Severity of depression and hypothalamic-pituitary-adrenal axis dysregulation: identification of contributing factors

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Severity of depression, as reflected by total scores on depression rating scales, has been established as one of several major sources of variance associated with hypothalamic-pituitary-adrenal axis dysregulation in patients with major depressive disorder. To determine which of the symptoms comprising clinically defined severity of illness contribute most to this relationship, we studied the associations between postdexamethasone plasma cortisol levels and components of the Hamilton Rating Scale for Depression (HRSD) in 114 patients with major depressive disorder. At pretreatment baseline, severity of depression was modestly but significantly correlated with postdexamethasone plasma cortisol; a large part of this relationship was associated with the anxiety components of the HRSD. When relationships between postdexamethasone plasma cortisol and severity measures were studied longitudinally during treatment, this contribution of the anxiety items persisted. The anxiety associated with depression appears to be a major clinical factor associated with the hypothalamic-pituitary-adrenal axis dysregulation in major depressive disorder.

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Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis occurs in many individuals with major depressive disorder (1–5). This disturbance has most often been studied by the dexamethasone suppression test (DST), although other challenge paradigms, such as corticotropin-releasing hormone (CRH) infusions, have been employed (6–8). The DST was originally conceived as a possible biological correlate specific to endogenous depression (1). As various investigative groups have accumulated neuroendocrine data on large groups of patients, however, it has become apparent that this dysregulation is complex and has many determinants, and the DST may better serve as a paradigm to study pathophysiology rather than as a diagnostic test.

Multiple clinical factors influence postdexamethasone plasma cortisol levels. These include severity of depressive episode (9–19), age (20–23), history of recent weight loss (24, 25), the presence of delusions (26–29), and recent use or withdrawal of psychotropic medication (30–33). Severity of depressive symptoms, as reflected by rating scale scores, is positively correlated with plasma postdexamethasone cortisol levels (9–14), as well as with circulating levels of pituitary hormones associated with the HPA axis (11). This severity relationship appears to account for approximately 20% of the total variance associated with the DST (9–14). The rating scales that are used for these types of investigations (most often the 17-item Hamilton Rating Scale for Depression (HRSD) (34)), however, are composed of many symptoms. We undertook this study to determine which of the items that comprise clinically defined severity of depressive illness account for the relationship between postdexamethasone plasma cortisol levels and severity of depression.

Material and methods

Subjects

A total of 114 patients of the Clinical Studies Unit (CSU) of the University of Michigan Depression Program of the Department of Psychiatry at the University of Michigan Medical Center were studied. Patients admitted to CSU undergo an extensive diagnostic evaluation, including 2 or more unstructured clinical interviews by psychiatrists, a

structured diagnostic interview using the Schedule for Affective Disorders and Schizophrenia (SADS) (35) by a trained research staff member, and a detailed family and social assessment by a staff social worker. Additionally, patients receive a thorough physical and laboratory examination, which routinely includes an electrocardiogram, complete blood count, electrolytes, tests of hepatic, pancreatic, renal and thyroid functions, plasma vitamin B_{12} and folate levels, VDRL, and a urine drug screen. At the conclusion of the assessment period, diagnosis is formulated by consensual agreement of involved clinicians using Research Diagnostic Criteria (RDC) (36). Patients included in this study were patients at CSU during the years 1981–1986.

Inclusion criteria were: patients met RDC for major depressive disorder (MDD); none were of the psychotic subtype; all underwent at least a 2-week medication-free washout period; each had a 1-mg oral dexamethasone suppression test at the conclusion of the drug-free period (baseline); none had identifiable technical exclusions that might invalidate DST results; and each gave written informed consent to participate in these research activities. The characteristics of this patient population are summarized in Table 1. In addition to this baseline data, a subgroup of patients ($n = 66$) was systematically monitored during treatment with weekly DST and HRSD scores. This subgroup of the total population was further studied to assess cortisol and severity rating scale changes over time.

Laboratory procedures

DST was administered in a standardized manner (1, 37). Patients received 1 mg dexamethasone orally at 2330, and plasma was obtained at 0800, 1600, and 2300 on the following day. Plasma cortisol was determined by a modification of Murphy's (38) competitive protein-binding technique. Prior to use of parametric statistics, the maximum postdexamethasone plasma cortisol levels underwent logarithmic transformation to improve normality of distribution.

Table 1. Clinical and demographic characteristics of study patients

Variable	Mean ± SD	Range
Age (years)	42.4 ± 16.4	19–85
Recent weight change (kg)	−0.7 ± 9.3	−25–+40
HRSD score	19.2 ± 10.9	9–34
Past depressive episodes	2.5 ± 3.0	0–8 (or more)
Age, first depressive episode	32.7 ± 15.7	12–80
Duration, current episode (weeks)	35.3 ± 34.6	0–98 (or more)
Sex		
Female	61%	
Male	39%	
Percentage unipolar	78%	

Clinical assessment

Each patient was rated for severity of depression using the 17-item HRSD (34) within 2 days of the DST by a clinician who was blind to all neuroendocrine measures, including current and previous DST results. The interrater reliability of the HRSD is studied at CSU every 6 months, and has consistently been within 2 points.

Data analysis

This database is stored within the University of Michigan Central Computer Facility on an IBM 3090-400 Mainframe, which houses the Michigan Terminal System. Statistical analysis was performed using the Michigan Interactive Data Analysis System (MIDAS) software package.

Results

Relationships between baseline severity and cortisol

To study the relationship between severity of depression and postdexamethasone plasma cortisol levels at baseline, Pearson's product-moment correlation coefficients were calculated for total HRSD scores and logarithmically transformed postdexamethasone plasma cortisol levels. As we and others have previously shown (9–14), these 2 variables are significantly correlated ($n = 114$, $r = 0.38$, $P < 0.0001$). To determine which of those items comprising the HRSD are responsible for this relationship, correlation coefficients were calculated between individual HRSD item scores and postdexamethasone plasma cortisol levels. Significant relationships were found between postdexamethasone plasma cortisol and middle and delayed insomnia, agitation, psychological and somatic anxiety, gastrointestinal and genital symptoms, loss of insight and weight loss (Table 2).

As 9 of the 17 HRSD items appeared to be significantly related to postdexamethasone plasma cortisol levels, it seemed possible that relationships between postdexamethasone plasma cortisol and any given HRSD item score might be confounded by the relationship of that variable to another HRSD item. To further explore this, the degree of association between the HRSD items themselves was explored. Table 3 demonstrates the matrix generated by correlating each HRSD item with the remaining items; only significant relationships are indicated. Many items are related to other items comprising the total HRSD score, and each item is significantly correlated with at least one other item. Because of the high degree of multicollinearity among HRSD variables, we attempted to simplify these items into less interrelated factors. Principal component

Table 2. Coefficients of correlation between HRSD items and postdexamethasone plasma cortisol levels at baseline

Item	r	P
Total HRSD	0.38	<0.0001
Depressed mood	0.03	
Guilt	0.15	
Suicide	−0.14	
Initial insomnia	0.14	
Middle insomnia	0.21	<0.05
Delayed insomnia	0.19	<0.05
Work and interest	0.07	
Retardation	0.05	
Agitation	0.42	<0.0001
Psychological anxiety	0.28	<0.005
Somatic anxiety	0.23	<0.05
Gastrointestinal	0.23	<0.05
General somatic	−0.03	
Genital	0.28	<0.005
Hypochondriasis	0.13	
Loss of insight	0.20	<0.05
Weight loss	0.21	<0.05

analysis was employed to generate orthogonal underlying factors, to determine whether any of these 9 items might contribute more than others to the relationship between HRSD and postdexamethasone plasma cortisol. Several methods are available to calculate such factors. Principal component analysis was selected instead of factor analysis; factor analysis requires that assumptions be made on the nature of the underlying factors as well as of a proper model, which may be quite difficult in practice. On the other hand, principal component analysis requires no assumptions of the underlying components, but simply generates orthogonal factors by a mathematical procedure. Accordingly, given the nature of this study, we felt the more conservative principal component analysis to be a more appropriate method of generating these factors (39).

Table 4 presents the results of this principal component analysis. Only the first 4 principal components generated were significant with eigenvalues >1.00; these 4 components accounted for 54% of the total variance. To determine which, if any, of these principal components are related to postdexamethasone plasma cortisol levels, coefficients of correlation were determined for each component and plasma cortisol. These results are summarized in Table 5. Only the first component exhibited a significant relationship with postdexamethasone plasma cortisol ($n = 114$, $r = 0.37$, $P < 0.0001$), having essentially the same degree of association with postdexamethasone plasma cortisol as the original total HRSD score ($r = 0.38$).

Examination of the first principal component re-

Table 4. Principal component analysis of individual HRSD items at baseline

Component	I	II	III	IV
Eigenvalue	2.24	1.71	1.25	1.03
Percentage of variance	20	14	11	9
Cumulative percentage of variance	20	34	45	54
Factor loadings:				
Depressed mood	0.24	0.39	0.08	0.09
Guilt	0.31	0.18	−0.07	−0.49
Suicide	0.22	0.36	−0.24	−0.41
Initial insomnia	0.17	−0.31	0.31	−0.14
Middle insomnia	0.18	−0.21	0.24	0.05
Delayed insomnia	0.31	−0.14	0.31	−0.22
Work and interest	0.25	0.39	0.02	0.29
Retardation	0.11	0.41	0.17	0.29
Agitation	0.24	−0.08	0.21	−0.13
Psychological anxiety	0.51	−0.20	−0.34	0.04
Somatic anxiety	0.41	−0.32	−0.41	0.39
Gastrointestinal	0.12	0.07	0.21	0.28
General somatic	0.02	0.12	−0.02	0.27
Genital	0.14	0.14	0.11	−0.06
Hypochondriasis	0.06	−0.10	−0.03	0.07
Loss of insight	0.04	0.06	0.05	0.02
Weight loss	0.17	−0.08	0.51	0.11

Table 3. Correlation matrix of HRSD items at baseline

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Depressed mood																	
2. Guilt	0.28																
3. Suicide	0.38	0.35															
4. Initial insomnia	–	–	–														
5. Middle insomnia	–	–	–	0.31													
6. Delayed insomnia	–	0.21	–	0.35	0.40												
7. Work and interest	0.52	–	0.29	–	–	–											
8. Retardation	0.48	–	0.18	–	–	–	0.45										
9. Agitation	0.21	0.32	–	0.27	–	0.37	–	–									
10. Psychological anxiety	–	0.28	–	–	–	0.29	–	–	0.26								
11. Somatic anxiety	–	–	–	–	0.19	–	–	–	–	0.51							
12. Gastrointestinal	0.33	–	–	–	–	–	0.23	0.23	–	–	–						
13. General somatic	0.20	–	–	–	–	–	0.31	0.33	–	–	–	–					
14. Genital	–	0.21	–	–	–	–	0.22	–	–	–	–	–	–				
15. Hypochondriasis	–	–	–	–	–	–	–	–	–	–	–	–	–	–			
16. Loss of insight	0.18	–	–	–	–	–	–	0.21	0.21	–	–	0.21	–	–	0.34		
17. Weight loss	–	–	–	0.29	0.18	0.29	–	–	0.33	–	–	0.36	–	–	–	–	

Table 5. Coefficients of correlation between postdexamethasone plasma cortisol levels and principal components of HRSD items at baseline

Principal component	r	P
I	0.37	<0.0001
II	−0.15	NS
III	0.17	NS
IV	0.10	NS

veals that the primary contributing HRSD items are somatic and psychological anxiety, both of which were found to be in the group of 9 HRSD items significantly correlated with postdexamethasone plasma cortisol levels. Seemingly, then, the 2 anxiety components of the HRSD appear to contribute significantly to the observed relationship between HRSD and postdexamethasone plasma cortisol. Linear regression analysis revealed that the sum of the 2 anxiety components of the HRSD contribute a large percentage of the variance observed in the relationship between total severity and postdexamethasone plasma cortisol. With logarithmically transformed postdexamethasone plasma cortisol as the dependent variable, and the combined anxiety scores from the HRSD and the HRSD less these 2 anxiety scores as independent variables, a significant linear relationship was established (multiple $r = 0.39$, $F = 9.95$, df = 2,113, $P < 0.0001$). Each of the independent variables has a significant partial correlation coefficient (anxiety items, $r = 0.21$, $P < 0.02$; anxiety-corrected HRSD, $r = 0.27$, $P < 0.005$). Thus, the anxiety items appear to contribute about half of the variance to the relationship between severity of depression and postdexamethasone plasma cortisol levels at baseline.

Relationships between longitudinal severity and cortisol

As these baseline studies suggested that the relationship between severity and cortisol was largely explained by the anxiety components of the HRSD, the relationships of postdexamethasone plasma cortisol, severity of depression ratings, and anxiety ratings were studied over time. Weekly changes in postdexamethasone plasma cortisol, anxiety-corrected HRSD scores (HRSD scores less psychological and somatic anxiety scores), and combined HRSD anxiety item scores (somatic and psychological anxiety) were compared by analysis of variance. Figs. 1–3 summarize the changes of logarithmically transformed postdexamethasone plasma cortisol (Fig. 1), anxiety-adjusted HRSD scores (Fig. 2), and the sum of the anxiety items from the HRSD (Fig. 3) over time. All 3 measures decrease over time in parallel; all first are significantly less than their respective baseline measures at week 4, and remain so

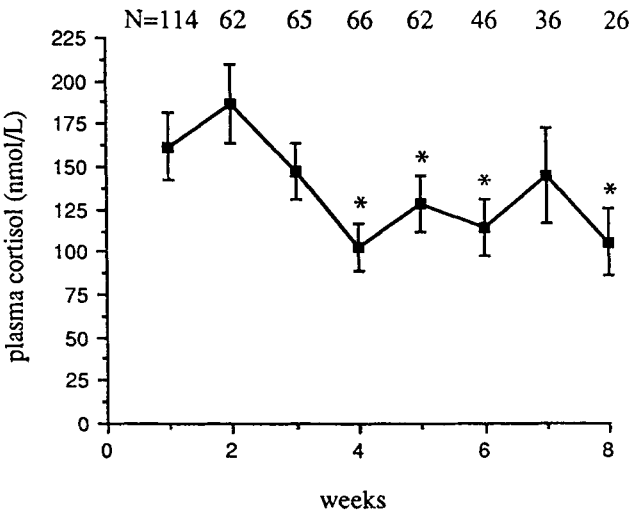

Fig. 1. Longitudinal course of postdexamethasone plasma cortisol from baseline through week 8 of treatment. Cases are not complete after week 1, and the number of patients remaining at each week are shown at the top of the figure. Results are means ± SE; *significantly different from baseline measure ($P < 0.05$).

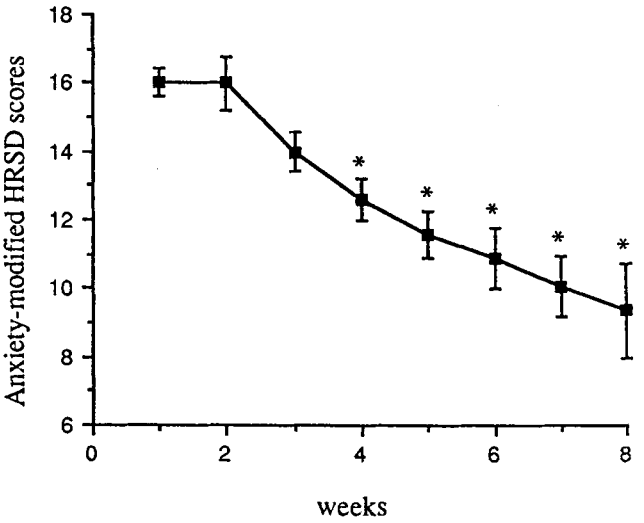

Fig. 2. Longitudinal course of anxiety-adjusted total HRSD scores from baseline through week 8 of treatment. For number of patients studied at each time point, see Fig. 1. Results are means ± SE; *significantly different from baseline measure ($P < 0.05$).

(with the sole exception of cortisol in week 7) for the 8 weeks surveyed.

To further address the longitudinal nature of these items, correlation coefficients were calculated at baseline, 4 weeks into treatment, and at discharge. At baseline, somatic and psychological anxiety were significantly correlated with postdexamethasone plasma cortisol, and were the 2 factors with the heaviest loading in the only principal component of the 17 HRSD items significantly correlated with postdexamethasone plasma cortisol. Fig. 1 reveals

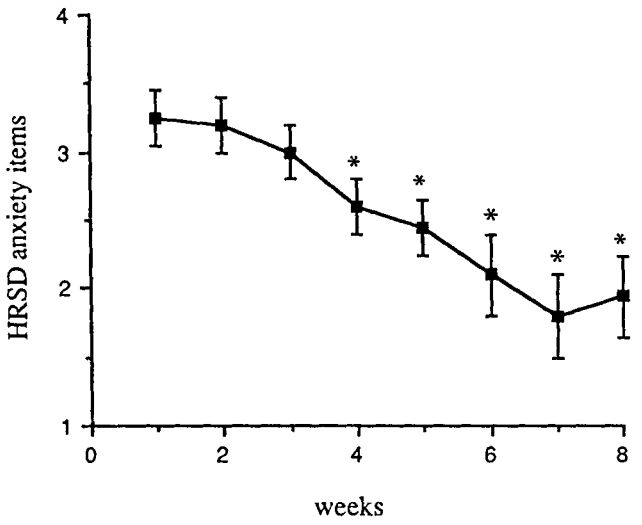

Fig. 3. Longitudinal course of the sum of both HRSD anxiety items from baseline through week 8 of treatment. For number of patients studied at each time point, see Fig. 1. Results are means ± SE; * significantly different from baseline measure ($P < 0.05$).

that the earliest time at which postdexamethasone plasma cortisol is significantly less than at baseline is week 4. Correlation coefficients for postdexamethasone plasma cortisol and total and individual HRSD items at week 4 are demonstrated in Table 6. Total HRSD remains significantly correlated with postdexamethasone plasma cortisol ($r = 0.24$, $n = 65$, $P < 0.05$). Of the 17 HRSD items, only somatic anxiety is correlated with postdexamethasone plasma cortisol. By the time of discharge, total HRSD score is no longer correlated with postdexamethasone plasma cortisol. As long as HRSD scores remain correlated with postdexamethasone plasma cortisol levels, the anxiety components appear to contribute significantly to the relationship.

To address the possibility of interactions of postdexamethasone plasma cortisol and combined HRSD anxiety item scores over time, profile analysis was used (40). Profile analysis is a longitudinal statistical method that allows comparisons of and elucidation of interactions of variables over time. In this particular case, logarithmically transformed postdexamethasone plasma cortisol was studied longitudinally at weekly intervals for weeks 1–6. The population was divided into thirds by HRSD somatic and psychological anxiety combined scores, corresponding to low, moderate, and high levels of anxiety on HRSD. These 3 groups were divided into subgroups with pretreatment anxiety total scores of 0–1 (low anxiety, $n = 11$), 2–3 (moderate anxiety, $n = 46$), and 4–8 (high anxiety, $n = 60$). Although the subgroups appear to have different numbers of patients at baseline, by week 2 all 3 groups were of similar size. The change in the 3 anxiety level profiles was examined over time for the entire population. In profile analysis, the first test is to determine if the profiles are parallel; nonparallelism of profiles in this particular study indicates significant anxiety × time interaction. If profiles are parallel, hence the pattern of change similar over time for all anxiety subgroups, one is able to then test for possible significant anxiety differences within the test group, as well as differences between groups over time.

The results of this analysis are shown in Table 7 and Fig. 4. For the entire population, the 3 profiles are parallel, hence there is no significant time × anxiety interaction. A significant ($P < 0.05$) between-group (anxiety) difference exists, as does a significant ($P < 0.0001$) main effect for time. Over time, postdexamethasone plasma cortisol decreases significantly, regardless of the anxiety stratum an individual is in. All 3 anxiety groups manifest this tendency, and all 3 change in a similar fashion over time. The high anxiety subgroup begins with the highest cortisol levels, however, followed by the moderate and then the low anxiety groups; this

Table 6. Coefficients of correlation between HRSD items and postdexamethasone plasma cortisol levels at week 4

Item	*r*	*P*
Total HRSD	0.24	<0.05
Depressed mood	0.20	
Guilt	−0.12	
Suicide	0.12	
Initial insomnia	0.21	
Middle insomnia	−0.05	
Delayed insomnia	−0.02	
Work and interest	0.12	
Retardation	0.04	
Agitation	0.10	
Psychological anxiety	0.20	
Somatic anxiety	0.32	<0.01
Gastrointestinal	0.14	
General somatic	0.12	
Genital	−0.10	
Hypochondriasis	0.18	
Loss of insight	−0.04	
Weight loss	0.22	

Table 7. Profile analysis of time and anxiety factors for longitudinal postdexamethasone plasma cortisol data

Parallelism of profiles
Maximum root = 0.052
df = 2,1,116
NS
Time
$F = 30.1$
df = 5,234
$P < 0.0001$
Anxiety
$F = 3.13$
df = 2,238
$P < 0.05$

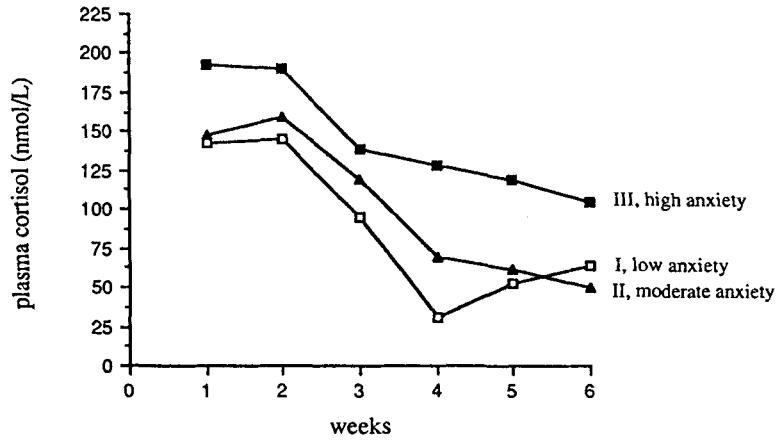

Fig. 4. Profile analysis of postdexamethasone plasma cortisol levels for low (I), medium (II), and high (III) anxiety groups over weeks 1–6.

relative relationship remains constant over time, despite the reduction in cortisol for all 3 groups. High pretreatment levels of anxiety (as reflected by HRSD anxiety items) then suggests that individuals will manifest relatively higher plasma cortisols over time than patients with lower levels of anxiety, although all patients tend to have a longitudinal reduction of cortisol during treatment. This finding implies a longitudinal correlation between postdexamethasone plasma cortisol and anxiety.

Discussion

These results replicate and extend previous studies demonstrating a relationship between postdexamethasone plasma cortisol levels and severity of depressive symptoms, as reflected by depression rating scale scores, in major depressive disorder (9–19). Similar to previous estimates, severity of depression was found to account for as much as 15–20% of the variance associated with DST (9–14). As indicated by the data from these 114 subjects, a significant portion of this relationship was found to be attributable to the anxiety symptoms of the HRSD at pretreatment baseline. Additionally, this association was preserved longitudinally over time, during treatment for depression.

Several previous investigations have attempted to identify depressive symptoms associated with dexamethasone nonsuppression in patients with affective disorders. Results of this type of study have been equivocal, and have been recently reviewed (9). Symptom differences that appear to be moderately consistent from study to study between dexamethasone suppressors and nonsuppressors include various patterns of insomnia (9, 15–17), weight loss (9, 15), and psychomotor agitation and retardation (9, 17, 19). Some investigators have variably found differences in anxiety levels (15–17, 19), lack of sexual interest (9, 16), decreased concentration (15, 16), and depressed mood (15). These results should be compared cautiously, however, since the studies often had small numbers of subjects, employed different experimental designs, and used different rating scales. No single items have been consistently demonstrated as being significantly different between dexamethasone suppressors and nonsuppressors.

More recently, various investigators have demonstrated that there is a modest but significant correlation between total severity of depression (as reflected by various rating scales) and postdexamethasone plasma cortisol levels. These studies have been remarkably consistent, indicating that 15–20% of the total variance associated with DST is attributable to clinical severity (9–14). In addition to this relationship at the adrenal level of the HPA axis, we have reported a similar correlation between severity of depression and circulating levels of the pituitary hormone, β-endorphin, following dexamethasone (11). Our present data are in agreement with these previous studies.

One recent study (9) has been reported in which a strategy similar to ours was employed. In this report, however, the authors found that the Yale Depression Inventory items of initial insomnia, agitation, loss of sexual interest, and weight loss were associated with dexamethasone nonsuppression and postdexamethasone plasma cortisol levels, whereas the 2 anxiety items on this particular rating instrument were not. At baseline, we did find associations between postdexamethasone plasma cortisol and the 4 items reported in this earlier study, but the main effect nonetheless appeared to be related to psychological and somatic anxiety. The discrepancy between this previous report and the present data is difficult to reconcile; both studies evaluated similar numbers of patients, and while this earlier report

appeared to have a more heterogeneous study population, it is doubtful that this is sufficient to account for these different findings. These authors did indicate in their review of previous studies in this area that the association between anxiety and cortisol levels has historically been equivocal.

Interestingly, many studies have been designed to explore the naturalistic clustering of depression rating scale scores in depressed individuals. A recent review (41) of 40 of these studies in which principal component analysis was used to explore this phenomenon concluded that, in every study, factor clusters existed for both depressive symptoms and anxiety symptoms. Interestingly, one of these studies was by Hamilton (42), using his 17-item HRSD. Two major orthogonal factors were identified in a group of 152 patients: Hamilton labelled these as a general measure of severity item (I) and a retarded *vs* agitated depression item (II). The heaviest loadings of these factors were, however, identified for I as suicide, depressed mood, work and interest, loss of insight, and retardation, and for II as somatic anxiety and psychic anxiety. These 2 factors found by Hamilton correspond very closely to factors II and I, respectively, in the present study. Indeed, our finding that the first 2 principal components consist of an anxiety component and a depression component replicates many early studies designed to explore underlying principal components of depression rating scales. It is intriguing that baseline postdexamethasone plasma cortisol was found to correlate with the anxiety component rather than the depression component; in fact, the magnitude of this correlation was the same as for total severity, suggesting that this component itself accounts for all of the variance associated with severity of depression and postdexamethasone plasma cortisol levels.

Finally, our data may provide some basis for another conceptual formulation of the hypothalamic-pituitary-adrenal axis dysregulation seen in depression. It has long been recognized that the HPA axis is the basic stress system, in effect protecting the organism from the deleterious effects of repeated stress (43–45). What has also become apparent is that patients with affective disorders share certain neuroendocrine similarities with endocrine disturbances associated with stress (1, 3, 4, 43–45). It is tempting to speculate that the anxiety components of the HRSD may reflect the subjective experience of stress in affected individuals, and hence the relationship between severity of depression and postdexamethasone plasma cortisol mirrors the degree of stress an individual with depression perceives. Clearly, this is tentative and requires further investigation.

The HPA axis is a complex system that is robustly dysregulated in certain depressed individuals. Severity of illness (9–19), age (20–23), degree of recent weight loss (24, 25), and the presence of delusions (26, 29) appear to be the major sources of variance associated with this pathophysiological alteration. The exact cause of this neuroendocrine defect in the affective disorders has eluded characterization, but may reflect central neurotransmitter and neuromodulator disturbances associated with depression. As data are collected on large populations of patients, however, studies such as this can be undertaken to begin to find the factors that either cause or modulate this endocrine disturbance; in this way, we can hopefully begin to more fully comprehend the chemical disturbances underlying the affective and other psychiatric disorders.

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References

1. Carroll BJ, Feinberg M, Greden JF et al. A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. Arch Gen Psychiatry 1981: 38: 15–22.
2. Charles G, Vandewalle J, Meunier JC et al. Plasma and urinary cortisol levels after dexamethasone in affective disorders. J Affective Disord 1981: 3: 397–406.
3. Brown WA, Keitner G, Qualls B, Haier R. The dexamethasone suppression test and pituitary-adrenocortical function. Arch Gen Psychiatry 1985: 42: 121–123.
4. Stokes PE, Stoll PM, Koslow SH et al. Pretreatment DST and hypothalamic-pituitary-adrenocortical function in depressed patients and comparison groups: a multicenter study. Arch Gen Psychiatry 1984: 41: 257–267.
5. Arana GW, Baldessarini RJ, Ornsteen M. The dexamethasone suppression test for diagnosis and prognosis in psychiatry. Arch Gen Psychiatry 1985: 42: 1193–1204.
6. Chrousos GP, Schulte HM, Oldfield EH et al. Corticotropin releasing factor: basic and clinical studies. Psychopharmacol Bull 1983: 19: 416–421.
7. Gold PW, Chrousos G, Kellner C et al. Psychiatric implications of basic and clinical studies with corticotropin releasing factor. Am J Psychiatry 1984: 141: 619–627.
8. Holsboer F, Gerken A, Stalla GK, Muller OA. ACTH, cortisol, and corticosterone output after ovine corticotropin releasing factor challenge during depression and after recovery. Biol Psychiatry 1985: 20: 276–286.
9. Miller KB, Nelson JC. Does the dexamethasone suppression test relate to subtypes, factors, symptoms, or severity? Arch Gen Psychiatry 1987: 44: 769–774.
10. Kumar A, Alcser K, Grunhaus L, Greden JF. Relationships of the dexamethasone suppression test to clinical severity and degree of melancholia. Biol Psychiatry 1986: 21: 436–444.
11. Meador-Woodruff JH, Haskett RF, Grunhaus L,

AKIL H, WATSON SJ, GREDEN JF. Postdexamethasone plasma cortisol and β-endorphin levels in depression: relationship to severity of illness. Biol Psychiatry 1987: 22: 1137–1150.
12. KLEIN HE, BENDER W, MAYR H, NIEDERSCHWEIBERER A, SCHMAUSS M. The DST and its relationship to psychiatric diagnosis, symptoms and treatment outcome. Br J Psychiatry 1984: 145: 591–599.
13. MAES M, DE RUYTER M, HOBIN P, SUY E. The dexamethasone suppression test, the Hamilton Depression Rating Scale and the DSM-III depression categories. J Affective Disord 1986: 10: 207–214.
14. WHITEFORD HA, PEABODY CA, CSERNANSKY JG, BERGER PA. The severity of depression and nonsuppression on the DST. Am J Psychiatry 1986: 143: 1634–1635.
15. KRISHNAN KRR, FRANCE RD, PELTON S, MCCANN UD, MANEPALLI AN, DAVIDSON JRT. What does the dexamethasone suppression test identify? Biol Psychiatry 1985: 20: 957–964.
16. REUS VI. Pituitary-adrenal disinhibition as the independent variable in the assessment of behavioral symptoms. Biol Psychiatry 1982: 17: 317–326.
17. NASR SJ, GIBBONS RD. Depressive symptoms associated with dexamethasone resistance. Psychiatry Res 1983: 10: 183–189.
18. BROWN WA, SHUEY I. Response to dexamethasone and subtype of depression. Arch Gen Psychiatry 1980: 37: 747–751.
19. KASPER S, BECKMANN H. Dexamethasone suppression test in a pluridiagnostic approach: its relationship to psychopathological and clinical variables. Acta Psychiatr Scand 1983: 68: 31–37.
20. OXENKRUG GF, POMARA N, MCINTYRE IM, BRANCONNIER RJ, STANLEY M, GERSHON S. Aging and cortisol resistance to suppression by dexamethasone: a positive correlation. Psychiatry Res 1983: 10: 125–130.
21. DAVIS KL, DAVIS BM, MATHE AA et al. Age and the dexamethasone suppression test in depression. Am J Psychiatry 1984: 141: 872–874.
22. LEWIS DA, PFOHL B, SCHLECHTE J, CORYELL W. Influence of age on the cortisol response to dexamethasone. Psychiatry Res 1984: 13: 213–220.
23. GREDEN JF, FLEGEL P, HASKETT R et al. Age effects in serial hypothalamic-pituitary-adrenal monitoring. Psychoneuroendocrinology 1986: 11: 195–204.
24. KEITNER GI, BROWN WA, QUALLS CB, HAIER RJ, BARNES KT. Results of the dexamethasone suppression test in psychiatric patients with and without weight loss. 1985: Am J Psychiatry 142: 246–248.
25. KRISHNAN KRR, FRANCE RD, SNIPES MT, PELTON S. Weight change and the dexamethasone suppression test. Biol Psychiatry 1985: 20: 1018–1022.
26. RUDORFER MV, HWA H-G, CLAYTON PJ. Dexamethasone suppression test in primary depression: significance of family history and psychosis. Biol Psychiatry 1982: 17: 41–48.
27. RIHMER Z, ARATO M, SZADOCZKY E et al. The dexamethasone suppression test in psychotic versus non-psychotic endogenous depression. Br J Psychiatry 1984: 145: 508–511.
28. SCHATZBERG AF, ROTHSCHILD AJ, STAHL JB et al. The dexamethasone suppression test: identification of subtypes of depression. Am J Psychiatry 1983: 140: 88–91.
29. MENDLEWICZ J, CHARLES G, FRANCKSON JM. The dexamethasone suppression test in affective disorder: relationship to clinical and genetic subgroups. Br J Psychiatry 1982: 141: 464–470.
30. MEADOR-WOODRUFF JH, GREDEN JF. Effects of psychotropic medications on hypothalamic-pituitary-adrenal regulation. Endocrinol Metab Clin North Am 1988: 17: 225–234.
31. KRAUS RP, HUX M, GROF P. Psychotropic drug withdrawal and the dexamethasone suppression test. Am J Psychiatry 1987: 144: 82–85.
32. DILSAVER SC, GREDEN JF. Effects of antidepressant withdrawal on the dexamethasone suppression test. Psychiatry Res 1985: 14: 111–122.
33. NABER D, ALBUS M, BURKE H et al. Neuroleptic withdrawal in chronic schizophrenia: CT and endocrine variables relating to psychopathology. Psychiatry Res 1985: 16: 207–219.
34. HAMILTON M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960: 23: 56–62.
35. SPITZER RL, ENDICOTT J. Schedule for Affective Disorders and Schizophrenia. New York: Biometrics Research Division, New York State Psychiatric Institute, 1975.
36. SPITZER RL, ENDICOTT J, ROBINS E. Research Diagnostic Criteria (RDC). New York: Biometrics Research Division, New York State Psychiatric Institute, 1977.
37. GREDEN JF. Biological laboratory tests in psychiatry. In: SADOCK BJ, KAPLAN HI, eds. Comprehensive textbook of psychiatry. 4th ed. Baltimore: Williams & Wilkins, 1985.
38. MURPHY BE. Some studies of the protein-binding of steroids and their application to the routine micro- and ultra-micro measurement of various steroids in body fluids by competitive protein-binding radioassay. J Clin Endocrinol Metab 1967: 27: 973–990.
39. CHATFIELD C, COLLINS AJ. Introduction to multivariate analysis. London: Chapman & Hall, 1980.
40. MORRISON D. Multivariate statistical methods. New York: McGraw-Hill, 1967.
41. MULLANEY JA. The relationship between anxiety and depression: a review of some principal component analytic studies. J Affective Disord 1984: 7: 139–148.
42. HAMILTON M. Development of a rating scale for primary depressive illness. J Clin Soc Psychol 1967: 6: 278–296.
43. SAPOLSKY RM, KREY LC, MCEWEN BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr Rev 1986: 7: 284–301.
44. AXELROD J, REISINE TD. Stress hormones: their interaction and regulation. Science 1984: 224: 452–459.
45. YOUNG EA, AKIL H. Corticotropin releasing factor stimulation of adrenocorticotropin and β-endorphin release: effects of acute and chronic stress. Endocrinology 1985: 117: 23–30.