Melancholia: Does This Ancient Concept Have Contemporary Utility?

by

Gabriele Sani,[a,b] Leonardo Tondo,[c,d,e] Juan Undurraga,[e,f,g] Gustavo H. Vázquez,[e,h] Paola Salvatore,[d,e,i] Ross J. Baldessarini [d,e]

a. Department of Neuroscience, Section of Psychiatry, Università Cattolica del Sacro Cuore, Rome, Italy;

b. Department of Psychiatry, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy;

c. Centro Lucio Bini, Cagliari & Rome, Italy;

d. Department of Psychiatry, Harvard Medical School, Boston, MA USA;

e. International Consortium for the Research on Mood & Psychotic Disorders, McLean Hospital, Belmont, MA USA.

f. Department of Neurology and Psychiatry, Faculty of Medicine, Clínica Alemana Universidad del Desarrollo. Santiago, Chile.

g. Early Intervention Program, Instituto Psiquiátrico Dr. J. Horwitz Barak, Santiago, Chile.

h. Department of Psychiatry, Queen's University, Kingston, Ontario, Canada;

i. Section of Psychiatry, Department of Medicine and Surgery. University of Parma, Italy.

Running title: *Melancholia*

Acknowledgments: Supported in part by a grant from the Aretaeus Foundation of Rome (to LT), by grants (FONDECYT-1180358) from CONICYT and from Clínica Alemana de Santiago (to JU), and a grant from the Bruce J Anderson Foundation and by the McLean Private Donors Research Fund (to RJB),

Disclosures: No author or immediate family member has financial relationships with commercial organizations that might appear to represent a potential conflict of interest with the material presented.

Submitted to: *International Review of Psychiatry* as an invited commentary as MS CIRP-2019-0085, December, 2019 [200 word summary, 1916 word text, 38 references, no tables].

Correspondence to: Prof. Gabriele Sani, [Largo Francesco Vito 1, 00168, Rome, Italy; Tel +39 06 30155807, Fax +39 06 30155767]; e-mail: gabriele.sani@unicatt.it.

Abstract

Many efforts have been made to develop coherent and clinically useful categories of depressive illness, especially to facilitate prediction of morbidity and guide treatment-response. They include proposals to resurrect the ancient concept of *melancholia*, a form of severe depression with particular symptomatic and proposed psychobiological characteristics. However, modern research is inconsistent in supporting differences between melancholic and nonmelancholic depression. In our recent study of over 3200 patient-subjects with DSM-5 major depressive episodes with/without melancholic characteristics, and matched for illness severity, prevalence of melancholic features was 35.2% with remarkably few clinical differences between melancholic and nonmelancholic subjects. Also, our systematic review of trials comparing melancholic and nonmelancholic subjects found little difference in responses to antidepressant treatments. These findings indicate that the concept of melancholia may have limited value for clinical prediction and treatment-selection. Overlap of symptoms in melancholic and nonmelancholic depression, based on DSM criteria, may limit distinction of melancholia; alternative definitions can be sought, and psychomotor retardation is a particularly strong differentiating feature. For now, however, melancholia seems best considered a state-dependent depression-type strongly associated with greater symptomatic severity, rather than a distinct syndrome. Its current status as a depression-type specifier seems appropriate, and it is a logical target for genetic and other biomedical studies.

Key words: bipolar disorder, DSM-5, major depression, melancholia, treatment

Introduction

Since the late 1800s, psychiatry has considered that major mental disorders occur in at least two basic groups, marked either by irrational thinking, altered speech, and abnormal behavior, or by abnormal moods with characteristic changes in thinking, speech, and behavior. Influential contributions to this two-family organization were made by Kraepelin (dementia praecox and manic-depressive illness [MDI]) and others [Shorter 1997; Trede et al. 2005]. Over the past century these groupings have undergone major challenges and modifications. Kraepelin's MDI concept was criticized as overly broad, although not until 1980 was a bipolar form of MDI (Bipolar Disorder [BD]) formally distinguished from a new concept of nonbipolar Major Depressive Disorder (MDD) [APA 1980].

MDD was a hybrid concept representing a compromise of two influential academic traditions [Shorter 1997]. One arose largely from hospital psychiatry and descriptive psychopathology from the 19th century, in which the dominant model of severe depression was largely synonymous with the ancient concept of *melancholia*. Another tradition arose in the

early 20th century, largely from office- and clinic-based practice, involved less severe depression and dysfunction, and was a candidate for treatment with psychotherapy. The broad, compromise concept MDD covered both illness-types. As such, MDD has been the target of intense debate, owing largely to evident clinical and biomedical heterogeneity of the syndrome and to the broad range of clinical responses to medical as well as psychological treatments provided for patients so-diagnosed, including a substantial proportion who respond unsatisfactorily to any available treatment [Baldessarini 2013].

Since 1980, many efforts have been made to develop a more coherent and clinically useful scheme for conceptualizing and diagnosing anticipated subgroups within the broad MDD category. Hoped-for clinical utility would include both more reliable and scientifically plausible diagnostic schemes, improved prognosis, or clinical prediction of the likely future course of depressive illness, as well as improved prediction of treatment response and more reliable selection of particular treatments. A proposed contribution to these important efforts has been to revisit the old concept of melancholia, as a particularly distinct and readily recognizable form of severe depression, and perhaps a separate syndrome with a unique pathophysiology and predictable responses to particular treatments [Taylor & Fink 2006]. The present discussion addresses the evolution and current status of the concept of melancholia.

Historical evolution

To ancient physicians, melancholia referred to a hypothetical excess of "black bile," considered to be a crucial causal contributor to clinical conditions represented by the term, and arising from the hypothesis of four humors (blood, phlegm, yellow and black bile, in turn, associated respectively with the elements air, water, fire, and earth). The basic concept of melancholia dates to ancient Greco-Roman medical texts proposing that appropriate balance of the basic humors led to good health, whereas imbalances were responsible for various diseases of body or mind. An excess of black bile, in particular, was associated with negative emotions including sadness, fear, and rage, and various forms of insanity not associated with fever, though not

necessarily implying clinical depression as conceived currently [Shorter 1997; Taylor & Fink 2006].

Between the 16th and 19th centuries, the association of melancholia with conditions marked by depressed mood and fearful preoccupations grew in strength and acceptance. It was eventually considered a form of "partial insanity" with severe, but relatively focused, fixed ideas but not pervasive loss of reason [Shorter 1997; Taylor & Fink 2006]. In the 20th century melancholia competed with the concept of "endogenous" depression, implying relatively severe, function-impairing depression seeming to arise spontaneously, as opposed to "reactive" depression associated with stressful experiences [Shorter 1997].

Current concept of melancholia

Recent efforts to resurrect the concept of melancholia have been associated with the search for a rational basis for categorizing conditions marked by depressed mood with improved clinical, pathophysiological, and therapeutic coherence [Taylor & Fink 2006]. It has been proposed that particular clinical features, such as psychomotor retardation or agitation, morbid fears and preoccupations approaching the level of delusion, as well as abnormal physiological responses all were much more likely in melancholic depression compared to other nonmelancholic types [Parker 2000; Taylor & Fink 2006]. Physiological measures included neuroendocrinological abnormalities—notably, excessive production of cortisol despite suppression with a test dose of the synthetic corticosteroid dexamethasone (dexamethasone suppression test, DST) [Carroll 1985; Arana et al. 1985], or deficient release of pituitary thyroid stimulating hormone (TSH) by administered thyrotropin releasing hormone (TRH) [Christaens & Maes 1992]; as well as altered circadian activity rhythms, delayed onset of rapid-eye-movement (REM) sleep, and altered sense of time-passage [Armitage 2007; Salvatore et al. 2012; Fuchs 2013; Baglioni et al. 2016]. In addition, there were proposals that melancholic depressions responded selectively to older tricyclic-type antidepressant drugs (TCAs) or to electroconvulsive treatment (ECT) more than to modern serotonin-reuptake inhibitors (SRIs), but less well to psychotherapies or to placebo than nonmelancholic patients [Fairchild et al. 1986; Taylor & Fink 2006]. It remains uncertain

whether such characteristics are sufficiently consistent and selective as to justify "disorder" or even "syndrome" status of melancholia [Parker et al. 2015]. Currently, DSM-5 considers that major depressive episodes in MDD or BD can sometimes include "melancholic features" [APA 2013]. In contrast, ICD-10 does not include a specific category for melancholia within its depression code (F32.9) [WHO 1992].

Assessment of proposed characteristics of melancholia

In order to evaluate several features that have traditionally been ascribed to melancholic depression, we recently compared those who did or did not meet DSM-5 criteria for melancholic features among over 3200 subjects in a major depressive episode and diagnosed with DSM-5 MDD or BD [Tondo et al. 2019]. The prevalence of DSM-5 melancholic features determined by criteria derived from eight corresponding items in the 21-item Hamilton Depression Rating Scale ($HDRS_{21}$) was 35.2% among adult subjects with moderate-severe depression (total $HDRS_{21}$ score $\geq$18). Prevalence was very strongly associated with depression-severity assessed in several ways, and was 5.0% higher in BD than in MDD. A striking finding was that, among subjects with major depression matched for severity, with or without melancholic features, there were very few differences in a broad range of clinical features, including family history, sex, onset-age, recurrence rate, proportion of time ill, risk of hospitalization, or response to clinical treatment. There was considerable overlap of risk of individual melancholic features between depressed subjects meeting DSM-5 criteria for having melancholic features or not, ranging from greater than three-fold difference for psychomotor retardation to 62% greater prevalence of excessive guilt feelings [Tondo et al. 2019]. The especially strongly differentiating effect of psychomotor retardation accords with previous reports [Parker 2000; Parker & McCraw 2017]. In addition, there was a 27% higher lifetime risk of being suicidal (mainly suicidal ideation rather than attempts or fatalities) in association with melancholic features. In an additional study, we systematically reviewed reports of clinical responses to TCA versus SRI-type antidepressants among depressed patients diagnosed as melancholic or endogenous or not. In meta-analyses of data from such studies, there was no overall difference in responses to various

types of antidepressants between the clinical subgroups, although TCAs were superior with melancholia [Undurraga et al. 2019].

Previous research has also questioned the specificity of associations of melancholia with particular pathophysiological changes, including neuroendocrine responses in the DST [Arana et al. 1985; Gitlin & Gerner 1986; Myers 1988] and the TSH-releasing test [Christaens & Maes 1992; Rush et al. 1997], as well as altered circadian activity rhythms and delay of onset of rapid-eye-movement (REM) sleep [Armitage 2007]. Such responses occur in other psychiatric disorders as well as melancholic depression, to limit their specificity [Arana et al. 1985].

These several findings raise questions about the nature and potential clinical value of the melancholia concept. The lack of clear differences between similarly severely depressed subjects who did or did not meet DSM-5 criteria for melancholic features [Tondo et al. 2019] suggests that melancholia be considered a state-dependent type of severe depression rather than a separate syndrome or disorder, and that the designation may have little clinical value for either prognosis or treatment-selection. The very strong association of melancholic features with depression-severity [Tondo et al. 2019] raises the question of whether severity alone may be a sufficient characterization. It has been pointed out previously that the overlapping DSM diagnostic criteria for major depression itself and melancholic features may limit their differentiation and association with clinically-relevant outcome measures [Parker et al. 2015].

Discussion

Efforts to develop more coherent, consistent, and predictive subgroups within the broad concept of major depression have included distinction of more versus less severe illness [Peselow et al. 1992; Zimmerman 2019], as well as apparent “endogenicity” or unexplained origin versus conditions that seem to be "reactive" to external stresses, or depression of mild or moderate severity often associated with anxiety and various "neurotic" clinical characteristics [Paykel 2008; Showraki 2019]. In addition, distinctions have been based on the presence of psychotic features, often pertaining to irrational or exaggerated fears or gloomy, mood-congruent preoccupations [Wijstra et al. 2006]. Another proposed subtype of depression is characterized

by "atypical" features, such as retained affective reactivity to environmental changes, overeating, oversleeping, severe psychomotor retardation ("leaden paralysis"), and sensitivity to interpersonal rejection, which may respond selectively to monoamine oxidase (MAO) inhibitor antidepressants [Quitkin et al. 1993]. Another depressive subtype with some clinical predictive value is major depression (in MDD or BD) with mixed (hypomanic or agitated) features [Tondo et al. 2018]. Such depressions may overlap with some features of melancholia [Koukopoulos et al. 2007, Sani & Swann 2020], as might psychotic and atypical depression [Taylor & Fink 2006]. In recent years, there have been enthusiastic proposals to resurrect the concept of melancholia, possibly as a distinct syndrome, with particular symptomatic features, pathophysiological characteristics, and selective responses to ECT, TCAs and perhaps also mood-stabilizing anticonvulsants or lithium and antipsychotics more than to psychotherapies or inert placebos [Fairchild et al. 1986; Peselow et al. 1992; Perry et al. 1996; Centorrino et al. 2005; Taylor & Fink 2006; Brown 2007; Parker et al. 2010; Koukopoulos & Sani 2014; Tondo et al. 2017].

Renewed interest in the concept of melancholia emerged following introduction of the concept of major depression in 1980 as a very broad, clinically heterogeneous condition. Despite the intuitive appeal of the concept of melancholic depression, recent research tends to challenge its security as a clinically or biomedically distinct disorder or syndrome, as addressed above. In particular, the ability of DSM-5 "melancholic features" to provide clinically important predictions (e.g., future morbidity, risk of suicide attempts or fatalities, or particular treatment-responses) or associations (e.g., family history, sex, current age or age-at-onset, previous or future morbidity) seems to be surprisingly limited, especially when DSM-5 nonmelancholic and melancholic patient-subjects have similar depression-severity [Tondo et al. 2019; Undurraga et al. 2019].

Conclusions

The clinically and scientifically appealing concept of melancholia may be of more limited value than has been recognized, particularly regarding clinical prediction and treatment-selection. The overlap of particular symptoms and behavioral dimensions in melancholic and nonmelancholic

depressed patient-subjects, based on current DSM criteria, may well contribute to this impression, and alternative definitions might be sought. Psychomotor retardation appears to be a particularly strong basis of differentiating melancholic from nonmelancholic depressions, and various biological measures have shown some ability to differentiate melancholic depression. Nevertheless, for now, we propose that melancholia seems to be best understood as a state-dependent type of depression, strongly associated with greater symptomatic severity, rather than a robustly distinct syndrome or disorder, and consider its status as a set of subtype-defining characteristics as in DSM-5 to be appropriate. Finally, despite its limitations, melancholic depression remains a logical target for genetic and other biomedical studies.

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