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Research report

The validity of diagnosis of melancholic depression according to different diagnostic systems ☆

M. Hakan Türkçapar[a,*], Asena Akdemir[a], Sibel D. Örsel[a], Nalan Demirergi[a], Ayhan Sirin[a], Emine Z. Kiliç[b], M. Haluk Özbay[a]

[a] *SSK Ankara Training Hospital, Department of Psychiatry, Ankara, Turkey*
[b] *Ankara University, Faculty of Medicine, Department of Child Psychiatry, Ankara, Turkey*

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Abstract

Background: Melancholic versus nonmelancholic depression dichotomy is perhaps the most widely accepted distinction in categorization of depression. This research aims to compare RDC, DSM-III, DSM-III-R, DSM-IV and ICD-10 melancholic/endogenous/somatic and nomelancholic/nonendogenous/nonsomatic depressive patients with regards to biological variables thyroid stimulating hormone (TSH), basal and post dexamethasone cortisol levels, age, age of onset of depression, psychosocial stressors, and severity of depression. *Methods:* Sixty-five patients who had been diagnosed as having major depression according to DSM III-R, using SCID were included in this study. Patients were divided into melancholic and nonmelancholic subtypes using RDC, DSM-III, DSM III-R, DSM-IV and ICD-10 criteria and groups were compared on the basis of biological variables, as well as age, psychosocial stressors and the severity of depression. *Results:* RDC endogenous depressives were older, more severely depressed and had higher cortisol levels then RDC nonendogenous depressives. DSM III-R melancholics were older, more severely depressed, reported fewer numbers of psychosocial stressors and had lower levels of TSH than nonmelancholics. DSM-IV melancholics were more severely depressed, had higher basal and post dexamethasone cortisol levels and lower TSH levels. The ICD 10 somatic depression group contained more severe, older depressives with lower TSH levels. *Conclusion:* The results of this research show that different criteria may identify different groups of patients as having melancholic depression. They also partly support the hypothesis that endogenous or melancholic depression have a biological basis. *Limitations of study:* The study involved a relatively small sample size from a single centre and the results are based on this relatively small sample.

Keywords: Melancholia; Endogenous depression; Depression subtypes; Biological markers; Cortisol; TSH

1. Introduction

Melancholic, endogenous, endogenomorphic, somatic or vital form of depression is one of the

*Corresponding author. Tel.: +90-312-4315643; fax: +91-312-4338213.

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most commonly described subtypes of major depression. These terms are qualifying phrases used synonymously for those major depressive disorders in which anhedonia, guilt, psychomotor and vegetative disturbances dominate the clinical picture (Akiskal, 1995). It has been shown by a good deal of research findings that melancholic patients are less likely to have a clear precipitant for the episode and that these patients show hyperadrenocorticism (American Psychiatric Association, 1994). Biological studies mostly support the hypothesis that endogenous or melancholic depression have a biological basis (Maes et al., 1992, 1996; Rush and Weissenburger, 1994; Deger et al., 1996).

Over the past 70 years, a number of operational definitions have been proposed to identify the endogenous/melancholic depressive subtype. In this study, five current definitions of melancholic depression are compared, namely: DSM-III, DSM-III-R, DSM-IV melancholic depression, RDC endogenous depression and ICD-10 somatic depression criteria. The RDC for endogenous depression served as the model for the DSM-III. The definition of DSM-III was revised when research suggested that DSM-III criteria did not identify a qualitatively distinct depressive subtype, but instead differentiated patients solely along a severity dimension (Zimmerman et al., 1986a). DST (dexamethasone suppression test) studies suggest that the DSM-III definition of melancholia may be too restrictive to adequately discriminate cortisol supressors from nonsupressors (Rush and Weissenburger, 1994). Zimmerman and Spitzer (1989), after reviewing studies of the DSM-III melancholia criteria, concluded that DSM-III melancholia criteria were too restrictive.

Validation of psychiatric diagnoses establishes them as 'real entities'. Comparison of the external validators is a good way of validating the diagnostic categories (Andreasen, 1995). It becomes important to compare the performance of diagnostic scales on clinical and biological measures. In our study, the diagnostic validity of these five definitions were examined using biological variables [baseline thyroid stimulating hormone (TSH), basal cortisol, postdexamethasone cortisol levels], age, age of onset of depression, psychosocial stressors, and severity of depression. The biological and clinical variables were compared between melancholic and nonmelancholic patient groups in each diagnostic system and then all of the findings were compared across diagnostic systems.

2. Materials and methods

2.1. Patients and assessments

Seventy-nine depressed outpatients were evaluated for inclusion in this study between December 1993 and December 1994. Of these, 65 who were diagnosed as having major depression using SCID (Spitzer et al., 1990) were included in this study. The remaining 14 patients were diagnosed as having dysthymic disorder and adjustment disorder with depressed mood and were excluded from the study for diagnostic homogeneity. All subjects were caucasians. The severity of depression was measured using the 17 item version of the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Personality disorders were assessed using SCID-II (Spitzer et al., 1989). SCID used in this study was extended to cover all of the criteria for melancholia. DSM-III-R (American Psychiatric Association, 1987) and DSM-III melancholic depression (American Psychiatric Association, 1980), RDC endogenous depression (Spitzer et al., 1977) and ICD-10 somatic syndrome (WHO, 1993) criteria that are not included in SCID were added to the diagnostic interview. The symptoms required for DSM-IV (American Psychiatric Association, 1994) melancholia criteria are the same as for DSM-III except that DSM-IV includes either pervasive anhedonia or unreactive mood, whereas DSM-III required both. Although DSM-III melancholia criteria were used to assess DSM-IV melancholia diagnosis, psychosocial stressors were assessed by using axis III of DSM-III-R.

The study was approved by the Ethics Committee of SSK Ankara Hospital. All patients gave written informed consent for their participation in the study. The exclusion criteria were high suicidal risk, the presence of significant organic illness, alcohol or drug abuse, severe allergic or multidrug reactions, anorexia nervosa, bulimia nervosa, purgative abuse, ECT within the last six months, depot neuroleptic use within the last one month. Women with childbearing potential who were not using an effective

form of contraception and women who were pregnant or breast feeding were also excluded. Baseline measures for blood pressure, heart rate and body weight were obtained on the first visit. A physical and a neurological examination were performed on admission to the study. An ECG and laboratory panel were done at first evaluation.

The subjects who were still on antidepressants had a wash-out period of at least one week for Tricyclic antidepressants TCAs, two weeks for monoamine oxidase inhibitors (MAOIs), one month for fluoxetine and two weeks for selective serotonin reuptake inhibitors SSRIs other than fluoxetine.

2.2. Biochemical assays

After the psychiatric evaluation (SCID, HDRS), blood was drawn at 8.00 a.m. (±15 min) following an overnight fast, for the laboratory panel, basal TSH and basal cortisol levels. The same day, patients ingested 1 mg of dexamethasone at 11.00 p.m., with fasting blood being collected the next day at 8.00 a.m. (±15 min), for postdexamethasone cortisol. On several occasions, it was shown that the assay of post-DST cortisol at 8.00 a.m. provides a better index of the dysfunction in negative feedback of dexamethasone on the HPA-axis in major depression then the assays performed on 4.00 or 11.00 p.m. post-DST cortisol (Maes et al., 1989). Cortisol levels were measured using a radioimmunoassay (RIA) method (Coat-A-Count® Cortisol Diagnostic Products Corporation, Los Angeles, CA, USA) in the same laboratory. The Coat-A-Count® cortisol assay has a detection limit of approximately 0.2 μg/dl. The intra-assay coefficient of variation (CV) was 5.1% and the inter-assay coefficient of variation was 6.4%. TSH levels were measured using a microparticle enzyme immunoassay (MEIA) technique (Imx R system, Abbott Laboratories). The sensitivity of the ImX ultrasensitive hTSH assay was calculated to be 0.03 μIU hTSH/ml. Inter- and intra-assay CV values for basal TSH were 3.0 and 4.0%, respectively.

In 12 patients, biological variables were not available due to technical problems (e.g. not enough plasma, broken tubes, hemolysis problems, refusing blood sampling, forgetting to take dexamethasone on time, not arriving at the clinic on time for blood sampling).

2.3. Statistical analysis

Statistical analyses were done using the SPSS Win (version 5.0.1) statistical programme. Independent sample *t*-tests were used for two group comparisons of continuous variables and the χ^2 tests were used for categorical data. The significance level was set at $\alpha = 0.05$.

3. Results

3.1. Demographic and clinical features

The majority of the patients were female (63.1%). No significant sex differences were found between melancholic and nonmelancholic patients in any of the diagnostic systems. The mean age of the patients was 33.3±9.9 (SD) and the mean age of onset of the illness was 28.5±9.3 (SD). The mean HDRS score of the patients was 24.0±6.3 (SD).

3.2. Prevalence and overlap among the five definitions

Table 1 gives the prevalence of endogenous/melancholic/somatic depression according to each set of criteria. Melancholic/endogenous/somatic depression is most frequently diagnosed by RDC (43 patients, 66.2%), while DSM-III diagnosed the least (16 patients, 24.6%). Considering the degree of overlap between the definitions, the chance-corrected agreement between the systems is as follows: DSM-IV vs. DSM-III-R, $\chi^2 = 21.5$; DSM-IV vs. DSM-III, $\chi^2 = 11.3$; DSM-IV vs. RDC, $\chi^2 = 30.5$; DSM-IV vs. ICD-10, $\chi^2 = 36.0$; DSM-III-R vs. DSM-III, $\chi^2 = 9.9$; DSM-III-R vs. RDC, $\chi^2 = 10.4$; DSM-III-R vs. ICD-10, $\chi^2 = 22.3$; DSM-III vs. RDC, $\chi^2 = 10.7$; DSM-III vs. ICD-10, $\chi^2 = 12.2$; RDC vs. ICD-10, $\chi^2 = 28.3$.

3.3. Age, age of onset, biological variables and severity of depression according to different diagnostic systems

Table 2 lists the age, age of onset and biological measurements in the DSM-III, DSM-III-R and DSM-IV melancholic and nonmelancholic patients. There was no statistically significant difference between the

Table 1
Diagnostic concordance (%) among five definitions of melancholic depression

	N[a] (%)	RDC (%)	DSM-III (%)	DSM-III-R (%)	DSM-IV (%)	ICD-10 (%)
RDC	43[b] (66.2%)	–	37	66	81	86
DSM-III	16 (24.6%)	100	–	86	94	100
DSM-III-R	32 (50.8%)	84	40	–	84	90
DSM-IV	37 (56.9%)	94	40	77	–	94
ICD-10	41 (63.1%)	90	39	74	85	–

The values denote the percentage agreement for melancholic depression.
The reference definition is on the left-hand-side of the table. (Thus, of 43 RDC endogenous depressive patients, 37% were melancholic according to the DSM III, 66% were DSM-III-R melancholics, 81% were DSM-IV melancholics, 86% were ICD-10 somatic depressives, etc.).
[a]Number of patients diagnosed as being melancholics.
[b]Definite endogenous depression according to the RDC.

Table 2
Age, onset of depression, biological variables and severity of depression in DSM-III, DSM-III-R, DSM-IV melancholic and nonmelancholic patients

Variables	DSM-III			DSM-III-R			DSM-IV		
	M[a] mean (±SD)	Nm[b] mean (±SD)	*p*	M[a] mean (±SD)	Nm[b] mean (±SD)	*p*	M[a] mean (±SD)	Nm[b] mean (±SD)	*p*
Onset (mean year±S.D)	27.1 (±10)	28.9 (±9.1)	0.5	31(±10.6)	25.9 (±7.3)	0.03	30 (±9.9)	26.7 (±8.3)	0.2
Age (mean year±S.D)	35 (±11.1)	32.6 (±10.8)	0.3	37 (±10.3)	28 (±7.3)	$1 \cdot 10^{-3}$	35.3 (±9.9)	30.7 (±9.4)	0.06
TSH (μIU hTSH/ml)	1.3 (±0.6)	1.4 (±0.8)	0.8	1.2 (±0.7)	1.7 (±0.8)	0.01	1.2 (±0.6)	1.8 (±0.9)	0.005
Basal Cort[c] (μg/dl)	23.8 (±11.7)	15.9 (±12.6)	0.06	19.3(±10.8)	16.3(±15.1)	0.4	22.6(±13.4)	10.3 (±6.3)	$1 \cdot 10^{-3}$
PD Cort[d] (μg/dl)	4.1 (±4.8)	2.7 (±7.6)	0.5	2.9 (±3.6)	3.1 (±9.8)	0.1	4.6 (±8.5)	0.5 (±0.9)	0.009
HDRS [e]	26.8 (±5.2)	23.2 (±6.4)	0.06	25 (±6.7)	23.1 (±5.9)	0.2	26.2 (±6.8)	21.3 (±4.4)	0.001

[a] = Melancholic; [b] = Nonmelancholic; [c] = basal cortisol; [d] = Postdexamethasone cortisol, [e] = Hamilton Depression Rating Scale.

two groups using the DSM-III system with respect to these variables. Compared to DSM-III-R nonmelancholics, DSM-III-R melancholics were significantly older and had a younger age of onset than nonmelancholics. With regard to biological variables, DSM-III-R melancholic depressive patients had lower TSH levels and DSM-IV melancholics had higher basal and postdexamethasone cortisol levels. Basal TSH levels were also significantly lower in DSM-IV melancholic patients. In addition, patients with DSM-IV melancholia had significantly higher mean scores on HDRS.

Table 3 summarizes the comparison of the endogenous (definite) and nonendogenous patients according to RDC and ICD-10. The age of onset for the RDC-diagnosed endogenous depressive patient is younger than that of the nonendogenous patient. Basal cortisol and postdexamethasone cortisol levels were significantly higher in endogenous depressives. Patients with RDC endogenous depression had significantly higher mean scores on the HDRS. There were statistically significant differences between ICD-10 somatic and nonsomatic depressives with regard to age, TSH levels and HDRS scores. Somatic depressive patients were significantly older than nonsomatic depressive patients. They had significantly lower TSH levels and higher HDRS mean scores compared to nonsomatic patients.

Table 3
Age, onset of depression, biological variables and severity of depression according to RDC and ICD-10 classifications

Variables	ICD-10			RDC		
	Somatic	Nonsomatic	*p*	End[a]	Nnend[b]	*p*
Onset (mean year±S.D)	29.7 (±9.8)	26.5 (±8.2)	0.2	31 (±10.0)	24 (±5.1)	0.001
Age (mean year±S.D)	35.6 (±10.3)	29.4 (±7.9)	0.01	35.2 (±9.8)	29.6 (±9.3)	0.03
TSH (μIU hTSH/ml)	1.2 (±0.7)	1.8 (±0.9)	0.01	1.3 (±0.8)	1.6 (±0.8)	0.2
Basal cortisol (μg/dl)	19.4 (±11.1)	15.3 (±15.4)	0.3	21.5 (±13.5)	10.5 (±6.1)	$<10^{-3}$
PD cortisol[c] (μg/dl)	3.2 (±3.7)	3 (±10.1)	0.9	4.1 (±8.1)	0.5 (±1.0)	0.01
HDRS	25.9 (±6.6)	21.0 (±4.4)	0.001	26.2 (±6.1)	20.0 (±4.5)	$<10^{-3}$

[a] = Melancholic; [b] = Nonmelancholic; [c] = postdexamethasone cortisol.

Table 4
Incidence of pychosocial stressor events before the episode in melancholic and nonmelancholic patients according to the various diagnostic systems

Diagnostic Systems	M[a]		NM[b]		*p*
	Stressor[c] *N*	No Stressor *N*	Stressor *N*	No Stressor *N*	(χ^2)
DSM III	9	7	29	20	0.83
DSM-III-R	15	17	22	9	0.05*
DSM-IV	20	17	18	10	0.40
ICD-10	21	20	17	7	0.12
RDC	23	20	15	7	0.25

[a] = melancholic; [b] = nonmelancholic; [c] = stressor.

3.4. Psychosocial stressors

Table 4 shows the incidence of psychosocial stressor events before the episode in melancholic and nonmelancholic patient groups across the diagnostic systems.

Significant differences emerged only in the DSM-III-R diagnostic system. More DSM-III-R nonmelancholic patients had stressor events before the depressive episodes compared with the melancholic patients.

4. Discussion

In this study, the relationship between biological and clinical variables and melancholic/nonmelancholic depression according to RDC, DSM-III, DSM-III-R, DSM-IV, ICD-10 were examined. Basal and postdexamethasone cortisol levels, TSH levels, age, clinical severity and psychosocial stressor events were used as validators.

The results suggest that DSM-III melancholia has the most restrictive definition among these diagnostic systems (24.6% of the patients were diagnosed as being melancholic according to DSM-III criteria). On the other hand, RDC had the least restrictive criteria set (66.2% of the patients were diagnosed as having definite endogenous depression according to RDC). It is difficult to compare our prevalence rates of melancholic depression diagnoses with those of other investigators because of sample differences, but similar trends were observed in most of the studies (Davidson et al., 1984; Zimmerman et al., 1985,

1986b). In their study, Lafer et al. (1996) found that, of 176 consecutive outpatients with unipolar depression, 40 (22.7%) met DSM-III-R criteria and 29 (16.5%) met DSM-IV criteria for melancholia. In our study, these percentages were 50.8 and 56.9%, respectively (Table 2).

The results of our study show that RDC endogenous depressives were older, more severely depressed and had higher cortisol levels than RDC nonendogenous depressives. DSM-III-R melancholics were older, more severely depressed, had a pre-episodic pychosocial stressor less often, and had lower levels of TSH than DSM-III-R nonmelancholics. In a study on DSM-III-R and DSM-III criteria, Zimmerman and Spitzer (1989) reported that DSM-III-R melancholic subtyping is associated with the presence of a personality disorder, older age and a tendency to blame others for the depression.

Most studies on the DST in depression agree that nonendogenous patients show abnormal results. However, this depends largely on the diagnostic system used. For example, six of eight outpatient studies on DST and its relation to the RDC endogenous/nonendogenous dichotomy had positive results. However, only three of nine studies using DSM-III criteria for melancholia found that DST differentiated melancholic patients from nonmelancholics (Rush and Weissenburger, 1994). In our study, DSM-III melancholics did not differ from DSM-III nonmelancholics with regards to any of the variables. It seems that DSM-III was the most restrictive, although its criteria were not supported by any of the external validators. Using the DST, Davidson et al. (1984) compared four sets of diagnostic criteria: the New Castle Index, DSM-III, RDC and the Michigan Diagnostic Index for the diagnosis of melancholia. As a result, they reported that DSM-III showed the lowest specificity and predictive value (Davidson et al., 1984).

DSM-IV melancholic patients were more severely depressed, had higher cortisol levels and lower TSH levels compared to nonmelancholic patients. In a cluster analysis, which was carried out on a sample of 80 depressed men, Maes et al. (1992) found that melancholic (vital) depressives were significantly older and exhibited biological disturbances (abnormal dexamethasone suppression test, lower basal TSH) compared to nonmelancholic (nonvital) depressives (Maes et al., 1992).

In a study that compares the DSM-III-R and DSM-IV melancholia definition, Lafer et al. (1996) found that patients with DSM-IV melancholia had higher mean scores on measurements of clinical severity compared with DSM-III-R-diagnosed melancholics. DSM-IV criteria were supported by biological differences between the groups but the presence of psychosocial stressors did not show any difference.

The results of our study support the melancholic–nonmelancholic distinction but the criteria for melancholic depression are not yet clear. Although the highest validity was found with the DSM-IV melancholia criteria, we still need to develop more precise validators for melancholic depression.

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