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The dexamethasone suppression test in schizophrenia

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ABSTRACT

Background. Cortisol non-suppression following the dexamethasone suppression test (DST) has been found to a variable extent in schizophrenia. The aetiology is unclear but may be related to depression or negative symptoms.

Methods. The DST was administered to 64 patients with DSM-IV schizophrenia. All patients were screened for DSM-IV major depression and rated on the Hamilton Rating Scale for Depression (HRSD), Scale for Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale (BPRS).

Results. DSM-IV criteria for major depression was fulfilled by 36% of the patients and 42% of patients had a history of parasuicide. Four patients had undetectable levels of dexamethasone and were excluded from the endocrine analyses. Only one remaining patient had a cortisol level above the cut-off point (> 138 nmol/l), indicating escape from dexamethasone suppression. The post-dexamethasone cortisol level correlated significantly with HRSD and BPRS scores but not with the SANS. The SANS and HRSD scores were not correlated, but they were independently correlated with the BPRS score.

Conclusions. In contrast to some other work, rates of dexamethasone non-suppression were very low; together with the high rates of depression, this suggests that depression in schizophrenia may have a different neuroendocrine profile from major depressive disorders. Failure to measure dexamethasone levels can be misleading.

INTRODUCTION

Non-suppression of cortisol following the dexamethasone suppression test (DST) was considered by Carroll *et al.* (1981) to be a specific marker for major depression. Subsequent investigators have since reported that DST non-suppression is also frequently found in schizophrenia (Sharma *et al.* 1988; Yeragani, 1990). A meta-analysis of 26 studies performed by Sharma *et al.* (1988) reported that 19% of patients with schizophrenia failed to suppress cortisol following dexamethasone administration compared with 51% of patients with psychotic depression and 7% of normal controls.

The pathophysiology of hypercortisolaemia in schizophrenia remains unclear. Following Carroll's work, some investigators have suggested that concurrent depression is the major determinant of DST non-suppression (Addington & Addington, 1990). Depression affects approximately a third of patients with schizophrenia (Roy, 1981) and suicide accounts for 10% of deaths in this population (Miles, 1977). Some studies reporting higher rates of non-suppression in depressed schizophrenic patients are methodologically flawed in that operational criteria for depression were not used, negative symptoms were not measured and sample sizes were small (Munro *et al.* 1984; Sawyer & Jeffries, 1984). Addington & Addington (1990) did assess negative symptoms, used operational criteria for diagnosis, and reported an association between major depressive illness and non-suppression.

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However, their sample had been recently admitted to hospital and this is associated with high rates of non-suppression (Baumgartner *et al*. 1985). Yet other investigators have found no differences in the rate of non-suppression between depressed and non-depressed schizophrenics when depression is measured using the Hamilton Rating Scale for Depression (HRSD) (Whiteford *et al*. 1988; Minas *et al*. 1990; Yeragani, 1990).

The possibility that non-suppression is associated with negative symptoms of schizophrenia has also been studied. These studies also yielded discrepant results. Coppen *et al*. (1983) reported that DST non-suppression was associated with negative symptoms. In a later study (Saffer *et al*. 1985), the same investigators found that a higher proportion of patients with Crow's Type II schizophrenia had abnormal DST results; but neither study measured depression. Altamura *et al*. (1989) also reported higher rates of non-suppression in patients with higher scores on the Scale for Assessment of Negative Symptoms (SANS) but again they did not measure depression. McGauley *et al*. (1989) found that the mean post-dexamethasone cortisol (PDC) was correlated with the SANS score while depression, as rated by the HRSD, was not. Yet other investigators have been unable to demonstrate an association between the SANS score and non-suppression (Whiteford *et al*. 1988; Addington & Addington, 1990; Minas *et al*. 1990). Garyfallos *et al*. (1993) measured negative symptoms using an anergia subscale (items 3, 13, 16 and 18) of the Brief Psychiatric Rating Scale (BPRS), as well as the SANS and were still unable to find an association with non-suppression.

Interpretation of non-suppression in schizophrenia is further complicated by the possibility that, in contrast to positive symptoms of schizophrenia, measures of negative symptoms and depression may not be mutually exclusive (Andreasen, 1982). Addington & Addington (1990) found that the HRSD score correlated with the negative symptoms score. Kulhara *et al*. (1989) found significant relationships between negative symptoms and depressive syndromes. However, other investigators have reported that depression and negative symptoms can be measured independently (Barnes *et al*. 1989; Newcomer *et al*. 1990).

Increasing age, particularly over 55 years, is associated with increasing rates of non-suppression in depression (Davis *et al*. 1984; Sharma *et al*. 1988) although not in all studies (Carroll *et al*. 1981; Yeragani, 1990). This may explain the higher rates of non-suppression where the patients have been described as chronic schizophrenia with negative symptoms, but are in fact an older population (Coppen *et al*. 1983; Saffer *et al*. 1985).

In summary, the pathophysiology of DST non-suppression in schizophrenia remains unclear. DST non-suppression can only be meaningfully studied using strict operational criteria for both schizophrenia and depression, controlling for acute stress by sampling a stable population, assessing compliance with the DST, and excluding patients who may be false positives (American Psychiatric Association Task Force, 1987). This study aims: (*i*) to test the hypothesis that DST non-suppression in patients with DSM-IV schizophrenia is associated with concurrent depression rather than with negative symptoms; (*ii*) to examine whether DST non-suppression is associated with severity of illness; (*iii*) to examine whether serum dexamethasone levels are associated with post-dexamethasone cortisol.

METHOD

Sample

Sixty-four patients fulfilling DSM-IV criteria for schizophrenia were selected from both in-patient and out-patient populations with a clinical diagnosis of schizophrenia at the Maudsley Hospital. Out-patients were recruited from Depot and Clozapine Clinics. All in-patients recruited had been admitted for at least 1 week. Patients with a substance abuse disorder, acute or chronic medical condition known to be associated with positive DST, such as pneumonia and diabetes mellitus, and age greater than 65 years, were excluded.

Measurements

Sociodemographic and clinical details were recorded: patient's age, sex, hospital status (in-patient or out-patient) and current psychotropic medication. All patients were assessed for DSM-IV major depression (American Psychiatric Association, 1994) and were also rated using the

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HRSD (Hamilton, 1967). The SANS was used to assess negative symptoms. This scale has five subscales: affective flattening, alogia, avolition–apathy, anhedonia–asociality and attentional impairment. As suggested by Andreasen (1982), the global score for each subscale (items 8, 13, 17, 22 and 25) is considered the most significant measure of that subscale and the sum of the five global rating scores represents the total severity of negative symptoms. Severity of illness was assessed on the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962). Past history of suicide attempt was recorded as present on direct questioning and confirmed by case-note review.

The dexamethasone suppression test

The DST was administered according to the procedure described by Carroll *et al*. (1981). The patients took an oral dose of 1 mg dexamethasone at 22.00 h and blood samples were taken at 16.00 h the following day. For in-patients, dexamethasone was prescribed on the regular drug chart and administration by nursing staff was confirmed by signature. All out-patients were contacted by telephone at 22.00 h by one of the researchers to check that they had taken the dexamethasone tablets. Blood was centrifuged and serum removed and stored in a −80 °C freezer within 1 h of being drawn. Plasma cortisol levels were determined using two different commercial kits: a fluorescent polarization immunoassay kit on a TDx Abbott machine (Abbott Diagnostics, Maidenhead, UK) and an ELISA immunoassay kit using a Boehinger ES-700 machine (Boehinger, Mannheim, Germany). Cortisol levels measured by the Abbott kit was used for the endocrine analyses. The sensitivity of the Abbott assay was 13 nmol/l. A post-dexamethasone cortisol (PDC) level of > 138 nm/l was defined as dexamethasone non-suppression. Compliance with the ingestion of the dexamethasone tablets was confirmed by measuring dexamethasone levels on the 16.00 h blood sample. Dexamethasone was measured using radio-immunoassay after ether extraction. The lowest detectable concentration of dexamethasone was 1 nmol/l. In order to exclude possible non-compliance, patients whose dexamethasone concentration was below this level were excluded from the statistical analyses involving endocrine variables. The cross-reactivity of dexamethasone with cortisol was 0·6%. The researchers were blind to assay results until all independent ratings had been completed.

Statistical analysis

The data were analysed using the computerized statistical package, SPSS (Windows 6.1 version). Results were expressed as the mean ± standard deviation. Measures of association were performed using Student's *t* tests, chi-square analyses (with degrees of freedom) and Pearson's product moment correlation coefficient, with 95% confidence intervals (CI) of the differences in proportions (%) or means, as appropriate.

RESULTS

Sixty-four patients were recruited: 52 males and 12 females. The mean age was 37·5 ± 10 years. All patients had DSM-IV diagnosis of paranoid schizophrenia. Twenty-three patients fulfilled DSM-IV criteria for major depression (36%) and 27 patients gave a history of parasuicide (42%). A history of parasuicide was significantly more common in patients with DSM-IV depression ($\chi 2(1) = 5{\cdot}14$, $P = 0{\cdot}023$, 95% CI 4·6 to 53·7).

The mean dexamethasone level was 4·72 ± 2·42 nmol/l. Four patients had dexamethasone levels < 1 nmol/l and these patients were excluded from further endocrine analysis: two of these patients had cortisol levels greater than 138 nmol/l. There was no significant correlation between PDC and dexamethasone levels ($r = -0{\cdot}14$, $P = 0{\cdot}295$).

Of the remaining sample ($N = 60$), only one patient was a definite DST non-suppressor (1·7%). Dexamethasone nonsuppression was not associated with DSM-IV depression ($\chi 2(1) = 1{\cdot}89$, $P = 0{\cdot}169$, 95% CI −4 to 13·9). An analysis including the four patients with undetectable dexamethasone levels gave a significant result ($\chi 2(1) = 5{\cdot}61$, $P = 0{\cdot}018$, 95% CI −0·7 to 26·8). A history of parasuicide was not associated with non-suppression ($\chi 2(1) = 1{\cdot}42$, $P = 0{\cdot}233$, 95% CI −3·7 to 11·7). Female sex was associated with DST non-suppression ($\chi 2(1) = 4{\cdot}5$, $P = 0{\cdot}033$, 95% CI −7·9 to 26). The other main findings are illustrated in Tables 1 and 2, PDC levels correlated with the HRDS score ($r = 0{\cdot}26$, $P = 0{\cdot}048$) and the BPRS

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Table 1. *Comparison of rating scales* (*means*) *with depression status and history of suicide attempt*

	DSM-IV depression		History of suicide attempt	
	D $N = 23$	ND $N = 41$	Present $N = 27$	Not present $N = 37$
HRSD	19·7	5·4*	14·7	7·5*
BPRS	31·3	21·3*	28·1	22·5*
SANS	11·5	9·4	12·1	8·7*
Anergia subscale of BPRS	5·8	4·6	5·5	4·7

D, depressed; ND, not depressed.
* Difference between groups significant at $P < 0{\cdot}05$, calculated with independent Student's t test.

Table 2. *Correlation coefficients between cortisol and clinical rating scales* (*HRSD*, *BPRS*, *global SANS*, *subscales of SANS and anergia subscale of BPRS*)

	HRSD	BPRS	SANS	Anergia
Cortisol (PDC) nmol/l	0·26*	0·27*	0·14	0·24
Anergia	0·23	0·56*	0·58*	—
SANS	0·19	0·35*	—	—
SANS8	0·12	0·39	—	—
SANS13	−0·60	0·24	—	—
SANS17	0·10	0·27	—	—
SANS22	0·18	0·18	—	—
SANS25	0·09	0·21	—	—
BPRS	0·58*	—	—	—

* $P < 0{\cdot}05$.

scores ($r = 0{\cdot}27$, $P = 0{\cdot}035$). PDC levels did not correlate with the global SANS ($r = 0{\cdot}14$, $P = 0{\cdot}289$) or the anergia subscale of the BPRS ($r = 0{\cdot}24$, $P = 0{\cdot}069$).

The mean BPRS score was significantly greater in depressed patients compared with non-depressed patients ($P < 0{\cdot}0001$, 95% CI 5·3 to 14·7). As expected, depressed patients also had significantly higher HRSD scores ($P < 0{\cdot}0001$, 95% CI 11·4 to 17·2). There was no significant difference in the total SANS scores between depressed and non-depressed groups ($P = 0{\cdot}214$, 95% CI −5·6 to 1·3). There was a strong positive correlation between the total SANS score and the BPRS score ($r = 0{\cdot}35$, $P = 0{\cdot}005$) but not with the HRSD score ($r = 0{\cdot}19$, $P = 0{\cdot}144$). There were no significant associations between individual SANS subscales and HRSD scores.

A history of parasuicide was significantly associated with higher mean HRSD scores ($P = 0{\cdot}002$, 95% CI 3·0 to 11·3), BPRS scores ($P = 0{\cdot}030$, 95% CI 0·6 to 10·6) and SANS scores ($P = 0{\cdot}041$, 95% CI 0·1 to 6·7).

DISCUSSION

We found that approximately one-third of the patients with DSM-IV schizophrenia were depressed. In spite of the high rates of depression, less than 2% were non-suppressors: a rate lower than some normal populations (Sharma *et al.* 1988). Depression, when measured by operational criteria, was not associated with DST non-suppression. The cortisol was repeated in a separate laboratory using a different kit to confirm the initial unexpected result of low rates of non-suppression. The overall sensitivity of the DST protocol we used was approximately 45% (APA Task Force, 1987). It is possible that a second sample at 22.00 h on Day 2 may have improved the sensitivity by 20% but this was not implemented to avoid distress to the patients.

A history of parasuicide was associated with current depressive illness, as well as with negative symptoms and overall severity of illness. This partially agrees with the finding of Jones *et al.* (1994) who reported an association between parasuicide and the HRSD score but not with negative symptoms. They also found that a history of parasuicide correlated with DST non-suppression but we did not find such an association.

Our findings do not support the hypothesis suggested by McGauley *et al.* (1989) that hypercortisolaemia in schizophrenia is associated with negative symptoms. Some investigators hypothesize that DST non-suppression associated with negative symptoms can be explained by the structural brain abnormalities claimed to be found particularly in this type of schizophrenia, namely enlarged lateral ventricles and reduced cortical volume (Saffer *et al.* 1985; Coryell & Tsaung, 1992). However, Dewan *et al.* (1985) found no difference between suppressors and non-suppressors on a wide range of parameters, such as CT findings and neuropsychological function.

Our hypothesis that DST non-suppression is associated with depression rather than negative

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symptoms was supported when post-dexamethasone cortisol was examined as a quantitative variable. There was an association between PDC levels and depression, as measured by the HRSD, and with overall severity of illness, as measured by the BPRS, but not with negative symptoms. As has been suggested by the APA Task Force (1987), it may be of value to consider the DST as a quantitative test, as this utilizes the data more efficiently and circumvents the caution on the accuracy of PDC values dispersed around the threshold cut-off of 138 nm/l for non-suppression.

Our study also emphasizes the importance of distinguishing between negative symptoms and depression in schizophrenia. In this study these two behaviours do appear to be independent as there was no association between measures of depression and negative symptoms.

A number of confounding factors must be taken into account. First, does neuroleptic medication contribute to the low rate of non-suppression? All patients in our study were on neuroleptic medication. Carroll *et al*. (1981) and others (Arana *et al*. 1984) have stated that neuroleptic medication does not affect the DST but Tandon *et al*. (1991) reported that the correlation between cortisol and negative symptoms disappeared after 4 weeks of treatment and these findings were partially replicated by Wik *et al*. (1986).

Secondly, the gender of the patient may have alternatively explained the observed association between depression and non-suppression. An association between female sex and DST non-suppression was found but the interpretation of this estimate is limited as the 95% confidence interval was wide and crossed the null value. Previous studies have reported that gender does not influence the validity of the DST (Carroll *et al*. 1981).

Thirdly, the DST is influenced by the non-specific stress of an acute illness or recent admission (Baumgartner *et al*. 1985; Ceulemans *et al*. 1985; Holsboer-Trachsler *et al*. 1987) although some have disputed this finding (Herz *et al*. 1985; Minas *et al*. 1990). Our study attempted to eliminate the confounding effect of acute stress on the DST by recruiting from both established in-patient and out-patient populations, as the false positive rate secondary to acute illness and recent admission status decreases several weeks after admission (Wik *et al*. 1986).

Fourthly, the mean age of this sample was young and, therefore, confounding by age was restricted, unlike other studies which examined older populations (Coppen *et al*. 1983; Saffer *et al*. 1985).

Fifthly the wide variation in dexamethasone levels that has been noted by a few previous workers (Meikle, 1982; Arana *et al*. 1984; McGauley *et al*. 1989; O'Sullivan *et al*. 1997) may have affected the rate of DST non-suppression. Six per cent (four patients) of the original sample had undetectable levels of dexamethasone. Including these patients in the analysis increased the significance of the association between depression and non-suppression. Two possible explanations for undetectable dexamethasone levels are non-compliance and increased metabolism of dexamethasone. Non-compliance (which would lead to over-reporting of non-suppression) is unlikely as these four patients were in-patients and their prescription charts recorded that the dexamethasone had been administered. Alternatively, increased dexamethasone metabolism has been reported in depressed individuals (O'Sullivan *et al*. 1997). Holsboer *et al*. (1986) compared the pharmacokinetics of six DST non-suppressors and 14 DST suppressors with endogenous depression and found that the former had increased dexamethasone elimination. Under these circumstances, suppression of the hypothalamic–pituitary–adrenal axis would occur prior to sampling at 16.00 h on the second day of the DST. This raises the possibility that many studies of the DST in psychiatric populations may have unwittingly under-reported rates of non-suppression as serum dexamethasone levels are rarely recorded.

All the patients in our study were diagnosed paranoid schizophrenia. It is possible that other schizophrenia subtypes may have different rates of DST non-suppression. The evidence available for this is inconsistent; Coryell & Tsuang (1992) found that disorganized schizophrenia was more likely to be associated with non-suppression while Sharma *et al*. (1988) reported that schizophrenia subtypes could not be differentiated by the DST.

Lifestyles common in psychiatric populations such as excess caffeine intake are possibly

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associated with non-suppression (Udhe *et al.* 1985). Although we did not measure caffeine levels other investigators (Hoebsler-Taschsler *et al.* 1987) have not found an association.

The very low rates of non-suppression found in this study and the high rates of depression suggest that depression in schizophrenia may have a different neuroendocrine profile to depression in a non-schizophrenic population. For instance, 5HT function, as measured by the prolactin response to D-fenfluramine, is decreased in depression but increased in schizophrenia (Abel *et al.* 1996).

In summary, we found that depression is common in schizophrenia and correlated with a past history of suicide attempt. Nevertheless, the prevalence of DST non-suppression was extremely low. Further studies should explore the relationship between the pharmacokinetics of dexamethasone and DST non-suppression in schizophrenia. Future research should not assume that depression in schizophrenia shares a common pathophysiological pathway with uncomplicated affective illness.

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