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Clinical and Demographic Factors Associated With DSM-IV Melancholic Depression

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Background. *The purpose of this paper is to use demographic and clinical data from a large diverse group of outpatients diagnosed with non-psychotic major depression to investigate the validity of the DSM-IV concept of melancholic depression.*
Methods. *Baseline clinical and demographic data were collected on 1500 outpatients (1456 of whom melancholia could be determined) with non-psychotic major depressive disorder (MDD) participating in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Depressive symptom severity was assessed by clinical telephone interview using the 17-item Hamilton Rating Scale for Depression (HRS-D_{17}) and the 30-item Inventory of Depressive Symptomatology (IDS-C_{30}). The types and degrees of concurrent psychiatric symptoms were measured using a self report, the Psychiatric Diagnostic Screening Questionnaire (PDSQ), by recording the number of items relevant to each diagnostic category endorsed by study participants.*
Results. *Adjusting for severity of depression (as measured by the total HRS-D_{17} scores), no differences were found in the rate of melancholic depression by race, marital status, education, employment status, family history of depression, primary care versus specialty care, monthly income, and degree of psychiatric and medical co-morbidity. Melancholic depression was significantly more likely in men than women. Melancholic depression after adjustment for severity was associated with a slightly younger age at study entry, as well as with greater illness severity, and slightly shorter duration of current episode. Hispanic ethnicity was associated with lower melancholic depression rates at the .06 level of significance.*
Conclusions. *Among outpatients with MDD, melancholic features were less likely in Hispanic patients, but more likely in slightly younger patients and in men. Melancholic features were also related to a slightly shorter current episode. These findings are consistent with the notion that external socio-demographic factors do not play an important role in the pathophysiology of melancholic depression.*

Keywords endogenous depression, melancholic depression, sequence treatment alternatives to relieve depression

INTRODUCTION

Depressive disorders were among the earliest diseases described in the history of medicine. Greek physicians referred to depression as "melancholia." They considered it to be an

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endogenous disease attributable to an excess of black bile. Historically, endogenous depression (ED), was defined as depression that grows from within. It was characterized by absence of presumably precipitating life events, prominent vegetative symptoms, recurrent episodes, and family history (1).

Several studies have evaluated the validity of different definitions for ED/melancholia and tested for any association between a variety of factors and ED/melancholia versus Non-Endogenous Depression (NED)/non-melancholia. Zimmerman et al. applied four definitions of ED including Feinberg and Carroll, DSM-III, Research Diagnostic Criteria, and Newcastle Scale, and found that the following 14 variables were more common in ED than NED patients: older age, more severely ill, lower likelihood of alcoholism and antisocial personality in their first degree relatives, less likely to make a non-serious suicidal attempt, more stable life style, greater likelihood of a biological abnormality on such test as Dexamethasone Suppression Test (DST), better response to somatic therapies, poor response to psychotherapy, lower rate of marital separation and divorce, better social support, lower rate of pre-morbid personality disorder, lower likelihood of stressful life events before hospital admission, lower likelihood of overreacting to neutral or negative events (2–5). During that research, the validity of the Newcastle Scale was the most frequently supported, with the ED having a lower rate of personality disorder, marital separations and divorces, familial alcoholism, life events, and non-serious suicide attempts (6).

Andreasen et al. examined 2942 subjects, using four definitions of ED (the Newcastle Scale, Research Diagnostic Criteria, DSM-III, and Autonomous Depression). They found the relatives of patients with ED did not have higher rates of depression than those with NED by any definition (7). During the study, the Newcastle Scale was the most sensitive in picking up familial transmission of recurrent unipolar depression.

The symptom pattern of melancholic and non-melancholic depression continues to be a matter of controversy. Rush & Weissenburger reviewed nine different definitions of melancholia including Newcastle Scale both versions I & II, Research Diagnostic Criteria, Diagnostic & Statistical Manual (DSM-III-R), the World Health Organization Depression Scale, Michigan Discrimination Index, Chicago Medical School Index, and Yale Group (8,9). In terms of clinical features, psychomotor retardation is included in all nine systems, terminal insomnia in eight, diurnal mood variation in six, guilt in five, anhedonia, distinct quality of mood, appetite loss and delusions in four, and non-reactive mood and loss of interest in three (10–12). Melancholic features have not always been associated with poorer antidepressant response (13,14). Rates of personality disorders furthermore have been shown to be comparable to those of non-melancholic depressed patients (15,16). Parker et al. suggested that melancholia is associated with older age than non-melancholic depression (17). Some investigators identified biological abnormalities in patients with melancholic depression and proposed that these abnormalities can be used as diagnostic markers (18).

As noted, most previous studies/surveys have used different factors/criteria to differentiate the melancholic from non-melancholic depression, had small sample sizes (10,17,19,20), and many studies did not control for severity of depression. Larger studies, such as those by Fava et al. (14) and Tedlow et al. (15) tended to be negative, suggesting that type I errors may have played a significant role in the positive findings.

STAR*D is a large ongoing clinical trial engaging outpatients with non-psychotic major depressive disorder. It provides opportunity to evaluate socio-demographic factors, and clinical course factors that might distinguish between melancholic and non-melancholic depression. This study involves subjects from primary as well as mental health care settings and uses minimal exclusion criteria (21).

This preliminary data analysis was undertaken to define: what demographic (age, sex, employment status, marital status, education, ethnicity) and clinical (length of illness, number of episodes, age of onset, length of episodes, medical and psychiatric co-morbidity) features distinguish melancholic from non-melancholic depression independent of the severity of the depressive episode?

METHODS

In any research involving depressed patients, the differentiation of patients into melancholic and non-melancholic sub-classification may prove useful for studying the association between life events and depressive symptoms over the course of the study (22–25). In addition, in the previous studies it was found that severity would not be an adequate substitute for melancholic features because a large number of patients with moderately severe, non-psychotic depression also have melancholic features.

For the purpose of this analysis, the STAR*D research group developed a specific definition based on items of the 30-Item Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C_{30}) (26). This definition is very similar to the DSM-IV criteria of melancholic depression (8). The rationale to use DSM-IV melancholic criteria in our definition is because it is simple not lengthy, captures the essence of the concept as defined by RDC without redundancy, and finally describe each sign/symptom adequately to improve item reliability as well as the overall concept.

To meet our melancholic depression criteria, the patient must score 2 or 3 on the IDS-C_{30} mood reactivity item or pleasure item and meet at least three of the following criteria based on IDS-C_{30} items (quality of mood, mood variation, psychomotor retardation, psychomotor agitation, appetite decrease or weight decrease, self-outlook) obtained by the ROA at baseline (Table 1). While it should be noted that assessing psychomotor retardation over the telephone can be more problematic than assessing psychomotor agitation, we believe the overall effect on determining melancholia is trivial.

Study Design

STAR*D is designed to define prospectively which of several treatments are most effective for participants with non-psychotic

Table 1 Definition of Melancholic Depression

DSM-IV	IDS-C_{30}
Either of the following:	
Loss of pleasure in all, or almost all, activities	Pleasure/Enjoyment (excluding sexual activities): rarely derives pleasure from any activities **OR** is unable to register any sense of pleasure/enjoyment from anything
Lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens)	Reactivity of Mood responses: mood brightens only somewhat with few selected, extremely desired events OR mood does not brighten at all, even when very good or desired events occur
Three (or more) of the following:	
Distinct quality of depressed mood (i.e., the depressed mood is experienced as distinctly different from the kind of feeling experienced after the death of a loved one)	Quality of Mood: mood is qualitatively distinct from grief nearly all of the time
Depression regularly worse in the morning	Mood Variation (worse in morning): for most of the week, mood appears more related to time of day than to events OR mood is clearly, predictably, better or worse at a fixed time each day
Early morning awakening (at least 2 hours before usual time of awakening)	Early Morning Insomnia: awakens at least two hours before need be, more than half the time
Marked psychomotor retardation or agitation	Psychomotor Retardation: takes several seconds to respond to most questions; reports slowed thinking OR is largely unresponsive to most questions without strong encouragement OR Psychomotor Agitation: describes impulse to move about and displays motor restlessness OR unable to stay seated. Paces about with or without permission
Significant anorexia or weight loss	Appetite Decrease: eats much less than usual and only with personal effort OR eats rarely within a 24-hour period, and only with extreme personal effort or with persuasion by others OR Weight Decrease: has lost five pounds or more in the last two weeks
Excessive or inappropriate guilt	Outlook (Self): largely believes that he/she causes problems for others OR ruminates over major and minor defects in self

Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Washington, D.C., American Psychiatric Association, 1994.

MDD who have an unsatisfactory clinical outcome to an initial and, if necessary, subsequent treatment(s) (see (21,27) or www.star-d.org for a detailed description of the STAR*D protocol). Altogether, 14 Regional Centers (RCs) across the United States oversee protocol implementation at 2–4 clinical sites that provide primary or psychiatric care in either the public or private sectors. In all, nearly half of the sites (18 of 41) are primary care settings.

Research outcome data are collected by telephone interviews with trained Research Outcome Assessors (ROAs) masked to treatment and by a telephone-based Interactive Voice Response (IVR) system. The ROAs received extensive training in the administration of the study's primary efficacy measures through live and videotaped interviews, and their inter-rater reliability is periodically assessed throughout the study.

Study Population

STAR*D has recruited over 4000 participants. This preliminary report presents data from 1456 of the first 1500 consecutive participants enrolled into Level 1 for whom melancholia could be determined. Participants must be self-identified outpatients who present for care to avoid the use of advertising, since this method attracts a less representative spectrum of participants (28). Every effort is made to enroll a broad spectrum of participants representing all racial groups and both genders. The risks, benefits, and adverse events associated with each treatment within the randomized treatments are explained to study participants, who provide written informed consent prior to study participation. Participants were male or female (18–75 yrs) outpatients with non-psychotic MDD and a baseline $HAMD_{17}$ score ≥ 14 for whom the treating clinician had determined that outpatient treatment with an antidepressant would be both safe and appropriate.

Participants with schizophrenia, schizoaffective, or bipolar disorder, as well as anorexia nervosa, were excluded. Those with primary diagnoses of bulimia nervosa, obsessive compulsive disorder (OCD), or panic disorder were also excluded. Participants with active substance abuse or dependence were eligible (as long as inpatient care for detoxification is not required clinically at study entry).

Research Outcome Assessment

After obtaining written informed consent at the screening/baseline visit, clinical and demographic information was collected, as well as prior course of illness, current and past abuse, prior suicide attempts, family history of mood disorders, current general medical illnesses, and prior history of treatment in the current major depressive episode (both medication and psychotherapy). Participants also completed the 139 item paper and pencil version of the Psychiatric Diagnostic Screening Questionnaire (PDSQ) (29). The types of and degree of concurrent psychiatric symptoms were measured using the PDSQ, by recording the number of items endorsed by study participants for each diagnostic category. The presence or absence of each comorbidity was determined by 90% specificity thresholds estimated by Zimmerman and Mattia (30).

The Clinical Research Coordinator (CRC) at each site completed the baseline HAM-D_{17} and the baseline 16-item Quick Inventory of Depressive Symptomatology – Clinician Rating (QIDS-C_{16}) and reviewed inclusion/exclusion criteria. The QIDS-C_{16} is a clinician-rated scale assessing the nine diagnostic symptom domains of MDD (31,32). Current general medical conditions (GMCs) were assessed by the 14-item Cumulative Illness Rating Scale (CIRS), completed using a manual to guide scoring, and to gauge the severity/morbidity of GMCs relevant to different organ systems (33–35).

The ROA called the participant for a telephone interview within 5 days of the baseline visit to complete the baseline HRS-D_{17} (36) the IDS-C_{30}, and the 5-item Income and Public Assistance Questionnaire (IPAQ). The 5-item Income and Public assistance Questionnaire (IPAQ), collected by the ROAs, measured the participant's monthly income and the source of monthly income (e.g., employment wages, public assistance). Other research outcomes were collected by IVR (function, quality of life, side effect burden, and participant satisfaction) within 5 days of the visit.

Statistical Analysis

Bivariate logistic regression models were fit to assess each factors association with the presence of melancholia. In addition, logistic regression models were fit for each factor controlling for illness severity (HRS-D_{17}). For each adjusted logistic regression model, odds ratios and 95% confidence intervals were calculated for the estimated odds ratios. Monthly household income and duration of index episode were log-transformed to account for their heavily positive-skewed distributions. These analyses were intended to be exploratory and hypothesis generating. No adjustments of p values for multiple comparisons were performed, so results must be interpreted accordingly.

RESULTS

As shown in Tables 2 and 3, the majority of these (n = 1456) subjects were female (63%) and most (66%) were recruited in specialty care clinics. The racial composition was 76% White, 18% Black and 6% other. Hispanic ethnicity was endorsed by 10% of the subjects. Most subjects were employed (59%). The average age of the participant was 40.4 years, with 13.5 years of education and a monthly household income of $2432. The severity of depression was moderate to marked, with mean baseline scores with HRS-D_{17} of 20.4 (SD:6.6), with IDS-C_{30} (ROA) of 35.8 (SD:11.6) and with QIDS-SR_{16} of 15.4 (SD:4.2). Table 2 summarizes the association between socio-demographic baseline characteristics (gender, race, ethnicity, employment status, marital status, family history of depression, and primary vs. specialty care) and melancholia presence after adjusting for severity of depression.

Table 2 Socio-demographic Characteristics by Melancholia[a]

		Melancholic				
Characteristic	N	Yes (n = 308)	No (n = 1148)	Odds ratio[b]	Confidence interval	P
Age—yr	1454	39.5 ± 12.8	40.8 ± 13.3	0.984	0.973, 0.996	0.0089
Gender						0.0144
Male	542	127 (23.4)	415 (76.6)	1.463	1.079, 1.983	
Female	913	180 (19.7)	733 (80.3)			
Race						0.5163
White	1103	223 (20.2)	880 (79.8)			
Black	265	70 (26.4)	195 (73.6)	1.009	0.701, 1.452	
Other	86	14 (16.3)	72 (83.7)	0.674	0.341, 1.333	
Hispanic						0.0654
Yes	131	18 (13.7)	113 (86.3)	0.579	0.323, 1.036	
No	1323	288 (21.8)	1035 (78.2)			
Education—yr	1452	13.2 ± 3.3	13.7 ± 3.2	1.038	0.990, 1.089	0.1223
Employment						0.3959
Employed	856	164 (19.2)	692 (80.8)			
Unemployed	506	130 (25.7)	376 (74.3)	0.875	0.639, 1.198	
Retired	92	13 (14.1)	79 (85.9)	0.650	0.324, 1.306	
Monthly income—$	1411	2364 ± 3433	2461 ± 2840	1.044	0.978, 1.115	0.1957
Marital status						0.0633
Married	616	120 (19.5)	496 (80.5)			
Never	412	92 (22.3)	320 (77.7)	1.332	0.929, 1.910	
Divorced	388	90 (23.2)	298 (76.8)	1.047	0.727, 1.507	
Widowed	39	5 (12.8)	34 (87.2)	0.341	0.116, 1.005	
Clinic setting						0.0802
Primary	497	97 (19.5)	400 (80.5)	0.753	0.547, 1.035	
Specialty	959	211 (22.0)	748 (78.0)			

[a] Descriptive statistics are presented as mean ± SD and n(%N). Sums do not always equal N due to missing values. Percentages are based on available data.
[b] Adjusted for 17-item Hamilton Rating Scale for Depression.

Table 3 Clinical Characteristics by Melancholia[a]

Characteristic	N	Melancholia		Odds ratio[b]	Confidence interval	P
		Yes (n = 308)	No (n = 1148)			
Age at first episode—yr	1444	23.9 ± 12.5	25.5 ± 14.3	0.993	0.982, 1.004	0.2219
Duration of episodes—yr	1442	15.7 ± 12.7	15.4 ± 13.3	0.993	0.981, 1.004	0.2101
Number of episodes	1330	5.4 ± 9.3	5.8 ± 9.4	0.885	0.726, 1.079	0.2269
Family history of depression						0.6670
Yes	808	166 (20.5)	642 (79.5)	0.937	0.695, 1.262	
No	642	141 (22.0)	501 (78.0)			
CIRS N categories	1456	3.2 ± 2.3	3.0 ± 2.2	0.943	0.882, 1.009	0.0907
CIRS Total score	1456	4.5 ± 3.7	4.3 ± 3.6	0.960	0.921, 1.001	0.0544
CIRS Severity index	1456	1.2 ± 0.6	1.2 ± 0.6	0.799	0.622, 1.028	0.0813
PDSQ Agoraphobia						0.7059
Yes	136	48 (35.3)	88 (64.7)	0.916	0.580, 1.446	
No	1316	258 (19.6)	1058 (80.4)			
PDSQ Alcohol abuse						0.2945
Yes	169	47 (27.8)	122 (72.2)	1.253	0.822, 1.910	
No	1283	259 (20.2)	1024 (79.8)			
PDSQ Bulimia						0.1110
Yes	172	32 (18.6)	140 (81.4)	0.680	0.423, 1.093	
No	1280	274 (21.4)	1006 (78.6)			
PDSQ Drug abuse						0.4756
Yes	104	30 (28.8)	74 (71.2)	1.214	0.712, 2.069	
No	1348	276 (20.5)	1072 (79.5)			
PDSQ Generalized anxiety						0.1719
Yes	305	93 (30.5)	212 (69.5)	0.783	0.552, 1.112	
No	1147	213 (18.6)	934 (81.4)			
PDSQ Hypochondriasis						0.2652
Yes	58	19 (32.8)	39 (67.2)	0.684	0.350, 1.335	
No	1394	287 (20.6)	1107 (79.4)			
PDSQ Obsessive-compulsive						0.8402
Yes	195	60 (30.8)	135 (69.2)	1.042	0.700, 1.551	
No	1257	246 (19.6)	1011 (80.4)			
PDSQ Panic						0.5355
Yes	162	63 (38.9)	99 (61.1)	0.876	0.576, 1.332	
No	1290	243 (18.8)	1047 (81.2)			
PDSQ Post-traumatic stress						0.8895
Yes	273	89 (32.6)	184 (67.4)	1.025	0.724, 1.450	
No	1179	217 (18.4)	962 (81.6)			
PDSQ Social phobia						0.4345
Yes	410	110 (26.8)	300 (73.2)	0.879	0.636, 1.215	
No	1042	196 (18.8)	846 (81.2)			
PDSQ Somatoform						0.8016
Yes	35	13 (37.1)	22 (62.9)	0.901	0.399, 2.033	
No	1417	293 (20.7)	1124 (79.3)			
Duration of index MDE—mo	1338	20.3 ± 49.4	21.1 ± 49.1	0.868	0.759, 0.993	0.0385
HRS-D_{17}	1443	26.5 ± 5.2	18.8 ± 6.0	1.273	1.234, 1.312	<.0001
QIDS-SR_{16}	1449	17.9 ± 3.7	14.7 ± 4.1	1.053	1.008, 1.101	0.0215

MDE, major depressive episode; MDD, major depressive disorder; CIRS, Cumulative Illness Rating Scale; PDSQ, Psychiatric Diagnostic Screening Questionnaire; HRS-D_{17}, Hamilton Rating Scale for Depression-17 item; QIDS-SR_{16}, Quick Inventory of Depressive Symptomatology, Self-rated.

[a] Descriptive statistics are presented as Mean ± SD and n (%N). Sums do not always equal N due to missing values. Percentages are based on available data.

[b] Adjusted for HRS-D_{17}.

Demographic Variables after Adjusting for Severity

Age at study entry and gender were significantly associated with melancholia. Males exhibited higher rates of melancholic depression than females. Melancholic patients were slightly younger than the non-melancholic patients at study entry (Table 3). Race, employment status, education, family history of depression, marital status, monthly income, and care setting did not distinguish melancholic and non-melancholic patients, while Hispanic ethnicity was associated with lower melancholic rates at the .06 level of significance.

Clinical Variables

Melancholia was associated with greater severity of depression (as assessed by the HRS-D_{17} and QIDS-SR_{16}) and with a significantly shorter duration of the index episode (Table 3). There were no other significant differences in medical or psychiatric co-morbidity (as measured by the PDSQ).

DISCUSSION

This preliminary report is based on data obtained from the first 1500 participants in STAR*D. This large sample provides the opportunity for hypothesis generation to identify potential factors associated with melancholia, in addition to severity of depression. In our study, after adjusting for severity of depression, being male and non-Hispanic was associated with significantly higher rates of melancholia (23.4% vs. 20% and 22% vs. 14% respectively). No other adjusted significant differences were found in the rate of melancholic depression by race, marital status, education, employment status, family history of depression, primary care versus specialty care, and monthly income. These findings suggest that genetic, rather than external socio-demographic factors may play an important role in the pathophysiology of melancholic depression.

Most participants were White 76%, with Black 18%, and Other 6%. Data showed a positive association between Blacks and melancholia when not adjusted for the severity by HRS-D_{17} scores (p value 0.0291), but there is no difference between White and Other race, and both show negative association or a protective effect to melancholia. This association became weak with melancholia when adjusted for severity by the HRS-D_{17} scores. This finding is unique in that race has not been studied before as a predictor of melancholic depression.

The fact that our results found no difference between melancholic and non-melancholic patients in terms of family history of depressive disorder is certainly consistent with previous reports (7,37). Von Knorring found that the risk of depression did not differ in relatives of patients with ED/melancholia and NED/non-melancholia, but the rate of alcoholism in the relatives of patients with NED/non-melancholia was higher than the rate in relatives of patients with ED/melancholia (38). Similar results were reported by Zimmerman et al. and Andreasen et al. (2,7).

The finding of a slightly lower age at the time of study entry is not consistent with previous studies which reported melancholic patients were older than non-melancholic patients, but these reports did not adjust for severity (2,8,10,24,39).

From a clinical standpoint, melancholia was associated with greater illness severity, and slightly shorter duration of current episode. Some researchers believe that the only distinction between ED and NED is the severity of depression (40). The Research Diagnostic Criteria (RDC) by Spitzer in 1975 supports this view (41).

In our study, symptoms consistent with concurrent psychiatric conditions including Agoraphobia, Alcohol Abuse, Generalized Anxiety Disorder, Hypochondriasis, Obsessive Compulsive Disorder, Panic Disorder, Post Traumatic Stress Disorder, and Somatoform Disorder were not more common in melancholic versus non-melancholic patients, which is not consistent with the findings of previous studies (24,25,29), and with those linking family history of alcoholism and ED (7).

There are several limitations to this report:

First, the main study STAR*D was not designed specifically to answer this question but rather to answer other questions. This paper is an analysis of data collected for other reasons. It is essentially hypothesis generating rather than hypothesis testing, but these hypothesis can then be tested in the next 2500 participants.

Second, this study did not test whether the melancholic or non-melancholic distinction is stable. In other words, perhaps a patient at one time might qualify as melancholic while at another time within the same episode he/she might not exhibit melancholia.

Third, since only outpatients with non-psychotic MDD were enrolled, it is possible that the clinical correlates and symptom pattern associated with melancholic depression may be different for inpatients treated for depression.

Fourth, the methods used to define melancholic depression can be challenged. We relied on a clinical rating of symptoms present within the last week obtained by telephone interview. We did not assess symptoms over the full episode.

Despite these limitations, the present study has many strengths including well trained evaluators and treatment teams in both primary and specialty care settings, a large sample size, broad representation of outpatients across the United States, and finally the ability to test factors that have not been previously studied in relation to melancholic and non-melancholic depression.

CONCLUSIONS

The most significant and relevant finding from this study is that DSM-IV melancholic depression is correlated with depressive illness severity, but few other demographic or clinical variables including Hispanic ethnicity, age, gender, and duration of current episode. These findings indicates that genetic or biological factors, rather than external socio-demographic factors play an important role in the development of melancholic symptoms.

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