Published in final edited form as:

J Nerv Ment Dis. 2009 June ; 197(6): 395–400. doi:10.1097/NMD.0b013e3181a775cf.

Does the Dexamethasone Suppression Test Reliably Discriminate Between Psychotic and Nonpsychotic Major Depression? An Exploratory Analysis of Potential Confounds

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Abstract

Previous research has shown that psychotic major depression (PMD) is often associated with higher rates of nonsuppression on the dexamethasone suppression test (DST) compared with nonpsychotic major depression (NMD), suggesting the potential importance of cortisol hypersecretion in the psychotic subtype of the disorder. However, these patient groups also are known to differ from one another on a variety of other clinical variables, and there are numerous factors independent of diagnostic status known to affect the DST. Thus, we investigated possible confounds that could help account for the apparent DST abnormalities in PMD sometimes reported in past research. Hospitalized patients with PMD ($n = 11$) and NMD ($n = 58$) were compared on the DST and other clinical variables. As expected, PMD patients showed significantly higher rates of DST nonsuppression (55% vs 24%; $p = .04$). However, PMD patients also had significantly higher levels of anxiety severity ($p = .01$). The higher rates of nonsuppression in the PMD group were attenuated when these patients were compared with a subsample of NMD patients matched on anxiety severity (55% vs 55%). Implications for future research on biological markers of PMD are discussed.

Keywords

depression; psychosis; anxiety; hypothalamic-pituitary-adrenal axis; dexamethasone suppression test

The historical problems with the concepts of “endogenous” and melancholic depression are well known, and continue to generate considerable controversy in the literature and disagreement among researchers (Farmer & McGuffin, 1989; Kendell, 1976; Shorter, 2007; Zimmerman & Spitzer, 1989). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been hypothesized to be a biological marker that may help distinguish depression subtypes. One procedure for investigating HPA metabolism is the dexamethasone suppression test (DST), a measure of cortisol hypersecretion (Carroll et al, 1981). The DST was originally used to diagnose Cushing’s syndrome, but has become the most studied biological marker for major depression (Sher, 2006). The DST was quickly adopted among researchers and even clinicians in the 1980s after studies suggested that it could reliably discriminate among endogenous/melancholic/delusional/psychotic forms of depression, which were thought to have a clearer biological component, and reactive/neurotic/nonmelancholic forms of depression, which were assumed to be more environmentally determined (Fink, 2005). Although these dichotomous nature-nurture distinctions have

largely fallen out of favor in modern clinical psychiatry, being supplanted by a more integrated biopsychosocial model, interest in melancholic depression remains strong (Fink & Taylor, 2007), research on psychotic depression has increased in recent years (Meyers, 2006), and the attempt to identify biomarkers of depression is witnessing a resurgence (Mossner et al, 2007).

After decades of research on this topic, Nelson and Davis (1997) published what is widely cited as the definitive meta-analysis of studies comparing DST findings in psychotic versus nonpsychotic depression and melancholic versus nonmelancholic depression. They failed to find reliable differences among patients based on the melancholic-nonmelancholic distinction. In contrast, patients with psychotic depression had modestly higher rates of DST nonsuppression compared to those with nonpsychotic depression (64% vs 41%). Nelson and Davis interpreted these results as suggesting greater hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and thus a potentially different pathophysiology in the psychotic subtype. This finding emerged from the pooled data even though the majority of the original studies analyzed failed to find statistically significant between-group differences. Low statistical power was certainly an issue in some of these early studies, but other factors may also have affected the results. For example, 57% of the studies included in the meta-analysis failed to properly control for group differences on clinical variables other than diagnosis. Those studies that did report attempts to control for potential confounds often failed to do so systematically or by using proper statistical techniques.

There are many factors known to affect HPA metabolism and the DST irrespective of major depression diagnosis, including weight loss/malnutrition, sleep and circadian rhythm, general “stress,” dementia, diabetes mellitus, epilepsy, hypertension, obesity, pregnancy, alcohol consumption, infection, age, fever, as well as medications such as steroids and anticonvulsants (Brown et al, 1988; Keitner et al, 1989; Mullen et al, 1986; Rosse et al, 2000; Stangl et al, 1986). Furthermore, previous studies have suggested a diverse array of clinical differences among patients with psychotic (PMD) versus nonpsychotic (NMD) major depression in general. For example, research has shown that patients with PMD tend to have greater depression severity, dysfunctional cognitions, psychomotor disturbance, suicidality, anxiety, somatic complaints, personality dysfunction, and cognitive impairment (Gaudiano et al, in press-a; Gaudiano & Miller, 2007; Keller et al, 2007; Rothschild, 2003). Patients with PMD also tend to have longer depressive episodes, higher relapse rates and levels of functional impairment, as well as a poorer response to medication or psychotherapy (Gaudiano et al, 2005; Gaudiano et al, in press-a; Rothschild, 1996; Schatzberg, 2003). Thus, it is apparent that any attempts to investigate DST abnormalities between PMD and NMD would be fraught with difficulties given the variety of other ways in which these patients also appear to differ from one another.

Previous research showing differences in DST response rates are often cited in support of the notion that there is fundamental dissimilarity between PMD and NMD that supports the reclassification of PMD as a unique and distinct psychiatric syndrome, instead of merely a subtype of major depression as it is currently defined in the DSM (Schatzberg & Rothschild, 1992). An alternate conceptualization of the disorder views it as falling along a continuum between mood and psychotic disorders, and argues that the syndrome is associated with greater illness severity and multiple, semi-overlapping comorbid problems (Brown et al, 1988; Verdoux & van Os, 2002). This latter conceptualization, then, implies that the categorical distinction between PMD and NMD patients is less important than the specific clinical features of these patients, which may or may not implicate their most salient clinical features—namely, psychotic symptoms during depressive episodes.

Given the renewed interest in the treatment of PMD in recent years (e.g., the STOP-PD clinical trial of combined pharmacotherapy, Meyers et al, 2006), and increasing recognition of its negative long-term prognosis (Vythilingam et al, 2003), we believe that the DST issue is again emerging as an important topic that should be reexamined using more refined methodologies. In fact, reports continue to appear in the literature employing the classic DST in studies with PMD patients (e.g., Contreras et al, 2007; Vythilingam et al, 2003). When discussing the results of their meta-analysis, Nelson and Davis (1997) largely dismissed the idea that there was a “file drawer problem” with DST studies of PMD. Thus, we were interested in examining never before published DST data comparing severely depressed psychotic and nonpsychotic inpatients taking part in a larger clinical trial, which was conducted during the height of the popularity of the DST. We examined differences between PMD and NMD patients in the sample. Furthermore, we compared and contrasted group DST nonsuppression rates using an unmatched versus matched sample of NMD patients in an attempt to control for clinical variables other than the diagnosis itself that could affect the DST. We hypothesized that factors other than depression or psychosis, such as anxiety severity, would differ between the groups, and that matching NMD and PMD patients on relevant clinical variables would produce more comparable rates of DST nonsuppression regardless of diagnostic status.

Method

Sample

A total of 84 depressed patients (73 NMD and 11 PMD) completed DST assessment after admission to a psychiatric inpatient unit and enrollment in a larger clinical trial of combined treatment with pharmacotherapy plus psychotherapy for major depression (Miller et al, 1989; Miller et al, 1988). Only baseline data are reported here. Subject recruitment took place from 1981 to 1986. Subjects were included if they gave informed consent; met DSM-III criteria for major depression with or without psychotic features according to the Diagnostic Interview Schedule (DIS, Robins et al, 1981); were free from severe general medical conditions; were not taking medications known to affect dexamethasone metabolism (e.g., anticonvulsants, steroids); and did not meet criteria for schizophrenia, bipolar disorder, or a neurological condition. The DSM-III (APA, 1980) defined psychotic features during a major depressive episode using the same criteria as those found in the current version of the DSM-IV-TR (APA, 2004). Thus, patients with delusions and/or hallucinations during the current depressive episode were diagnosed with PMD. We no longer have detailed data on the specific psychotic symptoms of patients in the sample.

DST Procedure

Patients received 1 mg dexamethasone orally at midnight and blood samples were drawn at 4:00 p.m. the next day. Serum cortisol concentration was determined by solid phase radioimmunoassay (New England Nuclear, Boston, USA). The assay sensitivity was 0.3 mg % and coefficients of variation were less than 8%. Following the recommendations of Carroll et al (1981), a serum cortisol concentration greater than 5 µg/dl (138 nmol/L) signified nonsuppression. All of the original studies in the Nelson and Davis (1997) meta-analysis used the > 5 µg/dl serum cortisol concentration criterion (or some slight variation thereof; e.g., 5 µg/dl) and 79% used a 4:00 p.m. assessment point to define nonsuppression. Research suggests that afternoon assessment is most likely to show DST differences (Burke et al, 2005). During the course of the study the project staff were blind to DST results. Tests were completed within the first week of admission.

Symptom Assessments

The 17-item version of the *Modified Hamilton Rating Scale for Depression* (MHRSD, Miller et al, 1985) was used to assess depression severity. The MHRSD is an adapted form of the original Hamilton Rating Scale for Depression (Hamilton, 1960) that includes standardized question prompts to increase reliability. The MHRSD has good interrater reliability and convergent validity. Interrater reliability conducted by blind assessors on the MHRSD was $r = .93$.

The *Beck Depression Inventory* (BDI, Beck et al, 1961) is a 21-item self-report instrument that assesses symptoms of depression. The BDI is widely used and numerous studies have demonstrated its reliability and validity in clinical and nonclinical samples (Beck et al, 1988).

The *Symptom Checklist-90* (SCL-90, Derogatis et al, 1973) is a self-report measure that assesses a range of psychiatric symptoms. Research has demonstrated the validity and reliability of the measure in inpatient samples (Buchanan et al, 1997; Derogatis & Savitz, 2000). The scale contains several factor-derived symptom subscales. In the current study, analyses were limited to the Depression, Anxiety, and Psychoticism Subscales because of their theoretical relevance to the current investigation and in an effort to reduce the number of analyses conducted. The SCL-90 subscales have evidence of reliability and validity (Derogatis, 1994). For example, Wetzler and Marlowe (1993) found that psychotic patients exhibited higher scores on the Psychoticism Subscale relative to the Depression or Anxiety Subscales when compared with psychiatric controls. In contrast, depressed patients were found to have higher scores on the Depression Subscale relative to the Anxiety or Psychoticism Subscales. To reduce heterogeneity and obtain a “purer” sample, NMD patients who had a significant score on the Psychoticism Subscale (< 1.50) were removed from the following analyses ($n = 13$).

Statistical Analyses

First, baseline differences between the groups on demographic and clinical variables were analyzed using nonparametric Wilcoxon rank-sum tests due to uneven group sizes. These analyses were supplemented by effect size analyses (small = .20, medium = .50, large = .80, Cohen, 1988) and odds ratios (Bland & Altman, 2000) to describe the magnitude of effects. Also, rates of DST nonsuppression between the groups were investigated using chi square tests. Finally, we created a subsample of NMD patients matched on any confounding variables using the “nearest available” pair-matching procedure described by Rubin (1973). This matched group of NMD patients was then compared again with the PMD patients on their DST nonsuppression rates.

Results

Preliminary Analyses

First, we explored potential baseline differences among NMD ($n = 58$) and PMD ($n = 11$) patients (see Table 1 for descriptive and inferential statistics). As expected, PMD patients exhibited significantly higher SCL-90 Psychoticism Subscale scores ($p < .001$). In addition, PMD patients had significantly higher scores on the SCL-90 Anxiety Subscale ($p = .01$). Both groups had similar rates of comorbid anxiety disorder diagnoses based on the DIS. Nonsignificant differences were found for current depression severity (BDI, MHRSD, SCL-90 Depression Subscale); although the direction of these effects suggested slightly greater depression severity in the PMD patients as expected. Mean cortisol levels and demographic characteristics were similar between groups, which is consistent with many past DST studies. These results suggested that patients were comparable on most variables,

which was consistent with the fact that all patients were currently hospitalized due to acute illness.

DST Nonsuppression Rates

First, we examined the rates of nonsuppression between groups using the entire sample. Defining DST nonsuppression as a plasma cortisol concentration $> 5 \mu\text{g/dl}$, the difference between the groups was statistically significant ($\chi^2 = 4.15$, $df = 1$, $p = .042$). The magnitude of the difference between the PMD (54.5%) and NMD (24.1%) groups appeared clinically significant (OR = 3.8, 95% CI = 1.0–14.3), and was consistent with that found in the Nelson and Davis (1997) meta-analysis (64% vs. 41%).

Matched Comparisons

Based on previous analyses, NMD patients were matched in a 1:1 ratio with PMD patients according to their SCL-90 Anxiety Subscale scores. DST cortisol values were not matched and thus left to vary freely. After matching, the groups were much more comparable on anxiety severity (NMD Group: $n = 11$, $M = 2.33$, $SD = .60$; PMD Group: $n = 11$, $M = 2.43$, $SD = .73$; $Z = .53$, $p = .61$, $d = .15$), but remained highly significantly different on psychosis severity (NMD Group: $n = 11$, $M = .75$, $SD = .37$; PMD Group: $n = 11$, $M = 1.72$, $SD = .62$; $Z = 3.40$, $p < .001$, $d = 1.90$). The matched groups were both 90% female and remained similar in age ($Z = .79$, $p = .44$) and education ($\chi^2 = 1.53$, $p = .22$). Contrary to previous analysis using the nonmatched NMD comparison group, the matched NMD sample showed equal rates of nonsuppression (PMD group = 54.5%, NMD group = 54.5%, $\chi^2 = 0$, $df = 1$, $p = 1.0$). See Figure 1 for group comparisons of DST nonsuppression rates using the matched versus unmatched samples.

Discussion

The difference in DST nonsuppression rates between the PMD and NMD groups was statistically significant, and was of a magnitude (55% vs 24%, respectively) similar to that reported in the previous literature suggesting higher nonsuppression in the PMD group. Anxiety severity also was significantly higher in PMD compared with NMD patients at baseline. Previous research shows a relationship between DST nonsuppression and general anxiety and “stress” (Calloway et al, 1984; Kocsis et al, 1985; Mellsop et al, 1985). The relationship between the DST and anxiety may be particularly relevant in DST studies of PMD, as these patients tend to experience greater anxiety severity in general and often more anxiety disorder comorbidity compared with NMD patients (Charney & Nelson, 1981; Gaudiano et al, in press-a; Lattuada et al, 1999). Furthermore, psychomotor agitation, which is often associated with anxiety, has been found to distinguish patients with PMD versus NMD (Gaudiano et al, in press-b; Parker et al, 1995).

DST nonsuppression differences were completely attenuated (55% vs. 55%) when analyses were rerun using a subsample of NMD patients matched on anxiety severity. In other words, no differences in DST response rates were evident after we better isolated psychosis, which is the primary criterion required for the diagnosis of PMD versus NMD. It also should be noted that overall rates of nonsuppression *within* the NMD group increased using the matched NMD subsample (27% vs 55%), suggesting that DST response was more a function of certain clinical characteristics of these patients, and therefore at least partially independent of diagnostic status itself.

DST research on patients with primary anxiety disorders has produced inconsistent findings that typically have depended on the specific anxiety disorder studied (Ehlert et al, 2001). However, emerging evidence suggests that depression and anxiety *comorbidity* may be a

key factor in HPA axis dysregulation in mood disorders. For example, Heim et al. (2000) found that women with major depression and a childhood history of abuse showed greater adrenocorticotrophic hormone (ACTH) and cortisol levels in response to a psychosocial laboratory stressor compared with controls, particularly if they exhibited current depression and anxiety symptoms. Similarly, Young et al. (2004) found that adults diagnosed with major depression and comorbid anxiety disorders showed significantly greater ACTH and a trend toward greater cortisol levels in response to a psychosocial stress test compared with those with “pure” major depression or an anxiety disorder without major depression. Based on these findings, Young and colleagues proposed that: “Individuals with comorbid anxiety and depression might have increased activity in both noradrenergic (anxiety) and CRH [corticotropin-releasing hormone] systems (depression) and thus might show greater reactivity of the HPA axis than individuals with hyperactivity of the CRH system alone” (p. 118). The current study extended this line of research into the study of anxiety severity in depressed patients, and the HPA axis negative feedback loop activated by the DST.

The typical approach in previous DST studies comparing PMD and NMD patients has been to test for significant differences between groups on baseline demographic and clinical variables. But this strategy may be inadequate for controlling for potential DST confounds, given that the results will be more a function of sample size and statistical power than absolute differences among patients. Matching may be a useful method for comparing PMD and NMD groups on the DST even when group differences on other variables are not substantial. Some past DST studies also have utilized matching successfully (Keitner et al, 1989; Norman et al, 1990; Tiller et al, 1988), although not to our knowledge in PMD samples. It is important to note that less than half of the studies included in the Nelson and Davis (1997) meta-analysis even attempted to account for baseline clinical differences between groups when examining DST nonsuppression rates.

Some have argued that the DST should be considered a variable of primary importance relative to other factors in PMD (Schatzberg et al, 1983). Our findings suggest caution when interpreting DST differences between PMD and NMD as either necessary or sufficient evidence that these disorders are distinct diagnostic entities with unique neuroendocrine pathophysiologies. It is yet to be clearly established that hypercortisolemia has a direct role in the pathogenesis of DSM-defined major depressive disorder, or psychotic major depression more specifically, versus being a nonspecific factor related to a variety of stress-related conditions (Duval et al, 2000; Ehler et al, 2001; van Praag, 2000). Of course, we do not intend to discount the potential utility of further research on the DST in PMD patients. Such research would likely prove useful for increasing our understanding of the nature of the disorder, and lead to refinements in its diagnosis and treatment. Thus, researchers should be encouraged to continue to explore these biological measures like the DST, but to do so carefully, with high methodological and statistical rigor, and with the appropriate caveats offered to provide a proper context to findings, as originally recommended by Carroll (1985).

Even though studies continue to use the classic DST in investigations of PMD, it also should be noted that newer methods of examining HPA axis activity have emerged in recent years. These newer methods may confer certain advantages over the known limitations of the DST. Watson et al. (2006) recently reported that the dexamethasone suppression/corticotrophin-releasing-hormone (dex/CRH) test (which involves administration of the DST and an additional CRH challenge test) had similar sensitivity but greater specificity (71.4% vs 47.6%) than the standard DST in differentiating healthy controls from a mixed sample of mood disorders patients. Such investigations have produced a great deal of early enthusiasm about the dex/CRH test by some researchers (e.g., Sher, 2006). The dex/CRH test may prove superior to the original DST on certain parameters, but similar problems with inadequately

controlling for known confounds can be found in the dex/CRH literature to date. Thus, we would recommend caution until results can be independently replicated using higher degrees of methodological rigor in these studies.

The incremental validity of the DST and related procedures also requires careful evaluation. Haynes and Lench (2003) note that incremental validity addresses the following psychometric criteria: “does the new measure (a) predict the phenomenon more validly or accurately than other measures, (b) contribute meaningfully to predictive efficacy when added to already-existing or more readily obtaining measures, and (c) cost less than other measures?” (p. 456). Unfortunately, these issues have yet to be sufficiently addressed in the literature on biological markers of psychopathology such as the DST.

Several limitations exist in the current study that should be given consideration. The small sample of PMD patients in our study requires caution when attempting to generalize results to the larger population of patients with this diagnosis. Uneven sample sizes could have affected our statistical analyses. However, we chose to use nonparametric tests to lessen this concern. The particular characteristics of our sample also should be considered. For example, there was a possible selection bias due to recruitment of patients into a larger clinical trial. In addition, the sample had limited racial/ethnic and male gender representation, so caution should be taken when attempting to generalize to these specific subgroups. Furthermore, our measures of psychosis and anxiety severity were self-report, and it would have been useful to examine interviewer-rated measures of these variables as well. We should point out that self-reported psychosis severity was significantly higher in the PMD group as expected, suggesting the validity from this measure in reference to the interviewer-rated diagnoses. In addition, results did not differ when comparing self-report versus interviewer-rated measures of depression severity. Although the original study excluded patients who received medications known to affect the DST and HPA metabolism, a complete list of the prescribed medications for each individual was not available. Finally, when using a matching design, it is always possible that an unmeasured variable could be affecting the results. Data were not available for exploring other potential DST confounds (e.g., weight loss), and such factors need to be carefully examined in future research. Unfortunately, similar limitations can be found in previous published studies on the DST. Despite these issues, we would point out that our study would have met the criteria for inclusion in the original Nelson and Davis (1997) meta-analysis.

Brown et al. (1988) reached similar conclusions after their examination of potential confounds in the DST, and we believe that our results are consistent with their original interpretation: “The results of the present study suggest that the DST should not be used as a ‘biological marker’ for any depressive subtype....Delusional depressives may show such adrenocortical abnormalities partly due to the effects of agitation, severity of depression, and distress. These factors interact and coexist frequently, making it difficult to tease apart the contributions of each to disturbed adrenocortical function” (pp. 175–176). We hope that our analysis will encourage others to reexamine this issue with a greater effort toward accounting for potentially confounding variables in DST studies of PMD, especially as they proceed with investigations of newer techniques for assessing possible HPA axis dysfunction in mood and anxiety disorders.

Acknowledgments

We would like to thank Mark Zimmerman, M.D. and Audrey Tyrka, M.D., Ph.D. for their helpful feedback on an earlier draft of this manuscript.

This research was supported in part by grants from the National Institute of Mental Health (MH076937, MH035945).

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Figure 1.

Comparison of Dexamethasone Suppression Test Response in Psychotic Major Depression and Matched versus Unmatched Nonpsychotic Major Depression Groups

Note. * $\chi^2 = 4.15$, $p = .042$; DST nonsuppression defined as a plasma cortisol concentration $> 5 \mu\text{g/dl}$ at 4:00 p.m.

Table 1

Group Comparisons on Baseline Variables

Variables	PMD		NMD		Analysis			Effect	
	%	n	%	n	χ^2	p	OR	95% CI	
Gender (Female)	90.9	11	83.3	60	.41	.52	2.00	0.23–17.43	
Education Level (College Degree)	54.5	11	71.2	59	1.19	.28	2.06	0.55–7.66	
Married	45.5	11	60.0	60	.81	.37	1.80	0.49–6.57	
Comorbid Anxiety Disorder	54.5	11	55.9	60	.01	.93	1.06	0.29–3.89	
	<i>M (SD)</i>	<i>n</i>	<i>M (SD)</i>	<i>N</i>	<i>Z</i>	<i>p</i>	<i>d</i>	<i>95% CI</i>	
Age	33.6 (10.5)	11	37.5 (12.1)	60	.92	.35	.34	−0.30–0.99	
MHRSD-17 item	24.7 (6.2)	11	22.8 (5.1)	60	1.28	.20	.33	−0.31–0.98	
BDI	32.0 (10.4)	11	28.9 (8.8)	60	.76	.44	.32	−0.32–0.97	
SCL-90 Depression Subscale	2.8 (0.7)	11	2.3 (0.7)	39	1.53	.13	.71	0.03–1.40	
SCL-90 Anxiety Subscale	2.4 (0.7)	11	1.8 (0.8)	39	2.46	.01	.80	0.11–1.49	
SCL-90 Psychoticism Subscale	1.7 (0.6)	11	.9 (0.4)	39	3.74	.00	1.57	0.83–2.31	
Plasma cortisol at 4:00 pm (µg/dl)	4.4 (3.4)	11	4.0 (4.5)	58	.79	.43	.10	−0.54–0.75	

Note. PMD = Psychotic Major Depression; NMD = Nonpsychotic Major Depression; MHRSD = Modified Hamilton Rating Scale for Depression (17-item total); BDI = Beck Depression Inventory; SCL-90 = Symptom Checklist-90; sample sizes vary in some comparisons due to missing data.