Objectifying Psychiatric Diagnosis and Treatment with the Dexamethasone Suppression Test

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The application of the dexamethasone suppression test (DST) to the treatment of depressive illness is discussed from the perspectives of its use in diagnosis, the measurement of outcome, and the prediction of response to antidepressant medications. Patients with nonsuppressing depression occur in about one half of the endogenously depressed population and probably represent a norepinephrine-deficient subtype of the syndrome. There is clear evidence that a change in the DST from nonsuppression to suppression parallels recovery from a depressive illness, and this may be used as an objective measure of outcome. Early studies show promise that the DST can predict the antidepressant of choice, although there are some limitations of the DST in treatment choice.

The diagnosis of melancholia or endogenous depression until recently has been made on the basis of clinical symptoms alone. Treatment often includes the prescription of tricyclic antidepressants, and 70 percent of these prescriptions are written by physicians in family practice or internal medicine.[1] How appropriately these drugs are used has been questioned, and one of the major difficulties lies in the diagnosis itself. The clinical symptoms identifying endogenous depression can also be applied to nonendogenous depression (neurotic, reactive) or to depression associated with schizophrenia and schizoaffective disorders. Choice of antidepressants is still largely empirical; controlled trials of tricyclic antidepressants support their equivalency, yet some patients improve on one and not another. Although studies have shown that maintenance therapy with tricyclic antidepressants reduces the risk of relapse, the determination of the appropriate time to discontinue drug treatment is still somewhat arbitrary. There has been no clear correlation between return to normal mood state and biological change.

Extensive research on the dexamethasone suppression test (DST) is demonstrating that this

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Table 1. Evidence for Subtypes of Endogenous Depression

	Presumptive Norepinephrine Deficiency	Presumptive 5-Hydroxytryptamine
MHPG* urinary levels	Decreased	Normal
5HIAA** urinary levels	Normal	Decreased
Dexedrine response	Euphoria	Dysphoria
Depressive type	90% of bipolar 50% of unipolar	50% of unipolar

*MHPG: 2 methoxy, 3 hydroxy phenylethylglycol is the major central nervous system metabolite of norepinephrine
**5HIAA: 5-hydroxyindoleacetic acid is the major central nervous system metabolite of 5-hydroxytryptamine (5HT or serotonin)

simple procedure may prove to be an objective index to identify patients suffering from endogenous depression.[2-7] The DST can also be used as a biological indicator of the optimal time for withdrawal of medication.[8-10]

Hypothalamic Pituitary Axis and Depression

Numerous investigators have reported that the incidence of abnormal DSTs in patients with a diagnosis of a major depressive disorder is approximately 50 percent.[3-5,7,11] An abnormal DST is characterized by early escape from suppression of plasma cortisol levels following the administration of dexamethasone.[2]

It is speculated that the dysfunction of biogenic amines, which is generally accepted as the basis of affective disorder, is also responsible for the abnormalities in neuroendocrine function that have been observed in depressed patients.[12] These include hypothalamic pituitary axis regulatory defects such as high plasma cortisol levels and early escape from dexamethasone suppression, presumably indicating a failure in the normal inhibitory influence of the brain on the release of ACTH and cortisol.[2,3,12]

The 50 percent of depressed patients who exhibit abnormal dexamethasone suppression may represent a subgroup of depressed patients with norepinephrine deficiency within their limbic system. Evidence suggests that catecholamines exert inhibitory control of the hypothalamic pituitary axis, while stimulatory mechanisms for ACTH involve serotonin. Thus a subgroup of depressed patients deficient in norepinephrine would be characterized by ACTH release and elevated cortisol levels. A subgroup deficient in serotonin would suppress normally.[13] Studies of metabolites of norepinephrine and serotonin in depressed patients support the existence of subtypes of endogenous depression.[13-15]

These various theories are summarized in Table 1.

Protocol for Dexamethasone Suppression Test

Normally, the administration of dexamethasone orally at midnight suppresses ACTH secretion for 24 hours. An abnormal DST is characterized by early escape from suppression. The standard protocol, as established by Carroll et al,[7] is to give 1 mg of dexamethasone orally at 11:30 PM, followed by plasma cortisol levels drawn at 4 PM and 11:30 PM. A level of plasma cortisol greater than 5 μg/100 mL at either 4 PM or 11:30 PM is considered abnormal. With this test, the DST has a sensitivity of 65 percent, that is, it can identify 65 percent of patients with an affective disorder who are non-

suppressors. Ninety-six percent of patients with other psychiatric diagnoses show a normal DST, which is the measure of the specificity of the test. Thus 4 percent of normal patients may have false-positive DST results, although the incidence of false positives is similar for both nondepressed psychiatric patients and nonpatients.[7] The choice of 5 μg/100 mL was a balance between specificity and sensitivity over a range of 3 to 6 μg/100 mL.

Since the 4 PM and 11:30 PM blood samples can detect 98 percent of positive DSTs, the 8 AM sample can be eliminated.[7] In the outpatient population, it may be necessary for practical reasons to use only the 4 PM blood sample. This may result in a less sensitive test; however, the 4 PM sample alone can still detect 78 percent of positive DSTs.[7]

Since the hypothalamic pituitary axis responds to a number of stresses, including medical illness, weight loss, pregnancy, and drugs, there are a number of exclusion criteria that must be observed to avoid false-positive and false-negative results (Table 2).

Table 2. Medical Exclusion Criteria

False-positive tests
Pregnancy; high-dose estrogens
Cushing's disease or syndrome
Severe weight loss, malnutrition, anorexia nervosa (weight 80% of ideal weight)
Hepatic enzyme induction (phenytoin, barbiturates, meprobamate)
Uncontrolled diabetes mellitus (hypoglycemia, acidosis)
Major physical illness, trauma, fever, dehydration, nausea
Acute withdrawal from alcohol
False-negative tests
Addison's disease, corticosteroid therapy, hypopituitarism
High-dose benzodiazepines (> 25 mg/d of diazepam), cyproheptadine (possible)
Uncertain exclusion criteria
Other endocrine disease
Spironolactone

From Carroll et al[7]

Uses

Classification

A significant use of the dexamethasone suppression test is in the diagnosis of endogenous depression, or "melancholia," a classical definition used by Carroll et al.[7] An abnormal DST is found in approximately one half of patients with endogenous depression. Patients with other psychiatric disorders suppress normally.[3,5,7] In practice, a positive DST confirms the clinical diagnosis. A negative DST does not rule out a clinical diagnosis of depression; the patient may belong to the subgroup of depressed patients who suppress normally and therefore may benefit from treatment. Of patients in the depressed phase of bipolar illness, 90 percent have been found to suppress abnormally.[3] Suppression tends to return to normal while the patient is in the manic state.[5]

Schlesser et al[5] investigated the use of the DST in the differentiation of familial subtypes of unipolar depression. The test discriminated between familial pure depressive disease (FPDD—patients who have a first-degree relative with a history of depression, but no history of mania, alcoholism, or antisocial personality disorders) and depression spectrum disease (DSD—patients who have a first-degree relative with alcoholism or antisocial personality disorder with or without depression and no mania). The patients with FPDD were nonsuppressors, whereas the DSD patients along with secondary depressive patients suppressed normally. Although Schlesser's results used only an 8 AM plasma cortisol level, an inadequate DST by Carroll's standards, this line of research is promising.

The ability to confirm the diagnosis of endogenous depression objectively with a laboratory test is a major step toward clearing the confusion presently associated with the treatment of depression.

Objectifying Response to Treatment

The optimal time to discontinue treatment of depression has not been established. The relapse rate in patients abruptly discontinued from medication is high, and the timing of medication reduction or cessation is completely empirical. Numerous investigators of DST have demonstrated that recovery from depression can be biologically

Table 3. Comparative Actions of Antidepressants

Tricyclic Antidepressants	Type of Action
Maprotiline	Norepinephrine reuptake blocker
Desipramine	
Nortriptyline	↕
Imipramine	
Amitriptyline	
Cloipramine	5-Hydroxytryptamine reuptake blocker

demonstrated by the return to normal suppression.[6-10] Outcome studies indicate that after discontinuation of treatment patients still nonsuppressing to dexamethasone show a higher relapse rate than patients with a normalized DST. In fact, several investigators report that bipolar depressed patients who switch into mania have a parallel change in their DST from nonsuppression to suppression.[3,5]

The DST seems to be a reliable biological marker for resolution of the underlying neurohormonal imbalance, which suggests that patients should demonstrate both clinical and neuroendocrine evidence of remission before withdrawal of medication is considered. As there are no other biological indices that can successfully predict when antidepressant therapy can be discontinued, the direct measurement of the norepinephrine hormonal dynamics in the limbic system appears a promising indicator of a successful treatment.

Predicting Antidepressant Response

Antidepressants can be separated on the basis of their differential effects on the reuptake of norepinephrine and 5-hydroxytryptamine[14,16] as demonstrated in Table 3.

As the DST is presumed to indicate a functional deficit in norepinephrine in the hypothalamus, it is a logical assumption that nonsuppressing depressed patients will preferentially respond to a norepinephrine reuptake blocker. In fact, the practicality of the DST lies more in its potential in measuring response and predicting the antidepressant of choice than in confirming diagnosis.

The literature is shallow and murky on this issue, however. Brown et al[17] in a preliminary study demonstrated that nonsuppressing depressed patients improved with desipramine or imipramine and failed to respond to amitriptyline and cloipramine. Conversely, his data show that suppressors improved with amitriptyline and cloipramine and not on treatment with desipramine and imipramine. Other investigators such as Carroll[18] failed to notice any correlation between DST response and specific antidepressants. The underlying problem may be due to tricyclic antidepressant metabolites. Parent compounds that primarily block norepinephrine reuptake may be converted to metabolites that are primarily 5-hydroxytryptamine reuptake blockers. This confounds the task of trying to predict antidepressant response, since these drugs may have multiple effects. Assuming the DST accurately detects any norepinephrine deficiency in the limbic system and assuming the biochemical etiology of depressive illness lies in the relative deficiency of either norepinephrine or 5-hydroxytryptamine, the ultimate utility of the DST as a predictor of the antidepressant drug of choice awaits refinement of antidepressant into pure norepinephrine or 5-hydroxytryptamine reuptake blockers.

Discussion

With the DST comes a new generation of diagnostic tools for psychiatry. It permits physicians to objectify the diagnosis of affective disorder and may allow precision in the selection of antidepressants and the determination of their effect that hitherto has not been enjoyed.

The usefulness of the test as a diagnostic tool is considerable. In the many complicated cases for which the various contributions to the psychopathology could previously only be loosely inferred, the DST should give physicians an important method of determining whether there exists an affective component to the illness that might yield to specific treatment.

The test may be especially helpful in cases in which diagnosis is uncertain, such as in patients with atypical depression or those with depressive override, or in patients presenting with somatic symptoms without apparent mood change.

This test, however useful, should not be employed alone to make the diagnosis of depression. Good clinical practice requires the diagnosis to be made on clinical grounds, with the DST used as an adjunct to support the diagnosis.

Although the utility of the DST in selecting the antidepressant of choice is far from settled, the initial research suggests that this is a promising lead. According to the rationale of the test, there should be a straightforward prediction of response to specific antidepressants based on the neurotransmitter they effect. Difficulties in the exact prediction may be based on the lack of specificity of the response of these drugs. If the next generation of antidepressants has a specific effect on a target neurotransmitter system, there may be a much closer fit between prediction and response.

Psychotropic drugs, including benzodiazepines (low dose), lithium, tricyclic antidepressants, and antipsychotics, do not appear to interfere with the DST. No differences in psychotropic medication were found between suppressors and nonsuppressors in a number of studies.[4,6,7] A preliminary study in 12 patients specifically examined the effect of tricyclic antidepressants. No difference in DST results before tricyclic antidepressants and after three weeks at moderate doses was found.[19] On the other hand, L-tryptophan, a serotonin precursor used as an antidepressant, has been reported to alter DST results.[20] More systematic studies are required to ensure that psychotropic drugs are not affecting the outcome of the DST.

The studies reviewed here indicate unanimity in supporting the usefulness of this test in determining successful outcome. There is, however, much to be learned about the relationships between alterations in limbic function and cognitive change. It is unclear just when antidepressants should be discontinued. Nonetheless, this simple test of endocrine function has the potential to revolutionize the current treatment of affective disorders.

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