Biological Psychiatry

Archival Report

Combined Analysis of Mifepristone for Psychotic Depression: Plasma Levels Associated With Clinical Response

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ABSTRACT

BACKGROUND: Patients with psychotic depression exhibit elevated cortisol levels. Competitively antagonizing cortisol at the glucocorticoid receptor with mifepristone demonstrated therapeutic benefit in early studies of patients with psychotic depression. We present a combined analysis of all controlled phase 2 and 3 studies to report antipsychotic differences between treatment with mifepristone or placebo and to evaluate the relative contributions to response of attaining an a priori–defined, high mifepristone plasma level and markers of glucocorticoid receptor antagonism (increases in adrenocorticotropin hormone and cortisol) with treatment.

METHODS: Data from five similarly designed double-blind phase 2 or 3 studies evaluating the efficacy and safety of 7-day treatment with mifepristone for the psychotic symptoms of psychotic depression were pooled for analysis (mifepristone $n = 833$; placebo $n = 627$). Clinical assessments were performed at baseline and on days 7, 14, 28, 42, and 56. Mifepristone, adrenocorticotropin hormone, and cortisol samples were collected at baseline and day 7.

RESULTS: Combined results demonstrated meaningful efficacy ($p < .004$) for mifepristone in reducing psychotic symptoms with wide safety margins. Patients in the a priori–defined, high mifepristone plasma level group (≥1637 ng/mL) demonstrated a more significant treatment effect over placebo ($p = .0004$). A number needed to treat of 7 and 48 was observed in the high and low mifepristone plasma level groups, respectively. Adverse events were similar in mifepristone- and placebo-treated patients.

CONCLUSIONS: A high mifepristone plasma level carried the strongest association with response, followed by changes in adrenocorticotropin hormone and cortisol. Therapeutic plasma levels of mifepristone were most likely to be achieved with the 1200 mg/day dose.

Keywords: Combined analysis, Glucocorticoid receptor, HPA axis, Mifepristone, Plasma level, Psychotic depression

https://doi.org/10.1016/j.biopsych.2018.01.008

Psychotic depression (PD) is a severe form of major depression that is characterized by delusions and/or hallucinations and has a prevalence rate of 0.3% to 0.4% (1,2). PD is associated with higher mortality than non-PD because of more frequent suicide attempts (often by violent means) and increased all-cause mortality (3).

Hypercortisolism distinguishes PD from other depressive subtypes (4–8), as indicated by elevated levels of urinary free cortisol (5), elevated serum adrenocorticotropic hormone (ACTH) and cortisol levels (6), and high rates of nonsuppression on challenge with dexamethasone and high postdexamethasone serum cortisol levels (7,8). One hypothesis suggests that elevated cortisol in patients with PD leads to overstimulation of the glucocorticoid receptor (GR), which stimulates the glucocorticoid responsive elements that control dopamine and glutamate leading to psychosis in susceptible individuals (9).

There are no treatments for PD that are approved by the U.S. Food and Drug Administration despite the high rate of PD mortality and morbidity. Standard of care treatment for PD includes electroconvulsive therapy or combination antidepressant/antipsychotic therapy, despite limited supporting controlled study results.

Placebo response rates in psychopharmacologic studies have steadily increased over the past 3 decades, significantly hampering the development of new therapies (10,11). While earlier studies of PD reported relatively low placebo response rates, studies over the past decade have reported significantly higher rates of response to placebo (12,13).

In 1985, Schatzberg *et al.* (9) proposed that reducing the effects of cortisol (by lowering cortisol levels or antagonizing cortisol's effects at GR) could decrease psychotic symptoms in patients with PD. Belanoff *et al.* (14) observed that antagonism of GR with 4-day administration of mifepristone (a potent competitive GR antagonist) under double-blind, placebo-controlled crossover conditions rapidly and durably reversed the psychotic symptoms of PD in a small number of patients. Subsequently, a number of open-label and double-blind trials

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ISSN: 0006-3223

have been conducted by both Corcept Therapeutics (Menlo Park, CA) and independent researchers (13,15–21). In all studies, mifepristone has produced response rates numerically superior to placebo; however, statistical significance has been less consistently observed. GR antagonism with mifepristone leads to significant increases in plasma ACTH and serum cortisol through the inhibition of negative feedback loops in the hypothalamic-pituitary-adrenal (HPA) system (17). Higher plasma levels of mifepristone are associated with more robust changes to ACTH and cortisol (21). In one small pilot study, increases in cortisol after 1 week of treatment were associated with improvement in psychosis several weeks later (15). All of the trials have been published previously (13,17,18,20,21), and four were reviewed recently by Schatzberg (15).

We provide a combined analysis of the five similarly designed double-blind phase 2 and 3 studies of mifepristone to treat PD sponsored by Corcept Therapeutics. The composite data from these studies in patients with PD (mifepristone n = 833; placebo n = 627) indicate that 7 days of treatment with mifepristone can reduce the psychotic symptoms of PD for periods of up to 8 weeks and is both safe and well tolerated. Moreover, data indicate that the day 7 therapeutic mifepristone plasma level (≥1637 ng/mL) and two mediators demonstrating the extent of GR antagonism, posttreatment increased ACTH levels and cortisol, have a strong association with treated patients' reduction in psychotic symptoms.

METHODS AND MATERIALS

General Study Design

Patients with PD were randomized to 7 days of double-blind treatment with mifepristone or placebo. Entry criteria for four of the five studies (study 1 was the exception) also included a minimum derived baseline Brief Psychiatric Rating Scale (BPRS) positive symptom subscale (PSS) of 8 or above. An antidepressant that had been approved by the U.S. Food and Drug Administration was administered for 7 or 8 weeks of the 8-week trials. Patients enrolled in these studies had not been taking antidepressants or antipsychotics for 7 days (30 days for fluoxetine) before enrollment. Mifepristone doses varied across studies (300, 600, or 1200 mg/day). All patients signed informed consent, and four of five studies were listed at clinicaltrials.gov (study 1 was conducted before regulations were established).

Combined Analyses

The combined analysis of data from these five separate studies uses one set of consistent statistical methods, based on an a priori–defined statistical analysis plan.

Efficacy Measurements

For all five studies, efficacy was measured using the overall 18-item BPRS score, the 4-item PSS of the BPRS, and the 24-item Hamilton Depression Rating Scale (HDRS). The PSS subscale, the primary scale for these analyses, is derived by summing the ratings across all four items (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content) and subtracting 4 because absence of a symptom is designated as 1 on the scale. This is consistent with the previous reporting of all efficacy analyses.

The primary end point in all studies was the proportion of patients with a ≥50% reduction from baseline on the BPRS PSS. All studies used the intent-to-treat population as the basis for all primary analyses. All subjects needed at least one postbaseline BPRS measurement to be included in the analyses for the primary end point. Response was defined as a categorical reduction of ≥50% in BPRS PSS from baseline at both day 7 and the final visit (day 28 in studies 1 and 3 and day 56 in studies 2, 4, and 5).

Analyses of the BPRS PSS percentage change from baseline were carried out with both the last observation carried forward (LOCF) and observed cases methods. The LOCF analysis carries forward the last postbaseline observation. The observed cases analysis uses only observed data with no imputation of missing values. We show the LOCF analyses because LOCF was the primary imputation method stipulated in the individual study's statistical analysis plans, as it was the preferred regulatory imputation method at the time the studies were conducted. LOCF is used herein where specifically indicated.

Study 1 did not require a minimal baseline PSS score for study inclusion. For this combined analysis, we included only those patients with a derived BPRS PSS ≥8 (159 of 221 enrolled patients). In addition, study 1 was designed to use day 28 as the time point of sustained efficacy; one third of study 1 subjects also continued to a day 56 visit. The day 28 value from study 1 was used for analysis.

For all studies, day 7 denotes rapid response, and the primary day denoting sustained response (day 28 for studies 1 and 3; day 56 for studies 2, 4, and 5) is termed the primary sustained response day.

Laboratory Measurements

Trough mifepristone plasma samples were obtained in all studies on day 7, before administration of the final dose of study drug, with analysis conducted by high-pressure liquid chromatography by MicroConstants (San Diego, CA) (13). A receiver operating characteristic hypothesis-generating analysis was conducted on the combined data from previously completed trials 1, 2, and 4. This receiver operating characteristic approach identified the mifepristone plasma threshold of 1637 ng/mL as optimal for discriminating responders from nonresponders with the greatest specificity and sensitivity. A mifepristone plasma level ≥1637 ng/mL is defined as a high plasma level (HPL); a mifepristone plasma level <1637 ng/mL is defined as a low plasma level (LPL). This plasma mifepristone threshold of 1637 ng/mL was first selected as an a priori end point and applied to study 5 and was then later selected a priori for this combined analysis. Cortisol and ACTH levels were obtained in all studies at baseline and day 7 and were measured by radioimmunoassay. Because the cortisol and ACTH measurements were analyzed by different laboratories for different studies, their percentage change rather than their absolute change was calculated to standardize across studies.

Statistical Analyses

Data from all five studies were available for statistical analysis, representing mifepristone doses of 300 mg (n = 110), 600 mg

(n = 471), 1200 mg (n = 252), and placebo (n = 627). Results are presented by all doses combined (300 + 600 + 1200 mg, n = 833) versus placebo (n = 627), by individual dose versus placebo, and by groups above and below the mifepristone plasma level threshold of 1637 ng/mL. Patients with insufficient baseline PSS scores from study 1 (n = 72) were removed from the analysis, leading to an intent-to-treat efficacy sample size of n = 1388 (mifepristone n = 793, placebo n = 595).

An a priori statistical analysis plan was implemented for the combined analysis of the 1388 patients described above. Analysis of the primary efficacy end point used a Fisher's exact test to compare proportions and a 95% confidence interval to compare differences in two binomial proportions. Analysis of continuous measures of efficacy including the BPRS PSS percentage change from baseline and the HDRS total score percentage change from baseline to subsequent study visit is based on a mixed model repeated measures analysis of covariance in which treatment and visit are fixed effects, intercept and subject are random effects, and a treatment by visit interaction term, with the baseline value as a covariate, was included. The 95% confidence interval for differences in least square means are presented in forest plots. For interpretation of clinical relevance, the number needed to treat (NNT) was calculated for the primary efficacy end point. The NNT analysis was conducted for both HPL and LPL groups of patients. The number needed to harm (NNH) was calculated using dropouts due to adverse events (AEs). Effect size based on two independent samples was used. Cohen's d effect size descriptors are applicable herein (22). All analyses were performed using SAS software (version 9.2; SAS Institute, Inc, Cary, NC). $p \leq .05$ was considered statistically significant.

RESULTS

Combined Analysis (Studies 1–5)

The baseline characteristics of the 1460 patients are summarized in Table 1 (mifepristone n = 833; placebo n = 627). No statistically significant differences in baseline characteristics were identified.

Dropout rates were 18.5% and 19.2% for the patient groups who received mifepristone and placebo, respectively. The primary efficacy analyses for all intent-to-treat patients (n = 1388; mifepristone n = 793, placebo n = 595), independent of plasma level, indicated mifepristone separated significantly from placebo on the primary end point (mifepristone 36.8%, placebo 28.5%; p = .004) (Table 2).

In Supplemental Table S1, the percentage changes from baseline in BPRS PSS by visit (weeks 1, 2, 4, and 8) indicate significant separation of drug over placebo by week 2 and continuing through week 8. The 95% confidence interval for the mean differences from placebo are displayed in Figure 1.

To assess the clinical relevance of mifepristone plasma level, the NNT for meeting response criteria on the BPRS PSS was calculated by plasma level group. Table 3 provides the responder proportion based on days 7 and 56 by the LOCF method, and day 7 and primary sustained response day by the observed cases method. The group of patients with mifepristone plasma level ≥1637 ng/mL are referred to as HPL and the group of patients with mifepristone plasma level <1637 ng/mL as LPL. As indicated in Table 3, an NNT of 7 was observed in the HPL mifepristone-treated group compared with an NNT of 48 in the LPL mifepristone-treated group. Combined (HPL + LPL) demonstrated an NNT of 12 when compared with placebo. In the HPL group, the NNTs for each dose tested (300, 600, or 1200 mg/day) were 7, 8, and 8, respectively.

Although mifepristone does not have linear pharmacokinetics, higher doses do yield higher plasma levels that plateau at doses >1200 mg/day. Mifepristone plasma levels ≥1637 ng/mL were found in 25% (24/97) of the 300 mg/day group, 44% (173/396) of the 600 mg/day group, and 65% (146/225) of the 1200 mg/day group.

The magnitude of change from baseline in day 7 ACTH and cortisol levels was significantly correlated with day 7 mifepristone plasma level; the correlation was stronger for cortisol

Table 1. Baseline Characteristics of All Study Subjects

Characteristics	Mifepristone (n = 833)	Placebo (n = 627)	Total (N = 1460)	p Value
Gender, Female, %	57.9	60.4	59.0	.3[a]
Race, %				.4[a]
White	61.3	56.0	59.0	—
Black	32.7	36.4	34.3	—
Other	6.0	7.6	6.7	—
Country, %				
United States	85.1	80.4	83.1	.1
Eastern Europe (e.g, Bulgaria, Croatia, or Serbia)	14.9	19.6	16.9	
Age, Years, Mean (SD), Range 18–77	44.7 (11.6)	44.7 (11.2)	44.7 (11.4)	.99[b]
BPRS PSS Score, Mean (SD), Range 0–19	10.7 (2.5)	10.7 (2.6)	10.7 (2.5)	.8[b]
BPRS Total Score, Mean (SD), Range 30–100	53.9 (8.0)	53.6 (7.2)	53.7 (7.7)	.5[b]
HDRS Total Score, Mean (SD), Range 20–61	38.0 (7.7)	38.2 (6.7)	38.1 (7.3)	.7[b]
BPRS PSS >8.0, %	95.3	94.4	94.9	.5[a]

BPRS, Brief Psychiatric Rating Scale; HDRS, Hamilton Depression Rating Scale; PSS, positive symptom subscale.
[a]Fisher's exact test.
[b]t test.

Table 2. Primary and Secondary Efficacy Analyses, Intent to Treat Population, All Five Studies

	Mifepristone (n = 793)	Placebo (n = 595)	Difference Mifepristone − Placebo	p Value[a]
Populations, n				
ITT (n = 1388)	793	595		
ITT LOCF (n = 1335)	761	574		
ITT non-LOCF (n = 1145)	654	491		
Primary Analysis Endpoint: Rapid and Sustained Response (Day 7 and PSRD), % (± SE%)				
≥50% Reduction in BPRS PSS for day 7 and PSRD (LOCF)	37.2 (1.8)	29.4 (1.9)	7.8 (2.6)	.0035
Secondary Analyses, % (± SE%)				
≥50% Reduction in BPRS PSS for days 7 and 56 (non-LOCF)	35.1 (1.9)	27.3 (2.1)	7.8 (2.9)	.0076
≥50% Reduction in BPRS PSS for days 7 and 56 (LOCF)	37.2 (1.7)	29.8 (1.9)	7.4 (2.6)	.0051
≥50% Reduction in BPRS PSS for days 7 and 28 (non-LOCF)	37.0 (1.8)	29.9 (2.1)	7.1 (2.8)	.0107
≥50% Reduction in BPRS PSS for days 7 and 28 (LOCF)	37.6 (1.8)	30.0 (1.9)	7.6 (2.6)	.0043

If there was no postbaseline observation, then no LOCF was calculated.

BPRS, Brief Psychiatric Rating Scale; ITT, intent-to-treat; LOCF, last postbaseline observation carried forward; PSRD, primary sustained response day; PSS, positive symptom subscale; SE, standard error.

[a]Fisher's exact test.

(r = .30, $p < .0001$, n = 670) than it was for ACTH (r = .19, $p <$ .0001, n = 646). The change in ACTH significantly and strongly correlated with the change in cortisol levels (using logarithms, Pearson's r = .47, $p < .0001$, n = 655).

In Figure 1 and Table 4, the HPL group demonstrated significantly increased response rates on the primary efficacy variable (p = .0004), as well as in their increases in day 7 ACTH and cortisol values compared with the LPL and placebo groups. The HPL group's significantly greater increase in ACTH and cortisol (Table 4) demonstrates an increased level of GR antagonism. This greater level of biologic effect is correlated with statistically significant improvements in clinical outcome as measured by changes in the BPRS PSS.

We assessed the relative effects of mifepristone versus placebo on symptoms of depression as measured by HDRS scores. As indicated in Figure 2, mifepristone separated significantly from placebo on 50% reduction in HDRS from baseline at weeks 4 and 8 only in only those patients who attained the therapeutic blood level (HPL). In Supplemental Table S2 we present analyses of percentage change from baseline in HDRS by individual study day and by plasma level group.

We conducted an analysis of the relative mediation effects of ACTH, cortisol, and plasma level of drug as detailed in Figure 3. Path A represents the change in plasma ACTH and cortisol levels on day 7 based on the effect of treatment with mifepristone. Path B represents a weaker association between change in both ACTH and cortisol levels on day 7 and a reduction in psychotic symptoms for up to 8 weeks. Path C, the mifepristone plasma level, represents the strongest association observed with response, as measured by a reduction in psychosis. The difference between the HPL and LPL groups on response is seen in Table 4 and Figures 1 and 2. We also show the differences between the two groups in the five studies in Table 3.

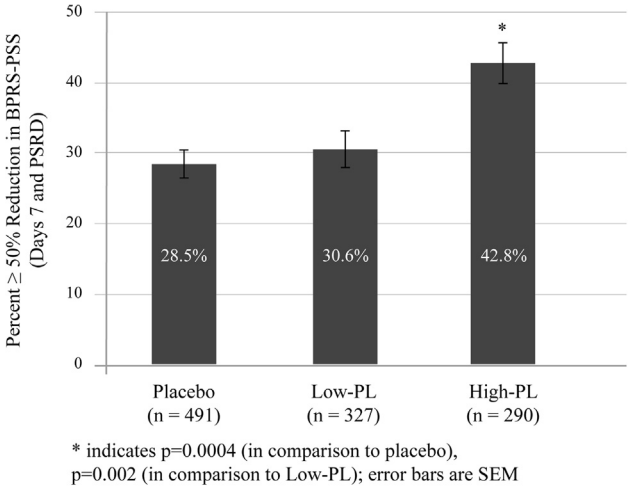


Figure 1. Mifepristone plasma level (PL): Clinical response. BPRS, Brief Psychiatric Rating Scale; PSS, positive symptom subscale; PSRD, primary sustained response day.

Safety

AEs from all five studies (n = 1460) were evaluated by dose group and by all doses combined. Treatment emergent AEs were reported in 556 (66.7%) mifepristone-treated patients and 386 (61.6%) placebo-treated patients. There were three deaths reported: two patients who received mifepristone and one patient who received placebo. More detailed AE descriptions are listed in Table 5.

Overall, the safety of mifepristone versus placebo was comparable, with a similar number of events noted in each group. The NNH was calculated using the outcome of study dropouts due to AEs. For all studies combined, the NNH for mifepristone was incalculable because dropouts due to side effects were higher for placebo (1.6%) than for mifepristone (1.4%). In two studies, dropouts because of AEs were higher for mifepristone than placebo (1.0% vs. 0.9%, NNH = 1000 in study 1; 2.4% vs. 1.6%, NNH = 126 in study 3). Mifepristone appeared safe and well tolerated across all three dosage groups. The rates of treatment emergent AEs were similar across placebo (62%), mifepristone total (67%), mifepristone

Table 3. Responders Number Needed to Treat Day 7 and Primary Sustained Response Day (Last Observation Carried Forward Not Used)

Studies, Doses	Treated Group Above vs. Below PK Threshold (n)	Treatment Group Response Rate (± SE)	Effect Size[a]	NNT, Placebo Rate, Study-Specific
All 5 Studies Combined	All treated (654)	36.8 (1.9)	0.18	12
	HPL (290)	42.8 (2.9)	0.30	7
	LPL (327)	30.6 (2.6)	0.05	48
	Placebo (491)	28.5 (2.0)	–	–
Study 1, 600 mg	All treated (57)	61.4 (6.4)	0.56	4
	HPL (26)	53.8 (9.8)	0.42	5
	LPL (30)	66.7 (8.6)	0.67	3
	Placebo (72)	33.3 (5.6)	–	–
Study 2, 600 mg	All treated (122)	30.3 (4.2)	0.16	14
	HPL (51)	37.2 (6.8)	0.31	7
	LPL (66)	24.2 (5.3)	0.02	125
	Placebo (111)	23.4 (4.0)	–	–
Study 3, 600 mg	All treated (106)	23.6 (4.1)	0.03	74
	HPL (39)	28.2 (7.2)	0.14	17
	LPL (64)	20.3 (5.0)	−0.05	–[b]
	Placebo (108)	22.2 (4.0)	–	–
Study 4, 300, 600, and 1200 mg	All treated (252)	39.3 (3.1)	0.15	14
	HPL (89)	52.8 (5.3)	0.42	5
	LPL (138)	30.4 (3.9)	−0.04	–[b]
	Placebo (81)	32.1 (5.2)	–	–
Study 5, 1200 mg	All treated (117)	38.5 (4.5)	0.10	21
	HPL (85)	38.8 (5.3)	0.11	19
	LPL (29)	31.0 (8.6)	−0.06	–[b]
	Placebo (119)	33.6 (4.3)	–	–

HPL, high mifepristone plasma level (≥1637 ng/mL); LPL, low mifepristone plasma level (<1637 ng/mL); NNT, number needed to treat; PK, pharmacokinetic; PSRD, primary sustained response day; SE, standard error.

[a]Effect size equals twice the two-sample *z* test for difference in proportions (vs placebo) divided by square root of total sample size. Negative effect sizes are based on treated proportion less than placebo proportion.

[b]Placebo > mifepristone, NNT is not calculable.

HPL (69%), and mifepristone LPL (65%) groups. There was no statistically significant difference in rates of AEs between mifepristone HPL and LPL groups.

DISCUSSION

The overall results of this combined analysis demonstrate statistical significance of mifepristone in reducing the psychotic symptoms of PD, especially in the HPL group, and with wide safety margins. The clinical impact of this treatment effect is best demonstrated by an NNT of 12 for all mifepristone-treated patients and an NNT of 7 in those patients in the HPL group.

The administration of an agent for 1 week produced a response lasting 8 weeks and suggests that the biologically targeted treatment may have long-term beneficial effects. The half-life of mifepristone is approximately 85 hours at steady state, so it would have been largely cleared two weeks after the last dose. In the combined analysis, mifepristone separated significantly from placebo in the percentage of patients who met the a priori–defined response criterion of a 50% reduction in BPRS PSS scores at day 7 and primary sustained response

Table 4. Association of Response and Mifepristone Plasma Concentration Levels, Treated Subjects Only

Mifepristone Plasma Concentration Levels (Day 7) Categories (*n* = 654)	≥50% Reduction in BPRS PSS for Day 7 and PSRD, % (*n*/*N*)	Mifepristone Plasma Concentration Levels, ng/mL, Mean ± SD	Day 7–Baseline, Mean ± SD (*n*)			
			Change in Cortisol Levels, nmol/L	Percent Change in Cortisol Levels	Change in ACTH Levels, nmol/L	Percent Change in ACTH Levels
HPL, ≥1637 ng/mL (*n* = 290)[a]	42.8 (124/290)	2575 ± 823 (*n* = 290)	590 ± 378 (269)	223 ± 179 (269)	44 ± 61 (262)	273 ± 372 (262)
LPL, <1637 ng/mL (*n* = 327)[a]	30.6 (100/327)	1125 ± 435 (*n* = 327)	423 ± 412 (304)	148 ± 189 (304)	28 ± 37 (292)	172 ± 230 (292)

ACTH, adrenocorticotropic hormone; BPRS, Brief Psychiatric Rating Scale; PSS, positive symptom subscale; HPL, high mifepristone plasma level; LPL, low mifepristone plasma level; PSRD, primary sustained response day.

[a]HPL vs. LPL group (p = .002).

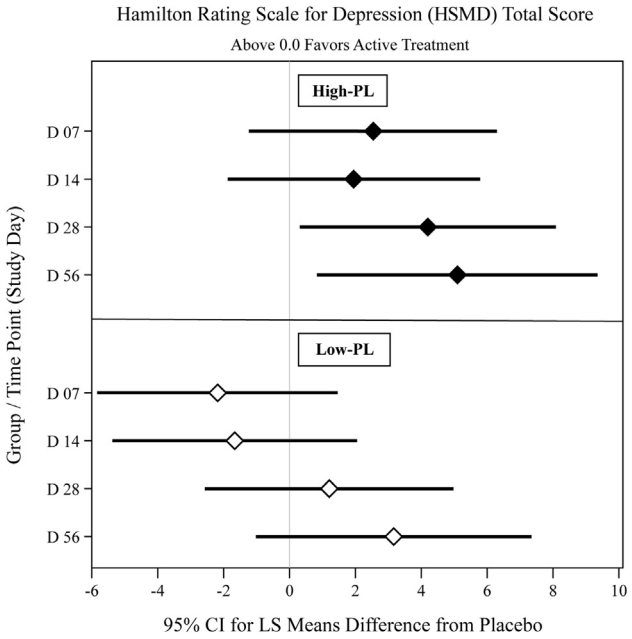


Figure 2. Hamilton Rating Scale for Depression total score. Percent change from baseline for high mifepristone plasma level (PL) and low PL vs. placebo. CI, confidence interval; LS, least significant.

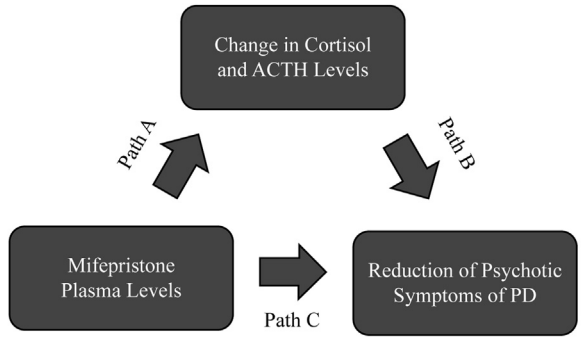
day ($p < .004$), independent of plasma level analyses. When the same analysis was conducted comparing the HPL versus placebo groups, the statistical separation from placebo was further increased ($p = .0004$), confirming the plasma level effect that was observed previously in each of the individual five studies (Figure 1).

Each individual study was characterized by relatively high placebo response rates starting at week 1. Study 1 did report statistically significant separation using a 50% reduction in BPRS PSS at weeks 1 and 4 and weeks 1 and 8 (18), but statistical significance was not achieved on the primary end point in studies 2 through 5.

Higher than anticipated placebo responses were observed in studies 2 through 5, consistent with the unfortunate trend noted in studies of many psychiatric indications (10,11,23). However, there may be additional contributing factors to the high placebo response rates in these studies. For one, estimates of placebo response rates from early PD studies were derived largely from single-blind studies, possibly underestimating the true double-blind placebo response rates. Second, many of the patients enrolled in the five studies reported here were recruited as outpatients but hospitalized as required by protocol, potentially introducing nonspecific treatment effects (12). Posener *et al.* (6) reported that in patients with PD (but not in control subjects) cortisol levels decline during hospitalization. Third, earlier literature suggested that tricyclic antidepressants alone were less effective in the treatment of PD than in non-PD, a view challenged by a more recent study evaluating selective serotonin reuptake inhibitor monotherapy in PD (24). In these five studies, all patients received an antidepressant that was approved by the U.S. Food and Drug Administration for 7 or 8 weeks of the 8-week trials.

A minimum PSS score of 12, indicating at least moderate levels of psychosis, was required for study entry. This could have led to baseline score inflation. A high response rate at week 1 is in keeping with score inflation at baseline. Arguing against this is study 5, which used centralized blinded raters for this study's entry assessment, and surprisingly had the highest 1-week placebo response rate of all five studies.

Despite high placebo response rates observed in the individual studies, the combined analysis of all mifepristone-treated patients separated from placebo-treated patients with statistical significance on the primary end points, and this effect was further accentuated when incorporating the a priori–defined therapeutic mifepristone plasma level of 1637 ng/mL. The receiver operating characteristic methodology used to determine the cut point between HPL and LPL is a statistical analysis that seeks to optimize the discrimination (i.e., sensitivity and specificity) between responders and nonresponders, and hence the cut point is a statistical value rather than a biological value. Figure 1 demonstrates that in this combined analysis of five studies, the mifepristone HPL group separates strongly from the placebo-treated group on the primary efficacy end point in contrast to the mifepristone LPL group, which did not. Results were similar for the LOCF and observed cases analyses. At 1200 mg of mifepristone per day, approximately 65% of subjects attained a therapeutic plasma level of mifepristone.



Path A represents the change in plasma ACTH and Cortisol levels on Day 7, based on the effect of treatment with mifepristone.

Path B represents a weaker association between change in both ACTH and Cortisol levels on Day 7 and reduction in psychotic symptoms up to eight weeks.

Path C represents the strongest associations observed with response, namely with the mifepristone plasma level.

Figure 3. Effect on reduction of psychotic symptoms of psychotic depression (PD), mifepristone plasma levels, and cortisol and adrenocorticotropic hormone (ACTH) analysis results. Using a stepwise logistic regression where the end point is a ≥50% reduction in Brief Psychiatric Rating Scale at each visit up to day 56, we find that the most significant reduction in Brief Psychiatric Rating Scale symptoms comes with visit or days since start of study medication. The longer from the start of treatment, the greater the response (≥50% reduction in Brief Psychiatric Rating Scale positive symptom subscale), with an odds ratio of 1.55 ± 0.017. The high mifepristone plasma level vs. low mifepristone plasma level odds ratio was 1.16 ± 0.058, which represents path C. The percentage change in cortisol as an effect of treatment with mifepristone had an odds ratio of 1.06 ± 0.02 per a 100% change in cortisol levels, which represents path B. The correlation between numerically continuous plasma levels and percentage change in cortisol levels on day 7 was 0.19 ($n = 610$), which represents path A. All p values are highly statistically significant.

Table 5. Safety Population (*N* = 1460): Preferred Terms With Frequency of at Least 5%

System Organ Class (Disorders)	Preferred Term	Mifepristone 300 mg (*n* = 110)	Mifepristone 600 mg (*n* = 471)	Mifepristone 1200 mg (*n* = 252)	Mifepristone All Doses (*n* = 833)	Placebo (*n* = 627)
Patients With ≥1 TEAE (%)		66.4	62.2	75.4	66.7	61.6
Gastrointestinal	Nausea	18.2	14.0	17.5	15.6	11.2
Nervous System	Headache	18.2	9.3	23.8	14.9	11.6
Nervous System	Dizziness	8.2	6.6	11.5	8.3	5.4
Gastrointestinal	Dry Mouth	4.5	5.1	11.5	7.0	5.4
Gastrointestinal	Diarrhea	9.1	4.0	9.1	6.2	5.1
Gastrointestinal	Constipation	2.7	4.2	9.5	5.6	5.7
Psychiatric	Insomnia	3.6	5.7	5.2	5.3	6.2
General Disorders and Administration Site Conditions	Fatigue	8.2	3.6	5.6	4.8	3.3
Gastrointestinal	Vomiting	4.5	3.8	7.5	5.0	2.6
Psychiatric	Anxiety	5.5	3.0	5.2	4.0	3.7
Gastrointestinal	Dyspepsia	1.8	2.1	9.5	4.3	3.2
Nervous System	Somnolence	7.3	2.8	3.2	3.5	3.8
Musculoskeletal and Connective Tissue	Back Pain	6.4	1.7	2.8	2.6	2.7
Skin and Subcutaneous Tissue	Rash	0.9	1.7	5.2	2.6	1.9

Multiple adverse events for each specific adverse event preferred term are only counted once for each subject. Adverse events are listed by highest percentage order in the "All Doses" column. The preferred term is listed if a frequency of ≥5% in any column is calculated.

TEAE, treatment emergent adverse event.

These statistically significant differences appeared clinically meaningful as evidenced by an overall NNT of 7 in the HPL mifepristone-treated patient group. In patients who did not attain the therapeutic mifepristone plasma level, the NNT was 48, indicating a substantially lower treatment effect than the HPL group. The NNT of 7 for the HPL group compares favorably to antipsychotic agents approved in the United States, including olanzapine (OLZ). The data presented indicate that the antipsychotic effect of mifepristone is indeed based on adequate mifepristone plasma level exposure. When results were assessed dividing the overall sample by dose received (300, 600, or 1200 mg/day), similar results were observed, with NNTs of 7 or 8 noted across the three doses. Thus, our data appear to support the hypothesis that 7 days of mifepristone, especially at sufficient plasma levels (HPL), is beneficial in reducing the psychosis of PD by the end of week 1 and sustains this reduction through week 8.

While inexact, it is informative to compare this study with others in psychotic disorders, including PD. A widely cited 6-week trial of clozapine versus chlorpromazine in patients with schizophrenia used a response criterion of a 20% reduction in BPRS total score, a far lower response threshold than was used here (25). In a review of antidepressants plus antipsychotics versus antidepressants alone in PD, an NNT of 10 was observed in favor of the combination on a 50% reduction in HDRS (25) with no assessment for the BPRS PSS. In another trial investigating treatments for PD (12), a comparison of OLZ–fluoxetine combination (OFC) versus placebo yielded an NNT of four for a 50% reduction in HDRS scores; OLZ monotherapy versus placebo produced an NNT of 18. No NNT was calculated for BPRS PSS. The percent reduction in BPRS PSS scores was smaller than what we observed in the mifepristone trials.

Across the 300 to 1200 mg/day doses, higher mifepristone plasma levels were associated not only with a greater likelihood of clinical response but also with significantly greater pharmacologic/biologic effects at the level of the GR as evidenced by a rise in day 7 ACTH and cortisol levels. A 200% rise (i.e., a tripling over baseline) in ACTH and/or cortisol levels observed for mifepristone plasma levels ≥1637 ng/mL reflected sufficient GR antagonism necessary to generate a clinical response, as can be seen in Table 4. The HPA axis is a closed negative feedback loop in which cortisol secreted by the adrenal glands feeds back to GRs in the pituitary and hypothalamus, resulting in reduced cortisol secretion. In contrast, antagonizing the pituitary and hypothalamic GRs with the GR antagonist mifepristone leads to an increase in cortisol secretion. However, this rise in cortisol levels is insufficient to overcome the central antagonism of cortisol by mifepristone, which readily crosses the blood-brain barrier. There is an overall lowering of the effect of cortisol with the use of mifepristone despite increased levels of circulating cortisol.

The association between therapeutic medication plasma levels and biological correlations related to medication are rare with agents in psychiatry. That mifepristone plasma level was a stronger predictor of a positive clinical outcome than was change in cortisol or ACTH suggests that the drug's effects on psychosis may be mediated by antagonism of GRs outside of the HPA axis. For example, Vendruscolo *et al.* (26) demonstrated that GR in the amygdala is under positive control rather than the negative control observed in the HPA axis. In the preclinical portion of the report, mifepristone blocked upregulated corticotropin-releasing hormone responses to cortisone and resulted in a reduction of alcohol consumption. In patients, mifepristone increased cortisol levels but reduced alcohol consumption, and hence the effect observed may be due to the effects of GR modulation outside of the HPA axis,

including effects on dopamine or glutamate. Thus, the change in the HPA axis may only be an indirect measure of antipsychotic effect.

In addition to low and clinically meaningful NNTs for mifepristone in the studies, the drug appeared to be safe and well tolerated. Overall dropout rates for any reason were less than 20% in the mifepristone trials compared with 56% in the OFC versus OLZ trial (12). In that trial, dropouts due to side effects were 10% for OLZ, 20% for OFC, and 6% for placebo. The NNHs were 25 for olanzapine and 7 for OFC. In the mifepristone combined dataset, dropout rates due to treatment emergent AEs were 1.4% in the placebo arm and 1.2% in the mifepristone arm. In three of the mifepristone studies, placebo dropout rates due to AEs were numerically larger than were those for mifepristone. NNHs using dropouts due to side effects in the remaining two were 126 and 1000, respectively. The NNH data for mifepristone indicate wide safety margins for 7 days of treatment in patients with PD.

When one takes into account the common cardiovascular and metabolic comorbidities that accompany PD (3), the safety profile of medications become especially relevant. The atypical antipsychotic medications commonly used in psychotic disorders can have profound adverse effects on weight and metabolic parameters, such as glucose tolerance, and can generate other serious AEs, including tardive dyskinesia. An effective medication that can be given for only 7 days to provide a clinical effect lasting up to 56 days with a superior safety profile would be welcome in the field. The administration of mifepristone was not associated with any of the usual side effects seen with atypical antipsychotics.

In summary, a pooled analysis of five studies evaluating the effectiveness of mifepristone in the treatment of the symptoms of PD demonstrated a reduction in psychosis when compared to placebo, especially at HPLs, that are best attained using a 1200 mg/day dose. In addition, the use of mifepristone appears to be safe and well tolerated. Taken together, these data support a high benefit to risk ratio for mifepristone in the treatment of PD, a serious psychiatric disorder for which there are no treatments approved by the U.S. Food and Drug Administration.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by National Institutes of Health/National Institutes of Mental Health Grant Nos. R01 MH0977669 (to CN; principal investigator, R. Scott Mackin), R01 MH101472 (to CN; principal investigator, R. Scott Mackin), and P50-MH100031, R01-MH046729, and R01-MH081884 (to NK).

TSB is an employee of and shareholder in Corcept Therapeutics. HK is an employee and officer of Biomedical Computer Research Institute, Inc., which has consulting contracts with a number of pharmaceutical and device companies, including Corcept Therapeutics. NK has received consulting fees from and previously held shares in Corcept Therapeutics. Corcept has made donations to the University of Wisconsin Department of Psychiatry and the Health Emotions Research Institute. NK has also received consultant fees from CME Outfitters, LLC, an annual honorarium from Pritzker Neuropsychiatric Disorders Research Consortium, and consultant fees from Elsevier for his role as Co-Editor. CN has received consulting fees from Corcept Therapeutics, Janssen, Lundbeck, and Otsuka and lecture honoraria from Lundbeck. JB is a cofounder, employee, and shareholder of Corcept Therapeutics. AS is a cofounder and shareholder of Corcept Therapeutics.

ClinicalTrials.gov: A United States Study of Corlux for Psychotic Symptoms in Psychotic Major Depression, https://clinicaltrials.gov/ct2/show/NCT00130676?term=NCT00130676&rank=1, NCT00130676; An International Study of the Safety and Tolerability of Corlux for Psychotic Symptoms in Psychotic Major Depression, https://clinicaltrials.gov/ct2/show/NCT00146523?term=NCT00146523&rank=1, NCT00146523; A United States Study of the Safety and Tolerability of Corlux for Psychotic Symptoms in Psychotic Major Depression, https://clinicaltrials.gov/ct2/show/NCT00128479?term=NCT00128479&rank=1, NCT00128479; A Study of Mifepristone vs. Placebo in the Treatment of Patients With Major Depression With Psychotic Features, https://clinicaltrials.gov/ct2/show/NCT00637494?term=NCT00637494&rank=1, NCT00637494.

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Received Jul 5, 2017; revised Dec 13, 2017; accepted Jan 12, 2018.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2018.01.008.

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