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Multiplicity of Depressive Episodes: Phenomenological and Neuroendocrine Correlates

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Sixty-four patients with a Research Diagnostic Criteria (RDC) diagnosis of major depressive disorder were categorized into three groups based on their number of depressive episodes (DE): Gr I (1 DE), n = 16, Gr II (2–4 DE), n = 25; and Gr III (5 or more DE), n = 23. All patients were nonsuppressors after 1 mg dexamethasone suppression test (DST) prior to the start of treatment. Patients were monitored during the course of their treatment using serial Hamilton Depression scores and post-DST plasma cortisol levels. A proportionately equal number of patients in the three groups had a favorable outcome, i.e., the number of depressive episodes did not predict recovery. Despite favorable clinical outcome, patients with higher numbers of depressive episodes had significantly higher post-DST plasma cortisol levels that were above the suppressive range (greater than 5 μg/dl). Patients with a higher number of depressive episodes had a significantly shorter duration of index episode and were younger at first depressive episode than patients in the other two groups. These results, however, were confounded with polarity, with a higher number of bipolars in Gr III than in the other two groups. Results are discussed in light of phenomenological and psychoendocrine findings of earlier studies.

Introduction

The chronic, episodic, and recurrent nature of major depressive disorder represents a prominent feature in its phenomenology. Therefore, studying the effect of time course on the phenomenology and neuroendocrinology of this illness could help further our understanding of the underlying pathophysiological mechanisms and prognostic aspects of depression. Particularly relevant to the neuroendocrinology of depression is the regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis over the course of time. Hypothetically, the dysregulation of this system may change as the illness becomes progressively chronic.

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Studies that have examined this longitudinal aspect showed that nonsuppression of plasma cortisol levels in response to dexamethasone is state dependent (Carroll et al. 1976; Nuller and Ostroumova 1980; Greden et al. 1982, 1983; Gerkin et al. 1985). Reversion to a nonsuppressive status, reportedly heralded relapse (Holsboer et al. 1983), and a high degree of consistency in dexamethasone suppression test (DST) status across hospitalizations was reported (Brown and Qualls 1982; Coryell and Schlesser 1983; Grunhaus et al. 1983; Yerevanian et al. 1984). Longitudinal follow-up during index depressive episode demonstrated that nonsuppressor patients had gradual decreases in their post-DST plasma cortisol levels as they showed gradual clinical improvement. This normalization process was observed with a variety of treatment modalities (Greden et al. 1980; Goldberg 1980; Gold et al. 1980; Dysken et al. 1979; Papakostas et al. 1981; Holsboer et al. 1982, 1983; Yerevanian et al. 1983; Albala and Greden 1980; Albala et al. 1981; Rothschild and Schatzberg 1982; Targum 1983). Yet, despite the close temporal relationship between clinical recovery and DST normalization, investigators documented a subpopulation of patients who maintained a nonsuppressor status after clinical recovery (Greden et al. 1983; Papakostas et al. 1981; Holsboer et al. 1982, Targum 1983); these patients were reportedly more prone to an earlier relapse (Greden et al. 1983; Holsboer et al. 1982; Targum 1983). It is not known if such failure to suppress despite symptomatic recovery was associated with any of the chronicity parameters such as age at first depressive episode, length of illness, number of depressive episodes, total duration of being depressed, duration of feeling well between episodes, age at index episode, and duration of index episode.

Sashidharan et al. (1984) found that a shorter duration of index episode was associated with DST nonsuppression in the absence of age, gender, polarity, and severity differences between the suppressors and nonsuppressors. Lenox et al. (1985) reported a trend for nonsuppressors to have a significantly longer duration index episode and length of illness and a significantly longer length of illness in nonconverters. However, age, severity, and clinical recovery represented methodological difficulties in that study. Finally, Meador-Woodruff et al. (1987) found no significant correlations between a variety of chronicity parameters and pretreatment post-DST plasma cortisol levels. These studies examined the relationship between DST status and chronicity parameters prior to treatment. We are not aware of other studies that have examined this relationship during and after treatment in a controlled fashion. In fact, chronicity parameters are more likely to be associated with the process of neuroendocrine recovery *from* rather than *with* the onset of an episode.

In this report, we studied the effect of the number of depressive episodes on DST status during the course of an index depressive episode. We tested the hypothesis that patients with a higher number of depressive episodes continued to have higher post-DST plasma cortisol levels at the conclusion of treatment. The relationship between the number of depressive episodes and other phenomenological aspects of depressive illness was also examined.

Methods

Sixty-four patients with major depressive disorder, endogenous subtype, met inclusion criteria for this study. These patients were seen at the Clinical Studies Unit of the Michigan Depression Program. Inclusion criteria were (1) an RDC diagnosis of major depressive disorder, endogenous subtype (Spitzer et al. 1977); (2) a Hamilton score for depression equal to or higher than 15; (3) absence of physical illness or technical exclusion criteria

that invalidate DST results; and (4) a plasma postdexamethasone level higher than 5 μg/dl. All patients underwent a comprehensive diagnostic evaluation by two clinicians using an unstructured interviewed. They all underwent a structured interview by a trained research staff member using the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer and Endicott 1975). Past medical records were reviewed, whenever possible, to confirm the longitudinal course of illness. Diagnosis was made by consensual agreement of two clinicians involved in treating the patient. A physical examination and full laboratory work-up were conducted.

Patients had a baseline 1 mg dexamethasone suppression test (Carroll et al. 1981) at the end of the drug-free period which lasted for 10–14 days. Serial DSTs were administered during the course of treatment. Blood samples were drawn for plasma cortisol level determination at 8 AM, 4 PM, and 11 PM. The maximum value of the three samples was used, usually the 4 PM value. Plasma samples were frozen immediately at −70°C until assayed using a modification of Murphy's competitive protein-binding assay (Murphy 1967).

A baseline 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960) was completed at the end of the drug-free period. Serial Hamilton scores, obtained during the course of treatment, were rated by the patient's same primary psychiatrist, who was blind to the DST results, and coincided with the DST.

Biological therapies entailed tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), electroconvulsive therapy (ECT), lithium carbonate, or a combination of these therapies. Choice of the modality of treatment was based on clinical considerations of each subject. All patients received adequate biological treatment. A clinically favorable outcome was operationally defined as having a Hamilton depression score lower than 10 and less than half the original score at the start of the study. This point in time was also operationally defined as the point of conclusion of treatment.

Patients were categorized, based on the number of depressive episodes, into three groups. Group I (acute): one depressive episode, Group II (moderately chronic): two to four depressive episodes, Group III (severely chronic): five or more depressive episodes.

Length of index depressive episode was operationally defined as number of weeks depressed before hospitalization plus number of weeks of hospitalizations until treatment was concluded. Age of first depressive episode was defined as age (in years) when the patient had a depressive episode that apparently met criteria for a major depressive episode, whether or not treatment was sought. This was retrospectively determined from the history, based on the clinician's best judgment and records whenever available, but no reliability studies were conducted.

One-way analysis of variance (ANOVA) was conducted for comparison of a variety of clinical parametric variables across the three groups. A X^2-test was used for comparing the distribution of categorical variables. Group comparison was conducted prior to, at two time-points during the course of, and at the conclusion of treatment. Logarithmic transformation of raw data was used in the statistical analysis when indicated.

Results

Sixty-four patients (21 men, 43 women) had a mean age at index episode of 56.3 (± 14.3) years, HRSD 24.7 ± 6.2, age at first depressive episode 41.2 (± 14.9) years, and mean length of index episode 40.1 ± 32.4 weeks. The mean pretreatment post-DST cortisol level was 13.1 (± 6.3) μg/dl. This cortisol level showed gradual decrease over the course of treatment (7.6 ± 5.9 to 6.1 ± 4.6 to 5.8 ± 5.6 μg/dl

Table 1. Characteristics of All Subjects and Subjects with Favorable Outcome According to Their Distribution Across the Three Groups

Parameter	Group I (1 episode)	Group II (2–4 episodes)	Group III (5 or more episodes)	Statistic	p
	All subjects				
	n = 16	n = 25	n = 23		
Age	54.5 (± 15.2)	58.3 (± 13.8)	55.4 (± 14.7)	$F = 0.397$	N.S.
Gender	M = 5, F = 11	M = 11, F = 14	M = 5, F = 18	$X^2 = 2.716$	N.S.
Polarity	UP = 15, BP = 1	UP = 22, BP = 3	UP = 8, BP = 15	$X^2 = 21.86$	0.001
Severity (HRSD)	25.9 (± 7.3)	25.3 (± 5.3)	23.4 (± 6.3)	$F = 0.914$	N.S.
Post-DST cortisol	12.3 (± 4.8)	11.8 (± 5.3)	15.1 (± 7.8)	$F = 1.812$	N.S.
Psychotic depression	N = 5	N = 7	N = 4	$X^2 = 3.39$	N.S.
	Subjects with favorable outcome				
	n = 13	n = 20	n = 19		
Age	55.5 (± 15.6)	62.4 (± 10.9)	55.9 (± 13.0)	$F = 1.619$	N.S.
Gender	M = 4, F = 9	M = 8, F = 12	M = 13, F = 16	$X^2 = 2.813$	N.S.
Polarity	UP = 12, BP = 1	UP = 17, BP = 3	UP = 6, BP = 13	$X^2 = 17.56$	0.0005
Severity (HRSD)	25.7 (± 8.1)	24.9 (± 5.9)	23.5 (± 6.5)	$F = 0.528$	N.S.
Post-DST cortisol	12.6 (± 4.6)	11.9 (± 5.9)	13.7 (± 6.1)	$F = 0.521$	N.S.

Values are means ± SD.
UP = unipolar; BP = bipolar.

at the conclusion of treatment). Forty-five patients had unipolar (UP) and 19 patients had bipolar (BP) depression. Of these 19 bipolar patients, 9 had a diagnosis of "probably bipolar-II." The general characteristics of patients according to their group distribution are summarized in Table 1.

Considering all patients, there were no group differences in severity and post-DST cortisol levels prior to, at two time points during the course of, or at the end of treatment. Considering only patients with favorable clinical outcome in each of the three groups, there were no group differences in HRSD scores and post-DST cortisol levels before and at two time points during the course of treatment. However, at the conclusion of treatment, there were statistically significant group differences in post-DST plasma cortisol levels (Group I 2.8 ± 1.8, Group II 5.3 ± 5.1, Group III 7.0 ± 5.5 μg/dl; $F = 3.19$, df = 2,48, $p < 0.05$) in the absence of differences in HRSD scores. Cortisol level differences were mainly between Groups I and III ($F = 6.38$, df = 29, $p < 0.01$). This was also true using log-transformed data (Figures 1 and 2). By classifying improved patients within each group into suppressors versus nonsuppressors, there was a trend towards significance (3/13 versus 8/20 versus 11/18, $X^2 = 4.58$, df = 2, $p < 0.10$), and a significantly higher number of nonsuppressors in Group III compared to Group I ($X^2 = 4.41$, df = 1, $p < 0.05$). Retrospective analysis of these patients with favorable clinical outcome showed no group differences in age at index episode, gender distribution, or severity; however, polarity distribution was significantly different (Table 1).

A proportionately equal number of patients in the three groups had a favorable clinical outcome: Group I 13/16 versus Group II 15/20 versus Group III 18/22; i.e., the number of depressive episodes did not predict clinical recovery ($X^2 = 0.54$, df = 2, p = NS). The mean length of index depressive episode (weeks) was as follows: Group I 50.72 ±

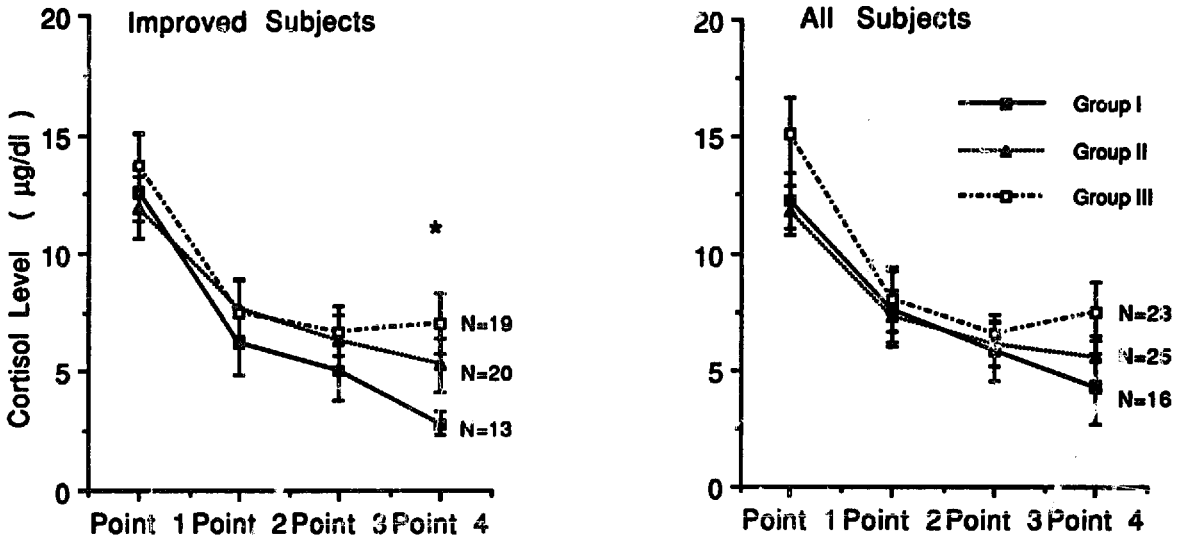

Figure 1. Cortisol levels over the course of treatment of the three groups. No group differences were observed at all time points when all subjects were considered. Improved subjects showed group differences only at the conclusion of treatment. * $p < 0.05$.

38.87, Group II 46.00 + 32.00, Group III 27.44 ± 25.54 (F = 2.41, df = 2,45, p < 0.10). Log-transformed data showed statistically significant group differences (F = 3.3, df = 2,45, $p < 0.04$) with the severely chronic group having a shorter duration of index episode than the other two groups. The mean age (years) at first depressive episode was as follows: Group I 54.5 ± 15.21, Gr II 42.87 ± 14.61, Gr III 36.21 ± 14.03 (F = 7.46, df = 2,60, p = 0.001) with the severely chronic group having a younger age of onset.

Comparison between the UP and BP patients before treatment, irrespective of their

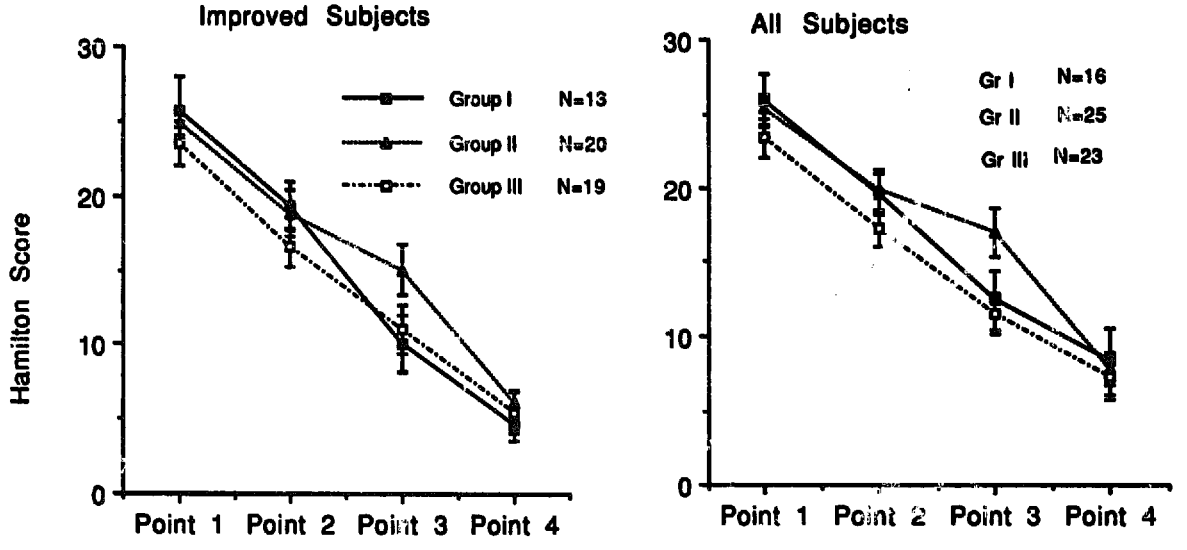

Figure 2. Hamilton scores for depression over the course of treatment of the three groups. No group differences were observed at all time points both for all subjects and improved subjects.

group distribution, showed that UPs had significantly higher HRSD scores (26.0 ± 6.3 versus 21.76 ± 4.7, $t = 2.63$, df = 62, $p < 0.01$) whereas BPs had a significantly higher number of depressive episodes (6.31 ± 2.7 versus 3.0 ± 2.4, $t = 4.64$, df = 62, $p < 0.001$), in absence of differences in clinical outcome ($X^2 = 1.19$, df = 1, p = NS), age at first depressive episode (40.4 ± 15.3 versus 38.2 ± 13.4, $t = 0.51$, df = 45, p = NS), age at index episode (57.5 ± 14.4 versus 53.6 ± 14.1, $t = 0.97$, df = 62, p = NS), and pretreatment post-DST cortisol levels (13.2 ± 5.4 versus 12.8 ± 8.1, $t = 0.21$, df = 62, p = NS). Finally, comparison between patients with favorable outcome and those with unfavorable outcome before treatment, irrespective of their group distribution, showed no differences in pretreatment post-DST plasma cortisol levels (12.7 ± 5.6 versus 14.6 ± 8.8, $t = 0.916$, df = 62, p = NS), in severity (24.5 ± 6.1 versus 25.66 ± 6.8, $t = 0.55$, df = 62, p = NS), in gender distribution ($X^2 = 1.97$, df = 1, p = NS), or in polarity ($X^2 = 1.19$, df = 1, p = NS). However, patients with favorable clinical outcome had a significantly higher mean age at index episode (58.3 ± 13.1 versus 47.66 ± 16.6, $t = 2.4$, df = 62, $p < 0.01$); i.e., older age predicted better outcome.

Discussion

In this study, we examined the DST normalization process and its relationship to a number of chronicity parameters in 64 patients with major depressive disorder. Phenomenological correlates of multiplicity of depressive episodes were also examined. Patients with a higher number of depressive episodes had significantly higher post-DST cortisol levels despite clinical recovery. Though there were no group differences in age, gender distribution, severity, or pretreatment post-DST plasma cortisol levels, there was a higher number of bipolar patients in Group III.

We believe this is the first study to document such a high incidence of nonsuppression among recovered patients with a high number of depressive episodes. The absence of a relationship between pretreatment post-DST cortisol levels and number of depressive episodes is consistent with earlier reports by Meader-Woodruff et al. (1987) and Lenox et al. (1985). These results are along the same lines as those of Lenox et al. regarding a significantly longer length of illness in nonconverters, though that study did not control for recovery.

Dexamethasone nonsuppression is reportedly state dependent and DST normalization is closely associated with clinical recovery, yet, several lines of evidence suggest that this may not be strictly so. First, DST normalization occurs prior to symptomatic recovery (Gerken et al. 1985). Second, our results, together with those of Targum (1983), Papakostas et al. (1981), Holsboer et al. (1982), and Greden et al. (1983), show that a number of patients maintain a nonsuppressive status despite clinical improvement. Third, Holsboer et al. (1983) showed that nonsuppression heralded clinical symptomatic relapse. These studies suggest the existence of a temporal lag between endocrine abnormalities and clinical symptomatology. It is likely that some of our patients who maintained a nonsuppressor status at the time of recovery converted later into suppressors; it would be of interest to find out how long it took them to normalize. We propose that delay in the endocrine recovery could be a correlate of chronicity of depressive illness.

Polarity distribution among the groups was different and could be a confounding variable, however, several points suggest otherwise. First, 9 of the 19 bipolar patients in this study carried a "probable bipolar II" diagnosis. This could have contributed to a

seemingly uneven distribution in polarity. Second, post-DST cortisol levels of unipolars and bipolars were not different. This is consistent with a study by Zisook et al. (1985) (and four other studies cited therein) who found no difference in post-DST cortisol levels between unipolar and bipolar depressed patients using a standard 1 mg DST. Therefore, it is unlikely that bipolar patients contributed to higher post-DST cortisol levels. Third, given the phenomenology of bipolar disorder (Goodwin and Jamison 1984), 25%–30% of the patients diagnosed as unipolars, on the basis of having a first depressive episode, would later develop a bipolar disorder. Collectively, these points argue that the differences in cortisol levels were mainly due to the effect of the number of episodes.

Keller et al. (1981) underlined the theoretical notion that predictors of recovery are different from those of relapse, and suggested that the duration of index episode predicts recovery, whereas the number of depressive episodes predicts relapse. Our results are in agreement with those of Keller et al. (1981, 1982a,b). In this study, a proportionately equal number of patients recovered in each group, i.e., the number of depressive episodes did not predict recovery. Earlier reports suggest that persistence of DST nonsuppression predicted a higher relapse rate (Targum 1983). In this study, nonsuppression, and consequently higher likelihood for relapse, was associated with a higher number of depressive episodes. Comparison between patients with favorable and those with poor outcome showed that older age predicted favorable outcome; otherwise, polarity, gender, severity, and post-DST cortisol levels did not predict outcome. These results are in partial agreement with those of Keller et al. (1981) regarding age, but not polarity or severity. The shorter length of index episode and younger age at onset observed in Group III could have been confounded with polarity. However, decrease in cycle length as a function of episode number was observed both in unipolar and bipolar patients (Zis and Goodwin 1979; Zis et al. 1980; Keller and Shapiro 1981).

In summary, this study shows that patients with a higher number of depressive episodes maintain higher post-DST cortisol levels despite symptomatic recovery and suggests the existence of a temporal lag between symptomatic and neuroendocrine recovery. These results require replication in prospectively designed studies that would, hopefully, not be confounded with polarity, and would explore other aspects of the relationship between various chronicity parameters and HPA axis regulation in depressive disorders.

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