Section 1 Introduction

Chapter 1

Models of depression

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Explanatory models of depression are constructed to serve multiple purposes including: (1) helping clinicians organize a body of knowledge to help in patient evaluation and treatment planning, (2) guiding research, and (3) informing about treatment outcome. Models are judged based on various types of validity, including predictive validity regarding prognosis and treatment outcome. Models exist at different levels, from more broad models that apply to all depressed patients, e.g., the gene–environment interaction, to the more specific that explain a particular dimension of the illness, e.g., the association between depression and ischemic heart disease. A model does not have to be comprehensive to be useful; a model may be constructed to understand treatment response or course of illness and have little if any explanatory value with respect to gender difference in rates of illness. A problem for all models of depression is the heterogeneity of the clinical picture of depression, raising the question as to what "depression" or subtype does the model apply? Patients who meet criteria for major depressive disorder (MDD) comprise a heterogeneous group that may share some phenomenology, but probably have disparate illnesses with multiple pathophysiologies. Indeed, biological abnormalities that have been shown to be associated with depression are present in only a moderate proportion of cases, indicating biologic heterogeneity. A model that is relevant for early-onset chronic depression may not be useful when applied to melancholia or "vascular depression." In this chapter we will discuss models of unipolar mood disorder that incorporate both current neuroscience and clinical research. It is hoped that these models will help the clinician both conceptualize the illness of a particular patient and formulate an effective individualized treatment plan.

There has been a long search for the gene or genes that carry the risk of depressive illness and though the research results have, to date, fallen short of this goal, they still have been illuminating and serve as a cornerstone for understanding the genesis of depression. Data come from adoption, twin, family, and population studies. In a meta-analysis of genetic studies of unipolar depression, Sullivan *et al.* (2000) estimated that 37% of the illness is accounted for by genetic factors and other compelling data suggest that the genetic contribution to bipolar disorder is greater than that for unipolar depression. Twin studies consistently report greater concordance rate for monozygotic vs. dizygotic twins, but even in the studies reporting the highest rates of concordance for bipolar disorder in monozygotic twins, they never report 100% concordance (Kendler *et al.* 1993), indicating that epigenetic modification, environment, or a gene interaction with environment must play a significant role in both unipolar and bipolar disorders.

Although genes are an important cause of major depression and bipolar disorder, we have not confirmed the identity of the responsible genes. For example, does genetic vulnerability produce a heightened sense of fear and anxiety so that life is experienced as a series of "stresses," i.e., events, including interpersonal failures and rejections, are experienced as overwhelming and as such ultimately lead to depressive illness? Depression could also result from early environmental deprivation or abusive experiences that produce epigenetic changes and recalibrate stress response systems to be hyper-reactive to stress in adult life. Perhaps the most compelling model is one in which genes and childhood adverse environmental conditions produce a gene–environment interaction that results in a diathesis for a mood disorder.

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There are considerable animal data to support variants of this model. During a critical period in early life, the experience of significant environmental stress, and in early life this primarily means some form of maternal deprivation, induces changes in brain structure that result in a demonstrable heightened reactivity to adverse conditions and specific patterns of behavior throughout adulthood (Hofer, 2003). There are genetic strains of mice that have the vulnerability to anxiety behaviors that are more intensely expressed in adverse environmental conditions. These consequences are reversed in adult mice by the administration of antidepressant medications, most specifically SSRIs (McEwen, 2003).

A major stress response system is the hypothalamic pituitary adrenal (HPA) axis. It is well documented that many patients with severe depression, in particular patients with melancholia or delusional depression, have marked dysfunction in the HPA axis, including loss of normal circadian rhythm of cortisol excretion and high cortisol levels (Nemeroff *et al.* 2002). Furthermore, genes and childhood adverse life events recalibrate such stress response systems in the brain and their components outside the brain. Maternal deprivation in lab animals is a model of early childhood stress and results in hypersensitivity in stress response systems that can persist into adulthood (Gutman and Nemeroff, 2002).

Cross-sectional studies in depressed patients reporting childhood physical or sexual abuse suggest such hyperactive stress responses may also be found in depressed patients (Heim *et al.* 2000, 2001). Severe MDD is associated with higher basal cortisol secretion and higher peak levels, as well as dexamethasone resistance, indicating failure of feedback inhibition at both the higher stimulated cortisol levels and the lower resting cortisol levels. Interestingly, post-traumatic stress disorder (PTSD) is associated with lower basal cortisol and increased glucocorticoid receptor (GCR) expression, indicating that the response to stress can be different in different disorders. In rodent models stress and glucocorticoids reduce neurogenesis and this can be reversed by antidepressant medication administration. Persistently elevated cortisol levels in rodents lead to hippocampal atrophy and both of these phenotypes are seen in moderate to severe depressions in humans. Therefore enhanced cortisol release in MDD may explain smaller hippocampal volume, which in turn has been reported to be proportional to duration of untreated depression lifetime, and progresses with lack of remission of depression (Sheline *et al.* 1999).

Another line of support for this model comes from the studies of humans that appear to demonstrate a gene–environment interaction that results in depression. The best-known example is the report that children exposed to childhood adversity who also carry the lower expressing gene variants of the promoter or regulatory region of the serotonin transporter gene (the target of SSRIs) have an elevated risk of major depression when exposed to stress in their mid-twenties (Caspi *et al.* 2003). Although the finding by Caspi has been both replicated and challenged, it is a compelling illustration of a gene–environment interaction.

The same variant of the serotonin transporter gene favors hyper-responsiveness of the amygdala when matching fearful or angry faces on functional magnetic resonance imaging. A hyperactive amygdala is also reported in PET studies of major depression and this over activity may facilitate encoding of painful memories contributing to stress sensitivity in adulthood and greater likelihood of depression when stressed (Hariri *et al.* 2005). The amygdala is the site where memories and associated affects are encoded. In non-human primates lower expressing serotonin transporter gene variants are associated with reduction of serotonin function in response to maternal deprivation, an effect that persists into adulthood and may explain part of the biologic impact of childhood adversity in the genetically susceptible individuals who are more prone to depression in adulthood (Bennett *et al.* 2002). Patients with MDD, who report childhood adversity, also have lower serotonin transporter binding on PET scanning, and this may be a biological endophenotype associated with a vulnerability to stress-induced MDD.

The fundamental concept of the gene–environment interaction model is that whether a result of genes or early environmental trauma, or both, early life stress results in functional and structural changes in the brain that confer a life-long hyperactive stress response mediated by the HPA axis. Direct genetic effects or purely environmental effects may result in depressions. For example, genes are associated with internalizing disorders or excessive sensitivity to the environment, and the experience of life events as more stressful, reinforcing a negative life experience whose final result is helplessness and despair, i.e., depression. Though much attention has

been given to the enduring impact of early stressful experiences, there are animal models and human stories in which conditions of repeated and unpredictable frustrations result in a state of "learned helplessness," a state that is characterized by behaviors that are associated with depression (Maier, 1984). This represents a model in which depression can result from external or interpersonal experiences in a person who does or does not have a genetic vulnerability to a mood disorder.

Another model of depression focuses on brain structure and neural circuits and asks the question, where in the brain does depression occur? Imaging studies of the depressed brain at baseline (MRI and PET studies), in response to stimuli (fMRI studies), and after treatment (PET and fMRI) have found alterations in structure and/or activity in a number of brain regions in major depression. Mayberg and others have found that MDD is characterized by increased brain activity in many ventral brain structures, including limbic structures, and hypoactivity in dorsal and lateral prefrontal cortex (Mayberg *et al.* 1999). Recovery from an episode of major depression is associated with reversal of much of this picture with changes in brain activity in the direction of that found in healthy volunteers. The disordered neurocircuitry of major depression more specifically includes hypoactivity in the ventral, medial, and dorsolateral prefrontal cortex, the anterior insula, the ventral striatum, the posterior cingulate gyrus, and hippocampus, and hyperactivity in the anterior cingulate cortex (ACC), medial thalamus, amygdala, and brainstem (Milak *et al.* 2005). These brain areas regulate emotional, cognitive, autonomic, sleep, and stress response behaviors, which are all impaired in MDD. Perhaps most intriguing is that a recent study found that children at risk for MDD by virtue of both parents having the illness had characteristic changes in brain structure, specificially cortical thinning (Peterson *et al.* 2009). Most recently deep brain stimulation treatments of patients with treatment-resistant MDD have focused interest on Brodmann area 25. The stimulation of this area by implanted electrodes can have a very swift and remarkable antidepressant effect (Mayberg *et al.* 2005).

Of course locating the areas in the brain that have altered activity in a patient with MDD still leaves unanswered the question of what is dysfunctional in these regions with respect to neurotransmitters, signal transduction, and circuitry. Perhaps the first compelling model of depression was the chatecholamine hyothesis (later extended to the biogenic amine hypothesis) that was formulated based on a limited understanding of the effects of antidepressant medications available in the 1960s (Schildkraut, 1965). This model postulates that depression is caused by a functional decrease in norepinephrine and/or serotonin activity in critical areas of the brain. This decrease may result from a deficiency in the amount of neurotansmitter available, abnormalities in metabolism and/or inadequete receptor response due to fewer receptors or lower receptor sensitivity. The longevity and popularity of this model may be due in large part because it offered an explanation of how antidepresant medications work, that is, TCAs and SSRIs block the reuptake of neurotransmitter from the synaptic cleft and MAOIs block the breakdown of monoamines and both thereby increase activation of postsynaptic receptors. There is a significant body of data that monoamine alterations characterize some depressions and that drugs raising monoamines are therapeutic, whereas depletion of monoamines reverses antidepressant effects, thus supporting the hypothesis. However, the biogenic amine hypothesis as originally stated posits that only two neurotransmitters are involved in MDD, norepinephrine and serotonin, and ignores dopamine, GABA, glutamate, neuropepetides, hormones, etc., and though blockade of neurotransmitter reuptake is an effect of some antidepressant medications, it is only one of several potential antidepressant mechanisms of action. This model also illustrates a potential negative consequence of a model if it is treated as "fact" rather than a useful paradigm. The development of new pharmacological treatments has probably been delayed because this model dictated looking for compounds that block the reuptake of serotonin or norepinephrine (Berton and Nestler, 2006). New antidepressants, such as ketamine, most likely act on other neurotransmitter systems and/or work through novel pathways to achieve antidepressant effects, raising questions about extrapolating from the presumed mechanism of action of a treatment to the pathogenesis of mood disorders. Nonetheless, regardless of how limited or inaccurate, the biogenic monoamine model of depression and the related view of antidepressant action continues to be a useful organizing and testable model that has been the stimulus for much valuable research.

Antidepressants are not the only treatments linked to a model of depression. Effective psychotherapies, whether CBT, IPT, or DBT, all offer a model of depression based on dysfunctional cognitions, relationships

or self-identity as outlined in Chapters 19, 20, and 21 respectively. Results of neuroimaging studies of depressed patients done pre- and post-treatment have led to a model that proposes that psychotherapy treatments for depression work "from top (cortex) down (amagdyla, hippocampus, and other structures) and medications the opposite" (Martin *et al.* 2001, Goldapple *et al.* 2004). Pre- and post-studies of different types of treatment, e.g., medication, psychotherapy, ECT, can provide persuasive data to support models of depressive illness when they can identify changes that only occur in responders, thereby deconstructing a general effect of treatment from the antidepressant mechanism of action. A caveat is that given the presumed heterogeneity in etiology among a group of patients, all of whom meet criteria for MDD, there may be an effect of medication that occurs in all patients, but only has an anitdepressant effect in a sub-group.

Another example of model building is the attempt to understand the relationship between depression and vascular disease. A replicated finding from multiple longitudinal studies is that depression early in life is a risk factor for development of coronary heart disease, the rate of depression in patients following myocardial infarction (MI) is approximately 20%, and an additional 20–25% have significant depressive symptoms (Roose and Krishnan, 2004).

One model has focused on the role of insulin resistance as an important mechanism to explain depression as a risk factor for vascular disease (Musselman *et al.* 2003). The hypercortisolemia associated with depression can induce hyperglycemia and insulin resistance. Furthermore, increased plasma cortisol, as well as other hormone abnormalities associated with depression, specifically decreases secretion of growth hormone and sex steroids, and can lead to increased visceral fat that subsequently contributes to insulin resistance. Once established, insulin resistance promotes hypertension through multiple mechanisms including: (1) increased renal tubular reabsorption of sodium, (2) increased sympathetic activity, and (3) proliferation of vascular smooth muscle. Independent of its stimulation of insulin resistance, visceral fat further promotes vascular damage by activating hepatic secretion of tumor necrosis factor that ultimately leads to an inflammatory process now recognized as a critical component in the pathogenesis of atherosclerosis (Troxler *et al.* 1977, Gold *et al.* 1999). Thus, the physiology of depression, specifically increased cortisol leading to insulin resistance, contributes to vascular damage, which in turn explains why patients with depression are at increased risk for myocardial infarction and stroke.

Although it has long been assumed that the depression follows the cardiac event as reflected in the phrase, "post-MI depression," Glassman *et al.* reported that in 50% of patients the depressive episode preceded the MI (Glassman *et al.* 2000). The physiology of depression may significantly contribute to the development of an ischemic event. Patients with depression have hyperactive platelets. When injury to blood vessel endothelium occurs, such as in patients with atherosclerosis, both platelets and circulating leukocytes attach to exposed sub-endothelial layers. This begins a cascade of events that includes conversion of platelet membrane GPIIB/IIIa complexes into receptors for fibrinogen and release from storage granules of chemotactic factors such as platelet factor 4, beta-thyroglobulin, and serotonin that stimulate other platelets and thereby induce the process of platelet aggregation. Mechanical obstruction secondary to platelet aggregation can play a central role in the development of acute ischemia in patients with atherosclerosis resulting in either MI or stroke. Thus depression can induce platelet activity that in turn contributes to an ischemic event. This sequence is a building block of a model of the relationship between depression and vascular disease in which the stress associated with an MI can lead to depression and equally depression can lead to an MI.

There is also a model of the relationship between late-life depression and cerebrovascular disease that hypothesizes that sub-clinical vascular disease is critical in the genesis of depression in late life (Krishnan *et al.* 2004). The vascular depression hypothesis (see Chapter 9) is that depression can occur as a consequence of structural damage in cortico-striatal circuits due to cerebral ischemia. Structural damage creates a vulnerability to depression and this vulnerability is further influenced by psychosocial risk factors, including negative life events and lack of social support.

Ideally models of mood disorders should have explanatory power, be able to be tested and disproven, help identify potential new treatment targets, and have predictive value for treatment response and prognosis. Perhaps most important, models should advance research and clinical care without inhibiting

innovative thinking to better understand disease pathophysiology, help develop treatments and prevention strategies, and stimulate the formulation of new models.

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Section 1 Introduction

Chapter 2

The diagnosis of mood disorders

Michael B. First and Jean Endicott

Introduction

The diagnosis of mood disorders, like the diagnosis of every other type of mental disorder, is based on a determination of whether a patient's presenting and lifetime symptomatology conforms to the standardized definitions of the various mood disorders included in one of the field's descriptive psychiatric nomenclatures: either the *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition – Text Revision* (DSM-IV-TR) (American Psychiatric Association, 2000) or the *International Classification of Diseases, Tenth Edition* (ICD-10) (World Health Organization, 1992). Clinicians working in the United States invariably rely on the DSM-IV-TR definitions, whereas clinicians working in most parts of the rest of the world use the definitions contacted in the ICD-10 (Reed *et al.* 2011). Researchers, regardless of where they are working, generally use the DSM-IV-TR definitions. Mood disorders in both of these systems are defined in terms of "syndromes," i.e., clusters of symptoms that co-occur. An overarching presumption has been that symptom co-occurrence within a syndrome reflects a common underlying pathophysiological process (or processes) that, with sufficient research efforts, can be elucidated and that will eventually form the basis for a more "objective" method for diagnosing mood disorders. Unfortunately, despite great efforts over the past 30 years and despite several initially promising candidates, such as the dexamethasone suppression test (The APA Task Force on Laboratory Tests in Psychiatry, 1987), not a single biomarker has been found that is useful in making a mood disorder diagnosis. Thus, for now and the foreseeable future, the diagnosis of mood disorders will continue to rely on a careful clinical assessment of the patient's signs, symptoms, and past history.

Basis for the organization of mood disorders in DSM

Unlike most other disorders which are defined in terms of self-contained criteria sets in DSM-IV-TR, the diagnostic criteria for mood disorders include separate uncoded criteria sets for mood episodes (i.e., major depressive episode, hypomanic episode, manic episode, and mixed episode) and coded criteria sets for mood disorders (i.e., major depressive disorder, dysthymic disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance-induced mood disorder, and mood disorder due to a general medical condition), which for the most part are expressed in terms of the mood episode criteria sets. Moreover, the adoption of a "lumping" rather than "splitting" strategy for the mood disorders (a strategy which is being continued in DSM-5) involves the extensive use of specifiers in order to define sub-groups of patients with mood disorders that might share a common treatment response pattern (e.g., seasonal pattern to indicate efficacy of light therapy) or possibly common pathophysiology (e.g., melancholic features).

Episodes vs. disorders

Historically, mood disorders occur in episodes of mood disturbance that are punctuated by periods of relatively symptom-free intervals of high functioning. Largely based on common treatment response patterns and family history, mood disorders have been divided into those that are characterized exclusively by episodes of depressed mood (so-called "unipolar depression") and those characterized by episodes of both depressed mood and mania ("bipolar depression"). Given the episodic nature of mood disorders, the basic "building blocks" of the mood disorders are

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mood episodes, as these embody the syndromal nature of these disorders. Accordingly, the major organizational division in the Mood Disorders chapter in DSM-IV is between Mood Episodes, which come first, followed by Mood Disorders. Reflecting its position as one of the most common psychiatric presentations seen by mental health professionals, the criteria for major depressive episode come first, followed by the criteria for manic episode, mixed episode, and hypomanic episode. The definitions of mood episodes are then followed by the definitions of the mood disorders, with depressive disorders coming first (again reflecting their relative commonality), followed by the criteria sets for bipolar disorders, substance-induced mood disorder and mood disorder due to a general medical condition. Since the mood episodes cannot be diagnosed on their own as free-standing diagnostic entities, there are no diagnostic codes associated with them.

Extensive use of specifiers for diagnostic homogeneity

There are two basic classificatory strategies that apply when deciding on the organization of diagnostic entities "lumping" and "splitting." A "lumping" strategy prefers relatively fewer diagnostic entities that are defined relatively broadly and heterogeneously, with the assumption that differences among cases are not as important as their commonalities in terms of understanding their etiology or selecting treatment. In contrast, a "splitting" strategy favors many more narrowly defined entities, with the assumption that the differences between cases are more important than their similarities in terms of defining etiologically and therapeutically homogeneous entities.

The adoption of a lumping strategy for mood disorders, particularly for classifying depressive disorders, reflects the perspective of depression as a unitary construct that represents a final common pathway derived from a variety of etiological and pathophysiological sources (Akiskal and McKinney, 1975), which "accounts for the shared clinical features seen in the heterogeneous groups of depressive disorders" (p. 300). Thus, starting with the first set of diagnostic criteria proposed for research (Feighner *et al.* 1972), continuing with the DSM-III (American Psychiatric Association, 1980), and subsequent DSM revisions, all episodes of clinical depression are defined using the same set of descriptive criteria, even those occurring in the context of bipolar disorder as opposed to major depressive disorder, despite evidence of heterogeneity in terms of pathophysiological mechanisms and treatment response.

As noted in the introduction to the DSM, its "highest priority has been to provide a helpful guide to clinical practice" (American Psychiatric Association, 2000, p. xxiii). One of the most important aspects of clinical utility is facilitating treatment selection. If it were the case that simply meeting the diagnostic criteria for a disorder like depression or bipolar disorder would be sufficient to determine the optimal treatment, then having a single unitary diagnosis of major depression or bipolar disorder would suffice. However, the long-recognized inconsistent response to various treatment options suggests the value of identifying sub-groups of cases that are more likely to respond to a specific treatment based on severity, phenomenological course, and other factors. DSM-IV thus encourages the use of multiple specifiers to describe the various aspects of the patient's mood disorder presentation in order to help with treatment selection. Fifteen different specifiers are provided in DSM-IV, more than for any other section of the DSM, with several additional specifiers (e.g., with mixed features, with anxious distress level of concern for suicide planned for DSM-5. While this approach has the advantage of providing clinicians with maximum flexibility in terms of allowing them to optionally specify the various important clinical features of the mood presentation, it has the disadvantage that, with the exception of severity, psychosis, and episode type, these specifiers cannot be reflected in the diagnostic coding system so that there is no way this information can be captured in most data systems.

Definitions of mood episodes in DSM-IV

Major depressive episode

A diagnosis of a major depressive episode (MDE) is made by recognizing the characteristic syndrome of symptoms that cluster together during the same period of time. There are two orthogonal dimensions to the major depressive syndrome: the number of characteristic symptoms and the duration/persistence of these symptoms. Nine symptom criteria are included in the syndrome, some of which are compound in the sense that they include several different possible symptoms, only one of which is required for that criterion to be

met: (1) depressed mood, (2) diminished interest or pleasure in all or almost all activities, (3) significant increase in appetite or increase in weight or significant decrease in appetite or weight, (4) insomnia or hypersomnia, (5) psychomotor agitation or psychomotor retardation, (6) fatigue or low energy, (7) feelings of worthlessness or excessive or inappropriate guilt, (8) diminished ability to think or indecisiveness, and (9) recurrent thoughts of death, suicidal ideation, or a suicide attempt. DSM-IV sets a diagnostic threshold of at least five out of these nine criteria, which must co-occur during the same period of time. Moreover, DSM-IV elevates two of these symptoms, depressed mood and diminished interest or pleasure to a position of special importance in the diagnosis of a depressive episode; one of these two must be part of the syndrome. This reflects the conventional wisdom that depressed mood should be a required element of a depressive episode. However, given that some individuals with depression (around 20%) do not report feeling sad, depressed, or tearful during an episode, a "depressive-equivalent," i.e., diminished interest in activities, is offered as an alternative. For the temporal dimension, 2 weeks has been chosen as the minimum duration for the symptoms in order to be considered an episode of clinical depression. Moreover, the symptoms have to be present nearly every day during this minimum 2-week period.

The individual symptom criteria in DSM-IV have purposely been worded in such a way as to emphasize the severity of each item. For example, the diminished interest or pleasure in criterion (2) must be "marked," weight loss or gain in criterion (3) must be "significant," psychomotor agitation or retardation in criter ion (5) must be sufficiently severe to be noticeable to others, and the feelings about oneself in criterion (7) have to rise to the level of worthlessness. A common error in the diagnosis of a major depressive episode is to stretch the diagnostic threshold so that it includes milder cases than intended by the diagnostic criteria; this has potential clinical implications, given the evidence that somatic treatments tend to be effective in more severe cases.

It should be noted that the threshold of five symptoms and the duration requirement of 2 weeks were not based on empirical evidence of any kind of discontinuity of zone or rarity (Kendell, 1989) that demarcates cases with four or fewer symptoms vs. five or more symptoms, or episodes of less than 2 weeks duration vs. episodes of more than 2 weeks duration. These thresholds were based on expert consensus that these thresholds defined a level of severity and persistence that would be reasonable to consider "disordered." However, many cases with three or four symptoms may be as ill as cases with five or more symptoms. Further complicating matters, doing a straight symptom count to define disorder as the DSM calls for ignores the reality that different symptoms may have inherently different severities or have differential impact on the need for treatment. For example, a case with only three symptoms but each one at a severe level (e.g., severe suicidal ideation, depressed mood, and inability to sleep) may be more severe than another case with five symptoms, but each of lesser severity. However, despite the potential negative impact of fixed thresholds on validity, their use has been shown to improve diagnostic reliability, especially in research settings. Clinicians using the DSM thresholds should exercise clinical judgment in their application and should view the duration and severity thresholds more as rules of thumb rather than as strict cutoffs to be applied rigidly. As noted in the introductory sections of the DSM-IV-TR, "the specific diagnostic criteria included in DSM-IV are meant to serve as guidelines to be informed by clinical judgment and are not meant to be used in a cookbook fashion. For example, the exercise of clinical judgment may justify giving a certain diagnosis to an individual even though the clinical presentation falls just short of meeting the full criteria for the diagnosis as long as the symptoms that are present are persistent and severe" (p. xxxii).

In addition to the syndromal requirements, the DSM-IV-TR definition has additional requirements to help differentiate between normal sadness and clinical depression. The first requirement is that the cluster of symptoms "cause clinically significant distress or impairment in social, occupational, or other important areas of functioning" (p. 356). Given that many of the symptoms that comprise a major depressive episode (e.g., insomnia, depressed mood, difficulty concentrating) can occur in individuals experiencing normal sadness, this "clinical significance criterion" has been added to the criteria set for a major depressive episode (as well as over 70% of the other disorders in DSM-IV) to help communicate to the clinician that the symptoms should be sufficiently severe so as to have a significant negative impact on the person's life. The other criterion that is intended to avoid inappropriately diagnosing normal individuals as suffering from clinical depression is

known as the "bereavement exclusion," which has been a part of the definition since DSM-III. It has long been recognized that individuals experiencing a normal grief reaction may experience many of the nine symptoms included in the definition of a major depressive episode (Clayton *et al.* 1971). In order to prevent normally grieving individuals who happen to have enough major-depressive-like symptoms to meet criteria for an MDE from being diagnosed as clinically depressed, the clinician is instructed *not* to give the diagnosis of MDE to such individuals unless there is evidence that the pattern or duration of the depressive symptoms is no longer consistent with a normal grief reaction, i.e., if the episode persists for longer than two months or certain uncharacteristic features such as morbid preoccupation with worthlessness, psychosis, suicidal ideation, psychomotor retardation, or marked functional impairment are present. This "exception" to the bereavement exclusion is important because for susceptible individuals, the loss of a loved one can trigger the development of a bona fide depressive episode needing psychiatric management.

One of the more controversial changes for DSM-5 is the elimination of the bereavement exclusion so that all cases that meet the syndromal requirement for a major depressive episode be given the diagnosis regardless of the context. This change was put forth on two grounds. First of all, several studies (Wakefield *et al.* 2007, Kendler *et al.* 2008) have suggested that episodes meeting syndromal criteria for a major depressive episode following loss of the loved one are no different than episodes following other severe losses such as divorce or job termination. Secondly, the validity of the bereavement exclusion has been challenged based on review articles which contend that bereavement-related depression is no different than other types of depression (Zisook *et al.* 2007, Lamb *et al.* 2010). Wakefield and First (2012), however, challenged the validity of these review articles, noting that the studies cited in the review article do not actually support the lack of validity of the bereavement exclusion and that two reanalyses of large epidemiological studies (Mojtabai, 2011, Wakefield and Schmitz, 2012) actually support its validity.

Two additional requirements are included in the definition to help differentiate a major depressive episode from other DSM-IV conditions also characterized by clinically significant depressed mood. First of all, following a system-wide DSM convention requiring that psychiatric symptoms that are due to a neurological or systemic general medical condition or that are due to the direct effects of a substance on the central nervous system be given a different diagnosis, the definition of an MDE has a criterion which excludes these etiologies ("the symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)"). In such situations the diagnosis would be a substance-induced mood disorder or a mood disorder due to a general medical condition. Finally, the definition also requires that the "criteria not be met for a mixed episode," which is a type of manic episode in which the criteria are simultaneously met for a manic and major depressive episode at the same time (see Mixed episode below). This is needed to prevent the clinician from mistakenly making the diagnosis of a major depressive episode without considering whether the criteria are also simultaneously met for a manic episode, thus justifying a diagnosis of mixed episode.

Manic episode/hypomanic episode

The hallmark of manic and hypomanic episodes is a discrete period of abnormally elevated, euphoric, expansive, or irritable mood that persists for at least a week in the case of mania or at least 4 days in the case of hypomania. Accompanying the elevated or irritable mood are a set of symptoms including inflated self-esteem or grandiosity, decreased need for sleep (for example, sleeping less than 3 hours yet still feeling rested), pressured speech, flight of ideas, distractibility to external stimuli, increase in social/sexual or occupational/academic activities or psychomotor agitation, and excessive involvement in pleasurable activities that have a high potential for painful consequences that the person ignores (e.g., making foolish business investments, going on unrestrained buying sprees). Unusual for DSM-IV, two different symptom thresholds are offered, depending on whether the mania is characterized by euphoric mood, in which case at least three symptoms must co-occur, or whether there is only irritable mood in which case a minimum of four symptoms are needed for the diagnosis. This requirement for an additional symptom was put into place to help differentiate irritable forms of mania from the irritability that often accompanies a depressive episode. In particular, while it is conceivable that an individual in a depressive episode might experience distractibility, psychomotor agitation, and