Efficacy and Safety of Mifepristone for the Treatment of Psychotic Depression

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Abstract: Open-label studies and randomized clinical trials have suggested that mifepristone may be effective for the treatment of major depression with psychotic features (psychotic depression). A recent study reported a correlation between mifepristone plasma concentration and clinical response.

The current study aimed to evaluate the safety and efficacy of mifepristone and, secondarily, to test whether response was significantly greater among patients with mifepristone plasma concentrations above an a priori hypothesized threshold.

A total of 433 patients who met criteria for psychotic depression were randomly assigned to receive 7 days of either mifepristone (300, 600, or 1200 mg) or placebo. Response was defined as a 50% reduction in psychotic symptoms on both days 7 and 56. Cochran-Mantel-Haenszel tests compared (1) the proportion of responders among patients assigned mifepristone versus placebo and (2) the proportion of responders among the subset of patients with plasma concentrations greater than 1660 ng/mL versus placebo.

Mifepristone was well tolerated at all 3 doses. The proportion of responders randomized to mifepristone did not statistically differ from placebo. Patients with trough mifepristone plasma concentrations greater than 1660 ng/mL were significantly more likely to have a rapid and sustained reduction in psychotic symptoms than those who received placebo.

The study failed to demonstrate efficacy on its primary end point. However, the replication of a statistically significant linear association between mifepristone plasma concentration and clinical response indicates that mifepristone at sufficient plasma levels may potentially be effective in rapidly and durably reducing the psychotic symptoms of patients with psychotic depression.

Key Words: psychotic depression, glucocorticoid receptor antagonists, mifepristone, cortisol, hypothalamic-pituitary-adrenal axis, ROC analyses, signal detection

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Major depression with psychotic features (psychotic depression) is a common and debilitating psychiatric illness, which affects up to 25% of depressed patients admitted to a psychiatric hospital.[1] It carries a 0.4% prevalence across the United States and Europe.[2] Psychotic depression differs from nonpsychotic depression in several ways, including increased risk of mortality,[3] increased severity and chronicity of depressive episodes, increased impairment, increased psychiatric comorbidity, increased suicidality,[4] and increased rate of relapse.[5,6] Some have argued that psychotic depression is a different clinical entity from nonpsychotic depression, despite being diagnostically coded as a subtype of major depression.[7,8] In addition, patients with psychotic depression tend to have a poor response to standard antidepressants,[9,10] often requiring more complex treatments such as electroconvulsive therapy (ECT) or combination pharmacotherapy with antipsychotics and antidepressants.

Dysregulation of the hypothalamic-pituitary-adrenal axis has been postulated in the pathophysiology of psychotic depression for many years.[11] Patients with psychotic depression have high rates of dexamethasone suppression test nonsuppression[12] and abnormalities in diurnal fluctuation of cortisol.[13] Mifepristone, an antagonist of the type 2 glucocorticoid receptor, has been proposed as a possible pharmacologic treatment of psychotic depression based on these biologic observations.[14] Prior studies of mifepristone in the treatment of psychotic depression have included both open-label and randomized controlled trials and have produced varying results.[15–19] In a previous randomized clinical trial published in 2006, efficacy of mifepristone was demonstrated in this patient population, particularly among patients with moderate to severe psychotic symptoms.[16]

Results from another previous randomized clinical trial of mifepristone testing the reduction of psychotic features in patients with psychotic depression were published in 2009. In this trial, there was a statistically significant correlation between plasma mifepristone level and clinical response.[19] Specifically, 42% of patients with mifepristone plasma concentrations greater than 1660 ng/mL versus 23% of patients randomized to placebo met the response criteria (a 50% reduction from baseline in psychotic symptoms at both study days 7 and 56). The plasma concentration–efficacy relationship was detected as statistically significant despite considerable background noise owing to the presence of a statistically significant site-by-treatment interaction.[19]

The current study was a placebo-controlled randomized clinical trial designed to evaluate the safety and efficacy of mifepristone for the reduction of psychotic symptoms in patients with psychotic depression. Secondarily, based on findings from a previous, separate clinical trial reported in 2009,[19] it was hypothesized that patients whose mifepristone plasma concentrations were greater than 1660 ng/mL would be significantly more likely to meet responder criteria when compared with placebo-treated patients.

MATERIALS AND METHODS

Participants

Participants were 433 patients who met current *Diagnostic and Statistical Manual, Fourth Edition, Text Revision*, diagnostic criteria for major depressive disorder with psychotic features by *Structured Clinical Interview for DSM Disorders* and had minimum baseline raw scores of 38 on the Brief Psychiatric Rating

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Scale (BPRS) total score, 12 on the BPRS Positive Symptom Subscale (PSS), and 20 on the 24-item Hamilton Depression Rating Scale. Eligible participants were between 18 and 75 years and were not on antidepressants, antipsychotics, and/or mood stabilizers for at least 7 days before randomization. Potential patients were excluded who had a primary psychiatric diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder. Other exclusion criteria included the following: presence of a major medical problem; history of clinically significant liver disease including viral hepatitis, steatohepatitis, and alcohol- or drug-induced liver disease; ECT within 3 months before randomization; currently taking medications known to significantly induce or inhibit the metabolism of CYP 3A4; used illicit drugs within 30 days before screen as per patient report and urine drug screen; history of drug dependence within 6 months of randomization; history of alcohol dependence within 6 months of randomization, in the judgment of the investigator at immediate risk of suicide or at risk for harming others; had received investigational therapy within 30 days of randomization; and previously participated in a mifepristone clinical trial.

Patients were enrolled in 40 outpatient clinical research centers across the United States and 5 sites in eastern Europe. After complete description of the study to subjects, written informed consent was obtained. The study protocol was reviewed at all research centers by a local or central institutional review board.

Design

This was a 56-day, double-blinded, 4-arm randomized clinical trial. Patients were randomly assigned 1:1:1:1 to receive either active treatment of mifepristone at 1 of 3 dose levels (300 mg, n = 107; 600 mg, n = 107; 1200 mg, n = 109) or placebo (n = 110). Patients were randomized to receive either mifepristone or placebo daily for 7 days. Throughout the study, patients were administered one of the following antidepressant medications at standard clinical doses: bupropion, venlafaxine, fluoxetine, citalopram, escitalopram, mirtazapine, paroxetine, or sertraline.

Blood samples were obtained on day 7, the last day of active dosing. After solvent extraction, trough plasma concentrations of mifepristone were measured using high-performance reverse-phase liquid chromatography followed by tandem mass spectrometry (MicroConstants, San Diego, Calif). The internal standard was mifepristone-d4. Liquid chromatographic separations were achieved using a ZORBAX (Agilent Technologies, Santa Clara, Calif) SB phenyl column (150 × 2.1 mm, 5 μm). The mobile phase consisted of solvent A (0.1% formic acid in water) and solvent B (0.1% formic acid in acetonitrile) and was delivered at a flow rate of 0.033 mL/min. The lower limit of quantitation (sensitivity) of the assay was 10 ng/mL. The gradient of mobile phase A/phase B = 59:49. The MS instrument settings were as follows: mass transition = 430.4 > 372.35; cone (V) = 50; collision (eV) = 21; and dwell time (seconds) = 0.2. There is a single charge associated with the compound mifepristone: the expected mass/charge (m/z) = MW + 1.

Plasma measurements were available for 87% of study participants. Missing data analysis indicated that patients with missing plasma data (13%) did not statistically differ from patients with valid data on baseline parameters.

Efficacy was measured using the BPRS-PSS, a Likert-type ratings scale with 4 items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.[20] Responses are rated from 1 (not present) to 7 (extremely severe). Scores on PSS are derived by summing the ratings across the 4 items and then subtracting 4, such that the derived scale scores range from 0 (no symptoms present) to 24 (all symptoms present at a severe level). The BPRS was administered by raters who were clinical researchers with at least 1 year of experience performing the BPRS and who completed training every 6 months throughout the study. Raters were certified by using online testing methods that evaluated rater scores against a criterion standard test (Hillicon Technologies, Austin, Tex).

Primary End Point

Responders were defined as patients with a 50% or greater reduction in their baseline PSS score on days 7 and 56. Patients with less than a 50% reduction from baseline at either day 7 or 56 were defined as nonresponders. Patients requiring rescue treatment with antipsychotic or mood stabilizer medications were also defined as nonresponders.

Statistical Analyses

The primary efficacy end point was the comparison of the proportion of responders in the active group (all 3 dose groups combined) versus the placebo group using the Cochran-Mantel-Haenszel procedure, with site used as a stratification variable. Efficacy analyses were conducted for 3 populations: intent to treat (ITT), modified intent to treat (mITT), and observed cases (OC). For the primary end point, missing BPRS scores were imputed using a mixed model for repeated measurements, with terms for treatment group, baseline PSS score, and time as categorical variables. The mITT population was defined a priori to the unblinding and comprised the ITT population minus the patients enrolled at 1 study site (n = 35). Quality control analyses confirmed that patients assigned to receive active treatment at this site had mifepristone plasma concentrations below the minimum measurable quantity. The OC population was defined as those patients with observed efficacy data on days 7 and 56. Missing data analyses were conducted to compare the 3 analysis populations on all study parameters.

Secondary efficacy analysis compared the proportion of responders among patients with plasma concentrations of mifepristone greater than 1660 ng/mL versus patients who received placebo using Pearson χ^2 test. The level of 1660 ng/mL provided maximal sensitivity and specificity for differentiating responders from nonresponders in a previous clinical trial using signal detection analysis of receiver operating characteristic (ROC) curves.[19,21] Exploratory analyses using ROC analyses[21] were conducted to determine the plasma level cut point for maximal discrimination between responders and nonresponders in this study.

Safety analyses were conducted on the population of all patients who were randomized and received at least 1 dose of study medication. All adverse events were tabulated and compared between treatment groups.

RESULTS

Table 1 shows the baseline characteristics of study participants.

Primary End Point: Mifepristone Versus Placebo

The Cochran-Mantel-Haenszel test adjusted for site indicated no statistically significant difference in the proportion of responders between those patients who received mifepristone (all dose groups combined) and those who received placebo on the primary end point. Figure 1 shows the response rates on the primary end point for the ITT, mITT, and OC populations. Post hoc analyses indicated that the 3 active dose groups did not differ from each other or from placebo in the proportion of responders.

TABLE 1. Baseline Characteristics of Study Participants

	Mifepristone 300 mg	Mifepristone 600 mg	Mifepristone 1200 mg	Placebo
mITT, n*	93	97	104	103
Age, mean (SD), y	44 (12)	46 (12)	47 (10)	43 (11)
Sex (% female)	60	59	66	65
Raw BPRS-PSS,† mean (SD)	14.4 (2)	14.7 (3)	14.8 (2)	14.6 (2)
24-item Hamilton Depression Rating Scale, mean (SD)	36.6 (8)	37.1 (8)	35.5 (8)	36.5 (7)
Mifepristone plasma concentration at day 7, mean (SD), ng/mL	1366 (556)	1819 (842)	2070 (957)	0

*Statistics presented in this table describes the mITT population.

†The scoring method for converting raw BPRS-PSS scores to derived scores is detailed in the Materials and Methods section.

Secondary End Point: Clinical Response and Mifepristone Plasma Concentration

Of patients assigned to active treatment and with observed plasma concentrations, 42% (108/255) had mifepristone plasma concentrations greater than 1660 ng/mL. As shown in Table 2, these patients were significantly more likely than patients assigned to placebo to meet the efficacy response criterion (52% vs 34%, $P = 0.02$). Of patients treated with mifepristone, but with plasma levels below 1660 ng/mL, 38% met the efficacy response criterion.

Exploratory signal detection analysis[21] detected that 1356 ng/mL was the optimal plasma level cut point for discriminating responders from nonresponders. Of the patients assigned to treatment with mifepristone, and whose plasma concentrations exceeded 1356 ng/mL, 51% were responders compared with 34% of patients assigned to placebo ($P = 0.02$). Patients treated with mifepristone, but with plasma levels below the threshold of 1356 ng/mL, had a response rate of 31%. Of patients with measurable plasma mifepristone levels at day 7, 65% had mifepristone plasma concentrations greater than 1356 ng/mL.

Table 3 shows the proportion of patients in each dose group with mifepristone plasma concentrations greater than the thresholds of 1660 and 1356 ng/mL, respectively. Patients in the 1200-mg dose group were most likely to have plasma levels greater than both the 1356- and 1660-ng/mL thresholds.

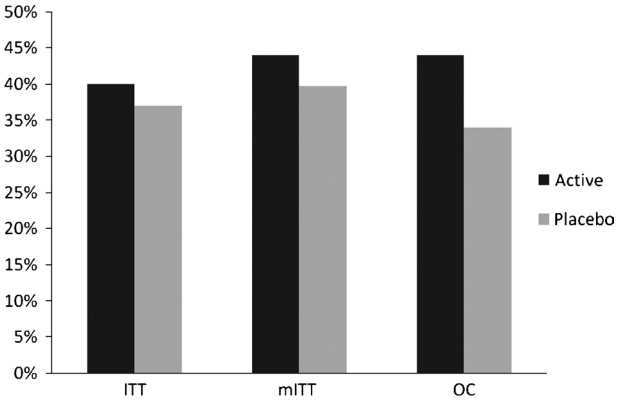

FIGURE 1. Primary end point: proportion of patients with rapid and sustained clinical response. Cochran-Mantel-Haenszel tests indicated that active and placebo groups did not differ in the proportion of responders (ITT, $P = 0.58$; mITT, $P = 0.60$; OC, $P = 0.14$). In each bar cluster, the bar on the left shows the response rate for patients assigned to active treatment and the right bar shows the response rate for patients assigned to placebo.

Safety

All 3 dose levels of mifepristone seemed to be well tolerated throughout the study, and similar percentages of patients experienced 1 or more treatment emergent adverse events throughout the study for all treatment groups including placebo (Table 4). Rates of headache, dizziness, and dyspepsia were higher in the mifepristone group, and rates of nausea and somnolence were higher in the placebo group. Sixty-nine percent (307/442) of the patients in the safety population (all patients enrolled) had 1 or more adverse events. There were a total of 18 serious adverse event (SAEs; placebo = 5, mifepristone 300 mg = 6, 600 mg = 2, and 1200 mg = 5), which occurred among 15 patients (placebo = 4, mifepristone 300 mg = 5, mifepristone 600 mg = 2, and 1200 mg = 4). Of the 18 SAEs, 14 were psychiatric in origin and included events such as "worsening psychosis, worsening depression, suicidal ideation, and acute anxiety." Four nonpsychiatric SAEs occurred in 3 patients, namely, gastritis, worsening asthma, and rash + bilateral pleural effusions, which occurred in the same patient. Sixteen patients experienced either an adverse event or SAE that led to premature discontinuation from the study (placebo = 6, 300 mg = 3, 600 mg = 3, 1200 mg = 4). Of the 15 patients with 1 or more SAEs, 7 terminated the study early because of the SAE. In only 1 patient with SAE (rash and bilateral pleural effusion) was the SAE judged to be related to

TABLE 2. Proportion of Responders With Plasma Concentrations Above Cut points

	Mifepristone, %	Placebo, %	*P**
All patients†	44	34	0.14
Patients with plasma concentration >1660 ng/mL‡	52	34	0.02
Patients with plasma concentration >1356 ng/mL‡	51	34	0.02

*Probability values derived from Pearson 2 × 2 χ^2 tests.

†Patients with observed mifepristone plasma concentration and observed efficacy data.

‡The concentration 1660 ng/mL was the a priori defined cut point for the study, and 1356 ng/mL was defined from post hoc signal detection analysis.

TABLE 3. Proportion of Patients in Each Dose Group With Mifepristone Plasma Concentrations Greater Than 1356 and 1661 ng/mL

Plasma Concentration	300 mg	600 mg	1200 mg
>1660 ng/mL,* %	21	45	55
>1356 ng/mL,† %	52	63	81

*The concentration 1660 ng/mL was specified a priori in the current study and was detected as an optimal cut point in a previously published clinical trial.[19]

†The concentration 1356 ng/mL was the threshold in the current study, which optimally discriminated responders and nonresponders using ROC signal detection methods.

study drug by the investigator. In all other cases, SAEs were judged to be not related to study drug by the investigator.

DISCUSSION

There were no statistically significant differences between mifepristone and placebo on the study's primary end point (ie, 50% or greater reduction in psychotic symptoms at days 7 and 56). The observed placebo response rate in all analysis populations was higher than expected. Previous studies of psychotic depression have reported placebo response rates close to zero.[22] However, the higher-than-expected placebo response is consistent with reports from the larger psychiatric literature, which has reported an upward trend in placebo response in studies of major depressive disorder. In a review of 75 placebo-controlled studies across several decades, Walsh et al[23] observed that placebo response rates increased an average of 7% per decade; placebo response ranged from 10% to 50% across the time span under review.

In our secondary analyses, a positive linear correlation between plasma concentration of mifepristone and efficacy, observed in a previous clinical trial,[19] was replicated and confirmed. As hypothesized, patients with higher mifepristone plasma concentrations (ie, >1660 ng/mL) were significantly more likely than placebo to have a rapid and sustained reduction in their psychotic symptoms.

This was the first clinical trial to use 3 dose levels of mifepristone. There was no statistically significant relationship between dose of mifepristone (300, 600, or 1200 mg) and clinical efficacy. Rather, trough plasma concentration of mifepristone on study day 7, regardless of dose, was positively correlated with clinical improvement. Patients receiving 1200 mg were more likely than patients receiving the lower doses to have mifepristone plasma concentrations greater than the threshold associated with response in a previous study (1660 ng/mL).[19]

The pharmacokinetics of mifepristone is complex and nonlinear. For a given population receiving a fixed dose of mifepristone, the variability of plasma concentrations is large.[24] In our study, a comparison of plasma concentration distributions across dose levels showed substantial overlap (Table 1). However, there was an observable linear relationship between dose and plasma concentration: 52% of patients dosed with 300 mg, 63% of patients dosed with 600 mg, and 81% of patients dosed with 1200 mg achieved the plasma threshold of 1356 ng/mL derived in the ROC analysis. These results suggest that the higher daily dose of mifepristone given to a patient, the higher their probability for experiencing a significant reduction in psychotic symptoms.

Previous work with mifepristone in psychotic depression has mostly been conducted with a dose of mifepristone 600 mg. This study provided the opportunity to compare the safety profile of mifepristone 1200 mg to placebo and lower doses of mifepristone. These data suggest that mifepristone 1200 mg is as safe and well tolerated in this patient population as the lower doses of mifepristone, while maximizing the probability of yielding mifepristone plasma concentrations greater than the ROC-defined plasma threshold.

Given the debilitating nature of psychotic depression, it is imperative to search for new treatments that improve on the current mainstays of psychiatric practice. Combination pharmacotherapy (antidepressant + antipsychotic) is often the first-line treatment for this patient population, and ECT is usually reserved for more severe cases. Although these treatment options have

TABLE 4. Patients With Treatment-Emergent Adverse Events*

Adverse Event	Mifepristone 300 mg	Mifepristone 600 mg	Mifepristone 1200 mg	Placebo
n (safety population)	110	109	112	111
Headache, n (%)	20 (18)	21 (19)	28 (25)	21 (18)
Nausea, n (%)	20 (18)	23 (21)	20 (18)	27 (24)
Dizziness, n (%)	9 (8)	12 (11)	18 (16)	7 (6)
Dry mouth, n (%)	5 (4)	10 (9)	14 (12)	12 (11)
Diarrhea, n (%)	10 (9)	9 (8)	12 (11)	7 (6)
Somnolence, n (%)	8 (7)	9 (8)	5 (4)	11 (10)
Dyspepsia, n (%)	2 (2)	4 (4)	11 (10)	3 (3)
Fatigue, n (%)	9 (8)	7 (6)	6 (5)	4 (4)
Constipation, n (%)	3 (3)	6 (5)	8 (7)	6 (5)
Vomiting, n (%)	5 (4)	7 (6)	8 (7)	5 (4)
Decreased appetite, n (%)	4 (4)	7 (7)	4 (4)	2 (2)
Back pain, n (%)	7 (6)	4 (4)	4 (4)	3 (3)
Insomnia, n (%)	4 (4)	7 (6)	6 (5)	6 (5)
Tremor, n (%)	4 (4)	6 (5)	3 (3)	2 (2)
Anxiety, n (%)	6 (5)	5 (5)	6 (5)	3 (3)
Patient with any of the listed events, n (%)	73 (66)	83 (76)	77 (68)	74 (66)

*Adverse events are listed for conditions that are reported by at least 5% of the study's safety population (all patients enrolled).

some utility in this patient population, they also present very real drawbacks. The newer-generation antipsychotics often prescribed for this condition are known to increase patients' risk of obesity, diabetes, and metabolic syndrome.[25] Because patients with mental illness already have an approximately 2-fold higher all-cause mortality rate relative to the general population,[26] it is problematic to administer medication regimens known to induce metabolic syndrome and obesity. Electroconvulsive therapy is associated with cognitive adverse effects, financial burden, and is, unfortunately, associated with substantial social stigma.

This study replicated a linear association observed in a prior clinical trial[19] between trough plasma concentrations of mifepristone and reduction of psychotic symptoms. Future work evaluating the utility of mifepristone in treating psychotic depression will focus on the optimization of dose and plasma levels to increase the percentage of patients achieving a robust response. A multisite randomized clinical trial evaluating the 1200-mg dose of mifepristone versus placebo is currently underway to further elucidate the role mifepristone may play in the treatment of psychotic depression.

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