Impact, Diagnosis, Phenomenology, and Biology

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Abstract

This section provides summaries of the epidemiology, phenomenology, nosology, and the suspected biological substrates of the depressive disorders. It particularly emphasizes the historical evolution of the pertinent diagnostic constructs and the prognostic import both of the various diagnostic groupings and of the individual symptoms and symptom clusters.

Keywords

History · Melancholia · Neurotransmitter · Nosology · Phenomenology

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1 Section 1: Prevalence

According to the most definitive effort to estimate prevalence of specific mental disorders in the United States, the National Comorbidity Survey Replication, the 12-month prevalence rates for DSM-IV-TR major depressive disorder (MDD), dysthymia, and bipolar I/bipolar II disorders are 6.7%, 1.5%, and 2.6%, respectively (Kessler et al. 2003). Lifetime rates are 16.6%, 2.5%, and 3.9%, respectively. Twelve-month prevalence rates from an earlier, large-scale study that used nearly identical methods were somewhat higher for MDD (10.3%), but were similar for dysthymia (1.3%) and bipolar I/bipolar II (2.5%) (Kessler et al. 1994).

Notably, the lifetime prevalence of MDD was approximately twofold higher for individuals below the age of 60 than for older individuals. Among those with a lifetime MDD diagnosis, those aged 18–29 years had 12-month prevalence rates that were threefold higher than those 60 and over. Individuals with incomes below the poverty line were nearly four times as likely to be depressed than those with incomes significantly above the poverty line.

Three-quarters of those with a lifetime history of MDD met criteria for another DSM-IV-TR diagnosis which, in a large majority of cases, began before MDD. A meta-analysis of the prevalence of MDD episodes among primary care patients given structured interviews estimated a point prevalence of 17% (Mitchell et al. 2009). Comparisons against whether the provider considered depression to be present, as stated in the medical record, showed a higher rate of false positives than false negatives. Diagnostic accuracy improved with repeated examinations.

Important caveats apply to these numbers. An earlier prevalence study that canvased over one million individuals at five centers across the United States reported a 1-year prevalence rate for MDD of 3.0% and a lifetime rate of 5.2%. These figures are less than one-half and one-third, respectively, those from the NCS-R study. It seems unlikely that secular trends or differences in sampling methods would account for discrepancies of this magnitude. Rather much of the difference has been attributed to variables such as subtle as differences in the number of probe questions built into the structured interviews used in the two studies (Kessler et al. 1994).

The assessment of lifetime rates of MDD is prone to particular difficulties. An example is the observation that, in numerous cross-sectional studies of adults across international settings, older individuals were reported to have substantially lower lifetime rates of MDD than younger ones (Weissman et al. 1996; Cross-National Collaborative Group and Wittchen 1992). This leads to considerable speculation as to the reason for this finding. Yet, test-retest studies have shown that past MDD episodes are recalled with poor reliability and that individuals are more likely to underreport than overreport previously described major depressive episodes (Simon and VonKorff 1995; Giuffra and Risch 1994). Because younger adults are considerably more likely to be experiencing major depressive episodes in any given year than are older ones (Kessler et al. 2005), this “telescoping effect” is likely to be quite large.

Methodical differences preclude meaningful comparisons across separate studies undertaken in different countries. The Cross-National Collaborative Group report applied the same sampling and assessment methods across ten countries and found six-fold differences between countries with the lowest and highest 1-year prevalence rates of major depression (Weissman et al. 1996). No clear explanation for these differences emerged. Relative cross-national consistencies did exist, however, for higher female prevalence, for mean age of onset in the late 20s, and for the increased risk for MDD posed by comorbidity with substance abuse and with being separated or divorced.

2 Impact

2.1 Disability and Economic Impact

Depressive disorders are the fourth leading cause of disability worldwide and account for the most years with disability of all illnesses in the Americas (Ustun et al. 2004). The annual economic burden resulting from MDD in the United States was $210.5 billion in 2010 (Greenberg et al. 2015), approximately half of which results from the cost of treatment with the other half due to work place or other indirect costs. Moreover, the economic consequences of depressive disorders grew substantially between 2005 and 2010, due largely to increases in the size of the population and the cost of care.

MDD appears to carry substantial additional impairment and cost through its relationships with cardiovascular disease (Fiedorowicz et al. 2011a). According to an extensive literature, inflammatory markers are likely to be elevated in patients with depressive disorder (Munkholm et al. 2013; Howren et al. 2009), and this comprises a plausible link between depressive disorder and cardiovascular disease. It is notable, then, that treatment with antidepressants appears to decrease cytokine activity, an important marker for inflammatory activity (Hiles et al. 2012).

2.2 Suicide

Suicide is the leading cause of death worldwide, more so in western countries. According to results pooled from 27 psychological autopsy studies, nine of ten suicides had met criteria for a psychiatric disorder when they died, and mood disorders were the most common, followed by substance use disorders (Arsenault-Lapierre et al. 2004). In the longest prospective study of new disorders, 17.5% of 186 patients who have been hospitalized for unipolar depression committed suicide over a span of 40–44 years (Angst et al. 2005). Suicide rates are substantially lower among individuals who are outpatients at the beginning of follow-up (Bostwick and Pankratz 2000). Despite widespread efforts in the United States to improve screening and treatment access for individuals at risk for suicide,

age-adjusted rates for both males and females have increased steadily from 2000 to 2014 (Curtin et al. 2016).

Among the risk factors for completed suicide identified across many studies, a history of suicide attempts is the most consistently robust (Coryell and Young 2005). While the value of a suicide attempt history is a clinically useful risk factor, it is nevertheless quite modest in predictive power as can be deduced from prevalence rates of 50 to 1 for suicide attempts and suicides, respectively (Kessler et al. 2005). The relative frequency of suicide attempts, though, underscores the societal burden associated with attempt behaviors per se. One estimate of the medical costs associated with suicide attempts in 2013 in the United States was $1.5 billion (Shepard et al. 2016).

3 Diagnosis

3.1 History

Probably the earliest currently known descriptions of depressive illness appeared in the writings of Hippocrates in 1550 B.C. and he, as have most subsequent writers on the subject, used the term melancholia to label the condition.

Suppositions regarding the causes of melancholia have varied widely from an excess of black bile to religious, moral, and societal etiologies. In the early 1920s, psychoanalytic explanations centered on the experiences of loss. Across all of these periods writers consistently recognized that dominant features included a persistently low mood, lethargy and slowing, decreases in appetitive functions, fear and fretfulness, self-reproach, and, in more severe cases, delusions of sin or persecution.

Proposed sub-classifications have also been numerous. The separation of unipolar and bipolar depression, first proposed by Leonhard et al. (1962) and later by Angst (1966), Perris (1966), and Winokur et al. (1969), is now the most fundamental and widely accepted of these. Notably, these proposals were based principally on family history differences between unipolar and bipolar patients. Another subdivision, between reactive or endogenous depression and endogenous or melancholic depression, has had long-standing intuitive appeal (Shorter 2007).

3.2 Operational Definitions

The first widely used set of operational criteria for depressive disorders was published in 1972 (Feighner et al. 1972) along with criteria for other psychiatric disorders considered to have validity at the time. Dysphoria was a requisite symptom, and a minimum of five from a list of eight symptoms with a duration of 1 month was necessary for a diagnosis. The term "major depressive disorder" first appeared in the subsequently published Research Diagnostic Criteria (RDC) (Spitzer et al. 1978).

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders III* adopted the operational criteria format as did the subsequent iterations of DSM-III-R, DSM-IV, and DSM-5. The RDC shortened the minimum duration to 2 weeks and added anhedonia to dysphoria as an option for the single required symptom. It also required four rather than five of the eight other symptoms. The DSM additions from DSM-III onward maintained these changes. Otherwise, the eight core symptoms of depressive disorder have remained essentially unchanged through all six of these diagnostic revisions.

Despite this definitional continuity, an active and far from settled debate continues between those who view depressive disorder as a unitary concept, in which cases fall along a severity continuum, and those who hold the disorder to be inclusive of two or more fundamentally different biological disorders (Shorter 2007). Currently many who take the later position assert that melancholia is a discrete illness characterized by biological abnormalities with well-established connections to severe depressive disorders such as hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and reduced REM latency (Taylor and Fink 2008).

The DSM-5 work groups deliberated under an overarching and carefully enforced principle that the degree of empirical evidence required for major changes in the definition of a disorder increased in proportion to the length of time that the definition had been in wide use without undergoing major changes. The threshold for substantial changes in the definition of MDD was correspondingly quite high. The mood disorder work group was not convinced by published evidence that the distinction between melancholic and non-melancholic depressive disorders was more valid than the simple distinction based on severity alone.

The prevailing view that melancholia, or endogenous depression, is less a result of ongoing social stressors and more anchored in measurable biological abnormalities leads intuitively to the assumption that the former would be more amenable to antidepressant treatment and the later to psychotherapy. The results of several large-scale comparisons of specific psychotherapies and antidepressant treatment support this position (Brown 2007; Thase and Friedman 1999). These studies did not show, however, that the presence or absence of melancholia was a more effective predictor of such deferential treatment response than the cruder distinction between greater and lesser overall symptom severity. A more recent meta-analysis shows that melancholia does not predict deferential responses to antidepressant and psychotherapeutic treatments when baseline severity scores are included in the statistical model (Cuijpers et al. 2017).

The realization that DSM-5 would not evolve to incorporate biological measures into diagnostic criteria and that none of the many biologic abnormalities that had been demonstrated in psychiatric illness have, in fact, been shown to be adequately specific and sensitive to any given DSM disorder led the NIMH, in 2008, to propose the Research Domain Criteria (RDoC) for use in future funded research. This approach was designed to cut across diagnostic categories with the application of a matrix. Rows consist of domains or constructs such as negative valence systems and arousal/modulatory systems and columns consist of units of analysis. Among the seven specified units are genes, neuro-circuits, physiology, and behaviors. The

RDoC approach emphasizes continuation over categories to provide researchers with a wider range of measures and greater statistical power.

3.3 Subtypes

There is near universal recognition that criteria for major depressive disorder encompass conditions that vary markedly in phenomenology, severity, course of illness, family history, and response to treatment. Many subtypes have been proposed but, despite substantial efforts to validate many of them, none has gained an acceptance that is clearly greater than that for the others. However, some have accumulated enough evidence for validity that they warrant clinical recognition.

The only subdivision of unipolar depression included in the first of the operational criteria of psychiatric disorders (Feighner et al. 1972) was that of *primary and secondary depression*. Patients with secondary depression have experienced the onset of a list of certain other disorders antedating the first depressive episode. This grouping followed well-established precedence from the nosology of medical illnesses such as that for hypertension. Accordingly, a syndrome arising in the context of another might have some etiologic role and should be separated from the same syndrome that develops de novo. The course of the former, secondary, condition is likely to reflect the course of the underlying disorder and treatment should be selected that recognizes this. In the case of depressive disorders, examples include episodes that occur in the context of alcoholism that then resolve with detoxification, as well as those that develop in the context of anorexia nervosa that then clear with weight restoration. Continuing with the medical illness analogy, the course, treatment response, and family history of secondary depression are likely to differ according to which non-affective illness comprises the background condition. Thus, it is not surprising that efforts to validate the primary/secondary distinction in which the secondary depression group have varying primary diagnoses yield generally disappointing results.

A notable exception was a study of 146 patients hospitalized with primary depression who were compared to 42 patients with secondary depression based on responses to a 1 mg dexamethasone suppression test (DST). Rates of non-suppression, a response once thought to have specificity for melancholia or endogenous depressive disorder, were 45% and 0%, respectively (Schlesser et al. 1980).

Another study used course and family history to compare patients with episodes of primary depression that included panic attacks, but who had no prior panic attacks outside of depressive episodes, to patients who had panic attacks that clearly preceded the first depressive episode (secondary depression), and to depressed patients with no history of panic attacks (primary depression) (Coryell et al. 1992). Patients with primary depression complicated by panic attacks in comparison to those with primary depression without panic attacks suffered greater depressive symptom severity and more depressive morbidity during a 5-year follow-up. They did not, however, have a greater risk of panic disorder among their relatives and did not experience panic attacks outside of depressive episodes during follow-up. The

group with depression secondary to panic disorder, in contrast, did have significantly more panic disorder among their relatives and were more likely to experience freestanding panic attacks during follow-up.

Interest in the distinction between *psychotic and nonpsychotic depression* began with observations that patients with MDD who also had delusions and/or hallucinations were less likely to respond to tricyclic antidepressants (Glassman et al. 1975). An extensive literature has since accumulated to show that patients with psychotic features, in comparison to depressed patients without them, have greater symptom severity, particularly in regard to symptoms thought to comprise melancholic depression (Coryell et al. 1984, 1985). They also experience longer depressive episodes, shorter times to relapse, and more depressive morbidity over extended follow-up periods (Coryell et al. 1996). They are less likely to show placebo responses (Glassman and Roose 1981), and, probably because of this, patients with psychotic features are more likely to show a substantial response differential between real and sham electroconvulsive therapy (Buchan et al. 1992). Of greater relevance to the distinctiveness of psychotic depression, patients with this condition are significantly more likely to experience delusions or hallucinations in subsequent episodes (Coryell et al. 1992; Charney and Nelson 1981; Nelson et al. 2018) and to have increased risks for psychotic depression among their relatives (Leckman et al. 1984).

The separation between depression that develops in the context of adverse events and those that appear without apparent external cause has, perhaps, the most intuitive appeal of all of the subgroupings for major depressive episodes. The assumption underlying the separation of *situational and non-situational depression* would predict that the former would have fewer of the symptoms associated with melancholia, that they would have fewer episode recurrences, and that they would have a lower familial risk of MDD. They might also be expected to show smaller outcome differences between responses to antidepressants and placebo. Somewhat surprisingly, research has supported none of these predictions.

Findings from family and twin studies have particular import for the concept of reactive or situational depression. Contrary to expectations, a family study of patients with recurrently situational depressive episodes showed they had approximately twice the morbid risk for MDD among their first-degree relatives than did patients with recurrently non-situational depressive episodes (Coryell et al. 1994a). Results from twin studies give these findings more meaning because they provide clear evidence that those adverse life events that are, to some degree, under individual control are heritable (Kendler and Karkowski-Shuman 1997). The concordance for the presence of recent adverse life events at a random point in time was shown to be significantly greater in monozygotic than in dizygotic twin pairs. Thus, personality traits that foster adverse life events seem highly heritable. This is clear with such dimensions as neuroticism, as measured by the NEO (McCrae and Costa 1987), which has been shown to be both highly heritable and marked by an increased sensitivity to stressors (Kendler et al. 2004).

A special case of the nosological recognition of the role of stressors in the genesis of depressive symptoms is the *bereavement exclusion* that was part of the MDD

criteria in DSM-III, DSM-III-R, and DSM-IV, but not in DSM-5. In the earlier DSM iterations, depressive symptoms that developed following "the loss of a loved one" did not warrant the diagnosis of MDD unless symptoms had persisted longer than 2 months or were attended by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic features, or psychomotor retardation.

The DSM-5 mood disorders work group, however, determined that little evidence existed to separate depressive symptoms following the loss of loved ones from depressive symptoms that develop following other losses or those following significant stressors in general (Kendler et al. 2008). Thus, unless depressive symptoms that occur after any significant stressor are to be excluded as indications of an illness, retention of the bereavement exclusion criteria was untenable. This change was viewed in some quarters as a play by organized psychiatry to "pathologize" normal human reactions and to thus increase patient populations (New York Times). Others, though, put forward evidence that suspension of the bereavement criteria was likely to result in minimal increases in the numbers of individuals given diagnosis of MDD by providers (Zisook et al. 2013).

DSM-5 expanded the boundaries of *pregnancy-related mood disorder* from 1-month postpartum in DSM-IV to any onset during the pregnancy or during the 2 months following delivery. This change arose in large part from evidence that a large portion of women with a depressive syndrome during the postpartum period experienced onset during pregnancy (Gotlib et al. 1989). While much has been written concerning the risks for, and adverse effects of, depression during pregnancy, evidence that pregnancy is a high-risk period for depression onset is scant. A comparison of the risk for depressive episodes during pregnancy to the risk during the 9 months preceding pregnancy showed no significant difference in a large community sample (Vesga-Lopez et al. 2008) though episode frequency was significantly higher during the postpartum period. That pregnancy does not protect against depression is shown by observations that most euthymic women who discontinue an antidepressant when they discover their pregnancy eventually relapse during pregnancy (Cohen et al. 2006). Most postpartum onsets develop within 1 month of delivery, and psychotic, mixed, or manic episodes have particularly rapid postpartum onsets (Di Florio et al. 2013).

In addition to the clustering of onsets following parturition, family studies have provided evidence that mood disorder episodes with postpartum onset differ from those with onset at other times. At least three sib-pair studies (Forty et al. 2006; Jones and Craddock 2001; Murphy-Eberenz et al. 2006) and one twin study have shown that postpartum onset has a significant familial component.

DSM-5 criteria for a diagnosis of *catatonia* require at least 3 symptoms from a list of 12, of which mutism, stupor, and catalepsy are perhaps the most common (Krishna et al. 2011; Morrison 1973). This syndrome can complicate schizophrenia, mania or major depressive episodes, drug intoxication or withdrawal, or a wide variety of medical conditions. A substantial minority of cases do not appear to have an underlying medical or psychiatric diagnosis (Krishna et al. 2011; Barnes et al. 1986). Such cases may be highly recurrent with some consistency in the presence of

catatonic symptoms across episodes (Francis et al. 1997). Catatonia with or without other underlying illnesses also appears to be familial (Barnes et al. 1986).

A prompt response to benzodiazepine administration is widely accepted as diagnostic of catatonia. Because patients with catatonia are at increased risk for developing neuroleptic malignant syndrome (Berardi et al. 2002), it is prudent to treat a catatonic state with benzodiazepine before antipsychotics are introduced (Rasmussen et al. 2016). Maintenance treatment with benzodiazepines may prove necessary in some cases (Thamizh et al. 2016).

ICD and DSM iterations have long distinguished *single episode and recurrent MDD*. Many studies have shown that patients with a recurrent major depression have shorter times to relapse following recovery (Maj et al. 1992; Pintor et al. 2004; Keller et al. 1983a; Gonzales et al. 1985). The number of previous episodes is a stronger predictor of relapse risk than is the simple separation of single vs. one or more prior episodes. Others have found that patients with recurrent depression are more likely to have family histories that are positive for depressive disorders as well as earlier ages of onset (Hollon et al. 2006). Patients with multiple prior major depressive episodes are more likely to eventually switch to a bipolar diagnosis than are patients with fewer episodes (Angst et al. 2003).

According to DSM-5, "full remission has occurred when two months have passed with no significant signs or symptoms of the disturbance were present." Other groups have proposed more nuanced definitions to indicate the concepts of response, recovery, remission, relapse, and recurrence. The terms "response" or "remission" as applied to most antidepressant treatment trials require only that depressive symptoms over the preceding week fall beneath a specified severity threshold such as 7 or less on the 17-item Hamilton Depression Rating Scale (Nierenberg and DeCecco 2001). Definitions put forward by the American College of Neuropsychopharmacology incorporated minimum durations of severity levels such that remission required at least 3 weeks at a clearly defined sub-criteria level while recovery required 4 or more months (Rush et al. 2006). An increase in symptoms to the criteria level after remission, but before recovery, was termed a "relapse," while such a symptom increase after recovery was a recurrence.

It is now well established that even residual depressive symptoms well below the numbers needed to meet the criteria for a major depressive syndrome are powerfully predictive of impairment, as well as of risk for recurrence (Judd et al. 1998, 2000). Accordingly, Judd et al. (2016) have shown that a mere 1-month period of fully asymptomatic recovery was a more powerful predictor of subsequent time well than any of 18 other potential predictors.

Definitions of a *chronic major depressive episode* in the RBC, and in each of the DSM iterations from DSM-III through DSM-5, specify the persistence of depressive symptoms for 2 or more years. Other proposals have specified 1 year or 3 years. Origins of the 2-year threshold are obscure, and it probably was not empirically derived. The DSM-IV definition required the persistence of 2 or more years of a full major depressive syndrome for the diagnosis of chronic depressive disorder. Depressive symptoms that persisted for 2 or more years, but which fell beneath the symptom number threshold for major depression, were designated as dysthymic

disorder. The DSM-IV definition of dysthymia was inherently unreliable, however, in that it required the absence of any 2-week period in the first 2 years of the illness during which symptoms rose to the full number and persistence required for a major depressive episode. This is a distinction that often involved the presence or absence of only a few symptoms during a 2-week period over a span of 2 years that may have occurred many years previously. Moreover, direct comparisons with DSM chronic major depressive episodes and dysthymic disorder failed to find differences in demographic variables, symptom patterns, treatment response, or family history (McCullough et al. 2000, 2003; Klein et al. 2004; Yang and Dunner 2001; Blanco et al. 2010). This lead to the change in DSM-5 in which chronic major depressive disorder has been merged with dysthymic disorder under the new label of *persistent depressive disorder*.

Whether chronicity is captured under the older criteria for chronic major depressive episode or under that for dysthymic disorder, patients who are so identified, in comparison with patients who have non-chronic episodes, have earlier onsets (Gilmer et al. 2005), higher levels of depressive morbidity over long prospective follow-up periods (Keller et al. 1983a, b; Gonzales et al. 1985; Klein et al. 1988, 2000; Coryell et al. 1990; Rhebergen et al. 2009, 2010), greater familial loading for affective disorders (Klein et al. 1988), greater likelihood of a coexisting personality disorder (Klein et al. 1988), higher levels of neuroticism (Rhebergen et al. 2010), a higher likelihood of suicide behaviors (Gilmer et al. 2005; Garvey et al. 1986), and more early adversity (Barnhofer et al. 2014).

DSM definitions of chronic major depressive episodes, dysthymia, and persistent depressive disorder are confined to non-bipolar individuals. Historical reasons for this are unclear. Chronicity in bipolar illness does not appear to be less common than in unipolar illness (Benazzi 1999; Angst et al. 2009).

Anxiety symptoms are frequent concomitants to depressive disorders, and evidence for their prognostic importance has become increasingly well-established over the past several decades. Whether the co-occurrence of anxiety symptoms with major depressive episodes is expressed as categorical comorbidity, as the coexistence of an anxiety disorder diagnosis, or as a quantification of anxiety symptoms, individuals with both MDD and anxiety states have more depressive morbidity in the short and long term (Coryell et al. 1992, 2009; Otto et al. 2006). They also have poorer responses to antidepressants (Fava et al. 2008; Papakostas et al. 2008) and to psychotherapy (Feske et al. 1998), and are at greater risk for suicidal behaviors (Sareen et al. 2005; Goes et al. 2012). There also appears to be a continuous positive relationship between anxiety symptom severity and the persistence of depressive symptoms over time (Coryell et al. 2009, 2012). This is true across a variety of anxiety symptom types and is an effect that endures with little change over decades of prospective follow-up. The comorbidity of MDD with anxiety disorders is apparently also familial (Goes et al. 2012; Kendler 1995). Kraepelin devoted a chapter to *mixed states* in his book *Manic Depressive Illness and Paranoid States* (1921). In it he described six subtypes and concluded that "they often occur in the transition between the fundamental forms (mania or depression). It may, however, appear as an independent morbid attack and, when this occurs, there is a certain

probability that similar states will follow later. The course of those mixed states when occurring as independent attacks appears in general to be lingering."

DSM-III, DSM-III-R, and DSM-IV reserved the term "mixed states" for individuals who met full criteria for MDD and mania concurrently. Such individuals, by definition, had bipolar disorder. The nomenclature provided no means to describe those individuals who had no history of mania or hypomanic episodes but who had subthreshold manic symptoms embedded within a major depressive episode. It is clear, however, that such individuals exist in significant numbers (Zimmermann et al. 2009) and that they have, in comparison to those with MDD but without accompanying manic symptoms, longer episodes, more morbidity over extended periods (Zimmermann et al. 2009; Persons et al. 2017; Benazzi 2001), poorer responses to antidepressants (Koukopoulos et al. 2007), and a higher likelihood of suicidal behavior (Persons et al. 2017). Recent evidence shows that individuals with mixed episodes are at a higher risk for suicide attempts because they spend more time in depressive states than do patients with no history of mixed states (Persons et al. 2017).

Not surprisingly, patients who experience manic symptoms within an episode of major depressive disorder are more likely to eventually develop a separate episode of mania or hypomania (Fiedorowicz et al. 2011a). In accord with this, the presence of manic symptoms in an episode of major depressive disorder is associated with an earlier age of onset and with greater familial loading for bipolar disorder. The likelihood of a family history of bipolar illness appears to increase with the number of manic symptoms present (Zimmermann et al. 2009). A receiver operating curve analysis, however, shows that the presence of three manic symptoms is the most efficient predictor of an eventual diagnostic switch to bipolar disorder (Fiedorowicz et al. 2011a). This is the number necessary for DSM-5 designation of MDD with mixed features.

4 Measurement

Two broad categories of instruments are available to quantify the severity of depressive symptoms – self ratings and clinician ratings. Each type has certain advantages and disadvantages over the other, and therapeutic trials typically use both. Congruence between self and clinician ratings may be lower during the more severe phases of depressive illness (Prusoff et al. 1972).

4.1 Self-Rated Scales

The Beck Depression Inventory (BDI) (Beck et al. 1961), the Inventory for Depressive Symptomatology (IDS) (Rush et al. 1986), and the Patient Health Questionnaire (PHQ-9) (Kroenke et al. 2001) are among the most commonly used self-rating scales. In comparison to the IDS, the BDI is weighted toward cognitive symptoms and less so toward vegetative symptoms. The PHQ-9 simply quantifies each of the

DSM criteria symptoms for a major depressive episode by the persistence of that symptom over the preceding week.

4.2 Clinician-Rated Scales

The Hamilton Rating Scale for Depression (HRS-D) (Hamilton 1960) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) are probably the most extensively used clinician rating scales. The HRS-D places more emphasis on somatic symptoms than does the MADRS. Neither the HRS-D nor the MADRS reflect hypersomnia or hyperphagia. The clinician-rated counterpart to the self-rated IDS, the clinician-rated IDS-C (Rush et al. 1996), do take these symptoms into account.

5 Phenomenology

Dysphoria is one of the two A criteria symptoms for DSM-5 major depression and thus must be present for a diagnosis to be made if anhedonia is absent. While depressed mood is initially specified in criteria A for a major depressive episode, subsequent text indicates that a sad affect as reported by informants can be used to infer dysphoria. In many cases, particularly in medical settings, neither a depressed mood nor a depressed affect is apparent in the individual who satisfies many of the other criteria of a depressive syndrome. Alexithymia, as a stable feature, increases with age and may indicate dysfunction in the right rostral anterior cingulate cortex (Paradiso et al. 2008). A failure to manifest dysphoria either subjectively or objectively is also more likely in individuals who present with a focus on somatic symptoms. Such a presentation has been termed "masked depression" (Fisch 1987, 1997). Thus, self-rating screening tools may be particularly helpful in outpatient medical settings.

Anhedonia is also considered a core depressive symptom (criteria A). Depressed individuals may lose interest in, or derive no pleasure from, their work, hobbies, interactions with friends or family members, music, or sex. The inability to enjoy all facets of life, pervasive anhedonia, is nearly always included among symptoms of melancholia or endogenous depression, however defined.

A recent meta-analysis showed that anhedonia is strongly correlated with suicide ideation even after control for the severity of other depressive symptoms (Ducasse et al. 2017). A persistence of anhedonia also appears to account for most of the lag between improvement in depressive symptoms and psychosocial functioning during treatment (Vinckier et al. 2017).

Either "significant" *loss of weight or appetite*, or *gain in weight or appetite*, satisfies one of the nine criteria for a major depressive episode. Gains in weight or appetite, together with hypersomnia, are considered "reverse vegetative" symptoms and are more common in bipolar I or bipolar II depressive episodes than in non-bipolar depressive episodes (Andreasen et al. 1988; Coryell et al. 1985). They

also comprise two of the five features used to define the DSM-5 specifier "with atypical features." This syndrome was originally based on symptoms that appeared to separate responders to monoamine oxidase inhibitors from responders to tricyclic antidepressants (McGrath et al. 1992). Strong evidence subsequently appeared that reverse vegetative symptoms are the most important components or the atypical feature cluster (Benazzi 2002; Kendler et al. 1996). Atypical depression defined as such is associated with obesity and has a significant genetic determinant (Kendler et al. 1996). The association between obesity and depressive illness in general may be etiologically bidirectional (Coryell et al. 2016), and individuals who overeat are substantially more likely to be obese between episodes (Murphy et al. 2009).

Complaints within the same individual of both *insomnia* and *hypersomnia* in a major depressive episode are particularly characteristic of those with a bipolar diagnosis (Geoffroy et al. 2018). Insomnia, more than most other depressive symptoms, is a relatively robust risk factor for completed suicide (Bernert et al. 2015). This aligns with observations that the most likely time for suicide to occur in the United States population is from 2:00 to 3:00 a.m. (Perlis et al. 2016).

Fatigue, or the subjectively perceived lack of energy, is among the most consistently reported symptom in major depressive episodes and has been identified as the one that most interferes with work functioning (Lam et al. 2012). It is also one of the most common residual symptoms following antidepressant treatment, and this persistence accounts for much of the impairment in functioning associated with incomplete remission from depressive episodes (Fava et al. 2014).

The DSM describes the criteria symptom of *self-reproach* as "feelings of worthlessness or inappropriate guilt." More than the other criteria symptoms for major depressive episodes, it is often difficult to identify the threshold above which self-criticism and remorse reaches the symptomatic level. The qualities of guilty feeling described by a patient deserve particularly careful attention in that the boundary between a painful preoccupation and a delusion can be a subtle one. As noted earlier, the distinction between delusional and non-delusional depression has important implications for treatment selection and for prognosis.

Moreover, relatively few studies have focused on this component of the depressive syndrome. Those that have showed that self-blaming emotions occur in the large majority of depressive patients and that they correlate closely with depressed mood, hopelessness, and with overall depressive symptom severity (Zahn et al. 2015). A study that tested the robustness with which individual criteria symptoms separated individuals with depressive disorders from comparison groups found guilt to be the most important discriminator, both from individuals with no illness and from those with generalized anxiety disorder (Breslau and Davis 1985). Individuals with past major depressive episodes appear more likely than those with chronic medical illness to have persistent feelings of guilt (Ghatavi et al. 2002).

In psychiatry the term *agitation* refers to non-purposeful hyperactivity that is often manifest as fidgetiness, hand wringing or pacing, and that is accompanied by feeling of inner tension. It should be distinguished from the hyperactivity that characterizes manic or hypomanic states in that the latter is purposeful, albeit marked by inconstancy and distractibility. It is regularly included among the features of

melancholia and is more prominent in depressed patients with psychotic features than in non-psychotically depressed patients (Coryell et al. 1985).

Individuals with psychomotor agitation are also much more likely to have a history of *psychomotor retardation* (Maj et al. 2006). Some have argued that agitation should be diagnostically linked to bipolar disorder and considered, together with subthreshold manic symptoms, as indicative of a mixed state (Benazzi et al. 2004). Evidence for this was not sufficient for the inclusion of psychomotor agitation in the DSM-5 criteria for the MDD mixed states specifier, however.

As noted, histories of psychomotor retardation and those of agitation are likely to coexist. Taken together, depressive syndromes marked by agitation or retardation have some stability across repeated episodes (Coryell et al. 1994b). Retardation is also notable because it shades into catatonia as severity increases. Psychomotor retardation, together with psychotic features, are the only symptoms found to distinguish responders to real ECT from responders to sham ECT (Crow et al. 1984).

Self-described *concentration difficulties* experienced by depressed patients have been shown to correlated strongly with health-related quality of life, independent of the severity of other depressive symptoms (Fattori et al. 2017). Subjectively rated problems with concentration also correlate with objectively measured cognitive deficits. Research into the implications of such objectively measured cognitive deficits for consequent impairment, course of illness, and both neuroanatomical and neurofunctional abnormalities is extensive. Notably, both subjectively and objectively measured deficits make contributions to disability ratings beyond the contribution of other depressive symptoms (Naismith et al. 2007). The search for treatments that specifically target cognitive deficits in depressive disorder is understandable in this light (Salagre et al. 2017).

Nearly all psychiatric disorders confer an increased risk for *suicidal behavior*. Largely because of its relatively high prevalence, the majority of individuals who die by suicide do so while in a depressive syndrome (Yoshimasu et al. 2008). Of the nine criteria symptoms for major depressive episodes, only thoughts of suicide or suicidal behaviors necessitate a careful estimate of near- and long-term risks for future suicide attempts or suicide completions. The most consistently identified risk factor for completed suicide is a history of suicide attempts, even attempts in the distant past (Coryell and Young 2005). Among attempters, those that employed violent means carry much higher risks for eventual suicide (Runeson et al. 2010), and risks for all individuals admitted for suicidal ideas or behaviors are highest in the weeks following discharge (Mortensen et al. 2000). For patients psychiatrically admitted because of suicidal ideation or behaviors, the subsequent denial of suicidal plans should, of its self, not justify discharge. The illness, and other factors, that gave rise to the suicide threats or behaviors should have demonstrably improved as well.

6 Diagnostic Boundaries

Personality disorders often accompany MDD in clinical settings (Corruble et al. 1996) and have considerable importance when they do. Depressed patients with personality disorders have earlier onsets of depression (Charney et al. 1981;

Pfohl et al. 1984; Black et al. 1988), are more likely to have histories of suicide attempts (Pfohl et al. 1984; Black et al. 1988), have fewer melancholic symptoms (Charney et al. 1981; Black et al. 1988), and have higher rates of psychosocial adversity (Pfohl et al. 1984). Prospective studies show that depressed patients with personality disorders experience more depressive morbidity over time (Pfohl et al. 1984; Zimmerman et al. 1986; Shea et al. 1990) and a poorer response to treatment, whether that be treatment with antidepressants (Charney et al. 1981; Pfohl et al. 1984), with ETC (Zimmerman et al. 1986), or with psychotherapy (Shea et al. 1990).

Among the personality disorders listed in DSM-5, borderline and antisocial personality disorders are perhaps the most thoroughly studied. Patients with ASPD often present with suicidal thoughts or behaviors in the context of depressive symptoms, and an ASPD diagnosis maybe missed unless it is considered in the differential. If it is present, the likelihood of concurrent substance abuse is substantially higher and maybe the more appropriate treatment target.

The recognition of comorbid borderline personality disorder is particularly important for treatment selection and patient counseling. First, though many controlled trials have shown that some widely used antidepressants are globally effective for the various facets of BPD, some, such as SNRIs or bupropion, have not been tested in this population (Mercer et al. 2009). Similarly, RCTs have supported the use of valproate, carbamazepine, and topiramate, but lithium has not been tested. Moreover, the time in which depressive symptom ratings for placebo and active treatment groups separate is typically later than is the case at uncomplicated MDD. It is important that both the treating physician and patient know this.

Second, patients with depressive symptoms and BPD often have a history of multiple unsuccessful antidepressant trails and, in addition, often report auditory hallucinations that may be construed as psychotic features. This picture thus may result in referral for ECT treatment. However, direct comparisons of patients with depression and borderline personality to those with other personality disorders showed that the former group had significantly poorer ECT outcomes than did those with other personality disorders whose outcomes were no different from depressed patients without personality disorders (Feske et al. 2004).

Third, there exists a substantial overlap between features of BPD and those of bipolar illness. This overlap includes sudden shifts in mood, periods of irritability and recklessness, and a predisposition to substance abuse. Not surprisingly there is now convincing evidence that borderline personality disorder is being widely misdiagnosed as bipolar disorder in the United States (Zimmerman et al. 2010). Such misdiagnoses are likely to have the unfortunate effect of shifting treatment focus to one that emphasizes polypharmacy and an external locus of control. Indeed, there is some evidence that patients with borderline personality disorder who have been misdiagnosed with bipolar disorder have poorer outcomes than patients who have never been given a diagnosis of bipolar disorder (Zimmerman et al. 2010).

Many patients given a firm diagnosis of *schizophrenia* have received other diagnosis previously, and a mood disorder diagnosis is frequently among these. Such diagnostic instability is particularly likely among patients who present with major depressive episodes and psychotic features. In a rigorously designed study,

43% of patients who began follow-up with a diagnosis of MDD with psychotic features had a consensus diagnosis of schizophrenia at 10 years (Bromet et al. 2011). Notably, diagnostic shifts in the opposite direction, from schizophrenia to MDD, occurred in only 2.4% of cases. Those who switched from MDD to schizophrenia were more likely to have had an insidious onset and to have had a family history of MDD. Baseline variables were otherwise of little value in predicting this shift (Ruggero et al. 2011). Taken together these results show the importance of reassessments over time. A diagnosis of major depressive disorder with psychotic features that is based on a single assessment should be considered a provisional one.

Much more research addresses the likelihood of, and risk factors for, transitions from MDD to *bipolar disorder*. The rates of such switches are quite variable across studies but are generally lower in prospective studies that have employed structured diagnostic interviews in the baseline assessment. Manic symptoms are among the most consistent predictors in both adult (Fiedorowicz et al. 2011b) and child/adolescent samples (Biederman et al. 2014), and the risks appear to increase in a stepwise fashion with the number of manic symptoms observed. Perspective studies have also repeatedly identified an early onset, and a family history of bipolar disorder as robust risk factors for diagnostic shifts to bipolar disorder (Zimmermann et al. 2009; Fiedorowicz et al. 2011b).

7 Biology

Of the many labels assigned to syndromes now encompassed as depressive disorders, the term melancholia has been the most enduring and was described by Hippocrates over 2,400 years ago (Lewis 1934). Later physicians in the classical period, such as Aretaeus of Cappadocia and Galen, also provided similar descriptions. They noted its episodic nature and the frequent alternations with manic states. Efforts to systematically describe and classify psychiatric disorders were superseded by church teachings in the Dark and Middle Ages, and conditions that would now be considered psychiatric were attributed to demonic possession, witchcraft, and other supernatural causes. With the Renaissance the observations of the ancient writers again became influential. The attributions to a humoral imbalance with an excess of phlegm and black bile persisted.

In the seventeenth to the eighteenth centuries, writers proposed many classifications schemes for mental disorders. These were generally inclusive of melancholia, but none achieved clear ascendancy over the others. Early in the twentieth century, Kraepelin proposed the fundamental distinction between manic depressive illness and dementia praecox. Psychoanalytic thinking then dominated from the 1940s to the 1960s, particularly in American psychiatry. Psychoanalytic formulations generally viewed depressive states as being reactive or psychotic depending on whether an identifying loss could be identified in a given case. If it could, then the problem was assumed to arise from inwardly directed anger triggered by loss reminiscent of unresolved childhood conflict or by an overactive superego.

Coincident with the advent of effective pharmacotherapy for mood disorders and the advent of a medical model or "neo-Kraepelinian" school of thought, emphasis shifted to the value of explicit and inherently reliable criteria for mood disorder diagnosis. This strongly influenced DSM-III and its subsequent iterations. The perceived need for diagnostic reliability influenced the decision to apply the label of major depressive disorder to conditions widely acknowledged to be heterogeneous. Some have proposed a solution in which major depression is replaced by a distinction between melancholia and non-melancholic mood disorders (Shorter 2007). Questions as to whether the observed differences between melancholic and non-melancholic depression can be attributed solely to the greater severity associated with melancholic depression remain unresolved, however.

With effective drug therapies for schizophrenia and mood disorders came investigations into the role of neurotransmitters in these illnesses. For depressive orders this interest grew initially from evidence for the antidepressant effects of monoamine oxidase inhibitors that emerged in the late 1950s (Schildkraut et al. 1965; Schildkraut 1967), as well as the pro-depressant effects of reserpine (Harris 1957). In its simplest form, the *catecholamine hypothesis* posited that depressive illness resulted from a relative deficiency of *norepinephrine* and that its relative excess promoted mania. Subsequent studies of norepinephrine or of norepinephrine metabolite concentrations, whether in urine, blood, or cerebrospinal fluid, yielded very inconsistent results, however.

Interest in the role of *serotonin*, an indolamine, developed soon after that for the catecholamines. Replicated observations showed a bimodal distribution of CSF 5-HIAA concentrations in which groups with the lower concentrations were comprised of individuals with more severe or endogenous depressive symptoms (Asberg et al. 1976; Gibbons and Davis 1986).

Additional evidence that norepinephrine and serotonin play important roles in depressive illness derives from precursor depletion studies. A low tryptophan diet followed by a tryptophan-free drink of amino acids results in abrupt lowering of serotonin synthesis. Alternatively, the addition of alpha-methyl-para-tyrosine to the diet blocks the production of L-dopa and thus depletes norepinephrine (Berman et al. 1999). These manipulations result in the rapid onset of depressive symptoms among individuals who have responded to SSRIs (Delgado et al. 1990) or to norepinephrine reuptake inhibitors (Miller et al. 1996), respectively. These maneuvers do not produce depression in well controls or in individuals who have responded to the alternative type of antidepressant.

Far fewer studies have targeted the possible role of *dopamine* functioning in depressive disorder. However, because anhedonia is often given prominence in criteria for depressive disorders and because it appears to be associated with much of the resulting disability (Vinckier et al. 2017), the fact that the dopamine system is integral to motivational arousal makes it also a likely candidate. Evidence for this includes lower dopamine metabolite concentrations in the CSF (Reddy et al. 1992) and lower dopamine transport binding (Sarchiapone et al. 2006). Some controlled trials of augmentation with dopamine agonists in major depressive episodes exist (Madhoo et al. 2014), but their efficacy may be greater in bipolar depression (Szmulewicz et al. 2017).

Other systems are clearly involved in pathogenesis of MDD, but none of the drugs approved for treatment in the United States target them. Probably the most extensively researched of these is the *hypothalamic-pituitary-adrenal (HPA) axis*. Early evidence suggested that the HPA is hyperactive, as manifest in a positive dexamethasone suppression test (DST), and that this hyperactivity might be specific for melancholia (Carroll et al. 1981), bipolar depression (Schlesser et al. 1980), or psychotic depression (Nelson and Davis 1997). Other findings pointed to the utility of the DST in the prediction of long-term outcome in schizoaffective depression (Coryell et al. 1992; Coryell and Zimmerman 1989). Subsequent failures to show consistent levels of diagnostic specificity, however, resulted in disillusionment over the DST (Hirschfeld et al. 1983). The test is, consequently, not now in wide use. The recent review of 48 studies on this topic, though, pointed to the problems inherent and the varied definitions used for melancholia or endogenous depression and noted that HPA hyperactivity distinguishes melancholic from atypical depression with notable consistency (Juruena et al. 2017). Also of note is that follow-up studies have found positive DST results to be a robust predictor of eventual completed suicide among patients hospitalized for depressive disorder (Mann and Currier 2007).

Inescapable stress, a reliable inducer of a depression model in rodents, impairs long-term potentiation in portions of the hippocampus (Shors et al. 1989), an area rich in *N-methyl-D-aspartate (NMDA)*. Such observations prompted a search for drugs that had antidepressant effects through their effects, direct or indirect, on NMDA receptors (Trullas and Skolnick 1990). While a number of glutamate or NMDA receptor modulators have shown preclinical antidepressant effects (Jaso et al. 2017), ketamine, an NMDA antagonist, has shown the most promise. The first controlled trial of ketamine infusion (Berman et al. 2000) has been followed by at least nine controlled trials (Kishimoto et al. 2016). The fact that the administration of ketamine produces antidepressant effects that peak at day 1 has created considerable notice, particularly because reductions in suicidal thinking appear to show an especially robust and rapid response, even after control for the effects of ketamine on other depressive symptoms (Ballard et al. 2014; Murrough et al. 2015; Grunebaum et al. 2018). Several open trials (aan het Rot et al. 2010; Ghasemi et al. 2014; Vande Voort et al. 2016) and at least one RTC (Singh et al. 2016) have demonstrated that repeated administration of ketamine can sustain the antidepressant effects. Only one of these reports followed patients more than a week after the final infusion, and this one described a high relapse rate within a month of the last treatment (aan het Rot et al. 2010). A substantial minority of depressed patients, however, show sustained response even after a single administration. The means to identify such individuals would be of obvious importance, and a positive family history for alcoholism is the most replicated of the potential predictors studied (Pennybaker et al. 2017). This is notable because individuals with family histories that are positive for alcoholism, even if they are not alcoholics themselves, react to alcohol differently from those that lack such a family history (Schuckit 1994) and the behavioral effects of alcohol on humans prominently involve NMDA receptors (Krystal et al. 2003).

Though research into the neuropathogenesis of depressive illness has focused on monoaminergic systems, a role for gamma-aminobutyric acid (GABA) deficits is also likely (Luscher et al. 2011). GABA-A receptor function comprises an integral link between stress and the HPA axis (Mody and Maguire 2011) and thus between stress, either in childhood or later in life, and depressive illness. Lower GABA levels in the brain have been shown in the CSF (Kasa et al. 1982; Gerner and Hare 1981) and in the brain through the use of magnetic resonance spectroscopy (Sanacora et al. 1999). There is some evidence that these deficits are associated with symptom severity or with the melancholic subtype (Sanacora et al. 2004).

GABA levels are increased by various antidepressant treatments (Luscher et al. 2011), and one study indicated that such increases can be induced acutely by an infusion of an SSRI in well individuals (Bhagwagar et al. 2004). This implies that 5-HT receptor changes associated with antidepressant response exist downstream from acute changes in GABA.

The GABA deficit hypothesis also indicates the potential of neuroactive steroids as antidepressants. Thus, such positive allosteric modulators of the $GABA_A$-R receptor as pregnanolone and allopregnanolone have been tested recently as treatments for depressive illness (Brown et al. 2014) and for postpartum depression in particular (Deligiannidis et al. 2016; Kanes et al. 2017). In contrast to conventional antidepressants, and akin to ketamine, the response to infusions of allopregnanolone occurs within the first 24 h.

Yet another pathogenic mechanism, that of inflammation, holds promise for new antidepressant approaches. The administration of pro-inflammatory agents in the treatment of autoimmune disorders regularly results in depressive syndromes (Capuron et al. 2001, 2002, 2008), and many reports have described elevated cytokine levels in individuals with depressive disorders in comparison to well controls (Baumeister et al. 2014; Dowlati et al. 2010).

Increased inflammation may explain, at least in part, links between specific underlying risk factors and the onset of depressive illness. Supporting evidence exists for adiposity (Bond et al. 2016; Miller et al. 2003), childhood trauma (Cattaneo et al. 2015; Danese et al. 2007; Li et al. 2013), metabolic syndrome (Capuron et al. 2008; Vogelzangs et al. 2014), and relative deficiencies in omega-3 fatty acids (Dinan et al. 2009). Some studies have also reported elevations in cytokine levels among individuals who have depressive illness and a history of suicide attempts in comparison to those with depressive illness but without past suicide attempts. Other reports have shown that levels of inflammatory markers decrease with antidepressant treatment (Li et al. 2013; Basterzi et al. 2005), but some have not (Brunoni et al. 2015; Eller et al. 2008; Hernandez et al. 2008), and it is unclear whether the benefits of conventional antidepressants accrue at least in part, through their anti-inflammatory effects.

There have been efforts to take a more direct approach and to use medications known as anti-inflammatory agents as antidepressants. These have included polyunsaturated fatty acids, cyclooxygenase (COX) inhibitors, anti-TNF-alpha, and minocycline (Fond et al. 2014). Efforts have met with some success (Akhondzadeh et al. 2009; Kappelmann et al. 2018; Muller et al. 2006) though this approach may have more benefit for those with elevated inflammatory levels at baseline (Raison et al. 2013).

References

aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, Mathew SJ (2010) Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry 67(2):139–145. https://doi.org/10.1016/j.biopsych.2009.08.038

Akhondzadeh S, Jafari S, Raisi F, Nasehi AA, Ghoreishi A, Salehi B, Mohebbi-Rasa S, Raznahan M, Kamalipour A (2009) Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Depress Anxiety 26(7):607–611. https://doi.org/10.1002/da.20589

Andreasen NC, Grove WM, Coryell WH, Endicott J, Clayton PJ (1988) Bipolar versus unipolar and primary versus secondary affective disorder: which diagnosis takes precedence? J Affect Disord 15(1):69–80

Angst J (1966) On the etiology and nosology of endogenous depressive psychoses. A genetic, sociologic and clinical study. Monogr Gesamtgeb Neurol Psychiatr 112:1–118

Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W (2003) Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 73(1):133–146

Angst J, Angst F, Gerber-Werder R, Gamma A (2005) Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Arch Suicide Res 9(3):279–300. https://doi.org/10.1080/13811110590929488

Angst J, Gamma A, Rossler W, Ajdacic V, Klein DN (2009) Long-term depression versus episodic major depression: results from the prospective Zurich study of a community sample. J Affect Disord 115(1–2):112–121. https://doi.org/10.1016/j.jad.2008.09.023

Arsenault-Lapierre G, Kim C, Turecki G (2004) Psychiatric diagnoses in 3275 suicides: a meta-analysis. BMC Psychiatry 4(1):37

Asberg M, Thoren P, Traskman L, Bertilsson L, Ringberger V (1976) "Serotonin depression" – a biochemical subgroup within the affective disorders? Science 191(4226):478–480

Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA, Brutsche NE, Ameli R, Furey ML, Zarate CA Jr (2014) Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res 58:161–166. https://doi.org/10.1016/j.jpsychires.2014.07.027

Barnes MP, Saunders M, Walls TJ, Saunders I, Kirk CA (1986) The syndrome of Karl Ludwig Kahlbaum. J Neurol Neurosurg Psychiatry 49(9):991–996

Barnhofer T, Brennan K, Crane C, Duggan D, Williams JM (2014) A comparison of vulnerability factors in patients with persistent and remitting lifetime symptom course of depression. J Affect Disord 152–154:155–161. https://doi.org/10.1016/j.jad.2013.09.001

Basterzi AD, Aydemir C, Kisa C, Aksaray S, Tuzer V, Yazici K, Goka E (2005) IL-6 levels decrease with SSRI treatment in patients with major depression. Hum Psychopharmacol 20(7):473–476. https://doi.org/10.1002/hup.717

Baumeister D, Russell A, Pariante CM, Mondelli V (2014) Inflammatory biomarker profiles of mental disorders and their relation to clinical, social and lifestyle factors. Soc Psychiatry Psychiatr Epidemiol 49(6):841–849. https://doi.org/10.1007/s00127-014-0887-z

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571

Benazzi F (1999) Bipolar II versus unipolar chronic depression: a 312-case study. Compr Psychiatry 40(6):418–421

Benazzi F (2001) Atypical depression with hypomanic symptoms. J Affect Disord 65(2):179–183

Benazzi F (2002) Can only reversed vegetative symptoms define atypical depression? Eur Arch Psychiatry Clin Neurosci 252(6):288–293. https://doi.org/10.1007/s00406-002-0395-0

Benazzi F, Koukopoulos A, Akiskal HS (2004) Toward a validation of a new definition of agitated depression as a bipolar mixed state (mixed depression). Eur Psychiatry 19(2):85–90. https://doi.org/10.1016/j.eurpsy.2003.09.008

Berardi D, Dell'Atti M, Amore M, De Ronchi D, Ferrari G (2002) Clinical risk factors for neuroleptic malignant syndrome. Hum Psychopharmacol Clin Exp 17(2):99–102

Berman RM, Narasimhan M, Miller HL, Anand A, Cappiello A, Oren DA, Heninger GR, Charney DS (1999) Transient depressive relapse induced by catecholamine depletion: potential phenotypic vulnerability marker? Arch Gen Psychiatry 56(5):395–403

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47(4):351–354

Bernert RA, Kim JS, Iwata NG, Perlis ML (2015) Sleep disturbances as an evidence-based suicide risk factor. Curr Psychiatry Rep 17(3):554. https://doi.org/10.1007/s11920-015-0554-4

Bhagwagar Z, Wylezinska M, Taylor M, Jezzard P, Matthews PM, Cowen PJ (2004) Increased brain GABA concentrations following acute administration of a selective serotonin reuptake inhibitor. Am J Psychiatry 161(2):368–370. https://doi.org/10.1176/appi.ajp.161.2.368

Biederman J, Wozniak J, Tarko L, Serra G, Hernandez M, McDermott K, Woodsworth KY, Uchida M, Faraone SV (2014) Re-examining the risk for switch from unipolar to bipolar major depressive disorder in youth with ADHD: a long term prospective longitudinal controlled study. J Affect Disord 152–154:347–351. https://doi.org/10.1016/j.jad.2013.09.036

Black DW, Bell S, Hulbert J, Nasrallah A (1988) The importance of axis II in patients with major depression. A controlled study. J Affect Disord 14(2):115–122

Blanco C, Okuda M, Markowitz JC, Liu SM, Grant BF, Hasin DS (2010) The epidemiology of chronic major depressive disorder and dysthymic disorder: results from the National Epidemiologic Survey on alcohol and related conditions. J Clin Psychiatry 71(12):1645–1656. https://doi.org/10.4088/JCP.09m05663gry

Bond DJ, Andreazza AC, Hughes J, Dhanoa T, Torres IJ, Kozicky JM, Young LT, Lam RW, Yatham LN (2016) Association of peripheral inflammation with body mass index and depressive relapse in bipolar disorder. Psychoneuroendocrinology 65:76–83. https://doi.org/10.1016/j.psyneuen.2015.12.012

Bostwick JM, Pankratz VS (2000) Affective disorders and suicide risk: a reexamination. Am J Psychiatry 157(12):1925–1932. https://doi.org/10.1176/appi.ajp.157.12.1925

Breslau N, Davis GC (1985) Refining DSM-III criteria in major depression. An assessment of the descriptive validity of criterion symptoms. J Affect Disord 9(3):199–206

Bromet EJ, Kotov R, Fochtmann LJ, Carlson GA, Tanenberg-Karant M, Ruggero C, Chang SW (2011) Diagnostic shifts during the decade following first admission for psychosis. Am J Psychiatry 168(11):1186–1194. https://doi.org/10.1176/appi.ajp.2011.11010048

Brown WA (2007) Treatment response in melancholia. Acta Psychiatr Scand Suppl 433:125–129. https://doi.org/10.1111/j.1600-0447.2007.00970.x

Brown ES, Park J, Marx CE, Hynan LS, Gardner C, Davila D, Nakamura A, Sunderajan P, Lo A, Holmes T (2014) A randomized, double-blind, placebo-controlled trial of pregnenolone for bipolar depression. Neuropsychopharmacology 39(12):2867–2873. https://doi.org/10.1038/npp.2014.138

Brunoni AR, Machado-Vieira R, Sampaio-Junior B, Vieira EL, Valiengo L, Bensenor IM, Lotufo PA, Carvalho AF, Cho HJ, Gattaz WF, Teixeira AL (2015) Plasma levels of soluble TNF receptors 1 and 2 after tDCS and sertraline treatment in major depression: results from the SELECT-TDCS trial. J Affect Disord 185:209–213. https://doi.org/10.1016/j.jad.2015.07.006

Buchan H, Johnstone E, McPherson K, Palmer RL, Crow TJ, Brandon S (1992) Who benefits from electroconvulsive therapy? Combined results of the Leicester and Northwick Park trials. Br J Psychiatry 160:355–359

Capuron L, Ravaud A, Gualde N, Bosmans E, Dantzer R, Maes M, Neveu PJ (2001) Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. Psychoneuroendocrinology 26(8):797–808

Capuron L, Gumnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB, Miller AH (2002) Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 26(5):643–652. https://doi.org/10.1016/S0893-133X(01)00407-9

Capuron L, Su S, Miller AH, Bremner JD, Goldberg J, Vogt GJ, Maisano C, Jones L, Murrah NV, Vaccarino V (2008) Depressive symptoms and metabolic syndrome: is inflammation the underlying link? Biol Psychiatry 64(10):896–900. https://doi.org/10.1016/j.biopsych.2008.05.019

Carroll BJ, Feinberg M, Greden JF, Tarika J, Albala AA, Haskett RF, James NM, Kronfol Z, Lohr N, Steiner M, de Vigne JP, Young E (1981) A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. Arch Gen Psychiatry 38(1):15–22

Cattaneo A, Macchi F, Plazzotta G, Veronica B, Bocchio-Chiavetto L, Riva MA, Pariante CM (2015) Inflammation and neuronal plasticity: a link between childhood trauma and depression pathogenesis. Front Cell Neurosci 9:40. https://doi.org/10.3389/fncel.2015.00040

Charney DS, Nelson JC (1981) Delusional and nondelusional unipolar depression: further evidence for distinct subtypes. Am J Psychiatry 138(3):328–333. https://doi.org/10.1176/ajp.138.3.328

Charney DS, Nelson JC, Quinlan DM (1981) Personality traits and disorder in depression. Am J Psychiatry 138(12):1601–1604. https://doi.org/10.1176/ajp.138.12.1601

Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, Suri R, Burt VK, Hendrick V, Reminick AM, Loughead A, Vitonis AF, Stowe ZN (2006) Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 295(5):499–507. https://doi.org/10.1001/jama.295.5.499

Corruble E, Ginestet D, Guelfi JD (1996) Comorbidity of personality disorders and unipolar major depression: a review. J Affect Disord 37(2–3):157–170

Coryell W, Young EA (2005) Clinical predictors of suicide in primary major depressive disorder. J Clin Psychiatry 66(4):412–417

Coryell WH, Zimmerman M (1989) HPA axis hyperactivity and recovery from functional psychoses. Am J Psychiatry 146(4):473–477. https://doi.org/10.1176/ajp.146.4.473

Coryell W, Pfohl B, Zimmerman M (1984) The clinical and neuroendocrine features of psychotic depression. J Nerv Ment Dis 172(9):521–528

Coryell W, Endicott J, Keller M, Andreasen NC (1985) Phenomenology and family history in DSM-III psychotic depression. J Affect Disord 9(1):13–18

Coryell W, Endicott J, Keller M (1990) Outcome of patients with chronic affective disorder: a five-year follow-up. Am J Psychiatry 147(12):1627–1633. https://doi.org/10.1176/ajp.147.12.1627

Coryell W, Endicott J, Winokur G (1992) Anxiety syndromes as epiphenomena of primary major depression: outcome and familial psychopathology. Am J Psychiatry 149(1):100–107. https://doi.org/10.1176/ajp.149.1.100

Coryell W, Winokur G, Maser JD, Akiskal HS, Keller MB, Endicott J (1994a) Recurrently situational (reactive) depression: a study of course, phenomenology and familial psychopathology. J Affect Disord 31(3):203–210

Coryell W, Winokur G, Shea T, Maser JD, Endicott J, Akiskal HS (1994b) The long-term stability of depressive subtypes. Am J Psychiatry 151(2):199–204

Coryell W, Leon A, Winokur G, Endicott J, Keller M, Akiskal H, Solomon D (1996) Importance of psychotic features to long-term course in major depressive disorder. Am J Psychiatry 153(4):483–489. https://doi.org/10.1176/ajp.153.4.483

Coryell W, Solomon DA, Fiedorowicz JG, Endicott J, Schettler PJ, Judd LL (2009) Anxiety and outcome in bipolar disorder. Am J Psychiatry 166(11):1238–1243. https://doi.org/10.1176/appi.ajp.2009.09020218

Coryell W, Fiedorowicz JG, Solomon D, Leon AC, Rice JP, Keller MB (2012) Effects of anxiety on the long-term course of depressive disorders. Br J Psychiatry 200(3):210–215. https://doi.org/10.1192/bjp.bp.110.081992

Coryell WH, Butcher BD, Burns TL, Dindo LN, Schlechte JA, Calarge CA (2016) Fat distribution and major depressive disorder in late adolescence. J Clin Psychiatry 77(1):84–89. https://doi.org/10.4088/JCP.14m09169

Cross-National Collaborative Group, Wittchen H-U (1992) The changing rate of major depression: cross-national comparisons. JAMA 268(21):3098–3105

Crow TJ, Deakin JFW, Johnstone EC, MacMillan JF, Owens DGC, Lawler P, Frith CD, Stevens M, McPherson K (1984) The Northwick Park ECT trial. Predictors of response to real and simulated ECT. Clinical Research Centre, Division of Psychiatry. Br J Psychiatry 144:227–237

Cuijpers P, Weitz E, Lamers F, Penninx BW, Twisk J, DeRubeis RJ, Dimidjian S, Dunlop BW, Jarrett RB, Segal ZV (2017) Melancholic and atypical depression as predictor and moderator of outcome in cognitive behavior therapy and pharmacotherapy for adult depression. Depress Anxiety 34(3):246–256

Curtin SC, Warner M, Hedegaard H (2016) Increase in suicide in the United States, 1999–2014. NCHS Data Brief 241:1–8

Danese A, Pariante CM, Caspi A, Taylor A, Poulton R (2007) Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci U S A 104(4):1319–1324. https://doi.org/10.1073/pnas.0610362104

Delgado PL, Charney DS, Price LH, Aghajanian GK, Landis H, Heninger GR (1990) Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. Arch Gen Psychiatry 47(5):411–418

Deligiannidis KM, Kroll-Desrosiers AR, Mo S, Nguyen HP, Svenson A, Jaitly N, Hall JE, Barton BA, Rothschild AJ, Shaffer SA (2016) Peripartum neuroactive steroid and gamma-aminobutyric acid profiles in women at-risk for postpartum depression. Psychoneuroendocrinology 70:98–107. https://doi.org/10.1016/j.psyneuen.2016.05.010

Di Florio A, Forty L, Gordon-Smith K, Heron J, Jones L, Craddock N, Jones I (2013) Perinatal episodes across the mood disorder spectrum. JAMA Psychiat 70(2):168–175. https://doi.org/10.1001/jamapsychiatry.2013.279

Dinan T, Siggins L, Scully P, O'Brien S, Ross P, Stanton C (2009) Investigating the inflammatory phenotype of major depression: focus on cytokines and polyunsaturated fatty acids. J Psychiatr Res 43(4):471–476. https://doi.org/10.1016/j.jpsychires.2008.06.003

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctot KL (2010) A meta-analysis of cytokines in major depression. Biol Psychiatry 67(5):446–457. https://doi.org/10.1016/j.biopsych.2009.09.033

Ducasse D, Loas G, Dassa D, Gramaglia C, Zeppegno P, Guillaume S, Olie E, Courtet P (2017) Anhedonia is associated with suicidal ideation independently of depression: a meta-analysis. Depress Anxiety. https://doi.org/10.1002/da.22709

Eller T, Vasar V, Shlik J, Maron E (2008) Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry 32(2):445–450. https://doi.org/10.1016/j.pnpbp.2007.09.015

Fattori A, Neri L, Bellomo A, Vaggi M, Mencacci C, Group IS (2017) Depression severity and concentration difficulties are independently associated with HRQOL in patients with unipolar depressive disorders. Qual Life Res 26(9):2459–2469. https://doi.org/10.1007/s11136-017-1595-4

Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, Biggs MM, Zisook S, Leuchter A, Howland R, Warden D, Trivedi MH (2008) Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry 165(3):342–351. https://doi.org/10.1176/appi.ajp.2007.06111868

Fava M, Ball S, Nelson JC, Sparks J, Konechnik T, Classi P, Dube S, Thase ME (2014) Clinical relevance of fatigue as a residual symptom in major depressive disorder. Depress Anxiety 31(3):250–257. https://doi.org/10.1002/da.22199

Feighner JP, Robins E, Guze SB, Woodruff RA Jr, Winokur G, Munoz R (1972) Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 26(1):57–63

Feske U, Frank E, Kupfer DJ, Shear MK, Weaver E (1998) Anxiety as a predictor of response to interpersonal psychotherapy for recurrent major depression: an exploratory investigation. Depress Anxiety 8(4):135–141

Feske U, Mulsant BH, Pilkonis PA, Soloff P, Dolata D, Sackeim HA, Haskett RF (2004) Clinical outcome of ECT in patients with major depression and comorbid borderline personality disorder. Am J Psychiatry 161(11):2073–2080. https://doi.org/10.1176/appi.ajp.161.11.2073

Fiedorowicz JG, He J, Merikangas KR (2011a) The association between mood and anxiety disorders with vascular diseases and risk factors in a nationally representative sample. J Psychosom Res 70(2):145–154. https://doi.org/10.1016/j.jpsychores.2010.07.010

Fiedorowicz JG, Endicott J, Leon AC, Solomon DA, Keller MB, Coryell WH (2011b) Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. Am J Psychiatry 168(1):40–48. https://doi.org/10.1176/appi.ajp.2010.10030328

Fisch RZ (1987) Masked depression: its interrelations with somatization, hypochondriasis and conversion. Int J Psychiatry Med 17(4):367–379

Fisch RZ, Tadmor OP, Dankner R, Diamant YZ (1997) Postnatal depression: a prospective study of its prevalence, incidence and psychosocial determinants in an Israeli sample. J Obstet Gynaecol Res 23(6):547–554

Fond G, Hamdani N, Kapczinski F, Boukouaci W, Drancourt N, Dargel A, Oliveira J, Le Guen E, Marlinge E, Tamouza R, Leboyer M (2014) Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review. Acta Psychiatr Scand 129(3):163–179. https://doi.org/10.1111/acps.12211

Forty L, Jones L, Macgregor S, Caesar S, Cooper C, Hough A, Dean L, Dave S, Farmer A, McGuffin P, Brewster S, Craddock N, Jones I (2006) Familiality of postpartum depression in unipolar disorder: results of a family study. Am J Psychiatry 163(9):1549–1553. https://doi.org/10.1176/ajp.2006.163.9.1549

Francis A, Divadeenam KM, Bush G, Petrides G (1997) Consistency of symptoms in recurrent catatonia. Compr Psychiatry 38(1):56–60

Garvey MJ, Tollefson GD, Tuason VB (1986) Is chronic primary major depression a distinct depression subtype? Compr Psychiatry 27(5):446–448

Geoffroy PA, Hoertel N, Etain B, Bellivier F, Delorme R, Limosin F, Peyre H (2018) Insomnia and hypersomnia in major depressive episode: prevalence, sociodemographic characteristics and psychiatric comorbidity in a population-based study. J Affect Disord 226:132–141. https://doi.org/10.1016/j.jad.2017.09.032

Gerner RH, Hare TA (1981) CSF GABA in normal subjects and patients with depression, schizophrenia, mania, and anorexia nervosa. Am J Psychiatry 138(8):1098–1101. https://doi.org/10.1176/ajp.138.8.1098

Ghasemi M, Kazemi MH, Yoosefi A, Ghasemi A, Paragomi P, Amini H, Afzali MH (2014) Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. Psychiatry Res 215(2):355–361. https://doi.org/10.1016/j.psychres.2013.12.008

Ghatavi K, Nicolson R, MacDonald C, Osher S, Levitt A (2002) Defining guilt in depression: a comparison of subjects with major depression, chronic medical illness and healthy controls. J Affect Disord 68(2–3):307–315

Gibbons RD, Davis JM (1986) Consistent evidence for a biological subtype of depression characterized by low CSF monoamine levels. Acta Psychiatr Scand 74(1):8–12

Gilmer WS, Trivedi MH, Rush AJ, Wisniewski SR, Luther J, Howland RH, Yohanna D, Khan A, Alpert J (2005) Factors associated with chronic depressive episodes: a preliminary report from the STAR-D project. Acta Psychiatr Scand 112(6):425–433. https://doi.org/10.1111/j.1600-0447.2005.00633.x

Giuffra LA, Risch N (1994) Diminished recall and the cohort effect of major depression: a simulation study. Psychol Med 24(2):375–383

Glassman AH, Roose SP (1981) Delusional depression. A distinct clinical entity? Arch Gen Psychiatry 38(4):424–427

Glassman AH, Kantor SJ, Shostak M (1975) Depression, delusions, and drug response. Am J Psychiatry 132(7):716–719. https://doi.org/10.1176/ajp.132.7.716

Goes FS, McCusker MG, Bienvenu OJ, Mackinnon DF, Mondimore FM, Schweizer B, National Institute of Mental Health Genetics Initiative Bipolar Disorder C, Depaulo JR, Potash JB (2012) Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and

obsessive-compulsive disorder. Psychol Med 42(7):1449–1459. https://doi.org/10.1017/S0033291711002637

Gonzales LR, Lewinsohn PM, Clarke GN (1985) Longitudinal follow-up of unipolar depressives: an investigation of predictors of relapse. J Consult Clin Psychol 53(4):461–469

Gotlib IH, Whiffen VE, Mount JH, Milne K, Cordy NI (1989) Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum. J Consult Clin Psychol 57(2):269–274

Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC (2015) The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry 76(2):155–162. https://doi.org/10.4088/JCP.14m09298

Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, Marver JE, Burke AK, Milak MS, Sublette ME, Oquendo MA, Mann JJ (2018) Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am J Psychiatry 175(4):327–335. https://doi.org/10.1176/appi.ajp.2017.17060647

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23(1):56

Harris TH (1957) Depression induced by Rauwolfia compounds. Am J Psychiatry 113(10):950. https://doi.org/10.1176/ajp.113.10.950

Hernandez ME, Mendieta D, Martinez-Fong D, Loria F, Moreno J, Estrada I, Bojalil R, Pavon L (2008) Variations in circulating cytokine levels during 52 week course of treatment with SSRI for major depressive disorder. Eur Neuropsychopharmacol 18(12):917–924. https://doi.org/10.1016/j.euroneuro.2008.08.001

Hiles SA, Baker AL, de Malmanche T, Attia J (2012) Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis. Psychol Med 42(10):2015–2026. https://doi.org/10.1017/S0033291712000128

Hirschfeld RM, Koslow SH, Kupfer DJ (1983) The clinical utility of the dexamethasone suppression test in psychiatry. Summary of a National Institute of Mental Health workshop. JAMA 250(16):2172–2174

Hollon SD, Shelton RC, Wisniewski S, Warden D, Biggs MM, Friedman ES, Husain M, Kupfer DJ, Nierenberg AA, Petersen TJ, Shores-Wilson K, Rush AJ (2006) Presenting characteristics of depressed outpatients as a function of recurrence: preliminary findings from the STAR*D clinical trial. J Psychiatr Res 40(1):59–69. https://doi.org/10.1016/j.jpsychires.2005.07.008

Howren MB, Lamkin DM, Suls J (2009) Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 71(2):171–186. https://doi.org/10.1097/PSY.0b013e3181907c1b

Jaso BA, Niciu MJ, Iadarola ND, Lally N, Richards EM, Park M, Ballard ED, Nugent AC, Machado-Vieira R, Zarate CA (2017) Therapeutic modulation of glutamate receptors in major depressive disorder. Curr Neuropharmacol 15(1):57–70

Jones I, Craddock N (2001) Familiality of the puerperal trigger in bipolar disorder: results of a family study. Am J Psychiatry 158(6):913–917. https://doi.org/10.1176/appi.ajp.158.6.913

Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Paulus MP, Kunovac JL, Leon AC, Mueller TI, Rice JA, Keller MB (1998) Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J Affect Disord 50(2–3):97–108

Judd LL, Paulus MJ, Schettler PJ, Akiskal HS, Endicott J, Leon AC, Maser JD, Mueller T, Solomon DA, Keller MB (2000) Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? Am J Psychiatry 157(9):1501–1504. https://doi.org/10.1176/appi.ajp.157.9.1501

Judd LL, Schettler PJ, Rush AJ, Coryell WH, Fiedorowicz JG, Solomon DA (2016) A new empirical definition of major depressive episode recovery and its positive impact on future course of illness. J Clin Psychiatry 77(8):1065–1073. https://doi.org/10.4088/JCP.15m09918

Juruena MF, Bocharova M, Agustini B, Young AH (2017) Atypical depression and non-atypical depression: is HPA axis function a biomarker? A systematic review. J Affect Disord 233:45–67. https://doi.org/10.1016/j.jad.2017.09.052

Kanes S, Colquhoun H, Gunduz-Bruce H, Raines S, Arnold R, Schacterle A, Doherty J, Epperson CN, Deligiannidis KM, Riesenberg R, Hoffmann E, Rubinow D, Jonas J, Paul S, Meltzer-Brody S (2017) Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet 390(10093):480–489. https://doi.org/10.1016/S0140-6736(17)31264-3

Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM (2018) Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol Psychiatry 23(2):335–343. https://doi.org/10.1038/mp.2016.167

Kasa K, Otsuki S, Yamamoto M, Sato M, Kuroda H, Ogawa N (1982) Cerebrospinal fluid gamma-aminobutyric acid and homovanillic acid in depressive disorders. Biol Psychiatry 17(8):877–883

Keller MB, Lavori PW, Endicott J, Coryell W, Klerman GL (1983a) "Double depression": two-year follow-up. Am J Psychiatry 140(6):689–694. https://doi.org/10.1176/ajp.140.6.689

Keller MB, Lavori PW, Lewis CE, Klerman GL (1983b) Predictors of relapse in major depressive disorder. JAMA 250(24):3299–3304

Kendler KS (1995) Is seeking treatment for depression predicted by a history of depression in relatives? Implications for family studies of affective disorder. Psychol Med 25(4):807–814

Kendler KS, Karkowski-Shuman L (1997) Stressful life events and genetic liability to major depression: genetic control of exposure to the environment? Psychol Med 27(3):539–547

Kendler KS, Eaves LJ, Walters EE, Neale MC, Heath AC, Kessler RC (1996) The identification and validation of distinct depressive syndromes in a population-based sample of female twins. Arch Gen Psychiatry 53(5):391–399

Kendler KS, Kuhn J, Prescott CA (2004) The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. Am J Psychiatry 161(4):631–636. https://doi.org/10.1176/appi.ajp.161.4.631

Kendler KS, Myers J, Zisook S (2008) Does bereavement-related major depression differ from major depression associated with other stressful life events? Am J Psychiatry 165(11):1449–1455. https://doi.org/10.1176/appi.ajp.2008.07111757

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 51(1):8–19

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS, National Comorbidity Survey R (2003) The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289(23):3095–3105. https://doi.org/10.1001/jama.289.23.3095

Kessler RC, Berglund P, Borges G, Nock M, Wang PS (2005) Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. JAMA 293(20):2487–2495. https://doi.org/10.1001/jama.293.20.2487

Kishimoto T, Chawla JM, Hagi K, Zarate CA, Kane JM, Bauer M, Correll CU (2016) Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. Psychol Med 46(7):1459–1472. https://doi.org/10.1017/S0033291716000064

Klein DN, Taylor EB, Harding K, Dickstein S (1988) Double depression and episodic major depression: demographic, clinical, familial, personality, and socioenvironmental characteristics and short-term outcome. Am J Psychiatry 145(10):1226–1231. https://doi.org/10.1176/ajp.145.10.1226

Klein DN, Schwartz JE, Rose S, Leader JB (2000) Five-year course and outcome of dysthymic disorder: a prospective, naturalistic follow-up study. Am J Psychiatry 157(6):931–939. https://doi.org/10.1176/appi.ajp.157.6.931

Klein DN, Shankman SA, Lewinsohn PM, Rohde P, Seeley JR (2004) Family study of chronic depression in a community sample of young adults. Am J Psychiatry 161(4):646–653. https://doi.org/10.1176/appi.ajp.161.4.646

Koukopoulos A, Sani G, Koukopoulos AE, Manfredi G, Pacchiarotti I, Girardi P (2007) Melancholia agitata and mixed depression. Acta Psychiatr Scand Suppl 433:50–57. https://doi.org/10.1111/j.1600-0447.2007.00963.x

Kraepelin E (1921) In: Carlson ET (ed) Manic-depressive insanity and paranoia. Arno Press

Krishna KR, Maniar RC, Harbishettar VS (2011) A comparative study of "idiopathic catatonia" with catatonia in schizophrenia. Asian J Psychiatr 4(2):129–133. https://doi.org/10.1016/j.ajp.2011.04.007

Kroenke K, Spitzer RL, Williams JB (2001) The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16(9):606–613

Krystal JH, Petrakis IL, Mason G, Trevisan L, D'Souza DC (2003) N-methyl-D-aspartate glutamate receptors and alcoholism: reward, dependence, treatment, and vulnerability. Pharmacol Ther 99(1):79–94

Lam RW, Michalak EE, Bond DJ, Tam EM, Axler A, Yatham LN (2012) Which depressive symptoms and medication side effects are perceived by patients as interfering most with occupational functioning? Depress Res Treat 2012:630206. https://doi.org/10.1155/2012/630206

Leckman JF, Weissman MM, Prusoff BA, Caruso KA, Merikangas KR, Pauls DL, Kidd KK (1984) Subtypes of depression. Family study perspective. Arch Gen Psychiatry 41(9):833–838

Leonhard K, Korff I, Schulz H (1962) Temperament in families with monopolar and bipolar phasic psychoses. Psychiatr Neurol (Basel) 143:416–434

Lewis AJ (1934) Melancholia: a clinical survey of depressive states. J Ment Sci 80:277–378

Li Z, Qi D, Chen J, Zhang C, Yi Z, Yuan C, Wang Z, Hong W, Yu S, Cui D, Fang Y (2013) Venlafaxine inhibits the upregulation of plasma tumor necrosis factor-alpha (TNF-alpha) in the Chinese patients with major depressive disorder: a prospective longitudinal study. Psychoneuroendocrinology 38(1):107–114. https://doi.org/10.1016/j.psyneuen.2012.05.005

Luscher B, Shen Q, Sahir N (2011) The GABAergic deficit hypothesis of major depressive disorder. Mol Psychiatry 16(4):383–406. https://doi.org/10.1038/mp.2010.120

Madhoo M, Keefe RS, Roth RM, Sambunaris A, Wu J, Trivedi MH, Anderson CS, Lasser R (2014) Lisdexamfetamine dimesylate augmentation in adults with persistent executive dysfunction after partial or full remission of major depressive disorder. Neuropsychopharmacology 39(6):1388–1398. https://doi.org/10.1038/npp.2013.334

Maj M, Veltro F, Pirozzi R, Lobrace S, Magliano L (1992) Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. Am J Psychiatry 149(6):795–800. https://doi.org/10.1176/ajp.149.6.795

Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L (2006) Agitated "unipolar" major depression: prevalence, phenomenology, and outcome. J Clin Psychiatry 67(5):712–719

Mann JJ, Currier D (2007) A review of prospective studies of biologic predictors of suicidal behavior in mood disorders. Arch Suicide Res 11(1):3–16. https://doi.org/10.1080/13811110600993124

McCrae RR, Costa PT Jr (1987) Validation of the five-factor model of personality across instruments and observers. J Pers Soc Psychol 52(1):81–90

McCullough JP Jr, Klein DN, Keller MB, Holzer CE 3rd, Davis SM, Kornstein SG, Howland RH, Thase ME, Harrison WM (2000) Comparison of DSM-III-R chronic major depression and major depression superimposed on dysthymia (double depression): validity of the distinction. J Abnorm Psychol 109(3):419–427

McCullough JP Jr, Klein DN, Borian FE, Howland RH, Riso LP, Keller MB, Banks PL (2003) Group comparisons of DSM-IV subtypes of chronic depression: validity of the distinctions, part 2. J Abnorm Psychol 112(4):614–622. https://doi.org/10.1037/0021-843X.112.4.614

McGrath PJ, Stewart JW, Harrison WM, Ocepek-Welikson K, Rabkin JG, Nunes EN, Wager SG, Tricamo E, Quitkin FM, Klein DF (1992) Predictive value of symptoms of atypical depression for differential drug treatment outcome. J Clin Psychopharmacol 12(3):197–202

Mercer D, Douglass AB, Links PS (2009) Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. J Personal Disord 23(2):156–174. https://doi.org/10.1521/pedi.2009.23.2.156

Miller HL, Delgado PL, Salomon RM, Berman R, Krystal JH, Heninger GR, Charney DS (1996) Clinical and biochemical effects of catecholamine depletion on antidepressant-induced remission of depression. Arch Gen Psychiatry 53(2):117–128

Miller GE, Freedland KE, Carney RM, Stetler CA, Banks WA (2003) Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. Brain Behav Immun 17(4):276–285

Mitchell AJ, Vaze A, Rao S (2009) Clinical diagnosis of depression in primary care: a meta-analysis. Lancet 374(9690):609–619. https://doi.org/10.1016/S0140-6736(09)60879-5

Mody I, Maguire J (2011) The reciprocal regulation of stress hormones and GABA(A) receptors. Front Cell Neurosci 6:4. https://doi.org/10.3389/fncel.2012.00004

Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389

Morrison JR (1973) Catatonia. Retarded and excited types. Arch Gen Psychiatry 28(1):39–41

Mortensen PB, Agerbo E, Erikson T, Qin P, Westergaard-Nielsen N (2000) Psychiatric illness and risk factors for suicide in Denmark. Lancet 355(9197):9–12

Muller N, Schwarz MJ, Dehning S, Douhe A, Cerovecki A, Goldstein-Muller B, Spellmann I, Hetzel G, Maino K, Kleindienst N, Moller HJ, Arolt V, Riedel M (2006) The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. Mol Psychiatry 11(7):680–684. https://doi.org/10.1038/sj.mp.4001805

Munkholm K, Vinberg M, Vedel Kessing L (2013) Cytokines in bipolar disorder: a systematic review and meta-analysis. J Affect Disord 144(1–2):16–27. https://doi.org/10.1016/j.jad.2012.06.010

Murphy JM, Horton NJ, Burke JD Jr, Monson RR, Laird NM, Lesage A, Sobol AM (2009) Obesity and weight gain in relation to depression: findings from the Stirling County study. Int J Obes 33(3):335–341. https://doi.org/10.1038/ijo.2008.273

Murphy-Eberenz K, Zandi PP, March D, Crowe RR, Scheftner WA, Alexander M, McInnis MG, Coryell W, Adams P, DePaulo JR Jr, Miller EB, Marta DH, Potash JB, Payne J, Levinson DF (2006) Is perinatal depression familial? J Affect Disord 90(1):49–55. https://doi.org/10.1016/j.jad.2005.10.006

Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM, Lener M, Kautz M, Kim J, Stern JB, Price RB, Perez AM, Brallier JW, Rodriguez GJ, Goodman WK, Iosifescu DV, Charney DS (2015) Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med 45(16):3571–3580. https://doi.org/10.1017/S0033291715001506

Naismith SL, Longley WA, Scott EM, Hickie IB (2007) Disability in major depression related to self-rated and objectively-measured cognitive deficits: a preliminary study. BMC Psychiatry 7:32

Nelson JC, Davis JM (1997) DST studies in psychotic depression: a meta-analysis. Am J Psychiatry 154(11):1497–1503. https://doi.org/10.1176/ajp.154.11.1497

Nelson JC, Bickford D, Delucchi K, Fiedorowicz JG, Coryell WH (2018) Risk of psychosis in recurrent episodes of psychotic and nonpsychotic major depressive disorder: a systematic review and meta-analysis. Am J Psychiatry 175(9):897–904. https://doi.org/10.1176/appi.ajp.2018.17101138

Nierenberg AA, DeCecco LM (2001) Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. J Clin Psychiatry 62(Suppl 16):5–9

Otto MW, Simon NM, Wisniewski SR, Miklowitz DJ, Kogan JN, Reilly-Harrington NA, Frank E, Nierenberg AA, Marangell LB, Sagduyu K, Weiss RD, Miyahara S, Thas ME, Sachs GS, Pollack MH, Investigators S-B (2006) Prospective 12-month course of bipolar disorder in out-patients with and without comorbid anxiety disorders. Br J Psychiatry 189:20–25. https://doi.org/10.1192/bjp.bp.104.007773

Papakostas GI, McGrath P, Stewart J, Charles D, Chen Y, Mischoulon D, Dording C, Fava M (2008) Psychic and somatic anxiety symptoms as predictors of response to fluoxetine in major

depressive disorder. Psychiatry Res 161(1):116–120. https://doi.org/10.1016/j.psychres.2008.02.011

Paradiso S, Vaidya JG, McCormick LM, Jones A, Robinson RG (2008) Aging and alexithymia: association with reduced right rostral cingulate volume. Am J Geriatr Psychiatry 16(9):760–769. https://doi.org/10.1097/JGP.0b013e31817e73b0

Pennybaker SJ, Niciu MJ, Luckenbaugh DA, Zarate CA (2017) Symptomatology and predictors of antidepressant efficacy in extended responders to a single ketamine infusion. J Affect Disord 208:560–566. https://doi.org/10.1016/j.jad.2016.10.026

Perlis ML, Grandner MA, Brown GK, Basner M, Chakravorty S, Morales KH, Gehrman PR, Chaudhary NS, Thase ME, Dinges DF (2016) Nocturnal wakefulness as a previously unrecognized risk factor for suicide. J Clin Psychiatry 77(6):e726–e733. https://doi.org/10.4088/JCP.15m10131

Perris C (1966) A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. I. Genetic investigation. Acta Psychiatr Scand Suppl 194:15–44

Persons JE, Coryell WH, Solomon DA, Keller MB, Endicott J, Fiedorowicz JG (2017) Mixed state and suicide: is the effect of mixed state on suicidal behavior more than the sum of its parts? Bipolar Disord. https://doi.org/10.1111/bdi.12538

Pfohl B, Stangl D, Zimmerman M (1984) The implications of DSM-III personality disorders for patients with major depression. J Affect Disord 7(3–4):309–318

Pintor L, Torres X, Navarro V, Matrai S, Gasto C (2004) Is the type of remission after a major depressive episode an important risk factor to relapses in a 4-year follow up? J Affect Disord 82(2):291–296. https://doi.org/10.1016/j.jad.2003.11.008

Prusoff BA, Klerman GL, Paykel ES (1972) Concordance between clinical assessments and patients' self-report in depression. Arch Gen Psychiatry 26(6):546–552

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH (2013) A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiat 70(1):31–41. https://doi.org/10.1001/2013.jamapsychiatry.4

Rasmussen SA, Mazurek MF, Rosebush PI (2016) Catatonia: our current understanding of its diagnosis, treatment and pathophysiology. World J Psychiatry 6(4):391

Reddy PL, Khanna S, Subhash MN, Channabasavanna SM, Rao BS (1992) CSF amine metabolites in depression. Biol Psychiatry 31(2):112–118

Rhebergen D, Beekman AT, Rd G, Nolen WA, Spijker J, Hoogendijk WJ, Penninx BW (2009) The three-year naturalistic course of major depressive disorder, dysthymic disorder and double depression. J Affect Disord 115(3):450–459. https://doi.org/10.1016/j.jad.2008.10.018

Rhebergen D, Beekman AT, de Graaf R, Nolen WA, Spijker J, Hoogendijk WJ, Penninx BW (2010) Trajectories of recovery of social and physical functioning in major depression, dysthymic disorder and double depression: a 3-year follow-up. J Affect Disord 124(1–2):148–156. https://doi.org/10.1016/j.jad.2009.10.029

Ruggero CJ, Kotov R, Carlson GA, Tanenberg-Karant M, Gonzalez DA, Bromet EJ (2011) Diagnostic consistency of major depression with psychosis across 10 years. J Clin Psychiatry 72(9):1207–1213. https://doi.org/10.4088/JCP.10m06774

Runeson B, Tidemalm D, Dahlin M, Lichtenstein P, Langstrom N (2010) Method of attempted suicide as predictor of subsequent successful suicide: national long term cohort study. BMJ 341:c3222. https://doi.org/10.1136/bmj.c3222

Rush AJ, Giles DE, Schlesser MA, Fulton CL, Weissenburger J, Burns C (1986) The inventory for depressive symptomatology (IDS): preliminary findings. Psychiatry Res 18(1):65–87

Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH (1996) The inventory of depressive symptomatology (IDS): psychometric properties. Psychol Med 26(3):477–486

Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, Ninan PT, Thase ME, Gelenberg AJ, Kupfer DJ, Regier DA, Rosenbaum JF, Ray O, Schatzberg AF, Force AT (2006) Report by the ACNP task force on response and remission in major depressive disorder. Neuropsychopharmacology 31(9):1841–1853. https://doi.org/10.1038/sj.npp.1301131

Salagre E, Sole B, Tomioka Y, Fernandes BS, Hidalgo-Mazzei D, Garriga M, Jimenez E, Sanchez-Moreno J, Vieta E, Grande I (2017) Treatment of neurocognitive symptoms in unipolar

depression: a systematic review and future perspectives. J Affect Disord 221:205–221. https://doi.org/10.1016/j.jad.2017.06.034

Sanacora G, Mason GF, Rothman DL, Behar KL, Hyder F, Petroff OA, Berman RM, Charney DS, Krystal JH (1999) Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. Arch Gen Psychiatry 56(11):1043–1047

Sanacora G, Gueorguieva R, Epperson CN, Wu YT, Appel M, Rothman DL, Krystal JH, Mason GF (2004) Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. Arch Gen Psychiatry 61(7):705–713. https://doi.org/10.1001/archpsyc.61.7.705

Sarchiapone M, Carli V, Camardese G, Cuomo C, Di Giuda D, Calcagni ML, Focacci C, De Risio S (2006) Dopamine transporter binding in depressed patients with anhedonia. Psychiatry Res 147(2–3):243–248. https://doi.org/10.1016/j.pscychresns.2006.03.001

Sareen J, Cox BJ, Afifi TO, de Graaf R, Asmundson GJ, ten Have M, Stein MB (2005) Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. Arch Gen Psychiatry 62(11):1249–1257. https://doi.org/10.1001/archpsyc.62.11.1249

Schildkraut JJ (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 122(5):509–522

Schildkraut JJ (1967) The catecholamine hypothesis of affective disorders. A review of supporting evidence. Int J Psychiatry 4(3):203–217

Schlesser MA, Winokur G, Sherman BM (1980) Hypothalamic-pituitary-adrenal axis activity in depressive illness. Its relationship to classification. Arch Gen Psychiatry 37(7):737–743

Schuckit MA (1994) Low level of response to alcohol as a predictor of future alcoholism. Am J Psychiatry 151(2):184–189. https://doi.org/10.1176/ajp.151.2.184

Shea MT, Pilkonis PA, Beckham E, Collins JF, Elkin I, Sotsky SM, Docherty JP (1990) Personality disorders and treatment outcome in the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatry 147(6):711–718. https://doi.org/10.1176/ajp.147.6.711

Shepard DS, Gurewich D, Lwin AK, Reed GA Jr, Silverman MM (2016) Suicide and suicidal attempts in the United States: costs and policy implications. Suicide Life Threat Behav 46(3):352–362. https://doi.org/10.1111/sltb.12225

Shors TJ, Seib TB, Levine S, Thompson RF (1989) Inescapable versus escapable shock modulates long-term potentiation in the rat hippocampus. Science 244(4901):224–226

Shorter E (2007) The doctrine of the two depressions in historical perspective. Acta Psychiatr Scand Suppl 433:5–13. https://doi.org/10.1111/j.1600-0447.2007.00957.x

Simon GE, VonKorff M (1995) Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. Epidemiol Rev 17(1):221–227

Singh JB, Fedgchin M, Daly EJ, De Boer P, Cooper K, Lim P, Pinter C, Murrough JW, Sanacora G, Shelton RC, Kurian B, Winokur A, Fava M, Manji H, Drevets WC, Van Nueten L (2016) A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am J Psychiatry 173(8):816–826. https://doi.org/10.1176/appi.ajp.2016.16010037

Spitzer RL, Endicott J, Robins E (1978) Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry 35(6):773–782

Szmulewicz AG, Angriman F, Samame C, Ferraris A, Vigo D, Strejilevich SA (2017) Dopaminergic agents in the treatment of bipolar depression: a systematic review and meta-analysis. Acta Psychiatr Scand 135(6):527–538. https://doi.org/10.1111/acps.12712

Taylor MA, Fink M (2008) Restoring melancholia in the classification of mood disorders. J Affect Disord 105(1–3):1–14. https://doi.org/10.1016/j.jad.2007.05.023

Thamizh JS, Harshini M, Selvakumar N, Bharadwaj B, Menon V (2016) Maintenance lorazepam for treatment of recurrent catatonic states: a case series and implications. Asian J Psychiatr 22:147–149. https://doi.org/10.1016/j.ajp.2016.06.002

Thase ME, Friedman ES (1999) Is psychotherapy an effective treatment for melancholia and other severe depressive states? J Affect Disord 54(1–2):1–19

Trullas R, Skolnick P (1990) Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur J Pharmacol 185(1):1–10

Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ (2004) Global burden of depressive disorders in the year 2000. Br J Psychiatry 184:386–392

Vande Voort JL, Morgan RJ, Kung S, Rasmussen KG, Rico J, Palmer BA, Schak KM, Tye SJ, Ritter MJ, Frye MA, Bobo WV (2016) Continuation phase intravenous ketamine in adults with treatment-resistant depression. J Affect Disord 206:300–304. https://doi.org/10.1016/j.jad.2016.09.008

Vesga-Lopez O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS (2008) Psychiatric disorders in pregnant and postpartum women in the United States. Arch Gen Psychiatry 65(7):805–815. https://doi.org/10.1001/archpsyc.65.7.805

Vinckier F, Gourion D, Mouchabac S (2017) Anhedonia predicts poor psychosocial functioning: results from a large cohort of patients treated for major depressive disorder by general practitioners. Eur Psychiatry 44:1–8. https://doi.org/10.1016/j.eurpsy.2017.02.485

Vogelzangs N, Beekman AT, van Reedt Dortland AK, Schoevers RA, Giltay EJ, de Jonge P, Penninx BW (2014) Inflammatory and metabolic dysregulation and the 2-year course of depressive disorders in antidepressant users. Neuropsychopharmacology 39(7):1624–1634. https://doi.org/10.1038/npp.2014.9

Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Lellouch J, Lepine JP, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H, Yeh EK (1996) Cross-national epidemiology of major depression and bipolar disorder. JAMA 276(4):293–299

Winokur G, Clayton PJ, Reich T (1969) Manic depressive illness. C. V. Mosby, St. Louis 186 pp

Yang T, Dunner DL (2001) Differential subtyping of depression. Depress Anxiety 13(1):11–17

Yoshimasu K, Kiyohara C, Miyashita K, Stress Research Group of the Japanese Society for H (2008) Suicidal risk factors and completed suicide: meta-analyses based on psychological autopsy studies. Environ Health Prev Med 13(5):243–256. https://doi.org/10.1007/s12199-008-0037-x

Zahn R, Lythe KE, Gethin JA, Green S, Deakin JF, Young AH, Moll J (2015) The role of self-blame and worthlessness in the psychopathology of major depressive disorder. J Affect Disord 186:337–341. https://doi.org/10.1016/j.jad.2015.08.001

Zimmerman M, Coryell W, Pfohl B, Corenthal C, Stangl D (1986) ECT response in depressed patients with and without a DSM-III personality disorder. Am J Psychiatry 143(8):1030–1032. https://doi.org/10.1176/ajp.143.8.1030

Zimmerman M, Galione JN, Ruggero CJ, Chelminski I, Dalrymple K, Young D (2010) Overdiagnosis of bipolar disorder and disability payments. J Nerv Ment Dis 198(6):452–454. https://doi.org/10.1097/NMD.0b013e3181e084e1

Zimmermann P, Bruckl T, Nocon A, Pfister H, Lieb R, Wittchen HU, Holsboer F, Angst J (2009) Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. Arch Gen Psychiatry 66(12):1341–1352. https://doi.org/10.1001/archgenpsychiatry.2009.158

Zisook S, Pies R, Iglewicz A (2013) Grief, depression, and the DSM-5. J Psychiatr Pract 19(5):386–396. https://doi.org/10.1097/01.pra.0000435037.91049.2f