Published in final edited form as:

Acta Psychiatr Scand. 2007 February ; 115(2): 89–92. doi:10.1111/j.1600-0447.2006.00943.x.

Melancholia: restoration in psychiatric classification recommended

Max Fink, Tom G. Bolwig, Gordon Parker, and Edward Shorter

Invited Guest Editors

The classification of depressive disorders has varied considerably over the last 80 years, with quite contrasting models. Present-day DSM and ICD guidelines are based on a categorical model, using symptom check list criteria and weighting severity. The resulting heterogeneity of clinical and research populations has proved to be detrimental to effective clinical care and research.

Concerns about the utility of the criteria for the diagnosis of major depression led to a three-day conference in Copenhagen in May 2006. Eighteen researchers and clinicians from Australia, Canada, Italy, Scandinavia, Switzerland, the United Kingdom and the United States considered problems intrinsic to the concept of ‘major depression.’ Their reports and a summary of the discussions are published in the ‘*Melancholia: Beyond DSM, Beyond Neurotransmitters*’ supplement to *Acta Psychiatrica Scandinavica*.

The question

The heterogeneity of population samples based on the criteria of the present DSM and ICD classification systems is an impediment to effective clinical care, to the evaluation of new interventions, and to the studies of pathophysiology. Among the better defined psychiatric entities, melancholia stands out as a clinical entity with the best possibility for generating homogeneous samples.

The long persistence of melancholia as a diagnostic concept is an evidence of its inherent validity. Melancholia describes a distinctive clinical syndrome with a defined underlying biology that is distinguishable from other mood disorders. Clinicians and researchers are convinced that the syndrome currently termed ‘major depressive disorder’ encompasses multiple subgroups that differ meaningfully in phenomenology, natural history, treatment response, and pathophysiology. Delusional depression and melancholia have attracted the most empirical work, but efforts to define melancholia have declined in recent years following failures to validate a distinction between melancholia and non-melancholia.

History

The doctrine of two depressions characterizes psychiatric history with descriptions ascribed to Hippocrates and recognized by many medical and literary writers (1, 2). The two forms were distinguished as a ‘white’ and a ‘black’ melancholia, as ‘melancholia’ vs. ‘spleen,’ and as ‘episodic melancholia’ contrasted with ‘chronic neurasthenia.’ Kraepelin characterized

manic-depressive insanity as a single illness, although he also described psychogenic depressions. Many authors formally characterized melancholia in the 19th century.

Melancholia was a recognized disorder in the first two American Psychiatric Association DSM classifications. The DSM-III classification of 1980 diminished melancholia to a diagnosis specifier. It defined under a single term 'major depressive disorder' all forms of depressive illnesses, and a separate 'bipolar disorder' to describe those individuals with a history of manic episodes. For those meeting major depression criteria, a 'melancholic features specifier' was delineated, but several listed clinical criteria overlapped with 'major depression'. Major depression criteria homogenized heterogeneous depressive disorder populations for clinical drug trials and studies of pathophysiology. The failure of drug developers to identify specific medications for different depressive illnesses and in the rejection of laboratory tests and detailed measures of motor and vegetative functions to ensure more homogeneous population samples are evidence of the inadequacies of the present classification systems.

Definition of a melancholia syndrome

In the DSM-IV classifications, melancholia is defined by symptom aggregation alone. The criteria are insufficient to define the syndrome. Two conference reports argue, however, that melancholia is a categorically distinct depressive illness differentiated by observable psychomotor disturbance (3, 4) and by neuroendocrine markers (5, 6). Differential response to effective antidepressant treatments (ECT, TCA) validates the diagnosis.

Parker (3) and Parker and Hadzi-Pavlovic (4) defined abnormal psychomotor activity as the distinguishing feature of melancholia. They offer a rating scale (CORE) as a marker of psychomotor disturbance. These criteria identify homogeneous depressive populations that are highly responsive to ECT, showing an age-related superior response to TCA compared with SSRI antidepressant medications. In assessing melancholia today, Parker (3) sees a similarity to our understanding of Parkinson's disease before its biologic marker was identified.

Taylor and Fink emphasize abnormal vegetative signs and neuroendocrine tests to identify melancholia populations (5, 6). They note that the populations identified by DSM criteria for major depression as well as the SCID criteria for the specifier 'with melancholic features' are heterogeneous. Their defining criteria require unremitting mood of apprehension and gloom, psychomotor disturbance, and laboratory evidence of abnormal cortisol functions. The patients who meet these criteria respond differentially to lithium, tricyclic antidepressants and ECT, and are subsumed under the labels of psychotic (delusional) depressed, geriatric depressed, puerperal psychosis, and pharmacotherapy-resistant depressed.

In an analysis of the concept of melancholia, Coryell (7) concludes that the DSM-IV criteria are associated with greater overall severity of mood disorder, a low likelihood of placebo treatment response, an episodic course, a family history of depressive illness without alcoholism, a relatively healthy personality, and hypothalamic-pituitary-adrenal (HPA) axis

hyperactivity. Evidence for the validity of the melancholia concept lies in the fact that the presence of one characteristic increases the likelihood of one or more of the other characteristics.

A common feature of melancholia, especially for the patients with abnormal HPA-axis functions, is the lack of response to placebo and the definitive response to ECT and active antidepressants. They are less likely to respond to psychotherapy (8).

Differentiation from atypical depression

A concept of atypical depression arose with the reports of a differential response of depressed patients to tricyclic and monoamine oxidase inhibitor (MAOI) antidepressants. The MAOI-responsive patients exhibited clinical characteristics of mood reactivity with the symptoms of weight gain or increased appetite, hypersomnia, leaden paralysis, and long-standing interpersonal rejection sensitivity. These criteria define 'atypical depression' in the DSM-IV psychiatric classification. Such patients are separable from those with melancholia. Stewart and Klein review the literature on the syndrome and suggest the addition of course of illness to the criteria (9).

In a 20-year follow-up study of Swiss depressed patients, Angst identifies the limitations of the DSM specifiers for melancholia and atypical depression, reporting a considerable overlap of features (10). In the latest examination of the subjects, 29% met the criteria for both melancholia and atypical depression during their course of illness, 32% for melancholia alone, 15% for atypical depression alone, and 24% did not have signs of either subtype. In 48% of the subjects, melancholia was longitudinally associated with atypical depression. The re-examinations show a stability of the features, and no differentiable demographic characteristics other than a higher percentage of female patients meeting criteria for atypical depression. The patients who met melancholia characteristics were more severely ill with a higher chronicity of illness.

Melancholia and mixed depression

The co-occurrence of depressed mood and agitation in both melancholia and bipolar mixed states is described in two reports, suggesting that the two disorders are part of a common pathophysiology, and not distinct disorders. In an interesting reference to two dramatic paintings, 'Melancholia' by Dürer and the 'Red Melancholia' by Cranach the Elder, Akiskal and Akiskal see melancholia and bipolar disorder, now separated in the classification, as a single disorder (11). A point of similarity is the sensitivity of the patients to the stimulatory effects of antidepressants with an increase in suicidal risk.

Reviewing an extensive experience with more than a thousand depressed patients in a 6-year period, Koukopolous et al. (12) describe the same association of agitated unipolar major depression and bipolar mixed states. A mental anguish accompanies the physical agitation of the patients making them overly responsive to the stimulation of antidepressant medications. The stimulatory effect is not seen with ECT, offering a treatment that is less hazardous.

Epidemiology

Using a database of hospital admissions in a remote region of Wales, Healy undertook a service utilization study based on retrospective chart analysis to compare the records from 1875 to 1924 with the records between 1995 and 2005 for diagnoses of mania, melancholia, and postpartum psychoses (2). He reports stability in the diagnoses of mania and melancholia (with and without psychosis) but a decrease in the incidence of *de novo* onset psychoses in the postpartum period. In the early historical period, mania (the records included schizophrenia, agitated depression, and senility under this label) was diagnosed in 50% of the records and melancholia in 30%.

The failure of epidemiologic studies to define clear differences in clinical presentation or long-term outcome between patients with melancholia and those with other forms of depressive illness, or between mild, moderate, and severe depression, suggests a continuity of illness, rather than discrete categories. The severity of illness criteria exhibits a proportionate risk for relapse and suicide, prior episodes, duration of illness, family history, and psychosocial functioning. Kessing's (13) review fails to identify a unique population of melancholic patients but the failure is caused by the lack of effective criteria that can be feasibly applied in epidemiologic surveys.

Laboratory tests

Hypercortisolemia and its failure to be suppressed with exogenous steroid administration were formalized in the dexamethasone suppression test (DST) in the 1970s. The abnormality was characteristic of patients with endogenous depression and was normalized with effective ECT. A return of the abnormality heralded relapse. Examination of the DST as a criterion for DSM-III major depression found poor correlations with the diagnosis. The test was discarded because it added little to what was readily available in patient clinical assessments (14). Re-assessment of the DST has been stimulated by recent studies of the DST in ECT practice, leading to its reinstatement as a criterion of melancholia (6).

Over the four decades since the discovery of the association between hypercortisolemia and melancholia, many efforts have been made to broaden the understanding of the mechanism involved. In the latest study of pathophysiology, Carroll describes overdrive in the HPA-axis function with increased secretion of ACTH as characteristic of depressed in-patients, regardless of the cortisolemic status (15).

In addition to abnormal HPA-axis function, sleep disturbances are present in more than 80% of patients with depressive mood disorders (16). Yet, sleep EEG findings based on overnight polysomnography have not always differentiated depressed patients from healthy controls. In clinical studies, sleep EEG abnormalities are strongly affected by gender with abnormal findings better correlated in men than in women. The usefulness of sleep EEG measures for diagnostic purposes has yet to be demonstrated.

Pathophysiology

The mechanism of action of convulsive therapy in relieving the seeming diverse syndromes of melancholia, catatonia, and delirium is a challenge to neuroscience. Among the measurable effects of induced seizures is stimulation of the HPA-axis and of neurogenesis. In a review of the laboratory data, Bolwig and Madsen (17) point to a decreased size of hippocampus and suggest that this may result from the toxic effects of cortisol. The suppression of hippocampal neurogenesis is strongly counteracted by electroconvulsive seizures (ECS). The same effect, albeit weaker, is demonstrated with antidepressant agents but not anti-psychotics.

The inhibition of motor activities in both melancholia and Parkinson's disease suggests a similarity in mechanism in the dopamine system in both syndromes. Malhi argues that dopamine deficiency affects a pathophysiologic chain underlying the expression of both syndromes (18).

Conclusion

The participants in the Copenhagen Melancholia Conference found the present classification of mood disorders to be of such heterogeneity that the search for causes and more effective treatments has been clouded. They considered the proposition that 'melancholia,' a time-tested diagnostic concept, should be reinstated as a defined mood disorder in psychiatric classification. Other mood disorders would best be labeled 'Non-melancholic Mood Disorders,' until research identified additional distinctive syndromes. The term 'major depressive disorder' should be discarded.

The concept of a homogeneous melancholia syndrome is developed from clinical signs and symptoms (unremitting gloom, psychomotor disturbance, anhedonia), defined by laboratory tests, and verified by the treatment response to tricyclic antidepressants and electroconvulsive therapy. A more exacting clinical definition will encourage the search for the neural circuits and neuroendocrine systems involved in melancholia, as well as for biologic state markers and more specific effective interventions.

Differentiating the psychotic and non-psychotic forms of melancholia is necessary. The psychotic forms are preferentially responsive to electroconvulsive therapy and to the combinations of anti-psychotic and antidepressant medications compared with antidepressant agents alone.

Biologic treatments are the central intervention in the clinical management of melancholia, with psychological and social interventions offering adjunctive opportunities. The list of treatments currently approved for 'major depression' need to be re-evaluated with placebo-controlled trials in populations defined by criteria for melancholia.

References

1. Shorter E. The doctrine of two depressions in historical perspective. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):5–13.

2. Farquhar F, Le Noury J, Tschinkel S, Harris M, Kurian R, Healy D. The incidence and prevalence of manic-melancholic syndrome in northwest Wales: 1875–2005. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):37–43.
3. Parker G. Defining melancholia: the primacy of psychomotor disturbance. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):21–50. [PubMed: 17201862]
4. Parker, G., Hadzi-Pavlovic, D. *Melancholia: a disorder of movement and mood.* Cambridge: Cambridge University Press; 1996.
5. Fink M, Taylor MA. Resurrecting melancholia. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):14–20.
6. Taylor, MA., Fink, M. *Melancholia: the diagnosis, pathophysiology and treatment of depressive illness.* Cambridge: Cambridge University Press; 2006.
7. Coryell W. The facets of melancholia. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):31–36.
8. Brown WA. Treatment response in melancholia. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):125–129.
9. Stewart JW, McGrath PJ, Quitkin FM, Klein DF. Atypical depression: current status and relevance to melancholia. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):58–71.
10. Angst J, Gamma A, Benazzi F, Ajdacic V, Rössler W. Melancholia and atypical depression in the Zurich study: epidemiology, clinical characteristics, course, comorbidity and personality. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):72–84.
11. Akiskal HS, Akiskal KK. A mixed state for melancholia? *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):44–49.
12. Koukopolous A, Sani G, Koukopolous AE, Manfredi G, Pacchiarotti I, Girardi P. Melancholia agitata and mixed depression. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):50–57.
13. Kessing LV. Epidemiology of subtypes of depression. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):85–89.
14. Fink M. Should the dexamethasone suppression test be resurrected? *Acta Psychiatr Scand.* 2005; 112:245–249. [PubMed: 16156830]
15. Carroll BJ, Casidy F, Naftolowitz D, Jatham NE, Wilson WH, Iran Manesh A, Liu PY, Veldhuis JD. Pathophysiology of hypercortisolism in depression. *Acta Psychiatr Scand.* 2007; 115(Suppl 433):90–103.
16. Armitage R. Sleep and circadian rhythms in mood disorders. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):104–115.
17. Bolwig TG, Madsen TM. Electroconvulsive therapy in melancholia: The role of hippocampal neurogenesis. *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):130–135.
18. Malhi GS, Berk M. Does dopamine dysfunction drive depression? *Acta Psychiatr Scand.* 2007; 115 (Suppl 433):116–124.