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Mifepristone Plasma Level and Glucocorticoid Receptor Antagonism Associated With Response in Patients With Psychotic Depression

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Abstract:

Background: Psychotic depression has no Food and Drug Administration–approved treatment. Patients demonstrate significant dysregulation of the hypothalamic-pituitary-adrenal axis providing a biologically targeted treatment opportunity. The purpose of this study was to explore the clinical and biological effects of short-duration (7-day) glucocorticoid receptor antagonism with mifepristone and the role of mifepristone plasma levels in patients with psychotic depression.

Methods: This double-blind, randomized study took place at 34 US clinical research centers and included patients with a diagnosis of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* major depressive disorder, severe, with psychotic features. Patients underwent daily, observed, in-clinic administration of oral study drug (mifepristone 1200 mg or placebo) for days 1 to 7 of the 56-day trial, followed by treatment with a single Food and Drug Administration–approved antidepressant on days 8 to 56. The following scales were administered on days 0, 7, 14, 28, 42, and 56: Brief Psychiatric Rating Scale (BPRS), BPRS Positive Symptom Subscale, Hamilton Rating Scale for Depression, and Columbia-Suicide Severity Rating Scale. The primary end point was a categorical analysis evaluating the proportion of patients with 50% or greater reduction from baseline in BPRS Positive Symptom Subscale score on both days 7 and 56, demonstrating early and durable response. Cortisol and adrenocorticotropic hormone were measured on days 0, 7, 28, and 56. Mifepristone plasma levels were assessed on days 0 and 7.

Results: An interim analysis indicated that the primary efficacy end point was unlikely to be met, and the study was stopped early with 292 of the planned 450 patients enrolled. Although the primary end point was not met, in a secondary prespecified analysis, patients who attained a mifepristone plasma level of 1637 ng/mL or greater (defined a priori and termed the high plasma level; 66.7% of patients) demonstrated statistically significant reductions in psychotic symptoms compared with patients who received placebo starting on day 28. This group also showed nonsignificant, numeric superiority on Hamilton Rating Scale for Depression improvement. No significant improvements were observed in the low-mifepristone group (<1637 ng/mL) versus the placebo group. There were no significant differences in Columbia-Suicide Severity Rating Scale suicidality ratings between groups.

Conclusions: Mifepristone 1200 mg daily for 7 days was safe and well tolerated, allowing most treated patients to achieve the a priori defined therapeutic plasma level of 1637 ng/mL, the mifepristone level associated with biological effect and clinical benefit.

Key Words: mifepristone, plasma level, psychotic depression, glucocorticoid receptor antagonism, cortisol, HPA axis

(*J Clin Psychopharmacol* 2017;37: 505–511)

Nearly 20% of patients with major depression develop nihilistic, paranoid, guilty, or somatic delusions[1]—that is, major depressive disorder with psychotic features. Psychotic depression (PD) has serious consequences for both patients and their caregivers.[2,3] It is associated with cognitive problems, including impairment in attention, working memory, and executive functioning.[4] Patients are likely to be hospitalized and have elevated suicide risk.[5] Longer-term consequences include elevated all-cause mortality, mostly from cardiovascular and metabolic illness.[6] Such patients can have excellent interepisode function. There are no Food and Drug Administration (FDA)–approved treatments of PD.

Disruption of the hypothalamic-pituitary-adrenal axis has been implicated in the pathophysiology of PD. Cortisol binds to the glucocorticoid receptor (GR), which is found in all tissue types, including the central nervous system. Although cortisol is critical for maintaining homeostasis, excess stimulation of GR adversely affects metabolism, cardiovascular and immune function, cognition, and mood. Chronic use of high-dose prednisone can lead to severe depression or mania, psychosis, and impaired cognitive issues in susceptible patients.[7] Cushing syndrome, the classic example of GR overstimulation, is characterized by obesity, infections, diabetes, cardiovascular problems, depression, and psychosis.[8,9]

Patients with PD demonstrate dysregulation in cortisol activity, rhythm, and production, as evidenced by (*a*) high rates of nonsuppression on the dexamethasone suppression test,[10] (*b*) reduced diurnal fluctuation of cortisol, (*c*) high plasma cortisol and adrenocorticotropic hormone (ACTH) levels, and (*d*) increased excretion of 24-hour urinary free cortisol.[11,12]

Mifepristone, a competitive GR antagonist, was first proposed as a therapy for patients with PD based on the observation

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Received December 22, 2016; accepted after revision April 28, 2017.

Dr Block had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Corcept Therapeutics had a role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the article for publication.

Drs Block and Belanoff contributed to the study concept and design and the acquisition, analysis, or interpretation of data. Dr Kushner contributed to the statistical analysis. Dr Belanoff obtained funding. Dr Block contributed to the study supervision. All authors contributed to drafting of the manuscript and critical revision of the manuscript for important intellectual content.

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This study was funded by Corcept Therapeutics.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000000744

that these patients have prominent cortisol dysregulation.[13] In addition, mifepristone had been observed to reverse the psychiatric symptoms of psychosis and depression in patients with Cushing syndrome.[14]

Although many pharmacologic studies in depression focus on daily drug administration for 8 weeks, the proposed regimen with mifepristone is different. Some clinical trials in which mifepristone was dosed daily for only 1 week have been shown to significantly reduce psychotic symptoms at week 1,[15,16] with sustained effects noted for up to 8 weeks.[16] However, other clinical trials have failed to demonstrate statistically significant separation of mifepristone from placebo on primary end points.[17,18] Interestingly, these studies have consistently identified a reproducible and statistically significant association between plasma level of mifepristone (herein referred to as high PL) and clinical response as measured by reduction in psychotic symptoms.[17,18] High-PL patients significantly outperformed both the group of patients with plasma levels less than the identified threshold (herein referred to as low PL), as well as those administered with placebo.[18] Although the pharmacokinetics of mifepristone is complex and nonlinear, higher mifepristone plasma levels can be achieved with higher mifepristone doses. Most data from earlier studies were based on a mifepristone dose of 600 mg daily for 7 days, in which the therapeutic plasma level of high PL was achieved in only half of those patients treated with mifepristone. In 1 study that included a 1200-mg mifepristone treatment arm, 67% of patients at that dose attained high PL.[18] In addition to high PL, a high degree of GR antagonism (inferred by increase in posttreatment cortisol and ACTH levels) has also been associated with significantly greater likelihood ($P < 0.003$) of sustained clinical response.[19] Mifepristone blocks negative feedback of cortisol in the hypothalamus and pituitary, leading to increased circulating ACTH and cortisol while antagonizing GR more globally. Demonstrable biological mediators of treatment response are rare in psychiatry, particularly changes in levels or function of specific pharmacologic targets.

Applying experience from earlier studies in PD, this study was designed and conducted to test (*a*) the efficacy of 1200 mg of mifepristone per day for 7 days versus placebo for reducing psychotic symptoms at both days 7 and 56, (*b*) the hypothesis that the a priori defined high-PL group is associated with significantly greater clinical response than both low-PL and placebo groups, and (*c*) the relationships among mifepristone plasma level, degree of GR antagonism as measured by posttreatment increases in plasma ACTH or serum cortisol, and treatment response.

METHODS

Study Design and Participants

The protocol, consent forms, and all amendments were approved by the institutional review board or ethics committee of the participating study center. The investigator or designee obtained from each patient a signed and dated written informed consent/authorization consistent with FDA/International Council for Harmonization regulations, the HIPAA Privacy Rule (if applicable), and applicable state and local laws. This study was posted on clinicaltrials.gov (Clinicaltrials.gov identifier: NCT00637494).

This was an 8-week, multisite (34 sites), double-blind, randomized clinical trial conducted in the United States from April 2008 to June 2014. Randomization was 1:1 mifepristone 1200 mg/d or placebo daily for 7 days. The primary objective was to evaluate the safety and efficacy of short-duration treatment with mifepristone (followed by an antidepressant for 7 weeks) for reducing psychotic symptoms in patients with PD.

A total of 292 patients (men or nonpregnant women, age ≥ 22 y) with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnosis of major depressive disorder, severe, with psychotic features (ie, PD) and who had not been taking antidepressants or antipsychotics for at least 7 days were enrolled. Entry criteria at baseline included Brief Psychiatric Rating Scale (BPRS) Positive Symptom Subscale (PSS) unadjusted score of 12 or greater, BPRS total unadjusted score of 38 or greater, and Hamilton Rating Scale for Depression (HAMD-24) total score of 20 or greater. All patients were hospitalized for at least 3 nights on days 0, 1, and 2 with hospital discharge on day 3 if clinically appropriate. Observed dosing with study drug (mifepristone or placebo) took place on days 1 to 7 of the 56-day study, followed by treatment with a single FDA-approved antidepressant on days 8 to 56. Ninety-five percent (277/292) of the patients received study drug for all 7 days.

Study Assessments and End Points

After completion of a psychiatric evaluation by the study physician, a Structured Clinical Interview for Diagnosis was performed by a blinded certified centralized rater to confirm the PD diagnosis. Centralized diagnosis and ratings over encrypted IP VPN videoconference systems were used to reduce potential site bias. Patients were clinically assessed by the site staff during screening and on days 0 to 7, 14, 28, 42, and 56 or early termination with the following scales:

- HAMD-24: A 24-item patient questionnaire comprising the HAMD-17 and 7 additional items.
- BPRS: An 18-item evaluation to assess psychopathology; each item is scored on a numeric scale ranging from 1 ("not present") to 7 ("extremely severe").
- BPRS-PSS: A subset of the BPRS of 4 items to assess the degree of psychosis and symptom severity: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. The BPRS-PSS score was rescaled by subtracting 4 from the sum of the individual symptom scores and ranges from 0 to 24.
- Columbia-Suicide Severity Rating Scale (C-SSRS): A 12-item scale that measures the degree of suicide ideation or behavior.

Plasma trough mifepristone samples were collected on day 7, before administration of the last dose of study drug. All doses of study medication were observed by appropriately trained study staff. An a priori receiver operating characteristic curve analysis, based on data from previous clinical trials with mifepristone,[18] determined that the mifepristone plasma concentration of 1637 ng/mL was the optimal therapeutic plasma level threshold for differentiating responders from nonresponders. Patients with a trough day 7 mifepristone level of 1637 ng/mL or greater are referred to as the "high-PL" group, whereas those with a level less than 1637 ng/mL are referred to as the "low-PL group."

The primary efficacy end point was the proportion of patients with 50% or greater reduction from baseline in BPRS-PSS at both days 7 and 56. A secondary efficacy analysis was the prespecified comparison of a 50% or greater reduction in BPRS-PSS at days 7 and 56 in the high-PL and placebo groups.

The safety of mifepristone was evaluated using reported adverse events (AEs) coded using the Medical Dictionary for Regulatory Activities, standard clinical laboratory tests (hematology, chemistry, and urinalysis), physical examinations, vital signs, and electrocardiograms. Samples for laboratory analyses were collected at screening and on days 7, 28, and 56. Electrocardiograms (12-lead) were obtained at screening and on day 7. Samples for cortisol and ACTH were collected at study baseline (day 0) and on days 7, 28, and 56. The samples were collected in the morning before dosing with study drug and processed by 1 centralized laboratory.

An antidepressant (fluoxetine, citalopram, bupropion, or venlafaxine) was provided on study days 8 to 56. Limited doses of benzodiazepines for anxiety or zolpidem for sleep disturbance were used if clinically indicated. Changes in the selection of study antidepressant required sponsor approval. Other antidepressants, antipsychotics, and mood stabilizers were prohibited during the 7-day screening process and throughout the 56-day study.

STATISTICAL ANALYSIS

All numerically continuous data are summarized using mean (SD) unless otherwise specified. All categorical data are presented using percentages. A prospective statistical analysis plan was followed for all analyses. For the primary end point and all categorical end points, a Fisher exact test was used to compare proportions, and a 95% confidence interval for differences in 2 binomial proportions is presented. For categorical measures (with or without effect of plasma level) involving the proportion of patients with a BPRS-PSS of 50% or greater change from baseline, last-observation-carried-forward (LOCF) imputation was used. For continuous measures of efficacy (with or without effect of plasma level), comparisons are based on a mixed model repeated-measures analysis of covariance of the changes from baseline at each visit, with treatment and visits as fixed effects and intercept and subject as random effects, and a Treatment × Visit interaction term, with the baseline value as a covariate. For all analyses involving plasma levels, plasma level group was also included in the mixed model repeated-measures analysis of covariance model as a fixed effect. Mixed model repeated-measures analyses were performed based on observed data, and imputation methods were not used.

The intent-to-treat (ITT) population included all randomized patients who took at least 1 dose of drug. All analyses were performed using the ITT population and SAS version 9.2 (Cary, NC). The analysis of the primary end point was based on an LOCF imputation model. The safety evaluation was performed using all ITT patients who took at least 1 dose of mifepristone or placebo.

Interim Analysis

A prespecified interim analysis for efficacy and futility was conducted when 50% of the patients were enrolled (n = 226/450). The study was powered at 80% to detect a difference of 13% (37% vs 24%) in response rate between the mifepristone and placebo groups for 1-tailed α of 0.025 with 450 patients. After the interim analysis, the study was stopped by the independent, external Data Monitoring Committee based on the low probability of reaching statistical significance on the primary efficacy end point: mifepristone, 39/110 (35.5%), and placebo, 36/116 (31.0%), χ^2 $P = 0.5$. The study stopped enrolling new patients but did allow all enrolled patients to complete the study.

The present report and analysis is based on the final number of N = 292 enrolled ITT patients (mifepristone, n = 141; placebo, n = 151).

RESULTS

Each site enrolled between 1 and 47 patients. As shown in Table 1, the baseline demographics and characteristics were well balanced across groups. The mean age was 46 years; 55% were female; and two thirds (66%) were black, and one third (32%) were white. Of the 292 patients randomized, 75 discontinued early from the trial (43 placebo, 32 mifepristone) (Supplemental Fig. 1, http://links.lww.com/JCP/A455).

Efficacy

Primary Outcome

As indicated in Table 2, statistically significant differences were not observed between mifepristone and placebo on the categorical primary measure of response of the percentage of patients who demonstrated a 50% or greater reduction in BPRS-PSS scores at both days 7 and 56 (36% for mifepristone vs 32% for placebo, $P = 0.5$). On day 7, an unexpectedly high placebo response rate (44%) occurred versus mifepristone (47%) ($P = 0.6$). A significant difference in response rate was observed on day 28 (mifepristone, 60%; placebo, 48%; $P = 0.03$).

Mifepristone Plasma Level

Of the mifepristone patients, 66.7% (94/141) were in the a priori defined high-PL group (mean [SD], 2815 [1021]ng/mL), 24.8% (35/141) were in the low-PL group (mean [SD], 1257 [297]ng/mL), and 8.5% (12/141) had missing values. A secondary prespecified analysis of the high-PL group demonstrated statistically significant improvement versus placebo at individual time points on days 28, 42, and 56 (Fig. 1). By day 56, 69% of the high-PL group, 57% of the low-PL group, and 56% of the placebo group met the BPRS-PSS response criterion ($P = 0.04$, high-PL vs placebo).

TABLE 1. Baseline Characteristics of All Study Patients

Characteristic	Mifepristone (N = 141)	Placebo (N = 151)	Total (N = 292)	*P*
Age, mean (SD), y	45.4 (9.0); range, 22–62	47.0 (9.5); range, 25–69	46.2 (9.3); range, 22–69	0.1*
Sex, female, %	54	56	55	0.7†
Race, %				0.3†
White	34	29	32	—
Black	64	68	66	—
Other	2	3	2	—
BPRS total score, adjusted mean (SD)	32.9 (6.6); range, 20–49	33.2 (6.2); range, 20–51	33.1 (6.4); range, 20–51	0.4*
BPRS-PSS score, adjusted mean (SD)	11.5 (2.6); range, 8–18	11.9 (2.6); range, 8–19	11.7 (2.6); range, 8–19	0.1*
HAMD-24 score, mean (SD)	38.0 (6.0); range, 20–52	37.7 (6.0); range, 23–58	37.9 (6.0); range, 20–58	0.7*
HAMD suicide question score, mean (SD)	1.1 (1.2); range, 0–3	1.1 (1.2); range, 0–3	1.1 (1.2); range, 0–3	0.7*

*t Test.

†Fisher exact test.

TABLE 2. BPRS-PSS: Proportion With 50% or Greater Reduction at Visit From Baseline (LOCF)

	Proportion With ≥50% Reduction at Visit From Baseline, n (%)						
	Mifepristone				Fisher Exact Test, 2-Tailed *P*		
Study Day	All Mifepristone (N = 141)	High PL* (N = 94, 66.7%)	Low PL* (N = 35, 24.8%)	Placebo (N = 151)	All Mifepristone vs Placebo	High PL* vs Placebo	Low PL† vs Placebo
Primary efficacy end point							
Days 7 and 56	51 (36.17)	37 (39.36)	10 (28.57)	48 (31.79)	0.5	0.3	0.8
Individual study days							
Day 7	66 (46.81)	45 (47.87)	16 (45.71)	66 (43.71)	0.6	0.6	0.8
Day 14	78 (55.32)	56 (59.57)	19 (54.29)	75 (49.67)	0.3	0.1	0.7
Day 28	85 (60.28)	59 (62.77)	21 (60.0)	72 (47.68)	0.03	0.03	0.3
Day 42	86 (60.99)	62 (65.96)	21 (60.0)	80 (52.98)	0.2	0.047	0.6
Day 56	90 (63.83)	65 (69.15)	20 (57.14)	84 (55.63)	0.2	0.04	1.0

*High PL, mifepristone ≥ 1637 ng/mL.

†Low PL, mifepristone < 1637 ng/mL.

Figure 1 shows the results for the individual time points for cortisol, ACTH, and change from baseline in end points of BPRS-PSS, BPRS total, HAMD-24, and C-SSRS across the entire study. Brief Psychiatric Rating Scale measures reveal statistically significant effects for the high-PL group when compared with placebo; however, the data did not show statistical separation on the HAMD-24. The low-PL group was not significantly different from the placebo group on any measure at any time point.

ACTH and Cortisol Effects

We explored whether the attainment of a higher mifepristone plasma level was associated with a greater degree of GR antagonism, as measured by elevations in ACTH or cortisol levels, and whether the measurable biological effects of GR antagonism were related to the clinical antipsychotic effects of mifepristone. In patients receiving mifepristone, both cortisol and ACTH were elevated on day 7 and returned to baseline by day 28 (Figs. 1A, B). Significant correlations were observed among mifepristone-treated patients on day 7 for log mifepristone level and log increases in cortisol (r = 0.28, P = 0.002, n = 130) and ACTH (r = 0.17, P = 0.06, n = 125). As indicated in Figure 1, both the high- and low-PL groups were associated with significantly higher ACTH and cortisol levels at day 7 than the placebo group, with high-PL effect demonstrating the greatest effect.

Safety

Treatment-emergent AEs occurred in 114 (80.8%) and 103 (68.2%) mifepristone and placebo patients, respectively (Table 3). The only serious AEs occurred in 3 mifepristone patients who required hospitalization; the events resolved and were judged by the investigator to be unrelated to study drug. Two patients treated with mifepristone and 4 patients treated with placebo discontinued because of an AE.

No clinically relevant differences in laboratory measures, vital signs, physical findings, or electrocardiograms were observed between the mifepristone and placebo patients.

No statistically significant differences were observed among the 3 groups on suicidality as measured by the C-SSRS (Fig. 1D).

DISCUSSION

In the interim analysis, statistical significance was not met on the primary efficacy end point, and the study was stopped early with enrolment of 292 of a planned 450 patients. Despite the negative primary outcome, this study provides valuable insights:

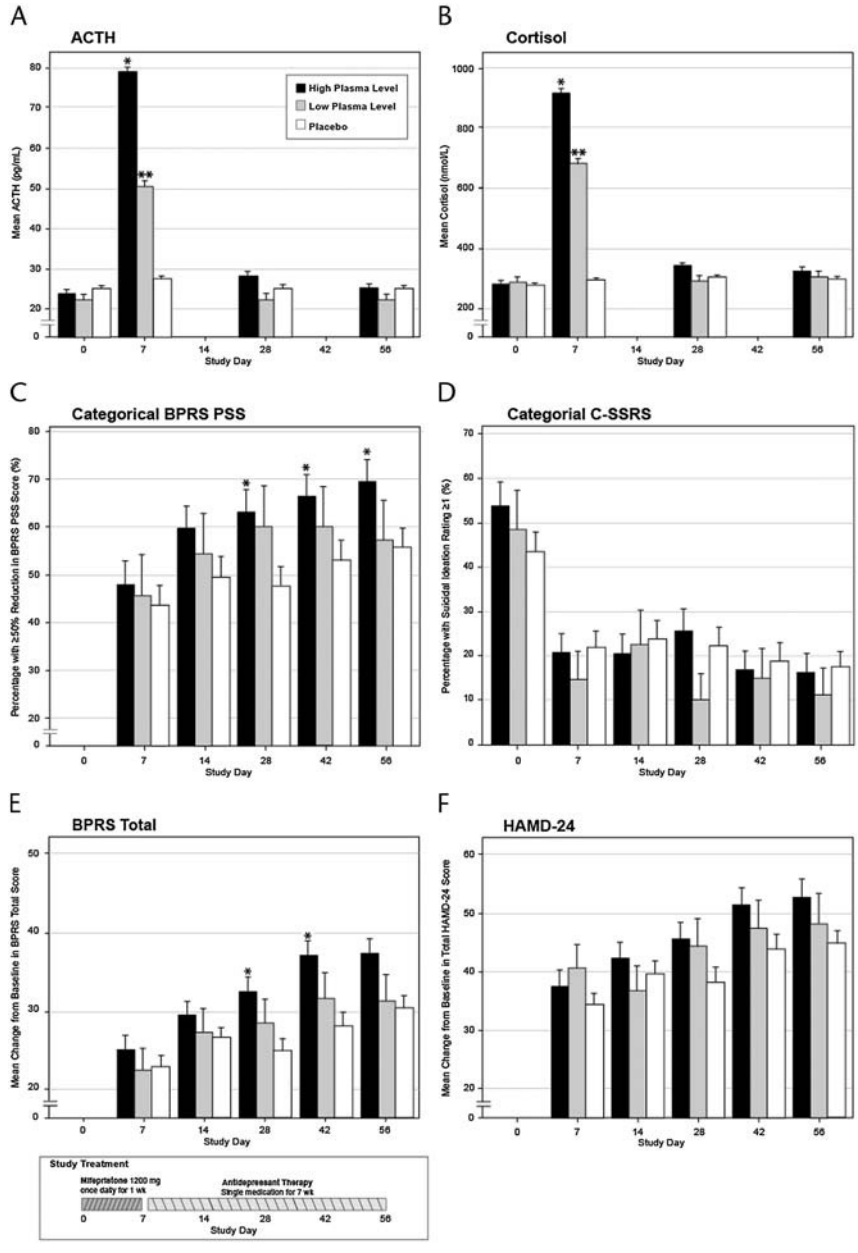
1. On the basis of a secondary prespecified analysis of the a priori mifepristone plasma threshold, this study demonstrated a clear mifepristone plasma level–response relationship, thereby replicating similar findings in previous studies.[17,18]
2. Biological markers of GR antagonism (cortisol and ACTH) were found to be mediators of antipsychotic effect of mifepristone.

Low-PL patients responded much like the patients who were administered with placebo, also confirming previous studies.[17,18] We hypothesize that a therapeutic mifepristone plasma level must be reached to develop a cerebrospinal fluid concentration sufficient to antagonize GR in the brain. Because patients were observed during study drug administration, the pharmacokinetics variability was not a function of treatment adherence.

Plasma ACTH levels and, to a lesser degree, plasma cortisol levels on day 7 were substantial mediators of clinical response. Although statistically significant correlations were observed among mifepristone-treated patients on day 7 for both cortisol and ACTH, the degree of correlation points to a limited amount of variance of change in cortisol or ACTH because of mifepristone plasma level. These data suggest that there may be other biological determinants of GR responsiveness (eg, GR genetic variation).

This study incorporated several design changes from previous studies, including increasing the dose of mifepristone from 600 to 1200 mg and incorporating centralized ratings. Centralized ratings were implemented to attempt to reduce the placebo response rate. However, the placebo response rate at day 7 (44%) was higher than expected and higher than in previous mifepristone PD studies, none of which used centralized ratings. It is plausible that conducting remote interviews over videoconference technology, for patients with PD, contributed to—rather than lessened—the placebo response rate. The third party who provided centralized ratings rotated raters within a patient's course of treatment, which may have intensified the problem.

We note that all patients enrolled in the study were administered a single antidepressant for 7 weeks after 1 week of mifepristone or placebo. The degree of improvement noted in both groups by study end may reflect positive effects of antidepressant monotherapy in this population. Benefits of monotherapy with selective serotonin reuptake inhibitors in PD have been



High plasma mifepristone level ≥1637 ng/mL, n = 94/141 (66.7%); low plasma mifepristone level <1637ng/mL, n=35/141 (24.8%); placebo: n = 151 (100%). In c, imputations are LOCF. In e and f, *P*-values are based on mixed model repeated measures of analysis of variance.

SE bars are presented.

* Statistically significant difference ($P \leq .05$) between high plasma level and placebo groups.

** Statistically significant difference ($P \leq .05$) between low plasma level and placebo groups.

Abbreviations: BPRS, Brief Psychiatric Rating Scale; C-SSRS, Columbia Suicide Severity Rating Scale; HAMD-24, Hamilton Rating Scale for Depression; LOCF, last observation carried forward; PSS, Positive Symptom Subscale.

FIGURE 1. Effects of mifepristone plasma level and antidepressant therapy in patients with PD.

reported.[20] Although such treatment may help explain the high response rates observed after day 7, it does not explain the high placebo response rate seen on day 7 before antidepressant therapy started.

Clinical trials with placebo response rates greater than 30% have diminished ability to statistically separate drug from placebo.[21] Despite the 44% placebo response rate on the BPRS-PSS observed at day 7, a robust signal of treatment effect on BPRS

TABLE 3. AEs Occurring in 5% of Patients or Greater in Any Group

AE	Mifepristone			Placebo (Based on N = 151), %	All Patients (Based on N = 292), %
	All Mifepristone (N = 141)	High PL* (N = 94, 66.7%)	Low PL† (N = 35, 24.8%)		
No. (n) patients who discontinued because of AE	2	1	1	4	76
Patients reporting AEs, %					
Patients with any AE	80.8	91.5	82.9	68.2	74.2
Headache	23.4	27.7	17.1	19.2	21.2
Nausea	17.7	21.3	8.6	12.6	15.1
Constipation	12.1	14.9	8.6	9.3	10.6
Diarrhea	7.8	11.7	0	9.3	8.6
Dry mouth	10.6	12.8	8.6	6.0	8.2
Insomnia	5.7	4.3	8.6	10.6	8.2
Dyspepsia	9.9	13.8	0	6.0	7.9
Dizziness	7.8	7.4	8.6	6.0	6.8
Vomiting	7.8	8.5	2.9	5.3	6.5
Anxiety	5.7	4.3	11.4	6.0	5.8
Pollakiuria	8.5	8.5	11.4	3.3	5.8
Rash	6.4	6.4	8.6	4.0	5.1
Fatigue	6.4	7.4	5.7	2.6	4.5
Abdominal pain	5.0	7.4	0	2.0	3.4

*High PL, mifepristone ≥ 1637 ng/mL.

†Low PL, mifepristone < 1637 ng/mL.

and positive trends on HAMD-24 in patients in the high-PL group were seen on days 28, 42, and 56 (Fig. 1).

Mifepristone 1200 mg daily for 7 days was safe and well tolerated when compared with placebo, confirming earlier safety findings.[18] Placebo- and mifepristone-treated patients discontinued the trial because of AEs at comparable rates (Supplemental Fig. 1, http://links.lww.com/JCP/A455). At the mifepristone dose of 1200 mg, approximately two thirds of the mifepristone patients attained the a priori therapeutic plasma level (1637-ng/mL mifepristone).

There are no FDA-approved medications for the treatment of PD. Targeting the specific biology of hypothalamic-pituitary-adrenal axis dysregulation in these patients could be a welcome advance for the field of psychiatry. A safe and tolerable side effect profile, coupled with a therapeutic plasma level and measurable biological effects associated with treatment response, makes GR modulation a reasonable line of inquiry in this disabling and potentially lethal illness. Future research should target the ability to stratify which patients would achieve high PL in advance of treatment with mifepristone with the hopes of improving the benefit-risk profile.

ACKNOWLEDGMENTS

The authors thank the study participants, without whom this study would never have been accomplished, and the investigators for their participation in this study. Agility Clinical, Inc, administered the interim analysis and received compensation from Corcept Therapeutics. The authors also thank Dat Nguyen, PharmD, and Ruth Ann Gover of Corcept Therapeutics for administrative assistance in review and submission of the manuscript and Caren Rickhoff, MWC, of MedGraphica Medical Writing Services for providing editorial assistance.

AUTHOR DISCLOSURE INFORMATION

Dr Block is an employee and shareholder of Corcept Therapeutics. Dr Belanoff is a cofounder, employee, and shareholder of Corcept Therapeutics. Dr Petrides received compensation as a principal investigator for this study. Dr Kushner received compensation as a consultant for Corcept Therapeutics. Dr Kalin has received compensation as a consultant for Corcept Therapeutics. Dr Schatzberg is a cofounder and shareholder of Corcept Therapeutics.

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