resistance using the MGH-TRD staging scale,[17] which included taking a treatment history and examination of hospital and family doctor records. We chose a minimum MGH-TRD score of 2 for inclusion, which represents no response to at

least two antidepressants, in view of usual UK practice in primary care of not augmenting or combining drugs for depression until after this stage.[1] Beyond this point, treatment sequencing for individual patients diverges greatly, with patients being referred to secondary care at different stages by individual clinicians. The maximum MGH-TRD score for inclusion in our study was 10, which in practice means the patient needed to have trialled five to six treatments, for at least the minimum recommended duration, incorporating different antidepressants or strategies that allowed for dose optimisation and augmentation or combination of drugs. Use of electroconvulsive therapy (ECT) was not an exclusion criterion. However, ECT scores 3 points on the MGH-TRD, and since most patients receiving ECT will also have had at least two antidepressants (often with dose optimisation and augmentation), few patients who received ECT would have scored lower than our maximum cutoff score of 10. Of the 165 randomly assigned patients, just seven (4%) had received ECT.

This sample, in which 70 (42%) patients were from primary care and most of the 95 (58%) patients who were from secondary care were outpatients, is very different from that in the exclusively inpatient study of metyrapone augmentation of conventional antidepressants by Jahn and colleagues.[8] The extent of treatment resistance is not described for the patients included in their study. Since recruitment in their study was based on the patients being acutely unwell and requiring admission to a hospital or psychiatric unit, the patients in that study might have been less treatment resistant than those in the ADD study, in which treatment-resistant depression was an inclusion criterion. Additionally, the metyrapone group in Jahn and colleagues' study had a slightly higher mean MADRS score at baseline of 31·5 points (SD 7·6) than the 28·1 points (55) in our study. However, the reverse was true of baseline BDI scores (30·0 points [SD 8·4] in Jahn and colleagues' study and 35·6 points [10·9] in our study). High BDI scores and a high BDI-to-MADRS ratio have been associated with poor outcome in patients with treatment-resistant depression.[33] Our patients therefore had clinical characteristics that are associated with worse outcomes, which is consistent with the overall low proportion of patients who achieved a response or remission in our study. These factors might explain the differences in findings between Jahn and colleagues' study and our study.

Several limitations should be considered in relation to our study. Although the trial did not reach its original target of 90% power, it achieved 84% power with respect to the primary outcome measure. In the binary outcomes of response and remission, the very wide CI suggests that the study is not adequately powered to detect differences in these measures of outcome, although response and remission rates were almost identical in the two groups. The 95% CI of the difference in MADRS scores between groups suggests that we cannot exclude an advantage to metyrapone of 3·5 points (or a disadvantage of 2·5 points). Therefore, although the results of this study do not support the efficacy of metyrapone, they cannot exclude a small effect (3·5 points, an effect size of 0·3). However, the prespecified analysis of only patients defined as adherent to treatment supports the interpretation that metyrapone is not efficacious in this population. This analysis was based on week 1 endocrine data and so some patients who were adherent to metyrapone up to that point might not have remained so for the subsequent 2 weeks of treatment. We did not assess the extent of adherence in the placebo group. Attrition in the follow-up phase was somewhat higher in the metyrapone group than in the placebo group, but this is unlikely to have substantially affected the primary clinical outcome measure since the difference in attrition was most marked after week 5. Nevertheless, we want to emphasise that the results of the study show no evidence of efficacy rather than showing evidence of no efficacy.

The assumption made in the study was that clinical effects on depression would be detectable after only 3 weeks of treatment with metyrapone. However, apart from Jahn and colleagues' study,[8] no empirical evidence confirms this assumption, and we cannot exclude that longer treatment with metyrapone could have had a positive effect. However, evidence suggests that antidepressant treatments start to work during the first week of treatment, and separation between the active and placebo groups is seen early on, even though a statistical difference might not occur for several weeks.[34] We saw no indication of this early effect occurring in our study (figure 3); indeed, patients in the metyrapone group had less improvement at the end of treatment than did patients in the placebo group, making it unlikely that extending treatment would have had a benefit.

The main conclusion is that in the population of patients with depression that we studied, the addition of metyrapone to standard serotonergic antidepressants was not efficacious and therefore cannot be recommended as a treatment option for treatment-resistant depression. A question remains as to why the ADD study was negative when an effect of antiglucocorticoid treatment is supported by preclinical data[32] and by Jahn and colleagues' previous RCT of metyrapone augmentation.[8] The negative finding might be related to the nature of the patients studied, as discussed already, or their relative absence of HPA axis dysfunction. Chronic depression has been shown to be associated with normal HPA axis function.[35] The initial hypercortisolaemia of depression might normalise with time in patients who continue to have symptoms; hence, normal cortisol concentrations might be a result or a cause of chronic treatment-resistant depression. This is an important issue for future research to clarify. Additionally, despite substantial heterogeneity between different patient subgroups, evidence for HPA axis dysfunction in patients with depression is available.[36]

HPA axis genes also seem to be central to the gene–environment interactions linking well established causal factors, such as early life trauma, with the development of depression,[37] as well as the genetic and epigenetic factors underlying the stress-diathesis model of depression.[38] Therefore, further exploration of treatments targeting the HPA axis for the prevention and treatment of depression is needed. For example, investigation of the efficacy of metyrapone augmentation in patients with acute depression would be interesting, particularly those with measurable hypercortisolaemia.

Contributors

All authors reviewed, revised and approved the final version of the manuscript. RHM-W was a co-applicant for the funding for the study, a principal investigator (PI) for the Newcastle site, and was involved in design of the study, particularly the electroencephalography aspects of the trial, and recruitment. RHM-W wrote the first draft of the report and incorporated comments from all other authors into the final version. IMA was a co-applicant for the funding for the study, a PI for the Manchester site, and was involved in the design of the study and recruitment. AF was a senior research associate for the study and analysed the hypothalamic–pituitary–adrenal axis data. PG reviewed all antiglucocorticoid treatments before the study and was involved in study conduct throughout. HCRG was a co-applicant for the funding for the study, a PI for the Newcastle site, and was involved in design of the study and recruitment. PMH was a co-applicant for the funding for the study, a PI for the Manchester site, and was involved in design of the study and recruitment. TH was a co-applicant for the funding for the study, a PI for the Leeds site, and was involved in design of the study and recruitment. AJL was a co-applicant for the funding for the study, a PI for the Newcastle site, and was involved in the design of the imaging components of the study. CM did all the statistical analyses. EM was a co-applicant for the funding for the study, a PI for the Newcastle site, and was involved in the design of the study and its protocols and governance. SP was a co-applicant for the funding for the study, a PI for the Newcastle site, and was involved in the design and supervision of the endocrine components of the study. NS was a PI for the Bradford site and was involved in the design of the study and recruitment. BNPS was a PI for the Durham and Teesside site and was involved in the design of the study and recruitment. NS was a co-applicant for the funding for the study and designed and oversaw all the statistical analyses. JW was a co-applicant for the funding for the study, a PI for the Newcastle site, and was involved in design of the study and recruitment, and liaison with the Mental Health Research Network. FHW was a co-applicant for the funding for the study, a PI for the Newcastle site, and was involved in the design of the study and recruitment. INF was the lead applicant for the funding for the study and the chief investigator. SW was a co-applicant for the funding for the study, a PI for the Newcastle site, and was involved in design of the study, particularly in the reviewing of its endocrine aspects, and recruitment. The ADD study team were involved in a range of activities, mainly recruitment, data collection, and data entry.

Declaration of interests

None of the authors, or members of the ADD study team, have any financial relationship with companies that manufacture or sell metyrapone. Several of the authors have, or had, financial relationships with pharmaceutical companies manufacturing or selling psychotropics within the last 3 years, as declared. These include: RHM-W—AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, Ferrer, Janssen-Cilag, Lundbeck, MyTomorrows, Otsuka, Pfizer, Pulse, Roche, Servier, SPIMACO, and Sunovian; IMA—Alkermes, Lundbeck, Lundbeck/Otsuka, and Servier; HCRG—Bristol-Myers Squibb, Desitin, Gedeon Richter, Lundbeck, Otsuka, and Hoffman-La Roche; PMH—Bristol-Myers Squibb, Eli Lilly, Janssen, Lundbeck, Otsuka, Roche, Servier, Sunovian, Takeda, Teva, and Quantum Pharmaceuticals; SP—Merck Serono and Viropharma; BNPS—Bristol-Myers Squibb, Eli Lilly, and Pfizer. AJL was a co-investigator of a study funded by EnVivo Pharmaceuticals. All other authors declare no competing interests.

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