The Dexamethasone Suppression Test in Patients With Mood Disorders

A. John Rush, M.D., Donna E. Giles, Ph.D., Michael A. Schlesser, M.D., Paul J. Orsulak, Ph.D., C. Richard Parker, Jr., Ph.D., Jan E. Weissenburger, Ph.D., George T. Crowley, Manoochehr Khatami, M.D., and Nishendu Vasavada, M.D.

Background: This study was undertaken to (1) determine whether the endogenous/nonendogenous mood disorder dichotomy is validated by the dexamethasone suppression test (DST); (2) determine whether other subtyping schemes (unipolar/bipolar, DSM-III melancholic/nonmelancholic, Winokur's family history subtypes) relate to the DST; (3) evaluate the relative contributions of symptom severity, weight loss, and other factors to DST status; and (4) assess the relative sensitivity of various post-dexamethasone cortisol determinations in the detection of dexamethasone nonsuppression.

Method: 487 consecutive adult inpatients (N = 131) and outpatients (N = 356) with unipolar (N = 422) or bipolar disorder (N = 65) underwent the 1.0-mg DST. Nonsuppression was defined as at least one post-dexamethasone cortisol measurement > 4.0 μg/dL.

Results: Nonsuppression occurred in 27% of all patients with major depression and 43% of all bipolar depressed phase patients. For outpatients, dexamethasone nonsuppression occurred in 35.2% of subjects with endogenous (unipolar + bipolar; N = 145) and 9.0% of those with nonendogenous (unipolar only; N = 211) depressions (single 4 p.m. post-dexamethasone cortisol). For inpatients, dexamethasone nonsuppression was found in 61.5% of subjects with endogenous (N = 104) and 18.5% of those with nonendogenous (N = 27) depressions (three post-dexamethasone cortisol determinations). For the inpatient and outpatient sample together, the DST had a sensitivity of 46.2% and a specificity of 89.9% in differentiating endogenous from nonendogenous major depressive episodes. Weight loss, gender, and symptom severity added little to the endogenous/nonendogenous dichotomy. The Research Diagnostic Criteria (RDC) primary/secondary and Winokur and colleagues' family history subtypes for unipolar depression were not strongly validated by the DST. The 4 p.m. and 11 p.m. samples together detected 91.0% of those inpatients with abnormal three-sample DST results. The 8 a.m. sample alone detected 30% of those, the 4 p.m. sample alone detected 67%, and the 11 p.m. sample alone detected 62%.

Conclusion: The RDC endogenous/nonendogenous dichotomy was validated by the DST.

(J Clin Psychiatry 1996;57:470–484)

Received June 21, 1995; accepted June 12, 1996. From the Mental Health Clinical Research Center and Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas (Drs. Rush, Khatami, and Vasavada), Department of Psychiatry and Neurology, University of Rochester Medical Center, Rochester, N.Y. (Dr. Giles), Dallas Neuropsychiatry Associates, Dallas (Dr. Schlesser), Psychiatric Clinical Diagnostic Laboratory, Department of Veterans Affairs Medical Center, Dallas, Tex. (Dr. Orsulak and Mr. Crowley), Department of Obstetrics and Gynecology, University of Alabama School of Medicine, Birmingham (Dr. Parker), and Audie L. Murphy Department of Veterans Affairs Medical Center, San Antonio, Tex. (Dr. Weissenburger). The first three authors contributed equally to the conduct of this study.

Supported by grants MH-35370 from the National Institute of Mental Health (NIMH) and M01RR00633 from the National Institutes of Health to the General Clinical Research Center, Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas; by Mental Health Clinical Research Center Grant MH-41115 from NIMH to the Department of Psychiatry, UT Southwestern; by a grant from the Biohumanics Foundation to the Department of Psychiatry, UT Southwestern; and by the Psychiatric Clinical Diagnostic Laboratory, Department of Veterans Affairs Medical Center, Dallas, Tex.

We thank Carol Fairchild, M.S.N., Nancy Johnson, M.S.N., and Lola Wilson, B.S.N., for clinical assistance, Christina M. Gullion, Ph.D., for statistical support, David Savage for secretarial support, and Kenneth Z. Altshuler, M.D., Stanton Sharp Distinguished Chair and Chairman, for administrative support.

Reprint requests to: A. John Rush, M.D., Department of Psychiatry at St. Paul POB I, Suite 600, 5959 Harry Hines Boulevard, Dallas, TX 75235-9101.

Over the past 20 years, cortisol hypersecretion has been reported frequently in many patients with mood disorders[1–4] (for a review, see Rubin[5]). More recent studies indicate that the cortisol response after a challenge with an exogenous glucocorticoid, dexamethasone, distinguishes some depressed patients from normal controls. These patients either fail to suppress their cortisol levels or escape from suppression abnormally early. A standard protocol has been proposed for employing the dexamethasone suppression test (DST) as a diagnostic tool.[6,7]

While the evidence that DST nonsuppression occurs in depression is substantial, the clinical implications of this phenomenon remain controversial.[8] Many studies find that DST nonsuppression is related to the endogenous or melancholic types,[6,9–12] while others fail to find such a relationship.[13–17] A variety of clinical, laboratory, methodological, design, and statistical factors most likely contribute to the differences between studies.[18–21]

In addition to the endogenous or melancholic subtypes, other diagnostic classifications have been evaluated in relation to the DST. Winokur and colleagues'[22] family his-

tory subtypes for unipolar depressions have been validated by some reports,[12,23–30] but not by others.[17,31–35] The positive studies generally reveal a higher incidence of DST nonsuppression in familial pure depressive disease than in either depression spectrum disease or sporadic depressive disease. Similarly, primary depression has a higher incidence of DST nonsuppression than does secondary depression by most reports,[26,28,32,36,37] but not by all.[12,38] For this dichotomy, the positive reports generally rest on inpatient samples, while negative findings are largely found in outpatients.

One of the major areas of controversy rests on findings indicating that DST nonsuppression is not specific to mood disorders.[39] The severity of dementia may relate to whether DST nonsuppression is found.[40] Most reports of carefully evaluated normal control subjects reveal a 3% to 6% DST nonsuppression rate.[6,12,13,41,42] Patients with moderate-to-severe dementia,[43–45] anorexia nervosa,[46,47] alcoholism,[48,49] schizophrenia,[50,51] mania and atypical psychoses,[52,53] obsessive-compulsive disorder,[54] borderline personality disorder,[24,55] and schizoaffective disorder,[56] as well as poststroke patients[57–59] evidence DST nonsuppression. This nonsuppression may be related to significant concurrent depressive symptoms in some of these patients.

Carroll[7,60,61] suggests that rather than being a uniquely specific concomitant of melancholic depressions, DST nonsuppression may indicate a limbic system derangement found in both classical cases of melancholia and in atypical presentations of "melancholia," such as catatonic depression, depressive pseudodementia, mixed manic depressive states, or atypical psychoses that resemble more typical episodes of major depression at follow-up. One study[62] suggests, however, that DST status does not relate to the presence or absence of major depression in patients with borderline personality disorder. Conversely, Olivera and colleagues[63] reported that DST nonsuppression in chronic psychiatric patients with substance dependence was related solely to the presence of affective symptomatology. Other studies have found *low* rates of DST nonsuppression in nondepressed patients with alcoholism,[64] panic disorder,[65] anxiety disorder,[66] schizophrenia,[2,3,26,67] mania,[26] and mild dementia.[68]

The relationship of the DST to several nondiagnostic factors has also been examined. Several reports have found an age effect on the DST,[16,69–75] which is in contrast to the original study[6] and subsequent reports by others.[76–80] Although age correlated significantly with DST status in a study by Maes et al.,[81] the authors point out that the percentage of variance accounted for was minimal (2.2%). In a more recent report, Maes et al.[82] found age to be a significant covariate of the 8 a.m. post-dexamethasone cortisol level, but not of the 4 p.m. post-dexamethasone level. For the 8 a.m. sample, the combination of age and baseline cortisol levels accounted for 59% of the variance, with the addition of diagnostic status not adding significantly to the predictive power. In addition, von Bardeleben and Holsboer[83] report findings suggesting an age effect on general glucocorticoid neuroregulation in depression.

It has been suggested that stress is an important determinant of DST nonsuppression.[84,85] Some evidence suggests that stress effects may be independent of the influence of endogenicity on DST results.[86–89] Haskett et al.[90] suggest that an increased rate of DST nonsuppression among recently admitted inpatients with diagnoses other than endogenous depression may reflect stress effects. This explanation is consistent with the fact that the rate of nonsuppression declined among these patients when the DST was repeated approximately 1 week later.

Weight loss in normal or obese subjects has been related to DST nonsuppression,[47,91,92] as has weight loss in some[82,91,93–95] but not all[10,90,96–100] depressed patient samples. Pfohl and coworkers[101] found that both self-reported weight change and measured weight change during the first week of hospitalization were *not* significantly related to DST results. The amount of measured weight loss between two successive admissions, however, was associated with DST nonsuppression, particularly in patients with below average body weight.

Gender differences have not been systematically examined in most studies of the DST. Carroll et al.[6] found no significant differences in the rates of nonsuppression among males and females in their study. Among their melancholic patients, 37% of males and 46% of females exhibited DST nonsuppression. Similarly, no gender differences have been found in subsequent reports.[81,102,103]

The severity of depressive symptoms may also relate to DST results,[81,104–111] although not all studies have found this relationship.[10,86,112–114] A recent study by Meador-Woodruff et al.[115] suggests that this effect may be significantly associated with the anxiety symptoms of the Hamilton Rating Scale for Depression (HAM-D).[116] In contrast, Staner et al.[117] found psychomotor change and weight loss to be the most discriminating symptoms when age, gender, and severity of illness were covaried. As reported by Georgotas and coworkers,[108] symptom severity and certain diagnostic subgroups (e.g., endogenous/nonendogenous or melancholic/nonmelancholic) are themselves confusing, and one subtype is somewhat more severe than the other. Thus, the relative contribution of symptom severity and diagnostic subtype to DST nonsuppression must be examined.

A methodological issue concerns the optimal sampling procedure to be used with the DST. Maes et al.[81] suggest that the 8 a.m. post-dexamethasone cortisol sample is optimal for maximizing sensitivity and specificity in identifying melancholic depression versus normal controls and minor depressives. This result is in contrast with earlier

reports noting nonsuppression at any one of the 8 a.m., 4 p.m., or 11 p.m. samples[6,36] or at the 4 p.m. sample only (with a threshold of 5.0 μg/dL).[86,118] A more recent study[119] concludes that the 11 p.m. post-dexamethasone cortisol measure is maximally sensitive, whereas the 3 p.m. post-dexamethasone measure is optimally specific, when comparing the matched samples of 40 endogenous depressed patients to 40 normal controls. All three post-dexamethasone cortisol samples (7 a.m., 3 p.m., and 11 p.m.) were similar in terms of their overall diagnostic efficiency.

The present study was undertaken to provide a comprehensive assessment of each of the areas of major controversy. We designed our study to (1) determine whether one or more descriptive subclassifications (primary/secondary and endogenous/nonendogenous by using Research Diagnostic Criteria [RDC],[120] melancholic/nonmelancholic by using DSM-III criteria,[121] family history subtypes by using Winokur and colleagues'[22] definitions) are validated by the DST; (2) evaluate the relative contributions of symptom severity, weight loss, and other factors to DST status; and (3) assess which of three post-dexamethasone cortisol levels contributed most to the identification of DST nonsuppression.

METHOD

Subjects

Outpatients were recruited from the Mood Disorders Program, University of Texas Southwestern Medical Center, Dallas. This program typically receives acutely symptomatic, depressed patients who are self-referred (approximately 80%), referred from private practitioners (approximately 10%), or referred from the Parkland Memorial Hospital (PMH) Psychiatric Emergency Service (ER) (approximately 10%).

Inpatients were recruited from the 18-bed inpatient Psychiatry Service of PMH. The referral source for the inpatient unit is largely from the Psychiatry ER. Of the 800 to 1000 patients assessed per month in the ER, 160 to 180 are hospitalized. Of those hospitalized, the more severely depressed are typically referred to this inpatient service.

The sample was developed from all consecutive patients admitted to either outpatient or inpatient services from 1980 to 1985 who met the inclusion and exclusion criteria (see below). Patients who had received barbiturates, phenytoin, carbamazepine, estrogens, or thyroid replacement within 14 days of testing were excluded. Patients with concomitant medical problems (e.g., diabetes, thyroid disease, congestive heart failure, hypertension that required drugs other than diuretics, concurrent infections, organic brain syndromes and dementia) and those with schizoaffective disorder by RDC were excluded.

Clinical Evaluations

Clinical diagnoses were made by experienced clinical researchers blind to DST results (one of the first three authors) on all patients. All patients were required to meet criteria for *definite* major depression by RDC. All outpatients received a structured interview, the Schedule for Affective Disorders and Schizophrenia, lifetime version (SADS-L),[122] to establish the clinical diagnosis and diagnostic subtypes according to RDC. RDC for definite endogenous depression (6 of 10 symptoms) were satisfied for all patients diagnosed as endogenous. RDC probable endogenous depressions were included in the nonendogenous group. RDC for endogenous depression, as well as DSM-III criteria for melancholia, were strictly applied for the nadir of the presenting episode. To illustrate the meaning of strictly applied, anhedonia, for example, was deemed present only if it were truly pervasive. If the patient's capacity for pleasure was significantly reduced compared with his/her premorbid level, but *not* pervasive, then pervasive anhedonia was deemed *not* present. Further, the clinician's personal belief as to whether the patient suffered endogenous or melancholic depression was not taken into account in rendering the diagnosis. Rather, both endogenous/nonendogenous (by RDC) and melancholic/nonmelancholic (by DSM-III) diagnoses were rendered based entirely on the number and nature of the symptoms occurring at the nadir of the presenting episode.

Outpatients were interviewed on two distinct occasions (usually separated by 4–7 days), with symptoms for affective disorder, RDC endogenous depression, and DSM-III melancholia assessed at both occasions. Outpatients who were taking psychotropic medications were required to discontinue them for 5 to 14 days, after which they were reevaluated by both RDC and DSM-III. This practice allowed the full symptomatic picture to express itself, thus clarifying diagnostic decisions. The final diagnostic judgment was rendered by the senior clinician (either of the first two authors) in all cases.

All inpatient diagnoses were rendered by the third author, using the same strictly applied RDC and DSM-III criteria for the nadir of the present episode. All subjects from this group were inpatients for at least 4 days prior to the DST; all were medication-free before testing, and most were medication-free for approximately 5 to 7 days prior to the DST.

History of psychiatric disorder among first-degree relatives was obtained from the patient. This information was used to classify patients according to the Winokur et al.[22] typology. According to this typology, patients with a family history of alcoholism in at least one first-degree relative receive a diagnosis of depression spectrum disease; those with a diagnosis of depression but no alcoholism in at least one first-degree family member are classified as familial pure depressive disease; and those patients

with no first-degree relatives with either depression or alcoholism are classified as sporadic depressive disease. To render a family history diagnosis, a procedure consistent with Andreasen et al.[123] was used in which there must be clear evidence of depressive symptoms, functional impairment, and/or help-seeking behavior. Therefore, diagnoses of first-degree relatives were made conservatively.

Diagnoses on all inpatients and outpatients were rendered independent of and blind to laboratory test results. Similarly, all laboratory measures were made independent of and blind to clinical diagnoses. Symptom severity was assessed with the 17-item HAM-D[116] within 2 days of the DST.

Dexamethasone Suppression Testing

The 1.0-mg overnight DST procedure was employed.[6,12,124] Patients were given 1.0 mg p.o. of dexamethasone at 11 p.m. (± 60 minutes). For inpatients, serum cortisol samples were drawn at 8 a.m., 4 p.m., and 11 p.m. the following day (± 60 minutes). In 92 (70.2%) of 131 inpatients, a blood sample at 11 p.m. immediately *before* dexamethasone administration was also obtained. For outpatients, only a 4 p.m. post-dexamethasone serum cortisol sample was obtained.

Cortisol concentrations were determined by radioimmunoassay as described elsewhere[124] using the Radioassay Systems Laboratory (Carson, Calif.) cortisol antibody (No. 1460) and tritiated cortisol tracer. Calibration standards for this assay are set at 0, 1.5, 3.0, 4.0, 5.3, 7.1, 9.5, 12.7, 17.0, 22.7, and 30.0 µg/dL. The ED_{50} for this assay is 6.0 µg/dL. The mean intraassay coefficient of variation over a recent 9-month period was 7.9% and the interassay coefficient of variation over this same time period was 12.5% at a nominal concentration of 6.0 µg/dL. Longitudinal quality control of this assay was accomplished by inclusion of two to six specimens of an assayed serum pool in each analysis batch. Data from repeated analysis of this pool permitted assessment of both interassay and intraassay performance as described previously.[125,126]

The criterion for an abnormal post-dexamethasone serum cortisol level was set at > 4.0 µg/dL. This threshold value was chosen based on our study of normal controls (N = 23) in which 8 a.m., 4 p.m., and 11 p.m. post-dexamethasone serum cortisol determinations were obtained.[124] From this study of normal controls, the specificity is 96% at the 4.0 µg/dL threshold. For inpatients, DST nonsuppression was recorded when one or more of the three post-dexamethasone cortisol levels exceeded 4.0 µg/dL. Although the threshold for nonsuppression was set a priori, our report retrospectively evaluated the diagnostic performance associated with serum cortisol levels of 3.0, 4.0, 5.0, and 6.0 µg/dL.

Statistical Analyses

Student t tests, analyses of variance, and chi-square analyses were used for between group comparisons. The influence of selected clinical variables on the DST was examined with stepwise discriminant (BMDP Statistical Software, Berkeley, Calif.)[127] and multiple regression analyses (SAS Institute Inc., Cary, N.C.).[128] For these analyses, the distribution of post-dexamethasone serum cortisol values was used and was normalized via logarithmic transformation.[129,130]

Table 1. Diagnostic Subgroups of Inpatients, Outpatients, and Total Sample*

	Inpatients		Outpatients		Total Sample	
Subgroup	N	%	N	%	N	%
RDC						
Unipolar endogenous	83	75	101	32	184	44
Unipolar nonendogenous	27	25	211	68	238	56
Unipolar primary	95	86	249	80	344	82
Unipolar secondary	15	14	63	20	78	18
Bipolar I, depressed	19	90	22	50	41	63
Bipolar II, depressed	2	10	22	50	24	37
DSM-III						
Unipolar melancholic	43	39	26	11	69	19
Unipolar nonmelancholic	66	61	219	89	285	81
Family history (unipolar, primary only)						
FPDD	32	34	70	28	102	30
DSD	30	32	80	32	110	32
SDD	28	29	88	35	116	34

*Abbreviations: DSD = depression spectrum disease, FPDD = familial pure depressive disease, RDC = Research Diagnostic Criteria, SDD = sporadic depressive disorder.

RESULTS

Sample Description

Data are presented first by each factor that has been associated with DST nonsuppression. Those factors that discriminated were then combined to assess the relative contributions of each to nonsuppression. A total of 487 patients were studied (356 [73.1%] outpatients; 131 [26.9%] inpatients). Endogenous/nonendogenous and primary/secondary subgroups of unipolar patients only (N = 422) were identified by RDC. Family history classification[22] was used to subgroup the RDC primary unipolar patients, excluding those with bipolar disorder in a first-degree relative (N = 328). Table 1 summarizes the combined diagnostic groupings in relation to patient status (unipolar endogenous and nonendogenous, primary and secondary, melancholic and nonmelancholic, and bipolar I depressed and bipolar II depressed). Table 2 compares descriptive characteristics for unipolar (endogenous + nonendogenous) and bipolar (I and II) depressed phase patients.

Diagnostic subgroups. A total of 354 unipolar patients were also classified as melancholic (69 or 19%) or nonmelancholic (285 or 80%) by DSM-III. Sixty-eight patients met both DSM-III melancholic and RDC endogenous criteria.

Table 3 shows the DST results for unipolar, bipolar, and family history diagnostic subgroups. RDC unipolar endogenous and nonendogenous patients significantly

Table 2. Diagnostic and Descriptive Characteristics of the Sample*

Characteristic	Unipolar (N = 422)	Bipolar[a] (N = 65)	Total (N = 487)
Age (y), mean ± SD	36.9 ± 12.4	36.8 ± 12.0	36.9 ± 12.3
Female	64.9%	49.2%	62.8%
HAM-D score, mean ± SD	22.6 ± 6.4	22.2 ± 7.7	22.6 ± 6.6
Psychotic	6.4%	20.6%	8.2%
Inpatients	26.1%	32.3%	26.9%

*Abbreviation: HAM-D = 17-item Hamilton Rating Scale for Depression.
[a]Includes 41 bipolar I depressed phase and 24 bipolar II depressed phase patients.

Table 3. DST Results for Diagnostic Subtypes of Unipolar Depression*

	Cortisol Level (μg/dL)				DST-NS	
	Highest		4 p.m.		Highest	4 p.m.
Subtype	Mean	SD	Mean	SD	(%)	(%)
Overall sample	3.6	3.9	3.2	3.6	29.0	24.4
Unipolar (N = 422)	3.4	3.8	3.0	3.6	26.8	22.5
Bipolar (N = 65)	4.6	4.0	3.9	3.9	43.1	36.9
Unipolar endogenous (N = 184)	5.1	5.0	4.4	4.7	47.8	39.1
Unipolar nonendogenous (N = 238)	2.2	1.8[a]	2.1	1.8[a]	10.5[a]	9.7[a]
Unipolar primary (N = 344)	3.6	4.0[b]	3.2	3.7	28.8	23.8
Unipolar secondary (N = 78)	2.7	2.9	2.5	2.8	18.0	16.7
FPDD (N = 102)	4.5	5.3	3.9	5.0	36.3	27.5
DSD (N = 110)	3.1	3.2	2.8	2.8	22.7	21.8
SDD (N = 116)	3.4	3.4	3.1	3.2	25.9	21.6

*Abbreviations: DST-NS = dexamethasone suppression test nonsuppression.
[a]$p < .001$, nonendogenous lower than endogenous.
[b]$p < .05$, primary higher than secondary.

differed in the overall incidence of DST nonsuppression, using the 4 p.m. sample ($\chi^2 = 50.0$, df = 1, $p < .001$) and the highest of three post-dexamethasone samples ($\chi^2 = 71.8$, df = 1, $p < .001$). They also differed in the mean 4 p.m. post-dexamethasone serum cortisol level ($F = 38.7$, df = 1,420; $p < .001$) and in the highest mean post-dexamethasone serum cortisol level ($F = 66.9$, df = 1,420; $p < .001$). A higher proportion of bipolar (versus unipolar) patients evidenced DST nonsuppression ($\chi^2 = 7.30$, df = 1, $p < .005$).

Unipolar Versus Bipolar Depression

On the basis of the highest post-dexamethasone cortisol sample, 43.1% of the 65 bipolar depressed phase patients evidenced DST nonsuppression. In comparison, 47.8% of the unipolar endogenous and 10.5% of the unipolar nonendogenous patients evidenced DST nonsuppression. Thus, bipolar depressed phase and unipolar endogenous patients had equivalent DST nonsuppression rates ($\chi^2 = 0.44$, df = 1, $p = .51$). Unipolar nonendogenous patients had significantly lower DST nonsuppression rates (10.5%) than either the bipolar depressed phase ($\chi^2 = 37.5$, df = 1, $p < .001$) or unipolar endogenous patients ($\chi^2 = 73.7$, df = 1, $p < .001$). Since the rates of DST nonsuppression were equivalent, bipolar and unipolar endogenous patient groups were combined for analyses in subsequent sections of this report.

Table 4. Characteristics of RDC Endogenous vs. Nonendogenous Unipolar Depressions

Characteristic	Endogenous (N = 184)	Nonendogenous (N = 238)	p
Age[a] (y), mean ± SD	37.5 ± 13.6	36.4 ± 11.4	NS
Female[b]	60.3%	68.5%	NS
HAM-D score,[a] mean ± SD	26.3 ± 6.2	19.8 ± 5.0	< .001
Psychotic[b]	13.0%	1.3%	< .001
Inpatient[b]	45.1%	11.3%	< .001
Primary[b]	88.6%	76.1%	< .001
FPDD[b]	38.5%	24.4%	< .01
DSD[b]	28.2%	38.4%	< .06
SDD[b]	33.3%	37.2%	NS

[a]p Values are based on Welch's approximate t statistic for unequal variances.
[b]p Values are based on chi-square.

DST results did not as strongly validate the RDC primary/secondary distinction. The highest post-dexamethasone cortisol value was significantly higher in the primary group ($F = 4.0$, df = 1,420; $p < .05$). On the basis of the 4 p.m. cortisol sample alone, however, the primary and secondary groups did not differ significantly ($F = 1.8$, df = 1,420; $p = .18$). The proportion of patients with DST nonsuppression, based on the 4 p.m. sample alone, did not differentiate primary and secondary groups ($\chi^2 = 1.5$, df = 1, $p = .22$), nor did the DST nonsuppression rate based on the highest post-dexamethasone cortisol level ($\chi^2 = 3.3$, df = 1, $p = .07$).

DST results also provided little validation for Winokur and colleagues'[22] family history subtypes for unipolar RDC primary depressives. Sixteen patients with primary depression could not be diagnosed by family history due to lack of information on first-degree relatives. The familial pure depressive disease group tended to evidence higher rates of DST nonsuppression than the other groups when the highest post-dexamethasone cortisol sample was analyzed ($\chi^2 = 5.2$, df = 2, $p = .07$). Family history groups did not differ, either using the rate of DST nonsuppression based on the 4 p.m. sample alone or using the cortisol value based on the highest value.

Table 4 describes patients with unipolar depression grouped by RDC endogenous/nonendogenous subtype. Endogenous patients were more severely depressed according to the 17-item HAM-D. More endogenous patients were psychotic and more were inpatients compared with the nonendogenous group. There were more patients with primary depression and a family history diagnosis of familial pure depressive disease among the endogenous group. This latter result reflects an overlap or partial correspondence among the three diagnostic schemes. Nonendogenous patients were more likely to have the family history diagnosis of depression spectrum

Table 5. Comparison of RDC Endogenous and DSM-III Melancholic Subtypes

Characteristic	Endogenous, Melancholic (N = 69)	Endogenous, Nonmelancholic (N = 94)	Nonendogenous, Nonmelancholic (N = 191)
Age (y)	40.9 ± 16.0	34.9 ± 11.3	36.1 ± 10.9
Female	54.4%	58.5%	68.1%
HAM-D score	28.3 ± 6.6	24.9 ± 5.6	19.4 ± 5.0
Psychotic	29.4%	2.1%	1.1%
Inpatient	63.2%	42.6%	13.6%
DST-NS (highest)	55.9%	39.4%	9.4%
DST-NS (4 p.m.)	41.2%	33.0%	8.4%
Highest post-dexamethasone cortisol level (μg/dL)	6.2 ± 5.9	4.2 ± 4.1	2.1 ± 1.9
4 p.m. post-dexamethasone cortisol level (μg/dL)	5.2 ± 5.8	3.6 ± 3.6	2.0 ± 1.8

Table 6. A Comparison of DST-NS Rates in Four Diagnostic Subclassifications of Unipolar Depression*

	Outpatients		Inpatients		Total Sample	
Classification	%	N	%	N	%	N
RDC						
Unipolar endogenous	40	40/101	39	32/83	39	72/184
Unipolar nonendogenous	9	20/211	11	3/27	10	23/238
Unipolar primary	19	48/249	36	34/95	24	82/344
Unipolar secondary	19	12/63	7	1/15	17	13/78
DSM-III						
Unipolar melancholic	46	12/26	37	16/43	41	28/69
Unipolar nonmelancholic	13	28/219	29	19/66	16	47/285
Family history (unipolar, primary only)						
FPDD	19	13/70	47	15/32	27	28/102
DSD	23	18/80	20	6/30	22	24/110
SDD	16	14/88	39	11/28	22	25/116

*Nonsuppression is defined as a 4 p.m. post-dexamethasone cortisol level > 4.0 μg/dL.

disease. Patients with a negative family history (sporadic depressive disease) were equally distributed among the RDC endogenous and nonendogenous subtypes.

DSM-III unipolar melancholic (N = 69) and unipolar nonmelancholic patients (N = 285) were also compared (Table 5). Of the nonmelancholic nonendogenous group (N = 191), only 16 (8.4%) evidenced DST nonsuppression at 4 p.m. Of those designated DSM-III nonmelancholic, but RDC endogenous, 31/94 (33.0%) showed DST nonsuppression at 4 p.m.

Table 6 presents a comparative summary of DST nonsuppression rates within diagnostic subtypes for inpatients and outpatients, both separately and combined. The percentages and numbers of patients showing DST nonsuppression are based on the 4 p.m. post-dexamethasone cortisol level, with a threshold for definition of nonsuppression set at > 4.0 μg/dL. Note that the percentage of nonsuppressors was no different for inpatients versus outpatients who met RDC for the endogenous subtype, or who met DSM-III for the melancholic subtype. However, family history of depression was associated with a higher rate of DST nonsuppression for inpatients versus outpatients, as was the presence of primary depression.

Table 7. Sensitivity, Specificity, and Diagnostic Confidence Values of 8 a.m., 4 p.m., and 11 p.m. Cortisol Samples (Separately and in Combination) for Inpatients

Sample Time	Sensitivity	Specificity	Diagnostic Confidence
8 a.m. (N = 127)	20	96	95
4 p.m. (N = 131)	41	89	93
11 p.m. (N = 118)	42	87	93
8 a.m. + 4 p.m.	48	85	92
8 a.m. + 11 p.m.	46	85	92
4 p.m. + 11 p.m.	57	85	94
8 a.m. + 4 p.m. + 11 p.m.	62	81	92

DST Method: Three Versus One Post-Dexamethasone Sampling

For inpatients, blood samples were collected and assayed for cortisol at 8 a.m., 4 p.m., and 11 p.m. after dexamethasone administration. DST nonsuppression was defined as one or more of the three samples having a cortisol level > 4.0 μg/dL. Based on this method, 69 (53%) of 131 patients evidenced DST nonsuppression. Of the 69 inpatients with DST nonsuppression, as defined by a positive serum cortisol level at one or more of the three sampling times, nonsuppression occurred in 30.4% (N = 21) at the 8 a.m. sampling time, in 66.7% (N = 46) at the 4 p.m. sampling time, and in 62.3% (N = 43) at the 11 p.m. sampling time. The combination of 4 and 11 p.m. samples detected 91% (N = 63) of DST nonsuppression, compared with 78% (N = 54) detected by the combination of 8 a.m. and 4 p.m. samples. These results suggest that the 4 and 11 p.m. samples suffice for differentiating endogenous from nonendogenous inpatients. Table 7 presents sensitivity, specificity, and diagnostic confidence values for the 8 a.m., 4 p.m., and 11 p.m. DST samples, as well as results of the pair-wise combinations of the three samples (separately and then combined) for inpatients.

Of the three samples, the one collected at 4 p.m. was the most sensitive in detecting DST nonsuppression. By using only the 4 p.m. sample, as done with the outpatients in this study, 46 (35%) of 131 inpatients showed DST nonsuppression. Thus, the single 4 p.m. sampling method "missed" detecting 23 cases (33.3%) of nonsuppression that were identified with the three-sample method. The 35% nonsuppression rate obtained when using the single 4 p.m. sample with inpatients contrasts with the 20% nonsuppression rate found among outpatients in the present study. That is, using the same procedure, inpatients as a group evidenced more frequent DST nonsuppression than their outpatient counterparts.

Nocturnal Hypersecretion of Cortisol

An 11 p.m. pre-dexamethasone serum sample was obtained for cortisol determination from 93 of 131 inpatients

studied. Based on a threshold value for nonsuppression of 4.0 μg/dL for any post-dexamethasone sample, 56 (60%) of 93 patients showed DST nonsuppression. Of the 74 endogenous patients in this sample, 47 (64%) had an elevated nocturnal cortisol level of > 4.0 μg/dL. However, 9 (47%) of 19 nonendogenous patients also had elevated cortisol levels. Thus, the sensitivity of this measure for endogenous depression was 64%, but its specificity was only 53%. The diagnostic confidence was 84% in this sample with a low incidence of nonendogenous depression. In a sample with 50% nonendogenous depressions, the diagnostic confidence would be 57%. These figures compared unfavorably with figures obtained from post-dexamethasone cortisol concentrations with respect to the level of specificity. Table 8 shows the results for the 11 p.m. pre-dexamethasone sample of other threshold values for nonsuppression. Even varying the threshold levels did not meaningfully improve the specificity of the 11 p.m. pre-dexamethasone cortisol level. This measure is, therefore, not as useful for diagnostic purposes as are post-dexamethasone cortisol values.

Table 8. Sensitivity, Specificity, and Diagnostic Confidence Values of Various 11 p.m. Pre-Dexamethasone Threshold Values From Bipolar (N = 15) and Unipolar (N = 78) Inpatients for Distinguishing RDC Endogenous and Nonendogenous Depressions*

	Nonsuppression Threshold			
Value	3.0 μg/dL	4.0 μg/dL	5.0 μg/dL	6.0 μg/dL
Sensitivity	77.0 (67.6)	63.5 (63.5)	54.1 (54.1)	48.7 (44.6)
Specificity	42.1 (77.8)	52.6 (83.3)	57.9 (83.3)	63.2 (100.0)
Diagnostic confidence	83.8 (92.6)	83.9 (94.0)	83.3 (93.0)	83.7 (100.0)

*Figures in parentheses are values using the highest post-dexamethasone cortisol finding for comparison. Bipolar patients were all bipolar I depressed phase patients, all of whom were classified as endogenous for this analysis.

Other Factors and the DST

As noted above, several factors in addition to diagnostic type may influence the DST. The relationship of several of these factors to the DST was examined in the present study, including age and sex, severity of depressive symptoms, recent weight loss, patient status (inpatient vs. outpatient) and psychotic features.

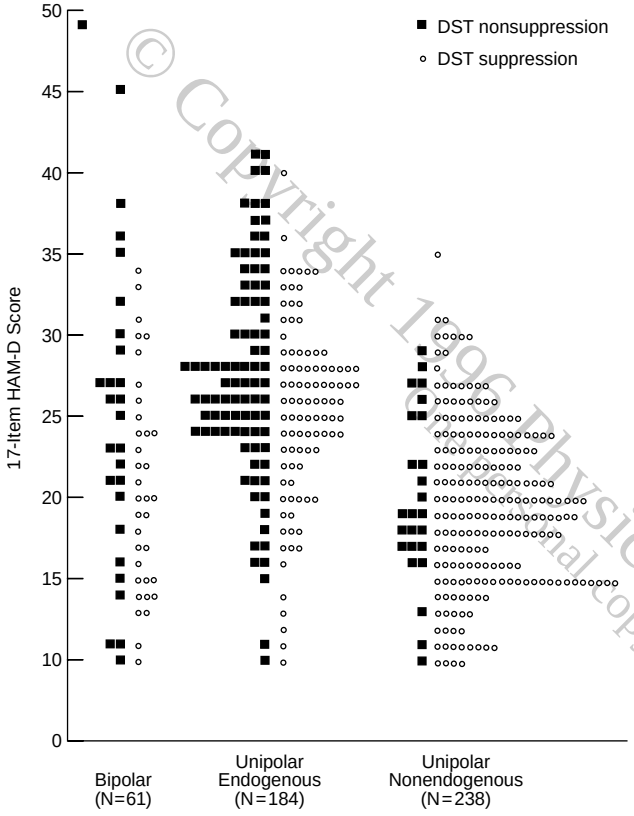
Age. To examine the relationship of age and DST, the total sample (N = 487) was divided by decades: < 20 years (N = 13), 20–29 years (N = 143), 30–39 years (N = 175), 40–49 years (N = 75), 50–59 years (N = 57), 60–69 years (N = 18), and > 69 years (N = 6). By using the highest post-dexamethasone cortisol value, the nonsuppression rates across ascending age groups were 70%, 47%, 34%, 48%, 61%, 58%, and 80%, respectively. The incidence of endogenous depression (unipolar endogenous and bipolar depressed phase) was 77% for < 20 years, 51% for 20–29 years, 51% for 30–39 years, 39% for 40–49 years, 54% for 50–59 years, 67% for 60–69 years, and 83% for > 69 years. Thus, the apparent increase in DST nonsuppression among the oldest and youngest decade groups is, in part, accounted for by a higher proportion of endogenous patients. Those under the age of 20 and over the age of 60 account for a very limited number of subjects in this sample, however.

Gender. The proportion of DST nonsuppression among males and females was compared. Thirty-three percent (60/181) of males and 26% (81/306) of females in the sample evidenced DST nonsuppression ($\chi^2 = 2.3$, df = 1, p = .13). The potential interaction between gender and endogenous depression on the DST was also examined. The percentage of females in the endogenous group was lower (57%) (including both unipolar endogenous and bipolar depressed phase patients) than the percentage of females in the nonendogenous group (68%) ($\chi^2 = 5.9$, df = 1, p < .02). This difference may be due to the gender ratio differences between unipolar and bipolar groups, since the bipolar depressed phase patients were defined a priori as endogenous. When we examined the unipolar endogenous patient group alone (N = 249), the DST nonsuppression rate was 48% for males and 46% for females ($\chi^2 = 0.2$, df = 1, p = .68). For nonendogenous patients, the DST nonsuppression rate was 12% for males and 10% for females ($\chi^2 = 0.3$, df = 1, p = .61). In conclusion, there was no effect of gender on DST nonsuppression in this sample when diagnostic subtype was controlled.

Inpatient vs. outpatient status. Nonsuppression rates differed for inpatients and outpatients in the present sample. Of 131 inpatients, 69 (53%) had DST nonsuppression. In contrast, only 72 (20%) of the 356 outpatients showed nonsuppression ($\chi^2 = 49.0$, df = 1, p < .001). In addition, a significant difference was found in the sensitivity of the DST for endogenous depression among inpatients (62%) and outpatients (36%) ($\chi^2 = 16.0$, df = 1, p < .001). This difference is due to the increased sensitivity of the DST with three post-dexamethasone samples, as was the protocol conducted on inpatients. Differences in sensitivity between inpatients and outpatients disappear when results are based on the 4 p.m. sample alone. The sensitivity of the DST for endogenous depression, using the 4 p.m. sample only, was 42% for inpatients and 36% for outpatients ($\chi^2 = 1.1$, df = 1, p = .30).

Severity. Patients with DST nonsuppression had a mean ± SD HAM-D score of 25.5 ± 7.4. In contrast, patients with DST suppression had a mean HAM-D score of 21.4 ± 5.8 (t = 6.4, df = 486, p < .001). These results are confounded by endogenous status, as the endogenous group was more severely ill than the nonendogenous group (Welch's t = 10.2, df = 446.3, p < .001). HAM-D scores for DST suppressors and nonsuppressors within unipolar endogenous, unipolar nonendogenous, and bipolar depressed phase groups are shown in Figure 1, which suggests that within these diagnostic subgroups,

Figure 1. Relationship Between Severity of Depressive Symptoms and DST Status Using the Highest Post-Dexamethasone Cortisol Sample and a > 4.0 μg/dL Cortisol Threshold for Declaring DST-NS*



*Four of the 65 bipolar patients had missing HAM-D scores.

symptom severity does not relate to DST status until the HAM-D score exceeds 34. Above this level, the percentage of patients with DST nonsuppression is greatly increased, to 86%. The very severely depressed patients were almost exclusively inpatients (21 of 22), for whom the more sensitive three-sample DST methodology was used. When the 4 p.m. sample alone was considered for this severely depressed group, the DST nonsuppression rate was still 77%. Of these 22 patients, 41% were psychotic. Thus, it appears that DST nonsuppression was related to greater severity of depression for the total sample because the rate of nonsuppression was higher among inpatients with severe or psychotic depression.

Weight loss. The weight loss item of the HAM-D was used to evaluate the relationship between recent weight loss (within the past 7 days) and DST status. Weight loss over the prior week was scored as 0 = no loss, 1 = probable weight loss, and 2 = definite weight loss. The percentage of patients with DST nonsuppression in each of the three weight-loss categories is shown in Table 9. Because weight loss is a symptom used to diagnose endogenous depression, results for endogenous and nonendogenous groups were examined separately. DST nonsuppression was significantly related to weight loss in the endogenous group, but not in the nonendogenous group. The positive result for the endogenous group is confounded by the inclusion of weight loss as a diagnostic symptom for endogenous depression, however. A higher score on the weight-loss item is associated with more weight loss. The mean ± SD symptom severity score for each of the three weight loss categories for endogenous patients was no weight loss (21.1 ± 5.7), probable weight loss (24.7 ± 4.5), and definite weight loss (29.0 ± 5.9). Diagnostic confidence for the endogenous versus nonendogenous distinction was higher in the definite weight loss compared with the no weight loss groups (94.3% and 66.7%, respectively).

Psychosis. Psychotic status was assessed in all but 3 (N = 484) patients. A higher percentage of psychotic (48%) than nonpsychotic (27%) patients ($\chi^2 = 6.2$, df = 1, p = .013) were DST nonsuppressors when using the highest post-dexamethasone cortisol level. However, percentages of DST nonsuppressors in psychotic (35%) and nonpsychotic (24%) groups were not significantly different when the 4 p.m. sample alone was used to declare DST status ($\chi^2 = 2.0$, df = 1, p = .16). The larger number of endogenous patients in the psychotic group confounded these results. No significant differences in nonsuppression rates were found when psychotic and nonpsychotic endogenous patients were compared. Among endogenous patients, 38% of the psychotic group (N = 37) showed nonsuppression by the 4 p.m. sample, compared with 39% of the nonpsychotic group (N = 210). Similarly, within the group of nonendogenous patients, those with psychosis (N = 3) had a nonsuppression rate at 4 p.m. of 0%, equivalent to those without psychosis (10%; N = 235).

Combined predictive analyses. The relative contributions to DST status of the factors discussed above were examined with multivariate analyses. For inpatients, all three post-dexamethasone cortisol levels were considered in declaring DST status. For this analysis, all bipolar patients were classified as endogenous. The variables included in stepwise discriminant and multiple regression models for predicting DST results included severity of depression (HAM-D score), weight loss, psychosis, endogenous/nonendogenous diagnosis, patient status (inpatient or outpatient), and polarity (unipolar vs. bipolar). Patient age and gender were not included because the number of subjects at the extremes of the age spectrum was small, and gender was unrelated to DST results.

Stepwise discriminant analysis evaluated the relationship of the six predictor variables to DST status (suppressor vs. nonsuppressor) using a serum cortisol threshold value of 4.0 μg/dL. Endogenous/nonendogenous subtype and inpatient/outpatient status were the only significant discriminating variables. The discriminant model correctly classified 61.8% of DST suppressors and 82.3% of DST nonsuppressors, using a jackknifed classification.

Table 9. Percentage of DST-NS for Each Weight Item Response in Endogenous and Nonendogenous Groups*

	HAM-D Weight Item Response						
	No Weight Loss (0)		Probable Weight Loss (1)		Definite Weight Loss (2)		
Group	%	N	%	N	%	N	p
Endogenous (N = 245)[a]	38.5	40/104	35.0	7/20	55.4	67/121	.02
Nonendogenous (N = 238)	12.5	20/160	4.5	1/22	7.1	4/56	NS
Total sample (N = 483)	22.7	60/264	19.0	8/42	40.1	71/177	< .001

*The highest post-dexamethasone cortisol level was used to determine suppression status for inpatients.
[a]Endogenous here includes 184 unipolar and 65 bipolar depressed phase patients. Four of the latter had missing items on the HAM-D.

These results suggest that of the variables analyzed, the RDC endogenous/nonendogenous classification and patient status (or the associated sampling method) contributed significantly and independently to the discrimination of DST suppressors and nonsuppressors. The patient status variable, as noted above, affects the sensitivity of the DST based on the one- versus three-sampling method. To eliminate this bias, the above analysis was repeated, using only the 4 p.m. post-dexamethasone sample to define DST status for inpatients. This analysis found that only the endogenous/nonendogenous subtype discriminated DST suppressors from nonsuppressors. A jackknifed classification correctly classified 58.4% of suppressors and 80.7% of nonsuppressors.

A stepwise multiple regression analyzed the relationship between the six predictor variables and the log-transformed highest post-dexamethasone serum cortisol level. Results were similar to the discriminant analysis, in that the RDC endogenous/nonendogenous dichotomy entered the equation first ($F = 71.7$, $df = 1,478$; $p < .0001$), followed by HAM-D score ($F = 24.7$, $df = 2,477$; $p = .0001$) and, finally, by inpatient/outpatient status ($F = 7.4$, $df = 3,476$; $p = .007$). The R^2 value associated with this three-variable model was .19. This multiple regression was repeated, using only the 4 p.m. post-dexamethasone cortisol level to declare DST status for inpatients. In this analysis, the same variables entered the model (endogenous/nonendogenous, HAM-D score, and inpatient/outpatient status), and the R^2 was .11.

DISCUSSION

The primary purpose of this study was to evaluate the DST in relation to several distinct, but overlapping diagnostic classifications for depression. Secondary aims included an evaluation of potential nondiagnostic factors in relation to DST status and an appraisal of DST methodology (one sample vs. three samples post-dexamethasone and an evaluation of the performance of the 11 p.m. pre-dexamethasone cortisol).

The present results reveal the following: (1) the RDC endogenous/nonendogenous dichotomy was clearly validated by DST response; (2) the DSM-III melancholic criteria are too restrictive when using the DST as the validating criterion; (3) there is an increased incidence of DST nonsuppression in RDC primary versus secondary depressions, which is accounted for by a higher incidence of RDC endogenous depressions in the primary group; (4) Winokur and colleagues' family history subtypes tended to be differentiated by DST response, and the familial pure depressive disease group was more likely to evidence DST nonsuppression, which was also accounted for by a greater incidence of RDC endogenous patients in the familial pure depressive disease group; (5) the three-sample post-dexamethasone methodology increases the probability of detecting DST nonsuppression by 36% over the single-sample method; (6) gender did not affect DST results; (7) overall depressive severity significantly contributed to DST status, but this result was confounded by a more significant effect of endogenous status; (8) inpatients were no more likely to evidence DST nonsuppression when evaluated in the same DST protocol as outpatients; (9) recent weight loss within the endogenous, but not the nonendogenous, group was related to the incidence of DST nonsuppression; (10) the 8 a.m. cortisol sample was the least sensitive of the three samples; and (11) pre-dexamethasone (11 p.m.) cortisol levels were of little value in differentiating RDC endogenous/nonendogenous subtypes. Our combined predictive analyses revealed the major predictor of DST status was the RDC endogenous/nonendogenous dichotomy.

Tables 10 and 11 summarize the studies comparing diagnostic subgroups with major depressed samples of > 10 subjects/subgroup or > 40 major depressed subjects total, in which the 1.0-, 1.5-, or 2.0-mg DST was used. Studies were divided into those that examined primarily or exclusively inpatients (Table 10) and those that involved primarily or exclusively outpatients (Table 11). Studies are further divided into those examining the diagnostic subtypes of RDC endogenous/nonendogenous, International Classification of Diseases (ICD-8 and ICD-9)[131,132] endogenous/neurotic, DSM-III melancholic/nonmelancholic, Newcastle Scale[133,134] endogenous/neurotic, Winokur and colleagues'[22] family history subtypes, and RDC primary/secondary.

Descriptive Classifications: RDC Endogenous Versus Nonendogenous Depression

This subdivision was the most clearly validated for both inpatients and outpatients in the present study. This

Table 10. Summary of DST Results and Depressive Subtypes in Inpatients*

System/Subtype	N	DST-NS	Studies
RDC			
Endogenous	480	46%	Brown and Shuey,[36a] Carroll et al,[6a] Rush et al,[124a] Davidson et al,[137a] Stokes et al,[16]
Nonendogenous	152	20%	Zimmerman et al,[29] Kumar et al,[109a] Haskett et al[90a]
RDC			
Primary	412	54%	Brown and Shuey,[36a] Schlesser et al,[26a] Charles et al,[150a] Papakostas et al,[151a] Asnis et al,[33]
Secondary	198	12%	Berger et al,[152] Coryell et al,[28a] Mendlewicz et al[32,153a]
DSM-III			
Melancholic	310	49%	Coryell et al,[28] Arana et al,[52] Johnson et al,[154] Stokes et al,[16] Zimmerman et al,[29a]
Nonmelancholic	372	28%	Cook et al,[141a] Rubin et al,[155] Brown et al,[142a] Maes et al[81]
ICD			
Endogenous	184	39%	Berger et al,[152] Kasper and Beckmann,[31a] Berger et al,[156a] Dam et al[11]
Neurotic	138	31%	
Newcastle Scale			
Endogenous	325	56%	McIntyre et al,[157a] Coppen et al,[10a] Holden,[158a] Kasper and Beckmann,[31a] Ames et al,[143]
Neurotic	294	22%	Davidson et al,[137a] Zimmerman et al[29a]
Winokur and colleagues' family history[b]			
FPDD	149	62%	Schlesser et al,[26a] Coryell et al,[28] Targum et al,[30] Fleming et al,[136] Zimmerman et al[29]
DSD	122	21%	
SDD	227	38%	

*Abbreviation: ICD = International Classification of Diseases.
[a]Studies with positive results by adjusted chi-square.
[b]Based on adjusted chi-square comparison between the familial pure depressive disease and sporadic depressive disease groups.

Table 11. Summary of DST Results and Depressive Subtypes in Outpatients

System/Subtype	N	DST-NS	Studies
RDC			
Endogenous	354	39%	Carroll et al,[23a]
Nonendogenous	338	13%	Giles and Rush,[86a] Rush et al,[12a] Peselow et al,[13,146a] Rabkin et al,[139] Calloway et al,[138a] Giles et al,[38a]
RDC			
Primary	224	25%	Carroll et al,[23]
Secondary	66	28%	Rush et al,[12] Giles et al[38,135]
DSM-III			
Melancholic	86	38%	Gitlin et al[145]
Nonmelancholic	23	35%	
ICD			
Endogenous	59	24%	Holsboer et al[15]
Neurotic	34	15%	
Newcastle Scale			
Endogenous	73	38%	Holsboer et al,[15]
Neurotic	92	28%	Calloway et al[138]
Winokur and colleagues' family history[b]			
FPDD	92	31%	Rush et al,[12a]
DSD	69	22%	Amsterdam et al,[34]
SDD	94	25%	Calloway et al,[138] Giles et al[38]

[a]Studies with positive results by adjusted chi-square.
[b]Based on adjusted chi-square comparison between the familial pure depressive disease and sporadic depressive disease groups.

finding corroborates six of eight prior inpatient DST studies and six of eight prior outpatient studies. In the Stokes et al.[16] inpatient study (which was reported with a negative finding), several key design issues deserve comment. Their study was part of an ongoing investigation—The Collaborative NIMH Psychobiology Study—that was aimed at determining whether cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA) and/or urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) excretion predicted differential response to amitriptyline or imipramine. Therefore, the sample chosen consisted of inpatients who had agreed to a demanding protocol. It did not contain consecutive admissions; thus, it cannot be used to establish laboratory norms. Secondly, the Stokes et al. study reported an unusually high rate of DST nonsuppression in normals, even when using the 8 a.m. postdexamethasone cortisol value, which suggests a higher cortisol threshold was indicated for declaring DST nonsuppression. Thirdly, and most importantly, most patients received *only* the 8 a.m. post-dexamethasone cortisol determination, which by the current report and those by others, impairs the sensitivity of the test. Finally, the number of nonendogenous patients was small. The negative findings of Zimmerman et al.[29] may have resulted from the inclusion of some bipolar depressed phase patients in the nonendogenous group, which itself was small in number.

Both outpatient studies that failed to validate the RDC endogenous/nonendogenous dichotomy with the DST found higher (albeit not statistically significant) DST nonsuppression rates in the endogenous group. Both used only clinical rather than structured interviews, which may have introduced more variability in the diagnoses.

In the present study, the RDC primary/secondary distinction was validated on the inpatient sample only. Primary depressed inpatients evidenced a 36% rate of DST nonsuppression, compared with a 7% rate in secondary depressed inpatients. The DST did not discriminate primary and secondary depressed outpatients, which concurs with prior results. Of the nine inpatient studies examined,

seven reported primary/secondary differences in DST nonsuppression rates (see Table 10). In contrast, but consistent with the present results, none of the four outpatient studies found DST validation for the primary/secondary distinction. It should be noted, however, that two of these studies were conducted by our own group and employed samples that overlapped with the present report. Giles et al.[38] studied a new series of patients (N = 103) in a replication and extension of the Rush et al.[12] findings of increased incidence of biological dysregulation in endogenous depression. Giles et al.,[135] using St. Louis criteria, studied patients who met RDC for secondary depression (N = 45) and found that neither DST response nor reduced rapid eye movement (REM) latency differentiated RDC secondary subtypes.

The family history–based classification of Winokur et al.[22] was also not generally validated by present DST results. Although almost one half (47%) of inpatients with a positive family history of depression evidenced nonsuppression, outpatients with familial pure depressive disease showed no correspondingly high DST nonsuppression rates. More importantly, nonsuppression rates for patients with a negative family history (sporadic depressive disease) were not significantly different from the rates shown by those with a positive family history (familial pure depressive disease), for either inpatients or outpatients. In general, present results of DST nonsuppression are similar to prior studies for both the depression spectrum disease and sporadic depressive disease groups, but lower for the familial pure depressive disease group than the 70% reported by others.[26,28,30] Two other studies in the literature reported nonsuppression rates in the familial pure depressive disease group (48%–49%) that are similar to the present findings.[29,136]

Our findings are in agreement with several studies from other sites that have evaluated the endogenous/nonendogenous dichotomy in relation to the DST,* and to prior studies by our own group.[12,38,86,124] However, four negative studies[13,16,29,139] have also been reported in which the DST did not reliably differentiate endogenous from nonendogenous depression.

These studies differ widely in laboratory methods, clinical diagnostic systems and methods in applying particular criteria, timing of the DST after hospitalization, the method of assaying the sample, and attention to longitudinal quality control in both clinical diagnosis and laboratory measurement. Such differences are likely to lead to different results.[19,20,140]

In fact, of the studies reviewed in Tables 9 and 10, none used the rigorous methods employed in this study including (1) structured interviews, (2) both inpatients and outpatients, (3) diagnoses rendered *only* by experienced clinicians utilizing RDC and DSM-III, (4) standard post-dexamethasone cortisol sampling time points per Carroll et al.[6] (8 a.m., 4 p.m., and 11 p.m. for inpatients and 4 p.m. only for outpatients), (5) consecutive admissions *not* related to another ongoing protocol, and (6) longitudinal quality controls in both laboratory determinations *and* clinical diagnoses.

Aguilar et al.[77] reported data that largely support Carroll et al.[6] and the present results. Unfortunately, their argument that giving 100 mg of secobarbital reduces false positives is rather unconvincing except by reference to other studies. Further, they used no structured interview, reported no normal control values with this unique methodology, and failed to differentiate endogenous from nonendogenous by any agreed-upon method. In addition, Mendlewicz et al.,[32] whose results also favor the Carroll et al.[6] original report, failed to use a structured interview, did not report normal control values, and did not differentiate endogenous from nonendogenous depressives by a clinically replicable method.

Many studies have relied upon a single post-dexamethasone cortisol level.† Present results suggest that this methodology renders DST results less sensitive. Extein and colleagues[144] have confirmed a significant increase in sensitivity of the DST with a six-point sampling method as compared with a two-point sampling method. A two-point sampling method, with samples taken at 4 p.m. and 12 midnight, yielded a 31% nonsuppression rate among inpatients with major depression. In contrast, the nonsuppression rate with a six-point method in this group was 44%.

Furthermore, most studies have sample sizes of 20 to 100 subjects. Few exceed 100 depressed subjects (whether inpatients or outpatients).‡

Finally, structured interviews, as opposed to specified criteria, have rarely been used in either those studies that do or those that do not validate the DST. Of those studies that used a structured interview, only Stokes et al.[16] used both a normal control group and a structured interview. However, this study was not a direct attempt at replication and has several of the limitations noted above. Since subjects were not consecutive inpatients, the population can not be said to be representative of the average inpatient depression.

A true "diagnostic laboratory test" in medicine is extremely rare. Most laboratory tests are adjuncts to diagnosis; they contribute to the complex pattern associated with particular syndromes that clinicians have learned to recognize. Most medical diagnoses are based on signs, symptoms, and history of illness, while laboratory test information provides additional clues to the diagnosis or

*References 2, 3, 23, 24, 36, 109, 137, 138.

†References 10, 11, 13, 15, 16, 26, 31, 32, 52, 137, 139, 141–143.

‡References 6, 10, 16, 26, 37, 38, 86, 145, 146.

differential diagnosis. Laboratory information may assist the clinician in differentially weighing the observed signs and symptoms or in rank ordering differential diagnoses.

Rarely will a laboratory test be so specifically related to the etiology of a clinical entity that it is truly diagnostic (e.g., hemoglobin SS for sickle cell anemia). The degree of diagnostic specificity associated with a particular laboratory test depends on the proximity of the laboratory test abnormality to the pathophysiologic sequence involved in the disorder. The DST is clearly not specific to depression, since nonsuppression occurs in certain general medical conditions (e.g., congestive heart failure, liver disease, uncontrolled diabetes, acute infections), with certain medications (e.g., phenytoin, barbiturates, carbamazepine), as well as in some nonaffective psychiatric disorders.[2,3] Conversely, within the group of major mood disorders (major depressive or unipolar disorder and bipolar disorder), the present results clearly indicate that the RDC endogenous/nonendogenous classification of major depression is validated by the DST. This finding is not the simple consequence of severity. Other clinical diagnostic subgroups were not validated. Severity, and by correlation, psychosis, also contribute to DST status. Recent weight loss relates to the DST, but does not contribute independent of endogenicity and severity. Finally, the three-sample method increased the sensitivity of the DST, compared with the single-sample (4 p.m.) method. The post-dexamethasone 4 p.m. and 11 p.m. samples combined were nearly as sensitive as all three samples. This difference accounted for observed differences in DST nonsuppression rates among inpatients and outpatients.

These findings have relevance for research into psychopathology in that they can assist in reducing the well-established heterogeneity of major depressive disorder (for a review, see Rush et al.[147]).

Indirect corroboration of these findings comes from studies relating the sleep electroencephalogram (EEG) to this differential subdivision and studies relating the DST to the sleep EEG. Virtually all of the earlier studies have found a relationship between selected sleep EEG measures and the endogenous/nonendogenous subgrouping (see Rush and Weissenburger[148]). For the more recent studies, all reports to date indicate that roughly 50% of patients with a reduced REM latency also evidence DST nonsuppression, which itself is unlikely to occur without a reduced REM latency. Thus, taken together, these physiologic and hypothalamic-pituitary-adrenal (HPA) axis evaluations are congruent in their evaluation (alone or together) of the endogenous/nonendogenous dichotomy.

Implications for clinical practice are less clear and depend highly on the potential clinical value of differentiating endogenous from nonendogenous depressions. Many, but not all, treatment studies are consistent with the notion that nonendogenous depression may preferentially respond to pill-placebo or psychotherapy alone, while the endogenous form is associated with a better response to tricyclic antidepressants or electroconvulsive therapy (ECT) (for a review, see Depression Guideline Panel[149]). Thus, the DST may be useful in clinical situations where this therapeutic choice is confronted and when the clinical descriptive differentiation between these two subgroups is uncertain.

Drug names: amitriptyline (Elavil and others), carbamazepine (Tegretol and others), imipramine (Tofranil and others), phenytoin (Dilantin and others), secobarbital (Seconal).

REFERENCES

1. Sachar EJ, Hellman L, Fukushima DK. Cortisol production in depressive illness: a clinical and biochemical clarification. Arch Gen Psychiatry 1970;23:289–298
2. Carroll BJ, Curtis GC, Mendels J. Neuroendocrine regulation in depression, I: limbic system-adrenocortical dysfunction. Arch Gen Psychiatry 1976;33:1039–1044
3. Carroll BJ, Curtis GC, Mendels J. Neuroendocrine regulation in depression, II: discrimination of depressed from nondepressed patients. Arch Gen Psychiatry 1976;33:1051–1057
4. Ettigi P, Brown GM. Psychoneuroendocrinology of affective disorders: an overview. Am J Psychiatry 1977;134:493–501
5. Rubin RT. Psychoendocrinology of major depression. Eur Arch Psychiatry Neurol Sci 1989;238:259–267
6. 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
7. Carroll BJ. The dexamethasone suppression test for melancholia. Br J Psychiatry 1982;140:292–304
8. American Psychiatric Association Task Force on Laboratory Tests in Psychiatry. The dexamethasone suppression test: an overview of its current status in psychiatry. Am J Psychiatry 1987;144:1253–1262
9. Nuller JL, Ostroumova MN. Resistance to inhibiting effect of dexamethasone in patients with endogenous depression. Acta Psychiatr Scand 1980; 61:169–177
10. Coppen A, Abou-Saleh M, Milln P, et al. Dexamethasone suppression test in depression and other psychiatric illness. Br J Psychiatry 1983;142: 498–504
11. Dam H, Mellerup ET, Rafaelson OJ. The dexamethasone suppression test in depression. J Affect Disord 1985;8:95–103
12. Rush AJ, Giles DE, Roffwarg HP, et al. Sleep EEG and dexamethasone suppression test findings in outpatients with unipolar major depressive disorders. Biol Psychiatry 1982;17:327–341
13. Peselow ED, Goldring N, Fieve RR, et al. The dexamethasone suppression test in depressed outpatients and normal control subjects. Am J Psychiatry 1983;140:245–247
14. Shulman R, Diewold P. A two-dose dexamethasone suppression test in patients with psychiatric illness. Can Psychiatr Assoc J 1977;22:417–422
15. Holsboer F, Bender W, Benkert O, et al. Diagnostic value of dexamethasone suppression test in depression [letter]. Lancet 1980;2:706
16. 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
17. Kocsis JH, Brockner N, Butler T, et al. Dexamethasone suppression in major depression. Biol Psychiatry 1984;19:1255–1259
18. Greden JF. Biological markers of melancholia and reclassification of depressive disorders. Encephale 1982;8:193–202
19. Kupfer DJ, Rush AJ. Recommendations for scientific reports on depression [editorial]. Am J Psychiatry 1983;40:1327–1328
20. Kraemer HC. The methodological and statistical evaluation of medical tests: the dexamethasone suppression test in psychiatry. Psychoneuroendocrinology 1987;12:411–427
21. Mossman D, Somoza E. Maximizing diagnostic information from the dexamethasone suppression test. Arch Gen Psychiatry 1989;46:653–660
22. Winokur G, Behar D, Van Valkenberg C, et al. Is familial definition of depression both feasible and valid? J Nerv Ment Dis 1978;166:764–768
23. Carroll BJ, Greden JF, Feinberg M, et al. Neuroendocrine dysfunction in

genetic subtypes of primary unipolar depression. Psychiatry Res 1980; 2:251–258
24. Carroll BJ, Greden JF, Feinberg M, et al. Neuroendocrine evaluation of depression in borderline patients. Psychiatr Clin North Am 1981;4: 89–99
25. Schlesser MA, Winokur G, Sherman BM. Genetic subtypes of unipolar primary depressive illness distinguished by hypothalamic-pituitary-adrenal axis activity. Lancet 1979;1:739–741
26. Schlesser MA, Winokur G, Sherman BM. Hypothalamic-pituitary-adrenal axis activity in depressive illness: its relationship to classification. Arch Gen Psychiatry 1980;37:737–743
27. Agren H, Wilde L. Patterns of depression reflected in pituitary-thyroid and pituitary-adrenal endocrine changes. Psychoneuroendocrinology 1982;7: 309–327
28. Coryell W, Gaffney G, Burkhardt PE. DSM-III melancholia and the primary-secondary distinction: a comparison of concurrent validity by means of the dexamethasone suppression test. Am J Psychiatry 1982;139: 120–122
29. Zimmerman M, Coryell WH, Pfohl B, et al. Four definitions of endogenous depression and the dexamethasone suppression test. J Affect Disord 1985;8:37–45
30. Targum SD, Byrnes SM, Sullivan AC. Subtypes of unipolar depression distinguished by the dexamethasone suppression test. J Affect Disord 1982;4:21–27
31. Kasper S, Beckmann H. Dexamethasone suppression test in a pluri-diagnostic approach: its relationship to psychopathological and clinical variables. Acta Psychiatr Scand 1983;68:31–37
32. Mendlewicz J, Charles GA, Franckson JM. The dexamethasone suppression test in affective disorder relationship to clinical and genetic subgroups. Br J Psychiatry 1982;141:464–470
33. Asnis GM, Halbreich U, Nathan RS, et al. The dexamethasone suppression test in depressive illness: clinical correlates. Psychoneuroendocrinology 1982;7:295–301
34. Amsterdam JD, Winokur A, Caroff SN, et al. The dexamethasone suppression test in outpatients with primary affective disorders and healthy control subjects. Am J Psychiatry 1982;199:287–291
35. Rudorfer MV, Hwu HG, Clayton PJ. Dexamethasone suppression test in primary depression: significance of family history and psychosis. Biol Psychiatry 1982;17:41–48
36. Brown WA, Shuey I. Response to dexamethasone and subtype of depression. Arch Gen Psychiatry 1980;37:747–751
37. Winokur G, Black DW, Nasrallah A. DST nonsuppressor status: relationship to specific aspects of the depressive syndrome. Biol Psychiatry 1987;22:360–368
38. Giles DE, Schlesser MA, Rush AJ, et al. Polysomnographic findings and dexamethasone nonsuppression in unipolar depression: a replication and extension. Biol Psychiatry 1987;22:872–882
39. Arana GW, Baldessarini RJ, Ornsteen M. The dexamethasone suppression test for diagnosis and prognosis in psychiatry. Arch Gen Psychiatry 1985; 42:1193–1204
40. Carnes M, Smith JC, Kalin NH, et al. The dexamethasone suppression test in demented outpatients with and without depression. Psychiatry Res 1983;9:337–344
41. Rothschild AJ, Schatzberg AF, Rosenbaum AH, et al. The dexamethasone suppression test as a discriminator among subtypes of psychotic patients. Br J Psychiatry 1982;141:471–474
42. Schatzberg AF, Rothschild AJ, Stahl JB, et al. The dexamethasone suppression test: identification of subtypes of depression. Am J Psychiatry 1983;140:88–91
43. Raskind M, Peskind E, Rivard MF, et al. Dexamethasone suppression test and cortisol circadian rhythm in primary degenerative dementia. Am J Psychiatry 1982;139:1468–1471
44. Spar JE, Gerner R. Does the dexamethasone suppression test distinguish dementia from depression? Am J Psychiatry 1982;139:238–240
45. Balidin J, Gottfries CG, Karlsson I, et al. Dexamethasone suppression test and serum prolactin in dementia disorders. Br J Psychiatry 1983;143:277–281
46. Gerner RH, Gwirtsmann HE. Abnormalities of dexamethasone suppression test and urinary MHPG in anorexia nervosa. Am J Psychiatry 1981; 138:650–653
47. Doerr P, Fichter M, Pirke KM, et al. Relationship between weight gain and hypothalamic pituitary adrenal function in patients with anorexia nervosa. Journal of Steroid Biochemistry 1980;13:529–537
48. Oxenkrug GF. Dexamethasone test in alcoholics [letter]. Lancet 1978;2:795
49. Swartz CM, Dunner FJ. Dexamethasone suppression testing of alcoholics. Arch Gen Psychiatry 1982;39:1309–1312
50. Castro P, LeMaire M, Toscano-Aguilar M. Abnormal DST results in patients with chronic schizophrenia [letter]. Am J Psychiatry 1983;140:1261
51. Dewan MJ, Pandurangi AK, Boucher ML, et al. Abnormal dexamethasone suppression test results in chronic schizophrenic patients. Am J Psychiatry 1982;139:1501–1503
52. Arana GW, Barreira PJ, Cohen BM, et al. The dexamethasone suppression test in psychotic disorders. Am J Psychiatry 1983;140:1521–1523
53. Coccaro EF, Prudic J, Rothpearl A, et al. Clinical utilization of the dexamethasone suppression test. J Clin Psychiatry 1984;45:382–384
54. Insel TR, Kalin NH, Guttmacher LB, et al. The dexamethasone suppression test in patients with primary obsessive-compulsive disorder. Psychiatry Res 1982;6:153–160
55. Steiner M, Links PS, Korzekwa M. Biological markers in borderline personality disorder. Can J Psychiatry 1988;33:350–354
56. Greden JF, Kronfol Z, Gardwen R, et al. Neuroendocrine evaluation of schizoaffectives with the dexamethasone suppression test. Presented at the Third World Congress of Biological Psychiatry; July 1981; Stockholm, Sweden
57. Finklestein S, Benowitz LI, Baldessarini RJ, et al. Mood, vegetative disturbance, and dexamethasone suppression test after stroke. Ann Neurol 1982; 12:463–468
58. Lipsey JR, Robinson RG, Pearlson GC, et al. The dexamethasone suppression test and mood following stroke. Am J Psychiatry 1985;142: 318–323
59. Harney JH, Fulton C, Ross ED, et al. Dexamethasone suppression test and onset of poststroke depression in patients with ischemic infarctions. J Clin Psychiatry 1993;54:343–348
60. Carroll BJ. Biologic markers and treatment response. J Clin Psychiatry 1983;44(8, sec 2):30–40
61. Carroll BJ. Dexamethasone suppression test: a review of contemporary confusion. J Clin Psychiatry 1985;46(2, sec 2):13–24
62. Korzekwa M, Steiner M, Links P, et al. The dexamethasone suppression test in borderlines: is it useful? Can J Psychiatry 1991;36:26–28
63. Olivera AA, Fero D, Scibilia J. Dexamethasone suppression test in psychiatric patients with psychoactive substance dependence. Am J Drug Alcohol Abuse 1991;17:295–305
64. Khan A, Ciraulo DA, Nelson WH, et al. Dexamethasone suppression test in recently detoxified alcoholics: clinical implications. J Clin Psychopharmacol 1984;4:94–97
65. Sheehan DV, Claycomb JB, Surman OS, et al. Panic attacks and the dexamethasone suppression test. Am J Psychiatry 1983;140:1063–1064
66. Curtis GC, Cameron OG, Nesse RM. The dexamethasone suppression test in panic disorder and agoraphobia. Am J Psychiatry 1982;139:1043–1045
67. Gold MS, Pottash ALC, Extein I, et al. Diagnosis of depression in the 1980's. JAMA 1981;245:1562–1564
68. Charles GA, Lefevre A, Mirel J, et al. Suppression of cortisol following dexamethasone in demented patients. Psychiatry Res 1986;17:173–182
69. Davis KL, Davis BM, Mathe AA, et al. Age and the dexamethasone suppression test. Am J Psychiatry 1984;141:872–874
70. Nelson WH, Khan A, Orr WW Jr, et al. The dexamethasone suppression test: interaction of diagnosis, sex and age in psychiatric inpatients. Biol Psychiatry 1984;9:1293–1304
71. Lewis DA, Pfohl B, Schlechte J, et al. Influence of age on the cortisol response to dexamethasone. Psychiatry Res 1984;13:213–220
72. Halbreich U, Asnis GM, Zumoff B, et al. Effect of age and sex on cortisol secretion in depressives and normals. Psychiatry Res 1984;13:221–229
73. Baumgartner A, Haack D, Vecsei P. Serial dexamethasone suppression tests in psychiatric illness, part III: the influence of intervening variables. Psychiatry Res 1986;18:45–64
74. Whiteford HA, Peabody CA, Thiemann S, et al. The effect of age on baseline and post-dexamethasone cortisol levels in depressive disorder. Biol Psychiatry 1987;22:1029–1032
75. Weiner MF. Age and cortisol suppression by dexamethasone in normal subjects. J Psychiatr Res 1989;23:163–168
76. Tourigny-Rivard MF, Raskind M, Rivard D. The dexamethasone suppression test in an elderly population. Biol Psychiatry 1981;16:1177–1184
77. Aguilar MT, Lemaire M, Castro P, et al. A study of the diagnostic value of the dexamethasone suppression test in endogenous depression. J Affect Disord 1984;6:33–42
78. Greden JF, Flegel P, Haskett R, et al. Age effects in serial hypothalamic-pituitary-adrenal monitoring. Psychoneuroendocrinology 1986;11:195–204

79. Ferrier IN, Pascual J, Charlton BG, et al. Cortisol, ACTH, and dexamethasone concentrations in a psychogeriatric population. Biol Psychiatry 1988;23:252–260
80. Schweitzer I, Tucknell VM, Maguire KP, et al. Plasma cortisol and 11-deoxycortisol activity in depressed patients and normal volunteers. Psychoneuroendocrinology 1991;16:375–382
81. Maes M, Vandewoude M, Schotte C, et al. Results of the 8 a.m. dexamethasone suppression test constitute a suitable tool for confirming the diagnosis of melancholia. Neuropsychobiology 1989;22:26–32
82. Maes M, Schotte C, D'Hondt P, et al. Biological heterogeneity of melancholia: results of pattern recognition methods. J Psychiatr Res 1991;25: 95–108
83. von Bardeleben U, Holsboer F. Effect of age on the cortisol response to human corticotropin-releasing hormone in depressed patients pretreated with dexamethasone. Biol Psychiatry 1991;29:1042–1050
84. Coccaro EF, Prudic J, Rothpearl A, et al. Effect of hospital admission on DST results. Am J Psychiatry 1984;141:982–985
85. Mellsop GW, Hutton JD, Delahunt JW. Dexamethasone suppression test as a simple measure of stress? BMJ 1985;290:1804–1806
86. Giles DE, Rush AJ. Relationship of dysfunctional attitudes and dexamethasone response in endogenous and nonendogenous depression. Biol Psychiatry 1982;17:1303–1314
87. Zimmerman M, Coryell W, Pfohl B. The validity of the dexamethasone suppression test as a marker for endogenous depression. Arch Gen Psychiatry 1986;43:347–355
88. Hwu HG, Lin HN. Serial dexamethasone suppression test in psychiatric inpatients. Biol Psychiatry 1990;27:609–616
89. Blouin J, Spindler E, Perez E, et al. The role of stress in interpreting the dexamethasone suppression test. Can J Psychiatry 1992;37:724–727
90. Haskett RF, Zis AP, Albala AA, et al. Comparison of early and delayed inpatient dexamethasone suppression tests. Psychiatry Res 1989;27: 161–171
91. Berger M, Pirke KM, Doerr P, et al. Influence of weight loss on the dexamethasone suppression test [letter]. Arch Gen Psychiatry 1983;40: 585–586
92. Edelstein CK, Roy-Byrne P, Fawzy FI, et al. Effects of weight loss on the dexamethasone suppression test. Am J Psychiatry 1983;140:338–341
93. Kline MD, Beeber AR. Weight loss and the dexamethasone suppression test. Arch Gen Psychiatry 1983;40:1034–1035
94. Targum SD. Reported weight change and the dexamethasone suppression test. Psychiatry Res 1983;9:173–174
95. Maes M, Maes L, Suy E. Symptom profiles of biological markers in depression: a multivariate study. Psychoneuroendocrinology 1990;15: 29–37
96. Feinberg M, Carroll BJ. Biological "markers" for endogenous depression: effect of age, severity of illness, weight loss, and polarity. Arch Gen Psychiatry 1984;41:1080–1085
97. Zimmerman M, Pfohl B, Coryell WH. Appetite and weight change and the dexamethasone suppression test. Biol Psychiatry 1984;19: 923–928
98. Gwirtsman HE, Roy-Byrne P, Gitlin MJ, et al. Reported weight loss and dexamethasone nonsuppression in depressed patients: a negative study. J Affect Disord 1985;9:193–196
99. Keitner GI, Brown WA, Qualls B, et al. Results of the dexamethasone suppression test in psychiatric patients with and without weight loss. Am J Psychiatry 1985;142:246–248
100. Krishan KRR, France RD, Snipes MT, et al. Weight change and the dexamethasone suppression test. Biol Psychiatry 1985;20:1015–1018
101. Pfohl B, Coryell W, Stangl D, et al. Body weight and reported versus measured weight loss as confounders of the dexamethasone suppression test. Biol Psychiatry 1986;21:931–938
102. Evans DL, Burnett GB, Nemeroff CB. The dexamethasone suppression test in the clinical setting. Am J Psychiatry 1983;140:586–589
103. Maes M, DeRuyter M, Suy E. Use of the dexamethasone suppression test in an inpatient setting: a replication and new findings. Psychoneuroendocrinology 1989;14:231–240
104. Brown WA, Johnston R, Mayfield D. The 24-hour dexamethasone suppression test in a clinical setting: relationship to diagnosis, symptoms, and response to treatment. Am J Psychiatry 1979;136:543–547
105. Stokes PE, Stoll PM, Mattson MR, et al. Diagnosis and psychopathology in psychiatric patients resistant to dexamethasone. In: Sachar EJ, ed. Hormones, Behavior and Psychopathology. New York, NY: Raven Press; 1976
106. Hwu HG, Chen TS, Yang YY. The clinical diagnostic value of dexamethasone suppression test in depressive illness. Ann Acad Med Singapore 1985;14:104–109
107. Carroll BJ, Martin FIR, Davies BM. Resistence to suppression by dexamethasone of plasma 11-OHCS levels in severe depressive illness. BMJ 1968;3:285–287
108. Georgotas A, Stokes PE, Hapworth WE, et al. The relationship of the dexamethasone suppression test to subtypes of depression and to symptom severity in the elderly. J Affect Disord 1986;10:51–57
109. Kumar A, Alcser K, Grunhaus L, et al. Relationships of the dexamethasone suppression test to clinical severity and degree of melancholia. Biol Psychiatry 1986;21:436–444
110. Meador-Woodruff JH, Haskett RF, Grunhaus L, et al. Postdexamethasone plasma cortisol and β-endorphin levels in depression: relationship to severity of illness. Biol Psychiatry 1987;22:1137–1150
111. Drateu L, Calil HM. The dexamethasone suppression test: its relationship to diagnosis, severity of depression and response to treatment. Prog Neuropsychopharmacol Biol Psychiatry 1989;13:99–117
112. Carroll BJ, Davies BM. Clinical associations of 11-hydroxycorticosteroid suppression and nonsuppression in severe depressive illness. BMJ 1970;1:789–791
113. Targum SD, Rosen L, Capodanno AE. The dexamethasone suppression test in suicidal patients with unipolar depression. Am J Psychiatry 1983;140:877–879
114. Steiner M, Brown GM, Goldman S. Nocturnal melatonin and cortisol secretion in newly admitted psychiatric inpatients: implications for affective disorders. Eur Arch Psychiatry Clin Neurosci 1990;240:21–27
115. Meador-Woodruff JH, Greden JF, Grunhaus L, et al. Severity of depression and hypothalamic-pituitary-adrenal axis dysregulation: identification of contributing factors. Acta Psychiatr Scand 1990;81:364–371
116. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
117. Staner L, Maes M, Bouillon E, et al. Biological correlates of the Newcastle scale in depressive illness: a multivariate approach. Acta Psychiatr Scand 1992;85:345–350
118. Klein HE, Bender W, Mayr H, et al. The DST and its relationships to psychiatric diagnosis, symptoms, and treatment outcome. Br J Psychiatry 1984;145:591–599
119. Thompson LM, Rubin RT, McCracken JT. Neuroendocrine aspects of primary endogenous depression, XII: receiver operator characteristic and kappa analyses of serum and urine cortisol measures in patients and matched controls. Psychoneuroendocrinology 1992;17:507–515
120. Spitzer RL, Endicott J, Robins E. Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 1978;35:773–782
121. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC: American Psychiatric Association; 1980
122. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978;35: 837–844
123. Andreasen NC, Endicott, J, Spitzer RL, et al. The family history method using diagnostic criteria. Arch Gen Psychiatry 1977;34:1229–1235
124. Rush AJ, Schlesser MA, Roffwarg HP, et al. Relationships among the TRH, REM latency, and dexamethasone suppression tests: preliminary findings. J Clin Psychiatry 1983;44:23–29
125. Orsulak PJ, Gershon ES. Therapeutic monitoring of tricyclic antidepressants: quality control considerations. Ther Drug Monit 1980;2:233–242
126. Orsulak PJ, Gershon ES. Clinical laboratory quality control: application to analysis of tricyclic antidepressants. In: Usdin E, ed. Clinical Pharmacology in Psychiatry. New York, NY: Elsevier; 1981:43–57
127. Dixon WJ, Brown MB, Engelman L, et al. BMDP Statistical Software. Berkeley, Calif: University of California Press; 1983
128. SAS Institute Inc. SAS/STAT User's Guide, Version 6, vol 1, 2. 4th ed. Cary, NC: SAS Institute Inc; 1990
129. Gaddum JH. Log-normal distributions. Nature 1945;156:463–466
130. Heath DF. Normal or log-normal: appropriate distribution. Nature 1967; 213:1159–1160
131. World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, 8th revision (ICD-8). Geneva, Switzerland: WHO; 1968
132. World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, 9th revision (ICD-9). Geneva, Switzerland: WHO; 1977

133. Gurney C. Diagnostic scales for affective disorders. In: Proceedings of the 5th World Congress of Psychiatry; 1971; Mexico City, Mexico. Page 330
134. Bech P, Gram LR, Reisby N, et al. The WHO depression scale: relationship to the Newcastle scales. Acta Psychiatr Scand 1980;62:140–155
135. Giles DE, Biggs MM, Roffwarg HP, et al. Secondary depression: a comparison among subtypes. J Affect Disord 1987;12:251–258
136. Fleming JE, Extein I, Sternbach HA, et al. The thyrotropin-releasing hormone and dexamethasone suppression tests in the familial classification of depression. Psychiatry Res 1983;9:53–58
137. Davidson J, Lipper S, Zung WWK, et al. Validation of four definitions of melancholia by the dexamethasone suppression test. Am J Psychiatry 1984;141:1220–1223
138. Calloway SP, Dolan RJ, Fonagy P, et al. Endocrine changes and clinical profiles in depression, I: the dexamethasone suppression test. Psychol Med 1984;14:749–758
139. Rabkin JG, Quitkin FM, Stewart JR, et al. The dexamethasone suppression test with mildly to moderately depressed outpatients. Am J Psychiatry 1983;140:926–927
140. Prabhu V, el-Guebaly N. Cortisol secretion and DST in affective disorders: methodological concerns. Can J Psychiatry 1983;28:602–611
141. Cook N, Harris B, Walker R, et al. Clinical utility of the dexamethasone suppression test assessed by plasma and salivary cortisol determinations. Psychiatry Res 1986;18:143–150
142. Brown RP, Stoll PM, Stokes PE, et al. Adrenocortical hyperactivity in depression: effects of agitation, delusions, melancholia and other illness variables. Psychiatry Res 1988;23:167–178
143. Ames D, Burrows G, Davies B, et al. A study of the dexamethasone suppression test in hospitalized depressed patients. Br J Psychiatry 1984; 144:311–313
144. Extein I, Pottash ALC, Gold MS. Number of cortisol time-points and dexamethasone suppression test sensitivity for major depression. Psychoneuroendocrinology 1985;10:281–288
145. Gitlin MJ, Gwirtsman H, Fairbanks L, et al. Dexamethasone suppression test and treatment response. J Clin Psychiatry 1984;45:387–389
146. Peselow ED, Baxter N, Fieve RR, et al. The dexamethasone suppression test as a monitor of clinical recovery. Am J Psychiatry 1987;144:30–35
147. Rush AJ, Cain JW, Raese J, et al. Neurobiological bases for psychiatric disorders. In: Rosenberg RN, ed. Comprehensive Neurology. New York, NY: Raven Press; 1991:555–603
148. Rush AJ, Weissenburger JE. Melancholic symptom features and DSM-IV. Am J Psychiatry 1994;151:489–498
149. Depression Guideline Panel. Clinical Practice Guideline Number 5. Depression in Primary Care, vol 2: Treatment of Major Depression. Rockville, Md: US Dept Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 93-0551;1993
150. Charles GA, Vanderwalle J, Meunier JC, et al. Plasma and urinary cortisol levels after dexamethasone in affective disorders. J Affect Disord 1981;3:397–406
151. Papakostas Y, Fink M, Lee J, et al. Neuroendocrine measures in psychiatric patients: course and outcome with ECT. Psychiatry Res 1981;4: 55–64
152. Berger M, Doerr P, Lund R, et al. Neuroendocrinological and neurophysiological studies in major depressive disorders: are there biological markers for the endogenous subtype? Biol Psychiatry 1982;17: 1217–1242
153. Mendlewicz J, Kerkhofs M, Hoffman G, et al. Dexamethasone suppression test and REM sleep in patients with major depressive disorder. Br J Psychiatry 1984;145:383–388
154. Johnson GF, Hunt G, Kerr K, et al. Dexamethasone suppression test (DST) and plasma dexamethasone levels in depressed patients. Psychiatry Res 1984;13:305–313
155. Rubin RT, Poland RE, Lesser IM, et al. Neuroendocrine aspects of primary endogenous depression, III: cortisol secretion in relation to diagnosis and symptom patterns. Psychol Med 1987;17:609–619
156. Berger M, Pirke KM, Doerr P, et al. The limited utility of the dexamethasone suppression test for the diagnostic process in psychiatry. Br J Psychiatry 1984;145:372–382
157. McIntyre IM, Norman TR, Burrows GD, et al. [letter]. BMJ 1981;283: 1609–1610
158. Holden NL. Depression and the Newcastle scale: their relationship to the dexamethasone suppression test. Br J Psychiatry 1983;142:505–507