

An Open Label Trial of C-1073 (Mifepristone) for Psychotic Major Depression*

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Background: *The rationale for treating patients with psychotic major depression (PMD) with glucocorticosteroid receptor (GR) antagonists is explained.*

Methods: *Thirty patients with PMD, with Hamilton Rating Scale for Depression (HAM-D-21) scores of 18 or greater, were assigned in an open label trial to receive 50 mg, 600 mg, or 1200 mg of mifepristone for 7 days.*

Results: *All the subjects completed the protocol; there were no dropouts. Side effects were mild and sporadic. Of 19 subjects in the combined 600- and 1200-mg group, 13 had a 30% or greater decline in their Brief Psychiatric Rating Scale (BPRS) scores, compared with 4 of 11 in the 50-mg group. In the 600- and 1200-mg group, 12 of 19 subjects showed a 50% decline in the BPRS positive symptom subscale, a more sensitive index for the symptoms seen in PMD, compared with 3 of 11 in the 50-mg group; 8 of 19 subjects in the 600- and 1200-mg group had a 50% decline in the HAM-D-21, compared with 2 of 11 in the 50-mg group.*

Conclusions: *These results suggest that short term use of GR antagonists may be effective in the treatment of psychotic major depression and that further blinded studies are warranted.* Biol Psychiatry 2002;52:386–392 © 2002 Society of Biological Psychiatry

Key Words: C-1073 Mifepristone, psychotic major depression, cortisol

*See accompanying Commentary, in this issue.

Introduction

There is strong evidence to support the hypothesis that psychotic major depression (PMD) is a distinct syndrome. Statistically significant differences between psychotic and nonpsychotic major depression have been noted

along many axes including presenting features (Charney and Nelson 1981; Coryell et al 1984; Frances et al 1981; Glassman and Roose 1981; Lykouras et al 1986; Nelson and Bowers 1978; Schatzberg and Rothschild 1992), neuropsychologic features (Belanoff 2001; Schatzberg et al 2000), biological features (Nelson and Davis 1997), familial transmission (Leckman et al 1984; Nelson et al 1984), course and outcome (Robinson and Spiker 1985), as well as response to treatment (Anton and Burch 1990; Chan et al 1987; Glassman and Roose 1986; Kantor and Glassman 1977; Nelson and Bowers 1978; Rothschild 1985; Spiker et al 1985).

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; Anton 1987; Anton and Burch 1990; Chan et al 1987; Kantor and Glassman 1977; Leckman et al 1984; Nelson and Davis 1997; Nelson et al 1984; Robinson and Spiker 1985; Rothschild 1985; Schatzberg et al 2000; Spiker et al 1985), and many have markedly elevated postdexamethasone cortisol levels. A meta-analysis of 12 studies, with a combined sample size of approximately 1000 depressed patients, indicated that when inpatient status was controlled for, psychosis, but not melancholic symptoms, was associated with increased DST nonsuppression rates (Nelson and Davis 1997). Significant elevation in 24-hour measures of urinary free cortisol levels and plasma adrenocorticotropin hormone (ACTH) have also been observed in patients with PMD (Anton 1987). Patients with nonaffective psychoses, such as schizophrenia, generally do not show a high DST nonsuppression rate (Arana et al 1983; Rothschild et al 1982), but not all studies concur (Muck-Seler et al 1999). We hypothesized a number of years ago that excessive glucocorticosteroid activity resulted in alterations in dopamine metabolism and the development of delusions (Schatzberg et al 1985). More recent data point to glucocorticoid administration causing cognitive deficits in humans and nonhuman primates that mirror impairments in PMD (Lyons 2000; Newcomer et al 1999).

Patients with PMD respond differently to pharmacologic therapies in comparison with patients with nonpsy-

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chotic major depression (Anton and Burch 1990; Chan et al 1987; Glassman and Roose 1986; Kantor and Glassman 1977; Nelson and Bowers 1978; Rothschild 1985; Spiker et al 1985). Important findings include a very low placebo response rate in PMD, as well as a poor response to antidepressant therapy alone (Avery and Lubrano 1979; Glassman et al 1975). Patients with PMD do respond to electroconvulsive therapy, or a combination of antipsychotics and antidepressants. (Charney and Nelson 1981; Frances et al 1981; Minter and Mandel 1979). In addition, some recent European trials suggest that there may be a role for monotherapy with selective serotonin reuptake inhibitors, particularly fluvoxamine (Gatti et al 1996; Zanardi et al 1996, 1997, 2000). There has been some debate as to whether these European patients may have represented depressed patients with obsessive features rather than classic PMD patients (Rothschild and Phillips 1999). In any case, both pharmacologic strategies and electroconvulsive therapy (ECT) may take weeks to months to be effective, and this results in an interim period of high morbidity.

The steroid mifepristone, also known as RU486 (C-1073), (17(-hydroxy-11(-(4-dimethylaminophenyl)17((1-propynyl)estra-4,9-dien-3-one), is not only an antiprogesterone but also, at higher concentrations, an effective antagonist of glucocorticosteroid action *in vitro* and *in vivo* (Gaillard et al 1984; Herrmann 1982; Lamberts et al 1984; Proulx-Ferland et al 1982). It is a potent antagonist at the low-affinity GR (glucocorticosteroid receptor, previously named GR-II) and with little affinity for the MR (mineralocorticosteroid receptor, previously named GR-I). Past studies have mapped GR-II in the nonhuman primate brain and have found GR-II in high concentrations in the prefrontal cortex (Sanchez 2000; Patel et al 2000). The effects and kinetics of GR-II blockade have been explored fairly extensively in humans (Bertagna et al 1994; Gaillard et al 1984) and do not appear to be associated with suppression of glucocorticosteroid actions peripherally. Mifepristone may be useful in revealing disturbance of the HPA neuroendocrine rhythm in major depressive disorders (Ammar et al 1986).

The use of mifepristone has been reported to ameliorate psychosis and depression in patients with Cushing's disease. Relatively high doses of mifepristone (400 mg to 800 mg/day) rapidly reversed psychosis and suicidal thinking in two patients with Cushing's syndrome (caused by metastatic adrenal cancer; Van der Lely et al 1991). Mifepristone use has also been reported in a patient with Cushing's syndrome who had both depressive and psychotic symptoms that were unresponsive to antidepressants alone and only partially responsive to an antidepressant-antipsychotic combination. Treatment with high doses of mifepristone (up to 1400 mg/day) resulted in both

his physical and psychiatric symptoms resolving quickly. (Nieman et al 1985). We recently reported on an extremely ill patient with refractory Cushing's disease who was treated with high doses of mifepristone (up to 2000 mg) for almost a year before the positive effects of radiotherapy took hold. His medical and psychiatric symptoms resolved completely on mifepristone (Chu et al 2001).

Mifepristone and other antiglucocorticoids have also been shown to have some benefit in major depression without psychotic features. For example, Murphy et al (1993) found that three of four patients with MDD had modest improvement with mifepristone when treated with 200 mg/day for up to 8 weeks. In addition, cortisol synthesis inhibitors such as ketoconazole have also shown some benefit in the treatment of MDD (Wolkowitz et al 1993, 1999).

Few adverse effects from mifepristone have been observed in studies in which subjects were given 10 mg/kg/day for up to 7 days (Nieman 1993). At daily doses of 200 mg, given for more than 7 days, mifepristone has been associated with fatigue, anorexia, and nausea (although not uniformly; (Grunberg et al 1993; Lamberts et al 1991). Mifepristone induced a maculopapular erythematous cutaneous eruption in 8 of 11 normal 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 unresectable meningioma at 200 mg daily for a median of 27 months (Grunberg et al 1993; Laue et al 1990). The cause of this spontaneously resolving rash is unknown. In a recently completed double-blind randomized placebo-controlled study of mifepristone for unresectable meningioma (200 mg/day for as long as 144 months) in 160 patients, mifepristone was well tolerated. Fatigue and hot flashes were reported more frequently in the mifepristone group, and 16% of the women in the mifepristone group developed endometrial hyperplasia (Grunberg et al unpublished data). At higher doses (up to 22 mg/kg/day) given to patients with Cushing syndrome, exanthema was not seen, although nausea was common in these patients (Chrousos et al 1989). The patient described earlier, who received up to 2000 mg/day, experienced neither a rash nor nausea (Chu et al 2001).

We recently reported a small-blinded study of mifepristone as a treatment for PMD (Belanoff et al 2001). Five patients with PMD participated in a 4-day, double-blind, placebo-controlled crossover study using 600 mg of mifepristone as monotherapy for PMD. In these patients, Brief Psychiatric Rating Scale (BPRS) scores declined by 34% while they were receiving mifepristone but rose 0.4% while receiving placebo. Similarly, scores on the Hamilton Rating Scale for Depression (HAM-D-21) declined by 25.5% during mifepristone administration versus 6% during placebo administration. Clinical Global Impression

Table 1. Raw Phase II Data by Mifepristone Dose

| (50 mg) | | | | | | | | | | | | | | | | | | | | |
|-----------|-----|---|----|-----|----|----|-----|---|-------|-------|-----------|------|------|----------|------|------|----------|--------|-------|--------|
| Pt. No. | Age | G | Hx | DCE | AD | AP | ADP | N | BPRS0 | BPRS7 | BPRS RESP | POS0 | POS7 | POS RESP | HAM0 | HAM7 | HAM RESP | CGI CH | CORT0 | CORT7 |
| 10-01 | 33 | F | Y | 6 | | | X | | 25 | 27 | N | 2 | 2 | N | 27 | 24 | N | 6 | 15.63 | 11.05 |
| 10-02 | 60 | F | Y | 36 | | | X | | 43 | 31 | N | 12 | 4 | Y | 25 | 17 | N | 2 | 14.28 | 6.05 |
| 10-09 | 32 | F | Y | 2 | | | X | | 32 | 11 | Y | 13 | 0 | Y | 24 | 14 | N | 2 | 9.82 | 3.00 |
| 10-15 | 53 | M | N | 52 | | | X | | 37 | 23 | Y | 15 | 10 | N | 27 | 19 | N | 3 | 8.42 | 9.77 |
| 03-20 | 38 | M | Y | 4 | | | | X | 33 | 14 | Y | 14 | 11 | N | 29 | 8 | Y | 2 | 4.45 | 1.90 |
| 04-21 | 31 | F | Y | 6 | | | X | | 44 | 34 | N | 16 | 11 | N | 34 | 25 | N | 3 | 6.12 | 12.37 |
| 04-22 | 38 | M | ? | 2 | | X | | | 33 | 24 | N | 14 | 11 | N | 22 | 15 | N | 3 | 9.57 | 13.62 |
| 04-28 | 51 | F | Y | 2 | X | | | | 34 | 30 | N | 14 | 11 | N | 19 | 19 | N | 3 | 12.26 | 16.90 |
| 10-30 | 60 | M | N | 18 | | | | X | 47 | 51 | N | 17 | 14 | N | 38 | 28 | N | 4 | 16.84 | 22.34 |
| 02-31 | 40 | M | Y | 26 | | | | X | 30 | 6 | Y | 6 | 0 | Y | 27 | 8 | Y | 1 | 13.14 | 14.23 |
| 04-32 | 29 | F | Y | 8 | | | X | | 27 | 20 | N | 9 | 7 | N | 21 | 14 | N | 3 | 6.36 | 17.89 |
| (600 mg) | | | | | | | | | | | | | | | | | | | | |
| Pt. No. | Age | G | Hx | DCE | AD | AP | ADP | N | BPRS0 | BPRS7 | BPRS RESP | POS0 | POS7 | POS RESP | HAM0 | HAM7 | HAM RESP | CGI CH | CORT0 | CORT7 |
| 02-04 | 40 | M | Y | 3 | | | | X | 38 | 25 | Y | 9 | 4 | Y | 27 | 21 | N | 2 | 9.13 | 57.68 |
| 04-05 | 23 | F | Y | 5 | | | X | | 41 | 31 | N | 17 | 12 | N | 23 | 4 | Y | 3 | 5.71 | 35.05 |
| 10-11 | 59 | F | Y | 6 | | | X | | 30 | 8 | Y | 6 | 0 | Y | 25 | 6 | Y | 1 | 9.87 | 12.01 |
| 02-14 | 37 | M | Y | 2 | | | X | | 23 | 15 | Y | 4 | 2 | Y | 18 | 9 | Y | 3 | 10.79 | 30.75 |
| 10-18 | 46 | F | ? | 13 | | | X | | 32 | 21 | Y | 5 | 2 | Y | 27 | 15 | N | 2 | 5.89 | 9.67 |
| 03-23 | 25 | F | Y | 2 | | | X | | 33 | 39 | N | 7 | 12 | N | 25 | 29 | N | 2 | 5.99 | 16.82 |
| 04-24 | 45 | F | Y | 1 | | | X | | 35 | 22 | Y | 13 | 10 | N | 20 | 13 | N | 3 | 3.13 | 6.23 |
| 11-27 | 67 | F | Y | 8 | | | X | | 51 | 35 | Y | 10 | 2 | Y | 38 | 22 | N | 3 | 16.89 | 46.22 |
| 10-29 | 31 | F | Y | 4 | | X | | | 30 | 4 | Y | 10 | 0 | Y | 20 | 3 | Y | 1 | 4.16 | >60.00 |
| 02-33 | 58 | M | Y | 4 | | | | X | 45 | 39 | N | 4 | 3 | N | 24 | 12 | Y | 2 | 6.66 | 27.94 |
| (1200 mg) | | | | | | | | | | | | | | | | | | | | |
| Pt. No. | Age | G | Hx | DCE | AD | AP | ADP | N | BPRS0 | BPRS7 | BPRS RESP | POS0 | POS7 | POS RESP | HAM0 | HAM7 | HAM RESP | CGI CH | CORT0 | CORT7 |
| 10-03 | 56 | F | N | 24 | | | | X | 32 | 13 | Y | 12 | 6 | Y | 19 | 12 | N | 3 | 7.68 | 36.97 |
| 10-07 | 53 | F | Y | 104 | | X | | | 30 | 9 | Y | 13 | 1 | Y | 21 | 7 | Y | 2 | 5.96 | 41.71 |
| 10-10 | 56 | M | ? | 52 | | | X | | 37 | 30 | N | 7 | 4 | N | 31 | 25 | N | 2 | 2.61 | 20.47 |
| 03-12 | 51 | M | Y | 12 | | | | X | 38 | 5 | Y | 13 | 0 | Y | 23 | 6 | Y | 1 | 5.90 | 18.21 |
| 08-16 | 64 | F | Y | 4 | | | X | | 26 | 23 | N | 10 | 6 | N | 18 | 12 | N | 4 | 10.50 | 41.80 |
| 10-19 | 25 | M | Y | 5 | | | X | | 24 | 25 | N | 8 | 4 | Y | 19 | 17 | N | 3 | 7.80 | 3.76 |
| 03-25 | 39 | F | Y | 52 | | | X | | 28 | 11 | Y | 10 | 5 | Y | 21 | 12 | N | 4 | 6.50 | 7.00 |
| 08-26 | 74 | F | Y | 7 | | | X | | 42 | 28 | Y | 9 | 5 | N | 26 | 16 | N | 2 | 13.56 | 31.44 |
| 10-34 | 45 | F | Y | 17 | | | X | | 20 | 6 | Y | 4 | 1 | Y | 19 | 8 | Y | 2 | 8.45 | n/a |

Pt. No., patient number (first two digits = site); G, gender (M, male; F, female); Hx, history of psychotic major depression; DCE, duration of current episode of psychotic major depression; AD, antidepressant; AP, antipsychotic; ADP, both antipsychotic and antidepressant; N, neither antipsychotic nor antidepressants; BPRS0 (7), Brief Psychiatric Rating Scale Score at day 0 and day 7 (individual items rated from 0-6); BPRS RESP, "responder" if 1, indicates 30+ % improvement (decline in score); POS0 (7), subscale of BPRS (items 4, 11, 12, and 15) day 0 and day 7; POS RESP, "responder" 1 indicates 50+ % decline in Positive Symptom Scale; HAM0 (7), Hamilton Depression Scale at day 0 and day 7; HAM RESP, "responder" if 1, indicates 50%+ decline in HAMD score; CGI/CH, Clinical Global Impression change scores; CORT0 (7), median afternoon cortisol value.

(CGI) scores declined by 33% during mifepristone administration and 8% during placebo administration. In this article, we present additional data supporting the earlier observations that mifepristone rapidly reverses symptoms of PMD and is well tolerated.

Methods and Materials

The subjects comprised 30 patients who met DSM-IV criteria, by clinician interview, for a diagnosis of major depression with

psychotic features and had a HAMD-21 score of 18 or greater (Hamilton 1960). The subjects were randomly assigned to receive 50 mg, 600 mg, or 1200 mg of mifepristone once daily for 7 days. (We chose to use a 50-mg dose because the placebo response rate in PMD is very low. In addition, a 50-mg/day dose does not appear to have significant antigluocorticoid effects in humans but still has antiprogesterone properties (Gaillard et al 1984). The study was an open-label, inpatient trial. Routine biological and hematologic studies were conducted at day 0, day 7, and day 28, and possible signs of adrenal insufficiency were

Table 2. Efficacy Measures: C-1073 (Mifepristone) for Psychotic Major Depression by Dose

| | 50 mg | 600 mg | 1200 mg | 600 mg + 1200 mg |
|-----------------------------|--------------|------------|-------------|------------------|
| HAM-D responders | 2/11 (18.2%) | 5/10 (50%) | 3/9 (33%) | 8/19 (42.1%) |
| BPRS responders | 4/11 (36.4%) | 7/10 (70%) | 6/9 (66.7%) | 13/19 (68.4%) |
| BPRS Positive Symptom Scale | 3/11 (27.3%) | 6/10 (60%) | 6/9 (66.7%) | 12/19 (63.2%) |

HAMD, Hamilton Rating Scale for Depression; BPRS, brief psychiatric rating scale.

monitored daily by specifically asking patients about the occurrence of decreased appetite, nausea or vomiting, fatigue or weakness, dizziness, and rash.

Subjects were between the ages of 18 and 75 and could not have an unstable medical problem. Women of childbearing potential could be included after a negative serum pregnancy test. Patients who admitted to using illicit drugs within the month before dosing, who had a positive drug screen at screening, or who consumed in excess of two ounces of alcohol daily were also excluded.

Patients were allowed to remain on antidepressants or antipsychotic medications (or both) if they had been on stable doses for at least 1 week. No patient was started on an antidepressant or an antipsychotic medication during the week before or during the week of dosing. In addition, medication-naïve patients were also allowed in the study. Benzodiazapines were permitted for insomnia, as was acetaminophen for headaches. All patients were required to give written consent to a protocol approved by their academic center's institutional review board.

Formal psychiatric assessments, including the HAMD-21, BPRS, and CGI were carried out on day 0, day 3, and day 7. The positive symptom subscale of the BPRS was used because it focuses on symptoms characteristic of PMD. The items of the BPRS included in this scale were items 4 (conceptual disorganization), 11 (suspiciousness), 12 (hallucinatory behavior), and 15 (unusual thought content). Our response criteria were a 30% reduction on the BPRS, a 50% reduction on the BPRS positive symptom subscale, and a 50% reduction on the HAMD-21 (Kane et al 1988; Kronig et al 1995; Nierenberg et al 2000; Nobler et al 1997). On day 0, day 7, and day 28, cortisol levels were measured serially every half hour from 1–4. (afternoon cortisol test; Halbreich et al 1982), and plasma ACTH was measured serially every hour from 1–4. Blood samples were spun down, and plasma was frozen at –80°F in each center before shipping to the Endocrine Laboratory at Brigham and Women's Hospital (Harvard University). Plasma cortisol determinations were made by radio immunoassay and plasma ACTH by immunoradiometric assay.

Results

Thirty patients at six academic centers (University of Massachusetts, Duke University, Cornell University Medical College, University of Michigan, University of Texas at Galveston, and Stanford University) were enrolled in the study. The groups did not differ significantly in age, gender, ethnicity, weight, or duration of the current episode of illness nor did they differ on baseline cortisol level, HAMD or BPRS (Table 1).

The number and percent of patients who met response criteria (50% or greater decline on HAM-D from baseline to day 7, 30% or greater decline on the BPRS from baseline to day 7, 50% or greater decline on the BPRS Positive Symptom Scale) are shown in Table 2.

Both the 600-mg/day and 1200-mg/day doses resulted in statistically significant increases in serum cortisol compared with the 50-mg dose at day 7 (Table 3). Mifepristone was well tolerated by all subjects, and none dropped out because of side effects. Two patients in the 600-mg group and one in the 1200-mg group reported uterine cramping, and one patient in the 50-mg group and one patient in the 1200-mg group (but none in the 600-mg group) reported a rash. The rash developed by the patient in the 50-mg group was noted to have completely abated 1 month after study completion; the rash developed by the patient in the 1200-mg group was noted to have completely abated 2 months after study completion.

Discussion

In this open-label study, mifepristone appeared to be effective in the patients with PMD. In the higher dose groups (600 mg and 1200 mg), nearly two thirds of the subjects showed

Table 3. Cortisol and Adrenocorticotropic Hormone (ACTH) Measures: C-1073 (Mifepristone) for Psychotic Major Depression by Dose

| | 50 mg <i>n</i> = 11 | 600 mg <i>n</i> = 10 | 1200 mg <i>n</i> = 9 |
|--|---------------------|--------------------------|--------------------------|
| Baseline cortisol (SD) (ug/dL) | 11.4 (4.1) | 8.9 (4.3) | 8.9 (4.4) |
| Day 7 change from baseline cortisol (SD) | .5 (6.5) | 20.5 (16.6) ^b | 15.7 (13.5) ^a |
| Baseline ACTH (SD) (pg/MI) | 23.9 (9.3) | 18.4 (9.7) | 16.4 (7.4) |
| Day 7 change from baseline ACTH (SD) | .5 (9.5) | 19.2 (19.2) ^a | 15.4 (17.1) ^a |

^a*p* < .05

^b*p* < .01

significant reductions in their psychosis in a week or less: each dose produced roughly equivalent benefits. Although the numbers are small, our data indicate that it made little difference whether patients were taking concomitant medications to experience a clinically meaningful reduction in symptoms, (e.g., 9 of 15 patients on concomitant medications vs. 3 of 4 patients without other medications met response criteria on the BPRS Positive Symptom Subscale.) In addition, three investigators noted that they each had a subject who was recorded as a nonresponder at day 7 but were clinically improved by day 10 (3 days after the last mifepristone dose.) Although our a priori sense was that mifepristone is not predominantly an antidepressant, in this group of patients with PMD, the fact that more than 40% of the subjects taking higher doses had a greater than 50% reduction in their HAM-D scores is noteworthy. Some of the observed effect on depression and psychosis could be carry over effects from their existing medication regimen, but the mean duration of the PMD episode was 17 weeks. Several patients had been on their psychotropic regimen for 1 year or longer. Thus, it is unlikely but possible that the responders experienced a carryover effect in the 7 days of the trial.

Placebo response rates are quite low in PMD, often in the range of 0–10% for 1 week of placebo run-in (Anton and Burch 1990; Glassman et al 1975) and certainly much lower than rates of response we observed in our higher dose groups. A recently presented study (Tollefson 2001) reported a higher placebo response rate in PMD patients, but the high placebo response rate (28%) in this trial is inconsistent with studies published to date. It should also be noted that 50 mg of C-1073 is not a placebo dose. Indeed, it is a biologically active dose on the ovarian cycle (Croxatto et al 1993; Kettel et al 1991, 1996; Ledger et al 1992; Luukkainen et al 1988; Murphy et al 1995a, 1995b; Shoupe et al 1987).

This open-label study supports our previously reported 4-day double-blind study of 600 mg of mifepristone for PMD. It also supports the dramatic reduction in psychosis and depression reported by investigators using mifepristone to treat symptoms secondary to Cushing's disease (Sartor and Cutler 1996).

We hypothesize that the psychosis in PMD is caused by excessive activation of the HPA axis. Actively blocking GR-II receptors in the prefrontal cortex and other areas in the brain with mifepristone may rapidly improve PMD patient's psychosis. Blocking this receptor also causes a rapid rise in cortisol (by blocking the feedback loop), which could downregulate MR. Perhaps this perturbation of the HPA axis causes a resetting of HPA normal rhythm. Additional well-controlled scientific research should test these possibilities. Interestingly, ECT, a mainstay in the treatment of psychotic major depression, creates a similar perturbation of the HPA axis (Mitchell et al 1990; Swartz

and Chen 1985). Mifepristone, of course, is much more specific than ECT, which probably accounts for its more benign side-effect profile. It is also difficult for the patient to receive ECT more than every other day or every third day as the brain becomes more refractory to seizures and side effects, particularly cognitive side effects, increase. Mifepristone can be given daily which, compared with ECT, cuts down on the length between first and last "dosing." At this time, we know little about repeated exposure to mifepristone in patients who relapse. On the other hand, ECT is known to be a safe and effective strategy for some PMD and appears effective in repeated trials. Combination therapy with antipsychotics and antidepressants also appear safe and effective for both acute treatment and in repeated exposures; however, both maintenance ECT and maintenance pharmacotherapy may have a significant side-effect burden for the PMD patient and have a delayed onset of action.

These data, although based on a relatively small number of subjects, raise the possibility that mifepristone, used alone or as an adjunct to antidepressant or antipsychotic medications, appears to substantially improve the psychotic and depressive symptoms seen in psychotic major depression. This finding adds to the growing body of literature indicating that hormonal dysregulation may be causally related to the expression of affective disorders. We are planning to conduct a large, random-assignment, double-blind study of mifepristone in psychotic major depression in the near future.

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