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Journal of Affective Disorders 105 (2008) 1 – 14

JOURNAL OF AFFECTIVE DISORDERS

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Review

Restoring melancholia in the classification of mood disorders

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Received 8 January 2007; received in revised form 21 May 2007; accepted 29 May 2007
Available online 19 July 2007

Abstract

The present DSM criteria for major depression poorly identify samples for treatment selection, prognosis, and assessments of pathophysiology. Melancholia, in contrast, is a disorder with definable clinical signs that can be verified by laboratory tests and treatment response. It identifies more specific populations than the present system and deserves individual identification in psychiatric classification. Its re-introduction will refine diagnosis, prognosis, treatment selection, and studies of pathophysiology of a large segment of the psychiatrically ill.

Keywords: Melancholia; Diagnosis; Classification; Major depression; Bipolar disorder

Contents

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doi:10.1016/j.jad.2007.05.023

Since 1980, DSM iterations have sought to define major depression as a homogeneous condition by a few symptoms. Neither biological tests nor treatment response are part of the diagnostic criteria. Patients meeting the DSM criteria for major depression vary widely in severity, pathophysiology, and treatment response. In contrast, melancholia is a syndrome that has been well described for centuries. Empirically derived diagnostic criteria reliably identify it. Laboratory tests support the syndrome's recognition, encouraging a simpler and more effective treatment algorithm (Taylor and Fink, 2006). Dividing the major depression category into melancholic and non-melancholic classes defines clinically specific populations for pathophysiologic and treatment response studies.

The DSM-III committee decision not to identify "melancholia" as a separate diagnosis was supported by many investigators who saw no clear depression subtypes other than major and minor forms (Winokur and Coryell, 1992). The criteria that emerged, however, were not consistent with the original view of "major" or "primary" depression. RDC defined endogenous depression, the forerunner of the DSM-III criteria, is not stable across episodes (Young et al., 1987), while the patients with psychotic depression and endogenous depression who are defined with melancholic features are consistent with the original major depression construct and are stable across episodes (Coryell et al., 1994).

The construct of major depression was further distorted by the NIMH catchment area study that relied on lay interviewers using a structured interview of low psychopathological sophistication (the DIS) that identified many non-ill respondents as having a psychiatric illness sufficient to be labeled with a psychiatric diagnosis, including an array of depression subtypes (Eaton et al., 1984, 1989). The study has been harshly criticized (Burvill, 1987), but its conclusions were adopted by the framers of DSM-IV (APA, 1994).

The DSM-IV committee remained anchored to the DSM-III construct with a low threshold for a major depression and found further support in analyses of empirical research for "endogenous" and "melancholic" depression. Rush and Weissenburger (1994), for example, after examining clinical, treatment, laboratory, and family history studies found psychomotor retardation, non-reactive mood, pervasive anhedonia, and quality of mood as identifiable clinical features of melancholia. These were associated with non-suppression of cortisol in the dexamethasone suppression test (DST) and with shorter REM-sleep latencies. Melancholic symptoms were predictive of a positive response to ECT and to tricyclic antidepressants. They concluded: "The available evidence suggests some clinical utility and some validity for the concept of melancholic features." And yet, inexplicably they decided: "Consequently, DSM-IV will retain the designation 'with melancholic features,' return to the shorter DSM-III feature listing, and broaden the designation by requiring either unreactive mood or pervasive anhedonia, but not both." This decision is inconsistent with their findings.

Rush and Weissenburger minimized the importance of multifactorial studies that show heterogeneity in samples of depressed patients and the clearly defined melancholic group in these samples (Taylor and Fink, 2006). In citing "antecedent adversity does not separate endogenous from reactive depression" they ignored the evidence linking melancholia episodes to antecedent stress and considerations of melancholia as a process that elicits an aberrant stress response state. They minimized the reliable efficacy of ECT in melancholia and the poor, even worsening, response in non-melancholic depression indicating that if depressive mood disorders were a continuum of severities, the milder forms should do best, not worst. They ignored their conclusion that the modest predictive response to TCA in defining depressive illnesses reflected high placebo rates in non-melancholic patients. They questioned the consistency of melancholia across episodes because some episodes are associated with psychosis while others are not, and some but not most patients develop manic episodes. But exacerbations of many illnesses vary symptomatically across episodes. Their conclusion of a weak consistency because "non-endogenous depressives may develop endogenous features during subsequent episodes but that endogenous depressives are likely to remain that way" could just as well result from the use of short lists of symptoms and

antecedent events to delineate diagnoses. They point out that the inconsistent findings of a higher incidence of depression in relatives of melancholic patients could result from differing diagnostic criteria, and conclude that the present criteria are acceptable.

But they are not.

The DSM diagnostic criteria are non-specific, blurring boundaries between melancholia and other depressive mood disorders and confounding diagnoses. The major depression construct has poor validity. The number of symptoms (the hallmark of the criteria), their duration, and resulting impairment in one twin does not predict the presence of depressive illness in a co-twin or future episodes in the proband (Kendler and Gardner, 1998). The DSM melancholia criteria have poor agreement with core features of melancholia derived from empirical studies cited below (Joyce et al., 2002).

The threshold for the diagnosis is artificially low as seen in the swelling population prevalence rates for depression from 6–8% in the 1960s to recent rates of over 10% for men and 20% for women (Ayuso-Mateos et al., 2001; Blazer et al., 1988, 1994; Kessler, 2003; Olsson and von Knorring, 1999; Silverman, 1968). Rates of almost 27% for men and a staggering 45% for women are reported in one Swedish study, but only eight men and nine women from more than 2000 subjects were identified as having a "serious" depressive illness (Rorsman et al., 1990). The inflation of depression base-rates by the use of ill-defined criteria has profound adverse effects on genetic research and health policy. Efforts to delineate more specific forms of depressive illness are needed. We propose that the melancholia syndrome be recognized as a specific depressive disorder that is recognized in a separate diagnostic class.

1. Defining melancholia

1.1. By psychopathology

The historically recognized melancholia syndrome is confirmed by over 70 multivariate analyses of patient and community samples of depressed persons (Taylor and Fink, 2006). Studies find several definable groups of depressed ill, not a single major depression, and, depending on the source of the sample, from 20% to 80% of the patients are described as "melancholic". Studies that do not separate depressed patients into melancholic and non-melancholic groups have been challenged and re-interpreted (Benazzi, 2002; Kendell, 1976; Kessing, 2004; Sullivan et al., 2002; Young et al., 1986).

The Kendell analysis of hospital discharge forms collected by trainee psychiatrists at the Maudsley Hospital between 1949 and 1963, for example, failed to find a bimodal distribution of patient characteristics and concluded that depressive disorders were best viewed as a continuum (Kendell, 1968). But, the Maudsley discharge form did not include items essential to delineate melancholia and the inter-rater reliability of the registrar raters is unknown but was likely poor. Two factors were nevertheless identified, one a longitudinal pattern of "neurotic" traits and a second with the cross-sectional features of psychotic depression (Taylor and Fink, 2006).

In contrast to the DSM short list criteria, the empirically defined melancholia syndrome is characterized by three symptom clusters, *all* present early in an episode and *all* required for proper identification (Table 1). An *abnormal emotional state* dominated by apprehension, anhedonia and overwhelming gloom is always present and interferes with efficient cognitive function. *Psychomotor disturbance* is always featured. Motor functions and cognitive activity are slowed and stupor and catatonia may occur. Other patients with melancholia are agitated, restless, with perseverative ruminations and actions. *Disturbances in basic body functions* or *vegetative signs* are always present. Patients lose their appetites and weight, sleep little, and lose interest in sex and family activities. Recall and concentration are so impaired that most are unable to work. Self-care is abandoned. Thoughts are pre-occupied by despondency, death and considerations of self-harm. Delusions are common with thoughts of illness, guilt, worthlessness and danger overwhelming their actions.

1.2. Verification of diagnosis by pathophysiology

A connection between hypercortisolemia and the clinical features of melancholia characterizes the syndrome, and melancholia is best considered a process that elicits, sometimes without a definable precipitating stress, an abnormal state in which the stress-response feedback shutdown mechanisms are faulty (Taylor and

Table 1
Diagnostic criteria for melancholia (*all* must be present)

A. An episode of illness with reduced functioning characterized by an unremitting mood of apprehension and gloom that compromises normal daily activities and persists for at least two weeks.
B. Psychomotor disturbance as agitation, retardation (including stupor and catatonia), or both.
C. Vegetative signs of poor sleep, appetite, libido, cognition (at least two).
D. At least one of the following:
Abnormal DST and CRH tests or high nighttime cortisol levels
Decreased REM latency or other sleep abnormalities

Fink, 2006). Measures of brain metabolism in patients with depression delineate abnormality in the stress-response system. The data for this understanding are most secure, however, when the focus is on severely ill, hospitalized, or psychotically depressed patients, suggesting that what is now considered the pathophysiology of major depression is best restricted to melancholia.

1.2.1. Physiology

The behavioral and physiologic effects associated with a strong and sustained stress response are consistent with the classic features of melancholia, offering face validity to the conclusion that an abnormal stress response is a core component of the syndrome (Heim and Nemeroff, 2001; Rothschild, 2003). Sustained severe stress is associated with fearfulness and irritability, increased stereotyped fear-related and defensive behavior, anhedonia, hypertension and tachycardia, decreased food intake and weight loss, decreased sleep and grooming, impotency, amenorrhea, immune suppression, and acute learning and memory problems. These are also features of melancholia.

An abnormal stress response state is reflected by HPA hyperactivity, increased cortisol production, high serum levels throughout the day with normal serum ACTH levels, and DST non-suppression. CRH hypersecretion and blunted ACTH responses to intravenous CRH are also observed (Meyer et al., 2001).

The hyper-glucocorticoid state perturbs noradrenergic and serotonergic systems (Keck and Holsboer, 2001; Sheline et al., 2003). The altered brain neurochemistry seen in patients with severe depression may be a "downstream" effect of the stress-response rather than the initiating cause of the illness. Serotonin, for example, is reduced in chronic states of elevated corticosteroids in laboratory animals and humans (Lopez et al., 1998; Meijer and de Kloet, 1998).

Up to 90% of identified melancholic patients show HPA hyperactivity. Centrally administered CRH, affecting HPA pathways, induces increased arousal and vigilance, decreased appetite and sexual behavior, and increased heart rate and blood pressure, features of melancholia (Arborelius et al., 1999; Holsboer, 2001). Postmortem data from persons who suffered from depression are consistent with these perturbations (Raadsheer et al., 1995). Postmortem and functional imaging reports of reduced numbers of hippocampal $5HT_{1A}$ receptors and reduced binding in melancholic patients (Lopez et al., 1998; Sargent et al., 2000)) and in suicide victims (Cheetham et al., 1990; Gonzalez et al., 1994; Yehuda et al., 1993) reflect a chronic exposure to cortisol, placing receptor dysfunction as a secondary phenomenon (Parianti and Miller, 2001).

1.2.2. Laboratory tests

The dexamethasone suppression test (DST) was adopted as a strategy to assess the abnormality in cortisol response and to identify melancholia. As a diagnostic measure, the DST is controversial. Positive DST test results were reported in only half the patients meeting DSM-III criteria for major depression leading to its rejection in clinical practice. When melancholia is defined by its three symptom clusters rather than the short-list DSM criteria, however, 70% or more of patients show a positive test *i.e.* non-suppression (Carroll et al., 1976, 1980).

All psychotically depressed patients meet criteria for melancholia and almost all exhibit abnormal cortisol measures. Elevated serum cortisol, loss of diurnal rhythmicity, and DST non-suppression are prominent in psychotic depressed patients when ill, normalize with successful treatment, and re-emerge in relapse. Carroll et al. (1980) concluded that, "*the DST identified melancholic patients with a sensitivity of 67% and a specificity of 96%.*" A meta-analysis of 14 studies comparing DST results in psychotic and non-psychotic depressed patients found the non-suppression rate to be substantially higher in psychotic depressed patients (64%) than in non-psychotic patients (36%) (Nelson and Davis, 1997). Patients with schizophrenia typically do not show abnormal cortisol levels or non-suppress ion, arguing that increased HPA activity is not characteristic of psychosis but of mood disorder. Among recent observers, Rush et al. (1996) reported cortisol non-suppression in 62% of endogenously depressed and 19% of non-endogenously ill in-patients in large samples of both unipolar and bipolar patients defined by RDC depression criteria. In outpatients, abnormal cortisol functions were found in 35% of the endogenously depressed and in 9% of non-endogenous depressed. Although the RDC criteria do not delineate endogenous from non-endogenous depression, the reported test sensitivity of 40% and specificity at 90% is equivalent to the sensitivity and specificity observed in the identification of a seizure disorder by standard EEG criteria (Parra et al., 2001).

Abnormal cortisol function in melancholia impacts the management of the patients. The suicide risk in those with an abnormal DST was 27% compared to 3% among patients with a normal DST in a 15-year follow-up study (Coryell and Schlesser, 2001). The risk for suicide and for hospitalization for suicide was higher in those with abnormal DST in a review of 101 patients re-examined

over two years (Yerevanian et al., 2004). In medication trials, 70% of DST suppressors (*i.e.* non-melancholic) are placebo responders compared to only 10% of DST non-suppressors (*i.e.* melancholic).

Abnormality in sleep EEG measures is also associated with melancholia. A meta-analysis of 115 sleep studies with over 36,200 psychiatric patients concluded that patients with mood disorders differed most from normal subjects (Benca et al., 1992). REM latency correlated best with severity of depressive mood disorder. Patients who had an endogenous, melancholic, or psychotic depression differed the most from controls. Greater sleep disturbance predicted a greater likelihood of relapse (Benca et al., 1992; Nofzinger et al., 1999). The findings in over 1400 severely depressed patients, mostly those with melancholia, can be summarized as having a pattern of reduced total sleep time, prolonged sleep latency, decreased percent time slow-wave sleep, shortened REM latency, and increased REM percent time. While these sleep EEG measures are less secure than measures of cortisol, they are useful in identifying the melancholia syndrome.

1.2.3. Structure

In functional imaging studies, brain areas activated by stress are abnormal in severely depressed patients. Such evidence offers a neurologic understanding of the classic features of melancholia (Gray, 1993; Van de Kar and Blair, 1999). Functional imaging finds the amygdala, hippocampus and several prefrontal cortical circuits to be dysfunctional in persons with severe depression, many of whom exhibit melancholia (Maes et al., 1993; Drevets, 1998).

Volumes of anterior cingulate cortex ventral to the genu of the corpus callosum (Drevets et al., 1997; Hirayasu et al., 1999) and the hippocampus (Bremner et al., 2000; Saxena et al., 2001; Shah et al., 1998; Sheline et al., 1996) are reduced in MRI and postmortem studies of depressed patients. The hippocampus, a primary site for glucocorticoid receptors (GR I) that are activated by elevated cortisol levels, exhibits negative feedback following glucocorticoid release. Loss of hippocampal neurons and reduced hippocampal metabolic activity in melancholia is an explanation for the inability to inhibit the hypothalamic-pituitary-adrenal axis with subsequent hypercortisolemia in these patients (Young et al., 1991). Hippocampal neuronal loss correlates with the patients' cognitive problems (Paradiso et al., 1997). Postmortem, the cerebral gray matter is reduced in the orbital cortex and posterior ventrolateral prefrontal cortex of depressed patients. The density and size of neurons and glia is reduced in the anterior dorsolateral prefrontal cortex.

1.2.4. Metabolism

Decreased dorsolateral and increased anterior cingulate and ventrolateral frontal activity, driven by increased amygdala activity, are hallmarks of severe depression and the dysfunction in these areas is associated with the features of melancholia. The greater the metabolic perturbation, the more severe is the depressive illness (Drevets, 2000).

In unmedicated severely depressed patients, amygdala resting blood flow and glucose metabolism is substantially increased with illness severity (Drevets, 1999a,b; Drevets et al., 1997; Wu et al., 1992). Increased metabolic rate in the right amygdala is associated with negative mood in depressed patients (Abercrombie et al., 1998). The abnormality is not found in patients with anxiety disorder or schizophrenia suggesting it may be specific to depressive illness (Drevets and Botteron, 1997). Successful antidepressant drug treatment normalizes these elevations (Brody et al., 2001a,b; Drevets, 1999a,b).

Deep brain electrical stimulation of the amygdala in humans induces anxiety and fear, and ruminations of past emotionally disturbing events (Drevets et al., 2002; Gloor et al., 1982; Okun et al., 2003). These features are observed in melancholia accompanied by cortisol release. Continuous amygdala overactivity during severe depression is thought to account for the unremitting apprehension and ruminations in melancholia. Successful antidepressant treatment normalizes the metabolic activity in these structures (Brody et al., 2001a,b; Buchsbaum et al., 1997).

Anterior cingulate lesions in humans are associated with abnormal emotional responses to emotionally laden concepts. The lesions are also the basis for akinetic mutism, stupor and catatonia. Severe melancholia is the second most common cause of catatonia (Fink and Taylor, 2003).

Blood flow and glucose metabolism are decreased in the dorsolateral prefrontal cortex anteriorally and medially in depressed patients (Brody et al., 2001a,b; Bremner et al., 1997). Lesions in these cortical regions and their corresponding subcortical circuitry produce avolitional and apathetic syndromes that mimic depression. The reduced metabolism in the dorsolateral prefrontal cortex in depression correlates with the degree of psychomotor retardation, anhedonia, and cognitive impairment, all features of melancholia (Gloor et al., 1982).

In contrast, increased metabolism is reported in the ventrolateral and posterior orbital cortex and the anterior insula of some unmedicated depressed patients. The increases are normalized with successful antidepressant drug therapy (Biver et al., 1994; Drevets et al., 1999; Rubin et al., 1994; Saxena et al., 2002) and ECT

(Navarro et al., 2002, 2004; Nobler et al., 1994). These increases, however, are also observed in patients with obsessive-compulsive and anxiety disorders, suggesting that the changes are non-specific expressions of anxiety. The increase in ventrolateral cortex metabolism is inversely related to the severity of depressive mood. Behavioral, visceral, and cognitive responses in flight/fight situations and in reward responses are modulated by activity of the ventrolateral prefrontal cortex posteriorally. Lesions in this cortical area result in a disinhibited syndrome similar to mania (Drevets et al., 1995; Rauch et al., 1994; Schneider et al., 1995).

1.3. Verifying diagnosis by family studies

The evidence verifying melancholia by family illness is circumstantial. While studies consistently report that children of parents who suffered depressive illness and the relatives of depressed children are both at increased risk for depressive illness (Goodman and Gotlib, 1999; Kendler et al., 2001; Klein et al., 2001; Kovacs et al., 1997; Lieb et al., 2002; Neuman et al., 1997), it must be inferred that the increased risks are specific to melancholia.

The first-degree relatives of depressed probands have a two-to-three fold increased risk than the general population for all forms of depressive illness (Sullivan et al., 2001). Genetic and environmental contributions are about equal and the degree of a person's risk increases in a linear fashion with the number of affected relatives (Sanders et al., 1999; Todd et al., 1993). Also, the more severe the illness is expressed in relatives, the younger the first episode of depression occurs in offspring (Todd et al., 1993; Williamson et al., 2004). Adoption (Ingraham and Wender, 1992) and linkage studies of candidate genes (Frodl et al., 2004; Huang et al., 2003; Koper et al., 1997; Lemonde et al., 2003) do not further clarify the determinants of depression.

Heritability estimates are also clearest for more severely ill depressed patients where population lifetime base rates are estimated at 5% to 10%, less than half the estimate for all forms of depression (Puig-Antich et al., 1989; Moldin et al., 1991; Tsuang et al., 1994). In family studies of more severely ill depressed patients, the adult first-degree relatives have a morbid risk for depressive illness four to five times greater than lower population risk figures (Tsuang and Faraone, 1990). While the proportion of melancholic patients is likely high in the samples of the "severely" depressed, melancholia is rarely specifically identified.

Some studies conclude, however, that substantial familial aggregation is specific for different forms of depression (Kendler et al., 1996; Klein et al., 2001). In twin data, a "severe typical" group (with a melancholic pattern of psychopathology) had high monozygotic twin concordance. Also, women with high familial aggregation are more likely to experience postpartum depressive illness, often melancholic. Children of mothers with early onset depression, particularly postpartum depression, have a high heritability for mood disorder. These findings are consistent with the reports that melancholia is associated with as much as a 14-fold increased risk for depressive mood disorder before the age of 13 in children whose mothers had their first illness before age 20 (Weissman, 1988; Weissman et al., 1984, 1988). High familial risk is associated with persistent HPA abnormal function, another link to melancholia (Modell et al., 1998).

The results are mixed in the few studies that identify endogenously depressed probands. Higher rates are reported in the relatives of endogenously depressed probands (Leckman et al., 1984). High rates of depressed mood are also reported in the relatives of children with endogenous depression (Puig-Antich et al., 1989). These associations, however, are not supported by others (Price et al., 1984; Zimmerman et al., 1986). The differences likely reflect the severity of the probands' illnesses, with the more severely ill having the greater familial aggregation.

1.4. Verification of diagnosis by treatment response

The dramatic response of melancholia to electroconvulsive therapy (ECT) and to a lesser extent, to tricyclic antidepressants (TCA) and lithium augmentation, further validate the syndrome.

1.4.1. Convulsive therapy

The efficacy of ECT to relieve melancholia and manic–depressive illness has been repeatedly verified (Abrams, 2002). The remission of illness in psychotic depressed patients with ECT is higher than with medications, either singly or in combinations (Taylor and Fink, 2006). The most recent verification is in two NIMH supported multi-site studies of ECT that defined depressive illness by DSM-III criteria for unipolar major depression (Kellner et al., 2006; Sackeim et al., 2001). Participants in both studies had been severely ill for many years and had failed multiple medication and psychotherapy trials.

In the 3-hospital study, the remission rate with unilateral ECT was 54.8% for patients completing treatment (Sackeim et al., 2001). In the 4-hospital study using bilateral ECT, the remission rate for all patients

(including dropouts) was 75% for the non-psychotic and 83% for the psychotic depressed (Kellner et al., 2006). For treatment completers the remission rate was 87% and 95% for non-psychotic and psychotic patients, respectively (Petrides et al., 2001).

1.4.2. Antidepressant drugs

The efficacy of TCA in melancholia further supports the separation of melancholia from other forms of depression. Their efficacy is under-recognized in treatment algorithms in which the more recently introduced SSRI and SNRI are preferentially recommended (Freemantle et al., 2000). The overall 30% to 40% remission rates of SSRI/SNRI agents, however, differ only minimally from placebo rates (Khan et al., 2003). Comparison studies rarely use nortriptyline or desipramine (the TCA with lesser anticholinergic effects) but prescribe imipramine and amitriptyline, thus maximizing the likelihood of medication intolerance and investigator awareness of the patient's medication assignment (Freemantle et al., 2000). Sample sizes are typically too small to reflect real differences and do not allow analyses of efficacy for varieties of depressive illness. The use of inadequate TCA dosing is the rule rather than the exception (Furukawa et al., 2002). Avoiding low dosing is critical. A review of 186 randomized control trials, found that adequately dosed amitriptyline elicited a better recovery rate than any of the alternative drugs, although it was less well tolerated (Barbui and Hotopf, 2001).

The advantage of TCA in melancholia is well documented (Anderson and Tomenson, 1994; Perry, 1996; Schatzberg, 1998; Navarro et al., 2001). Studies by Paykel and colleagues found the best responses to amitriptyline among the most severely ill and psychotic patients and the least responses in the anxious depressed patients with abnormal personality traits, concluding that the differences in treatment response implied different pathophysiologies (Paykel, 1971; Paykel et al., 1973; Prusoff and Paykel, 1977).

An advantage for TCA over other antidepressants is reported when remission is used as the outcome criterion (Thase, 2003). When treatment is guided by plasma level monitoring, 40% to 55% of depressed patients remit on an SSRI while 60% to 70% remit with a TCA (Preskorn and Fast, 1991, Preskorn and Burke, 1992). Randomized controlled studies find this advantage in melancholic and more severely depressed patients (Bagby et al., 2002; Danish University Antidepressant Group, 1986, 1990, 1993; Nobler and Roose, 1998; Perry, 1996; Roose et al., 1994).

In a meta-analysis of controlled trials comparing amitriptyline with other TCA, heterocyclic antidepressants, and an SSRI, the overall efficacy favored amitriptyline (Barbui and Hotopf, 2001). Another meta-analysis reported greater efficacy for TCA in hospitalized depressed patients, but not for other groups (Anderson, 2000). Hospitalized depressed patients are also more likely to be melancholic (Danish University Antidepressant Group, 1999).

A recent comparison found nortriptyline superior to fluoxetine in moderate to severely depressed patients with similar drop-out rates and without measurable cardiovascular problems with nortriptyline (Akhondzadeh et al., 2003).

Danish double-blind randomized controlled antidepressant drug trials that included 292 inpatients, most of whom with melancholia, report clomipramine to be superior to the comparison drug (citalopram, paroxetine or moclobemide) (Hildebrandt et al., 2003).

1.4.3. Lithium

The efficacy of lithium therapy in depressed patients also supports the separation of melancholia from other mood disorders. While lithium therapy for mania is well documented, it is also effective for patients with recurrent depression. Double-blind placebo-controlled studies of lithium augmentation report response rates of 50% to 63% (Bauer and Dopfmer, 1999; Block et al., 1977; Fava et al., 2002; Price et al., 2001). Melancholic patients benefit most, with 57% responding to augmentation compared to 25% in non-melancholic patients. Melancholic patients who suffer recurrent depression or who have both manic and depressive episodes have similar response rates (Alvarez et al., 1997). Maintenance lithium therapy prevents future depressive episodes, even in patients without a history of mania or hypomania (Baethge et al., 2003). When prescribed continuously for several years, lithium substantially lowers the risk of suicide in patients with mood disorder (Baldessarini and Tondo, 2003; Burgess et al., 2001; Cipriani et al., 2005). The effectiveness of lithium in patients with melancholia is also consistent with the construct that bipolar depression is a form of melancholia and that what is now considered unipolar depression is non-melancholic depression (see below).

2. Discussion

Empirical evidence justifies separating the DSM major depression category into melancholia and non-melancholic depressive disorders. Melancholia is a clinically and biologically definable syndrome that optimizes treatment selection and outcome, and refines samples for pathophysiologic study. Melancholia characterized by

the present DSM/ICD criteria only approximates the empirically defined and historically recognized syndrome. A specific disturbance in mood with abnormal vegetative and psychomotor functions is essential to the diagnosis. Separating melancholia will also encourage better delineation of other depression syndromes.

2.1. Impact on the classification of mood disorders

Empirically defined melancholia encompasses several mood disorder categories now separately classified. Psychotic depression, depression with catatonia or stupor, parapartum depression, and abnormal bereavement are best viewed as forms of melancholia (Taylor and Fink, 2006). The recognition that psychotic depression, most perinatal depressions, and severe depression following a death of a loved one are melancholic depressions broadens the domain, but does not affect the validity of the melancholia construct. The recognition simplifies the classification and accepts observations that these conditions are alike other than in their circumstances.

The depressive syndromes associated with manic–depressive illness are also best viewed as melancholic depression. This understanding resolves the unipolar-bipolar controversy. Melancholic depressions include persons who on occasion have manic or hypomanic episodes – bipolar illness. When ill, however, such persons mostly suffer from depression. The alternative abnormal moods reflect additional liability factors, just as psychosis, stupor, and catatonia are severity features. While all persons with psychotic depression are melancholic, only about 30% of melancholic patients are psychotic. While all manic–depressive patients should be considered melancholic when depressed, only about 20% of melancholic patients also experience alternative abnormal mood states. Many, however, experience some features of mania or hypomania over their lifetimes. Why such patients have these experiences is as unclear as why some melancholic patients experience psychosis or catatonia.

The evidence is strong that the depressive illness of manic–depression is melancholia. The historical record reflects this understanding, and melancholia not associated with mania or hypomania cannot be distinguished from melancholia associated with such mood states. Family illness studies show an increased risk for unipolar and bipolar disorder in the first-degree relatives of both unipolar and bipolar patients when unipolar depression is defined as melancholia. In the families of the bipolar patients the risk for recurrent depression (i.e. unipolar) is higher than the risk for bipolar mood disorder (Duffy et al., 2000; Jones et al., 2002; McGuffin and Katz, 1989; Taylor et al., 1980; Taylor and Abrams, 1980). Studies of twin pairs concordant for mood disorder, 20% to 30% are "mixed," one twin's illness characterized by recurrent depressions and the other by both depression and mania (Bertelsen et al., 1977; McGuffin et al., 2003; Torgersen, 1986). The hypothesis that the twins with both mania and depression and other manic–depressive patients have a genetic predisposition for mood instability in addition to the predisposition for melancholia remains uncertain (McGuffin et al., 2003). This additional genetic liability is said to elicit unstable cerebral hemispheric activation with left hemisphere activation associated with approach and manic-like behaviors and right hemisphere activation associated with withdrawal and depression (Hirshfeld-Becker et al., 2003; Harmon-Jones et al., 2002).

That manic–depression is a variation of melancholia can also be concluded from many studies of psychopathology, laboratory markers, and treatment response (Taylor and Fink, 2006). Goodwin and Jamison (1990), in their landmark review of manic–depressive illness reached a similar conclusion (Page 65):

> "Despite the heterogeneity in both the bipolar and unipolar groups, the breadth of reported bipolar–unipolar differences is impressive. They include four separate spheres of data — genetic, clinical, biological and pharmacological. Bipolar and recurrent unipolar disorders, nevertheless, appear to be very similar in some important respects (e.g., prophylactic response to lithium). Taken together, the data suggest that they are best considered as two subgroups of manic–depressive illness rather than separate and distinct illnesses. The available data also support a continuum model, with "pure" bipolar illness at one end and unipolar illness at the other."

And (page 62):

> "Some family history studies are consistent with a model in which bipolar and unipolar are variants of the same fundamental disorder, with bipolar representing the more severe end of the spectrum."

More recently, Cassano et al. (2004) presented clinical data from 117 patients initially designated as having "remitted recurrent unipolar depression" and 106 said to have bipolar I disorder. Paranoid ideation, auditory hallucinations, suicide attempts, and features of melancholia were more commonly experienced in the bipolar I patients. The authors concluded:

> "Cumulatively our empirical findings support a continuous view of the mood spectrum as a unitary

phenomenon that is best understood from a longitudinal perspective. Our data suggest that unipolar disorder and bipolar disorder are not two discrete and dichotomous phenomena but that mood fluctuations – up and down – are common to both conditions…."

2.2. Impact on clinical trials

The protocols for the STAR*D (Rush et al., 2006) and the two multi-center ECT studies (Kellner et al., 2006; Sackeim et al., 2001) used DSM criteria to identify patients with major depression. The samples, however, are divergent in illness severity and in the mixture of melancholic and atypical features. The patent heterogeneity of the STAR*D sample likely influenced the poor outcomes. The homogeneity of the ECT referred samples and the treatment's greater efficacy offered better outcomes. Dividing patients with major depression into those with melancholic or non-melancholic illness offers more phenotypically distinct population samples and optimizes treatment outcomes, much as staging breast and prostate cancer has optimized treatment algorithms for these conditions.

2.3. Laboratory tests

DST non-suppression supports the identification of melancholia (Fink, 2005; Taylor and Fink, 2006). The electroencephalogram offers similar specificity and sensitivity in identifying patients with seizure disorders, and is an analogous laboratory test (Parra et al., 2001). It is an accepted standard procedure in the diagnosis of seizure disorders despite the experience that a single inter-ictal recording shows seizure rhythms in 50% to 55% of patients with well-defined epilepsy. Two recordings increase sensitivity to 92%. Improvements in measures of cortisol and neuroendocrine physiology offer a similar opportunity to design better laboratory test criteria for melancholia.

Confirming melancholia by the DST in clinical trials will minimize the influence of placebo-response rates on estimated efficacy rates. Only about 10% of DST non-suppressors respond to placebo. The test also offers an objective criterion for predicting remission and relapse. For example, while TCA are reported to be ineffective in children and are rarely used in adolescent patients, efficacy studies of responders to TCA include young patients who tolerated the medications. Melancholic features, high cortisol levels later in the day, and DST non-suppression identify the younger depressed persons more likely to respond to TCA, thereby avoiding SSRI and the association with increased suicide risk (Taylor and Fink, 2006).

Others have recently called for a re-assessment of the decision in the DSM-III and DSM-IV classifications not to include laboratory test criteria (First and Zimmerman, 2006). The recommendation for consideration of measures of cortisol and sleep EEG for melancholia is a consistent recommendation.

2.4. Impact on studies of pathophysiology

Genetic, brain imaging, family, or neurochemical studies of pathophysiology are expensive and fraught with technical difficulties. To identify a common biological feature is made more difficult by the imprecise criteria that identify heterogeneous populations. In the assessment of hypercortisolemia and failure of steroid suppression among depressed patients, the best results are reported in those identified by melancholia and psychosis, and in those verified by treatment response to ECT. Study samples identified by the defined criteria for melancholia offer better populations to dissect their biological characteristics among other psychiatric illnesses.

2.5. A home of its own

The evidence demarcating the melancholia syndrome as an identifiable disorder with defined symptoms, pathophysiology, and effective treatments compels its consideration as a distinct entity in psychiatric classification. Studies of the psychopathology of depression, however, demonstrate that a symptom check-list alone does not identify the syndrome and that characteristic features of mood, motor and physiologic disturbance must all be present. Rather than lump all depressive disorders into a major depression group and then characterize such patients by severity and historical features while presenting other depressions as if their contextual circumstances define their pathophysiology, we propose bringing depressive disorders into two categories: melancholia and non-melancholia (Taylor and Fink, 2006).

Parker and Hadzi-Pavlovic (1996) presented a similar argument for the separate identification of melancholia. The delineation of melancholia by defined clinical features, validation by physiologic tests and by treatment response, offers a more systematic and operationally reliable paradigm for the classification of psychiatric disorders than the present symptom check-list criteria established in DSM-III and DSM-IV classifications.

Role of funding source
Nothing declared.

Conflict of interest
No conflict declared.

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