The Dexamethasone Suppression Test in Psychiatric Disorders

Introduction of the DST led to greater interest among psychiatric researchers in the hypothalamic-pituitary-adrenal (HPA) axis.

by ANTHONY J. ROTHSCILD, MD

The dexamethasone suppression test (DST) has been one of the most studied biological tests in clinical psychiatry. As has happened with many other new ideas and technologies in the history of science, the DST was first openly embraced by psychiatrists after its standardization and introduction for use in clinical psychiatry in 1981.1 After wide use and further study in the 1980s, the DST went through a negativistic period in which many clinicians and researchers argued that the DST had little value as a biological test in clinical psychiatry. However, the introduction of the DST led to greater interest among psychiatric researchers in the hypothalamic-pituitary-adrenal (HPA) axis; from the major physiological regulator corticotropin-releasing factor (see Musselman and Nemeroff, this issue3) to the effects of elevated cortisol levels on outcome and treatment4 (see Murphy and Wolkowitz, this issue5).

The purpose of this paper is to review the current knowledge on the use of the DST in a variety of clinical situations. Current controversies and issues remaining for future research will also be discussed.

ADMINISTRATION OF THE DST

The most widely employed procedure for administering the DST is as follows: 1.0 mg of dexamethasone, a potent, long-acting synthetic steroid, is taken at 11:00 PM. On the day after the administration of dexamethasone, blood samples for determination of plasma cortisol concentration are most commonly drawn at 8:00 AM, 4:00 PM, and 11:00 PM. For convenience, often only an afternoon sample is obtained from outpatients, but this does result in a modest loss of test sensitivity.6 A number of medical conditions, including severe weight loss and use of alcohol and certain other medications, can produce false positive results.1,6,7 Although not always clinically possible, ideally patients should be drug-free, physically healthy, and physiologically stable to ensure unambiguous interpretation of DST results.6

DEFINITION OF NONSUPPRESSION

The criterion level to define normal plasma concentrations of cortisol under the test conditions described above is commonly set at 5.0μg/dl.1 The cutoff was developed with the modified Murphy competitive protein-binding (CPB) technique,8 Rubin and colleagues9 have suggested a cutoff of 3.5 μg/dl when using the more specific radioimmunoassay (RIA) technique, while others9 have argued that the utility of the
DST in the clinical setting would be enhanced by using a cutoff of 7 μg/dl. It also remains unclear whether the cortisol abnormality (as measured by the DST) is perhaps better viewed as a spectrum of cortisol levels rather than a binary, all-or-none, nonsuppression versus suppression classification.

**AFFECTIVE DISORDERS**

There is now abundant evidence for hyperactivity of the HPA axis in endogenous or melancholic depression. The sensitivity of the DST (rate of a positive outcome, or nonsuppression of cortisol) in major depression is about 40% to 50% but it is higher (about 60% to 70%) in very severe, especially psychotic, affective disorders, including major depression with psychotic as well as melancholic features, mania, and schizoaffective disorder. The specificity of the DST (the chance of a negative finding when the person tested is free of the condition under study) has been reported to be over 90%. With most studies of the DST (involving hundreds of subjects using 1.0 mg of dexamethasone) reporting rates of cortisol nonsuppression in normal controls of approximately 5% to 10%. Since a physician is seldom interested in distinguishing a patient with affective disorder from a normal person, a more important question is the specificity of the DST among patients with other psychiatric or medical illnesses that might be confused with major depression. As the nonsuppression groups have expanded to other diseases, the specificity of the DST (as is the case with all diagnostic tests) has decreased.

The rate of nonsuppression of cortisol following dexamethasone administration in depressed patients (test sensitivity) is dependent on many technical, physiologic, and clinical factors. These include, but are not limited to, dose of dexamethasone used, time of sampling of cortisol, criteria for nonsuppression, cortisol sampling methodology, nonspecific stress factors (e.g., hospitalization, medical illnesses), effects of treatment with and withdrawal from psychotropic or other medications, changes in diet and weight, and age.

**MAJOR DEPRESSION WITH PSYCHOTIC FEATURES**

(PSYCHOTIC DEPRESSION, DELUSIONAL DEPRESSION)

One of the most replicable findings in the DST literature is the high rate of DST nonsuppression and markedly elevated postdexamethasone cortisol levels in patients with psychotic major depression (PMD). For example, our group reported on a study of 88 patients treated at McLean Hospital and 31 healthy control subjects using the DST to identify subtypes of depression. A review of the case histories indicated that those patients with major depression and very high plasma cortisol levels (15 μg/dl or more at 4:00 PM) had a propensity for exhibiting mood-congruent psychotic features (e.g., nihilistic delusions) at the time of study. For example, of the nine patients with major depression who had plasma cortisol levels of 15 μg/dl or more, seven showed psychotic features; and all six with plasma cortisol levels of 17 μg/dl at 4:00 PM or more were psychotic. In contrast, of the remaining 36 patients with major depression whose plasma cortisol levels were less than 15 μg/dl, only seven showed psychotic features ($x^2 = 11.4, df = 1, p < .001$). In this study the frequency of nonsuppression (10 of 14, or 71.4%) was higher in the PMD patients than in the nonpsychotic patients with major depression (18 of 31, or 58.1%).

We then compared these psychotically depressed patients with a group of schizophrenic patients to ascertain whether the high postdexamethasone cortisol levels in the patients with psychotic depression reflected a nonspecific effect due to psychosis. Eight of the 14 psychotic patients with major depressive illness had a postdexamethasone 4:00 PM cortisol level $>14 \mu g/dl$. In contrast, none of the psychotic schizophrenic patients had a postdexamethasone 4:00 PM cortisol level $>14 \mu g/dl$.

The mean postdexamethasone cortisol levels for the unipolar psychotically depressed patients (13.5 ± 8.1 μg/dl) was significantly higher than for psychotic schizophrenic patients (2.4 ± 5.8 μg/dl, $p < .05$). Thus, the high cortisol levels seen in our patients with unipolar psychotic depression was not due to the psychosis per se, but rather to the presence of psychosis in the context of an affective disorder. Given the high rate of DST nonsuppression in PMD and the lower rates of DST nonsuppression in schizophrenia (see below), the DST may be of clinical utility in the differential diagnosis of PMD from schizophrenia; a differential diagnosis that is often difficult, particularly in a young person.

**GERIATRIC DEPRESSION**

Studies of the DST in major depression have demonstrated an association between the frequency and degree of dysregulation and increasing age. DST abnormalities in major depression that are associated with increased posture...
One of the most replicable findings is the high rate of DST nonsuppression and markedly elevated postdexamethasone cortisol levels in patients with psychotic major depression.

age include a greater proportion of DST nonsuppressors and increased postdexamethasone cortisol levels. Most, but not all, studies carried out in normal subjects have failed to show an age effect on cortisol levels after dexamethasone administration. In one study, over 90% of normal elderly controls demonstrated suppression on the DST.

The interpretation of nonsuppression on the DST in the geriatric population is complicated by the occurrence of DST abnormalities in Alzheimer's disease, in multinfarct dementia, and by false positives due to unstable physical illnesses that accompany aging, presumably as the direct effect of the illnesses or because of the medications taken by the patients.

A recent study of physically healthy and cognitively intact elderly patients with major depression demonstrated that treatment is associated with DST normalization. In this sample of 30 subjects, 60% were nonsuppressors at baseline compared with 17% after intensive treatment. A strong correlation was identified between clinical improvement and decreases in afternoon cortisol levels. The authors argued that there are advantages in using cortisol as a continuous rather than a categorical measure in assessing the relationship between reversal of depression and DST results in the geriatric population.

DYSTHYMIC DISORDER/BORDERLINE PERSONALITY DISORDER

Several studies have investigated the rate of nonsuppression on the DST in dysthyemic disorder and borderline personality disorder. Generally, the rate of DST nonsuppression is less than in major depression and similar to what is observed in normal control subjects. For example, in a metaanalysis of 10 studies that used DSM-III criteria comparing DST results in dysthyemic disorder, major depression, and other psychiatric disorders in adults, the rate of DST nonsuppression was significantly different between patients with dysthyemic disorder and those with major depression but not between dysthyemic disorder and normal controls.

A review of studies of the DST in borderline personality disorder (BPD) indicated that the majority of studies had low rates of DST nonsuppression. Most of the BPD nonsuppressors were depressed, and the rates of nonsuppression in the group that had coexisting BPD and major depressive disorder had nonsuppression rates lower than the published rates of nonsuppression for patients with major depressive disorder alone. In general, nondepressed BPD patients were suppressors on the DST.

These studies are consistent with an earlier report by our group that investigated the rates of DST nonsuppression in patients with dysthymic disorder and BPD. We reported a rate of DST nonsuppression in the dysthymic disorder/borderline personality disorder group of 16% compared with a rate of DST nonsuppression of 61% in the major depression group. We also found that the mean (±SD) 4:00 PM postdexamethasone cortisol level for patients with major depression (8.8 ± 6.7 μg/dl) was significantly higher than that seen in the dysthymic disorder/borderline personality disorder group (2.9 ± 1.0 μg/dl, p < .05). We did not observe any significant differences between the dysthymic disorder/borderline personality disorder group and the control group on mean (±SD) 4:00 PM postdexamethasone cortisol levels.

SCHIZOPHRENIA

Studies of the DST in schizophrenia have yielded rates of nonsuppression ranging from 0% to 73%. Higher rates of DST nonsuppression in schizophrenia have been associated with depressive symptomatology, negative symptoms, and the nonparanoid subtype.

Reviews of the DST literature in patients with schizophrenia suggest that variances in DST results may be due to the phase of the illness and the medication status of the patient when the test is performed. Several groups have observed a reduction in rates of DST nonsuppression in patients with schizophrenia after three to four weeks of neuroleptic treatment. Furthermore, rates of DST nonsuppression are higher in drug-free schizophrenic patients than in medicated patients. Although antipsychotic medication regimens are believed to have no effect on the DST, other groups have suggested that withdrawal of neuroleptics/anticholinergics may produce DST nonsuppression lasting up to 21 days.

While further studies are needed to examine the frequency of nonsuppression in patients with schizophrenia, it does appear that
the rate of nonsuppression is greater than in normal controls, but not as high as the rate seen in affective disorders.

**PANIC DISORDER**

In general, outpatients with panic disorder are more likely than normal controls, but less likely than patients with major depression, to exhibit dexamethasone nonsuppression, a phenomenon that does not simply reflect coexisting depression. In a study using multiple DST testing over a two-month period, Coryell and colleagues reported that 18 of 44 (40.9%) panic disorder patients were nonsuppressors on at least one of three DST tests compared with only five of 36 (14.3%) controls ($p = 0.006$).

Most studies of the DST in panic disorder patients have generally not been designed to address the issue of possible differences between agoraphobic and nonagoraphobic subjects. One study reported that panic disorder patients with agoraphobia had higher postdexamethasone serum cortisol and a higher rate of nonsuppression on the DST than panic disorder patients without agoraphobia or normal controls. DST nonsuppression in panic disorder has been associated with a more persistent and chronically disabling condition.

**OBSESSIVE-COMPULSIVE DISORDER**

Varying rates of nonsuppression on the DST have been reported in obsessive-compulsive disorder (OCD). Several studies have reported low rates of nonsuppression while others have reported higher rates of nonsuppression. Insel and colleagues reported that inpatients with OCD were much more likely to be nonsuppressors than were outpatients, suggesting that severity might be an important factor. One study has suggested that depressive symptoms are associated with higher postdexamethasone cortisol values in OCD patients, but not all studies agree.

**POSTTRAUMATIC STRESS DISORDER**

Data from DST studies of posttraumatic stress disorder (PTSD) patients have yielded inconclusive results. Four studies have reported normal suppression of cortisol in nondepressed PTSD patients given the standard 1 mg DST. In PTSD patients who met criteria for major depression, two studies reported a nonsuppression pattern on the DST in some patients, and two other studies showed normal suppression in this subgroup. Moreover, recently, Yehuda and colleagues have suggested that PTSD patients have enhanced negative feedback sensitivity of the HPA axis because they exhibit an exaggerated suppression response to low doses of dexamethasone. These results are also consistent with previous reports that PTSD patients show low mean basal 24-hour urinary cortisol excretion and a higher than normal number of lymphocyte glucocorticoid receptors. These recent studies suggest abnormalities in HPA axis activity in PTSD patients, which is the opposite of what is seen in major depression, raising interesting questions for future research. For example, would there be an HPA axis abnormality (and of what type) in patients who concurrently suffer from major depression and PTSD or major depression with psychotic features and PTSD? In particular, there are clinical situations in which the specific diagnosis of the patient is difficult to ascertain. For example, there are patients who suffer from psychotic depression and have a history of abuse or trauma. Are these PTSD patients who exhibit psychotic symptoms or are they patients with major depression with psychotic features and who have a history of trauma? The low-dose DST may be a potentially useful clinical and experimental tool for distinguishing what is primarily a PTSD disorder from major depression with psychotic features.

**EATING DISORDERS**

HPA axis hyperactivity has been reported in patients suffering from anorexia nervosa. However, since hypercortisolemia occurs with protein-caloric malnutrition and since weight loss of greater than 20% of ideal body weight has been found to cause false-positive DST results, the weight loss alone may be responsible for some of the observed abnormalities. Walsh and colleagues have suggested that some patients with anorexia nervosa exhibit hypercortisolemia that cannot be accounted for solely by weight loss; however, the interpretation of DST results in patients with anorexia nervosa remains difficult.

Several studies have reported nonsuppression on the DST in patients with bulimia. In one study, nonsuppressors were more likely to report a family history of treat-
Generally, the rate of DST nonsuppression in BPD is less than in major depression and similar to what is observed in normal control subjects.

Studies of the DST in children and adolescents, the sensitivity of the DST appeared to be higher among children than among adolescents, higher in subjects from inpatient settings than in outpatient settings, and more specific in adolescent samples. Few differences were observed in rates of nonsuppression for different psychiatric conditions. Questions still remain as to the appropriate amount of dexamethasone that should be given when the DST is administered to children and adolescents.

PLASMA DEXAMETHASON CONCENTRATIONS

The bioavailability of dexamethasone may be a factor influencing DST results. Postdexamethasone cortisol values show a significant inverse relationship with plasma dexamethasone concentrations, and patients with major depression who are DST suppressors have higher plasma dexamethasone concentrations than DST nonsuppressors.

One study has suggested that DST nonsuppressors have a significantly shorter half-life of dexamethasone than DST suppressors, suggesting that DST nonsuppressors may have accelerated metabolism of dexamethasone rather than decreased absorption.

Another study found that clinical response in depressed patients receiving ECT was associated with increased plasma dexamethasone levels, whereas changes in cortisol levels were independent of clinical outcome. This study raises the intriguing question as to whether clinical recovery is associated with altered bioavailability of dexamethasone. While the preponderance of the evidence suggests that the simultaneous measurement of serum dexamethasone and cortisol values is helpful to interpret DST results, the relationship of plasma dexamethasone levels to clinical outcome suggests that there may be abnormalities in the metabolism and/or bioavailability of dexamethasone itself in depressed patients.

DEXAMETHASONE SUPPRESSION TEST AND CLINICAL OUTCOME

Prolonged elevation of cortisol levels in depressed patients, as evidenced by failure to convert to normal suppression on the DST, even after an apparently adequate initial clinical response to treatment, has been reported in many studies to be a warning of increased risk for relapse, although not all studies agree.

Our group recently completed a study on the relationships between one-year cortisol measures and outcome at one year in depressed patients. We observed significant correlations between measures of cortisol activity (DST, urinary free cortisol [UFC]) at one year and measures of social and occupational functioning at one year. Patients with UFC values...
greater than 100 μg/24 hours at one year had significantly poorer functioning as measured by the Social Adjustment Scale—Self Report (SAS-SR)\textsuperscript{109} total score at one year, than did patients with UPC values less than 100 μg/24 hours. A similar relationship was observed between DST nonsuppressor status at one year and poorer social and occupational functioning at one year.\textsuperscript{3}

The relationship between higher cortisol levels at one year and poor overall functioning at one year was observed in both psychotic and nonpsychotic depressed patients and appeared even stronger statistically when degree of depression (as measured by total HRDS score) was partialed out. We have hypothesized that the association between higher levels of cortisol at one year and poorer social/occupational functioning is secondary to subtle cognitive deficits caused by the higher cortisol levels seen in depressed patients.\textsuperscript{3} Our hypothesis is based on observations that increased HPA axis activity in depressed patients is associated with larger ventricle-to-brain ratios (VBRs)\textsuperscript{110-112} and cognitive disturbances.\textsuperscript{111,113-119} These studies suggest possible associations among cognitive disturbances, cortisol hypersecretion, and enlarged ventricles.

Similar observations of relationships between cortisol and outcome have been reported in patients with schizophrenia. Tandon and colleagues\textsuperscript{4} reported that persistent DST nonsuppression in schizophrenic patients was associated with greater negative symptom severity at four weeks and poorer outcome at one year. Conversely, conversion of DST nonsuppression at baseline to normal suppression after four weeks of neuroleptic treatment was associated with significantly greater improvement in both negative symptoms and global severity at four weeks. This observation is consistent with previous reports by the same group\textsuperscript{61} and others.\textsuperscript{56} Analogous to observations by our group in patients with depression,\textsuperscript{111} persistent DST nonsuppression in the schizophrenic patients was associated with greater VBRs (although not statistically significant because of the small sample size, \(n = 6\)) and poorer one-year outcome.\textsuperscript{4}

Further studies using larger samples and standardized treatments are needed and are in progress to explore, in a systematic way, the relationships among increased HPA activity, cognition, brain scan abnormalities, and social and occupational functioning in patients with depression and schizophrenia.

**CONCLUSIONS**

The DST, as one of the first laboratory tests introduced in psychiatry, represents an important milestone in the history of psychiatry. As has been reviewed in this paper, the rate of nonsuppression of cortisol following dexamethasone administration is dependent on diagnosis as well as many technical and physiologic factors. Although the use of the DST in the clinical setting has decreased, the test may have utility in certain situations such as the differentiation of major depression with psychotic features (high nonsuppression rate) from schizophrenia (low nonsuppression rate), a diagnosis that can be clinically difficult, particularly in a young person with a first episode of psychosis.

Attempts to correlate abnormalities observed on administration of the DST with specific psychiatric disorders (with the exception of psychotic depression) has met with limited success. However, it is important to remember that diagnostic classification systems undergo frequent update and revision. If results on measurements of HPA axis activity do not precisely match up with our current diagnostic criteria, it does not necessarily mean that the biological test does not have validity. In the meantime, we are left with the observation that many psychiatric patients have abnormalities on measurements of HPA activity. By further exploring the reasons for and consequences of HPA axis hyperactivity, we hope to learn more about the pathophysiology and treatment of these disorders.

**REFERENCES**

7. Kraus RF, Graf P, Brown M. Drugs and the DST: need


