The empirical status of melancholia: Implications for psychology

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Abstract

The concept of a subtype of depression with a biological rather than a psychological set of causes has been more prominent in the psychiatric literature than in the psychological literature on depression. There has been dispute as to whether research on melancholia supports the distinction of a separate subtype with a distinct symptomatic profile characterized by marked anhedonia, psychomotor difficulties, excessive guilt or hopelessness, suicidal features, and appetite and weight disturbances. Research suggests that individuals with melancholic depression are qualitatively different from those with non-melancholic depression in their symptomatology. Examination of biological functioning, personality traits, responsiveness to treatment, and suicidality also tend to support the melancholic–non-melancholic distinction. This paper reviews the status of the melancholia concept and explores its implications for psychological research and practice.

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1. Introduction

Depression has been conceptualized as a heterogeneous mixture of conditions and disorders, but finding meaningful groupings has been a difficult endeavor. The idea of somatogenesis, manifest disease arising from internal biological dysfunction, is at least as old as Hippocrates’ writings in the 5th century BC. Melancholia preceded the term depression to describe human despondency. The word is derived...
from the Greek term “melaina chole” or “black bile,” the bodily humor that was identified with black moods. In recent history, the idea of a somatic genesis for depression has been contrasted with a psychological genesis, and the terms “endogenous” versus “exogenous” or “reactive” have been used to contrast these two sources of depression.

Establishing subgroups of patients based on putative etiology has long been a goal of diagnostic classification. Those with endogenous symptoms should lack precipitating events, although a number of investigators have failed to find group differences in the incidence of stressful life events between individuals with endogenous and non-endogenous symptomatic profiles (e.g., Forrest, Frazer, & Priest, 1965; Lafer, Nierenberg, Rosenbaum, & Fava, 1996; Leff, Roatch, & Bunney, 1970; Thomson & Hendrie, 1972). In fact, Mundt, Reck, and Backenstrass (2000) demonstrated that stressful experiences often precede onset of melancholic episodes. Findings from other investigations indicate that depressed individuals with melancholic symptomatology may undergo more adverse experiences than non-melancholic individuals (Harkness & Monroe, 2002; Willner, Wilkes, & Orwin, 1990). Two studies have provided support for the idea of fewer precipitating events in depressive episodes with endogenous symptoms (e.g., Kohn, Zislin, & Agid, 2001; Tomaszewska, Peeslow, Barouche, & Fieve, 1996). Overall, the inconsistencies across investigations demonstrate the difficulty in establishing groupings based on supposed etiology.

2. The constructs of endogeneity and melancholia

The term endogenous has been used to identify a syndrome of depression identified by symptoms of pervasive anhedonia, anorexia, weight loss, early morning awakening, diurnal variation of mood, psychomotor agitation or retardation, guilt, and sometimes psychotic features (Coplov et al., 1986). The grouping of a separate melancholic subtype of depression was introduced in the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III; American Psychiatric Association, 1980). Klein (1974) summarized the rationale for this distinction in patients who show a regular impairment in the capacity to experience pleasure or to respond effectively to the anticipation of pleasure. Klein described “neurotic depression,” as a “chronic emotional or personality disorder related to low self-esteem, overly severe disappointment reactions, feelings of helplessness, reliance on external sources of self-esteem, and an irritable, grasping, angry, unhappy, other-blaming, and histrionic attitude” (Klein, 1974, p. 448). He contrasted this with melancholic depression, typified by a loss of interest or pleasure, anorexia, suicidal preoccupation, fearful perplexity, retardation, or agitation. Klein characterized melancholia as “endogenomorphic” depression, that is, having the form or appearance of endogenous depression. Klein believed that the key feature of true endogenous depression is persistent and severe anhedonia, which he hypothesized results from inhibition of the brain’s “pleasure mechanism”. In the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association, 1994), melancholia is a specifier for a Major Depressive Episode in either unipolar or bipolar depression. It requires (A) during the most severe period of the episode that the patient shows either (1) loss of pleasure in all, or almost all, activities; or (2) lack of reactivity to usually pleasurable stimuli; and (B) three or more of the following: (1) distinct quality of depressed mood; (2) depression regularly worse in the morning; (3) early morning awakening; (4) marked psychomotor retardation or agitation; (5) significant anorexia or weight loss; and (6) excessive or inappropriate guilt. Loss of interest or lack of reactivity is stressed as the essential feature.
Evidence supports the existence of qualitatively distinct dimensions of depression, one of which is identifiable as melancholia that is highly associated with anhedonia. Factor analytic studies have generally confirmed a melancholic dimension of depression (Biro & Till, 1989; Kiloh & Garside, 1963; Marcos & Salamero, 1990). Kiloh and Garside (1963) examined personality traits and present depressive symptoms and reported a two-factor solution with the second factor interpreted as a bipolar melancholic versus non-melancholic dimension. They listed melancholic clinical features as: early awakening, depression worse in the morning, distinct quality of depression, retardation, episode duration of 1 year or less, age 40 or above, depth of depression, failure of concentration, and weight changes. Another psychometric analysis of 200 diagnostically heterogeneous depressed patients (Biro & Till, 1989) led to a four-factor solution interpreted to represent dimensions of depression subtypes: melancholic, psychotic, anxious, and retarded depression. The melancholic factor was weighted with anhedonia, loss of interest, retardation, reduced efficacy, guilty feelings, diurnal variation, insomnia, and hopelessness. Marcos and Salamero (1990) reported a three-factor solution and identified the primary factor as one of melancholia. Clark and Watson (1991) conducted an extensive review of the depression assessment literature spanning many self-report and clinician ratings of mood, symptom, and syndrome measures. Their findings confirmed two independent factors in depression: anhedonia and general distress.

While factor-analytic methods can identify separate dimensions, they cannot detect whether underlying structure of psychological disorders is taxonic (categorical) or dimensional (continuous). Examinations using taxometric analysis, a set of statistical techniques able to assess latent structure, have provided support for a qualitatively discrete melancholic subtype (Ambrosini, Bennett, Cleland, & Haslam, 2002; Beach & Amir, 2003; Grove et al., 1987; Haslam & Beck, 1994). An analysis of 531 patients with a primary major depressive diagnosis demonstrated that sleep disturbance and loss of satisfaction, appetite, weight, and libido were indicators of a unique melancholic taxon (Haslam & Beck, 1994). These results parallel those found by Beach and Amir (2003) in four samples of 984 undergraduates, who demonstrated that in addition to symptoms identified in the Haslam and Beck (1994) study, preoccupation with health and social anhedonia were good indicators of a categorically discrete melancholic syndrome. Melancholic features tended to be part of a structurally distinct entity, whereas cognitive and affective depressive symptoms were more consistent with a dimensional structure (Beach & Amir, 2003). These findings suggest that melancholia is a constellation of clinical features and not solely a marker of those who are most severely and chronically depressed. In fact, at least 50% of the depressed people who score in the upper half of severity range do not have melancholia (Thase, Hersen, Bellack, Himmelhock, & Kupfer, 1983). Benazzi (2000) demonstrated no differences in chronicity between melancholic and non-melancholic forms of bipolar II depression. Taken together, these findings suggest that melancholia may be a naturally occurring phenotype, qualitatively distinguishable from non-melancholic depression, and not solely an artifact of a symptom-defined system of disease classification.

Based on a literature review and an empirical examination of 152 inpatients with unipolar major depression, Zimmerman, Coryell, Pfohl, and Stangl (1986) suggested additional features of the melancholic construct such as, a greater family history of depression, a lower family history of alcoholism, a lower family history of antisocial personality, older age, higher scores on symptom severity indexes, less frequent non-serious suicide attempts, lower prevalence of divorce or marital separations, fewer stressful life events, lower probability of premorbid personality disorder, better social support, less cognitive distortion, a higher frequency of neuroendocrine or other biologic abnormalities, a better response to
somatic therapies, and a poorer response to psychotherapy. Examination of the biological and psychological factors in melancholia has supported the association with some of these features.

3. Biological factors in melancholia

When it was introduced, the dexamethasone suppression test (DST; Carroll, Martin, & Davies, 1968) was offered as a specific laboratory test and biological marker for the presence of melancholia in depression. In normals, dexamethasone suppressed cortisol whereas a non-suppression response, indicative of a pituitary–adrenal hypothalamic dysfunction, was associated with melancholic depression (Carroll et al., 1981). Although these findings were only correlational and could not demonstrate a causal relationship, DST results supported the hypothesis that the key component of melancholic depression is a dysfunction of physiological mechanisms that regulate emotion. Most investigations have found that 35–60% of individuals with melancholia show an abnormal DST response (Giles & Rush, 1982; Mitchell et al., 1996; Rush et al., 1997).

Other investigators, however, have found no relation between a diagnosis of melancholic depression and non-suppression DST results (Brown & Shuey, 1980; Mendlewicz, Charles, & Franckson, 1983). A study evaluating 231 psychiatric inpatients found that DST responses were related to intervening variables such as stress due to hospital admission, drug withdrawal, suicidal turmoil, and weight loss (Berger, Pirke, Doerr, Krieg, & von Zerssen, 1984). These variables were found to enhance the rate of abnormal DST results regardless of diagnostic classification. Klein and Berger (1987) argued that the DST does not reliably indicate hypercortisolism, a reflection of pituitary–adrenal hypothalamic dysfunction. Whether or not failure to suppress plasma cortisol is a reliable correlate of melancholia, the DST may lack sufficient sensitivity or specificity for an accurate diagnosis of melancholia.

Besides dexamethasone suppression response, other neuroendocrine variables have shown some ability to discriminate melancholic and non-melancholic forms of depression. Thyroid axis dysfunction may be related to psychomotor abnormalities, weight loss, and sleep disturbances in melancholia (Thase & Howland, 1995). Basal levels of thyroid stimulating hormone (TSH) and response to thyrotropin-releasing hormone, indices of thyroid axis functioning, have been used as biological measures of depression (Thase & Howland, 1995). Türçapar et al. (1999) demonstrated that DSM-IV-diagnosed melancholic patients have higher cortisol levels and lower levels TSH of than non-melancholic individuals with depression. In concordance with these findings, Rush et al. (1997) found that melancholic patients were more likely to have a blunted thyrotropin-releasing hormone stimulation test (TRH-ST) results and DST non-suppression than non-melancholic depressed patients. Other studies assessing depression through neuroendocrine measures have indicated that the presence of weight loss and depressive psychomotor abnormalities may better account for abnormal TSH levels, blunted DST response, (Staner, Maes, Bouillon, & Linkowski, 1992) and lower melatonin levels (Fontoulakis et al., 2001) than the constellation of symptoms required for research diagnostic criteria (RDC) and DSM-IV melancholia diagnoses.

A separate area of research indicates that sleep patterns differ in depressed individuals with and without melancholia (Kupfer, Foster, Coble, McPartland, & Ulrich, 1978; Rush et al., 1997; Staner et al., 1992; Simons & Thase, 1992). Individuals with melancholic depression display a reduced REM latency (Rush et al., 1997) and a higher REM frequency (Coble, Foster, and Kupfer, 1976) than those with non-melancholic depression. REM latency has demonstrated the greatest sensitivity but lowest specificity in
the differentiation of melancholic from non-melancholic depression as compared to the DST and the TRH-ST (Rush et al., 1997). Temporal mood patterns and sleep-related symptoms suggest that circadian rhythms are shifted in people with melancholia. Vogel, Thurmond, Gibbons, Sloan, Boyd, and Walker (1975) found that melancholic patients whose circadian rhythms were altered by REM sleep deprivation improved more than patients with unaffected circadian rhythms deprived of only non-REM sleep. The same circadian manipulation did not significantly alter symptoms in non-melancholic depressed patients. In another paper, Vogel, Vogel, McAbee, and Thrumond (1980) proposed that depressive clinical characteristics represent a damaged sleep cycle “oscillator”, which results in circadian rhythm disturbances. They suggested that REM sleep deprivation improved depressive symptoms in melancholia because it stimulated the oscillator and corrected the circadian rhythm disruption. Other laboratories have replicated findings that REM sleep deprivation improves depressive symptoms, (Elsenga & van den Hoofdakker, 1983, 1987; Reynolds et al., 1987). Newly developed software for the real time detection of REM sleep in conjunction with computer-operated awakening procedures is making this phenomenon easier to assess and study (Groezinger, Koegel, & Roeschke, 2002).

Studies demonstrating reduced REM latency and the efficacy of sleep deprivation in melancholic individuals suggest that disrupted circadian rhythms may be a significant feature of melancholic depression. An interesting corollary to the sleep research findings is found in the time experience of patients with melancholic depression (Kuhs, Herman, & Töle 1991; Raamsayer, 1990; Tysk, 1984). When melancholically depressed inpatients are asked to approximate a 30-s interval, they tend to underestimate by about 6 s, suggesting that time subjectively passes slowly for them (Kuhs et al., 1991). Misjudgment in time estimation tasks has been interpreted as evidence of altered “internal clock” functioning in melancholia (Tysk, 1984). Raamsayer (1990) investigated temporal discrimination tasks in melancholic patients and also found results indicative of dysfunctional internal clock regulation. Animal research provides evidence suggesting that the rate of internal clock functioning depends on the effective level of dopaminergic activity (Maricq & Church, 1983; Meck, 1983). Thus, internal clock dysregulation in melancholia may be a consequence of abnormal functioning of dopaminergic systems, a phenomenon which has been demonstrated in other studies that report dysfunction in the brain’s reward system (BRS) in depression (Naranjo, Tremblay, & Busto, 2001; Willner, 1997). Future research using neuropharmacological techniques may clarify the extent of any alterations in dopaminergic functioning present in melancholia (e.g., Rampello, Nicoletti, & Raffaele, 1991; Thase, Mallinger, McKnight, & Himmelhoch, 1992).

A common finding is that rates of melancholia increase with age leading some to propose that biological correlates of aging may play a role in producing melancholic symptoms (Thase & Friedman, 1999). For example, levels of serotonin or dopamine, neurotransmitters associated with the pathophysiology of depression, tend to be inversely related with age (Thase & Howland, 1995). In addition, inhibitory mechanisms that reduce the effects of stress on brain functioning may decline with age (Thase & Howland, 1995). Another set of explanations for these findings involves the notion that various forms of reinforcement may be unattainable or lost in older age due to reduced physical health, inability to travel, and death of friends and loved ones. Reductions in positive reinforcement may cause a decline in hedonic tone, which may eventually develop into a more pervasive form of anhedonia. Whether or not anhedonia is present, it is common for elderly patients with depression to report somatic symptoms, such as diminished energy, strained effort, and sleep disturbance (Gottfries, 1998; Norris, Snow-Turek, & Blankenship, 1995). Because sexual activity and appetite changes may not be related to depression in the elderly (Norris et al., 1995), melancholia assessment of this population should focus more on anhedonic symptoms and daily variations in mood.
Animal research has been used to examine models of the etiology of melancholic symptoms and their neurobiological correlates. Animal models of depression use highly controlled techniques such as repeated psychostimulant exposures and chronic stress to induce anhedonia and other melancholic symptoms that can be reversed with antidepressant medication (Leith & Barret, 1975; Phillips & Barr, 1997; Willner, 1997). These methods produce anhedonia by dysregulating the BRS. The BRS is a complex neural network with active sites along the medial forebrain bundle, particularly in the lateral hypothalamic, posterior hypothalamic, and ventral tegmental levels (Wise, 1988). The BRS is stimulated during reward behavior and has been shown to drive hedonic processes through activation of the mesocorticolimbic dopamine system (Naranjo et al., 2001). Only recently have investigators begun to examine the BRS in humans with depression. Naranjo et al. (2001) measured the response of subjects with major depressive disorder (MDD) to d-amphetamine, a pharmacological agent known to activate the BRS and its dopaminergic network. They found that the MDD subjects reported increases in subjective reward differently than non-depressed controls. This was interpreted as evidence for BRS dysfunction in depression. Measures of biological variables, such as DST and TSH response, are thought to assess the brain’s stress response. BRS alterations may assess the physiological source of anhedonia in melancholia directly, although current evidence supporting this notion is primarily correlational (e.g., Naranjo et al., 2001).

Recently, investigators have utilized neuroimagining techniques to examine regional brain structure and function in emotionally disordered individuals (see Davidson, 2000; Davidson & Irwin, 1999; Davidson, Pizzagalli, Nitschke, and Putnum, 2002 for reviews). Davidson et al. (2002) found that individuals with depression demonstrate structural and functional abnormalities in the prefrontal cortex, anterior cingulated cortex, hippocampus, amygdala, and other neural sites. A few studies have examined impact of melancholic depressive symptomatology on brain function (Bench et al., 1992; Galynker et al., 1998; Pizzagalli et al., 2002). Psychomotor retardation, anhedonia, and flat affect have been associated with decreased left dorsolateral prefrontal cortex activity (Bench et al., 1992; Galynker et al., 1998), whereas comorbid anxiety has been related to more right- than left-sided neural activity (Bruder et al., 1997). Pizzagalli et al. (2002) examined imaging correlates of depressive symptomatology in melancholic and non-melancholic depressed individuals. One of the more interesting findings in this study was that state measures of anxiety demonstrated a more robust correlation with right frontal lobe activity in melancholic subjects than in non-melancholic subjects. This is consistent with evidence that melancholia involves more extensive physiological dysregulation than non-melancholic depression.

Overall, there appears to be some consistent biological factors associated with the presence of melancholia in depression (e.g., REM latency). While these correlates add to our understanding of melancholia, many studies that have examined biological factors were cross-sectional which precludes certain interpretations of the temporal ordering and directional causation of biological dysfunction and melancholic symptoms. Moreover, none of these factors have developed into definitive biological markers or practical assessment devices. Consequently, assessment of the melancholia construct remains at the level of evaluating current behavioral symptomology.

4. Psychological factors in melancholia

A number of assessment techniques have been used to determine whether an individual meets criteria for melancholic depression. The standard for research is to conduct a semistructured interview, such as
the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995) to obtain both a diagnosis of depression and the specifier “with melancholic features.” While DSM-IV criteria are the most frequently used, expanded criteria were proposed in the Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978). RDC lists 10 depressive symptoms to diagnose melancholic depression very similar to DSM criteria but lacking items on poor reactivity to usually pleasurable events. Symptoms on the RDC are rated as either present or absent. RDC classification separates depressed individuals into “definite endogenous”, “probable or uncertain endogenous”, and “non-endogenous.” The RDC category of “probable endogenous” is more inclusive than the DSM-IV specifier “with melancholic features.”

In addition to RDC and DSM-IV specifier criteria, empirical scales have also been developed for identifying items that differentiate melancholic from non-melancholic patients. The Newcastle Index (Carney, Roth, & Garside, 1965; Gurney, 1971) is a 10-item scale based on multiple regression analyses of 35 items rated on 116 depressed patients who seemed to fit the melancholic category. The Feinberg–Carroll Discriminate Index (Feinberg & Carroll, 1982) sums ratings on eight clinical items, each multiplied by a given weight that allows for a distinction between definite melancholic, probable or uncertain melancholic, and nonmelancholic. This index has high agreement with clinical diagnoses and biological correlates of melancholia (Staner et al., 1992) and may be useful to clinicians who wish to confirm a diagnostic impression of melancholia with a formal assessment procedure.

Melancholia can also be measured as a continuous variable, so that severity can be assessed and tracked during a course of treatment. The most commonly used clinician rating scale for assessing severity of depression, the Hamilton Depression Rating Scale (Hamilton, 1960), has been adapted to assess melancholia. Of the 17-item version of the Hamilton, a subset of questions that make up a Hamilton Endogenomorphy Scale that has been used to assess melancholia in research studies (e.g., Thase et al., 1983). The Inventory of Depressive Symptomatology-Clinical Ratings (IDS-C; Rush, Guillon, Basco, Jarret, & Trivedi, 1996) includes items that assess all melancholic and non-melancholic depressive symptoms listed in the DSM-IV. There is also a Quick-IDS-C (QIDS-C; Rush et al., 2003) that only takes 5–7 min to complete. However, the QIDS does not measure all melancholic or atypical features. The Bech–Rafaelsen Melancholia Scale (Bech & Rafaelsen, 1980) is an 11-item clinician rating measure that lacks items that assess psychomotor agitation or diurnal variation of mood, both of which appear to be important symptoms associated with melancholia. Overall, clinician ratings that gauge the severity of melancholia may be useful, especially when used in conjunction with comprehensive diagnostic tools such as the DSM-IV.

The most frequently used self-report measures of depression give only partial information about melancholic symptomatology. The BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) is the most commonly used self-report index of depression. Items tapping increased appetite, weight gain, increased sleep, psychomotor agitation, psychomotor retardation, problems with concentration, and nonsuicidal death wishes were not included in the first edition (Zimmerman & Coryell, 1987); however, a factor-analytically derived subscale of the BDI that correlates highly with somatic and vegetative symptoms reliably distinguished between melancholic and non-melancholic forms of depression (Schotte, Maes, Cluydts, De Doncker, & Cosyns, 1997). The second edition of the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996) offered questions on atypical symptoms, concentration difficulties, and psychomotor problems, but still lacks melancholic items on daily mood variation and whether mood improves after positive events. Similarly, other commonly used self-report measures, the Zung Depression Inventory (Zung, 1965) and the Center for Epidemiological Studies—Depression Scale
(Radloff, 1977) do not contain items measuring guilt, diurnal variation of mood, early morning awakening, and responsiveness of mood. These self-report measures can not substitute for a specific measure of melancholia, but may be used to screen out non-melancholic individuals who endorse few or no items assessing anhedonia or somatic and vegetative features. They are also useful for tracking overall treatment progress.

One self-report scale, The Inventory to Diagnose Depression (IDD; Zimmerman and Coryell, 1987) was developed to diagnose depression and melancholia according to DSM-III-R criteria. The benefits of the IDD are its user-friendly language, assessment of subthreshold MDD symptoms (i.e., “less than or more than two weeks”), and the five-level severity rating of each symptom. The Inventory of Depressive Symptomatology-Self Report (IDS-SR; Rush et al., 1996) is much like the IDD but is updated to include items that assess all melancholic and non-melancholic depressive symptoms listed in the DSM-IV. The IDS-SR includes a shortened versions, the Quick-IDS-SR (QIDS-SR; Rush et al., 2003), but like the QIDS-C, the QIDS-SR also does not assess all melancholic symptoms. The IDS-SR uses DSM-IV wording in its descriptions of symptoms (e.g., “Is your mood variation attributed to the environment” and “My mood is sad, but this sadness is different from the type of sadness associated with grief or loss”). Thus, the language may not be easily understood by respondents. Nonetheless, both the IDS-SR and the IDD are adequate means of assessing melancholic symptomatology. The Levine–Pilowsky Depression Questionnaire (LPDQ; Pilowsky, Levine, & Boulton, 1969) is a 57-item test with questions to assess endogenous and non-endogenous depression. It contains 28 questions that are usually answered yes by individuals with endogenous depression. However, the LPDQ was developed before DSM-III consensus on melancholic symptoms, and it omits some consensus criteria and adds some idiosyncratic items.

Anhedonia is traditionally conceptualized as the core symptom of melancholia (Klein, 1974). It may be pervasive or confined to a specific aspect of experience, such as a food and drink palatability, sexual activity, social interaction, sensory stimulation, or one’s usual interests and pastimes (Snaith, 1993). Presence and severity of anhedonia is typically measured in most depression assessment tools through one or two items. To obtain a more accurate quantitative measure of anhedonia, practitioners and researchers can use one of three self-report questionnaires: Chapman Physical and Social Anhedonia Scale (CAS; Chapman, Chapman, & Raulin, 1976), Fawcett–Clark Pleasure Capacity Scale (FCPS; Fawcett, Clark, & Scheftner, 1983), and Snaith–Hamilton Pleasure Scale (SHAPS; Snaith, Hamilton & Morely, 1995). All have been shown to correlate with measures of melancholia (Fawcett et al., 1983; Loas & Boyer, 1996; Snaith, Hamilton, & Morely, 1995).

The CAS asks about past experiences and trait-like anhedonic characteristics (i.e., “The taste of food has always been important to me”). The CAS allows users to assess both social and physical anhedonia in separate subscales of 40 and 48 items. The SHAPS and FCPS ask about hypothetical responses to pleasurable stimuli and assess anhedonia as a state, while the CAS examines anhedonia as trait-like. The SHAPS uses 14 items to measure for differences in hedonic response to social contact, appetite for food, hobbies and pastimes, and sensory experiences with one or a few items on each category. D’haenen (1996) pointed out that paper and pencil anhedonia measures are subject to bias according to age, gender, social, and ethnic group. Nonetheless, using anhedonia measures in conjunction with traditional melancholia assessment tools such as the Newcastle Index, DSM-IV, or RDC can provide additional information on the pervasiveness and severity of this symptom. Therapists may potentially plan more successful behavioral activity schedules by utilizing information gained from anhedonia assessment. Using these symptoms specific measures may be useful in learning more about the helpfulness of specific interventions.
Personality traits have also been associated with melancholic depression, although, due to methodological limitations, it is unclear whether such traits may be causes or effects of the disorder. A number of studies report that “autonomous” personality traits occur frequently in individuals with melancholia, and “sociotropic” traits are common in non-melancholically depressed people (Beck, 1983; Robins & Luten, 1991). Autonomous individuals are sensitive to achievement losses. When they experience defeat, their clinical features are more likely melancholic. Sociotropic individuals are sensitive to interpersonal loss and present clinical characteristics related with reactive depression. The relation of these personality traits to depression type may assist researchers and clinicians in understanding etiologies of depression from a stress–diathesis point of view. Other studies investigating personality traits report that patients with melancholic depression have less vulnerable personality styles and are less neurotic and more obsessive than individuals with non-melancholic depression (Benjaminsen, 1981; Boyce, Parker, & Hickie, 1990; Charney, Nelson, & Quinlan, 1981). However, because these findings are primarily correlational, it is difficult to determine whether certain personality types are risk factors for melancholia.

Examinations of life events suggest that stressful experiences often precede the onset of melancholia (Forrest et al., 1965; Leff et al., 1970; Thomson & Hendrie, 1972). Reports of significant increases in stressful life events during the pre-episode year (up to 12 months before the onset of the depressive episode) in people with depression have been found whether or not melancholic symptomatology is present (Brown, Harris, & Hepworth, 1994; Cornell, Milden, & Shimp, 1985). Although some studies have found that individuals with melancholia report fewer stressful life events than those with non-melancholic depression (e.g., Kohn et al., 2001; Tomaszewska et al., 1996), periods of distress have been shown to predict episodes of melancholia as well (Mundt et al., 2000). Whether or not incidence of distressing events can differentiate between melancholic versus non-melancholic depressions, it should be noted that individuals who display melancholic symptomatology may have undergone prior stressful experiences (Mundt et al., 2000).

Recently, research has examined stress in childhood and its effect on adult depression (e.g., Bifulco, Brown, Moran, Ball, & Cambell, 1998; Harkness & Monroe, 2002). Harkness and Monroe (2002) examined a group of depressed 76 women, 31 of whom met RDC for melancholia, and found that women with melancholia experienced more severe early childhood adversity (i.e., severe physical abuse, sexual abuse, antipathy, and neglect) than non-melancholic women. Other studies have demonstrated that less severe forms of childhood adversity, such as a dysfunctional parental marriage, dysfunctional parenting, and rejection, were more associated with non-melancholic depression (Parker, Gladstone, et al, 1997; Parker, Kiloh, & Hayword, 1987; Parker, Roussos, et al, 1997). Harkness and Monroe (2002) hypothesized that severe, prolonged, and uncontrollable stress may cause neuroadaptations that mediate the development of melancholia in adulthood. As a general rule, clinicians applying psychological interventions should be cognizant of potential psychosocial precipitants that can occur before the onset of melancholic depressive episodes.

5. Suicide in melancholic patients

Melancholic patients may have a heightened risk for suicide. Van Praag and Plutchik (1984) studied suicide attempts, depression type, and depression severity in hospital patients with non-psychotic depression. Their data showed that violent suicide attempts occurred with greatest frequency in
individuals with melancholic depression. Goldney, Adam, O’Brien, and Termansen (1981) studied 100 female suicide attempters in four Australian inpatient wards and assessed for melancholia. One-third of those assessed were classified with melancholia. Another study examined the relation between suicidality and DST response in 49 newly hospitalized patients and found significantly more of the suicidal patients had abnormal DSTs (Tagrum, Rosen, & Capodanno, 1983). Five out of six of those who later made a suicide attempt had abnormal DST results.

A recent review suggested that individuals classified with melancholia may not be at greater risk for suicide (O’Leary, 1996). It appears that certain melancholic symptoms, such as guilty feelings, loss of interest, and pervasive anhedonia, may better predict suicidality than RDC or DSM based classification (Davis, 1998; Van Gastel, Schotte, & Maes, 1997). In the Swedish Lundby Study, over 3500 patients were monitored over a 25-year period (Hagnell & Rorsman, 1978). The records of 28 subjects who successfully committed suicide were analyzed and revealed that 10 out of the 14 with a depressive diagnosis experienced a number of melancholic features (waking up early, extreme guilt, diurnal rhythm). Fawcett et al. (1990) studied 954 psychiatric patients with affective disorders and found that severe loss of interest or pleasure to be a predictor of future suicide. Other symptoms that appear to be related to suicidality are hopelessness, depressed mood, feelings of guilt, loss of interest, and low self-esteem (Van Gastel et al., 1997). Thus, while the data are not uniform in suggesting that melancholia may be associated with elevated suicide risk, clinicians should be aware of the possibility, especially when specific symptoms are present such as severe anhedonia and loss of interest, hopelessness, and inappropriate guilt.

6. Somatic treatment of melancholic depression

There is disagreement about whether melancholic and non-melancholic depressed individuals respond differently to pharmacotherapy and pill placebos. Because of the large number of studies with conflicting data, two papers with alternate viewpoints are cited here. Feinberg (1992) suggested that accurate diagnosis and subtyping of depression is crucial in determining response to treatment. He cited studies demonstrating that melancholic depressed individuals responded to imipramine but not placebo, whereas non-melancholic depressed patients responded to active treatment or placebo (Kiloh, Ball, & Garside, 1961; Rogers & Clay, 1975). Other studies have reported similar findings (Peselow, Sanfilipo, & Difiglia, 1992; Raskin & Crook, 1976). Feinberg indicated that these results suggest that individuals with melancholic depression may be less responsive to psychosocial interventions. These broad statements may not be warranted as studies demonstrating that melancholic patients do not respond to placebo merely provide evidence that these patients are less responsive to the psychological effects of pill placebos. In response to Feinberg’s article, Greenberg, Bornstein, Greenberg, and Fisher (1992) wrote that the studies reviewed by Feinberg judged the efficacy of antidepressants and placebos without double-blind conditions. Following the publication of these papers, a double-blind antidepressant treatment study found that individuals with melancholia are in fact less likely to respond to placebo than non-melancholic patients (Peselow et al., 1992).

Although research examining melancholic versus non-melancholic differences in treatment response is useful, it is important that investigators of treatment efficacy extend beyond subtype, e.g., evaluating symptom-specific improvements within melancholic and non-melancholic patients. Nevertheless, it
appears that individuals with melancholic depression are less likely to be placebo responders than those with non-melancholic depression.

It is clear that antidepressant medication is an effective treatment for individuals who meet RDC, or DSM criteria for melancholia. Angst, Scheidegger, and Stabl (1993) published data from 38 double-blind and 2 single-blind studies examining moclobemide and other antidepressants versus placebo that were available for an intent-to-treat meta-analysis of individuals with melancholia. Response rates to moclobemide were highest in patients with unipolar melancholic (66%) followed by bipolar (57%), neurotic (52%), and reactive (43%) depression. Studies examining the efficacy of newer antidepressant medication treatments for melancholia indicate that fluoxetine is less effective than nortryptiline (Roese, Glassman, & Attia, 1994), venlafaxine (Dierick, 1997; Tzanakaki, Guazzelli, & Nimatoudis, 2000) and sertraline (Flament, Lane, & Zhu, 1999). Nevertheless, fluoxetine has been shown to be superior to placebo in the treatment of melancholia (Heiligenstein, Tollefson, & Faries, 1993).

Some suggest that melancholic patients respond better to somatic treatment than individuals with non-melancholic depression (American Psychiatric Association, 1993). However, the clearest predictors of pharmacological response appear to be biological correlates of melancholia rather than explicit behavioral symptomatology (Akiskal et al., 1980; Rush et al., 1986, 1989; Svendsen & Christensen, 1981). In fact, some studies have shown no differences between subtype diagnosis and somatic treatment response (Coryell & Turner, 1985; Paykel, Hollyman, Freeling, & Sedgwick, 1988; Peselow et al., 1992).

Resistance to pharmacotherapy is rare but does occur in some melancholically depressed individuals (Puzyznski, Koszew ska, & Kalinowski, 1995). Melancholic patients who are resistant to psychosocial or pharmacological treatment may be treated successfully by ECT (Puzyznski et al., 1995; Strober, Rao, & DeAntonio, 1998). When investigators looked at group differences in depression subtype and temporal response to ECT, melancholic patients tended to respond to treatment more quickly and more favorably than non-melancholic subjects (Viissides & Jenner, 1982). On the whole, ECT and antidepressant medication are effective treatments for melancholia.

7. Psychosocial treatment for melancholic depression

The widespread clinical belief that melancholia should be treated pharmacologically has not been challenged until recently. This notion originally stemmed from older conceptualizations of melancholia as an endogenous disorder. In comparison to the extensive research base on somatic treatments, few studies have examined the efficacy of psychotherapy for melancholic depression. Prusoff, Weissman, Klerman, and Rounsiville (1980) were the first to evaluate psychosocial treatments in melancholia. They investigated the effectiveness of short-term interpersonal psychotherapy (IPT) and amitriptyline in a 16-week, randomized controlled trial. Study results demonstrated that melancholic depressed individuals defined by RDC responded well to medication and combined medication and IPT, but failed to respond to IPT alone. However, a recent analysis of treatment efficacy, using a sample size large enough to detect smaller effects, suggests that IPT may be helpful for treating melancholia (Sotsky et al., 1991).

A small body of literature has addressed the effectiveness of Cognitive-Behavioral Therapy (CBT) for treating melancholic depression. Cappeliez (2000) used RDC to assess melancholia in a sample of 21 elderly participants, six of whom were classified as melancholic. In this study, two of the six participants reached non-depressed status at the end of CBT. Gallager and Thompson (1983) and Thompson and Gallager (1984) also reported that around one-third of elderly depressed individuals with melancholic
symptoms improved after CBT. Nevertheless, interpretations of these studies are limited because of small sample size \((N=15)\) and restricted age of participants (mean age of 67 years). Thase, Simons, Cahalane, and McGeeary (1991) assessed 38 melancholically depressed individuals prior to treatment and administered a 16-week, 20-session outpatient protocol of Beck’s CBT (Beck, Rush, Shaw, & Emery, 1979). At post treatment, 75% of the participants did not meet response criteria for depression as measured by Hamilton Depression Rating Scale, Beck Depression Inventory, and the Global Assessment Scale. Other investigations have found cognitive therapy effective for individuals with melancholic depression (Blackburn, Bishop, Glen, Whalley, & Christie, 1981; Kovacs, Rush, Beck, & Hollon, 1981; Teasdale, Fennell, Hibbert, & Amies, 1984). It is difficult to compare these findings with those found in larger studies because of small sample sizes and other methodological differences. In addition, most of these studies included patients who satisfied less restrictive RDC criteria of probable endogenous, which limited the generalizability of these investigations to patients with more extensive melancholic symptoms.

The National Institute of Mental Health Treatment of Depression Collaborative Research Program examined depression subtype as a patient predictor of response to four treatment conditions: imipramine+clinical management, placebo+clinical management, Cognitive Therapy, and IPT (Sotsky et al., 1991). The large sample size permitted sufficient power to detect the effects of psychotherapy in melancholic patients. In their analysis, melancholia was an overall predictor of lower depression severity at termination across all conditions. Additionally, the analysis indicated that melancholic patients treated with IPT improved more than those treated with Cognitive Therapy. A separate investigation examined maintenance data following psychosocial and pharmacological treatment for the prevention of relapse in melancholia (Frank, Kupfer, Hamer, Grochocinski, & McEachran, 1992). In this study, 52 patients who received IPT-maintenance therapy without active medication did not fare very well. On the whole, it appears that interpersonal psychotherapy approaches may be somewhat helpful in the treatment of active melancholia, but may be less effective in preventing relapse. One study examining follow-up data in RDC classified melancholic patients treated with CBT employed a single group analysis of biological predictors of treatment response (Simons & Thase, 1992). Fourteen percent of those who remitted following treatment were categorized as relapsers and tended to have longer REM latency values than those who remained well.

To organize this literature, Thase and Friedman (1999) published an informative review on the effectiveness of psychotherapy for melancholia and severe depressive states. They hypothesized that IPT may be better suited for melancholically depressed patients because it avoids unnecessary strain to the therapeutic alliance. For instance, if a melancholic client fails to engage in scheduled activities or complete assignments, cognitive interventions to overcome such obstacles may further de-emotionalize the relationship. Addressing noncompliance from an interpersonal perspective may be more likely to keep the alliance intact.

Pervasive anhedonia in melancholia may present particular challenges to psychotherapeutic approaches. Young, Weinberger, and Beck (2001) recommend that behavioral techniques are especially “necessary for those more severely depressed patients who are passive, anhedonic, socially withdrawn and unable to concentrate for extended periods of time” (p. 281). Behavioral approaches to therapy emphasize encouraging the patient to engage in activities that were formerly pleasurable, to restore positive mood. In that anhedonia is characterized as a biologically based inability to experience pleasure and by a lack of reactivity to positive stimuli, it may be that at least some anhedonic patients may not respond to behavioral activation interventions. No studies to date have
looked at the specific responses of melancholic patients to behavioral activation interventions, nor has anyone specifically assessed anhedonia as treatment progresses. For activation methods to be effective, it may require extra attention to the anhedonia. For example, in session exercises with pleasurable sensations or practice of pleasurable experiences in imagination may be helpful in cueing anhedonic patients to pleasurable stimuli. Homework exercises that involve rating pleasurable events involved in daily experiences may also help the person be more aware of small changes in pleasure and mood.

Cognitive approaches to therapy involve exploring automatic thoughts associated with depressed moods recorded by patients between sessions. With poor affective reactivity to emotionally-laden events, patients may not be experiencing situational downswings in mood in response to negative interpretations of events or situational upswings in mood in reaction to more positive interpretations. They may instead remain apathetic. This may be problematic because some experts assert that for cognitive techniques to work, the patient must be able to examine their negative thoughts while experiencing negative mood (Beck, et al., 1979). Melancholic patients may be less likely to experience noticeable mood shifts and less likely to be able to re-experience the emotion in the therapy session. In session exercises, recalling the events in imagery may help to reproduce and identify feelings and accompanying thoughts. McCullough (2003) recommends several other techniques that can be used to target the cognitive components of inactivity, anhedonia, and lack of reactivity to environmental events. Because melancholic patients may believe that they will remain miserable and unhappy no matter what happens to them or what they do, discussing the consequences of behavior in response to specific environmental events may be helpful. In addition, in session arrangements of contingencies may help patients recognize the effects of their behavior and develop causal thought about their interpersonal experiences, potentially helping to enhance emotional responsivity. Periodic monitoring of melancholia and especially using anhedonia scales described in the present paper could be helpful in assessing the success of these behavioral or cognitive interventions.

8. Summary and conclusions

The proportion of cases with melancholia in an outpatient setting is much lower than non-melancholic forms of depression (Thase & Friedman, 1999). Although it is an uncommon problem, practitioners should be aware that individuals with melancholic symptomatology may require separate assessment tools and the consideration of different treatment options. Unfortunately, there is still debate over what features define melancholia. The DSM-IV specifier “with melancholic features” and RDC of “definite endogenous” are the most researched and restrictive definitions of melancholia. Yet there is still uncertainty as to what some of the criteria in these diagnoses mean (Carrol, 1984; Parker, Gladstone, et al., 1997, Parker, Roussos, et al., 1997). For example, how distinct is “distinct quality” of mood? Empirical analysis has lead to the suggestion that this criterion be removed from the DSM-IV diagnosis of melancholia until its definition be improved (Parker, Gladstone, et al., 1997; Parker, Roussos, et al., 1997). Some investigators have tried to avoid vague symptom criteria altogether by utilizing a sign-based measure of melancholia (Parker et al., 1994). In addition to disagreement over what defines the syndrome, there is also debate as to whether melancholia is a true phenotype. While it is possible that melancholia is solely a consequence of diagnostic categorization or a cluster of symptoms present in chronic and severe cases of depression, empirical
evidence tends to support the phenotype model (Ambrosini et al., 2002; Beach & Amir, 2003; Benazzi, 2000; Grove et al., 1987; Haslam & Beck, 1994; Thase et al., 1983). Melancholia is not always present in severe and chronic forms of depression (Benazzi, 2000; Thase et al., 1983). Moreover, taxometric analyses have isolated specific clinical features that define a melancholic syndrome that is qualitatively distinct from non-melancholic symptomatology (Ambrosini et al., 2002; Beach & Amir, 2003; Grove et al., 1987; Haslam & Beck, 1994), supporting a unique melancholic phenotype. Generally, patients fitting this syndrome tend to be older and demonstrate severe anhedonia, psychomotor abnormalities, and neurovegetative features. Assessment of melancholic symptoms as defined by the DSM-IV can be performed via clinician ratings (e.g., Newcastle Index) or self-report (e.g., IDS-SR).

The current review indicates that there is empirical support for a melancholic subtype that qualitatively is distinct from other forms of depression. Individuals with melancholia are different than other depressed individuals in their patterns of symptomatology, psychological and biological factors, and treatment response. Although endogenous and melancholic depression share the same constellation of symptoms, findings from empirical research suggests that there is a clear distinction between these two constructs. Individuals described as melancholic can experience severe life stress, which may play a role in the etiology of their disorder (Forrest et al., 1965; Harkness & Monroe, 2002; Lafer et al., 1996; Leff et al., 1970; Mundt et al., 2000; Thomson & Hendrie 1972; Willner et al., 1990, but see Kohn et al., 2001; Tomaszewska et al., 1996), whereas endogenous depression by definition lacks any clear environmental precipitants. Future research of the interrelation between genetic and environmental factors may better elucidate the epigenetics involved in the development of melancholia. Biological dysfunction may also influence melancholic symptomatology. While much evidence is correlational, measures of basal neuroendocrine levels and neuroendocrine response and REM sleep data provide evidence for a pathophysiology of melancholia. Thus, endogenous and melancholic forms of depression may both include internal biological dysfunction; however, episodes of melancholia appear to be initiated by life stress in some circumstances. The future of biological assessment of depression appears to be directed towards identifying the association between regional brain activity and specific symptomatology (Davidson, 2000; Stahl, Zhang, & Damatarca, 2003). Other empirical efforts may focus on the relationship between biological indicators and environmental stress. Currently, research indicates that biological abnormalities and melancholic features in depression predict a poor response to psychotherapy (Frank et al., 1992; Thase, Dubé, & Bower, 1996). Does this mean that depressed patients with melancholia do not respond well to psychosocial interventions because of their underlying biological dysfunction? This question may remain unanswered until newer research techniques can better uncover the physiological bases of emotional disorders.

Current research literature indicates that somatic treatments are generally effective for melancholic and non-melancholic depression. The empirical status of psychosocial interventions are less conclusive. Findings from smaller studies support the efficacy of psychosocial treatments for melancholia (Blackburn et al., 1981; Kovacs et al., 1981; Teasdale et al., 1984; Thase et al., 1991; Sotsky et al., 1991), but larger studies with more conservative inclusion criteria have indicated that some forms of psychotherapy may be ineffective (Frank et al., 1992; Prusoff et al., 1980; Sotsky et al., 1991). Given the impact of psychosocial stressors on the course of melancholia, the combination of psychosocial and somatic techniques may be the most favorable option for melancholia treatment.
**References**


