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Research report

Impairment and distress patterns distinguishing the melancholic depression subtype: An iSPOT-D report ☆

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ABSTRACT

Background: This study seeks to provide a comprehensive and systematic evaluation of baseline clinical and psychological features and treatment response characteristics that differentiate Major Depressive Disorder (MDD) outpatients with and without melancholic features. Reflecting the emphasis in DSM-5, we also include impairment and distress.

Methods: Participants were assessed pre-treatment on clinical features (severity, risk factors, comorbid conditions, illness course), psychological profile (personality, emotion regulation), functional capacity (social and occupational function, quality of life) and distress/coping (negativity bias, emotional resilience, social skills, satisfaction with life). Participants were randomized to sertraline, escitalopram or venlafaxine extended-release and re-assessed post-treatment at 8 weeks regarding remission, response, and change in impairment and distress.

Results: Patients with melancholic features ($n=339$; 33.7%) were distinguished clinically from non-melancholics by more severe depressive symptoms and greater exposure to abuse in childhood. Psychologically, melancholic patients were defined by introversion, and a greater use of suppression to regulate negative emotion. Melancholics also had poorer capacity for social and occupational function, and physical and psychological quality of life, along with poorer coping, reflected in less emotional resilience and capacity for social skills. Post-treatment, melancholic patients had lower remission and response, but some of this effect was due to the more severe symptoms pre-treatment. The distress/coping outcome measure of capacity for social skills remained significantly lower for melancholic participants.

Limitations: Due to the cross-sectional nature of this study, causal pathways cannot be concluded.

Conclusions: Findings provide new insights into a melancholic profile of reduced ability to function interpersonally or effectively deal with one's emotions. This distinctly poorer capacity for social skills remained post-treatment. The pre-treatment profile may account for some of the difficulty in achieving remission or response with treatment.

1. Introduction

The debate over the defining features of melancholic depression can be traced back to the third century (Day and Williams, 2012). Previous attempts to differentiate the melancholic and non-melancholic type have shown some patterns in baseline and treatment response characteristics (Bobo et al., 2011; McGrath

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et al., 2008; Parker and Hadzi-Pavlovic, 1996; Taylor and Fink, 2006), but not enough to impact our current diagnostic definition of this subtype. This is reflected in the unchanged nature of melancholic features according to the DSM-5, released in May 2013. What has changed is the increased importance of clinical distress or impairment in social, occupational or other important areas of life for the definition of Major Depressive Disorder (MDD), now listed as criterion B instead of C. In light of the change, the defining features of melancholic depression will be re-investigated, but this time including the under-investigated areas of distress and impairment.

Melancholic features of MDD have been defined by criteria related to disturbances in affect (including one's ability to interact), psychomotor disturbances (retardation or agitation), cognitive processes and other vegetative dysfunction symptoms (Parker and Hadzi-Pavlovic, 1996; Roger et al., 2010). According to the DSM-IV and DSM-5, the cardinal criterion is anhedonia, the loss of pleasure in all or almost all activities or the lack of reactivity to stimuli that are normally pleasurable (American Psychiatric Association, 2000). Melancholic depression is commonly conceptualized as the biological form of MDD (Parker and Hadzi-Pavlovic, 1996), characterized by a more severe clinical presentation and poorer prognosis. Yet empirical data is currently lacking and questions remain on whether melancholia is qualitatively distinct enough to be considered a clinically useful marker that could inform clinicians about treatment choice.

To date, the most consistent findings are those that suggest greater clinical symptom severity among melancholic compared to non-melancholic patients (Bobo et al., 2011; Caldieraro et al., 2013; McGrath et al., 2008; Parker et al., 2003; Quinn et al., 2012; Schotte et al., 1997) and other depressed subtypes (Angst et al., 2007; Uher et al., 2011), as well as a greater likelihood of psychiatric comorbidities (Bobo et al., 2011; McGrath et al., 2008; Szadoczky et al., 2003) including anxiety (Bobo et al., 2011, Kendler, 1997; McGrath et al., 2008; Wiethoff et al., 2010). Evidence that melancholic MDD is associated with other unique clinical characteristics is less consistent. Some findings suggest that melancholic MDD is distinguished by a greater number of depressive episodes (Alvarez et al., 2011; Uher et al., 2011), greater physiological dysfunction (e.g., a central hypernoradrenergic state (Wong et al., 2000) or hypothalamic-pituitary-adrenal axis hyperactivity (Lamers et al., 2013)), less dysfunction of personality—namely exhibiting higher perfectionism, cooperativeness and effectiveness (with some resemblance to characteristics of conscientiousness and openness) (Rubino et al., 2009)—and less neuroticism (Kendler, 1997).

Specific demographic factors that may distinguish melancholic from non-melancholic MDD are mixed. Previous literature suggests minor trends of a greater likelihood to be male (Gili et al., 2012; Khan et al., 2006; McGrath et al., 2008); greater unemployment (Bobo et al., 2011; McGrath et al., 2008) and non-significant trends of lower mean age (Bobo et al., 2011; McGrath et al., 2008; Tedlow et al., 2002). Despite its conceptualization as biological in origin, melancholic MDD has not been associated with family history of MDD (Alvarez et al., 2011). The melancholic subtype has been significantly associated with a history of greater exposure to early life trauma, particularly to experiences of abuse (Bobo et al., 2011; Lamers et al., 2010); however, early-life stress as a whole does not always reach the level of significance (Bobo et al., 2011). Regarding outcomes, some studies have linked melancholic MDD to greater suicidality or suicidal vulnerability (Bobo et al., 2011; McGrath et al., 2008; Szadoczky et al., 2003), while others have observed a lower suicide rate in this subtype compared to non-melancholic MDD (Hansen et al., 2003).

Findings on whether DSM-IV criterion melancholic MDD is useful in predicting the general response to antidepressant medications are decidedly variable. Studies have reported melancholics to be less responsive to antidepressant medication to a clinically significant (Gili et al., 2012) or insignificant (Uher et al., 2011) degree, more responsive than non-melancholics (Yang et al., 2013) or to show no differences (Bobo et al., 2011). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, melancholics were significantly less likely than non-melancholics to achieve remission with citalopram (a selective serotonin reuptake inhibitor; SSRI), but the difference was no longer significant after adjusting for baseline severity (McGrath et al., 2008).

Findings on preferential antidepressant drug types are also inconclusive. For example, in the second phase of the outpatient STAR*D study, citalopram non-responders had a non-significantly lower probability of remission among melancholics compared to non-melancholics prior to controlling for baseline severity, but no evidence of preferential response to any of the three second-step medications [sertraline, an SSRI; venlafaxine-extended release, a serotonin norepinephrine reuptake inhibitor (SNRI) or bupropion sustained release, an aminoketone] (Rush et al., 2008). However, in an inpatient melancholic sample, Sheehan et al. (2009) found venlafaxine (an SNRI) superior to fluoxetine (an SSRI) on one of five primary outcome measures.

Given the mixed findings regarding distinguishing features and antidepressant response in melancholic patients, this report seeks to provide the a comprehensive review of pre-treatment and outcome characteristics in a large international outpatient sample to answer the following questions:

1) Which pre-treatment baseline clinical features and psychological profile characteristics distinguish those with MDD who have and do not have melancholic features?
2) Which pre-treatment baseline domains of functional capacity and distress/coping characteristics distinguish those with MDD who have and do not have melancholic features?
3) How are the MDD participants with melancholic features distinguishable from those without regarding symptom response and remission, functional or distress/coping outcomes post-treatment?

2. Methods

2.1. Study overview

The International Study to Predict Optimized Treatment for Depression (iSPOT-D) is a phase IV, multi-site, international, randomized open-label trial designed to define markers of treatment response to commonly prescribed medications in an adult depressed, outpatient population. All participants were either antidepressant medication naïve or washed-out. Assessments were collected at pre-treatment baseline and post-treatment at 8 weeks. The iSPOT-D trial was designed with no placebo arm as to best mimic real-world practice. In this way, findings also reflect the biases that exist in routine practice and promote the translatability of the findings. For more details on the study protocol design, rationale and methods, see Williams et al. (2011).

2.2. Study participants

Potential participants were screened by telephone. Those appearing to meet the inclusion/exclusion criteria attended an in-person baseline visit. Those eligible were outpatient adults (18–65 years old) diagnosed with current single-episode or recurrent nonpsychotic MDD. Patients were excluded if they had certain disorders (i.e. psychotic, bipolar, eating, obsessive compulsive, post-traumatic stress, axis II personality), current drug or alcohol dependence, history of head trauma with loss of consciousness, or

any condition contraindicating any study antidepressant (including previous non-response). Inclusion/exclusion criteria were framed to recruit participants representative of patients seen in primary care and outpatient psychiatric services who would typically receive antidepressant medication in routine practice.

MDD participants were drawn from a total of 17 sites in 5 countries. These included 9 sites in the USA (3 academic sites at Ohio State University, Stanford University, University of Missouri and 6 clinical sites at the ADD Treatment Center, Mission Viejo California, Brain Resource Center, Manhattan, New York, Brain Resource Center, New Jersey, the Center for Healing the Human Spirit, Tarzana California, NeuroDevelopment Center, Providence Rhode Island, Shanti Clinical Trials, Colton California), 4 academic sites in Australia (Flinders University, Adelaide South Australia, Monash University, Melbourne Victoria, Swinburne University, Melbourne Victoria and the University of Sydney, NSW), 2 clinical sites in the Netherlands (Brainclinics, Nijmegen and Psy-care, Valkenburg), 1 academic site in New Zealand (University of Auckland), and 1 clinical site for South Africa (Brain Health, Johannesburg Gauteng). Further details about the clinical characteristics of the study sample are reported in Saveanu et al. (in press).

This study complies with the "Good Clinical Practice" principles in the US FDA Code of Federal Regulation as well as the laws and regulations of each country the study was conducted in. The study was approved by each site's governing Institutional Review Board and was conducted according to the principles of the Declaration of Helsinki 2008, the International Conference on Harmonization (ICH) guidelines. All participants were provided an information and consent form, and had the opportunity to ask research personnel questions prior to signing the consent form. All participants were assessed to ensure that they had appropriate decision making capacity and understood all procedures involved in the study. Participants were also informed that, if they chose to participant, they are able to withdraw from the study at any time.

2.3. Definition of melancholic features

Face-to-face assessments for study inclusion included the Mini-International Neuropsychiatric Interview (MINI Plus) (Sheehan et al., 1998) and the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) (Hamilton, 1960), the latter to confirm a severity score of ≥ 16. Melancholic status was defined according to DSM-IV criteria from the MINI Plus as well as a sign-based rating system of psychomotor disturbance (CORE, Parker and Hadzi-Pavlovic, 1996) score of > 7.

The CORE scale is an 18-item scale that provides an observer-rated assessment of cognitive symptoms, agitation and psychomotor retardation characteristic of melancholic MDD (Kaplan et al., 2010; Parker and Hadzi-Pavlovic, 1996; Rush and Weissenburger, 1994). It is a scale constructed to capture the utility of considering psychomotor disturbance as a surface marker rather than as a symptom. Scores on this measure (in comparison to symptom reports of psychomotor disturbance) are reported to show marked specificity of "substantial" observable psychomotor disturbance being present in melancholic depression and absent in nonmelancholic depression with a score of 8 or more (Parker, 2000). Validation studies were supported by sociodemographic, psychosocial and biological variables, as well as the capacity to predict ECT response (Parker, 2000). In one validation study involving dexamethasone suppression testing (DST) of 100 depressed patients (Mitchell, 1996), DST nonsuppression rates rose linearly (from 30% to 90%) as CORE scores increased. In comparison to other measures of melancholia (e.g., DSM-III, DSM-III-R, Newcastle), CORE scores have shown superior discrimination across a range of clinical givens or ascriptions to melancholia (Parker and Hadzi-Pavlovic, 1996), including psychosocial risk factors, neuropsychological testing (e.g., higher rates of cognitive processing problems), and treatment response (e.g., strong prediction of ECT response). We included the CORE to limit the possibility of overestimating melancholic status (Pier et al., 2004; Austin et al., 1999; Parker et al., 1994). Our iSPOT-D sample includes patients with comorbid anxiety. Previous studies suggest that use of the CORE limits the possibility of falsely allocating a patient to the melancholic group when the apparent melancholia is in fact due to the consequences of anxiety (Parker and Hadzi-Pavlovic, 1996, p. 121). Given that psychosis was an exclusion criteria for iSPOT-D it is unlikely that the use of the CORE, and the psychomotor symptoms it assesses, produced a greater emphasis on psychotic depression.

2.4. Protocol treatment

Participants were randomized to receive escitalopram, sertraline or venlafaxine-XR at a 1:1:1 ratio. Any psychotropic medication, except occasional use of sleep aid and anxiolytics, were discontinued and washed-out prior to baseline assessments. Randomization was carried out using PhaseForward's™ validated, Web-based Interactive Response Technology. A blocked randomization procedure (block size: 12) was undertaken centrally and applied irrespective of the clinically defined subtypes. Investigators/raters and participants were not blind to treatment assignment.

The assigned antidepressant was prescribed and doses were adjusted by the participant's treating physician according to routine clinical practice. Additional medication for associated symptoms (e.g., insomnia) or medication-induced side effects (e.g., nausea) were allowed as they reflect common practice. Any treatment for concurrent general medical conditions, except medications contraindicated with the study-assigned antidepressants, were allowed and recorded. Psychotherapy was proscribed during the first 8 weeks of treatment.

2.5. Pre-treatment baseline measures

2.5.1. Clinical features

Symptom severity scores were assessed at baseline using the clinician rated $HRSD_{17}$, the self-rated 16-item Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$) (Rush et al., 2003; Trivedi et al., 2004), and the self-rated Depression Anxiety Stress Scale (DASS) (Lovibond, 1998; Lovibond and Lovibond, 1995), for a Depression severity sub-score, as well as Anxiety and Stress sub-scores.

Risk factors were assessed as part of the clinical interview, including age, sex, race and education level completed. Family history of illness, early life stress events and work status were collected in computer based self-report questionnaires.

Course of illness and comorbidities were collected at baseline using the MINI Plus.

2.5.2. Psychological profile

This information was collected using the self-report questionnaires the NEO-Five Factor Inventory (NEO-FFI) and the Emotion Regulation Questionnaire (ERQ) (Gross and John, 2003).

2.5.3. Functional capacity

This was assessed using the clinician-rated Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992) and the self-report World Health Organization Quality Of Life (WHOQOL) scale (World Health Organization, 1998).

2.5.4. Distress and coping measures

These included the self-report Brief Risk-resilience Index for Screening (BRISC) (Williams et al., 2012) assessment and the Satisfaction with Life Scale (SWLS) (Diener et al., 1985).

2.6. Post-treatment outcome

The primary outcome measure was remission, defined by a week 8 $HRSD_{17}$ score ≤ 7. Secondary outcome measures included remission (week 8 QIDS-SR_{16} score ≤ 5), response ($\geq 50\%$ decrease from baseline on the $HRSD_{17}$ or QIDS-SR_{16}) and significant change in total scores from baseline to week 8 for the measures of social and occupational function (SOFAS), quality and satisfaction with life (WHOQOL and SWLS), and emotional risk and resilience (BRISC).

Study site personnel contacted participants by telephone at day 4 and weeks 2, 4 and 6 to monitor antidepressant dosage, compliance, concomitant medications and adverse events. At these same time points, participants completed two Web-questionnaires: the QIDS-SR_{16} and the Self-Rated Global Measure of the Frequency, Intensity and Burden of Side Effects Rating (FIBSER) (Wisniewski et al., 2006) to measure severity and side effect burden.

2.7. Statistical analyses

Of the 1008 participants enrolled in the study, two were missing information necessary to categorize the melancholic subtype, leading to a final baseline sample of 1006 participants, 339 of which met the criteria for melancholia. Participants were considered to complete the study if they had a complete week 8 QIDS-SR_{16}, $HRSD_{17}$, or SOFAS. All treatment response analyses were conducted using a per protocol sample. From the 1006 initial participants with valid melancholic information, 160 participants were excluded for not starting the study treatment or receiving a medication that did not match the randomized medication. An additional 192 participants were excluded from the analysis for not receiving at least 6.0 weeks of treatment, missing the week 8 assessment, having a dose value that was inconsistent with the randomized medication, or washing out of the medication prior to the week 8 assessment. This results in a total of 654 participants used in this analysis. Not all participants had complete data. The specific number of participants for each measure is reported. Additionally, percentages are reported using the total number of observed cases as the denominator.

To determine distinguishing features at baseline and avoid false positives, a predictive model of melancholia was used. Logistic regression analyses were run with melancholia as the outcome and the baseline measure as the predictor on the full sample. *p*-Values are reported for unadjusted models and for models adjusted for clinical site and baseline level of severity ($HRSD_{17}$).

To assess whether melancholia predicts treatment response, logistic or linear regression analyses were run with the primary or secondary outcomes as the dependent variable and melancholia as a predictor using the observed cases. Odds ratios and *p*-values are reported in unadjusted models and models adjusted for clinical site, interaction with medication arm (when medication arms were combined), and baseline level of severity ($HRSD_{17}$). Clinical site and medication arm were treated as a categorical measures.

As previously specified for the iSPOT-D trial (Williams et al., 2011), the first half of the sample (reported here) are intended to be an exploratory study to generate hypotheses, while the second half is intended to be used for replication of the hypotheses generated. Therefore, in our analyses we used an alpha level of .05 to determine significance and results should be interpreted accordingly.

3. Results

3.1. Do pre-treatment baseline clinical features and psychological profile characteristics distinguish melancholic MDD?

Compared with non-melancholics, melancholic MDD participants had significantly more severe symptoms of depression, as assessed by the $HRSD_{17}$ ($p < 0.01$), QIDS-SR_{16} ($p < 0.01$) and DASS depression scale ($p < 0.01$). Regarding risk factors, melancholic MDD was distinguished by a lower level of education in both the unadjusted model ($p < 0.01$) and adjusted model, after co-varying for site and baseline severity ($p < 0.01$). The presence of early life stress did not significantly predict the presence of melancholic MDD. However, when categorized by type of stress (i.e., abuse, family breakup, disaster/war, familial health, personal health, bullying/birth complications, adoption), abuse-type early-life stress was significant both after ($p=0.01$) and after adjusting for site and baseline severity($p=0.02$) (see Table 1). Neither family history of depression nor age of MDD onset distinguished melancholic MDD.

Melancholic MDD was distinguished by the comorbid disorders of DSM-IV dysthymia and specific phobia in the unadjusted model, but this effect was moderated by covariates. Distinguishing psychological factors (beyond the influence of baseline characteristics) include the personality traits of lower extraversion ($p=0.01$) on the NEO-FFI and higher levels of suppression of negative emotion ($p=0.01$) on the ERQ. Lower NEO-FFI conscientiousness was also distinguishing ($p=0.02$), however only present in the unadjusted model. Dimensional severity of anxious arousal and generalized stress, assessed by the DASS, did not contribute to predicting melancholic MDD (Table 1).

3.2. Baseline impairment in functional capacity and distress/coping characteristics

On functional status measures, melancholic MDD was predicted by lower social and occupational functioning (SOFAS) ($p < 0.01$), and poorer quality of physical ($p=0.03$) and psychological health ($p < 0.01$) (WHOQOL) in the melancholic group beyond the influence of baseline depression severity or site. Distress and coping was also distinct, reflected in less emotional resilience ($p=0.01$) and capacity for social skills ($p < 0.01$) again beyond the influence of baseline depression severity or site. Negativity bias (BRISC), Satisfaction with life (SWLS) and the quality of social relationships and environment (WHOQOL) did not predict the melancholic subtype (Table 1).

3.3. Treatment outcome

After an average of 7.7 weeks of treatment, melancholic MDD was distinguished by a lower rate of remission ($p < 0.01$) and response ($p < 0.01$) on the $HRSD_{17}$ in the unadjusted model (Table 2). Beyond the influence of site and severity, the melancholic MDD group was distinguished by poorer capacity for social skills post treatment (according to BRISC). Other outcome measures, such as remission and response according to the QIDS-SR_{16} and functional (SOFAS and WHOQOL) and distress measures (BRISC negativity bias, emotional resilience and SWLS) demonstrated a non-significantly poorer outcome for the melancholic group compared to the non-melancholic group. When outcome measures are adjusted for baseline characteristics, differences in remission between melancholic and non-melancholic participants on the $HRSD_{17}$ become non-significant (Table 2), indicating that this outcome difference was due in large part to higher baseline severity. The response data (according to $HRSD_{17}$), after controlling for baseline characteristics, was bordering significance ($p=0.05$) indicating that the melancholic group was less likely to response to treatment.

Melancholia was not a significant differential moderator of response or remission to a particular type of medication for either $HRSD_{17}$ or QIDS-SR_{16}, or for significant change across functional outcomes of SOFAS, WHOQOL or SWLS (Supplementary Table 1). While the average dose of venlafaxine-XR dosage was lower than the suggested noradrenergic threshold of 150 mg (Clerc et al.,

Table 1
Baseline clinical features, psychological profile, functional capacity and distress/coping of the melancholic MDD and non-melancholic MDD groups.

Baseline characteristics	Melancholic MDD			Non-melancholic			*p*-Value[+]	*p*-Value[++]
Clinical features								
Symptom severity	***N***	**Mean**	**SD**	***N***	**Mean**	**SD**		
$HRSD_{17}$	339	23.7	4.4	667	21.0	3.6	0.00**	0.00**
$QIDS\text{-}SR_{16}$	317	15.2	3.8	644	14.1	3.8	0.00**	0.12
DASS depression	301	23.6	9.7	617	21.5	9.4	0.00**	0.09
DASS anxiety	301	9.4	6.9	617	8.5	6.6	0.06	0.68
DASS stress	301	18.4	8.7	617	18.1	8.2	0.56	0.08
Risk factors	***N***	**Count**	**%**	***N***	**Count**	**%**		
Family history of MDD	339	75	22.1	667	158	23.7	0.58	0.44
Gender (males)	339	183	54.0	667	387	58.0	0.22	0.80
Age (years)	339	37.7	12.6	667	37.9	12.6	0.78	0.95
Education (years)	339	14.1	2.9	667	14.7	2.7	0.00**	0.00**
Exposure to Early Life Stressors (binary presence)	302	273	90.4	615	543	88.3	0.34	0.32
Specific exposure to early life Abuse	306	200	65.4	618	345	55.8	0.01**	0.02*
Race							0.02**	0.08
Black	339	71	20.9	667	96	14.4		
Other	339	64	18.9	667	148	22.2		
Unknown	339	3	0.9	667	1	0.1		
White	339	201	59.3	667	422	63.3		
Employment							0.39	0.09
Employed	339	157	46.3	667	347	52.0		
Other	339	26	7.7	667	47	7.0		
Retired	339	13	3.8	667	30	4.5		
Student	339	69	20.4	667	120	18.0		
Unemployed	339	21	6.2	667	45	6.7		
Unknown	339	53	15.6	667	78	11.7		
Comorbid conditions								
Dysthymia	339	95	28.0	667	124	18.6	0.00**	0.06
Panic Disorder	339	36	10.6	667	49	7.3	0.08	0.97
Agoraphobia	339	32	9.4	666	42	6.3	0.07	0.18
Social phobia	339	34	10.0	667	59	8.8	0.54	0.84
Specific phobia	339	26	7.7	666	29	4.4	0.03*	0.32
GAD	339	24	7.1	667	45	6.7	0.84	0.37
Illness course								
Age at first episode (years)	333	22.3	12.3	656	23.2	11.9	0.29	0.95
Duration of MDD (years)	333	14.8	12.1	656	14.2	12.2	0.42	0.95
Number of episodes							0.56	0.83
0 (current episode)	330	0	0.0	653	2	0.3		
1	330	36	10.9	653	66	10.1		
2	330	24	7.3	653	61	9.3		
3	330	39	11.8	653	66	10.1		
4	330	37	11.2	653	83	12.7		
5 or more	330	194	58.8	653	375	57.4		
Previous suicide attempt	339	42	12.4	667	75	11.2	0.59	0.27
Psychological profile								
NEO personality								
Agreeableness	298	28.7	6.1	611	28.4	6.5	0.44	0.05
Conscientiousness	298	25.2	7.4	611	26.5	7.6	0.02*	0.08
Extraversion	298	19.6	6.8	611	21.0	6.5	0.00**	0.01**
Openness	298	28.3	7.1	611	28.4	7.1	0.83	0.22
Neuroticism	298	31.3	6.8	611	31.3	6.9	0.92	0.15
ERQ								
Reappraisal	321	4.2	1.2	648	4.4	1.2	0.08	0.17
Suppression	322	4.3	1.4	647	4.1	1.3	0.00**	0.01**
Functional capacity								
SOFAS	338	52.9	8.9	666	57.4	8.9	0.00**	0.00**
WHOQOL								
Overall	311	2.6	1.0	630	2.8	0.9	0.00**	0.01**
Physical health	310	50.1	14.5	626	52.7	14.3	0.01**	0.03*
Psychological	308	32.3	14.0	627	35.8	13.6	0.00**	0.00**
Social relationships	309	36.6	19.9	628	39.6	19.8	0.03*	0.25
Environment	308	50.9	15.7	624	52.1	15.8	0.27	0.86
Distress and coping								
BRISC								
Negativity bias	317	64.4	12.7	632	66.2	11.7	0.03*	0.79
Emotional resilience	322	42.9	6.4	636	44.3	6.4	0.00**	0.01**
Social skills	322	33.2	6.3	640	34.8	5.9	0.00**	0.00**

1994; Redrobe et al., 1998), remission and response did not significantly differ when the sample was grouped into < 150 mg and ≥ 150 mg.

Similarly, melancholic MDD was also not distinguished on other treatment factors of attrition, dose, weeks of treatment received and side effect burden, with all items not significantly different

Table 1 (*continued*)

Baseline characteristics	Melancholic MDD			Non-melancholic			*p*-Value[+]	*p*-Value[++]
SWLS	320	11.2	5.3	645	11.7	5.4	0.13	0.99

Note: baseline $HRSD_{17}$ is not appropriated when adjusted for $HRSD_{17}$. Also, the non-significant result of the QIDS-SR and DASS, when adjusted for site and baseline severity, is indicative of the analogous depression severity construct that is being measures. There is a statistically significant effect for years of education but this effect is not likely to represent a meaningful difference given the mean difference is less than a full year and because of the tight standard deviation.
Abbreviation: MDD, Major Depressive Disorder; SD, Standard Deviation; $HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; $QIDS\text{-}SR_{16}$, 16-item Quick Inventory of Depressive Symptomatology; DASS, Depression Anxiety Stress Scale; GAD, Generalized Anxiety Disorder; NEO, NEO-Five Factor Inventory; ERQ, Emotion Regulation Questionnaire; SOFAS, Social and Occupational Functioning Assessment Scale; WHOQOL, World Health Organization Quality Of Life; BRISC, Brief Risk-resilience Index for Screening; SWLS, Satisfaction with Life Scale.

[+] Unadjusted linear regression.
[++] Linear regression adjusted for clinical site and baseline severity as measured by $HRSD_{17}$.
* $p < .05$.
** $p < .005$.

Table 2
Remission, response, functioning and quality of life outcomes by melancholic/non-melancholic MDD groups (unadjusted[+] and adjusted[++]).

Treatment outcome	Melancholic MDD			Non-melancholic MDD			*p*-Value[+]	*p*-Value[++]
	N	**Count**	**%**	***N***	**Count**	**%**		
Remission/response defined by change in symptom severity								
$HRSD_{17}$ remission	208	74	35.6	446	228	51.1	0.00**	0.53
$HRSD_{17}$ response	208	117	56.3	446	298	66.8	0.01**	0.05
$QIDS\text{-}SR_{16}$ remission	201	68	33.8	433	173	40.0	0.14	0.80
$QIDS\text{-}SR_{16}$ response	190	93	48.9	426	235	55.2	0.15	0.47
	N	**Mean**	**SD**	***N***	**Mean**	**SD**	***p*-Value[+]**	***p*-Value[++]**
Post-treatment functional capacity and distress/coping								
SOFAS	208	67.5	11.0	446	71.3	10.7	0.15	0.12
WHOQOL	198	3.1	1.0	430	3.3	0.9	0.14	0.13
BRISC negativity bias	202	76.9	12.4	432	79.2	11.4	0.54	0.45
Emotional resilience	202	46.4	7.1	435	47.6	6.9	0.79	0.99
Social skills	203	36.1	6.0	439	37.8	5.6	0.05	0.03*
SWLS	203	15.0	7.2	435	16.1	6.9	0.68	0.86

Note: logistic regression, with no covariates, was used to assess the prediction of melancholia for $HRSD_{17}$ and $QIDS\text{-}SR_{16}$ remission/response. Linear regression, with and without covariates were used to assess the prediction of melancholia for the week 8 score of SOFAS, WHOQOL, BRISC and SWLS.
Abbreviations: MDD, Major Depressive Disorder; $HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; $QIDS\text{-}SR_{16}$, 16-item Quick Inventory of Depressive Symptomatology; SD, Standard Deviation; SOFAS, Social and Occupational Functioning Assessment Scale; WHOQOL, World Health Organization Quality Of Life; BRISC, Brief Risk-resilience Index for Screening; SWLS, Satisfaction with Life Scale.

[+] Unadjusted linear regression.
[++] Linear regression adjusted for clinical site and baseline severity as measured by $HRSD_{17}$.
* $p < .05$.
** $p < .005$.

between the melancholic and non-melancholic groups (Table 3). These factors also did not differ between treatment arms.

4. Discussion

4.1. Which pre-treatment baseline clinical features and psychological profile characteristics distinguish those with MDD who have and do not have melancholic features?

Consistent with previous literature the melancholic group has distinctly greater symptom severity across all measures of depression severity (HDRS, QIDS-RS and DASS depression subscale). However severity alone did not characterize this subtype. Beyond the influence of baseline severity, the outpatient MDD group with melancholic features was distinguished in clinical features of a lower level of education and greater exposure to early-life abuse, and had psychological profile of higher introversion and poorer emotional regulation by the suppression of negative emotions. The distinctive psychological profile indicates that the melancholic type finds more pleasure in being alone and will suppress negative emotions instead of dealing with them. While this introversion finding is not congruent with Kendler's work (1997), which found no significant association between extroversion and history of MDD or melancholia (Kendler, 1997), this personality trait has been linked to melancholic symptoms, namely blunted processing of incentive motivation and lower affect (Depue and Collins, 1999). Introversion's association with poorer reward processing (Smillie, 2013) and reinforcement learning (Skatova et al., 2013) could also be indicative of the avoidance of potential conflicts (agreeableness, which is bordering significance) or negative emotions (ERQ) where reward is reduced for dealing with the unpleasant short-term.

Consistent with Bobo et al. (2011), only the abuse type of early-life trauma significantly predicted melancholic MDD after controlling for baseline severity. This idea of different depressive symptomatic profiles being associated with different classes of stressful life events was supported by Keller et al. (2007). Exposure to abuse could potentially cause a vulnerability to melancholic MDD later in life, an idea supported by the animal model of 'learned helplessness' in which animals that experience inescapable stressors exhibit decreased spontaneous activity (Sherman et al., 1982). The finding that lower years of education predicted melancholic MDD was not consistent with Bobo et al. (2011), who found this effect to

Table 3
Attrition, treatment and side effects by melancholic/non-melancholic MDD groups.

Outcome	Melancholic MDD			Non-melancholic MDD			*p*-Value[+]	*p*-Value[++]
	N	Mean	SD	*N*	Mean	SD		
Weeks of treatment	208	7.7	0.6	446	7.7	0.5	0.91	0.38
Dose at 8 weeks (mg/day) escitalopram	72	12.3	5.7	114	12.3	7.8	0.99	0.85
Sertraline	67	54.4	25.1	166	64.1	35.4	0.04	0.14
Venlafaxine-XR	69	85.9	36.4	135	82.4	39.8	0.54	0.42
	N	Count	%	*N*	Count	%		
Attrition	339	103	30.4	667	182	27.3	0.30	0.52
Maximum side effect frequency (% of the time)							0.78	0.87
None	198	79	39.9.	428	167	56.8		
10–25%	198	83	42.4	428	183	32.5		
50–75%	198	26	13.1	428	43	10.0		
90–100%	198	10	5.1	428	3	0.7		
Maximum side effect intensity							0.88	0.80
None	198	77	38.9	428	167	39.0		
Trivial	198	84	42.4	428	183	42.8		
Moderate	198	33	16.7	428	73	17.1		
Severe	198	4	2.0	428	5	1.2		
Maximum side effect burden (impairment)							0.38	0.26
None	198	104	52.5	428	243	56.8		
Minimal-mild	198	72	36.4	428	139	32.5		
Moderate-marked	198	18	9.1	428	43	10.0		
Severe/unable to function	198	4	2.0	428	3	0.7		

Note: attrition figures here are defined as missing face-to-face and self-report week 8 of QIDS-SR_{16}, SOFAS, and $HRSD_{17}$. Percentages are calculated using the baseline sample as the denominator. Side-effect measures are according to the Self-Rated Global Measure of the Frequency, Intensity and Burden of Side Effects Rating (FIBSER)[37] recorded at or close to the week 8 visits.
Note: recommended treatment arms doses ranges were: escitalopram 10–20 mg/day, sertraline 50–200 mg/day, venlafaxine-XR 75 mg/day increased to 150–225 mg/day as required.
Abbreviations: MDD, Major Depressive Disorder; SD, Standard Deviation; QIDS-SR_{16}, 16-item Quick Inventory of Depressive Symptomatology; SOFAS, Social and Occupational Functioning Assessment Scale; $HRSD_{17}$, 17-item Hamilton Rating Scale for Depression.
[+] Unadjusted linear regression.
[++] Linear regression adjusted for clinical site and baseline severity as measured by $HRSD_{17}$.

be non-significant. However, Kendler et al. (2013) found that the two factors that best predicted melancholic MDD (cognitive/psychomotor and neurovegetative symptoms) were also significantly associated with lower education attainment.

Our results suggest that the long-standing theory that melancholia is 'endogenous' or biologically-based was not supported by our clinical or demographic data of family history, age of onset or onset at $\leq$18 years of age, which were non-significant even prior to controlling for site and symptom severity. These null findings accord with empirical research (Alvarez et al., 2011; Dougherty et al., 2009; Kendler, 1997; McGrath et al., 2008), but not with the earlier conception that melancholia is familially transmitted. Twin studies or genetic analyses may help to clarify the inconsistent findings on whether melancholia is biologically based.

Our null results for the comparison of melancholic and non-melancholic groups on clinical characteristics of stress and anxiety suggest some departures from the traditional characterization of melancholic MDD. Among the prevailing theories of melancholia are the stress models that propose chronic mild stress, hyperarousal and hyperactivity may lead to the hypoactive responses that characterizes melancholia (Day and Williams, 2012). In our large cohort, melancholia was not predicted by symptoms of anxiety and stress, nor by co-morbid anxiety disorder diagnoses of panic disorder, social or specific phobias, or generalized anxiety. These findings suggest self-reported current symptoms related to stress and arousal are not necessarily characteristic of the melancholic subtype. By contrast, prior exposure to early life trauma, particularly abuse, was a predictor of melancholia. This latter finding is consistent evidence that early life trauma enhances risk for particular forms of depression by altering the physiology of stress systems (Heim et al., 2008; Nemeroff and Vale, 2005).

4.2. Which pre-treatment baseline domains of functional capacity and distress/coping characteristics distinguish those with MDD who have and do not have melancholic features?

A profile of distinct functional impairments and patterns of distress were distinguishable in the melancholic group compared to the MDD group without melancholic features. After controlling for baseline depression severity, the melancholic MDD was predicted by a pattern of reduced ability to function interpersonally as indicated in lower social and occupation function, and the distress/coping characteristic of emotional resilience and social skills. Poorer psychological and physical health quality of life was distinguishable to melancholia, yet this distress was not apparent in their self-rated quality of social relationships, which was not significantly different from non-melancholics.

Considering the above clinical and psychological findings, interpersonal impairments may be considered congruent with distinguishing psychological factors, such as the suppression of negative emotions and introversion. Also, literature has linked reduced interpersonal functioning to abuse early in life (Lamoureux et al., 2012; Sperry and Widom, 2013); however, future investigations would need to be undertaken to confirm if this is true for this sample. While social and occupational functioning and capacity for social skills were distinctly lower for melancholic participants, the self-rated quality of social relationships was undifferentiated, indicating perhaps no distress at their social impairments or preference for the social interactions reflective of the sample's higher introversion.

These findings do not support the dimensional or homogeneous view of depression (Judd et al., 2002), in which melancholic MDD is simply a more severe form of MDD. Beyond the influence of depression severity, melancholic MDD represented a patient

group with reduced functioning and lower quality of physical and psychological health. Instead, findings support the view that melancholia is a distinct subtype of MDD, distinguishable from non-melancholia by distinct social and emotional impairments as well as psychological distress.

4.3. How are the MDD participants with melancholic features distinguishable from those without regarding symptom remission and response, impairment or distress outcomes post-treatment?

Our findings indicated that a participant with melancholic features had a reduced likelihood of reaching remission or response ($HRSD_{17}$). This was not reflected in the self-rated $QIDS\text{-}SR_{16}$, which was inconsistent with STAR*D findings (McGrath et al., 2008). When the analysis was adjusted for baseline between-group differences of severity and site (including clinical setting and geographical location), the effect of melancholia on remission was no longer significant and response was bordering significance. The same non-significant outcome occurred when other depression severity scales were applied, removing the possibility of a scale-specific pattern. This indicates that the melancholic remission and response to antidepressant treatment is related in part to other variables associated with the melancholic subtype, such as the higher pre-treatment symptom severity that contributes to these poorer outcomes, an idea supported in other literature (Kirsch et al., 2008). The distress/coping outcome measure of capacity to seek out social supports was distinctively lower for melancholic participants beyond the influence of baseline site and severity, again supporting melancholia to be a distinct group with poorer capacity for social skills both before and after treatment. The difference in their capacity for social skills was not significantly different across treatment arms (see Supplementary Table 1). The non-significant difference between treatment arms also indicates that treatment outcomes were not influenced by choosing an SSRI verses an SNRI, which is congruent with this being an outpatient sample (Rush et al., 2008). Melancholic and non-melancholic MDD did not differ significantly regarding dose of medication, an outcome notable as melancholic MDD participants did not have a higher dose compared to non-melancholic participants despite having greater severity and poorer function.

Since melancholic MDD had poorer psychosocial impairments both before and after treatment, and may have some chronic tendencies (indicated by dysthymia), it could be suggested that these patients may benefit from the addition of psychotherapy, particularly therapy that builds social skills. This suggestion is contrary to conventional wisdom, which suggests psychotherapy is more likely to benefit non-melancholic patients. However, therapies such as Cognitive Behavior Analysis System of Psychotherapy (CBASP) (McCullough, 2000) combined with antidepressant medication have been reported to be superior to monotherapy for achieving partial or full remission in MDD (Kocsis et al., 2003). Hirschfeld et al. (2002) also found combination therapy (CBASP and nefazdone) to be more effective for improving social functioning, an improvement that appeared to be independent of depression severity. Other studies, such as Vittengl et al. (2004), did not find this heightened improvement of social function with combination therapy, but this is likely due to the type of therapy received (participants in Vittengl et al. (2004) received cognitive therapy only).

4.4. Limitations

While the follow up period in the study allowed for investigation of acute response to antidepressant medication, and suggested that acute response is due to severity of pre-treatment symptoms in melancholic MDD, we can infer that baseline severity would predict longer-term outcomes. We recognize that the study focused on three commonly used antidepressants and that it remains possible that differential moderation effects in melancholic MDD would be revealed with other medications based on differing mechanisms of action (for example, medications that involve a dopaminergic mechanism). We also recognized that the randomization of medication was not conditional of the melancholic subtype and suggest future studies seek to undertake controlled investigations into how the melancholia "microphenotype" relates to antidepressant treatment outcomes by a priori selecting patients based on their melancholic versus non-melancholic status. To promote the validity of these findings a replication study has been planned to confirm whether results replicate.

4.5. Conclusions

In this comprehensive review of pre-treatment and outcome characteristics in a large international outpatient sample, some new insights have been demonstrated. Compared to non-melancholic MDD, melancholic MDD findings reveal a profile of distinctive social and emotional impairments and some distress. Specifically, melancholia was distinguishable by characteristics of introversion, avoidance of negative emotions, poorer social and occupational function, poorer physical and psychological quality of life, poorer emotional resilience and a lower capacity for social skills. Consistent with other research, melancholic depression is also characterized by greater depression severity, in addition to greater exposure to abuse-type early-life trauma and lower years of education. While findings do suggest the melancholic group to exhibit poorer remission and response post-treatment, it is these pre-treatment characteristics that account for some of this treatment outcome difference. With the inclusion of impairment and distress measures post-treatment, for the first time findings demonstrate that the melancholic participants have a lower capacity to seek out social support even after treatment (beyond the influence of baseline severity and site). Our findings did not support the homogenous view of depression, nor did it support the endogenous and stress theories that dominate the current melancholic MDD models. Instead, the data suggest melancholic MDD is qualitatively distinct from non-melancholic MDD particularly in their capacity to interact socially. Data may also indicates the potential role of exposure to abuse early in life and a characteristic pattern of reduced ability to function interpersonally or effectively deal with one's emotions. This study has created a platform from which to test clinical and neurobiological predictors of treatment outcome in melancholic MDD. Given the presence of pre-treatment differences in melancholic psychological profile, functional impairments and distress, and poorer post-treatment outcomes, our findings support the importance of physicians routinely assessing their depressed patients, particularly melancholic patients, on "real-world" outcomes such as social functioning (Langlieb and Guico-Pabia, 2010).

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Appendix A. Supplementary material

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