An 8-Week Open-Label Trial of a 6-Day Course of Mifepristone for the Treatment of Psychotic Depression

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Objective: Several investigations suggest that mifepristone leads to the rapid amelioration of psychotic depression. However, these studies were of short duration (1 week or less) and included subjects who were taking other psychotropic medications. The goals of this study were to extend these findings by conducting an 8-week trial of mifepristone for subjects with psychotic depression who were taking no concomitant psychiatric medications.

Method: Twenty subjects with a DSM-IV major depressive episode with psychotic features (for convenience we use the term *psychotic depression)* taking no psychotropic medications were given a 6-day course of mifepristone and followed as inpatients for a total of 8 weeks. Nonblinded ratings using the Hamilton Rating Scale for Depression (HAM-D) and Clinical Global Impressions scale (CGI) were performed at baseline and at the end of weeks 1, 4, and 8. The Brief Psychiatric Rating Scale (BPRS) was also administered at baseline and after weeks 4 and 8. Subjects were recruited between February 2003 and December 2003.

Results: Significant improvements in HAM-D and CGI scores were shown after 1 week and between weeks 1 and 4 but not between weeks 4 and 8. BPRS scores improved significantly after week 4, while the improvement in BPRS scores between weeks 4 and 8 was of borderline significance.

Conclusion: Mifepristone appears to be a useful intervention for psychotic depression, leading to significant improvements even after a 1-week course of administration. Issues related to its optimal dosing and to prediction of response are discussed, as are the implications of lack of a placebo group and the use of nonblinded ratings in the present study.

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Despite the debate concerning whether unipolar depression with psychosis is a qualitatively distinct, separate syndrome from unipolar depression without psychosis rather than just a quantitatively more severe variant of nonpsychotic depression,[1,2] there is general agreement concerning differences between these 2 presentations of depression. In general, such differences have been found in family history,[3] neuroimaging,[4] and neuropsychological testing studies[5] as well as in other areas.

One major area in which differences have been found has shown that excessive hypothalamic-pituitary-adrenal axis activity is much more prevalent in psychotic depression than in nonpsychotic depression. Two markers of this difference have been higher levels of 24-hour urinary free cortisol[6] and higher rates of nonsuppression when using the dexamethasone suppression test[7] for patients with psychotic depression.

Elevated cortisol activity has been associated with neuropsychological test impairment in patients with Cushing's disease[8] and in depressed patients.[9] Repeated administration of glucocorticoids to healthy test subjects has been reported to result in a variety of cognitive impairments,[10] further suggesting that hypercortisolemia may contribute to the cognitive deficits seen in some depressed patients.

In psychotic depression, the natural feedback loop involving cortisol is thought to be awry, with sustained levels of the hormone creating a chronic stress reaction. El-

evated cortisol leads to elevated dopamine levels, and together these 2 factors may help cause some of the serious problems of psychotic depression, including hallucinations, sleep disturbances, and memory problems.[11]

Another major area in which differences have been found is the response to antidepressants when used alone. Psychotic depression has been shown to respond much more poorly than nonpsychotic depression to tricyclic antidepressants[12] and, in some reports, to the selective serotonin reuptake inhibitors.[13] Patients with psychotic depression typically receive 1 of 2 treatments: an antidepressant given in conjunction with an antipsychotic medication or electroconvulsive therapy (ECT).[14]

Mifepristone (RU486) is a medication that acts as a progesterone antagonist and that shows glucocorticoid receptor antagonism at higher doses.[15,16] It demonstrates high affinity for the low-affinity glucocorticosteroid receptor while showing only weak affinity for the mineralocorticoid receptor, thereby minimizing cushingoid side effects. Case studies have shown mifepristone to effectively treat depression and psychosis associated with Cushing's disease and to produce only a few side effects.[17,18]

Two recent reports have also demonstrated that mifepristone can treat psychotic depression not associated with Cushing's disease.[19,20] In both of these reports, patients showed marked improvements of their condition in 1 week using formal rating scales. There was also the observation that these improvements were maintained after the mifepristone treatment, which lasted 4 days in 1 study[19] and 7 days in the other,[20] although formal data collection did not extend beyond 1 week. However, many of the subjects in both of these studies were taking concomitant medications, thereby making inferences concerning the therapeutic effects of mifepristone less clear.

The purpose of the present study was to extend our understanding of the therapeutic effects of mifepristone in psychotic depression. Unlike previous studies, no subject in the present study was taking concomitant antidepressants, antipsychotics, or mood stabilizers. Unlike previous studies that examined the effects of mifepristone for time periods of less than 1 week, the present study was 8 weeks in length, allowing a better understanding of the time course of therapeutic effects.

METHOD

The study was carried out collaboratively at Alexandria Psychiatric Hospital, Alexandria, Egypt, and at Behman Psychiatric Hospital in Cairo, Egypt. Each site continued enrolling subjects until a combined total of 20 consecutive subjects was entered.

Subjects

All patients admitted to either participating hospital who met DSM-IV-TR[21] criteria for a major depressive episode with psychotic features were screened for inclusion in this study. Patients were between the ages of 18 and 65 years. Female patients were eligible only if they were postmenopausal. Subjects were recruited between February 2003 and December 2003. As part of their routine admission, all potential subjects had routine laboratory tests drawn, an electrocardiogram (ECG) performed, and no concurrent unstable medical conditions or a comorbid substance abuse or dependence diagnosis. All patients were followed as inpatients for the duration of the 8-week study.

Procedure

Either of 2 study doctors (A.R., W.F.) approached eligible patients at each site, and explained the study to them. If agreement to participate was given, subjects were given an informed consent statement to read, discuss, and sign. Informed consent statements were approved by the institutional review boards connected with each hospital.

After the informed consent form was signed, the patient's diagnosis was independently confirmed by the other study doctor at the site. Raters were instructed on the potential difficulties in diagnosing psychotic depression, with emphasis on excluding posttraumatic stress disorder plus depression and on cultural beliefs that could possibly be interpreted as delusions. All ratings were carried out by 1 person at each site. An initial meeting and a second meeting at 6 months were held to insure inter-rater reliability for the scales used. In those meetings, both raters watched several live interviews; independently rated the patients on the Hamilton Rating Scale for Depression (HAM-D), the Brief Psychiatric Rating Scale (BPRS), and the Clinical Global Impressions Scale (CGI); and then discussed rating differences to arrive at an agreement. The eligible subjects were then rated on the 21-item HAM-D,[22] the BPRS,[23] and the CGI).[24] To be eligible to participate, subjects needed a score of 23 or greater on the HAM-D.

After the baseline ratings, all subjects began a 6-day open-label trial of mifepristone given as 200 mg t.i.d., after which the drug was discontinued. Subjects were taking no other psychotropic medications for at least 1 week prior to the baseline ratings but were permitted lorazepam for sleep. The HAM-D was repeated after weeks 1, 4, and 8 of the trial; the BPRS, after weeks 4 and 8; and the CGI, after weeks 1, 4, and 8. Side effects were inquired about at each visit. Subjects who responded poorly after week 1 were evaluated for treatment with ECT.

Statistical Analyses

Results were analyzed using a repeated-measure analysis of variance. Because of dropouts and removals of subjects for ECT, a last-observation-carried-forward (LOCF) analysis was used. However, since there were dropouts due to both therapeutic failure and therapeutic

success, analyses of completers at each point were also performed. When discrepant, both are reported; otherwise, only the LOCF analyses are reported. All statistics were performed using SYSTAT, version 10.2.01 (Point Richmond, Calif.).

The number of responders and remitters was also examined. Since there are no widely accepted criteria for response or remission in psychotic depression, the standard definitions for response and remission of nonpsychotic depression were used, with response meaning a reduction of HAM-D score to 50% or less of baseline score and remission meaning a HAM-D score equal to or less than 7.[25] Alpha was set at .05.

RESULTS

Twenty subjects participated: 14 in Alexandria (10 men and 4 women) and 6 in Cairo (4 men and 2 women). The female subjects were significantly older than the male subjects because of selection criteria (58.17 [SD = 6.5] years vs. 40.86 [SD = 12.0] years, respectively) ($F = 8.343$, $df = 1,16$; $p = .011$), although there was no significant difference in age of subjects between the sites ($F = .514$, $df = 1,16$; $p = .484$) or in the mean age of men and women across the 2 sites ($F = .047$, $df = 1,16$; $p = .831$).

After week 1, 2 subjects were removed from the study because they were judged to be responding poorly, and both received ECT. One, a 68-year-old woman, had a baseline HAM-D score of 32, a baseline BPRS score of 52, and a baseline CGI score of 6. After 1 week, her HAM-D score was 24. She did not receive a 1-week CGI rating. The second, a 53-year-old woman, had a baseline HAM-D score of 34, a baseline BPRS score of 43, and a baseline CGI score of 5. After 1 week, her HAM-D score was 16 and her CGI score was 3. However, within 2 days of these ratings, she showed a significant relapse, with psychosis and severe depression reoccurring.

Eight other subjects left the study after week 4. Seven of these subjects, 5 men and 2 women, were judged to be significantly improved, chose to leave the hospital, and were lost to follow-up. One male patient was judged to be unimproved, withdrew from the study, and received standard treatment.

Two other subjects, who initially responded, relapsed and were withdrawn from the study at week 6. The first was a male patient who received a second 6-day course of mifepristone. This subject had responded dramatically by week 4, with his HAM-D score dropping from 30 to 5, his CGI score dropping from 6 to 1, and his BPRS score dropping from 60 to 20. However, by week 6, he was clinically judged to be relapsing; therefore, another trial of mifepristone was given, to which he responded a second time. The second was a 70-year-old female subject who initially appeared to respond, but by week 6, her condition worsened significantly and she was withdrawn from the study to receive standard treatment.

Table 1. LOCF Data for Each Follow-Up Timepoint After a 6-Day Open-Label Course of Mifepristone for Psychotic Depression[a]

Measure	Baseline	Week 1	Week 4	Week 8
HAM-D	34.15 (6.03)	25.55 (9.25)	10.55 (7.89)	9.30 (7.99)
BPRS	49.75 (8.78)	NA	27.00 (8.73)	25.90 (8.84)
CGI	5.55 (0.69)	4.20 (1.01)	2.15 (1.57)	2.00 (1.62)

[a]All values shown as mean (SD).
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, NA = not applicable.

Using LOCF repeated-measure analyses, subjects showed a significant improvement in HAM-D scores after week 1 ($F = 45.272$, $df = 1,19$; $p < .001$), after week 4 ($F = 75.894$, $df = 2,38$; $p < .001$), and after week 8 ($F = 65.072$, $df = 3,57$; $p < .001$). This same pattern of results was obtained with the CGI scores after week 1 ($F = 30.712$, $df = 1,19$; $p < .001$), after week 4 ($F = 53.759$, $df = 2,38$; $p < .001$), and after week 8 ($F = 55.728$, $df = 3,57$; $p < .001$), and with the BPRS scores after week 4 ($F = 64.362$, $df = 1,19$; $p < .001$) and after week 8 ($F = 62.580$, $df = 2,38$; $p < .001$). Using only data from completers did not change the results for the HAM-D, the CGI, or the BPRS at any timepoint, with all analyses significant at $p < .001$. The means and standard deviations for the HAM-D, the CGI, and the BPRS scores at each week are shown in Table 1 for the LOCF results. Completer results are shown in Table 2.

The time course of the therapeutic response was examined further. Both HAM-D scores ($F = 40.87$, $df = 1,19$; $p < .001$) and CGI scores ($F = 37.18$, $df = 1,19$; $p < .001$) dropped significantly between weeks 1 and 4. However, the HAM-D ($F = 1.54$, $df = 1,19$; $p = .230$), CGI ($F = 1.31$, $df = 1,19$; $p = .267$), and BPRS ($F = 3.03$, $df = 1,19$; $p = .098$) ratings did not significantly change between weeks 4 and 8, although the BPRS rating change was of borderline significance. Using data from completers, again, did not change the results.

After week 1, 2 of the 20 subjects met the criterion for a response, with 1 of those meeting the remission criterion. Two subjects were removed from the study at this time for failure to respond; 1 of these had initially responded but quickly relapsed. After week 4, all 18 of the remaining subjects achieved a response. Eleven of the 18 achieved remission. At week 6, 3 more subjects relapsed. At week 8, 3 subjects who were responders but not remitters at week 4 became remitters. One subject who achieved remission at week 4 no longer met the criterion for remission at week 8, although he still met the criterion for response. This subject's HAM-D score decreased from a baseline score of 27 to a score of 7 on week 4 and a score of 11 on week 8.

Table 2. Completer Data For Each Follow-Up Timepoint After a 6-Day Open-Label Course of Mifepristone for Psychotic Depression

	Baseline		Week 1		Week 4		Week 8	
Measure	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
HAM-D	20	34.15 (6.03)	20	25.55 (9.25)	18	9.50 (7.49)	10	6.10 (4.58)
BPRS	20	49.75 (8.78)	NA	NA	17	24.35 (5.20)	10	23.00 (4.30)
CGI	20	5.55 (0.69)	19	4.11 (0.94)	18	1.72 (1.23)	10	1.50 (1.08)

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, NA = not applicable.

At baseline, there were no significant laboratory, ECG, or physical findings for any subject, nor did any abnormalities appear over the course of the study. Similarly, the subjects did not report any significant side effects from the mifepristone during this study.

DISCUSSION

The present study extends the results of 2 previously reported studies.[19,20] As in those studies, a brief course of mifepristone appeared to significantly impact psychotic depression. Our study also demonstrated that these effects significantly build over the 3 weeks following a 6-day course of mifepristone and generally persist for the following 4 weeks despite no further use of any psychoactive medications.

If replicated, these findings would suggest a resetting of the glucocorticoid system that impacts the expression of psychotic depression for some patients with psychotic depression. Mifepristone has been found to have a half-life of 20 to 30 hours,[15,16] and so a persistence of active medication cannot be invoked to explain these results.

A number of important questions remain unanswered. The optimal dose, dosage schedule, length of a course of treatment, and appropriate follow-up for a course of treatment all need to be determined. For example, after a successful course of treatment with mifepristone, should patients receive antidepressants, as in Belanoff et al.[20]; antipsychotics with antidepressants, as is the recommended treatment for psychotic depression[26]; or another course of mifepristone, as was successfully done with 1 of our patients at week 6?

Similarly, the range of applicability of mifepristone needs further exploration. Several studies have suggested that hypercortisolemia may predict response,[20,27] but further examination is warranted. Similarly, at least 1 study has suggested that mifepristone may be effective in major depression without psychotic features,[28] a finding that needs replication. Mifepristone's utility in other forms of depression such as that in bipolar disorder, postpsychotic depression in schizophrenia, and atypical depression may also be warranted.

Problems with the present study should be noted. First, it was neither blinded nor placebo controlled. However, previous studies[29,30] have shown a low placebo response rate with psychotic depression, and placebo use with this seriously ill group could be ethically challenged. Second, it would have been more helpful to have weekly ratings on all the measures used to better understand the time course for the therapeutic response. Third, no statistical tests were used to assess inter-rater reliability. More systematic collection of side effect data would also have been helpful. Finally, follow-up of early responders would have provided important data.

Nevertheless, the present findings are of note. They hold promise for a more rapid, relatively safe treatment for psychotic depression, and they further confirm the research exploring the role of hormonal influences in the pathophysiology of psychotic depression.

Drug names: dexamethasone (Hexadrol, Decadron, and others), lorazepam (Ativan and others), mifepristone (Mifeprex).

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