Mifepristone versus Placebo in the Treatment of Psychosis in Patients with Psychotic Major Depression

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Background: *Abnormalities in the hypothalamic pituitary adrenal axis have been implicated in the pathophysiology of psychotic major depression (PMD). Recent studies have suggested that the antiglucocorticoid, mifepristone might have a role in the treatment of PMD. The current study tested the efficacy of mifepristone treatment of the psychotic symptoms of PMD.*

Methods: *221 patients, aged 19 to 75 years, who met DSM-IV and SCID criteria for PMD and were not receiving antidepressants or antipsychotics, participated in a double blind, randomized, placebo controlled study. Patients were randomly assigned to either 7 days of mifepristone (*n = *105) or placebo (*n = *116) followed by 21 days of usual treatment.*

Results: *Patients treated with mifepristone were significantly more likely to achieve response, defined as a 30% reduction in the Brief Psychiatric Rating Scale (BPRS). In addition, mifepristone treated patients were significantly more likely to achieve a 50% reduction in the BPRS Positive Symptom Scale (PSS). No significant differences were observed on measures of depression.*

Conclusion: *A seven day course of mifepristone followed by usual treatment appears to be effective and well tolerated in the treatment of psychosis in PMD. This study suggests that the antiglucocorticoid, mifepristone, might represent an alternative to traditional treatments of psychosis in psychotic depression.*

Key Words: Psychotic major depression, mifepristone, cortisol, GR

Although psychotic major depression (PMD) is simply classified as a severe form of depression in DSM IV(TR), PMD may represent a unique subtype of depression with its own phenomenology, treatment response, and biology (Schatzberg and Rothschild 1996). Psychotic features occur in about 14–25% of patients with major depression (Coryell 1996; Johnson et al 1991). PMD may be associated with a more chronic course, more frequent hospitalizations, higher risk of suicide, and greater disability than other forms of depression (Angst 1986; Coryell et al 1986).

The most commonly employed treatments for PMD are the combination of an antidepressant with an antipsychotic (Amore et al 1996; Rothschild et al 1993; Schatzberg 1992; Simpson et al 1999; Wheeler Vega et al 2000) or electroconvulsive therapy (ECT) (Buchan et al 1992; Minter and Mandel 1979). ECT appears to be effective in the treatment of PMD even when pharmacotherapy is unsuccessful (Avery and Lubrano 1979; Petrides 2001). Unfortunately, both ECT and combination pharmacotherapy have drawbacks, including substantial side effects, social stigma, and a delayed onset of therapeutic benefit (Challiner and Griffiths 2000; Datto 2000; Fogg-Waberski and Waberski 2000).

Abnormalities in the hypothalamic pituitary adrenal axis (HPA) have long been implicated in the pathophysiology of PMD. Patients with psychotic depression consistently show a high rate of non-suppression on the dexamethasone suppression test (DST) and/or high post dexamethasone cortisol levles (Arana et al 1983; Ayuso-Gutierrez et al 1985; Bond et al 1986; Caroff et al 1983; Mendlewicz et al 1982; Rothschild et al 1982). Other HPA abnormalities found in PMD include higher 24 hour urinary free cortisol relative to non-psychotic major depression (NPMD) patients (Anton 1987) and higher serum ACTH and nocturnal cortisol levels in PMD patients compared to NPMD patients (Keller et al, in press). It has been suggested that psychosis in PMD is driven in part by the effects of glucocorticoids on dopamine synthesis and activity (Schatzberg et al 1985). Exogenous glucocorticoid administration as well as Cushing's disease may be associated with changes in mood, cognition, and perception that parallel symptoms seen in PMD (de Quervain et al 2000; Forget et al 2000; Gifford and Gunderson 1970; Jeffcoate et al 1979; Mauri et al 1993; Starkman 1993).

Cortisol synthesis inhibitors, such as ketoconazole and metyrapone, may have therapeutic benefits in some depressed patients. For example, ketoconazole was shown to have antidepressant effects in a subset of depressed patients with hypercortisolemia (Wolkowitz et al 1999; Wolkowitz et al 1993). More recently, Jahn and colleagues (Jahn et al 2004) found that the addition of metyrapone to a standard serotonergic antidepressant was more effective than the addition of a placebo in augmenting antidepressant response. In addition, metyrapone treated patients exhibited a more rapid antidepressant response than did placebo treated patients. However, cortisol synthesis inhibitors are limited by a variety of potentially serious side effects at doses necessary to suppress cortisol synthesis (Sonino 1987).

Mifepristone is a potent and specific antagonist of the type II glucocorticoid receptor (GR-II) and the progesterone receptor (Gaillard et al 1984; Herrmann 1982; Lamberts et al 1984; Proulx-Ferland et al 1982). Although mifepristone is a potent GR-II antagonist, it has little effect on the mineralocorticoid receptors MR (previously named GR-1). In addition, mifepristone has no known affinity to monoamine, histamine, or cholinergic receptors. The GR-II receptor has a low affinity for cortisol and appears to play a part in the termination of the stress response. Mifepristone does not appear to be associated with suppression of glucocorticosteroid actions peripherally (Bertagna et al 1994; Gaillard et al 1984).

Several studies have indicated that mifepristone might be effective in the treatment of PMD and that the effects on psychosis might be more consistent and robust than the effects on depression (Belanoff et al 2001; Belanoff et al 2002; Simpson et al 2005; Flores et al 2006). These studies also suggested that

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the benefits of mifepristone might be seen with only 6 or 7 days of treatment and the effects might be sustained for at least 3 weeks after treatment with mifepristone was discontinued. Similarly, mifepristone might have value in the treatment of bipolar depression (Young 2004). These preliminary studies have been small, and only limited conclusions can be drawn from them. A larger double blind study of 208 PMD patients examined the effect of adding 7 days of mifepristone or placebo to usual treatment in patients hospitalized for the purposes of the study (DeBattista 2003). Both treatment groups improved significantly from baseline but did not differ from each other on the primary end point (a 30% reduction in the BPRS at 7 and 28 days). However, in post hoc analyses patients who received mifepristone were more likely to achieve a rigorous response (i.e., HamD $\leq$ 7, BPRS $\leq$ 25) require less antipsychotics, and were more likely to be discharged earlier from the hospital than were placebo-treated patients. The concomitant use of treatments known to be effective (concurrent antidepressant/antipsychotic use and hospitalization) may have reduced the ability to demonstrate a difference between groups on the primary endpoint.

While most of the work involving anti-glucocortioid strategies has focused on antidepressant effects, there is reason to believe that the antipsychotic effects of these drugs in the treatment of psychotic depression might be greater than their effects on depression. In 1985, Schatzberg and colleagues proposed a corticosteroid hypothesis/dopamine hypothesis for psychotic depression which postulated that steroid mechanisms were driving the psychotic symptoms of PMD (Schatzberg et al 1985). Specifically, they stated "This hypothesis is not intended to primarily account for why patients become depressed but rather why some depressed patients become psychotic." While preliminary studies with mifepristone in the treatment of PMD have suggested an antidepressant effect, the most robust and consistent effects have been seen on scales that measure psychosis, such as the BPRS. In particular, mifepristone appeared to impact the positive symptom subscale, which measures core psychotic symptoms including delusions, paranoia and hallucinations.

In this study, the antipsychotic efficacy of mifepristone is compared with placebo in PMD patients who are not taking antidepressants or antipsychotics during and prior to study drug administration. We hypothesized that patients taking mifepristone would have a rapid reduction of psychotic symptoms evident after 7 days of treatment, and that this response would be sustained for three weeks post treatment. Furthermore, we hypothesized that differences between response rates to treatment and placebo would be more pronounced among patients with higher baseline psychotic symptom severity. It was expected that improvements in psychotic symptoms would be greater than improvements in depressive symptoms.

Methods and Materials

Twenty-nine sites in the continental United States participated in this study after obtaining institutional review board approval. All patients provided written informed consent before participation.

Patients were included if they met DSM-IV criteria for PMD by clinical interview and by SCID. In addition, hospital admission notes were reviewed by the sponsor's medical monitor to further confirm the diagnosis of PMD. Enrolled patients were required to achieve a score of 38 or greater on the BPRS and 20 or greater on the HamD-24. Patients were required to have a negative serum pregnancy test and to use two acceptable methods of contraception throughout the study.

Exclusion criteria included an unstable medical condition, the use of systemic or inhaled corticosteroids, ECT in the 3 months prior to randomization, antidepressant and/or antipsychotic use during the 7 days before randomization, a history of illicit drug use in the previous month or alcohol or drug dependence in the previous 6 months.

Patients who met the study criteria were randomized 1:1 to 7 days of inpatient treatment in a double blind, placebo controlled, parallel group design. Patients received either mifepristone 600mg/day or placebo for seven consecutive days. Patients were evaluated prior to dosing at day 0 and then daily during dosing (days 1–7). Psychiatric assessments included the BPRS and HAMD scales performed at days 0, 3, 7, 14, and 28. Antipsychotics and antidepressants were not allowed for at least 7 days prior to randomization and for the 7 days of study drug administration. From day 8 onward, the investigator could prescribe any medication regimen or treatment that was clinically indicated. At the request of the FDA, a subset of patients (chronologically, the patients enrolled in the latter part of the study) had efficacy measures at day 56 to further assess the durability of response. All patients were hospitalized for at least the first three days of the trial. Thereafter, any patient deemed stable for discharge could continue to receive study medication as an outpatient. Patients discharged from the inpatient setting before day 7 were seen daily by research staff for clinical assessments and witnessed administration of study medication.

Safety was assessed by spontaneous report of adverse events, physical examination, and laboratory assessments including a serum chemistry panel, a complete blood count with differential, and an electrocardiogram at days 0 and 7.

Statistical Analysis

The primary endpoint measure for efficacy, defined a priori, was a "responder analysis" based on BPRS scale level of response. This endpoint compared the percentage of patients who had Rapid Response (at least a 30% reduction in the BPRS Total at days 7 and 28), Response (at least a 30% reduction in BPRS Total at day 28 but not at day 7), and No Response. A categorical 30% reduction in the BPRS had been used in a previous trial of mifepristone in PMD (DeBattista 2003) and was thought to represent a clinically meaningful reduction in psychotic symptoms. There were two prominent secondary measures of efficacy: 1) a 50% reduction in the BPRS positive symptom subscale (PSS), the 4 core psychotic items including suspiciousness, hallucinatory behavior, disorganized thinking, and unusual thought content; and 2) a 50% reduction on the HamD at day 7 and sustained to day 28.

Efficacy analyses were performed on the Intent to Treat (ITT) sample (n = 221), which consisted of all randomized subjects who received at least one dose of study medication. Data were observed at day 28 for 170 of the 221 patients (77%). For the 51 patients with missing data at either day 7 or day 28, BPRS and HAMD data were imputed using a mixed effects model for repeated measurements (MMRM). The response variable was the natural logarithm of the BPRS total, BPRS PSS (rescaled by subtracting 4 from each value), and HAMD scores. Values of zero were replaced with .25. The model included fixed effects categorical terms for treatment group, visit, and their interaction. An unstructured covariance matrix was used to model the interdependence of the within-subject repeated measures. The calculations were carried out using SAS PROC MIXED. Scores on the three outcome measures were imputed using the MMRM model,

Table 1. Demographic Characteristics of the ITT Sample ($n = 221$)

	Mifepristone ($n = 105$)	Placebo ($n = 116$)	p-Value
Age (Mean, SD)	40.9 ± 10.8	41.6 ± 11.0	.62[a]
Age group (n, %)			
18 to 34	31 (29.5%)	33 (28.4%)	.86[b]
35 to 64	72 (68.6%)	79 (68.1%)	
65+	2 (1.9%)	4 (3.4%)	
Gender (n, %)			.45[c]
Male	56 (53.3)	56 (48.3)	
Female	49 (46.7)	60 (51.7)	
Race, (n, %)			.74[b]
White	57 (54.3)	59 (50.9)	
Black	38 (36.2)	42 (36.2)	
Asian	1 (1.0)	4 (3.4)	
Hispanic or Latino	9 (8.6)	10 (8.6)	
Baseline Measures			
BPRS Total	55.8 ± 11.6	55.7 ± 9.2	.56[a]
BPRS PSS Scale	13.7 ± 3.6	13.4 ± 3.2	.95[a]
HAMD	37.3 ± 8.4	37.3 ± 7.5	.96[a]

[a]Significance level from a one-way ANOVA with treatment as a factor.
[b]From a Fisher's Exact test.
[c]From a Pearson chi-square test.

and then responder status was determined based on the definitions described above.

The proportion of rapid and sustained responders, responders, and non-responders were compared across treatments using Cochran-Mantel-Haenszel tests adjusting for site. The test statistic is the Cochran-Armitage linear trend test with p-values computed using a z-score approximation (equivalent to the Cochran-Mantel-Haenszel test for nonzero correlation). The test was carried out using a permutation approach, in which 10,000,000 resamples without replacement will be drawn independently within centers. The calculations were carried out using SAS PROC MULTTEST.

Results are also presented for the completer sample or observed cases (OC) data.

After completing the efficacy analyses on the ITT sample, statistical analyses targeted a focal population of interest: patients with more substantial psychotic symptoms ($n = 159$). This group was defined a priori as patients having a BPRS PSS ≥ 12 at baseline. The cutpoint of 12 was derived from a moderator analysis of efficacy data from a previous double blind PMD mifepristone trial which found that patients with a BPRS PSS ≥ 12 at baseline were more likely to have marked response. For this subset of the ITT sample ($n = 159$), proportions of rapid and sustained responders were again compared using Cochran-Mantel-Haenszel tests, adjusted for site. For exploratory purposes, analyses were conducted on a subset of patients who were asked, based on a FDA request, to complete a follow-up efficacy assessment at day 56. Chronologically, these patients were enrolled at the latter end of the study. All statistical tests were conducted using an alpha of .05 (two-tailed).

Results

A total of 221 patients ($n = 221$) were randomized and received at least one dose of study medication. The demographics of the ITT sample are described in Table 1. A randomization check indicated no significant differences between groups at baseline on demographic, BRPS, and HAMD measures. There were no statistical differences between groups on the rate of antidepressant use after day 7 (58% mifepristone, 62% placebo) or in the rate of antipsychotic use after day 7 (36% mifepristone, 42 % placebo), In addition, there was no significant difference between groups in the rate of ECT use after day 7 (2% on mifepristone, 3% on placebo) or the rate of combination treatment with both an antidepressant and antipsychotic after day 7 (29% mifepristone, 37% placebo).

Efficacy Analyses: Primary and Secondary Endpoints

As shown in Table 2, patients in the mifepristone treated group were more likely to achieve the response criterion on the primary measure, a 30% improvement in the total BPRS (Rapid and Sustained Response and Response). This difference was statistically significant in the ITT sample ($p = .041$) and compl-

Table 2. Primary and Secondary Endpoints: Response Status by Treatment Group

	Intent-to-Treat		Observed Cases	
	Mifepristone ($n = 105$)	Placebo ($n = 116$)	Mifepristone ($n = 78$)	Placebo ($n = 92$)
BPRS Total				
Rapid and Sustained	51 (48.6%)	49 (42.2%)	40 (51.3%)	36 (39.1%)
Response	31 (29.1%)	23 (19.8%)	18 (23.1%)	17 (18.5%)
Non-Response	23 (21.9%)	44 (37.9%)	20 (25.6%)	39 (42.4%)
	p value[b] = .041		p value[b] = .020	
BPRS PSS				
Rapid and Sustained	50 (47.6%)	40 (34.5%)	39 (50.0%)	30 (32.6%)
Response	23 (21.9%)	17 (14.7%)	13 (16.7%)	14 (15.2%)
Non-Response	32 (30.5%)	59 (50.9%)	26 (33.3%)	48 (52.2%)
	p value[b] = .006		p value[b] = .019	
HamD				
Rapid and Sustained	50 (47.6%)	56 (48.3%)	37 (47.4%)	42 (45.7%)
Response	21 (20.0%)	15 (12.9%)	22 (28.2%)	30 (32.6%)
Non-Response	34 (32.4%)	45 (38.8%)	19 (24.4%)	20 (21.7%)
	p value[b] = .668		p value[b] = .546	

[a]Rapid and Sustained Response, Response achieved at day 7 and sustained at day 28; Response, Response achieved by day 28; Non-Response, Response achieved at day 7 but not sustained at day 28, or not achieved at days 7 and 28.
[b]From a Cochran-Mantel-Haenszel test adjusted by pooled site.

Table 3. Patients with Baseline PSS Scores > = 12 (n = 159): Response Status by Treatment Group

	Intent-to-Treat			Observed Cases		
	Mifepristone (n = 74)	Placebo (n = 85)	p^a	Mifepristone (n = 53)	Placebo (n = 65)	p^a
BPRS PSS						
Rapid and Sustained	43 (58.1%)	28 (32.9%)		32 (60.4%)	20 (30.8%)	
Response	11 (14.9%)	11 (12.9%)		6 (11.3%)	9 (13.8%)	
Non-response	20 (27.0%)	46 (54.1%)		15 (28.3%)	36 (55.5%)	
			.001			.003

[a]Rapid and Sustained Response, 50% reduction in BPRS PSS score achieved at day 7 and sustained at day 28; Response, 50% reduction in BPRS PSS score achieved by day 28; Non-Response, 50% reduction in BPRS PSS score achieved at day 7 but not sustained at day 28, or not achieved at days 7 and 28.
[b]From a Cochran-Mantel-Haenszel test adjusted by pooled site.

eter samples (p = .020). Mifepristone treated patients were more likely to achieve response on one of two secondary measures, a 50% improvement in the BPRS PSS. This difference was statistically significant in both the ITT (p = .006) and completer populations (p = .019). Both mifepristone and placebo treated patients had improvement on their HAMD scores, but the difference between groups on responder status was not statistically significant (ITT: p = .668; OC: p = .546). Table 2 shows the proportion of rapid responders by treatment group for primary and secondary endpoints.

Other Analyses

After completing the efficacy analyses on the ITT sample, statistical analyses targeted a focal population of interest, defined a priori as patients having a BPRS PSS ≥ 12 at baseline. As stated earlier, the cutpoint of 12 was derived from a moderator analysis of efficacy data from a previous double blind PMD mifepristone trial which found that patients with a BPRS PSS ≥ 12 at baseline were more likely to have marked response. Of the 221 patients in the ITT sample, 159 patients had a BPRS PSS score ≥ 12 at baseline (n = 159), indicating the presence of at least minimal psychotic symptoms. These patients did not differ from other patients in the ITT sample on baseline demographic variables (age: t = .17, df = 219, p = .87; gender: X^2 = .02, df = 1, p = .90). Among this a priori designated group of interest, differences between the treatment and placebo groups were larger in terms of effect size. As shown in Table 3, a greater percentage of patients receiving mifepristone had a rapid reduction in psychotic symptoms, measured by the BPRS PSS, by day 7 and sustained their response at day 28. The difference in responder rate was statistically significant for the ITT (p = .003) and observed cases samples (p = .001). The group receiving mifepristone showed a significantly greater mean reduction in PSS scores at day 28 using both ITT (treatment: −7.2 ± 3.4; placebo: −5.2 ± 4.4; t = −3.2, df = 157, p = .001) and observed cases data (treatment: −7.0 ± 3.6; placebo: −4.7 ± 4.5; t = −3.04, df = 121, p = .003).

Among this target group of interest, forty-two participants (mifepristone: n = 19; placebo: n = 23) were observed at the FDA's request; these patients were assessed 7 weeks after the end of study drug administration. Responder analysis of the day 56 data indicated that a greater percentage of patients in the mifepristone group showed a 50% reduction in the PSS at days 7 and 56. Fifty-three (53%) of patients receiving treatment and twenty-two percent (22%) of patients randomized to placebo responded by day 7 and sustained their response at day 56 (p = .038). Mean change from baseline PSS scores at both day 7 and day 56 were significantly different across groups (Day 7 treatment −6.1 ± 3.4; placebo 4.7 ± 4.2 df = 157, t = 2.21, (p = .028); Day 56 treatment: −8.1 ± 3.5; placebo: −4.9 ± 3.6; t = −2.86, df = 40, p = .007). There was also a trend favoring mifepristone on improvement in the HamD absolute change from baseline at day 56 (treatment −20.2 ± 11.3; placebo −13.0 ± 12.0, df = 40, t = 1.96, (p = .056).

Adverse Events

Mifepristone appeared to be well tolerated with no AEs occurring at significantly higher rates than with placebo (see Table 4). While the rates of nausea, vomiting, rash and toothache trended higher in the mifepristone group, these differences did not achieve statistical significance. Likewise, the higher trended rates of constipation, dyspepsia, abdominal pain, and somnolence in the placebo groups were not statistically different. The rate of serious adverse events in the placebo group was higher than in the mifepristone group but these differences were not statistically significant. The rate of withdrawal due to adverse events in both the placebo and drug treated was very low, with 1 patient withdrawing from both the placebo and C-1073 treated groups secondary to AEs.

Table 4. Adverse Events in Most Frequently Affected Body Systems (≥ 5% for Any Group)

	Mifepristone n (%)[a]	Placebo n (%)	Total n (%)	p^b
Patients Studied				
Total Patients Studied	105	116	221	
Total Patients with TEAEs	71 (67.6)	85 (73.3)	156 (70.6)	
Body System Affected				
Headache NOS	17 (16.2)	21 (18.1)	38 (17.2)	.73
Nausea	12 (11.4)	7 (6.0)	19 (8.6)	.23
Vomiting NOS	10 (9.5)	5 (4.3)	15 (6.8)	.18
Constipation	5 (4.8)	12 (10.3)	17 (7.7)	.14
Dizziness	6 (5.7)	10 (8.6)	16 (7.2)	.45
Insomnia	5 (4.8)	6 (5.2)	11 (5.0)	1.00
Sedation	7 (6.7)	8 (6.9)	15 (6.8)	1.00
Abdominal pain NOS	6 (5.7)	4 (3.4)	10 (4.5)	.52
Rash NOS	6 (5.7)	2 (1.7)	8 (3.6)	.16
Abdominal pain upper	1 (1.0)	6 (5.2)	7 (3.2)	.12
Toothache	6 (5.7)	1 (0.9)	7 (3.2)	.06

TEAE, treatment-emergent adverse event.
[a]The denominator for the percentages is the total number of patients in each treatment.
[b]Fisher's Exact.

Discussion

Mifepristone appears to significantly reduce psychotic symptoms in patients with PMD as measured by the BPRS. The effects of mifepristone were most evident on the positive symptom subscale, which assesses core psychotic symptoms including delusions, hallucinations, suspiciousness, and disorganized thinking. As previously seen in patients with PMD, the effects of mifepristone were seen in psychosis but no significant effects were seen in depression. There might be several reasons for a differential effect on psychotic symptoms relative to depressive symptoms. Schatzberg and colleagues (Schatzberg et al 1985) have postulated a corticosteroid-mediated abnormality in dopamine function in PMD. Thus, an antiglucocorticoid might relieve psychotic symptoms in PMD more than depressive symptoms. Another possibility is that depressive symptoms might be more sensitive to non-specific treatment effects, such as being in the hospital, or to concurrent therapy than psychotic symptoms (Stolk et al 2001). Thus, even though mifepristone might have had effects on depressive symptoms, a high placebo response rate on depressive symptoms might have been difficult to overcome. Finally, it is possible that antipsychotic effect might occur early and antidepressant effects later. While there were no differences in the HamD between groups at days 7 or 28 in the secondary analysis, a post hoc analysis at day 56 suggests a strong trend favoring mifepristone ($p = .056$). However, the post hoc nature of this analysis in a subset of the total sample that were evaluated at day 56 renders this finding inconclusive.

Another notable finding of the study is the placebo response rate. Historically the placebo response rate in PMD was thought to be quite low with rates have ranging from 0 to 28 (Spiker and Kupfer 1988; Kocsis et al 1990; Schatzberg and Rothschild 1992). More recently, higher placebo responses have been observed in two PMD inpatient trials (DeBattista et al 2003; Rothschild et al 2004). There are a number of possibilities for the relatively high placebo response rate in this trial. One is that hospitalization and concurrent medications contributed to a higher placebo response rate than has been historically reported. Despite the precautions taken, it is also conceivable that patients may have entered the trial with a diagnosis that has a higher placebo response rate than does PMD. However, the high baseline HamD and BPRS scores suggest that the population was quite ill. The most likely alternative diagnoses were depression without psychosis, schizoaffective disorder or schizophrenia. Placebo response in depression without psychotic features is inversely related to HamD scores and the high HamD scores in this population would predict a comparably lower placebo response rate (Khan et al 2002). Neither schizophrenia nor schizoaffective disorder is associated with high placebo response rates. Another possible contributor to the relatively high placebo response rate is that an open label extension study may have confounded results. Patient who had an adequate response to study drug in the current study were eligible to participate in an open label extension study if they relapsed. Thus, it is possible that the motivation to be assured of open label treatment in the extension study might have contributed in some way, to the higher response rate in the acute study.

The effects of mifepristone on psychosis seemed to be evident both 3 weeks (day 28) and 7 weeks (day 56) after the drug was stopped. Studies employing antiglucocorticoid agents such as ketoconazole and metyrapone have reported that the clinical effects of these agents might persist for up to 8 months after the drug is stopped (Ghadirian 1995; Murphy 1998). The saturation of the GR II receptor for 7 days might also have effects on the HPA axis for a prolonged period. It is speculative but conceivable that an overactive HPA axis might be reset by acute blockade of the GRII receptor (Belanoff et al 2002). The persistent effects of mifepristone on the treatment of psychosis are not adequately explained by antipsychotic use after day 7. An antipsychotic effect was evident by day 7 when patients were not on antipsychotics. In addition, a minority of patients in both arms of the study (36% of mifepristone and 41% of placebo treated patients) were put on antipsychotics after day 7, predominately atypical antipsychotics such as olanzapine and risperidone. Since the majority of patients were not treated with antipsychotics, it seems unlikely that the difference between groups could be explained by concurrent medications.

There are a number of limitations to this study. Among them is that antipsychotics were allowed after day 7. Perhaps the antipsychotic effects seen were primarily related to the use of concurrent antipsychotics. However, this is unlikely for at least 2 reasons. One, only a minority of patients were administered antipsychotics at any point in the study. In addition, placebo treated patients were numerically more likely to have received follow-on antipsychotics than were patients who received mifepristone. Another possibility is that the concurrent antidepressant use after day 7 contributed to antipsychotic effects in these PMD patients. While a few studies have suggested antidepressants might treat the entire syndrome of PMD (Gatti et al 1996; Zanardi et al 1997; Zanardi et al 2000), most studies have not found this to be true. In any case, the rate of antidepressant use was similar in both groups and thus would not adequately explain a difference in the BPRS score. Missing data were imputed by MMRM, and inherent to all imputation methods is the risk of misestimation. However, MMRM is considered advantageous to other available methods (e.g., Last Observation Carried Forward).

Despite the limitations, this study suggests that there may be therapeutic benefits of mifepristone in the treatment of psychosis in psychotic major depression. If proven in subsequent trials, the targeting of a purported pathophysiology with a specific pharmacotherapy would be largely unprecedented in psychiatry. The discovery of psychotropics to date has rested on serendipity and repetition of drugs with similar pharmacological profiles.

Currently available therapies for PMD have significant limitations. While antipsychotics are effective, they are sometimes associated with extrapyramidal symptoms and potentially serious metabolic effects. In addition, antipsychotics tend to work in a slow measured manner in the treatment of any psychosis. Likewise ECT, while effective, requires repeated treatments under general anesthesia, is associated with cognitive side effects, and carries a significant stigma. An effective alternative to these treatments would be welcome.

This study suggests that mifepristone may have clinically significant antipsychotic effects in the treatment of PMD. Additional controlled trials are needed to replicate this effect. However, if replicated in additional studies, it may indicate that antiglucocorticoid drugs might have important applications in the treatment of psychotic depression.

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Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

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Sync your system to PACER to automate legal marketing.