Metyrapone as Additive Treatment in Major Depression

A Double-blind and Placebo-Controlled Trial

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Background: Inhibitors of steroid synthesis have been reported to exert antidepressive effects, according to preliminary findings.

Objective: To test whether the addition of metyrapone to standard antidepressants induces a more rapid, more efficacious, and sustained treatment response in patients with major depression.

Design: Double-blind, randomized, placebo-controlled trial.

Setting: Hospitalized care.

Patients: Sixty-three inpatients with a DSM-IV diagnosis of major depression and a baseline score 18 points or higher on the Hamilton Rating Scale for Depression.

Interventions: Random allocation to 2 treatment groups receiving either placebo or metyrapone (1 g/d) for the first 3 weeks during a 5-week treatment with standard serotonergic antidepressants (nefazodone or fluvoxamine).

Main Outcome Measures: Primary outcome criteria were the number of responders and the time to onset of action. Responder rates were considered twice after 3 and 5 weeks with a definition of treatment response as 30% and 50% reduction, respectively, of baseline Hamilton Rating Scale for Depression scores. Onset of action was defined as the time point at which at least a 20% reduction of baseline Hamilton Rating Scale for Depression scores occurred.

Results: Using intention-to-treat analysis, we found that a higher proportion of patients receiving metyrapone showed a positive treatment response at day 21 (23 of 33 patients) and at day 35 (19 of 33 patients) compared with placebo patients (day 21: 13 of 30 patients; Fisher exact P = .031; day 35: 10 of 30 patients; Fisher exact P = .047). The clinical course of patients treated with metyrapone showed an earlier onset of action (Kaplan-Meier analysis; log-rank test P < .006) beginning in the first week. The plasma concentrations of corticotropin and deoxycortisol were significantly higher during metyrapone treatment (multivariate analysis of covariance, P < .05), whereas cortisol remained largely unchanged. Metyrapone treatment was well tolerated without serious adverse effects.

Conclusions: Metyrapone is an effective adjunct in the treatment of major depression, accelerating the onset of antidepressant action. A better treatment outcome compared with standard treatment and a sustained antidepressive effect were observed.

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Our understanding of the neuroendocrine pathophysiology of depression has made significant progress in recent years, which should help to develop new remedies. Alterations of the hypothalamic-pituitary-adrenal (HPA) axis are the most consistent pathological endocrine findings in depression. The key regulator of HPA axis activity, corticotropin-releasing hormone (CRH), is increased in depression. The effects of CRH are modulated by neuropeptides and monoaminergic transmitters. The exaggerated HPA function in depression appears to be also the result of an impaired glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) feedback control. Whether HPA-axis hyperactivity is initially caused by a CRH overdrive resulting in MR/GR dysfunction or vice versa by dysregulation at another level is yet undecided.

Hence, attempts have been made to treat depression by directly targeting HPA-axis activity. Currently, 3 major pathways are investigated: (1) administration...
of CRH antagonists like R121919,36,37, (2) administration of GR antagonists like RU 486 or Org 3451718-21, and (3) treatment with steroid-synthesis inhibitors like metyrapone.22

Preclinical studies nurture the hope for new therapeutic strategies based on steroid-synthesis inhibition,23 but clinical data about the antidepressive efficacy of these compounds are mainly confined to small open-label trials and case reports.24-30 First reports date back to the 1970s when Jeffcoate et al31 treated depressed Cushing patients with metyrapone. In 1991, Murphy32 reported the first case of a successfully treated depressed patient. One single-blind crossover trial of metyrapone and 2 small double-blind studies on ketoconazole in the treatment of depression have been published.33-35

Our aim was to conduct the first prospective, randomized, placebo-controlled, and double-blind clinical trial of metyrapone as additive treatment in depression. Metyrapone was preferred because this compound inhibits selectively the 11β-hydroxylase and the 11β-hydroxysteroid-dehydrogenase type 1 (11β-HSD-1),36,37 thereby exerting direct effects within the central nervous system.38 The additive approach was applied because the intended inclusion of severely depressed patients made a pure placebo group ethically challenging.39 Furthermore, the continuous use of an antidepressant allowed a standardized follow-up after the double-blind period.

The questions to be answered were whether metyrapone exerts potentiating effects during a standard antidepressant therapy and whether an earlier onset of action and an improved overall and sustained treatment response can be achieved. Because GR/MR distribution as well as 11β-HSD-1 activities are subject to sexual dimorphism in humans, the sample was prospectively stratified for sex and balanced for treatment with 2 selected serotonergic antidepressants.

Figure 1. Flow chart of the study recruiting and randomization procedures.
PSYCHOPATHOLOGIC ASSESSMENTS

Following the assessment of inclusion and exclusion criteria on day 0, data were collected, including information about the history of illness and sociodemographic data concerning family and social, psychological, and medical problems. The psychopathometric assessments were performed at days 0, 3, 7, 14, 21, 28, and 35 between 10 AM and 1 PM. External ratings were the HAMD-21,44 the Montgomery-Asberg Depression Rating Scale (MADRS),43 and the Clinical Global Impressions scale.46 Self-rating instruments were the Beck Depression Inventory (revised 21-item version)47 and the Zung Self-Rating Depression Scale (20-item version).48 Adverse effects were assessed by a German adaptation of the Udvalg for Kliniske Undersøgelser (UKU) side effect scale.49 External rating instruments were applied by 2 authors (H.J. and M.S.), who had training sessions to assure high quality and interrater reliability.

BIOCHEMISTRY

Blood samples were drawn between 8:30 and 9:30 AM on days 0, 1, 3, 7, 10, 14, 21, 28, and 35 for clinical chemistry, endocrine parameters (cortisol, 11-deoxycortisol, corticotropin [ACTH], and dehydroepiandrosterone [DHEA]), and drug monitoring of fluvoxamine and nefazodone during the steady-state phase (data given for day 14).

Endocrine parameters were determined by commercial radioimmunoassays with coated tube techniques (cortisol, 11-deoxycortisol, DHEA; DRG-Instruments, Marburg, Germany) or immunoradiometrically (ACTH; Nichols Institute, San Juan Capistrano, Calif). The cross-reactivity of cortisol determinations with 11-deoxycortisol was less than 0.1%.

Fluvoxamine and nefazodone were determined after automated extraction via column switching by reverse-phase high-performance liquid chromatography using UV detection.50 During the trial, only 1 author (K.W.) had access to laboratory data to control for clinically relevant changes.

STATISTICS

The intention-to-treat sample of 63 patients was estimated to be sufficient to detect large effect sizes with a power of 85% at an α level of .05. For the statistical evaluation of outcome criteria, the intention-to-treat sample of 63 patients with the dropouts classified as nonresponders has been taken into consideration, whereas for hormones, the statistical evaluation was based on those 60 patients who actually received medication during the study. Missing values were substituted using a last observation carried forward approach.

A priori primary outcome criteria were (1) 2 psychometric criteria defined by the number of responders and the time to onset of action and (2) the course of concentrations of ACTH, cortisol, 11-deoxycortisol, and DHEA. The number of responders was considered twice after 3 and 3 weeks by defining the treatment response as a 30% and 50% reduction, respectively, from baseline HAMD scores. Onset of action was determined by the survival analytical approach of Stassen,51 which defines the onset of action as the time point at which at least a 20% reduction of baseline HAMD scores occurred. Other psychometric scores, demographic parameters, and adverse effects were considered as secondary variables.

Differences in the responder rates between the treatment groups were tested by Fisher exact test. The other main criterion, the time to onset of action, was analyzed with a Kaplan-Meier survival analysis and embedded log-rank test as described,39 considering dropouts as censored cases.

Multivariate analyses of covariance (MANCOVA) with sex as a covariate were further applied for testing the effects of treatment, antidepressant medication, and time on secondary variables like HAMD and MADRS. According to the underlying data structure, differences between metyrapone and placebo in demographic baseline variables or adverse effects were tested by MANCOVA or nonparametric tests (Fisher exact test or median test). Associations between some variables in the various experimental conditions were tested with the Pearson correlation coefficients. To characterize the study sample on a descriptive level, rates of remission defined as a HAMD score of less than 8 at day 35 were calculated, and a Quitkin pattern analysis based on the Clinical Global Impressions scale to define the time point, when at least a marked improvement was detectable, was performed.51 Also, the relapse rates after week 3, defined as a persistent 20% increase in HAMD scores, and the treatment effect sizes were derived.

For the hormonal variables, sex was considered a covariate. Multivariate analyses of covariance with repeated-measures design were applied to test the effects of treatment and antidepressant medication (between-subject factors with 2 levels: metyrapone or placebo; nefazodone or fluvoxamine) and time (a within-subject factor with 9 levels) on ACTH, cortisol, 11-deoxycortisol, and DHEA as dependent variables. A complementary statistical evaluation (post hoc analysis) by MANCOVA focused on possible differences in the endocrine parameters between responders and nonresponders at the end of the study (day 35). Response, treatment, and time were considered as influential variables and sex and baseline concentrations as covariables.

In cases of significant factor effects in the MANCOVA, univariate F tests and tests with contrasts were conducted to identify those variables contributing significantly to these effects and to locate the time points of significant differences. As a nominal level of significance, α = .05 was accepted. All post hoc tests (univariate F tests and tests with contrasts) were performed at a reduced level of significance (Bonferroni correction) to keep the type I error less than or equal to 0.05. Measures are given in mean ± SEM unless otherwise stated.

RESULTS

STUDY SAMPLE

Eleven patients of the metyrapone group and 9 of the placebo group received a DSM-IV 296.2x diagnosis, and 22 of the metyrapone-treated and 21 of the placebo-treated patients were classified as recurrently depressed patients (DSM-IV 296.3x). Regarding diagnoses, history of depression (duration of illness, age at time of onset, number of episodes, severity of current episode, and duration of current episode), and baseline psychopathometric scores (HAMD, MADRS, Clinical Global Impressions-Severity Grade scale, Beck Depression Inventory, and Zung Self-Rating Depression Scale), no significant differences between metyrapone and placebo were detected (Table 1 and Table 2). Women had suffered more previous episodes than men. The median for previous episodes in women was 3 (minimum/maximum, 1/21), compared with 2 in men (minimum/maximum, 1/8). Furthermore, the duration of the current index episode prior to study inclusion was longer in men (median, 4 months; minimum/maximum, 1/24 months) than in women (median, 2 months; minimum/maximum, 0.5/19 months).
Table 1. Study Sample

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 30)</th>
<th>Metyrapone (n = 33)</th>
</tr>
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<td>Men, No.</td>
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<td>15</td>
</tr>
<tr>
<td>Women, No.</td>
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<td>18</td>
</tr>
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<td>Fluvoxamine, No.</td>
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<td>18</td>
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<td>Nefazodone, No.</td>
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<td>15</td>
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<td>Age, y, mean ± SD</td>
<td>46.5 ± 13.0</td>
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<tr>
<td>Age at first episode, y (minimum/maximum)</td>
<td>36 (15/61)</td>
<td>53 (10/64)</td>
</tr>
<tr>
<td>Previous episodes, No. (minimum/maximum)</td>
<td>2 (1/16)</td>
<td>2 (1/21)</td>
</tr>
<tr>
<td>Duration of index episode, mo (minimum/maximum)</td>
<td>3.5 (1/24)</td>
<td>3 (0.5/24)</td>
</tr>
</tbody>
</table>

Of the 63 patients randomized, 56 patients completed the trial and 7 patients dropped out. Three dropouts revoked their consent after inclusion and before the treatment was started, and 4 patients left during the study because of adverse effects. Four dropouts were assigned to the placebo group, 3 to the metyrapone group, 4 to the fluvoxamine group, and 3 to the nefazodone group. Five of 7 dropouts were women.

With regard to premedication, 2 of 33 patients in the metyrapone group received fluoxetine 4 weeks prior to the inclusion date. Both patients took it for fewer than 10 days. In the placebo group, 1 of 30 patients had taken fluoxetine for a few days 2 weeks before inclusion. In the metyrapone group, 1 patient received nefazodone prior to inclusion and was switched to fluvoxamine because of previous adverse effects; 1 patient received fluvoxamine for 3 days, 11 days before inclusion in the trial. In the placebo group, 1 patient was exposed to fluvoxamine for 1 day, a week before entering the hospital. Regarding data of all antidepressants taken within a 4-week period prior to inclusion as well as lifetime exposure to antidepressants, no differences between the treatment groups were detectable. One patient in each group received a β-blocker in low dose.

PSYCHOPATHOLOGICAL OUTCOME

Considering the main outcome, the responder rates in the metyrapone group at day 21 and day 35 were significantly greater than those in the placebo group. Twenty-three of 33 patients in the metyrapone group vs 13 of 30 patients in the placebo group showed a positive treatment response using the 30% reduction criterion of the HAMD at day 21 (Fisher exact P = .031). At day 35, 19 responders in the metyrapone group vs 10 responders in the placebo group yielded a significantly better response rate and better treatment outcome in the metyrapone group (50% reduction criterion; Fisher exact P = .047). The course of the HAMD scores is shown for both treatments in Figure 2, and the treatment efficacy is similarly detectable with HAMD, MADRS, Beck Depression Inventory, and Zung Self-Rating Depression Scale with effect sizes ranging from 0.37 to 0.73 (Table 2).

Concerning the time to onset of action, the Kaplan-Meier survival analysis (Figure 3) indicated a significantly shorter time to improvement for the metyrapone group than for the placebo group (log-rank test, P < .006). Fifty percent of the metyrapone-treated patients showed early improvement by a HAMD score reduction of at least 20% at day 7. In the placebo group, a 20% improvement was reached by 50% of the patients only at day 14. At day 35, all patients from the metyrapone group showed at least a 20% improvement, whereas in the placebo group, 5 of 30 did not show any improvement. The lower panel of Figure 3 depicts the Quitkin pattern of the Clinical Global Impressions scale scores also indicating a faster onset of action induced by metyrapone. About the same proportion of patients in both groups showed no marked improvement on the Clinical Global Impressions scale until the study’s end (metyrapone, 6/33; placebo, 10/30). The remission rates at week 5, defined as a total HAMD score of less than 8 points, were 10/33 in the metyrapone group and 7/30 in the placebo group. The relapse rate after day 21, defined as a persistent 20% increase in HAMD scores to day 35, was very low and similar for the metyrapone group (3/33) and the placebo group (3/30). Analysing the influence of treatment, antidepressant medication, and time on the sum scores of the HAMD and MADRS, with sex and baseline scores as covariates, we observed significant effects of treatment (F[3, 65] = 4.52; significance of F = 0.02) and time (F[10, 47] = 6.16; significance of F < 0.001) on each of the considered scales (univariate F tests, P < .05). Fluvoxamine and nefazodone did not significantly differ in their antidepressant efficacy, neither alone nor in interaction with the factors treatment and time. Tests with polynomial contrasts revealed significantly stronger reductions of HAMD (F[1, 36] = 42.63; significance of F < 0.001) and MADRS (F[1, 36] = 52.75; significance of F < 0.001) scores by metyrapone compared with placebo at each time point until day 35 (Figure 2).

The MADRS scores showed an earlier and more pronounced reduction than the HAMD scores in the metyrapone group, verifying the statement that the MADRS is sensitive to early antidepressant actions. Item 3 (inner tension) and item 10 (suicidal ideation) showed especially fast reductions for patients treated with metyrapone.

ENDOCRINE MEASURES

The MANCOVA of the endocrine data showed significant main effects of treatment (F[4, 52] = 8.05; significance of F = 0.05), time (F[32, 1642] = 9.18; significance of F = 0), and antidepressant medication (F[1, 52] = 3.61; significance of F = 0.02), as well as a significant interaction effect of all 3 factors (F[32, 1642] = 1.83; significance of F = 0.003) attributed to all hormones except DHEA (univariate F tests, P < .05). Subsequent univariate F tests showed that cortisol showed slightly higher concentrations in the fluvoxamine group after commencing treatment. Both antidepressants did not show different effects on ACTH, 11-deoxycortisol, and DHEA. By analyses of simple effects of antidepressant medication within the factors treatment and time, significant differences did not emerge at the various time points of the study for any of the endo-
crine variables. Therefore, it is not necessary to differentiate between the antidepressants regarding the endocrine variables. Also, sex as a covariate did not significantly influence the investigated hormones.

By analysis of the simple effects of treatment and time, we found that during metyrapone treatment, ACTH, 11-deoxycortisol, and DHEA showed significant elevations of plasma concentrations compared with baseline (test with polynomial contrasts; $P$ values for a second-degree polynomial $<.05$) (Table 3). These elevations were already significant at day 1 for 11-deoxycortisol, ACTH, and DHEA. These hormones were also significantly increased during the entire 3-week treatment period compared with placebo (tests with contrasts, $P<.05$). For cortisol, there was a trend toward slightly higher cortisol concentrations ($P$ values for a first-degree polynomial $=.052$).

After discontinuation of metyrapone, the concentrations of ACTH, 11-deoxycortisol, and DHEA decreased reasonably, and, apart from still-increased ACTH concentrations at day 35 in the metyrapone group, no significant differences from placebo remained (test with contrasts, $P<.05$). During placebo, analyses of time effects also showed slightly increased ACTH and 11-deoxy-
cortisol concentrations compared with baseline, which were similar for fluvoxamine and nefazodone. Cortisol for the whole placebo group and DHEA concentrations remained largely unchanged.

With metyrapone, a significant correlation between ACTH and 11-deoxycortisol plasma concentrations emerged ($r_{beta}=0.953; P<.001$ at day 21), and a similar but less robust correlation was found between ACTH and DHEA ($r_{beta}=0.518; P<.01$ at day 21). No significant correlations between these parameters appeared in the placebo group. Also, no significant correlation was detected between ACTH and cortisol levels during metyrapone administration as evidence of a sufficient enzyme block.

**RESPONSE AND ENDOCRINE VARIABLES**

Comparing responders and nonresponders in the metyrapone group, a positive treatment response after 5 weeks appeared to be associated with greater elevations of ACTH and 11-deoxycortisol plasma concentrations (Table 4) (Figure 4), although this difference failed to reach statistical significance in a post hoc MANCOVA.

There was no significant association between basal cortisol levels at day 0 and treatment outcome at day 21 or day 35, although baseline cortisol concentrations were

### Table 2. Psychometric Data*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 30)</th>
<th>Metyrapone (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End Point</td>
</tr>
<tr>
<td>HAMD-21</td>
<td>28.0 ± 5.7</td>
<td>17.5 ± 11.0</td>
</tr>
<tr>
<td>MADRS</td>
<td>34.8 ± 6.4</td>
<td>21.4 ± 12.0</td>
</tr>
<tr>
<td>CGI-SG</td>
<td>6.1 ± 0.7</td>
<td>5.2 ± 1.5</td>
</tr>
<tr>
<td>BDI</td>
<td>31.3 ± 7.8</td>
<td>22.9 ± 11.2</td>
</tr>
<tr>
<td>SDS</td>
<td>72.3 ± 8.1</td>
<td>64.3 ± 11.1</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD.

**Abbreviations:** BDI, Beck Depression Inventory; CGI-SG, Clinical Global Impressions-Severity Grade scale; HAMD-21, Hamilton Rating Scale for Depression, 21-item version; MADRS, Montgomery-Asberg Depression Rating Scale; SDS, Zung Self-Rating Depression Scale.
higher for the responders taking metyrapone. No difference emerged in the response rate by splitting the patient sample at a cutoff of greater than 30 μg/dL of cortisol at baseline. Higher basal cortisol concentrations were not associated with a more favorable outcome during metyrapone treatment.

SAFETY AND TOLERABILITY

The metyrapone treatment was well tolerated, and no serious adverse effects occurred. Minor adverse effects had a low incidence (Table 5) and were predominantly reported by women (mean±SEM adverse events reported: women, 3.32±0.47; men, 2.55±0.40). Only nausea and headaches were reported significantly more often during metyrapone treatment compared with placebo (Fisher exact P=.037 and P=.048, respectively). Adverse effects were mainly due to the serotonergic antidepressant treatment, especially in the first 2 weeks. Patients receiving fluvoxamine reported more nausea and restlessness, while patients taking nefazodone complained more frequently of a dry mouth. We did not observe any alterations in general clinical chemistry parameters.

COMPLIANCE AND COMEDICATION

All patients taking metyrapone showed significant elevations of 11-deoxycortisol; therefore, full compliance can be assumed. At the end of the treatment course, both raters and patients guessed whether placebo or metyrapone had been taken. An association analysis (r coefficient) showed no agreement between raters’ and patients’ guesses and the identity of the given medication.

Plasma concentrations of both antidepressants showed that all patients were compliant with the respective treatment. Mean±SEM plasma concentration at steady state for nefazodone was 691±23 ng/mL, for the metabolite meta-chlorophenylpiperazine (mCPP) 41±1.6 ng/mL, and for fluvoxamine 77±3.4 ng/mL. No effect of metyrapone on these concentrations was detected, and no associations between plasma concentrations of antidepressants and outcome parameters emerged.

Lorazepam was restricted to the first 8 days (day 0 to day 7) of the study, according to our protocol. Thirteen of 30 patients in the placebo group (mean±SEM dose, 1.18±0.24 mg/d of lorazepam) and 11 of 33 patients in the metyrapone group (mean±SEM dose, 1.47±0.28 mg/d of lorazepam) reported more frequently of a dry mouth. We did not observe any alterations in general clinical chemistry parameters.

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**Table 3. Endocrine Parameters for the Metyrapone and Placebo Groups**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Treatment</th>
<th>Day Within Study Phase</th>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Corticotropin, pg/mL</td>
<td>Metyrapone</td>
<td>5.0±0.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.5±0.6</td>
<td>6.8±1.3</td>
</tr>
<tr>
<td>Cortisol, μg/dL</td>
<td>Metyrapone</td>
<td>28.7±1.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>26.3±0.8</td>
<td>24.6±1.7</td>
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<tr>
<td>Deoxycortisol, ng/mL</td>
<td>Metyrapone</td>
<td>1.8±0.1</td>
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<tr>
<td>Placebo</td>
<td>2.6±0.2</td>
<td>5.4±1.2</td>
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<tr>
<td>Dehydroepiandrosterone, ng/mL</td>
<td>Metyrapone</td>
<td>6.7±0.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.2±0.4</td>
<td>6.0±0.6</td>
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</table>

Abbreviations: N, nonresponder; R, responder.

*Data are presented as mean±SEM.

**Table 4. Endocrine Parameters for the Responder and Nonresponder Fractions of the Metyrapone and Placebo Groups**

<table>
<thead>
<tr>
<th>Hormone</th>
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<th>Faction</th>
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<th>1</th>
<th>3</th>
<th>7</th>
<th>10</th>
<th>14</th>
<th>21</th>
<th>28</th>
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<tr>
<td>Corticotropin, pg/mL</td>
<td>Metyrapone</td>
<td>R</td>
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<tr>
<td>Cortisol, μg/dL</td>
<td>Metyrapone</td>
<td>R</td>
<td>6.3±1.6</td>
<td>6.3±1.7</td>
<td>11.3±2.2</td>
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<td>Deoxycortisol, ng/mL</td>
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<td>Dehydroepiandrosterone, ng/mL</td>
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</table>

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lorazepam) received lorazepam. No association between administration of lorazepam and treatment response emerged.

**COMMENT**

Major results of this study were that the addition of metyrapone to a standard serotonergic antidepressant treatment led to a significantly better overall treatment outcome and a significantly more rapid onset of therapeutic action. These beneficial effects outlasted the 21-day treatment period independently of the serotonergic antidepressant used, ie, nefazodone or fluvoxamine.

Our study is the first placebo-controlled, double-blind trial of metyrapone used as an augmentation agent in the treatment of patients with major depression. Our findings validate the results of an earlier open-label study and the only other placebo-controlled, single-blind crossover study on metyrapone. This latter study is not directly comparable to ours because 30 mg/d of hydrocortisone, which itself has psychotropic effects, was co-administered. Antidepressant effects were also observed applying the cortisol-synthesis inhibitor ketoconazole in a controlled study with 20 depressed patients, where merely the cortisol-synthesis inhibitor ketoconazole in a controlled study with 20 depressed patients, where merely 3 hypercortisolemic patients improved. Malison et al found only limited efficacy in treatment-refractory major depression. In our substantially larger sample, metyrapone enhanced antidepressant efficacy independently of eucortisolemic or hypercortisolemic basal morning plasma cortisol concentrations.

As expected, the major findings were that metyrapone intervened with cortisol synthesis, inducing marked increases of plasma ACTH, the cortisol precursor 11-deoxycortisol, and the neurosteroid DHEA. During metyrapone treatment, we did not observe significant decreases in basal morning plasma cortisol concentrations, which is in line with the findings of Raven et al. These observations can be explained by the dosage regimen, administering metyrapone during daytime until the nadir of cortisol secretion, when HPA-axis feedback mechanisms are especially responsive. A considerable rebound of plasma cortisol concentrations occurs in the morning hours, driven by the elevated ACTH concentrations. During placebo, both antidepressants, which are known to interact with the Cytochrom P450 system, increased ACTH and 11-deoxycortisol concentrations compared with baseline, while cortisol for the whole group and DHEA remained largely unchanged. However, no differential interaction of both antidepressants with metyrapone was detected.

No apparent correlation emerged between basal plasma cortisol concentrations before starting metyrapone treatment and the overall outcome. The responders in the metyrapone group had insignificantly higher cortisol concentrations, but morning cortisol concentrations show a large variability and are a weak measure of overall HPA-axis activity. Patients showing improvement with metyrapone developed larger increases of ACTH and 11-deoxycortisol compared with nonresponders, although this effect did not reach significance. One explanation would be that patients taking metyrapone improved according to the extent of steroid-synthesis inhibition. However, leaner patients who received higher average doses of metyrapone per kg showed the same differences in treatment response, and no correlation with the body weight index emerged (data not shown). Hence, our findings in the responder fraction may reflect a more sensitive hypothalamic or hippocampal feedback, leading to a reset of the circadian rhythm of the HPA axis or unmasking of central CRH overdrive.

Metyrapone also significantly increased the plasma concentrations of the cortisol precursor 11-deoxycortisol, which itself has psychotropic effects, and of the neuroactive steroid DHEA, which exerts antiglucocorticoid, anxiolytic, and antidepressive actions. Neuroactive steroids act on \( \gamma \)-aminobutyric acid A and progesterone receptors in humans. Metyrapone induces profound long-term changes of synthesis and concentrations of such steroids, and a correlation between a reduction in MADRS scores and an increase of neuroactive urinary and plasma steroids has been found. Whereas Raven et al did not find changes in the urinary secretion of DHEA, we observed significant elevations of plasma DHEA.

Although the antidepressive and neuroendocrine effects of metyrapone are clearly demonstrated by our study,

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**Table 5. Frequencies of Adverse Effects**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Metyrapone Group (n = 32)</th>
<th>Placebo Group (n = 28)</th>
<th>Fisher Exact P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal discomfort</td>
<td>5</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>3</td>
<td>.037</td>
</tr>
<tr>
<td>Headaches</td>
<td>11</td>
<td>4</td>
<td>.048</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>10</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Nervousness/agitation</td>
<td>6</td>
<td>6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.
the mechanisms of actions are still far from elucidated. Besides the reset of HPA-axis activity and the enhanced release of neuroactive steroids, we surmise that alternative mechanisms cooperate to yield the therapeutic effects. Steroid actions and feedback regulation are determined by their tissue concentrations, which are largely regulated by prerreceptor metabolism. The enzyme 11β-HSD regulates the steroid access to receptors, catalyzing the conversion of active 11-hydroxy-glucocorticoids like cortisol into their inactive keto-forms. One form, the 11β-HSD-1, is widely expressed in the hypothalamus, hippocampus, cerebellum, and neocortex, maybe acting as a tissue-specific modulator of glucocorticoid action. This enzyme’s reaction is bidirectional, and in intact neurons the reduced nicotinamide-adenine dinucleotide phosphate (NADPH)–dependent reduction of 11-ketosteroids is the predominant reaction, regenerating active glucocorticoids in neuronal target cells.99 Whereas ketoconazole mainly blocks steroid synthesis at the adrenal level, metyrapone crosses the blood-brain barrier63 and inhibits the conversion of the endogenous precursor 11-deoxycortisol to cortisol both at the adrenals and in the brain, acting on the 11-beta-hydroxylase. In addition, metyrapone blocks the 11-oxoreductase activity of the 11β-HSD-1 either directly or indirectly by increased formation of endogenous inhibitors, eg, progestosterone-derivates. Thus, metyrapone is able to decrease cortisol concentrations in the brain independently of circulating steroid levels. This potential to decouple central nervous tissues from peripheral steroid concentrations has been demonstrated in humans, and behavioral consequences of altered hippocampal 11β-HSD-1 activity were recently shown in an animal model.

A specific site of action of metyrapone could be the hippocampus, where 11β-hydroxylase and 11β-HSD-1 are colocalized with MR. Inhibition of cortisol synthesis in this region would deplete MR from their ligands, and MR should subsequently be up-regulated. This regulatory sequel can be demonstrated for many antidepressant drugs, which increase the binding capacity and gene expression of MR in the hippocampus in the rat. Increases of hippocampal MR levels precede the decrease in CRH messenger RNA in the hypothalamic paraventricular nucleus and the readjustment of the HPA-axis activity. Complementarily, the MR antagonist spironolactone hampered antidepressive effects of amitriptyline in humans. Therefore, metyrapone might assist a faster restoration of MR function, which accelerates the attainment of new allostatic equilibrium.

The reduced occupation of GR and MR by cortisol in the hippocampus could consecutively accelerate the up-regulation of 5HT-1A receptors, which are essential for the action of serotonergic antidepressants. A reduced availability of cortisol in the central nervous system, especially during the evening, could directly promote the reset in positive feedback loops. Such cortisol-dependent circuits are demonstrated in several brain areas, like the amygdala and hypothalamus and notably the hippocampus.

Furthermore, the neogenesis of neurons within the hippocampus may be involved in the etiology of depression. Preliminary experiments show that metyrapone increases the number of new cells in the gyrus dentatus of the hippocampal formation in mice, maybe partly mediated by neurosteroids like DHEA. Moreover, metyrapone induces c-fos expression in limbic regions. Again, a restoration of hippocampal feedback onto HPA-axis activity could be assisted.

Several mechanisms are potentially responsible for the antidepressant efficacy of metyrapone. Shortcomings of our study were that HPA-axis activity was characterized merely by morning cortisol concentrations. Seemingly eu cortisolemic patients frequently show other signs of HPA dysregulation in depression. More sensitive tests, like the combined dexamethason suppression test (DST)/CRH challenge, would allow a more refined analysis of hidden perturbations. The wash-out phase was short because our severely ill patients needed acute treatment. Although steroid-synthesis inhibitors are not quite ready for routine clinical application, the findings of this study clearly warrant further studies aimed at identifying subgroups of depressed patients who will benefit most from this approach and surrogate markers to find the optimal dose regimen.

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