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## Multiple Depressive Episodes and Plasma Postdexamethasone Cortisol Levels

James H. Meador-Woodruff, George Gurguis, Leon Grunhaus,  
Roger F. Haskett, and John F. Greden

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*The hypothalamic-pituitary-adrenal (HPA) axis is dysregulated in many patients with major depressive disorder (MDD). To determine whether or not a past history of depressive episodes is associated with this dysregulation, we studied the relationships among number of past depressive episodes, number of previous hospitalizations for depression, and number of years since first depressive episode and biological markers of depression (postdexamethasone plasma cortisol levels and dexamethasone suppressor/nonsuppressor status). No significant relationships were detected.*

### Introduction

Many patients with major depressive disorder (MDD) develop hypothalamic-pituitary-adrenal (HPA) axis dysregulation during episodes of depression (Carroll et al. 1981). This dysregulation in depressed individuals appears to exist at both the adrenal and pituitary levels, as reflected by abnormal postdexamethasone responses of plasma cortisol (Carroll et al. 1981; Charles et al. 1981; Brown et al. 1985) and proopiomelanocortin-derived peptides:  $\beta$ -endorphin (Matthews et al. 1982; 1986) and adrenocorticotrophic hormone (ACTH) (Kalin et al. 1982; Nasr et al. 1983b; Pfohl et al. 1985; Sherman and Pfohl 1985). The possible dysregulation of the hypothalamic hormone corticotrophin-releasing factor (CRF) in depression is also being explored (Chrousos et al. 1983; Gold et al. 1984; Halsboer et al. 1985).

Numerous factors have been shown to influence the apparent degree of HPA axis dysregulation in MDD. Age (Oxenkrug et al. 1983; Davis et al. 1984; Lewis et al. 1984), recent weight change (Keitner et al. 1985; Krishnan et al. 1985b), polarity (Zisook et al. 1985), psychosis (Rudorfer et al. 1982), and severity of illness (Reus 1982; Nasr and Gibbons 1983; Nasr et al. 1983a; Sangal et al. 1984; Krishnan et al. 1985a) have been found to affect postdexamethasone cortisol responses. In addition, antidepressant withdrawal (Dilsaver and Greden 1985), alcoholism (Kroll et al. 1983), dose of dexamethasone

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From the Clinical Studies Unit for Affective Disorders, Department of Psychiatry, University of Michigan, Ann Arbor, MI. Supported in part by NIMH Grant 1 RO1-40216-01 (J.F.G.) and the Department of Psychiatry and the Theophile Raphael Fund at the University of Michigan Medical Center. Presented in part at the 41st Annual Meeting of the Society of Biological Psychiatry, Washington, D.C., May 7-11, 1986.

Address reprint requests to Dr. James H. Meador-Woodruff, Department of Psychiatry, Mental Health Research Institute, University of Michigan Medical Center, 205 Washtenaw Place, Ann Arbor, MI 48109-0720.

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(Brown et al. 1983), timing and frequency of plasma samples (Goldberg 1980), and cortisol assay characteristics (Demers and Derck 1977; Meltzer and Fang 1983) can influence Dexamethasone Suppression Test (DST) results.

In view of the pervasiveness of these changes, it would be of great interest to determine whether or not the HPA axis dysregulation seen in MDD is modulated by the past history of depressive episodes. Does the HPA axis return completely to its pre-morbid state following resolution of each depressive episode, or does some degree of dysregulation persist and interact with changes occurring during subsequent episodes? Surprisingly few studies have addressed this issue, and findings to date have been contradictory. Lenox et al. (1985) studied 20 depressed patients and noted a trend for DST nonsuppressors to report more prior depressive episodes than suppressors. They also observed that more years had elapsed since the first episode of MDD (i.e., age at index episode minus age of first episode) in patients who were DST nonsuppressors than the suppressors in their population. However, other investigators (Brown and Qualls 1982; Grunhaus et al. 1983; Yerevanian et al. 1984) have reported that DST suppression status did not change between hospitalizations for sequential depressive episodes in most of the MDD patients they studied, suggesting that number of depressive episodes does not affect the degree of HPA axis dysregulation in MDD. In an attempt to clarify these issues, we investigated a large population of patients with MDD for whom these data were available; to maximize the descriptive power of our data, we explored this problem by several different methods.

## Methods

### *Patients*

Eighty-one patients in the Clinical Studies Unit (CSU) for Affective Disorders of the Department of Psychiatry at the University of Michigan from 1980 to 1985 were identified. All patients admitted to the CSU undergo a comprehensive diagnostic evaluation, including several clinical interviews by psychiatrists, a structured interview by a trained research staff member using the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer and Endicott 1975), and a detailed family history and social assessment by a social worker, as well as a thorough physical and laboratory evaluation. Diagnosis is made by consensual agreement of the clinicians involved in gathering the above information, using Research Diagnostic Criteria (RDC) (Spitzer et al. 1977).

Patients included in the present study (1) met RDC (Spitzer et al. 1977) for major depressive disorder (MDD); (2) did not meet psychotic subtype; (3) had 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960) scores of at least 16; (4) completed a Dexamethasone Suppression Test (DST) following a medication-free period of 2 weeks; (5) had no identifiable technical exclusions known to invalidate the DST (Carroll et al. 1981); and (6) gave written informed consent to participate in these research activities.

### *Laboratory Procedures*

Each patient received 1 mg of dexamethasone at 11:30 PM on the night prior to study, and blood was collected the following day for cortisol determination. Samples were typically obtained at 8:00 AM, 4:00 PM, and 11:00 PM, although fewer than all three samples were collected for most patients. Plasma cortisol concentration was determined by a modification of Murphy's (1967) competitive protein-binding technique.

### *Data Acquisition*

Three parameters were available in our database to express multiplicity of depressive episodes: (1) number of previous lifetime major depressive episodes ("depressive episodes" or DE), (2) number of previous lifetime hospitalizations for MDD ("depressive hospitalizations" or DH), and (3) number of years since the patient's first depressive episode ("years depressed" or YD). Empirically, one might expect DE and DH to be highly related to each other; examination revealed, however, that although the two are significantly correlated, only 48% of the variance is attributable to this relationship. Accordingly, we included DH as a separate parameter of multiplicity of depressive episodes. The data DE, DH, and YD are routinely obtained at the time of hospitalization from interviews with the patient, family members, and current and previous therapists; this information is entered into our database at the time it is obtained. As any analysis depends on the accuracy of these data, every effort is made at the time of hospitalization to corroborate this information by obtaining the actual records of as many past psychiatric hospitalizations of each patient as possible. Additionally, other variables, such as age, degree of recent weight change, and HRSD score at the time of the DST, are entered into our dataset and were available for this study.

### *Data Analysis*

As the direction of causality is not well understood, the relationship between these three parameters (DE, DH, and YD) and postdexamethasone cortisol values was studied by three different methods. All results are expressed  $\pm$  SEM, unless otherwise specified.

*Method 1.* For each multiplicity parameter, the patient population was divided into tertiles of approximately equal size, representing mild, moderate, and severe patterns. For DE, 0, 1-3, and 4-8 previous depressive episodes characterized the respective groups; for DH, 0, 1-2, and 3-8 previous hospitalizations for depression; and for YD, 0-10, 10-20, and >20 years since first depressive episode. Mean age, HRSD score, degree of recent weight change, and logarithmically transformed postdexamethasone plasma cortisol values at the three sampling times were calculated for each group for each parameter. Between-group differences were tested by one-way Analysis of Variance (ANOVA).

*Method 2.* Correlation coefficients were calculated among DE, DH, and YD, and logarithmically transformed postdexamethasone cortisol values at 8:00 AM, 4:00 PM, and 11:00 PM, age, recent weight loss, and HRSD score. Pearson's product-moment correlation coefficient was calculated for the tests of association between YD and the other listed variables. As DE and DH are not continuously distributed variables, Kendall's Tau-B coefficient of rank correlation, corrected for tied ranks (Conover 1971; Gibbons 1971) was employed for tests of association between DE and DH and the other variables.

*Method 3.* For this method, we reversed dependent and independent variables to study this phenomenon in a more traditional manner (Carroll et al. 1981). Patients were defined as DST suppressors or nonsuppressors: nonsuppression was defined as having a maximum postdexamethasone cortisol value of  $>5$   $\mu\text{g}/\text{dl}$ . We compared mean age, degree of weight change, HRSD scores, and the three multiplicity parameters for suppressors and nonsuppressors; comparison was by one-way ANOVA.

## Results

### Method 1

The results of studying postdexamethasone cortisol levels as a function of degree of number of DE is shown in Figure 1. Although there was a trend toward higher cortisol levels at 8:00 AM and 4:00 PM as a function of number of previous depressive episodes, for none of the three time points were the across-group differences significant. There were, however, significant across-group differences for degree of recent weight change. Age and HRSD scores were not significantly different among the three groups.

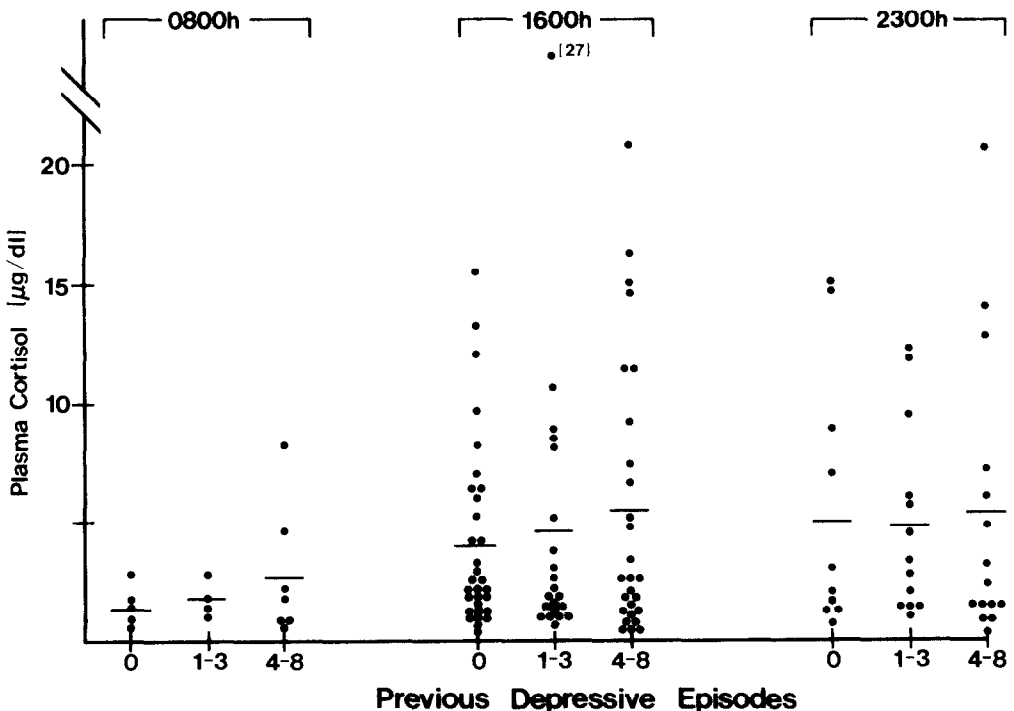
A similar analysis of cortisol levels as a function of degree of number of DH is summarized in Figure 2. None of the between-group differences was significant for any of the three cortisol sampling times. Age and HRSD scores did show trends toward being higher as a function of DH. Recent weight loss was not significantly related to DH.

Figure 3 shows the results of examining cortisol levels as a function of number of YD. Again, none of the across-group differences attained statistical significance. As might be expected, however, age was significantly related to this parameter. HRSD scores and recent weight change were not significantly different among the groups.

### Method 2

The results of correlating the multiplicity parameters DE, DH, and YD with cortisol values are shown in Table 1. None of the parameters was significantly correlated with

Figure 1. Postdexamethasone cortisol levels as a function of number of previous depressive episodes at 8:00 AM, 4:00 PM, and 11:00 PM. The between-group differences are not significant for any of the three time points.



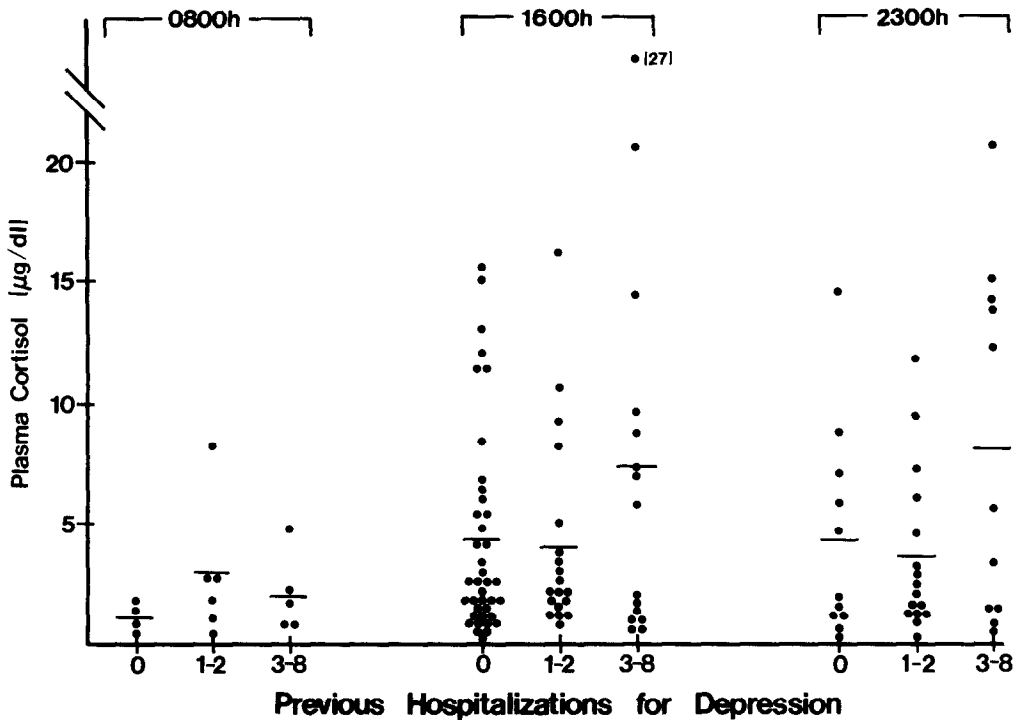


Figure 2. Postdexamethasone cortisol levels as a function of number of past hospitalizations for depression at 8:00 AM, 4:00 PM, and 11:00 PM. The between-group differences are not significant for any of the three time points.

any of the three postdexamethasone cortisol samples. Significant correlations, however, existed between DH and age and YD and both age and HRSD score.

### Method 3

Table 2 summarizes the results of comparing the multiplicity parameters and other variables for DST suppressors and nonsuppressors. None of the three multiplicity parameters was significantly different among these groups. DST nonsuppressors, however, were significantly older than DST suppressors.

## Discussion

These results indicate that past history of depressive experience does not affect the degree of HPA axis dysregulation seen in MDD as indicated by postdexamethasone cortisol levels. We initially designed this study to examine the effects of mild, moderate, and severe degrees of the three multiplicity parameters on postdexamethasone cortisol levels. Due to the negative findings, we reexamined the data by using correlation coefficients to insure that the stratification procedure had not biased the results. Finally, we studied the problem using the more conventional method (Carroll et al. 1981) of identifying patients as DST suppressors and nonsuppressors and comparing the three multiplicity parameters for each group. Regardless of the method employed, we found no significant

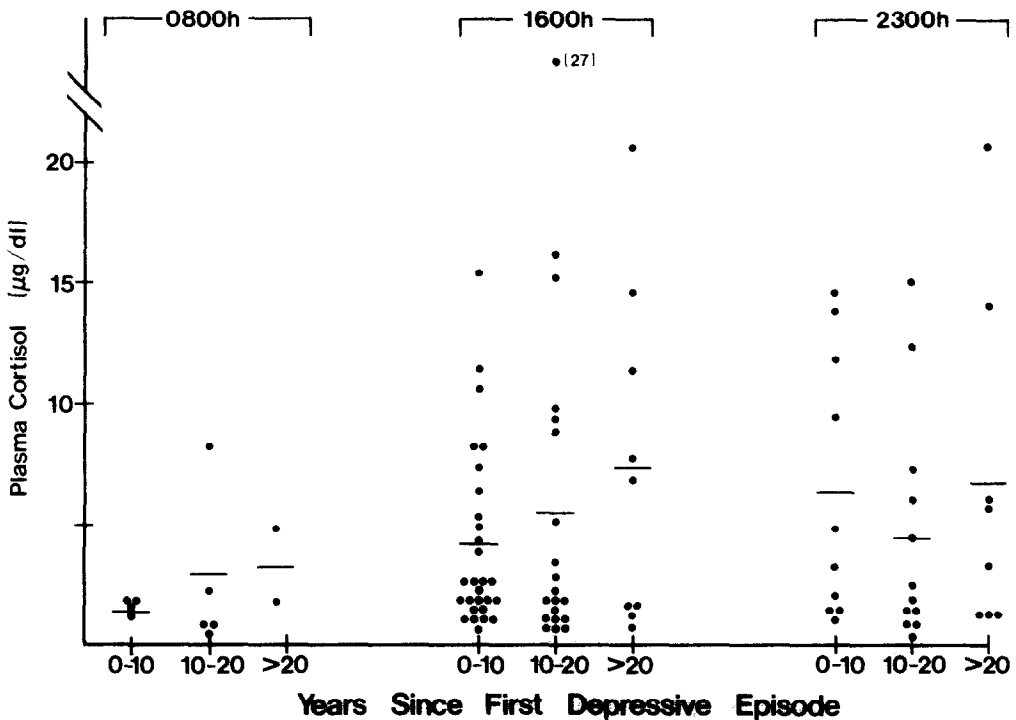


Figure 3. Postdexamethasone cortisol levels as a function of number of years since first depressive episode at 8:00 AM, 4:00 PM, and 11:00 PM. The between-group differences are not significant for any of the three time points.

relationships between postdexamethasone cortisol levels and any of the three multiplicity parameters (number of previous depressive episodes, number of previous hospitalizations for depression, and number of years since first depressive episode).

The 81 patients we studied in this investigation represent the largest group of subjects yet employed to examine this phenomenon. Yerevanian et al. (1984) found that DST suppressor/nonsuppressor status was unchanged upon readmission to the hospital for recurrent depressive episodes in 11 of 12 patients studied, which is in agreement with our findings. Similarly, Grunhaus et al. (1983) found that DST suppressor/nonsuppressor status was unchanged in 7 of 10 patients upon readmission for recurrent MDD. Brown and Qualls (1982) studied 11 patients and found that the 6 patients who were DST suppressors during the index episode of MDD remained suppressors in subsequent episodes, but several of 5 initial nonsuppressors became suppressors. In a study of 20 patients with MDD, however, Lenox et al. (1985) found that DST suppressors had a significantly shorter length of illness (YD in the present study) than did nonsuppressors. The nonsuppressors were older than the suppressors in their study, however, and an examination of the data they presented suggests that if age were introduced as a covariate in their analysis, this apparent trend might fail to reach statistical significance. In addition, they found no difference in number of previous depressive episodes between DST suppressors and nonsuppressors. The findings of the present study and of the previous studies, taken together, suggest that the magnitude of dysregulation of the HPA axis is not a function

Table 1. Coefficients of Correlation of Indices of Multiplicity of Depressive Episodes with Postdexamethasone Plasma Cortisol Levels and Clinically Relevant Variables<sup>a</sup>

Variable	Past depressive episodes	Past depressive hospitalizations	Years since first depressive episode
8:00 AM cortisol <sup>b</sup>	+0.06	+0.08	-0.03
4:00 PM cortisol	+0.03	+0.06	+0.03
11:00 PM cortisol	-0.01	+0.15	-0.10
Age	+0.09	+0.19 <sup>c</sup>	+0.46 <sup>d</sup>
HRSD score	+0.15	+0.15	+0.23 <sup>c</sup>
Recent weight change	-0.15	-0.13	+0.05

<sup>a</sup>Values reported are Pearson product-moment correlation coefficients for the continuously distributed variable (years since first depressive episode) and Kendall's Tau-B coefficients of rank correlation for the noncontinuously distributed variables (past depressive episodes and hospitalizations).

<sup>b</sup>All cortisol values were logarithmically transformed prior to analysis.

<sup>c</sup> $p < 0.05$ .

<sup>d</sup> $p < 0.01$ .

of the number of previous depressive episodes; the axis does not "know" if the patient has been depressed only once or a dozen times, responding similarly during each depressive episode.

The neuroendocrinology of depression is complex and incompletely understood. The hypercortisolemia (Carpenter and Bunney 1971; Carroll et al. 1976, 1981) and DST abnormalities seen at both the adrenal (Carroll et al. 1981; Charles et al. 1981; Brown et al. 1985) and pituitary (Kalin et al. 1982; Matthews et al. 1982, 1986; Nasr et al. 1983b; Pfohl et al. 1985; Sherman and Pfohl 1985) levels are presumably related to limbic neurotransmitter disorganization, resulting in altered hypothalamic CRF secretion. Interestingly, however, depressed patients appear to be hyporesponsive to infusions of CRF, which is clearly different from the response of the pituitary in Cushing's disease (Gold et al. 1984; Holsboer et al. 1984a, 1984b). Multiple levels of feedback regulation are operative in the HPA axis and complicate interpretation of this system.

To definitively answer the question of whether or not the HPA axis dysregulation seen in MDD is modulated by the past history of the axis would require prospectively performing serial HPA measures on a large sample of patients between and during multiple

Table 2. Multiplicity of Depressive Episode Parameters as a Function of DST Suppression State

Variable	DST suppressor	DST nonsuppressor	<i>p</i>
n	51	30	
Years since first depressive episode	9.3 ± 1.1	12.8 ± 1.7	NS
Previous hospitalizations for depression	2.2 ± 0.3	2.7 ± 0.4	NS
Past depressive episodes	3.8 ± 0.4	3.7 ± 0.5	NS
Age (years)	37.8 ± 2.0	47.5 ± 3.0	0.006
HRSD score	21.1 ± 0.6	22.6 ± 0.9	NS
Weight change (kg)	-0.73 ± 1.1	-3.3 ± 1.3	NS

depressive episodes. Several investigators (Carroll et al. 1976; Greden et al. 1983) have followed depressed DST nonsuppressors through recovery from single episodes and have noted that many become DST suppressors once patients are euthymic. It may be, of course, that higher levels of the HPA axis (i.e., pituitary and hypothalamic) are dysregulated as a function of number of previous depressive episodes and that feedback mechanisms are able to maintain cortisol homeostasis so that the adrenal response would not appear to be dependent on the number of past episodes. Following serial HPA measures (including plasma cortisol, ACTH,  $\beta$ -endorphin, and responsiveness to CRF infusion) in patients as they go through multiple depressive episodes has yet to be reported on a large scale, but would be the most reasonable strategy to thoroughly address this issue.

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