

24-Hour Monitoring of Cortisol and Corticotropin Secretion in Psychotic and Nonpsychotic Major Depression

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Background: Considerable research has been devoted to the hypothalamic-pituitary-adrenal (HPA) axis in depression, but relatively little attention has been given to intensive monitoring of hormone secretion over time. Such research is potentially important because the HPA axis has prominent circadian and ultradian periodicity. Comparison of depressed patients with and without psychotic features is also important because HPA axis abnormalities may be especially pronounced in psychotic depressed patients.

Methods: Eleven patients with psychotic major depression (PMD patients), 38 patients with nonpsychotic major depression (NPMD patients), and 33 healthy control subjects, all drug free, were studied. Patients with PMD and NPMD were outpatients recruited primarily by advertisement. Subjects were admitted to a General Clinical

Research Center and had blood drawn through an intravenous line for determination of cortisol and corticotropin (ACTH) levels every hour for 24 hours.

Results: Among NPMD patients, the 24-hour cortisol amplitude was significantly ($P=.02$) reduced in comparison with control subjects, while ACTH indices did not differ between NPMD patients and the control group. Among PMD patients, the ACTH 24-hour mean was significantly ($P=.03$) increased compared with controls, while PMD patients and the control group did not differ significantly in cortisol indices.

Conclusion: In the population studied, PMD and NPMD patients have distinct profiles of HPA axis dysregulation.

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CONSIDERABLE research has been devoted to the hypothalamic-pituitary-adrenal (HPA) axis in depression, with the general conclusion that the HPA axis is hyperactive in this disorder.¹ However, relatively little attention has been given to the intensive monitoring of HPA axis hormones over time in depressed patients. Such research is potentially important because the secretion of these hormones involves complex circadian and ultradian periodicity,^{2,3} which can only be addressed by frequent measurement of hormone levels over 24-hour periods. Ten previous studies with a total of 151 depressed patients have measured basal cortisol or corticotropin (ACTH) levels at a frequency of at least every hour for 24 hours.⁴⁻¹⁶ The largest involved 32 depressed patients and reported increased mean cortisol levels among depressed patients, but age effects make interpretation of this finding difficult.^{8,9} The second largest included 25 depressed patients, and opposite conclusions regarding the ex-

istence of significant differences between patients and controls were reported in different publications.⁵⁻⁷ The remaining 8 studies had sample sizes of between 6 and 18 depressed patients. Of these, 5 reported increases in cortisol and/or ACTH levels among the depressed patients,^{4,10-12,16} 2 had negative results,^{14,15} and in 1 the relationships between cortisol, age, and diagnosis make conclusions difficult.¹³ Methodological issues that may be problematic in this group of studies include the pooling of subjects with unipolar and bipolar depression^{5-10,12,13} and the inclusion of subjects receiving medication.⁵⁻⁹

Research on the HPA axis in depression should also give particular attention to the distinction between psychotic and nonpsychotic subtypes of this illness. Patients with psychotic major depression (PMD patients) have been reported to exhibit very high rates of cortisol nonsuppression after administration of dexamethasone and markedly elevated postdexamethasone cortisol levels in comparison with patients with nonpsychotic major depression (NPMD patients).¹⁷⁻²¹ A recent

SUBJECTS AND METHODS

SUBJECTS

Subjects were recruited by advertisement and from outpatient psychiatric services at Stanford University Medical Center (SUMC), Stanford, Calif; McLean Hospital, Belmont, Mass; and Washington University School of Medicine (WUSM), St Louis, Mo. Screening involved a psychiatric interview conducted by a psychiatrist (J.A.P. or C.D.) and administration of the Structured Clinical Interview for *DSM-III-R*,²³ the 21-item Hamilton Depression Rating Scale (HDRS),²⁴ the Brief Psychiatric Rating Scale,²⁵ the Clinical Global Impressions (CGI) Scale,²⁶ and the Family History–Research Diagnostic Criteria.²⁷ Ratings were conducted by psychiatrists (J.A.P. or C.D.) or research assistants who had demonstrated adequate interrater reliability within and across the sites. A medical history was taken and a physical examination conducted by a physician (J.A.P. or C.D.). Screening laboratory tests included complete blood cell count, standard biochemistry panel, and serum thyrotropin level. All subjects were required to have no active medical problems, no significant laboratory abnormalities, no weight loss greater than 2.25 kg in the previous month, and no current medication use, with no medications specifically for the 2 weeks before being studied. Depressed patients were required to have a *DSM-III-R*²⁸ diagnosis of unipolar major depressive disorder in a current episode of at least moderate severity, either with or without psychotic features; a minimum HDRS total score of 21; a Thase Core Endogenomorphic Scale²⁹ score of at least 7 on the 8 items included in the HDRS; no psychiatric medications in the 2 weeks before the study, with no fluoxetine in the previous 6 weeks and no depot neuroleptics in the previous 3 months; no electroconvulsive therapy in the 6 months before the study; and no abuse of alcohol or other drugs in the 12 months before the study. Control subjects were required to have no lifetime history of Axis I or II disorders, an HDRS score less than 5, and no history of Axis I disorders in first-degree relatives, in addition to meeting the requirements noted above for all subjects. In addition, all subjects were required to abstain from alcohol for the previous 7 days and throughout the protocol; for the previous 3 days and throughout the protocol they had no more than 3 cups of caffeinated beverages daily. Informed consent was obtained from all subjects.

PROCEDURE

A standard protocol was conducted in a General Clinical Research Center (GCRC). Initially, the GCRCs at SUMC and Brigham and Women's Hospital (BWH), Boston, Mass, were used, and later the protocol was also conducted in the WUSM GCRC. Subjects were admitted to the GCRC at noon, and by 4 PM an intravenous line was started with an isotonic

sodium chloride solution drip to keep the vein open. Beginning at 6 PM, blood was drawn through the intravenous line for serum cortisol and plasma ACTH level determinations every hour until 6 PM the next day. No medications were allowed, and standard meals were given at uniform times. Subjects did not smoke in the GCRC, but were permitted brief periods in nearby smoking areas in between blood draws. Subjects were required to be supine in bed for 15 minutes before each blood draw. This protocol was part of a larger study in which subjects remained in the GCRC for an additional 48 hours and underwent additional testing of the HPA axis, including the administration of hydrocortisone and corticotropin-releasing factor.

HORMONE MEASUREMENTS

Serum and plasma samples were quick-frozen and kept at -20°C for cortisol assays and at -70°C for ACTH assays. Hormone assays were conducted in the Endocrinology Laboratory of BWH. Cortisol levels were determined by radioimmunoassay,³⁰ for which the intra-assay coefficient of variation is 4% and the inter-assay coefficient of variation, 6%. Levels of ACTH were determined by immunoradiometric assay,³⁰ for which the intra-assay and inter-assay coefficients of variation are 3.1% and 7.3%, respectively.

DATA ANALYSIS

Following procedures used in the majority of previous studies of 24-hour cortisol and ACTH levels in depression,^{5,9,11-13,15} cortisol and ACTH data were examined with a cosinor analysis, which models hormone levels over time as a sinusoidal function. The cosinor analysis uses a least squares procedure to fit individual subject data to the equation: $Y(t) = \alpha + \beta \cos(2\pi t/24 + \gamma) + e(t)$, where $Y(t)$ is the subject's value at time t (hours on a 24-hour clock starting at midnight). The mesor, or 24-hour mean, is α ; the amplitude, defined as the distance from the mean to the peak, or half the peak-to-trough distance, is β ; the acrophase, which indicates the time of the peak and trough, is γ ; and $e(t)$ represents random error of measurement. Within subjects, but not across subjects, the errors are assumed to have constant variance and are independent from one time point to another. The parameters α , β , and γ have some trivariate distribution across subjects, but no assumptions are made in the analysis about this distribution. The parameters obtained by cosinor analysis were compared between groups by means of a one-way analysis of covariance, in which diagnosis (PMD patients vs NPMD patients vs control subjects) was the single factor tested, and sex, age, and site were covariates. The significance level (α) was set at .05. If the test of diagnostic group differences was statistically significant, pairwise t tests of differences between the groups were computed.

meta-analysis confirmed this observation and showed that the psychotic subtype is the category of depression most strongly associated with an abnormal response to dexamethasone.²² Of the 10 studies employing intensive monitoring of cortisol or ACTH levels, 1 excluded PMD patients,¹⁰ while the 2 largest studies pooled PMD and NPMD patients,⁵⁻⁹ and several did not specify whether PMD patients were included.¹¹⁻¹⁶ There has been no previous re-

port of 24-hour HPA axis hormone secretion in a separate group of PMD patients compared with NPMD patients and healthy control subjects. We present herein a study of 24-hour cortisol and ACTH secretion, in which drug-free patients with unipolar major depression were stratified according to the presence or absence of psychotic features, and which involved a relatively large patient sample.

Table 1. Demographic and Clinical Characteristics of Patients and Controls*

Variable	Patients With PMD (n = 11)	Patients With NPMD (n = 38)	Control Subjects (n = 33)
Male-female ratio	7:4	14:24	18:15
Age, y	40.1 (11.4)	43.7 (13.9)	41.4 (15.1)
Score			
HDRS	28.2 (6.3)	25.1 (4.1)	2.1 (1.3)
CES	9.2 (2.9)	8.6 (1.4)	0.6 (0.8)
BPRS	42.4 (9.6)	33.2 (5.6)	19.9 (1.9)
CGI	5.3 (0.7)	4.4 (0.9)	1.0 (0)
Episode length, mo†	63.3 (47.5)	59.8 (102.4)	...
No. of previous depressive episodes	6.0 (6.6)	4.4 (5.2)	...

*Mean (SD) shown for continuous variables. PMD indicates psychotic major depression; NPMD, nonpsychotic major depression; HDRS, 21-item Hamilton Depression Rating Scale; CES, Thase Core Endogenomorphic Scale; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impressions Scale; and ellipses, not applicable.

†For current depressive episode.

RESULTS

SAMPLE CHARACTERISTICS

Eleven PMD patients, 38 NPMD patients, and 33 control subjects were studied. Differences between groups in sex distribution and age were not statistically significant, and differences in clinical ratings were consistent with the way the groups were defined (**Table 1**). In general, PMD patients were more severely ill than NPMD patients. Mean values for length of the current episode and number of previous episodes suggest depressive illnesses that are chronic and recurrent. However, 22 of the 38 NPMD patients had index episodes 2 years or less, whereas 16 had longer episodes, indicating that most of the NPMD patients did not suffer from chronic depression. Of the 11 patients with PMD, only 1 had an index episode 2 years or less, while 4 of the 11 had episodes 3 years or less, indicating that the PMD patients suffered from more chronic illnesses. The specific psychotic symptoms among PMD patients were as follows: delusional guilt in 3 patients, somatic delusions in 3 patients, delusions of being controlled in 2 patients, and delusions of mind reading, thought insertion, and thought withdrawal in 1 patient each. Auditory hallucinations occurred in 3 PMD patients, visual hallucinations in 2 patients, and somatic hallucinations in 1 patient. Comorbid psychiatric diagnoses were as follows: dysthymia in 7 NPMD patients, posttraumatic stress disorder in 6 NPMD patients and 1 PMD patient, panic disorder in 1 NPMD patient, agoraphobia without panic attacks in 1 PMD patient and 1 NPMD patient, social phobia in 3 NPMD patients, obsessive-compulsive disorder in 1 PMD patient and 1 NPMD patient, generalized anxiety disorder in 1 PMD patient, and hypochondriasis in 1 PMD patient. The distribution of subjects across the 3 sites was as follows: for PMD patients, 8 at SUMC, 2 at BWH, and 1 at WUSM; for NPMD patients, 28 at SUMC, 9 at BWH, and 1 at WUSM; and for controls, 19 at SUMC, 11 at BWH, and 3 at WUSM. Nine PMD patients were recruited by ad-

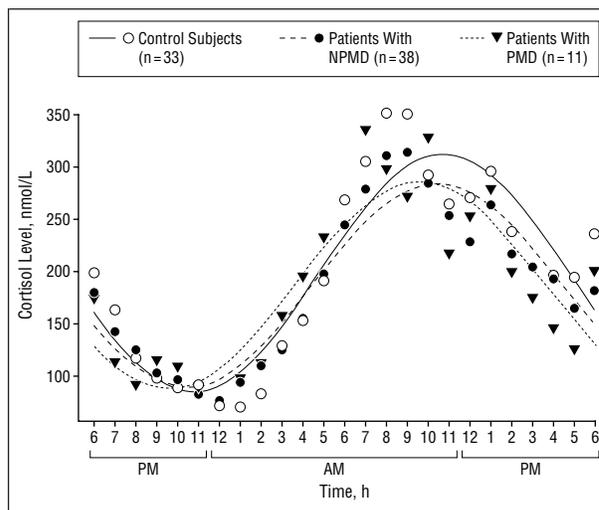


Figure 1. Cortisol levels across 24 hours in patients with psychotic major depression (PMD), patients with nonpsychotic major depression (NPMD), and healthy control subjects. Lines show curves predicted by the cosinor model based on observed group mean values for 24-hour mean, amplitude, and peak time; symbols, actual group means at each time point.

vertisement in community media, whereas 2 were recruited from the SUMC Mood Disorders Clinic; of the NPMD patients, 34 were recruited by advertisement and 4 from the SUMC clinic.

24-HOUR CORTISOL AND ACTH LEVELS

The cosinor model showed a moderately good fit to the cortisol data (**Figure 1**). Mean (SD) percent of variance accounted for by the model (R^2) was $50.7\% \pm 19.2\%$ in the PMD group, $54.8\% \pm 12.1\%$ in the NPMD group, and $57.7\% \pm 12.3\%$ in the controls. These figures mean that the correlation between predicted and observed values for an individual subject exceeded, on average, 0.70 (the square root of R^2). The fit is illustrated in Figure 1 by presentation of actual group means at each time point, together with the curve for each group predicted by the cosinor model using the group mean values for 24-hour mean, amplitude, and peak time. As will be seen (**Table 2**), there were considerable individual differences between subjects in the values of these parameters. Thus, the curve based on averaging individual values does not fit observed mean values as well as the individual curves fit the individual observed values. Nevertheless, similarities of patterns in the 2 presentations are apparent.

Statistically significant differences between groups were found in the cortisol amplitude ($F_{2,76} = 3.2$; $P = .046$). Post hoc tests indicated that the cortisol amplitude was lower in the NPMD group than in the controls ($t = 2.5$; $P = .02$), while PMD patients did not differ significantly from either of the other groups. This phenomenon can be seen in both the average and fitted curves in Figure 1. No significant differences were found in either the 24-hour mean or the peak time for cortisol.

The cosinor model fit was slightly less good for ACTH (**Figure 2**), with mean \pm SD R^2 of $43.9\% \pm 19.6\%$ in PMD patients, $44.3\% \pm 16.0\%$ in NPMD patients, and $42.2\% \pm 18.7\%$ in controls, indicating on average a cor-

Table 2. Twenty-Four-Hour Cortisol and ACTH Levels*

Variable	PMD (n = 11)	NPMD (n = 38)	C (n = 33)	F _{2,76}	Post Hoc Tests
Cortisol, nmol/L					
24-h Mean	186.6 (29.4)	185.9 (39.1)	198.0 (40.7)	0.9	...
Amplitude	113.3 (29.6)	109.1 (29.2)	128.6 (32.5)	3.2†	NPMD < Controls
Peak time, in hours of 24-h clock‡	0924 (0156)	0951 (0112)	1004 (0105)	1.3	...
ACTH, pmol/L					
24-h Mean§	4.51 (1.62)	3.49 (1.26)	3.33 (1.15)	3.8	PMD > Controls
Amplitude‡§¶	2.25 (1.09)	1.76 (0.84)	1.62 (0.92)	3.0	...
Peak time, in hours of 24-h clock‡	0843 (0209)	0933 (0130)	0947 (0126)	2.1	...

*Data are given as mean (SD). ACTH indicates corticotropin; PMD, psychotic major depression; NPMD, nonpsychotic major depression; C, control subjects; and ellipses, not applicable.

†P = .046.

‡Age covariate P < .05.

§Sex covariate P < .01.

¶P = .03.

||Site covariate P < .01.

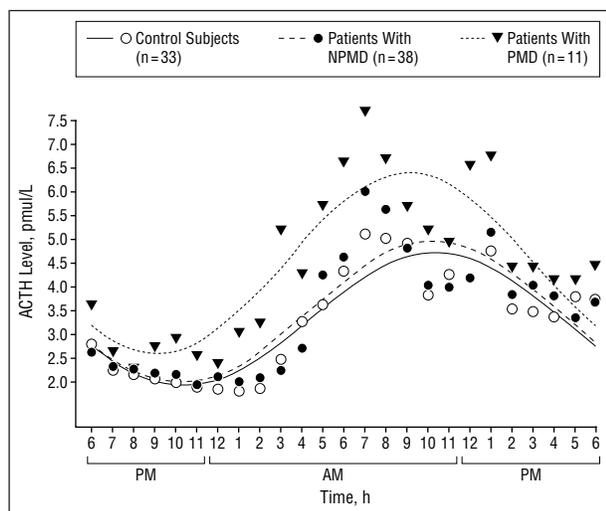


Figure 2. Corticotropin (ACTH) levels across 24 hours in patients with psychotic major depression (PMD), patients with nonpsychotic major depression (NPMD), and healthy control subjects. Lines show curves predicted by the cosinor model based on observed group mean values for 24-hour mean, amplitude, and peak time; symbols, actual group means at each time point.

relation within subjects of more than 0.65. The group means at each time point and the curves based on the average individual cosinor parameters are presented in Figure 2.

Statistically significant differences between groups were found in the 24-hour mean for ACTH ($F_{2,76} = 3.8$; $P = .03$), with PMD patients significantly higher than the controls ($t = 2.3$; $P = .03$), while the NPMD patients did not differ significantly from either of the other 2 groups. For this variable, the sex covariate had a significant effect ($F_{1,76} = 11.0$; $P = .001$), with males having higher 24-hour mean ACTH levels than females. No significant differences were found in amplitude or peak time for ACTH.

The observation that cortisol amplitude is significantly reduced in NPMD patients could be potentially affected by the inclusion of 6 patients with posttraumatic stress disorder, a condition that has been associated with decreased cortisol levels.^{15,31} Cortisol amplitude was compared between the NPMD patients and the

control group after excluding subjects with posttraumatic stress disorder, and in this analysis the NPMD patients continued to show a significant reduction in cortisol amplitude ($F_{1,63} = 5.4$; $P = .02$).

We also examined whether the inclusion of patients with chronic depression could be responsible for the observed reduction in cortisol amplitude in the NPMD group. The 22 NPMD patients having a current depressive episode of less than 2 years actually had lower cortisol amplitude (mean \pm SD of 103.1 ± 31.4 nmol/L) than the 16 NPMD patients with longer current episodes (mean \pm SD of 117.2 ± 24.5 nmol/L). Cortisol amplitude was compared between NPMD patients and the control group after excluding the 16 NPMD patients with chronic depression. In this analysis, the decrease in cortisol amplitude among the NPMD patients continued to be statistically significant ($F_{1,53} = 8.3$; $P = .006$).

COMMENT

Results of this study suggest that psychotic and nonpsychotic major depressive disorders are associated with distinct patterns of HPA axis dysregulation. Patients with NPMD had significantly lower cortisol amplitude than control subjects. Together with the nonsignificant reduction in the 24-hour mean for cortisol, this finding suggests that peak cortisol secretion is reduced in NPMD patients. No significant differences in ACTH indices were found between NPMD patients and controls, and conclusions cannot be drawn regarding the question of whether the reduced peak cortisol secretion may be primary or secondary to an abnormality at a higher level of the HPA axis. The finding of reduced peak cortisol secretion in our NPMD patients differs from the results of previous studies employing 24-hour monitoring of cortisol secretion. In those reports, the preponderance of evidence suggested increased cortisol secretion among the depressed patients studied,^{4,10-12,16} although there were important negative findings as well.^{7,14,15}

In contrast, our PMD patients had increased 24-hour mean ACTH secretion compared with healthy subjects, while cortisol indices did not differ between PMD

patients and controls. These results are generally consistent with previous findings that HPA axis hyperactivity is particularly pronounced in this subtype of depression.¹⁷⁻²² However, interpretation of the ACTH and cortisol findings together is not straightforward. The increase in ACTH output could be due to an increase in the central drive regulating secretion of corticotropin-releasing factor. However, this explanation would require a compensatory decrease in the adrenal response to ACTH, and there is no direct evidence for decreased adrenal responsiveness in any category of depression.

Some additional, preliminary data may be pertinent to interpretation of our findings in PMD patients. After the 24-hour monitoring of basal hormone levels, subjects were randomly assigned to receive infusions of hydrocortisone hemisuccinate, corticotropin-releasing factor, or placebo, and hormone levels continued to be monitored at 1- to 2-hour intervals for the 2 subsequent 24-hour periods. In the case of the subjects randomized to placebo, unstimulated cortisol and ACTH levels were thus followed for 72 hours. The subjects in the placebo condition consisted of 5 PMD patients, 16 NPMD patients, and 14 control subjects. In the control group, mean \pm SD values for the cortisol 24-hour mean were 184.6 \pm 33.1 nmol/L the first day, 184.6 \pm 33.1 nmol/L the second day, and 201.1 \pm 35.8 nmol/L the third day. Patients with NPMD had corresponding values of 176.3 \pm 33.1 nmol/L the first day, 170.8 \pm 35.8 nmol/L the second day, and 176.3 \pm 44.1 nmol/L the third day. In contrast, the PMD patients showed an increase in 24-hour mean cortisol from 198.3 \pm 30.3 nmol/L the first day to 214.9 \pm 27.5 nmol/L the second day and 253.4 \pm 38.6 nmol/L the third day. The ACTH values in the PMD patients continued to be elevated, and peak cortisol levels in the NPMD patients continued to be reduced, throughout the 72 hours. These preliminary observations suggest that when basal hormone levels are followed for longer periods, PMD patients may show an increase in cortisol secretion, as would be consistent with the previous research. However, any conclusion about HPA axis function over an extended period of observation would be premature.

Some of the differences between our findings and those of previous studies may relate to having sampled a different population of depressed patients. Seven of the 10 previous studies having similar methods, including the largest studies, employed depressed inpatients as subjects,^{4-10,12,13,16} while 2 studies employed outpatients,^{11,15} and the source of patients was not specified in 1.¹⁴ In contrast, none of the patients in our sample were inpatients, and the large majority were recruited by advertisement. Other evidence suggests that HPA axis hyperactivity may be less pronounced in depressed outpatients compared with inpatients. Nelson and Davis²² reviewed studies comparing dexamethasone suppression test results in melancholic and nonmelancholic patients and found an overall nonsuppression rate of 36% among inpatients and 22% among outpatients; among outpatients who did not meet criteria for melancholia the nonsuppression rate was only 12%. Rush et al³² presented dexamethasone suppression test results for 109 inpatients and 245 outpatients with major depression and reported nonsuppression rates of 32% among inpatients and 16% among outpatients. Thus, our

results may in part reflect studying outpatients with illnesses that are less severe than those of the inpatients included in previous studies.

Another factor that bears on the interpretation of our findings concerns the chronicity of illness. Although the average duration of the current depressive episode was similar in the PMD and NPMD groups, most of the NPMD patients had depressive episodes shorter than 24 months and, according to usual criteria, did not have chronic depression, whereas most of the PMD patients had an episode of chronic major depression. To our knowledge, there are no published data addressing the question of whether psychotic or nonpsychotic depressions are more likely to be chronic.³³ Thus, the difference between the groups on this variable may be inherent in the difference between the 2 types of depressive illness.

The duration of the depressive episodes may also bear on the generalizability of our findings. With respect to illness chronicity, it is not clear how similar our samples are to those in previous studies. Most reports of HPA axis function in depression simply do not contain information about this variable. Of the 10 previous studies that conducted 24-hour monitoring of HPA axis hormones in depression, only 2 provided data on chronicity. In the largest of the 10 studies, mean duration of the current depressive episode was 92 weeks, a value close to the usual criterion for chronicity.^{8,9} In a smaller study, the length of the current depressive episode was noted to range from 2 to 6.4 months.¹³ Among studies of dexamethasone suppression test response in depressed outpatients, 2 were identified that had relatively large samples and provided data on episode duration. In a study of 86 patients, the mean episode duration was 43 months,³⁴ while a study of 64 patients had a mean episode duration of 6 months.³⁵ Thus, illness duration should be considered a variable that potentially may limit the generalizability of our findings, but no definitive statement can be made in this regard.

In conclusion, NPMD patients were found to have a reduced amplitude of 24-hour cortisol secretion, whereas PMD patients had increased ACTH secretion. These observations suggest distinct mechanisms of HPA axis dysregulation in PMD and NPMD patients, but conclusions about the pathophysiology underlying our findings cannot be drawn. The discrepancies between our findings and those of previous studies may be due to sampling an outpatient population and, possibly, a population with relatively long duration of the depressive episode. Conclusions about HPA axis abnormalities in psychotic depression should be considered tentative in view of the small number of subjects studied. Efforts to replicate these results using similar recruitment strategies, larger numbers of PMD patients, and longer periods of observation are warranted.

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