Response to a Selective Serotonin Reuptake Inhibitor (Citalopram) in Major Depressive Disorder With Melancholic Features: A STAR*D Report

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Objective: This study examined demographic and clinical correlates of DSM-IV major depressive disorder with melancholic features and assessed whether melancholic features were predictive of response to a selective serotonin reuptake inhibitor antidepressant.

Method: Participants with major depressive disorder (N = 2875) at primary and specialty care sites who received the first step treatment with citalopram in the Sequenced Treatment Alternatives to Relieve Depression study were included. Patients were enrolled between July 2001 and April 2004. Melancholic features were ascribed by previously developed algorithms of telephone interview ratings prior to treatment. Demographics, clinical features, and treatment response were compared between those with and without melancholic features.

Results: The 23.5% of participants with melancholic features were characterized by higher severity scores, greater rates of previous suicide attempts and ratings of current suicidal risk, and more concurrent psychiatric comorbidity. Unadjusted remission rates for those with melancholic features were statistically significantly reduced in absolute terms by up to 8.4% compared to those without melancholic features, which is a 24.1% decrease in relative chance of remission ($p < .0001$). Following adjustments for between-group baseline differences, remission rates were no longer different.

Conclusion: Melancholic features are associated with a significantly reduced remission rate with an SSRI. This effect appears to be accounted for by demographic and clinical features associated with melancholic features.

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The concept of melancholia has a long tradition in the nosology of depressive disorders. It has been used to describe depression conceptualized as "endogenous" or mainly biologically based, rather than determined mainly by personality or life circumstances. Klein reformulated this concept in his description of "endogenomorphic depression."[1] He postulated that endogenomorphic depression was characterized by pervasive anhedonia caused by a marked biological impairment in the brain reward system, which markedly impaired the capacity to experience consummatory pleasure. This concept was influential in the formulation of criteria for melancholia in the 1980 *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, in which the designation of melancholic features to describe a major depressive episode (MDE) was first introduced.

A recent review concluded that available research supports the idea that melancholic features appear to be qualitatively different from nonmelancholic depression in terms of biological functioning, personality traits, treatment response, and suicidality.[2] There are data supporting

the association of melancholia with biological abnormalities compared to nonmelancholic patients: a distinct genotype (the long allele of the serotonin promoter polymorphism),[3] loss of hippocampal volume,[4] and signal transduction abnormalities in the cultured fibroblasts of patients with melancholic depression compared to controls and those with nonmelancholic depression.[5] In a review of endophenotypes for major depression, the authors concluded that the anhedonic (melancholic) phenotype has the best empirical support.[6]

The clinical relevance of melancholic features in predicting treatment response to first-generation antidepressants has produced mixed findings. Several outpatient studies have suggested that melancholic features are more consistently associated with a good response to tricyclic antidepressants (TCAs) and a poorer response to placebo.[7–9] In addition, a meta-analysis of 38 double-blind studies of the monoamine oxidase inhibitor (MAOI) moclobemide concluded that response rates to the MAOI were highest in depressed patients with melancholic features.[10] Taken together, these studies suggest that both TCAs and MAOIs are effective in these patients.

Regarding the selective serotonin reuptake inhibitors (SSRIs), although an SSRI has shown efficacy compared to placebo in outpatients,[11] 1 study has found an SSRI to be less effective than a TCA in hospitalized elderly patients with melancholic features.[12] Two other studies also found an SSRI to be less effective than venlafaxine, a dual serotonin-norepinephrine reuptake inhibitor,[13,14] raising the question of whether SSRIs are less effective than TCAs or other antidepressants that affect multiple neurotransmitter systems when melancholic features are present, at least among inpatient samples.

In this study, we conducted an analysis examining demographic and clinical correlates of melancholic features and whether the melancholic features were predictive of response or remission in the large sample of outpatients treated with citalopram (an SSRI) in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[15–17]

METHOD

Participant Population

The study protocol was approved and monitored by the institutional review boards of the STAR*D National Coordinating Center (University of Texas Southwestern Medical Center, Dallas), the Data Coordinating Center (University of Pittsburgh), each regional center and relevant clinical site, and the Data Safety and Monitoring Board of the National Institutes of Health (Bethesda, Md.). All participants provided written informed consent prior to study enrollment.

The study enrolled outpatients with a primary diagnosis of nonpsychotic major depressive disorder (MDD) according to DSM-IV criteria,[18] established by routine clinical assessment and confirmed with a checklist completed by the clinical research coordinator.

Outpatients in routine clinical care 18 to 75 years of age with a score ≥ 14 on the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$)[19] were enrolled between July 2001 and April 2004 from 18 primary care and 23 psychiatric care practice settings. Recruitment of treatment-seeking outpatients as well as broad inclusion and minimal exclusion criteria were used to ensure recruitment of a sample representative of outpatients with MDD seen in typical clinical practice. Symptom remission for clinical decision making was defined as a score of ≤ 5 on the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rating ($QIDS\text{-}C_{16}$).[20–22]

Assessments

Clinical research coordinators collected clinical and demographic information, reviewed inclusion/exclusion criteria, and assessed current general medical conditions using the Cumulative Illness Rating Scale (CIRS)[23,24] to identify the number, average severity, and burden of concomitant general medical conditions. The self-report Psychiatric Diagnostic Screening Questionnaire (PDSQ)[25–27] was completed to determine the presence of 11 potential concurrent Axis I psychiatric disorders.

The presence of melancholic features was determined by using the 30-item Inventory of Depressive Symptomatology-Clinician Rating ($IDS\text{-}C_{30}$)[28] obtained by telephone interview with a research outcomes assessor at entry into the first treatment step.[17] Research outcomes assessors were graduate-level clinicians with psychiatric experience who were trained for reliability on research outcomes assessor ratings both before and during the study. An algorithm closely linked to DSM-IV criteria was constructed.[29] To meet our criteria for melancholic features, the patient had to score 2 or 3 in the $IDS\text{-}C_{30}$ mood reactivity or pleasure item and meet at least 3 of the following criteria based on $IDS\text{-}C_{30}$ items (quality of mood, mood variation, psychomotor retardation, psychomotor agitation, appetite decrease or weight decrease, self-outlook) obtained by a the research outcomes assessor at baseline. The $IDS\text{-}C_{30}$ scores both psychomotor retardation and psychomotor agitation over the telephone and in person largely by patient report with minimal reliance on current latency and speed of speech. Thus, the use of telephone interviews, we believe, should minimally affect these ratings.

Function and quality of life measures were collected by a telephone-based interactive voice response system.[30,31] These included the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[32] to assess quality of life, the 12-item Short-Form Health Survey (SF-12)[33] to evaluate participant perceptions of mental and physical function, and the Work and Social Adjust-

ment Scale (WSAS)[34] to measure occupational and interpersonal impairment.

Protocol Treatment

Open-label treatment with citalopram was delivered with management-based care[17] according to a treatment manual,[35] which recommended dosage based on symptom and side effects ratings obtained at each treatment visit. Depressive symptom severity over the prior week was assessed using the 16-item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR_{16}) and the QIDS-C_{16}, each of which rate the 9 diagnostic symptom domains of major depressive disorder.[20,21,36] Side effects were assessed at each visit using the Frequency, Intensity, and Burden of Side Effects Rating Scale.[16] Clinical research coordinators at each site assisted clinicians in implementing protocol treatments. To enhance appropriately vigorous dosing, a Web-based monitoring system alerted clinical research coordinators and clinicians when inadequate response had occurred in the context of acceptable side effects. The clinician manual, didactic instruction, clinical research coordinator support, and centralized monitoring with feedback constituted an intensive effort to ensure high quality care and adherence to treatment manual recommendations.[37]

The aim of treatment was defined a priori as symptom remission (QIDS-C_{16} score ≤ 5). The protocol recommended clinic visits at baseline and at weeks 2, 4, 6, 9, and 12, with additional visits as clinically indicated. While STAR*D entailed a series of randomized trials of treatments in participants without satisfactory benefit to an initial trial of citalopram, only the data on initial citalopram treatment are presented here. The planned length of each treatment trial was 12 weeks. However, participants could leave a trial early if (1) intolerable side effects occurred, (2) a remission was sustained for at least 2 weeks, or (3) minimal symptom reduction (QIDS-C_{16} total score > 9) had occurred after 6 weeks at maximally tolerated doses. Participants with at least a response ($\geq 50\%$ reduction in QIDS-C_{16} score at 12 weeks) could continue receiving treatment for up to an additional 2 weeks to determine if remission would occur with additional time.

End Points

The primary outcome (HAM-D_{17}) was obtained by independent, trained, certified, and treatment-masked research outcomes assessors using telephone-based structured interviews with participants at entry and exit from citalopram treatment. Secondary outcomes include the QIDS-SR_{16}, which was obtained by research outcomes assessors at baseline and subsequent treatment visits.

Serious Adverse Events

Common procedures were used to identify, monitor, and report adverse events and serious adverse events. Serious adverse events included death and events that were life threatening, led to hospitalization, or entailed clinically significant suicidal ideation or worsening of depression. For these analyses, we defined a suicide-related serious adverse event as one in which suicide occurred or a suicide attempt was made. We separately calculated worsening of depression and suicidal ideation of sufficient severity to require hospitalization.

Table 1. Baseline Demographic Characteristics Associated With Melancholic/Nonmelancholic Features

Demographic	Melancholic Features: No (N = 2200)	Melancholic Features: Yes (N = 675)	p
Setting, %			.0226
Primary care	39.1	34.2	
Specialty care	60.9	65.8	
Race, %			.0103
White	76.6	73.0	
African American	16.5	21.3	
Other	6.9	5.6	
Hispanic ethnicity, %			.0071
No	86.1	90.1	
Yes	13.9	9.9	
Sex, %			.0215
Male	35.1	40.0	
Female	64.9	60.0	
Marital status, %			.0928
Never married	28.4	29.6	
Married	42.6	39.0	
Divorced	25.7	29.2	
Widowed	3.4	2.2	
Employment status, %			.0008
Employed	57.1	53.0	
Unemployed	36.7	43.4	
Retired	6.2	3.6	
Insurance status, %			.4862
Private insurance	51.3	50.2	
Public insurance	14.5	13.3	
No insurance	34.2	36.5	
Age, mean (SD), y	41.1 (13.3)	39.8 (12.2)	.0526
Education, mean (SD), y	13.5 (3.3)	13.3 (3.2)	.0303
Income, mean (SD), $/mo	2361 (2796)	2345 (3695)	.0324

Statistical Methods

Summary statistics are presented as means and standard deviations for continuous variables and percentages for discrete variables. Student t tests, Wilcoxon tests, and χ^2 tests were used to compare the baseline clinical and demographic features, treatment features, side effects, and serious adverse event rates across treatments and for the entire sample.

All analyses were conducted by using all participants beginning citalopram treatment. Remission was defined as HAM-D_{17} total score ≤ 7 based on masked rater assessment and QIDS-SR_{16} total score ≤ 5 at exit from the treatment. Log-rank tests compared the cumulative proportion with remission and response across the 2 diagnostic groups. The remission threshold for the QIDS-SR_{16} of ≤ 5 was established using item response theory (IRT) analysis and was chosen as it corresponds to a score of ≤ 7 on the HAM-D_{17}.[21]

Table 2. Baseline Clinical Features Associated With Melancholic/Nonmelancholic Features

Clinical Feature	Melancholic Features: No (N = 2200), Mean (SD)	Melancholic Features: Yes (N = 675), Mean (SD)	p
CIRS			
Categories endorsed	3.1 (2.3)	3.1 (2.3)	.9356
Total score	4.4 (3.7)	4.5 (3.8)	.5847
Severity index	1.2 (0.6)	1.3 (0.6)	.1006
Symptom severity			
HAM-D_{17}	20.5 (4.5)	26.0 (5.2)	< .0001
IDS-C_{30}[a]	26.1 (7.1)	30.5 (6.9)	< .0001
QIDS-SR_{16}	15.6 (3.9)	18.2 (3.7)	< .0001
	Median (IQR)	Median (IQR)	
Age at onset of first MDE, y	21 (21)	21 (18)	.1201
No. of episodes	3 (4)	3 (4)	.5522
Length of current MDE, mo	8.1 (21)	7.9 (22)	.2995
Length of illness, y	12 (20)	13 (20)	.4407

[a]Without melancholic items.
Abbreviations: CIRS = Cumulative Illness Rating Scale, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, IDS-C_{30} = 30-item Inventory of Depressive Symptomatology-Clinician Rating, IQR = interquartile range, MDE = major depressive episode, QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology–Self-Report.

Table 3. Suicidal Risk and Course of Illness by Melancholic/Nonmelancholic Features

Clinical Feature	Melancholic Features: No (N = 2200), %	Melancholic Features: Yes (N = 675), %	p
Family history of depression			.3733
No	44.0	46.0	
Yes	56.0	54.0	
Family history of alcohol abuse			.3558
No	59.1	57.0	
Yes	40.9	43.0	
Family history of drug abuse			.2016
No	76.2	73.8	
Yes	23.8	26.2	
Family history of suicide			.9800
No	96.4	96.4	
Yes	3.6	3.6	
Family history of mood disorder			.2570
No	41.7	44.2	
Yes	58.3	55.8	
Attempted suicide			.0005
No	83.5	77.6	
Yes	16.5	22.4	
Present suicide risk			.0006
No	97.5	95.0	
Yes	2.5	5.0	
Age at onset			.9809
≤ 18 y	41.9	42.0	
> 18 y	58.1	58.0	
Anxious features			< .0001
No	52.3	28.9	
Yes	47.7	71.1	
Chronic depression			.8007
No	74.9	74.4	
Yes	25.1	25.6	
Recurrent depression			.9698
No	24.3	24.4	
Yes	75.7	75.6	
No. of general medical conditions			.3827
0	10.1	9.5	
1	15.5	14.7	
2	17.2	19.7	
3	15.3	13.0	
≥ 4	41.9	43.1	

When outcome HAM-D_{17} scores were missing, participants were assumed to be unremitted. Sensitivity analyses were conducted to determine if this method of addressing the missing data affected study results. Additionally, an imputed value for the HAM-D_{17} was generated from an IRT analysis of the relationship between the HAM-D_{17} and the QIDS-SR_{16} to evaluate the analysis of remission based on the HAM-D_{17}.

RESULTS

Demographic and Clinical Characteristics

Of 4041 participants enrolled in the STAR*D trial, 2875 met all inclusion criteria, including the specified severity by research outcomes assessor rating, and had at least 1 postbaseline visit. Baseline demographic and clinical characteristics are described in Tables 1–4. Almost two thirds of participants were female, ethnic and racial minorities were well represented, there was considerable general medical comorbidity, and the majority had a positive family history of depression and early onset recurrent major depressions. Symptom severity was in the moderately severe range (Table 2).[17]

Six hundred seventy-five subjects (23.5%) met criteria for melancholic symptom features, similar to the 21.2% in the initial STAR*D subsample already described.[29] As in that sample, melancholic features were slightly but significantly more common in men and less common in Hispanic subjects. In the present, larger sample, melancholic features were more common in specialty care settings, among African Americans, and among the unemployed, all of which were not found in the initial subsample.[29] There was a strong trend, which had previously achieved statistical significance, for participants with melancholic features to be slightly younger (Table 1). Patients with melancholic features were rated more severely ill than those without melancholic features by each depression rating scale, although this is probably accounted for, at least in part, by the fact that melancholic features include symptoms that are scored by these scales, making their selection biased toward higher scores (Table 2). However, when the IDS-C_{30} scores were compared without including melancholic features, subjects with melancholic features were still characterized by a higher severity score (Table 2). Also, anxious depression, according to a previously reported definition,[38] was significantly more common among those with melancholic features (Table 3). Age at onset, number of episodes, length of current

Table 4. Association of Melancholic/Nonmelancholic Features With Psychiatric Diagnostic Screening Questionnaire

	Melancholic Features		
Axis I Disorder	No (N = 2200), %	Yes (N = 675), %	p
GAD			< .0001
Absent	79.2	67.3	
Present	20.8	32.7	
OCD			< .0001
Absent	87.3	80.5	
Present	12.7	19.5	
Panic			< .0001
Absent	88.6	81.4	
Present	11.4	18.6	
Social phobia			.0128
Absent	69.9	64.8	
Present	30.1	35.2	
PTSD			< .0001
Absent	81.9	71.1	
Present	18.1	28.9	
Agoraphobia			< .0001
Absent	89.8	83.0	
Present	10.2	17.0	
Alcohol abuse			.0121
Absent	88.8	85.2	
Present	11.2	14.8	
Drug abuse			.0015
Absent	93.5	89.8	
Present	6.5	10.2	
Somatoform			.0018
Absent	98.1	96.0	
Present	1.9	4.0	
Hypochondriasis			.0010
Absent	96.3	93.2	
Present	3.7	6.8	
Bulimia			.3844
Absent	86.7	88.0	
Present	13.3	12.0	
No. of comorbid Axis I disorders			< .0001
0	45.0	32.8	
1	26.9	26.8	
2	14.1	15.1	
3	6.8	9.0	
≥ 4	7.2	16.3	

Abbreviations: GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder.

Table 5. Remission and Response Status by Melancholic/Nonmelancholic Features (unadjusted analysis)

	Melancholic Features			
Outcome	No (N = 2200), %	Yes (N = 675), %	Total (N = 2875), %	p
HAM-D_{17}, remission				.0050
No	71.2	76.7	72.5	
Yes	28.8	23.3	27.5	
QIDS-SR_{16}, remission				< .0001
No	65.2	73.6	67.1	
Yes	34.8	26.4	32.9	
QIDS-SR_{16}, response				.0450
No	52.1	56.5	53.1	
Yes	47.9	43.5	46.9	

Abbreviations: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology–Self-Report.

Table 6. Remission and Response Status by Melancholic/Nonmelancholic Features (adjusted analysis)

	Unadjusted		Adjusted[a]		Adjusted[b]	
Outcome	OR	p	OR	p	OR	p
HAM-D_{17}, remission	0.750	.0051	0.749	.0048	0.973	.8183
QIDS-SR_{16}, remission	0.671	< .0001	0.669	< .0001	0.895	.3159
QIDS-SR_{16}, response	0.837	.0452	0.835	.0421	1.010	.9381

[a]Adjusted for regional center.
[b]Adjusted for regional center, clinical setting, race, ethnicity, sex, employment status, years of education, total income, attempted suicide, present suicide risk, 30-item Inventory of Depressive Symptomatology-Clinician Rating severity score without melancholia items, anxious features, and number of Axis I disorders.
Abbreviations: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology–Self-Report.

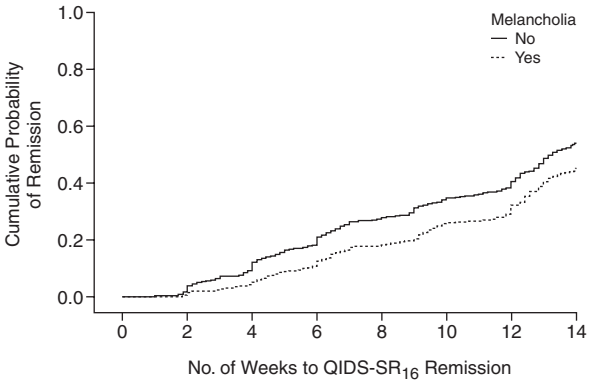
episode, and duration of illness did not distinguish those with and without melancholic features.

Participants with melancholic features were significantly more likely than those without melancholic features to have made prior suicide attempts and to be judged a present suicide risk at study entry. They did not differ in proportion with chronic depression or recurrent depression, in degree of concurrent general medical comorbidity, or on multiple family history variables (Table 3). Patients with melancholic features had more concurrent Axis I disorders on all anxiety and substance use disorders examined, as well as on somatoform disorder and hypochondriasis, and they were more likely to have at least 3 other concurrent Axis I psychiatric disorders (Table 4).

In unadjusted analyses, remission and response rates were significantly lower for those with melancholic features, and depressive symptoms were more severe at the end of treatment (Table 5). These differences remained robust when analyses were adjusted for regional center. However, the difference became insignificant on both the primary (HAM-D_{17}) and secondary (QIDS-SR_{16}) outcome measures following adjustments for baseline differences (clinical setting, race, ethnicity, sex, employment status, years of education, total income, attempted suicide, present suicidal risk, IDS-C_{30} severity scores excluding melancholia items, anxious depression, alcohol abuse, drug abuse, and count of psychiatric comorbidities [PDSQ count]) (Table 6).

Anxious depression has been associated with poorer outcome in the STAR*D study,[39] as it has in some,[40–42] but not all, previous studies.[43,44] Because of this, we sought to determine whether the effect of melancholia on remission was entirely accounted for by its association with anxious features. Therefore, we examined treatment outcomes after controlling only for regional center and the presence of anxious depression, using the definition employed in the STAR*D report of this effect.[39] In these analyses, the

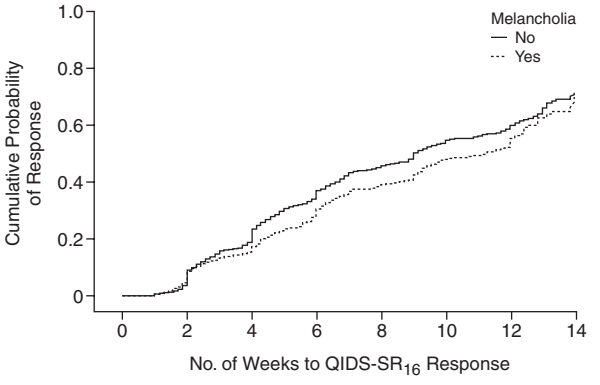
Figure 1. Cumulative Probability of Remission by Presence of Melancholic Features



Melancholia	N	N	N	N	N	N	N	N
No	2192	2020	1514	1062	742	468	318	118
Yes	671	614	478	350	254	154	109	38
Total	2863	2634	1992	1412	996	622	427	156

Abbreviation: QIDS-SR[16] = 16-item Quick Inventory of Depressive Symptomatology–Self-Report.

Figure 2. Cumulative Probability of Response by Presence of Melancholic Features



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presence of melancholic features resulted in a significantly decreased remission rate when calculated using the QIDS-SR_{16} (OR = 0.74, $p < .005$) but did not result in a significantly decreased remission rate when calculated using the HAM-D_{17} (OR = 0.847, $p = .11$) or in response when calculated using the QIDS-SR_{16} (OR = 0.923, $p = .38$). Therefore, while higher levels of anxiety among those with melancholic depression may account, at least in part, for the lower remission and response rates from the unadjusted analyses, melancholia still is associated with some evidence of decreased rate of remission even after the effect of anxiety is accounted for.

Survival curves representing the cumulative probability of remission and response by study week are presented in Figures 1 and 2, respectively. These show significant decreases in rate of both remission ($\chi^2 = 18.57$, df = 1, $p < .0001$) and response ($\chi^2 = 6.02$, df = 1, $p = .014$) over time. Compared with patients without melancholic features, those with melancholic features received both higher maximum citalopram dosages and higher dosages at study exit, but they remained in treatment for a slightly shorter time (Table 7). Correspondingly, they reported greater frequency, intensity, and burden of side effects, although the frequency with which they experienced serious adverse events and likelihood of intolerance of medication did not differ. They did experience a slightly greater number of psychiatric serious adverse events (Table 8), accounted for mainly by a few cases of increasing suicidal ideation without ensuing hospitalization.

DISCUSSION

This study provides an estimate of the prevalence and clinical features of melancholia in a clinical sample in usual treatment settings, both primary and specialty care, which should be widely generalizable. Consistent with our preliminary report[29] in this sample and with other studies,[45–47] almost one quarter of patients with major depressive disorder met criteria for melancholic features, which indicates that melancholic features occur in a clinically meaningful subset of patients in usual outpatient treatment settings. While there were some statistically significant differences on demographic variables, these were small and unlikely to be of clinical utility.

Descriptors of illness course and family history did not differ between groups. Those with melancholic features had higher depression severity scores, likely due in part to symptom overlap between melancholic and core depressive symptoms rated by these scales. Those with melancholic features were characterized by much greater Axis I comorbidity, which mainly included anxiety and substance use disorders. Presumably because of higher levels of symptomatology, patients with melancholic features were treated with higher dosages of medication and experienced a greater side effect frequency, intensity, and burden, possibly due to higher dosage.

Most importantly, the presence of melancholic features was associated with a lower likelihood of remission on the HAM-D_{17} (5.5% absolute decrease, which is a 19.1% decrease relative to those without melancholic features). However, since we assumed a priori that a patient with a missing HAM-D_{17} outcome score was a nonremitter, we also evaluated outcomes using the QIDS-SR_{16}, which was available for essentially all subjects. Melancholic features were associated with an even lower remission rate using the QIDS-SR_{16}. This decrease in remission rate was 8.4% in absolute rate, equivalent to a 24.1% decrease in rate

Table 7. Treatment Characteristics in Relation to Symptomatic Outcome by Melancholic/Nonmelancholic Features

	Melancholic Features						
	No (N = 2200)		Yes (N = 675)		Total (N = 2875)		
Treatment	N	%	N	%	N	%	p
Citalopram, maximum dose, mg/d							.0059
< 20	55	2.5	8	1.2	63	2.2	
20–39	557	25.4	137	20.4	694	24.2	
40–49	652	29.7	209	31.1	861	30.0	
≥ 50	932	42.4	318	47.3	1250	43.6	
Citalopram, dose at study exit, mg/d							.0123
< 20	92	4.2	13	1.9	105	3.7	
20–39	614	28.0	170	25.3	784	27.3	
40–49	651	29.6	204	30.4	855	29.8	
≥ 50	839	38.2	285	42.4	1124	39.2	
Time in treatment, wk							.0070
< 4	239	10.9	84	12.4	323	11.2	
≥ 4 but < 8	348	15.8	137	20.3	485	16.9	
≥ 8	1613	73.3	454	67.3	2067	71.9	
	Mean	SD	Mean	SD	Mean	SD	
No. of visits	4.8	1.5	4.7	1.6	4.8	1.5	.0013
Time to first treatment visit, wk	2.3	1.1	2.3	1.2	2.3	1.1	.5368
Time in treatment, wk	10.2	4.1	9.7	4.3	10.0	4.2	.0061
Time from final dose to study exit, wk	5.1	3.8	4.7	3.8	5.0	3.8	.0181

Table 8. Adverse Events and Side Effects by Melancholic/Nonmelancholic Features

	Melancholic Features						
	No (N = 2200 [76.5%])		Yes (N = 675 [23.5%])		Total (N = 2875)		
Variable	N	%	N	%	N	%	p
Maximum side effect frequency							.0005
None	327	15.0	121	18.0	448	15.7	
10%–25% of the time	635	29.0	173	25.7	808	28.2	
50%–75% of the time	728	33.3	186	27.6	914	32.0	
90%–100% of the time	497	22.7	193	28.7	690	24.1	
Maximum side effect intensity							.0003
None	321	14.7	121	18.0	442	15.5	
Trivial	626	28.6	167	24.8	793	27.7	
Moderate	915	41.8	257	38.2	1172	41.0	
Severe	325	14.9	128	19.0	453	15.8	
Maximum side effect burden							.0003
No impairment	434	19.8	149	22.1	583	20.4	
Minimal-mild impairment	931	42.6	242	36.0	1173	41.0	
Moderate-marked impairment	661	30.2	203	30.2	864	30.2	
Severe impairment—unable to function	161	7.4	79	11.7	240	8.4	
Serious adverse events	75	3.4	41	6.1	116	4.0	.8376
Death, nonsuicide	2	2.6	1	2.2	3	2.4	
Hospitalization for general medical conditions	37	47.4	21	46.7	58	47.2	
Medical illness without hospitalization	2	2.6	2	4.4	4	3.3	
Psychiatric hospitalization							
Substance abuse	6	7.7	2	4.4	8	6.5	
Suicidal ideation	24	30.8	12	26.7	36	29.3	
Worsening depression	4	5.1	2	4.4	6	4.9	
Other	1	1.3	1	2.2	2	1.6	
Suicidal ideation (without hospitalization)	2	2.6	4	8.9	6	4.9	
Any psychiatric serious adverse events	36	1.6	21	3.1	57	2.0	.0244
Intolerance	183	8.3	64	9.5	247	8.6	.3455

relative to those without melancholic features. Having an easily ascertained clinical category that predicts a 24% poorer response to usual starting treatment appears to be clinically useful.

When the analyses of the effect of melancholic features on remission were adjusted for baseline between-group differences, the effect of melancholic features on response and remission rates diminished in magnitude, although it was still significant on one measure. This finding indicates that some of the effect of melancholia is related to other variables that are associated with it, such as present and past suicidality and amount of other Axis I comorbidity—principally, anxiety disorders. Both anxious features and comorbid anxiety disorders have been associated with poorer treatment outcome[39] and appear to account for some, but not all, of the lower cumulative probability of both response and remission of patients with melancholic features in this study.

These data raise, but cannot answer, the important question of whether the poorer response to citalopram is reflective of lower efficacy with SSRIs for those with melancholic features, as shown for inpatients with melancholic features[12] as well as for samples of inpatients whose melancholic features were not assessed[48] but in which a higher proportion of subjects with melancholic features is likely.[49] A review of controlled studies[50] comparing the remission rates in melancholic depression with TCAs to those with SSRIs found that the remission rates were significantly better with TCAs (range, 56%–63%) than with SSRIs (range, 25%–34%) in 3 inpatient studies. However, in the subsequent levels of treatment in STAR*D, the presence of melancholic features was not predictive of differential response to sertraline compared to bupropion sustained release or venlafaxine extended release. (These data are detailed in another manuscript.[51]) This finding suggests that the presence of melancholic features does not assist in selection of medication for treatment for outpatients, although they appear to do so for inpatient samples.

The fact that the study did not include a placebo group limits the conclusions that may be drawn. It may be that the lower remission rate was actually due to a smaller probability of a placebo response to citalopram in patients with melancholic features, as shown in at least 1 controlled study.[7] Further controlled studies among outpatients, comparing an SSRI directly to other treatments and, ideally, to placebo, would be needed to definitively answer this question.

The clinical importance of these data is that it might be worthwhile to assess patients for the

presence of melancholic features prior to beginning treatment with an SSRI antidepressant, since they may be a negative prognostic factor for SSRI treatment. Further studies with a validated instrument would be required to confirm this.

There are several limitations of this study, arising mainly from the fact that STAR*D was not designed specifically to address the question we posed. We did not use a structured interview of known reliability to ascertain melancholic features. While the IDS-C_{30} algorithm to ascribe melancholic features has face validity, its performance against a structured interview has not been tested. In addition, the IDS-C_{30} was administered by telephone interview based on symptoms in the prior week rather than in the entire episode. One study[28] did find that the IDS-C_{30} items that defined endogenous symptoms were valid when compared to a structured interview assessing the entire episode. However, because ratings were based on only the patient's symptoms in the previous week, this procedure might not accurately represent the symptom profile of the entire episode. DSM-IV specifies that loss of pleasure and lack of reactivity should be assessed for the most severe period of the current episode. Therefore, we may have underestimated the prevalence of melancholic features in this sample. Additionally, our method could also not ascertain whether these melancholic features were stable either during the episode or across the multiple episodes experienced by most of our patients. Finally, since only outpatients with unipolar nonpsychotic MDD were enrolled, these results may not generalize to patients with bipolar disorders or to inpatients or other more severely ill patients.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), norepinephrine (Levophed and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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