Metyrapone is an effective adjuvant treatment for major depression

Jahn H, Schick M, Kiefer F, *et al*. Metyrapone as additive treatment in major depression: a double-blind and placebo-controlled trial. *Arch Gen Psychiatry* 2004;**61**:1235–44.

Q Does metyrapone potentiate the effects of antidepressants in people with major depression?

METHODS

Design: Randomised controlled trial.

Allocation: Concealed.

Blinding: Double blind (both assessors and participants blinded to treatment).

Follow up period: Five weeks.

Setting: Specialised wards for affective disorders at the University Hospital, Hamburg.

Patients: Sixty three people aged 18–75 years with a diagnosis of major depressive disorder (DSM-IV); a score of 18 or over on the Hamilton Rating Scale for Depression, 21 item version (HAMD-21); and free from antidepressant, antipsychotic, mood stabilising, and other medication for at least three days before the study began. Participants were excluded if they had any other axis I psychiatric disorders or other serious medical conditions, or if they were pregnant or breast feeding.

Intervention: Participants were randomised to receive either oral metyrapone (250 mg four times a day) or placebo for three weeks in addition to treatment with either nefazodone (300–400 mg/day) or fluvoxamine (150–200 mg/day). Addition of metyrapone or placebo was stopped after three weeks and standard antidepressant treatment continued for a further two weeks. After baseline, assessments occurred on day 3 and at the end of each week of the study.

Outcomes: Primary outcomes were number of responders to treatment (30% reduction in HAMD-21 score at three weeks and 50% reduction from baseline in HAMD-21 score at five weeks); time to treatment action (when at least 20% reduction in HAMD-21 scores had occurred); and endocrine levels (changes in concentrations of ACTH, cortisol, 11-deoxycortisol, and DHEA).

Patient follow up: 89% at five weeks.

MAIN RESULTS

At both three and five weeks, significantly more people had responded to treatment in the metyrapone group compared with the placebo group (>30% reduction in HAMD-21 at three weeks: 20/33 (60%) with metyrapone *v* 13/30 (43%) with placebo; $p = 0.031$, >50% reduction in HAMD-21 at five weeks: 10/33 (30%) with metyrapone *v* 10/30 (33%) with placebo; $p = 0.047$). Participants taking metyrapone in addition to standard antidepressants responded to treatment faster than those taking placebo (days to 20% improvement in HAMD score by 50% of participants: seven days with metyrapone *v* 14 days with placebo; $p<0.006$). Addition of metyrapone to antidepressant treatment lead to significantly greater plasma concentrations of ACTH, 11-deoxycortisol, and DHEA compared with addition of placebo ($p<0.05$). Cortisol concentrations were not significantly higher with metyrapone ($p = 0.052$). Significantly more headaches and nausea were reported in those taking metyrapone than placebo (headaches; $p = 0.048$, nausea; $p = 0.037$).

CONCLUSIONS

Addition of metyrapone to treatment with antidepressants improves symptoms of depression and accelerates the action of antidepressant drugs.

NOTES

Participants were stratified by sex and by antidepressant (nefazodone or fluvoxamine). Analysis of endocrine parameters was not done on an intention to treat basis.

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Sources of funding: one author was supported by a fellowship from the Graduiertenkolleg 255 (Deutsche Forschungsgemeinschaft, Bonn, Germany).

Commentary

It is widely believed that depressive illness is often provoked and may be perpetuated by stress. Despite this our physical treatments for the disorder, all of which were discovered serendipitously, do not directly target stress hormones. The study by Jahn *et al* builds on the notion that drugs acting on the stress hormone system may have potential antidepressive effects in major depressive disorder. Using intention to treat analysis, a higher proportion of participants receiving metyrapone showed a positive treatment response at day 21 and at day 35 compared with those receiving placebo. Participants treated with metyrapone also showed an earlier onset of antidepressive action.

This paper is very timely and builds on advances from preclinical research, which show that stress hormones impair the ability of antidepressants to increase forebrain 5-HT,[1] and clinical observations that suggest stress hormone antagonists may be antidepressant.[2] Large scale follow up studies are required to confirm the safety and efficacy of this treatment before this approach can be adopted widely. Nevertheless, this result is encouraging to clinicians and adds to the body of work which suggests that drugs targeting the stress hormone system may be potentially helpful treatments for depression.

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1 Gartside SE, Leitch MM, Young AH. Altered glucocorticoid rhythm attenuates the ability of a chronic SSRI to elevate forebrain 5-HT: implications for the treatment of depression. *Neuropsychopharmacology* 2003;**28**:1572–8.
2 Young AH, Gallagher P, Watson S, *et al*. Improvements in Neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology* 2004;**29**:1538–45.