

# DST non-suppression predicts suicide after attempted suicide

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## Abstract

Most prospective studies of HPA axis have found that non-suppressors in the dexamethasone suppression test (DST) are more likely to commit suicide during the follow-up. Attempted suicide is a strong clinical predictor of suicide. The aim of this study was to assess the predictive value of DST for suicide in a group of depressed inpatients with and without an index suicide attempt. Historical cohort of 382 psychiatric inpatients with mood disorder admitted to the department of Psychiatry at the Karolinska University Hospital between 1980 and 2000 were submitted to the DST and followed up for causes of death. During the follow-up (mean 18 years), 36 suicides (9.4%) occurred, 20 of these were non-suppressors and 16 were suppressors. There was no statistically significant difference in suicide risk between the suppressors and non-suppressors for the sample as a whole. An index suicide attempt predicted suicide. In suicide attempters with mood disorder, the non-suppressor status was significantly associated with suicide indicating that HPA axis hyperactivity is a risk factor for suicide in this group. The dexamethasone suppression test may be a useful predictor within this population.

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## 1. Introduction

Suicide is a major cause of mortality worldwide, according to WHO estimates approximately one million people die from suicide worldwide every year (WHO, 2001). Prediction of suicide risk is important for suicide prevention and inpatients with mood disorder are the obvious high-risk group with a lifetime prevalence of suicide of approximately 9% if ever hospitalized for suicidality (Bostwick and Pankratz, 2000). There is a

need for predictors among depressed inpatients to assist the clinician to focus on those most at risk. Clinical, psychological and demographic factors such as prior suicide attempt (Nordström et al., 1995), hopelessness (Beck et al., 1985), suicide intention (Harriss et al., 2005), age, gender, marital status, social and occupational functioning, and psychiatric comorbidity have all been identified as risk factors (Roy, 1983; Fawcett et al., 1990; Sokero et al., 2003). Still, the task of mental health professionals is difficult due to the many factors involved and the limited specificity of clinical predictors.

Incorporating a biological test to increase specificity and sensitivity of suicide prediction would be of clinical value if use of such a marker could enhance detection of

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high-risk patients and thereby improve clinical suicide prevention. Although the serotonin system has been the major focus of biological research on suicide (Nordström et al., 1994; Samuelsson et al., 2006), there is now substantial evidence that HPA axis abnormalities may be connected with serotonin abnormalities in the biology of suicidal behaviour (Lopez et al., 1998; Mann, 2003).

Elevated activity of the hypothalamic–pituitary–adrenal (HPA) axis is one of the most replicated biological findings in major depression. Relative to healthy control subjects, people with depression have consistently been reported to have elevated levels of cortisol in 24-h collections of plasma and urine, hypertrophy of the adrenal and pituitary glands and exaggerated cortisol response to adrenocorticotrophic hormone (ACTH) stimulation (reflecting adrenal hypertrophy) (Garlow et al., 1999). The diathesis toward HPA axis dysfunction in major depressive disorder appears associated with both a negative feedback disturbance and an increased drive by central processes (Drevets et al., 2002). Interest in cortisol functioning in psychiatric patients led to the development of the dexamethasone suppression test (DST) as a formal test of HPA function (Carroll et al., 1968).

The DST offers a clinical way to measure disturbance in the HPA axis. After its initial demonstration as a potential marker of endogenous depression (Carroll et al., 1976), the DST was extensively studied as a diagnostic tool. However, it failed to demonstrate utility as a diagnostic tool for depression, due to low sensitivity and variable specificity (American Psychiatric Association, 1987) and interest then waned.

Beginning with Bunney and Fawcett who suggested a possible association between HPA disturbance and suicide in 1965, a body of research has focused on such associations (Bunney and Fawcett, 1965). The most robust finding using dexamethasone suppression test (DST) is that suicide but not suicide attempt is associated with non-suppression on the DST (Lester, 1992).

Disturbances in the HPA system measured with DST have been associated with increased risk of suicide in depressed patients in several prospective studies. In one 15-year follow-up study by Coryell and Schlessler (2001) of 78 patients, DST non-suppression increased the likelihood of suicide 14-fold. The suicide risk was 27% compared with 3% among patients with a normal DST in this sample of mood disorder patients.

This hypothesis that an abnormal DST, which indicates a problem with the HPA or stress axis, is an indicator of heightened suicide risk has been replicated in several studies (Norman et al., 1990; Yerevanian et al., 2004). A review of 101 patients re-examined over 2 years confirmed the higher risk for suicide and higher risk for

hospitalization for suicidality in those with abnormal DST (Yerevanian et al., 2004).

However, not all studies have been able to show that non-suppressors are more likely to commit suicide (Träskman-Bendz et al., 1992). In a study of 423 mood disorder patients administered the DST from 1978 to 1981 Black et al. (2002) found that suppressors and non-suppressors did not differ significantly with respect to frequency of suicidal ideations or suicides. A recent study by Coryell et al. (2006) suggests, however, that DST results may not be a useful predictor for mood disorder outpatients or for those with no clinical evidence of suicidality.

In a recent meta-analysis Mann et al. (2005) concluded that non-suppressors have more than 4-fold increased risk of suicide compared with suppressors.

### 1.1. Aims of the study

The aim of the present study was to try to replicate the earlier finding of association between DST non-suppression and suicide and to assess the predictive value of non-suppressor status in the dexamethasone suppression test for suicide in a large group of depressed inpatients with and without history of a suicide attempt using the suicide mortality as the outcome criterion.

## 2. Methods

### 2.1. Subjects

This is a historical cohort study involving 382 psychiatric inpatients (126 men and 256 women, mean age 52 years, S.D. = 16,4) admitted to the psychiatric clinic at the Karolinska University Hospital between 1980–2000 with a DSM diagnosis of mood disorder: unipolar, major depressive disorder, single episode or recurrent, bipolar disorder, depressed or dysthymic disorder. Patients with substance abuse or psychotic disorder (schizophrenia spectrum) were excluded. Information about the index suicide attempt was registered. One hundred fourteen patients had attempted suicide just before admission.

Patients with a medical condition (or taking medication) known to interfere with the results at the time of the DST were excluded.

### 2.2. Dexamethasone test

At admission 1 mg of dexamethasone was given orally at 11:00 p.m., and plasma cortisol levels were determined from blood samples drawn the following day at 8:00 a.m., 4:00 p.m., and 11:00 p.m. The predictive

value of non-suppressor status (cortisol level 5 µg/dl or above in any sample the following day) for future completed suicide was analyzed.

All patients were followed up for the cause of death. The patients who died within the follow-up period were identified and the causes of death were obtained from Statistics Sweden, which keeps the National Swedish Cause of death register for a National Board of Health and Welfare. 36 suicides were identified during a mean follow-up time of 18 years. The subsequent analysis concerns the patients who committed suicide.

### 2.3. Data analysis

DST result and two other potential predictors of suicide: the presence of a suicide attempt during the index illness episode before admission and male sex were selected on the basis of the previously described literature review. Each potential predictor was dichotomized, and the two resulting groups were compared by using survival analysis.

The study was approved by the ethics committee of the Karolinska University Hospital.

## 3. Results

### 3.1. Patient characteristics

All analyses were based on a total of  $n=382$  cases. Of the 382 patients with DST results, 167 (44%) had an 8:00 a.m., 4:00 p.m., and/or 11 p.m. postdexamethasone cortisol level greater than 5 µg/dl and were considered non-suppressors, 215 (56%) patients were suppressors.

The DST non-suppressor and DST suppressor subjects did not differ in gender distribution (68% respective 66% females).

The DST non-suppressor ( $n=167$ ) group was followed for a mean of 18.7 years (S.D.=6) with a median of 20.1 years, range=5–25. The DST suppressor ( $n=215$ ) group was followed for a mean of 17.2 years (S.D.=6) with a median of 18.4 years and a range of 5–25.

Two groups differed in mean age. The DST non-suppressors had a mean age of 55 years (S.D. 15.5); the DST suppressor group had a mean age of 50 years (S.D. 16.8),  $P=0.0014$ .

114 patients (30%) had made a suicide attempt preceding admission, they had a mean age of 47 years (S.D.=17) compared with patients without index suicide attempt, mean age 54 (S.D.=16),  $P=0.0005$ .

### 3.2. Suicide risk and the dexamethasone suppression test

Thirty-six suicides (9.4%) occurred during the follow-up time: 22 women (8.6%) and 14 men (11.1%). Twenty of the suicide victims were non-suppressors (12 women and 8 men) and 16 suppressors (10 women and 6 men) in DST status. Outcome results are summarized in Table 1. The overall suicide risk among depressed inpatients with non-suppression was 12% and for suppressor groups 7.4% (N.S).

One major finding was that DST non-suppression did not distinguish between suicides and survivors in the group of depressed inpatients (N.S). The result remained non-significant even when adjusted for gender, for age and for violent versus non-violent method for completed suicide.

Table 1

Potential predictors of suicide during follow-up in 382 depressed inpatients with a baseline dexamethasone suppression test (DST) result

Potential predictor	<i>n</i>	Patients who committed suicide, <i>n</i>	Patients who committed suicide, %	Risk ratio	Analysis <i>P</i>
Male	126	14	11.1%	1.3	NS
Female	256	22	8.6%		
DST non-suppression	167	20	12%	1.6	NS
DST suppression	215	16	7.4%		
Suicide attempt in index episode	114	25	21.9%	5.3	$P<0.0001$ (Fisher's exact test, one-tailed)
No suicide attempt in index episode	265	11	4.2%		
Suicide attempt in index episode	44	16	36.4%	2.8	$P=0.0261$ (Fisher's exact test, one-tailed)
DST non-suppression					
Suicide attempt in index episode	70	9	12.9%		
DST suppression					
Index episode suicide attempt in men	13	6	46.2%	3.7	$P=0.0168$ (Fisher's exact test, one-tailed)
DST non-suppression					
Index episode suicide attempt in men	24	3	12.5%		
DST suppression					

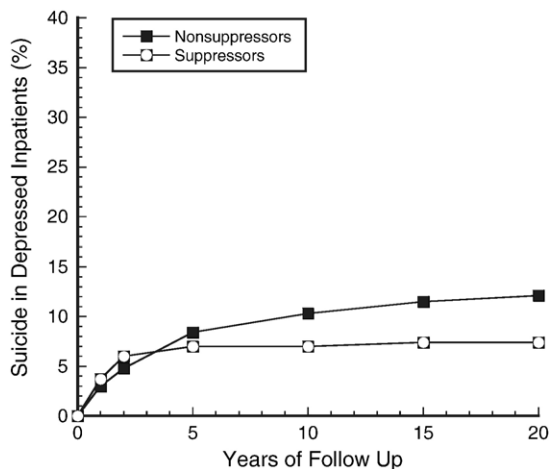


Fig. 1.

When survival time and cumulative suicide risk after DST are taken into account, the result still remains non-significant concerning the potential of DST to predict short- or long-term suicide risk in a group of psychiatric inpatients with mood disorder. Fig. 1.

In this cohort 114 patients had made a recent suicide attempt. The index episode suicide attempt before admission to the wards predicted suicide in this population ( $P < 0.0001$ ).

This variable was entered together with DST suppressor status as an independent variable in a regression analysis of the likelihood of suicide. In this model, non-suppression did not increase the likelihood of future suicide (risk ratio = 1.6,  $P = 0.64$ ). A suicide attempt in the index episode generated a risk ratio of 5.3 ( $P < 0.0001$ ).

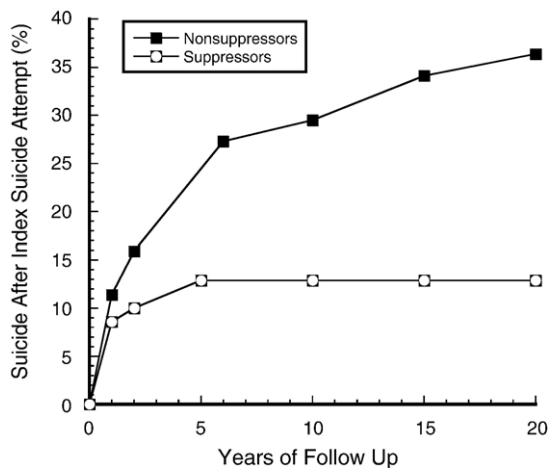


Fig. 2.

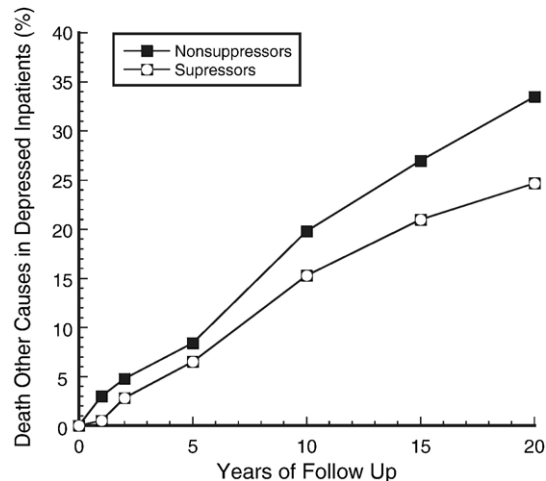


Fig. 3.

### 3.3. Suicide risk and the dexamethasone suppression test in suicide attempters

When we only included suicide attempters with mood disorder, the DST non-suppressor status predicted suicide (Fisher's exact test, one-tail  $P = 0.0261$ ) in this group. The five, ten and 20-year survival (Fisher's exact test, one-tail  $P = 0.0773$ ,  $P = 0.0457$ ,  $P = 0.0175$ , respectively) are presented in the Fig. 2. Gender specific analysis showed that the finding is significant for men (Fisher's exact test, one-tail  $P = 0.0168$ ) but not for women (Fisher's exact test, one-tail  $P = 0.1973$ ).

### 3.4. Overall mortality and dexamethasone suppression test

In this material non-suppressors had a higher total mortality compared with suppressors (Fig. 3). Non-suppressor status predicted death from causes other than suicide (Fisher's Exact Test one-tail  $P = 0.0088$ ) in the group in general. When analyzing further men and women separately the finding remained significant only for men (Fisher's Exact Test, one-tail  $P = 0.0147$ ) but not for women (Fisher's Exact Test, one-tail  $P = 0.1060$ ). Most natural causes were found, including respiratory disease, circulatory, neurological, endocrine, digestive disorders, and symptoms, signs, and ill-defined conditions. There was a predominance of circulatory and respiratory disorders as other causes of death.

## 4. Discussion

In this study of 382 hospitalised mood disorder patients with almost a 20-year follow-up 9.4% of the

patients committed suicide, confirming the suggestion that they constituted a group with a high suicide risk with a suicide mortality corresponding to lifetime prevalence rates published in the psychiatric literature (Bostwick and Pankratz, 2000).

Prospective biological studies, while producing at times divergent results, have reached some consensus in terms of a few key neurobiological systems involved in suicidal behaviour in mood disorders, including the serotonergic system and the HPA axis (Mann, 2003; Westrin and Nimeus, 2003; Mann et al., 2005). According to several studies and meta-analyses depressed patients with abnormal DST have a higher risk for suicide (Coryell and Schlessler, 1981; Lester, 1992; Coryell and Schlessler, 2001; Mann et al., 2005). In this large historical cohort of 382 mood disorder inpatients non-suppression in the dexamethasone suppression test did not increase suicide risk. In a recent meta-analysis by Mann et al. (2005), the odds ratio of suicide is estimated to be 4.5-fold greater among non-suppressors compared with suppressors. For inclusion in this DST meta-analysis, reports had to include both suppressors and non-suppressors, and to report DST results for both suicides and non-suicides. Seven of the twelve studies met these criteria (Mann et al., 2005). The total number of suicides included in this meta-analysis was 28 non-suppressors and 12 suppressors (Mann et al., 2005). In our study we analyzed 36 suicides.

We could not replicate the earlier findings of a correlation between abnormal DST and suicide in this large group of mood disorder inpatients. Compared with Coryell and Schlessler's study, which is often cited as a reference, we had almost a five times larger sample and a longer follow-up time.

Interestingly in this material the non-suppressor status predicted death from other causes than suicide for men but not for women.

The distinguishing factor that reached statistical significance was a suicide attempt in the index episode. This is in line with previous studies of suicide mortality among patients who have attempted suicide (Nordström et al., 1995) and emphasize the importance of this clinical predictor while assessing the suicide risk of psychiatric patients.

In the group of suicide attempters with mood disorder the DST non-suppression predicted future suicide while it did not in the whole group in general. Depressed patients with suicidal behaviour in their past have showed a differentially regulated HPA system compared with depressed patients without suicidal behaviour with less pathologic test outcomes (Pfennig et al., 2005). This is in line with our finding that the DST non-suppression predicted suicide in the suicide attempter group. In our

sample the non-suppression of cortisol was significantly associated with suicide in male suicide attempters with a mood disorder highlighting this group as high-risk group to focus in clinical settings (Samuelsson et al., 2006).

One hypothesis is that suicidal patients represent a distinct subgroup of depressed patients with a possibly different genetic background. Family, twin, and adoption studies imply that the overlap of genes predisposing to suicidal behaviour and affective disorders may not be complete (Mann, 2003), proposing possibility of separate genetic factors predisposing to suicidal behaviour and affective disorders. Additional pathophysiologic disturbances in suicide-prone patients could alter depression-related HPA axis hyperactivity.

To identify high-risk individuals and using biological tests in the assessment of suicide risk in this group may help to direct more resources to clinical suicide prevention. In this study the severity of illness and Axis II diagnoses were not assessed, which is a limitation.

All patients in this study were hospitalised. Given that patients with a hospitalization history, particularly when suicidal, have much elevated suicide prevalence over both psychiatric outpatients and nonpatients, the clinical decision to hospitalise appears to be a useful indicator of increased suicide risk (Bostwick and Pankratz, 2000).

The median age was higher in our material than in many referred studies. Regardless of diagnosis, patients 65 years and older have significantly higher non-suppression rates than those below age 65 (Keitner et al., 1992). Our finding that abnormal DST test did not predict suicide in an unselected group of mood disorder inpatients remained significant even when we in the data analysis excluded all patients above the age of 65. Limitations: Plasma dexamethasone levels are often necessary as the test is sensitive to steroid levels. Pregnancy, systemic disease inducing weight loss or requiring endocrine treatment, and starvation are conditions that may affect the test result and must be considered in assessing the test data (Fink, 2005). Moreover, any biological assessment needs to account for medication effects, as well as effects of substance and alcohol use, age and gender.

It has been recently suggested that the DST or the dexamethasone–corticotropin releasing hormone test DEX/CRH test, a modification of the DST, may have use as a marker for some aspects of depressive illness for example to predict the risk for relapse (Appelhof et al., 2006) or as a test for treatment effect of ECT to show that the abnormal HPA functioning in patients with major depression resolves with adequate treatment (Yuuki et al., 2005).

While there is increasing data that the DST is a useful index of the presence and severity of mood disorder and the change with treatment (Fink, 2005), our finding does not support the consensus of the potential usefulness of the dexamethasone suppression test as a biological suicide predictor in unselected groups of mood disorder patients. However patients who have attempted suicide might be a subgroup where this biological test could be useful as a complement in the assessment of suicide risk. The dexamethasone suppression test may have a place after prescreening with clinical and neuropsychological assessments. The clinical question that can be raised is whether it is clinically prudent (or warranted) to conduct routine DSTs on patients with depression because of the increased risk of suicide.

Variables such as gender, history of suicide attempts, and DST non-suppression can be conceptualized as trait-like vulnerability factors that increase the risk of eventual suicide, and therefore clinicians need to be aware of their historical presence in order to be appropriately vigilant to the increased risk. Given the multi-determined nature of suicidal behaviour, predicting risk for completed suicide requires a multidimensional approach. It is likely that future biological predictors will involve combination of the use of endophenotypes such as the neuroendocrinologic characterizations of patients using the dexamethasone test, brain receptor scans and haplotype analysis of candidate genes. Refining biological predictors and integrating them with clinical predictors is an important future challenge in the clinical psychiatric research.

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