Dexamethasone Suppression Test in Schizophrenia: Relationship to Symptomatology, Ventricular Enlargement, and Outcome

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To relieve confusion about the clinical correlates and prognostic implications of the dexamethasone suppression test (DST) in schizophrenia, we conducted a DST in 44 schizophrenic inpatients at drug-free baseline and approximately 4 weeks after neuroleptic treatment. Patients were rated on positive, negative, and depressive symptoms at both times. A head computed tomography (CT) scan was performed and measures of ventricle–brain ratio (VBR) obtained. Clinical improvement was monitored at four weeks, and longer-term outcome assessed at 1 year. Seventeen of the 44 patients were DST nonsuppressors at baseline, and five of these remained nonsuppressors at 4 weeks posttreatment. Postdexamethasone plasma cortisol levels were correlated with negative symptoms at baseline ($r = 0.45$; $p < 0.01$), but not after 4 weeks of neuroleptic treatment. Postdexamethasone plasma cortisols were not related to global severity, positive, or depressive symptoms at either timepoint or to VBR. Persistent nonsuppression was associated with poor outcome, but baseline postdexamethasone cortisol levels were unrelated to outcome at 4 weeks and 1 year. The literature on DST in schizophrenia is reviewed and attempts are made to reconcile discrepant findings and to discuss pathophysiological implications.

Introduction

Although the dexamethasone suppression test (DST) was originally proposed as a specific marker for major depressive disorder (Carroll et al 1981), studies in schizophrenia have yielded rates of nonsuppression ranging from 0% to 73% (Yeragani 1990). Higher rates of DST nonsuppression in schizophrenia have been attributed to depressive symptoms (Munro et al 1984; Sawyer and Jeffries 1984), negative symptoms (Coppen et al 1983; Shima et al 1986; Tandon et al 1989a), and the nonparanoid subtype (Banki et al 1984). It also has been suggested that DST nonsuppression in schizophrenia may prognosticate a better outcome (Targum 1983; Coryell and Zimmerman 1989). Most of these findings

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have not, however, been confirmed in other investigations and the approximately 50 studies of DST in schizophrenia have yielded discrepant findings.

The present study was conducted in an effort to define the clinical correlates and prognostic implications of the DST response in schizophrenia, and study the impact of phase of illness, neuroleptic treatment, and ventricular size. In a preliminary report (Tandon et al 1989a), we had observed a 35% nonsuppression rate in a sample of 20 medication-free schizophrenic patients, and an association between postdexamethasone cortisol levels and severity of negative symptoms. We now report findings on an expanded sample of 58 patients with regard to frequency of DST nonsuppression in medication-free and neuroleptic-treated phases of schizophrenic illness, and relationship of the DST response to symptomatology (positive, negative, and depressive symptoms). In this study, we additionally investigated the relationship of the DST response to ventricular size and 1-year outcome.

Methods

The original sample consisted of 58 consecutively hospitalized patients who were admitted to the Inpatient Schizophrenia Program at the University of Michigan from 1987–1989. All patients met DSM-III-R (American Psychiatric Association 1987) and Research Diagnostic Criteria (RDC) (Spitzer et al 1978) for schizophrenia. Patients with any medical criteria known to interfere with a valid DST (Carroll et al 1981) were excluded. No patient had received depot neuroleptics for at least 6 months before entering the study. Informed consent was obtained. After patients had been drug-free for a minimum of 2 weeks, clinical ratings, head computed tomography (CT) scan, and a 1 mg DST were performed. Patients were then treated with clinically determined doses of haloperidol, thiothixene, or chlorpromazine [doses of 8–30 mg haloperidol equivalents per day (Baldessarini 1984)], singly or in combination with 2–6 mg of trihexyphenidyl. After about 4 weeks of such treatment, clinical ratings and the DST were repeated. Approximately 1 year after the initial drug-free evaluation, outcome was assessed. Outcome could be assessed on 44 of the 58 patients in the original sample. The remaining patients could not be located. All subjects who had clinical ratings and a valid DST at the drug-free and 4-week posttreatment timepoints, and on whom outcome could be assessed at 1 year were included in the final sample. The final sample of 44 patients consisted of 29 men and 15 women, with a mean (±SD) age of 29 (±8) years (range 18–46 years). The mean duration of the illness was 7 (±5) years. Of these 44 patients, 15 were drug naive (never medicated), 12 had been noncompliant with prescribed treatment and were drug free for >4 weeks, and 17 were drug free for 2–4 weeks.

Patients were rated by one of the investigators (RT) on the 18-item Brief Psychiatric Rating Scale [BPRS (Overall and Gorham 1962)], Scale for the Assessment of Negative Symptoms [SANS (Andreasen 1983)], and the Hamilton Depression Rating Scale [HDRS (Hamilton 1960)] at baseline and about 4 weeks after neuroleptic treatment. Ratings were completed while blind to DST results and head CT findings. Global severity was assessed by the 18-item BPRS total score. Positive symptom severity was assessed by the sum of the following four BPRS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. Collectively, these items comprise the BPRS "THOT" factor (Guy 1976; Hedlund and Vieweg 1980) and are most commonly employed to rate positive symptoms. Negative symptoms were assessed by the SANS, the sum of

global scores being employed as the measure of negative symptom severity. The BPRS "ANER" factor, consisting of emotional withdrawal, motor retardation, and blunted affect, was utilized for comparison. Depressive symptom severity was assessed by the 17-item HDRS total score. Change in symptom ratings at 4 weeks was employed as the measure of improvement at 4 weeks.

A 1-mg DST (Carroll et al 1981) was performed at drug-free baseline and after about 4 weeks of neuroleptic treatment. The first DST was performed at least 1 week after the patient's hospital admission to permit adaptation (Haskett et al 1989). Clinical ratings and the corresponding DST were performed within 2 days of each other. Blood samples for postdexamethasone cortisol levels were obtained at 4 PM and 11 PM and the maximal cortisol levels were employed for analysis. Cortisol was assayed by Murphy's competitive protein-binding method (Murphy 1967). Maximal postdexamethasone cortisol levels > 5 μg/dl have been established in our clinical setting to be indicative of nonsuppression (Carroll et al 1981). Plasma dexamethasone levels were not measured in this study.

A head CT scan was performed on 36 of the 44 patients in the sample and measures of ventricle–brain ratio (VBR) obtained by videoscreen planimetry. Two raters (JD and JMW), blind to clinical ratings and DST findings, conducted these measurements and the mean of two ratings of the maximum VBR on the CT brain slices ($LVBR_{max}$) on each individual patient was employed for analysis.

Outcome was assessed by the Strauss-Carpenter scale (Strauss and Carpenter 1972; McGlashan 1984), on which hospitalization, employment, social activity, symptoms, global function, and compliance are all assessed on a 5-point (0–4) scale. A family member/careprovider, and the individual's treating psychiatrist or community mental health center casemanager were contacted for this assessment by two independent raters (CM and KC) about 1 year after the initial drug-free evaluation. After their independent assessments, a joint conference was held between these raters to arrive at final consensus ratings. The raters were blind to the clinical ratings, DST, and head CT findings.

The relationship between DST findings and other parameters was evaluated by calculating Pearson's product–moment correlations between log-transformed maximal postdexamethasone cortisol levels and clinical ratings, VBR, and outcome measures. Based on DST suppression/nonsuppression at the two timepoints, patients were then divided into the following three groups: patients who were suppressive following dexamethasone at both timepoints (S-S); patients who were nonsuppressive at drug-free baseline but who converted to normal suppression after 4 weeks (NS-S); and those who continued to be nonsuppressors even after 4 weeks of neuroleptic treatment (NS-NS). These groups were compared on clinical ratings, VBR, and outcome by analysis of variance (ANOVA).

Results

In the total sample, at drug-free baseline, postdexamethasone cortisol levels were significantly correlated with negative symptom scores measured either by the SANS ($r = 0.45$; $n = 44$; $p < 0.01$) or the BPRS "ANER" factor ($r = 0.41$; $p < 0.01$). Figure 1 illustrates the relationship between baseline postdexamethasone cortisol and the SANS sum of global scores. Baseline postdexamethasone cortisol levels were significantly correlated to four SANS subscale global scores ($r = 0.39$–0.49; $p < 0.05$ for affective blunting, avolition–apathy, anhedonia–asociality, and attentional impairment) and showed a trend toward significant relationship with the alogia subscale global score ($r = 0.31$;

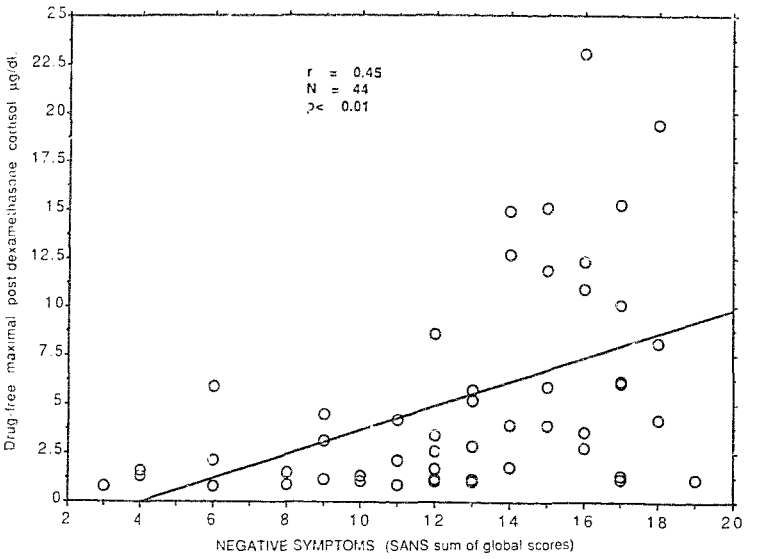

Figure 1. Association between postdex cortisol and negative symptoms ($r = 0.45$; $n = 44$; $p < 0.01$).

$p < 0.10$). There was no relationship to global severity ($r = 0.20$; NS), positive symptoms ($r = 0.20$; NS), or depressive symptoms ($r = 0.17$; NS). Similarly, baseline postdexamethasone cortisol levels were unrelated to age, sex, VBR, improvement of symptoms at 4 weeks, or any index of outcome at 1 year. (Similar findings were obtained when the larger sample of 58 patients, including 14 on whom outcome data not available, was considered.) Postdexamethasone cortisol levels were significantly correlated to change in SANS sum of global scores during neuroleptic treatment ($r = 0.38$; $p < 0.05$).

At the 4-week posttreatment timepoint, postdexamethasone cortisol levels were unrelated to negative symptoms ($r = 0.13$; NS), positive symptoms ($r = 0.15$; NS), depressive symptoms ($r = 0.13$; NS), or global severity ($r = 0.23$; NS). There also was no association with age, sex, VBR, or outcome at 1 year. Drug-free and 4-week posttreatment postdexamethasone cortisol levels were significantly correlated ($r = 0.42$; $p < 0.01$).

The BPRS total (mean ± SD) of the entire sample at medication-free baseline was 49 (± 7.5). The mean severity of positive symptoms (measured by the BPRS "THOT" subscale) and negative symptoms (measured by the SANS sum of global scores) were 15.7 (±3.0) and 13.2 (±3.9) respectively. Both positive and negative symptoms improved with neuroleptic treatment; the mean positive and negative symptom severity at 4-weeks posttreatment were 9.5 (±3.1) and 8.8 (±3.9) respectively. The mean maximal postdexamethasone cortisol was 5.5 (±5.0) at drug-free baseline and 2.6 (±2.6) at 4-weeks posttreatment. Head CT scans from 36 patients resulted in a mean ± SD $LVBR_{max}$ of 0.08 (±0.03).

Seventeen of the 44 patients (39%) were DST nonsuppressors at baseline, including five of 15 previously never-medicated patients. In the larger sample of 58 patients, 22 were nonsuppressors, yielding a similar nonsuppression rate of 38% at drug-free baseline. Although all patients were drug-free for at least 2 weeks before the initial DST, Kraus et al (1988) have suggested that withdrawal of neuroleptics–anticholinergics may produce DST nonsuppression lasting up to 21 days. Analysis of the data to examine for this possibility revealed that in our final sample, 15 patients were drug naive, 12 patients were drug free >4 weeks, and 17 patients were drug free for 2–4 weeks. Five of the 15 drug-naive patients (33%), five of the 12 patients drug free >4 weeks (42%), and seven of the 17 patients drug free for 2–4 weeks (41%) were DST nonsuppressors. Thus, psychotropic withdrawal effects apparently did not account for the DST findings observed in our study.

Of the 17 baseline DST nonsuppressors 12 became normally suppressive (NS-S) at 4-weeks posttreatment. Of the 27 patients who were DST suppressors at drug-free baseline, 26 remained suppressive (S-S), while one became a DST nonsuppressor at 4-weeks posttreatment. This patient was classified with the five persistent DST nonsuppressors in the NS-NS group. The three groups are compared on symptom ratings, VBR, and outcome in Table 1. The three groups did not differ in age or sex distribution. While there was no statistical difference in maximal VBR between the three groups, persistent DST nonsuppressors tended to have larger VBR ($F = 1.8$; df = 2,33; $p < 0.19$).

At drug-free baseline, the three groups did not differ with regard to severity of positive symptoms, depression, or global severity. Both persistent DST nonsuppressors and normalizing DST nonsuppressors had significantly higher negative symptom scores than the persistent DST suppressor group. By definition, both the DST nonsuppressor groups had significantly higher postdexamethasone cortisol levels than the DST suppressor group.

After 4 weeks of clinically determined neuroleptic treatment, the three groups did not differ with regard to severity of positive symptoms, depression, or global severity. The persistent DST nonsuppressor group had significantly higher negative symptom ratings than the persistent DST suppressor and normalizing DST nonsuppressor (suppressor at this timepoint) groups. Again by definition, the persistent DST nonsuppressor group had higher mean postdexamethasone cortisol than the other two groups.

After 4 weeks of neuroleptic treatment, the normalizing DST nonsuppressor group showed significantly greater improvement in both negative symptoms and global severity than the other two groups. There were no differences between the three groups with regard to degree of improvement of positive or depressive symptoms.

There were significant differences between the three groups with regard to 1-year outcome. The persistent DST nonsuppressor group had significantly worse total outcome than the other two groups. While the normalizing DST nonsuppressor group had somewhat better outcome than the persistent DST suppressor group, this difference was not statistically significant. The three groups did not differ with regard to treatment compliance.

Discussion

Thirty-nine percent (17 of 44) of schizophrenic patients were DST nonsuppressors at medication-free baseline. Four weeks after neuroleptic treatment, 14% (6 of 44) of these patients remained DST nonsuppressors. The rate of DST nonsuppression observed in our sample is intermediate between the 0% to 73% reported in the literature and is comparable to data reported in most recent studies (Table 2). All studies of the 1-mg DST in schizophrenia (not schizoaffective disorder) with a sample size >10, which employed a post-

Table 1. Comparison of Persistent DST Suppressors, Persistent DST Nonsuppressors, and DST Nonsuppressors Converting to Suppressor Status with Four Weeks Neuroleptic Treatment

Parameter	Persistent DST suppressors (S-S) $n = 26$	Normalizing DST nonsuppressors (NS-S) $n = 12$	Persistent DST nonsuppressors (NS-NS) $n = 6$	Significance (ANOVA)
Age	27 ± 8	32 ± 8	31 ± 7	NS
Sex (M/F)	18 M/8 F	7 M/5 F	4 M/2 F	NS
VBR	0.077 ± 0.03	0.080 ± 0.03	0.097 ± 0.05	NS
Medication-free				
Positive (BPRS "THOT")	15.3 ± 3.0	16.5 ± 3.4	15.8 ± 1.0	NS
Negative (SANS glob sum)	11.7 ± 4.2	15.1 ± 2.0	15.5 ± 1.9	$F = 5.2$; $p < 0.01$
Depression (HRSD tot)	13.1 ± 4.8	13.4 ± 2.7	12.3 ± 3.4	NS
Global severity (BPRS tot)	48.2 ± 7.4	50.5 ± 9.0	49.0 ± 4.7	NS
Post-dex cortisol μg/dl	2.4 ± 1.3	10.0 ± 4.7	12.8 ± 6.8	$p < 0.001$
Four-weeks posttreatment				
Positive	9.6 ± 3.1	8.8 ± 2.9	10.2 ± 3.8	NS
Negative	8.3 ± 4.0	8.8 ± 3.0	12.0 ± 2.7	$F = 3.3$; $p < 0.05$
Depression	7.0 ± 3.5	6.9 ± 2.4	6.7 ± 3.5	NS
Global severity	35.5 ± 7.1	32.8 ± 5.9	37.7 ± 6.7	NS
Post-dex cortisol	1.8 ± 0.8	1.8 ± 0.8	8.7 ± 3.2	$p < 0.001$
Change in symptoms 4 weeks				
Positive	5.7 ± 3.3	7.7 ± 4.7	5.7 ± 3.4	NS
Negative	3.4 ± 2.0	6.3 ± 2.6	3.5 ± 2.6	$F = 6.5$; $p < 0.01$
Depression	5.7 ± 2.4	6.6 ± 1.7	5.7 ± 2.5	NS
Global severity	12.7 ± 6.8	17.7 ± 6.5	11.3 ± 5.2	$F = 3.3$; $p < 0.05$
One-year outcome				
Hospitalization	3.6 ± 0.8	3.9 ± 0.3	3.3 ± 0.8	NS
Employment	1.7 ± 1.2	1.9 ± 0.9	1.0 ± 0.9	NS
Social activity	2.3 ± 1.4	2.8 ± 1.5	2.0 ± 1.4	NS
Symptoms	2.1 ± 1.0	2.0 ± 0.8	1.3 ± 0.8	NS
Global function	2.4 ± 1.1	2.7 ± 1.1	1.6 ± 0.9	NS
Total	12.1 ± 2.0	13.3 ± 2.1	9.2 ± 1.7	$F = 3.5$; $p < 0.05$
Compliance	3.2 ± 1.1	3.1 ± 1.4	3.5 ± 0.8	NS

dexamethasone cortisol value of 5 μg/dl as the cutoff for nonsuppression are enumerated in this table. A summary meta-analysis of these studies reveals a DST nonsuppression rate of 36% in the drug-free state (39% in our sample) and 20% in the medicated state (14% in our sample). These data suggest that phase of illness and medication status influence rates of DST nonsuppression in schizophrenia and may partially account for the discrepant findings in the literature. Rates of DST nonsuppression are higher in drug-free schizophrenic patients in the acute phase of the illness. The significant reduction in rates of DST nonsuppression that we observed after 3–4 weeks of neuroleptic treatment is consistent with this suggestion and with findings of other studies in which the DST was performed before and after neuroleptic treatment (Herz et al 1985; Holsboer-Trachsler et al 1987; Moller et al 1986; Tandon et al 1989a; Wik et al 1986).

The association between postdexamethasone cortisol levels and severity of negative symptoms observed in our study is in agreement with eight of the 12 other studies that evaluated this association (refer to Table 2). We observed an association between post-dexamethasone cortisol and negative symptoms in the drug-free state, but not after 3–4 weeks of neuroleptic treatment. These findings are similar to those of the Stanford group,

Table 2. Dexamethasone Suppression Test in Schizophrenia: Rates of Nonsuppression, Association with Symptomatology, Medication Status, and Outcome

Study	Nonsuppression rate		Associations		Outcome
	Med. free	Medicated	Negative	Depression	
Addington and Addington 1990	—	6/50(12%)	No	Yes	—
Aleem et al 1988	—	6/19(32%)	—	No	—
Altamura et al 1989	—	22/54(40%)	Yes	—	—
Asnis et al 1986	4/17(24%)	—	—	—	—
Banki et al 1984	19/45(42%)	—	—	—	—
Banki et al 1986	7/20(35%)	—	—	—	—
Baumgartner et al 1985	11/22(50%)	—	—	—	—
Berger et al 1984	—	4/21(19%)	—	—	—
Castro et al 1983	—	7/23(30%)	—	—	—
Coppen et al 1983	—	10/46(22%)	Yes	—	—
Coryell and Zimmerman 1989	—	8/31(26%)	—	—	good 1-year outcome
Dam et al 1985	—	5/15(33%)	—	—	—
Dewan et al 1982	—	6/20(30%)	—	No	—
Doran et al 1986	2/13(16%)	—	—	No	—
Faustman et al 1990	7/21(33%)	—	Yes	No	—
Gold et al 1981	—	0/25 (0%)	—	—	—
Harris 1985	—	4/12(33%)	Yes	—	—
Herz et al 1985	11/15(73%)	1/5 (20%)	—	—	—
Holsboer-Trachsler et al 1987	15/31(48%)	4/31(13%)	—	—	not related: 4 weeks
Hubain et al 1986	10/22(45%)	—	—	—	—
Hwang et al 1984	—	2/13(15%)	—	—	—
Jones et al 1990	6/17(35%)	—	No	Yes	—
Joseph et al 1987	—	2/39 (5%)	—	—	—
Keshavan et al 1989	3/27(11%)	—	No	No	worse outcome; 4 weeks
Kiriike et al 1988	—	2/22 (9%)	—	—	—
Krishnan et al 1987	—	2/15(13%)	—	No	—
McGauley et al 1989	—	4/28(14%)	Yes	No	—
McMahon et al 1986	—	2/12(17%)	—	—	—
Mellsop et al 1985	6/30(20%)	—	—	—	—
Moller et al 1986	12/20(60%)	6/13(46%)	—	—	—
Morphy et al 1985	—	6/13(46%)	—	—	—
Munro et al 1984	—	7/46(15%)	—	Yes	—
Nelson et al 1984	—	4/14(29%)	—	—	—
Nishimon et al 1984	—	16/67(25%)	—	—	—
Pandey et al 1987	4/22(18%)	—	—	—	—
Perenyi et al 1987	—	6/30(20%)	—	No	—
Rihmer and Arato 1984	—	1/20 (5%)	—	—	—
Rothschild et al 1982	—	2/14(14%)	—	—	—
Saffer et al 1985	—	10/50(20%)	Yes	No	—
Sawyer and Jeffries 1984	—	7/20(35%)	—	Yes/No	—
Schlesser et al 1980	—	0/48 (0%)	—	—	—
Sharma et al 1988	8/44(18%)	—	—	No	—
Shima et al 1986	—	5/22(23%)	Yes	No	—
Siris et al 1984	—	0/16(0%)	—	—	—
Sora et al 1986	—	7/28(25%)	—	—	—
Stokes et al 1984	2/12(17%)	—	—	—	—
Tandon et al 1989	7/20(35%)	0/20(0%)	Yes	No	good outcome. 4 weeks
Targum 1983	5/21(24%)	—	—	—	good outcome 6 months
Whiteford et al 1988	—	9/40(23%)	No	No	—
Wik et al 1986	15/21(71%)	3/15(20%)	—	—	—
Wolkowitz et al 1989	4/16(25%)	—	—	—	—
Zhou et al 1987	—	6/48(13%)	—	—	—

who observed no relationship between postdexamethasone cortisol and negative symptoms in chronic, medicated schizophrenic patients (Whiteford et al 1988), but observed such a relationship in acute, unmedicated patients (Faustman et al 1990). These data, in addition to the association between postdexamethasone cortisol levels and change in negative symptoms observed in our study, may indicate that in the acute phase of the illness, postdexamethasone cortisol levels are related to nonenduring negative symptoms (Carpenter et al 1988; Tandon et al 1990; Tandon and Greden 1990a).

Our failure to find any association between postdexamethasone cortisol and depressive symptoms is consistent with the findings of 13 of the 17 studies that assessed this association (refer to Table 2). Despite the phenomenological overlap between negative and depressive symptoms and consequent difficulty in differentiating between them (Sommers 1985; Addington and Addington 1990), recent studies indicate that these phenomena can be distinctly measured in schizophrenia (Barnes et al 1989; Newcomer et al 1990; Liberzon et al 1990). Our finding of an association between postdexamethasone cortisol levels and negative symptoms, but not with depressive symptoms, would support this contention. We found no other relationship between postdexamethasone cortisol and global severity, a finding consistent with other studies that evaluated this association (Dewan et al 1982; Shima et al 1986; Tandon et al 1989a).

The observed relationship between DST findings and outcome was complex. Baseline postdexamethasone cortisol itself was unrelated to outcome at 4 weeks or 1 year. The pattern of baseline DST nonsuppression converting to normal suppression after 4 weeks of neuroleptic treatment was associated with significantly greater improvement in both negative symptoms and global severity at 4 weeks; this finding is consistent with our previous finding (Tandon et al 1989a) and those of Holsboer-Trachsler et al (1987). Conversely, persistent DST nonsuppression was associated with greater negative symptom severity at 4 weeks and poor outcome at 1 year. These findings parallel those in major depression, where normalizing baseline DST nonsuppression is associated with greater clinical improvement (Greden et al 1983; Brown and Qualls 1981; Baldessarini and Arana 1985), and persistent DST nonsuppression is associated with poor outcome (Greden et al 1983; Baldessarini and Arana 1985).

Our findings appear to be at variance with those of Coryell and Zimmerman (1989); they observed an association between baseline DST nonsuppression and good 1-year outcome in functional psychosis, including schizophrenia. The following methodological differences may have contributed to this discrepancy: (1) in their study, the baseline DST was not always performed under drug-free conditions; (2) the association between postdexamethasone cortisol levels and good 1-year outcome noted in their study was somewhat equivocal with regard to the schizophrenic group (Tandon et al 1989b), and (3) because they were studying the association of *baseline drug-free DST*, their group of initial DST nonsuppressors included both normalizing nonsuppressors (associated with better 4-week outcome in our study) and persistent DST nonsuppressors (associated with worse 1-year outcome in our study).

Pathophysiological mechanisms that may underly these phenomena are not known. Normalizing DST nonsuppression may be related to stress, cholinergic hyperactivity (Carroll et al 1980; Tandon and Greden 1989, 1990b), or some other mechanism associated with better resolution of the index psychotic episode. The association between negative symptoms and postdexamethasone cortisol at drug-free baseline, but not at 4-weeks posttreatment is consistent with this suggestion (Tandon and Greden 1989, 1990b). The greater improvement in negative symptoms with 3–4 weeks of neuroleptic treatment in the normalizing DST nonsuppressor group and other data indicating that postdexamethasone cortisol levels

are related to nonenduring negative symptoms in the acute phase would also support this hypothesis. On the other hand, persistent DST nonsuppression may be related to some other mechanism (such as enlarged ventricles, Rothschild et al 1989) that may be associated with poor outcome (Coppen et al 1983). In the present study, the persistent DST nonsuppressor group tended to have greater VBR (although this difference was not statistically significant, perhaps related to the small number of patients in this group, $n = 6$) and poor 1-year outcome. However, these explanations remain speculative.

In summary, a significant proportion of schizophrenic patients exhibit abnormal feedback regulation in the hypothalamic–pituitary–adrenal axis, as reflected in DST nonsuppression. A greater proportion of schizophrenic patients exhibit DST nonsuppression in the medication-free phase than in the neuroleptic-treated phase. There is a significant association between postdexamethasone cortisol and severity of negative symptoms, particularly in the drug-free phase. There appears to be no association between DST findings in schizophrenia and severity of depressive symptoms. Normalizing DST nonsuppression appears to be associated with greater clinical improvement with neuroleptic treatment. Persistent DST nonsuppression appears to be associated with worse outcome. While distinct mechanisms may underlie these phenomena, the pathophysiological bases of DST nonsuppression in schizophrenia remain unclear. Future studies should take medication status and phase of illness into consideration, as these appear to be important confounding variables.

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