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BRIEF REPORTS

Rapid Reversal of Psychotic Depression Using Mifepristone

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The rationale for treating psychotic major depression with glucocorticoid receptor (GR) antagonists is reviewed. Five patients with psychotic major depression were given 600 mg of mifepristone in a 4-day, double-blind, placebo-controlled crossover study. All the patients completed the protocol and adverse effects were not observed or reported. All of the five patients showed substantial improvements in their Hamilton Rating Scale for Depression scores while they were receiving mifepristone, and four of the five patients showed substantial improvement in their Brief Psychiatric Rating Scale scores. Little, if any, improvement was seen with placebo. These preliminary results suggest that short-term use of GR antagonists may be effective in the treatment of psychotic major depression and that additional study, perhaps using higher doses or more treatment days, seems warranted. (J Clin Psychopharmacol 2001;21:516–521)

THERE IS STRONG evidence to support the theory that psychotic major depression (PMD) is a distinct syndrome.[1] Statistically significant differences between psychotic and nonpsychotic major depression have been noted along many axes, including presenting features,[2–7] biology,[8] familial transmission,[9, 10] course and outcome,[11] as well as response to treatment.[5, 6, 12–16]

Many centers have reported specific abnormalities in the hypothalamic-pituitary adrenal (HPA) axis activity of patients with psychotic depression. Patients with PMD are among those with the highest rates of nonsuppression on the dexamethasone suppression test (DST),[8–18] and many of them have markedly elevated postdexamethasone cortisol levels. A recent meta-analysis of 12 different studies, with a combined sample size of 700 patients, indicated that when inpatient status was controlled, psychosis, but not melancholic symptoms, were associated with DST nonsuppression rates.[17] Significant elevations in 24-hour measures of urinary free cortisol levels have also been observed in patients with psychotic major depression.[18]

Patients with nonaffective psychoses, such as schizophrenia, do not show high DST nonsuppression rates.[19, 20] Patients with PMD respond differently to pharmacologic therapies in comparison with patients with nonpsychotic major depression.[5, 6, 12–16] Important findings include a very low placebo response rate in PMD, as well as a poor response to antidepressant therapy alone.[21, 22] Patients with PMD do respond to electroconvulsive therapy, or a combination of currently available antipsychotic and antidepressant medication.[4, 7, 23] However, both of these methods act relatively slowly, which results in an interim period of high morbidity.

The progesterone-receptor antagonist mifepristone (17β-hydroxy-11β-(4-dimethylaminophenyl)17α-(1 propynyl) estra-4,9-dien-3-one) is also, at higher concentrations, an effective antagonist of glucocorticoid action *in vitro* and *in vivo*.[24, 25] It is specifically a GR-II receptor antagonist and has very little affinity for the GR-I receptor. The effects of GR-II blockade have been studied fairly extensively in humans[26]; an antiglucocorticoid effect is not associated with peripheral cortisol suppression.

The use of mifepristone has been reported to ameliorate psychosis and depression in patients with Cushing syndrome. Relatively high doses of mifepristone (400–800 mg/day) were useful in rapidly reversed psychosis

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and suicidal thinking in two patients with Cushing syndrome (caused in this case, by metastatic adrenal cancer).[27] Nieman and associates[28] have also reported a patient with Cushing syndrome who had PMD symptoms that were unresponsive to antidepressants alone, and only partially responsive to an antidepressant/antipsychotic combination. However, treatment with high doses of mifepristone (up to 1,400 mg every day) resulted in both his physical and psychiatric symptoms resolving quickly.

Few adverse effects from mifepristone have been observed in studies in which patients were given 10 mg/kg a day for as many as 7 days.[29] Mifepristone given at daily doses of 200 mg, for more than 7 days, has been associated with fatigue, anorexia, and nausea (although not uniformly).[30, 31] Mifepristone induced a maculopapular erythematous cutaneous eruption in 8 of 11 healthy men receiving the medicine at a dose of 10 mg/kg for 9 to 14 days, and in 5 of 28 patients receiving treatment for meningioma at 200 mg daily for a median of 27 months.[31, 32] The cause of this spontaneously resolving rash is unknown. At higher doses (up to 22 mg/kg a day) given to patients with Cushing syndrome, no exanthema was seen, although nausea was common in these patients.[33]

Unfortunately, neither extensive nor blinded studies of mifepristone as a treatment for PMD have taken place.[34] We are conducting such a study. In this article we present preliminary data, suggesting that mifepristone may potentially benefit PMD patients.

Materials and Methods

Five newly admitted patients, with an admitting diagnosis of major depression with psychotic features (DSM-IV criteria) were studied. The diagnoses at admission were confirmed independently by two psychiatrists. The patients served as their own controls in a random- assignment, double-blind crossover design. They were given either 600 mg of mifepristone for 4 days followed by 4 days of placebo, or 4 days of placebo followed by 600 mg of mifepristone. Routine biological and hematologic studies were conducted daily to watch for possible signs of relative adrenal insufficiency, such as hypoglycemia and eosinophilia.

The patients were required to be between the ages of 18 and 75, and without major medical problems. Apart from hypercortisolemia, patients were excluded if they had any signs of Cushing syndrome. Furthermore, because mifepristone, in the dose range we used, is reported to cause an abortion rate approaching 85%, women of childbearing potential were excluded from the study. All patients who admitted to having used illicit drugs within the month before admission, or who consumed in excess of 2 ounces of alcohol daily were also excluded. All patients had normal physical exams and normal routine labs at hospital admission.

Patients were required not to take antipsychotic medication for 3 days before entering the study. Concurrent antidepressant use did not lead to exclusion from the study, however, no patients were taking antidepressant medication upon entering the mifepristone trial. No patient was started on an antidepressant medication while participating in the study. Benzodiazepines were permitted for insomnia and acetaminophen for headaches. If a patient's condition was such that they could not tolerate the drug-free period (for example, if they were intensely suicidal), they were not eligible for the study. Finally, all patients were required to give written consent to a protocol approved by the Institutional Review Board at Stanford University Medical Center.

Formal psychiatric assessments, including the Hamilton Rating Scale for Depression (HAM-D),[35] Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impression Scale, were carried out on days 1, 3, 5, 7, and 9 at 10 a.m. Paragraph recall was tested at 11:30 a.m., cortisol levels were measured serially every half-hour from 1:00 p.m. to 4:00 p.m., and plasma adrenocorticotropic hormone (ACTH) was measured serially every hour from 1:00 p.m. to 4:00 p.m., on days 1, 5, and 9. Blood samples were spun down and plasma were frozen at −80°F in the General Clinical Research Center Laboratory. Plasma cortisol determinations were made by radioimmunoassay in the Endocrinology Laboratory at Brigham and Women's Hospital (Harvard University). Plasma ACTH was assayed by immunoradiometric assay in the same laboratory.

Brief patient histories

Patient 1. This 50-year-old man had no prior psychiatric history, and had received no mental health treatment, except for career-counseling in graduate school. He was employed as an executive in the high-tech industry, was in excellent physical health, and was married with no children. He took no medications other than daily vitamins. Three months before his entry into the study he noted increasing feelings of depression with anhedonia, insomnia, decreased appetite, and decreased concentration. A stressor at that time was his mother's entry into a skilled nursing facility because of advanced Alzheimer's disease. One month before entry into the study he began to grow increasingly suspicious that coworkers were talking about him and planning to get him fired. At entry into the study, he was extremely guarded with mood-congruent delusions that the hospital might be a prison where he would be executed. He had received no psychiatric care to that point.

At admission, the patient's mean afternoon cortisol level was 12.0 μg/dL and did not decline throughout the

afternoon collection period. He received mifepristone first, and by day 5 his mean afternoon cortisol level was 37.7 μg/dL and, in a striking example, the normal rhythm of a steady decline of cortisol levels throughout the afternoon had resumed (Table 1). His HAM-D scores declined from 29 to 21, and his BPRS declined from 47 to 40. Moreover, from day 5 to day 9, while receiving placebo, his HAM-D continued to decrease (21 to 10), as did his BPRS (40 to 25), suggesting that mifepristone continued to be active in his system, as indicated by the continued elevation of his afternoon cortisol values. At this time, his normal cortisol rhythm continued. The patient experienced no adverse effects and no lab values, other than cortisol and ACTH, changed significantly. The patient began taking paroxetine at discharge and returned to work 2 weeks later. His depressed mood resolved over the next several weeks and his paroxetine was discontinued 9 months after conclusion of the study. He remains asymptomatic 2 years later.

Patient 2. A 44-year-old European-American married woman and mother of two, had a past psychiatric history that was limited to one previous episode of PMD, 3 years before study admission, for which she had been hospitalized for 1 week. During this initial episode of PMD, she acknowledged being very depressed, and felt that the devil was controlling her. She knew this to be true because her bed was very cold and thought there might have been a machine under her bed. Against medical advice, she left the hospital because she came to believe that one of her physicians was also being controlled by the devil. After leaving the hospital, she continued to be severely depressed with both auditory hallucinations and somatic delusions. She tried paroxetine for several weeks but there was no change in her condition. The paroxetine was decreased and nortriptyline was started. Eventually lithium was added to her treatment regimen, and her depression improved, although her somatic delusions remained.

One year before study admission, all of her symptoms had resolved. Two months later, against medical advice, she discontinued her medications. For 9 months she remained asymptomatic, but then became depressed again.

TABLE 1. Results of the afternoon cortisol test (patient 1)

	Cortisol Levels (μg/dl)		
Time	Day 1	Day 5	Day 9
1:00 p.m.	11.8	56.0	22.1
1:30 p.m.	14.4	40.9	22.7
2:00 p.m.	11.6	34.4	16.9
2:30 p.m.	10.4	34.2	14.1
3:00 p.m.	11.6	34.6	13.4
3:30 p.m.	12.7	35.7	12.6
4:00 p.m.	11.8	28.4	18.7
Mean	12.0 μg/dl	37.7 μg/dl	17.2 μg/dl

She could not identify any particular precipitating event. She reported increasingly depressed mood, weight loss, decreased concentration, memory, and energy, anhedonia, and insomnia.

One month after the onset of this depressive episode, she attempted suicide by hanging. The attempt failed because her feet reached the floor. She then made a second suicide attempt by taking an overdose of the previously prescribed nortriptyline. At this point, she was brought to the emergency department and stabilized. During her examination, she revealed that she had recently been hearing strange noises in her house and seeing shadows. She also stated that the devil was manipulating her body and that she had been unwilling to drive because the devil had the power to destroy her. Her examination in the emergency department was also notable for significant psychomotor retardation. Her only long-standing medical problems were irritable bowel syndrome and back pain. Findings from her physical examination wer within normal limits, and she was receiving estradiol and medroxyprogesterone for perimenopausal symptoms.

She received placebo first, and then mifepristone. While receiving placebo, her HAM-D increased from 33 to 35 and her BPRS from 51 to 57. While receiving mifepristone, her HAM-D declined from 35 to 21 and her BPRS from 57 to 44. At the end of the 9-day study, the patient was no longer delusional and felt well enough to go home. She declined follow-up antidepressant medication. Six weeks after leaving the study, she was reported to be experiencing symptoms of PMD and did not return for follow-up.

Patient 3. The patient, a 67-year-old woman with a history of recurrent PMD, was admitted after taking 15 fluoxetine capsules in a suicide attempt. Her first episode of PMD was in 1980, during which she experienced delusions of persecution and reference, and was hospitalized after a suicide attempt. One year before study entry, she experienced an episode of PMD and was prescribed low-dose haloperidol and fluoxetine. Her condition improved to the point where she felt "back to normal," and after 2 to 3 months of combination therapy she decided to stop taking her prescribed haloperidol and fluoxetine. Two months before study admission, her condition began to deteriorate. She complained of very low energy, poor appetite, spontaneous crying, poor self-care, and increased guilt about being a burden to her family. She also expressed increasingly delusional thoughts, including that her phones were tapped, her family was trying to poison her, her neighbors were observing her through her windows and, most recently, that white automobiles were following her. There was a question of whether she had experienced auditory hallucinations, because she complained of hearing sirens and phones ringing, but this observation was complicated by her partial hearing loss.

The patient's psychiatric history has been marked by long periods when she is fully functional (working as a nursing aide) with intermittent episodes of severe depression and paranoid ideation. At admission, the patient was taking no medications of any kind on a regular basis. Other than a 65% hearing loss in one ear and a 35% loss in the other ear, she had no ongoing medical problems.

This patient received placebo first and then mifepristone. She showed little change on either regimen. She was discharged and treated with olanzapine and her condition continued to improve. Her mean afternoon cortisol was 9.4 μg/dL at entry into the study, 9.4 μg/dL after 4 days of placebo and more than 60 μg/dL after 4 days of mifepristone. When she returned for her follow-up visit, 8 weeks later, and was feeling well, her afternoon cortisol was only 3.1 μg/dL, perhaps indicating that 9.4 μg/dL was quite hypercortisolemic for her.

Patient 4. This patient was a 57-year-old, male professional, with an 18-month history of severe depression characterized by extreme insomnia, low energy, poor concentration, and somatic concerns that had resulted in an extensive medical workup. Despite an extraordinary physical workup, he could not be convinced that he was physically sound and planned even more extensive physical testing. He tried virtually all of the antidepressants currently available, often in combination with antipsychotic medication. He also had a round of electroconvulsive therapy (ECT), with eight treatments that led to a modest and short-lived improvement in his condition. He had not been able to work for the past 15 months, which was in sharp contrast to his very productive career before the onset of his depression. He linked the onset of his depression to treatment with prednisone for an allergic reaction. He had no previous history of depression and no medical problems, but his family history was significant for his mother had severe late-life depression. He had weaned himself off of all medications (with the exception of clonazepam for sleep) before study entry.

The patient received placebo first. While receiving placebo his HAM-D declined from 31 to 28 and his BPRS declined from 53 to 45. While receiving mifepristone his HAM-D declined from 28 to 21 and his BPRS from 45 to 28. He left the hospital at the end of the study and was treated with venlafaxine, a drug to which his depression had not previously responded. Although his course of recovery was not a straight line, his improvement continued over time and he required neither additional hospitalization, nor ECT, and eventually gained full recovery.

Patient 5. A 45-year-old man with a history of obsessive-compulsive disorder, who in the 8 months before study entry, became increasingly depressed, experienced poor sleep, anhedonia, poor concentration, low energy, feelings of guilt, and had developed a fixed belief that his hearing had been irreparably harmed by various noises in his environment. These noises included a phone ringing, a child's bell, and a car horn. He became convinced that he had lost almost all of his hearing and was not dissuaded by the many trips to the audiologist, who indicated normal hearing, nor by the fact that he could converse in normal tones with those around him. Several weeks before study admission, he contemplated suicide and was hospitalized briefly and involuntarily. After trying a first dose of several medications, he refused to take any medication because he believed that each previous one- or two-pill trial had added to his hearing loss. Shortly before study admission, he began to believe that the police were trailing him ever since his involuntary admission. This patient worked as a college professor and was married with three children. He used no illicit substances or alcohol, but did have a family history of depression, including several siblings with major depression and his mother who experienced both depression and dementia.

He received mifepristone first and then placebo. While receiving mifepristone, his HAM-D declined from 46 to 37 and his BPRS from 54 to 41. Particularly significant, item 11 (suspiciousness) declined from a 6 (severe) to a 1, (absent) and item 15 (unusual thought content) declined from a 6 to a 3, mild. He no longer believed that the police were trailing him, nor that his phone was tapped. However, he still obsessively believed that he had a hearing loss, and his desire to have his hearing tested again was even stronger than before. While receiving placebo, his HAM-D declined from 37 to 35, but his BPRS increased again from 41 to 54, with particularly high scores on somatic concern and anxiety. At discharge, he refused all medications, and he has remained quite debilitated with high levels of somatic anxiety.

Results

In all cases, HAM-D scores declined during mifepristone treatment (see Table 2). In both cases, where the patient received mifepristone first, their HAM-D declined during the placebo treatment also (case one significantly, case five marginally.) In the three cases where placebo was given first, HAM-D scores changed very little (rising slightly in case two and falling slightly in cases three and four.) Ignoring the carryover effect leaves five active treatment cells and three placebo cells. The mean decline in HAM-D while receiving mifepristone was 8.0 (25.5%), whereas while receiving placebo it was 1.7 (5.8%). The difference approaches statistical significance ($F = 5.01$, $p < 0.07$).

In all but one case, BPRS scores declined during mifepristone treatment (See Table 2). The exception was case three, the patient with the lowest BPRS at

TABLE 2. Individual HAM-D and BPRS scores[a]

	HAM-D			BPRS		
Subject No.	Day 1	Day 5	Day 9	Day 1	Day 5	Day 9
1 (mifepristone first)	29	21	10	49	40	25
2 (placebo first)	33	35	21	51	57	44
3 (placebo first)	23	19	17	32	35	36
4 (placebo first)	31	28	21	53	45	28
5 (mifepristone first)	46	37	35	54	41	54

[a]HAM-D, Hamilton Rating Scale for Depression; BPRS, Brief Psychiatric Rating Scale.

study entry. Her BPRS score increased by one point. In case one, where the patient received mifepristone first, their BPRS continued on a distinct decline during the placebo period. In the other patient who received mifepristone first (case 5), the patient's BPRS reversed to the pretreatment level during placebo treatment. The mean decline in BPRS score while receiving mifepristone was 10.2 points (34%), whereas while receiving placebo, the BPRS increased by 0.3 points (1.2%).

Discussion

Although only a small number of patients have received mifepristone for psychotic major depression, the results seem fairly promising. All the patients were discharged from the hospital at the end of the 9-day study period. All of the five patients showed improvement in their HAM-D scores while receiving mifepristone, and four of the five patients showed improvement in their BPRS scores. Moreover, the patient who did not, was the least symptomatic to start. The overall decline in BPRS scores was 32.5%, which approaches the 40% value frequently seen in 6- to 8-week trails of effective antipsychotic medication. None of the patients reported side effects of any kind, and both basic lab measures and measures of vital signs were unaffected by treatment.

Although HAM-D scores diminished during treatment, all the patients still had significant residual signs and symptoms of major depression. We recommended that all begin antidepressant treatment at the end of the study. We observed that the more significant clinical change was that four of the five patients were no longer psychotic at the end of the study, and all were more cognitively organized. Additionally, it seemed as if the reason that the patients' HAM-D scores declined was that they were more cognitively intact and felt in better control of their thinking.

Cortisol transmission takes place through two receptors, the mineralocorticoid (type I, MR) and the glucocorticoid receptor (type II, GR). Type I receptors bind cortisol with roughly 10 times the affinity of type II receptors.[36] As a consequence, type I receptors primarily regulate cortisol homeostasis and type II receptors do not fill until cortisol levels are relatively high.[37] Mifepristone is a specific type II antagonist, which means that although the creation of the gene product resulting from high levels of cortisol is blocked, normal cortisol homeostasis continues forward.[38] Perhaps this mechanism explains the paucity of patientive complaints and observed side effects in our study.

The mechanism of clinical improvement in our patients with psychotic major depression is not entirely clear. Type II receptors are found in relatively high abundance in nonhuman, frontal cortex and primate hippocampus,[39] and functions modulated by these regions appear to be decreased in PMD patients.[40] Blocking these receptors may aid in improving cognition. It also seems that the abruptly blocking type II-receptors may cause a "resetting" of the HPA axis. Cortisol levels rise when mifepristone is taken because the feedback mechanism is partially disrupted, however, normal cortisol rhythm returns and seems to remain intact after mifepristone is discontinued. Short-term use of mifepristone may prove to be its most effective regimen.

Although it is generally accepted that many patients with psychotic major depression have high levels of circulating cortisol, it has been noted that some patients do not. One explanation may be, because of wide interindividual differences in serum cortisol levels and a lack of longitudinal observation, some patients with psychotic major depression whose cortisol levels seem to be normal, actually may be experiencing quite high levels of cortisol for them. For instance, patient #3's average afternoon cortisol was a modestly elevated 9.4 μg/dL when she was quite ill. Eight weeks later when she was well, her average afternoon cortisol was 3.1 μg/dL.

Although the number of patients we have studied is small, their improved condition after just 4 days of treatment with mifepristone suggests that glucocorticoid antagonists may be useful for treating psychotic major depression. In fact, the paucity of adverse effects observed, leads us to believe that a slightly longer trial, (i.e., 7 or 8 days) might be equally safe and even more efficacious. Larger, double-blinded trials of mifepristone to treat psychotic major depression seem warranted in the near future.

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References

1. Schatzberg AF, Rothschild AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? Am J Psychiatry 1992;149:733–45.
2. Coryell W, Pfohl B, Zimmerman M. The clinical and neuroen-

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