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The Dexamethasone Suppression Test as a Predictor of Sleep Deprivation Antidepressant Effect

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Abstract. An abnormal dexamethasone suppression test (DST) result, a sensitive and specific marker for endogenous depression, was found to be associated with an antidepressant response to sleep deprivation in patients who met *DSM-III* criteria for Major Depressive Episode regardless of whether they met criteria for melancholia or psychotic subtypes of this disorder. These findings support previous reports of an association between an abnormal DST result and antidepressant effects of sleep deprivation in depressed patients. Our results extend the positive association between an abnormal DST result and the antidepressant response to sleep deprivation to include depressed patients who are clinically nonmelancholic during their current episode but who have an abnormal DST result.

Key Words. Sleep deprivation, dexamethasone suppression test, melancholia.

Total night sleep deprivation produces a definite but usually transient antidepressant effect (SDAE = sleep deprivation antidepressant effect) in 40 to 75% of depressed patients studied (King, 1977). This effect is most often, though not always, seen in patients with endogenous depression (Pflug, 1976). Thus diagnostic subtype does not totally account for the variability of response to sleep deprivation among depressed patients.

Nasrallah and Coryell (1982) have reported that an abnormal dexamethasone suppression test (DST) result is associated with the SDAE in patients who meet *DSM-III* (American Psychiatric Association, 1980) criteria for major depression. An abnormal DST result has been shown to be a sensitive and highly specific marker of endogenous depression (melancholia) (Carroll et al., 1981). Therefore, a positive association between an abnormal DST and SDAE is consistent with data which support an association between a clinical diagnosis of endogenous depression and SDAE. Because some patients with endogenous depression do not exhibit SDAE while some patients with nonendogenous depression do, it would be of interest to determine whether an abnormal DST distinguishes sleep deprivation responsive from nonresponsive patients with nonendogenous as well as endogenous depression.

In a study of the effect of 1 night of sleep deprivation in eight patients with endogenous depression, Albala et al. (1981) reported that an abnormal DST result did

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not distinguish sleep deprivation responsive from nonresponsive patients. Seventy-five percent of their sample exhibited SDAE. These results suggest that in a patient population with a high likelihood of exhibiting SDAE (endogenous depression) an abnormal DST result adds no predictive information with respect to SDAE.

In order to address further the issue of whether DST results predict sleep deprivation effects *independently* of clinical diagnosis, we retrospectively tested the following hypotheses: (1) in patients with major depression (not subtyped in terms of presence or absence of melancholia) an abnormal DST is positively associated with SDAE (i.e., replicating the findings of Nasrallah and Coryell, 1982); (2) in patients with major depression *without melancholia* an abnormal DST result is positively associated with SDAE; (3) in patients categorized by DST result and clinical diagnosis, the following rank order would be found with respect to SDAE: (melancholia *and* abnormal DST) > (*either* melancholia *or* abnormal DST) > (*neither* melancholia *nor* abnormal DST).

Methods

Subjects. Charts for all patients admitted during the preceding 12 months were screened (by S.D.) and a sample consisting of 10 depressed inpatients who met the following criteria was obtained: (1) *DSM-III* criteria for major depressive episode; diagnoses were derived by consensus of two raters (D.K. and R.J.) who independently diagnosed each patient using the following data: (a) psychiatric history and mental status examination obtained on admission (semistructured interview); (b) discharge summary; (c) all available records from previous psychiatric admissions. (2) DST performed within the first week of hospitalization (did not meet any of the medical exclusion criteria of Carroll et al., 1981, for the DST). (3) One night of sleep deprivation (36 to 42 hours without sleep) which occurred while the patient was moderately or severely depressed (global clinical impression) but after completion of the DST. Two patients were sleep-deprived within a week of having had the DST. All other patients were sleep-deprived at least a week after the DST. Demographic features of the sample are given in Table 1.

Diagnostic Criteria. All patients met *DSM-III* criteria for major depression for their current episode. In this study patients who met the criteria for melancholia or psychotic depression are referred to as melancholic, though the specific subclassification is indicated in Table 1. Patients were also diagnosed as bipolar or unipolar based on historical data.

Dexamethasone Suppression Test. Dexamethasone, 1.125 mg, p.o., was administered at 2300 h and a blood sample for serum cortisol was drawn at 1600 h on the following day. An abnormal result was considered to occur when serum cortisol was > 5 μg/dl. Serum cortisol levels were determined by Gamma Coat [^{125}I] Cortisol Radioimmunoassay Kit.[1]

Sleep Deprivation. In our sample there were three types of sleep deprivation: (1) therapeutic ($n = 4$); (2) sleep deprivation electroencephalogram (EEG) ($n = 4$); (3) self-imposed ($n = 2$) (Table 1). "Therapeutic" sleep deprivation was given for potential antidepressant benefit. Patients were informed of potential therapeutic outcome before the deprivation procedure. Sleep deprivation EEG studies were conducted to rule out seizure disorder. Patients with "self-imposed" sleep deprivation were not requested to stay awake for therapeutic effects or an EEG study but remained awake due to "total insomnia." In all cases, except when deprived for sleep EEG, patients remained awake for 36 to 42 hours. Patients deprived of sleep for EEG study slept up to 30 minutes, between 8 and 10 a.m., during the EEG. Patients who had sleep

1. Radioimmunoassay Kit available from Clinical Assays, Division of Travenol Laboratories, Inc., Cambridge, MA 02139.

deprivation EEGs were requested to remain awake until their regular bedtime after their EEG study in order to "maintain their sleep-wake cycle." During the deprivation night patients stayed in the ward "day room" in full view of the nurses station. They played cards, read, walked, and talked with ward staff. Patients were allowed to shower if necessary to remain awake. In all cases patients were moderately to severely depressed (global clinical assessment) when sleep-deprived. At the time of deprivation six patients were taking tricyclic antidepressants, two were taking monoamine oxidase inhibitors, one was taking a neuroleptic, and one was on no medication (Table 1). Medications were not withheld for sleep deprivation.

Table 1. Diagnosis, demographic data, medication, type of sleep deprivation and response to sleep deprivation for 10 inpatients meeting *DSM-III* criteria for major depressive episode

Subtype of major depression	Age	Sex	Medication	DST result	Type of sleep deprivation	Rated response
Bipolar (psychotic)	50	M	TCA	NS	EEG	6
Unipolar	72	F	TCA	NS	Therapy	3.5
Unipolar (melancholia)	61	F	TCA	NS	EEG	4
Unipolar	48	F	MAOI	NS	Therapy	5.25
Bipolar	38	M	none	NS	Self-imposed	4
Unipolar	30	M	TCA	S	Therapy	3
Unipolar	58	F	TCA	S	EEG	3.75
Bipolar (psychotic)	28	M	Neuroleptic	S	EEG	4
Unipolar	22	M	MAOI	S	Self-imposed	1.5
Unipolar	35	M	TCA	S	Therapy	1.75

Abbreviations: M = male; F = female; TCA = tricyclic; MAOI = monoamine oxidase inhibitor; NS = nonsuppression or abnormal result; S = suppression or normal result.
See Table 2 for response rating scale.

Sleep Deprivation Response Ratings. Composite descriptions of each patient's mental status and behavior for the day before and the day after sleep deprivation were obtained by extracting all descriptive material from nursing notes and progress notes. Progress notes (recorded daily by a psychiatric resident) routinely contained assessments of "target symptoms" (i.e., symptoms relevant to tracking an individual's progress) such as mood, vegetative symptoms, and psychomotor status, as well as descriptions of ward behavior and social interaction. The composite descriptions were coded (contained no information regarding identity of the patient or DST results) and were independently rated by four raters (three had no contact with patients) using the 6-point scale in Table 2. The mean of the four ratings for each patient is given in Table 1. These ratings reflect postdeprivation status for the day immediately following sleep deprivation relative to predeprivation status.

Results

Diagnosis, demographic data, medication, type of sleep deprivation and rated response to sleep deprivation for our 10 patients are given in Table 1. The mean age for

our sample was 44.2 years. Mean ages for DST nonsuppressor and suppressor subgroups, respectively, were 53.8 years and 34.6 years. The overall male:female ratio was 3:2. DST nonsuppressors had a 2:3 and suppressors a 4:1 male:female ratio.

Table 2. Sleep deprivation response rating scale

1. Worsening	Definite evidence, subjective or objective, of exacerbation of depression
2. No change	No subjective or objective evidence of improvement or worsening
3. Minimal improvement	Subjective report of some improvement in mood or energy, etc., but objective evidence is lacking or minimal
4. Moderate improvement	Subjective and objective evidence of improvement in *more than one dimension*, but patient cannot unequivocally be rated as as euthymic
5. Marked improvement	Subjective and objective evidence that the patient's mood has normalized. No evidence of residual symptoms of depression
6. Euphoria	Definite euphoria; some behavioral evidence of activation (e.g., increased rate of speech, or increased psychomotor activity); no residual symptoms of depression

Sleep deprivation response ratings were converted to ranked scores and Mann-Whitney *U* tests were run on each comparison in Table 3 (Blalock, 1979). Hypothesis 1 predicted that DST nonsuppression would be positively associated with SDAE. Based on a review of the literature, it was predicted that age, sex, and type of sleep deprivation would be unrelated (King, 1977).

Table 3. Subgrouping for 10 depressed inpatients (DST result, sex, age, type of sleep deprivation) with median rated response to sleep deprivation, DST results (number and percentage) and Mann-Whitney *U* test results for each comparison

	n	Median rated response	% NS[1]	*p*
Nonsuppressors	5	4	100%	< 0.03[2]
vs. suppressors	5	3	0%	
Males vs.	6	3.5	33%	< 0.61[3]
females	4	4.6	75%	
Age 45 or younger	5	3.5	20%	< 0.15[3]
vs. age 45 or older	5	3.9	80%	
Therapy vs.	4	3.3	50%	< 0.48[3]
others	6	3.5	50%	

1. Percent of DST nonsuppressors.
2. One-tailed comparison.
3. Two-tailed comparison.

DST nonsuppressors were rated as having a significantly greater SDAE than DST suppressors ($p < 0.028$, one-tailed). Types of sleep deprivation (therapeutic vs. other), age, and sex did not differentiate responders from nonresponders.

For subgroupings based on age and sex, the highest percentage of DST nonsuppressors was found in the subcategory associated with higher median sleep deprivation response ratings (Table 3). Thus females had a higher median response rating (i.e., better response) than males and also had a higher percentage of DST nonsuppressors (75%) than males (33%). The same relationship held for age. Patients who received sleep deprivation as therapy did not differ from patients sleep-deprived for other reasons (EEG, insomnia) in terms of percentage of DST nonsuppressors (50% vs. 50%) and these subgroups had the most similar median response ratings (3.3 vs. 3.5).

Our second hypothesis predicted that an abnormal DST result would be associated with SDAE in major depression patients without melancholia. Seven of our patients did not meet criteria for melancholia and three of these had an abnormal DST. A Mann-Whitney *U* test comparing these subgroups suggested that an abnormal DST was associated with SDAE in major depression patients without melancholia ($p <$ 0.057, one-tailed).

Our third hypothesis was that in patients categorized by diagnostic subtype *and* DST result the following rank order would be seen with respect to SDAE: subgroup I (melancholia *and* abnormal DST) > subgroup II (*either* melancholia *or* abnormal DST) > subgroup III (*neither* melancholia *nor* abnormal DST). Our data suggest a tendency for subgroups I and II to be associated with a higher rated sleep deprivation response than subgroup III, while subgroups I and II did not differ from each other (Table 4). Thus patients with a diagnosis of melancholia *and* an abnormal DST and patients with *either* a diagnosis of melancholia *or* an abnormal DST tended to exhibit a greater antidepressant effect than patients who had *neither* melancholia *nor* an abnormal DST.

Table 4. Comparisons between subgroups I, II, and III on sleep deprivation response ratings and results of Mann-Whitney *U* tests (one-tailed) for each comparison

Comparison	*p*
I vs. II	< 0.27
II vs. III	< 0.03
I vs. III	< 0.07

I = both melancholia and abnormal DST result ($n = 2$);
II = either melancholia or abnormal DST result ($n = 4$);
III = neither melancholia nor abnormal DST result ($n = 4$).

Discussion

These data suggest that an antidepressant response to sleep deprivation is associated with an early escape from dexamethasone suppression in patients with a *DSM-III*

diagnosis of major depressive episode. Two patients in our sample worsened (response rating ≤ 2) as a result of sleep deprivation. Both of these patients were DST suppressors. Fifty percent (5 of 10) of patients were rated as having at least moderate improvement (response rating ≥ 4). Four of these five (80%) were DST nonsuppressors.

These findings are consistent with those of Coryell and Nasrallah (1982). Since these investigators did not subcategorize their major depression patients (in terms of presence or absence of melancholia), their data do not lend themselves to sorting out the relative value of DST result and diagnostic subtype for predicting SDAE. By categorizing our sample both in terms of DST result and depressive subtype, we were able, in a preliminary way, to look at the relative predictive value of these variables.

Our data support hypothesis 2 and certain aspects of hypothesis 3. DST results in patients who meet criteria for major depression without melancholia have predictive value with respect to SDAE. On the other hand, patients with a clinical diagnosis of melancholia and an abnormal DST did not have a greater SDAE than patients having either but not both factors. Both subgroups (I and II) did, however, respond more favorably to sleep deprivation than patients who neither were melancholic nor had an abnormal DST. One hypothesis suggested by these findings is that patients who do not meet clinical criteria for melancholia but have an abnormal DST may be "biologically equivalent" (with respect to SDAE) to patients who meet clinical criteria for melancholia but have a normal DST.

Consistent with previous studies, neither age nor sex differentiated sleep deprivation responders from nonresponders. Interestingly, the type of sleep deprivation (therapy vs. other) did not discriminate responders from nonresponders. Patients who were sleep-deprived for EEG slept up to 30 minutes during their EEG (between 8 a.m. and 10 a.m.). There is some evidence to suggest that napping during sleep deprivation adversely affects outcome (King, 1977). Two of our "EEG" patients, however, had a moderate response while the third had slightly less than a moderate response (3.75). It is conceivable that these patients might have responded even more favorably had they not slept. It is also possible that napping which occurs outside the "critical period" (King, 1977) may not adversely affect results of deprivation. The results of one study which found partial sleep deprivation to be as effective as total sleep deprivation support this hypothesis (Schilgen and Tölle, 1980). Further work is clearly needed to determine under what circumstances napping interferes with the SDAE.

Since nine of our patients were on medication at the time of sleep deprivaton, the possibility that our findings (of an association between DST nonsuppression and an SDAE) could have resulted from drug effects or drug-deprivation interactions must be considered.

Though patients were on medication when sleep-deprived, they were all moderately to severely depressed on the day preceding deprivation. The improvement which occurred was transient, lasting 1 day, except for one patient who remained euphoric for 2 days after deprivation. The transience of response, the suddenness of onset, and the temporal relationship to sleep deprivation closely resemble the description of the sleep-deprivation response in drug-free depressed patients. These observations suggest that responses were not due solely to drug effect. Improvement could have been due, however, to sleep deprivation or an interaction between sleep deprivation and medication.

The fact that all five patients who exhibited less than a moderate response to sleep deprivation (response rating < 4) were on antidepressant medication at the time of deprivation is consistent with the hypothesis that the transient improvement was a function of sleep deprivation per se. However, because we did not control for serum tricyclic levels or percent of platelet monoamine oxidase inhibition, the possibility that our results may have been due to an interaction between drug therapy and sleep deprivation cannot be ruled out (i.e., that responders had adequate serum tricyclic levels or adequate percent MAO inhibition whereas nonresponders did not).

Studies which control for serum drug levels or which use sleep deprivation in drug-free patients are necessary to characterize further the relationship between DST result and response to sleep deprivation.

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