Depressive Disorders

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Sections

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Excerpt

Depressive disorders include disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. Unlike in DSM-IV, this chapter “Depressive Disorders” has been separated from the previous chapter “Bipolar and Related Disorders.” The common feature of all of these disorders is the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual’s capacity to function. What differs among them are issues of duration, timing, or presumed etiology.

SECTION QUICK LINKS

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In order to address concerns about the potential for the overdiagnosis of and treatment for bipolar disorder in children, a new diagnosis, disruptive mood dysregulation disorder, referring to the presentation of children with persistent irritability and frequent episodes of extreme behavioral dyscontrol, is added to the depressive disorders for children up to 12 years of age. Its placement in this chapter reflects the finding that children with this symptom pattern typically develop unipolar depressive disorders or anxiety disorders, rather than bipolar disorders, as they mature into adolescence and adulthood.

Major depressive disorder represents the classic condition in this group of disorders. It is characterized by discrete episodes of at least 2 weeks’ duration (although most episodes last considerably longer) involving clear-cut changes in affect, cognition, and neurovegetative functions and inter-episode remissions. A diagnosis based on a single episode is possible, although the disorder is a recurrent one in the majority of cases. Careful consideration is given to the delineation of normal sadness and grief from a major depressive episode. Bereavement may induce great suffering, but it does not typically induce an episode of major depressive disorder. When they do occur together, the depressive symptoms and functional impairment tend to be more severe and the prognosis is worse compared

with bereavement that is not accompanied by major depressive disorder. Bereavement-related depression tends to occur in persons with other vulnerabilities to depressive disorders, and recovery may be facilitated by antidepressant treatment.

A more chronic form of depression, persistent depressive disorder (dysthymia), can be diagnosed when the mood disturbance continues for at least 2 years in adults or 1 year in children. This diagnosis, new in DSM-5, includes both the DSM-IV diagnostic categories of chronic major depression and dysthymia.

After careful scientific review of the evidence, premenstrual dysphoric disorder has been moved from an appendix of DSM-IV ("Criteria Sets and Axes Provided for Further Study") to Section II of DSM-5. Almost 20 years of additional research on this condition has confirmed a specific and treatment-responsive form of depressive disorder that begins sometime following ovulation and remits within a few days of menses and has a marked impact on functioning.

A large number of substances of abuse, some prescribed medications, and several medical conditions can be associated with depression-like phenomena. This fact is recognized in the diagnoses of substance/medication-induced depressive disorder and depressive disorder due to another medical condition.

Disruptive Mood Dysregulation Disorder

Diagnostic Criteria

296.99 (F34.8)

1. Severe recurrent temper outbursts manifested verbally (e.g., verbal rages) and/or behaviorally (e.g., physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.
2. The temper outbursts are inconsistent with developmental level.
3. The temper outbursts occur, on average, three or more times per week.
4. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).
5. Criteria A–D have been present for 12 or more months. Throughout that time, the individual has not had a period lasting 3 or more consecutive months without all of the symptoms in Criteria A–D.
6. Criteria A and D are present in at least two of three settings (i.e., at home, at school, with peers) and are severe in at least one of these.
7. The diagnosis should not be made for the first time before age 6 years or after age 18 years.
8. By history or observation, the age at onset of Criteria A–E is before 10 years.
9. There has never been a distinct period lasting more than 1 day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.
    - **Note:** Developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation, and should not be considered as a symptom of mania or hypomania.
10. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by another mental disorder (e.g., autism spectrum disorder, posttraumatic stress disorder, separation anxiety disorder, persistent depressive disorder [dysthymia]).
    - **Note:** This diagnosis cannot coexist with oppositional defiant disorder, intermittent explosive disorder, or bipolar disorder, though it can coexist with others, including major depressive disorder, attention-deficit/hyperactivity disorder, conduct disorder, and substance use disorders. Individuals whose symptoms meet criteria for both disruptive mood dysregulation disorder and oppositional defiant disorder should only be given the diagnosis of disruptive mood dysregulation disorder. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of disruptive mood dysregulation disorder should not be assigned.
11. The symptoms are not attributable to the physiological effects of a substance or to another medical or neurological condition.

Diagnostic Features

The core feature of disruptive mood dysregulation disorder is chronic, severe persistent irritability. This severe irritability has two prominent clinical manifestations, the first of which is frequent temper outbursts. These outbursts typically occur in response to frustration and can be verbal or behavioral (the latter in the form of aggression against property, self, or others). They must occur frequently (i.e., on average, three or more times per week) (Criterion C) over at least 1 year in at least two settings (Criteria E and F), such as in the home and at school, and they must be developmentally inappropriate

(Criterion B). The second manifestation of severe irritability consists of chronic, persistently irritable or angry mood that is present between the severe temper outbursts. This irritable or angry mood must be characteristic of the child, being present most of the day, nearly every day, and noticeable by others in the child's environment (Criterion D).

The clinical presentation of disruptive mood dysregulation disorder must be carefully distinguished from presentations of other, related conditions, particularly pediatric bipolar disorder. In fact, disruptive mood dysregulation disorder was added to DSM-5 to address the considerable concern about the appropriate classification and treatment of children who present with chronic, persistent irritability relative to children who present with classic (i.e., episodic) bipolar disorder.

Some researchers view severe, non-episodic irritability as characteristic of bipolar disorder in children, although both DSM-IV and DSM-5 require that both children and adults have distinct episodes of mania or hypomania to qualify for the diagnosis of bipolar I disorder. During the latter decades of the 20th century, this contention by researchers that severe, non-episodic irritability is a manifestation of pediatric mania coincided with an upsurge in the rates at which clinicians assigned the diagnosis of bipolar disorder to their pediatric patients. This sharp increase in rates appears to be attributable to clinicians combining at least two clinical presentations into a single category. That is, both classic, episodic presentations of mania and non-episodic presentations of severe irritability have been labeled as bipolar disorder in children. In DSM-5, the term *bipolar disorder* is explicitly reserved for episodic presentations of bipolar symptoms. DSM-IV did not include a diagnosis designed to capture youths whose hallmark symptoms consisted of very severe, non-episodic irritability, whereas DSM-5, with the inclusion of disruptive mood dysregulation disorder, provides a distinct category for such presentations.

Prevalence

Disruptive mood dysregulation disorder is common among children presenting to pediatric mental health clinics. Prevalence estimates of the disorder in the community are unclear. Based on rates of chronic and severe persistent irritability, which is the core feature of the disorder, the overall 6-month to 1-year period-prevalence of disruptive mood dysregulation disorder among children and adolescents probably falls in the 2%–5% range. However, rates are expected to be higher in males and school-age children than in females and adolescents.

Development and Course

The onset of disruptive mood dysregulation disorder must be before age 10 years, and the diagnosis should not be applied to children with a developmental age of less than 6 years. It is unknown whether the condition presents only in this age-delimited fashion. Because the symptoms of disruptive mood dysregulation disorder are likely to change as children mature, use of the diagnosis should be restricted to age groups similar to those in which validity has been established (7–18 years). Approximately half of children with severe, chronic irritability will have a presentation that continues to meet criteria for the condition 1 year later. Rates of conversion from severe, nonepisodic irritability to bipolar disorder are very low. Instead, children with chronic irritability are at risk to develop unipolar depressive and/or anxiety disorders in adulthood.

Age-related variations also differentiate classic bipolar disorder and disruptive mood dysregulation disorder. Rates of bipolar disorder generally are very low prior to adolescence (<1%), with a steady increase into early adulthood (1%–2% prevalence). Disruptive mood dysregulation disorder is more common than bipolar disorder prior to adolescence, and symptoms of the condition generally become less common as children transition into adulthood.

Risk and Prognostic Factors

Temperamental

Children with chronic irritability typically exhibit complicated psychiatric histories. In such children, a relatively extensive history of chronic irritability is common, typically manifesting before full criteria for the syndrome are met. Such pre-diagnostic presentations may have qualified for a diagnosis of oppositional defiant disorder. Many children with disruptive mood dysregulation disorder have symptoms that also meet criteria for attention-deficit/hyperactivity disorder (ADHD) and for an anxiety disorder, with such diagnoses often being present from a relatively early age. For some children, the criteria for major depressive disorder may also be met.

Genetic and physiological

In terms of familial aggregation and genetics, it has been suggested that children presenting with chronic, non-episodic irritability can be differentiated from children with bipolar disorder in their family-

based risk. However, these two groups do not differ in familial rates of anxiety disorders, unipolar depressive disorders, or substance abuse. Compared with children with pediatric bipolar disorder or other mental illnesses, those with disruptive mood dysregulation disorder exhibit both commonalities and differences in information-processing deficits. For example, face-emotion labeling deficits, as well as perturbed decision making and cognitive control, are present in children with bipolar disorder and chronically irritable children, as well as in children with some other psychiatric conditions. There is also evidence for disorder-specific dysfunction, such as during tasks assessing attention deployment in response to emotional stimuli, which has demonstrated unique signs of dysfunction in children with chronic irritability.

Gender-Related Diagnostic Issues

Children presenting to clinics with features of disruptive mood dysregulation disorder are predominantly male. Among community samples, a male preponderance appears to be supported. This difference in prevalence between males and females differentiates disruptive mood dysregulation disorder from bipolar disorder, in which there is an equal gender prevalence.

Suicide Risk

In general, evidence documenting suicidal behavior and aggression, as well as other severe functional consequences, in disruptive mood dysregulation disorder should be noted when evaluating children with chronic irritability.

Functional Consequences of Disruptive Mood Dysregulation Disorder

Chronic, severe irritability, such as is seen in disruptive mood dysregulation disorder, is associated with marked disruption in a child's family and peer relationships, as well as in school performance. Because of their extremely low frustration tolerance, such children generally have difficulty succeeding in school; they are often unable to participate in the activities typically enjoyed by healthy children; their family life is severely disrupted by their outbursts and irritability; and they have trouble initiating or sustaining friendships. Levels of dysfunction in children with bipolar disorder and disruptive mood dysregulation disorder are generally comparable. Both conditions cause severe disruption in the lives of the affected individual and their families. In both disruptive mood dysregulation disorder and pediatric bipolar disorder, dangerous behavior, suicidal ideation or suicide attempts, severe aggression, and psychiatric hospitalization are common.

Differential Diagnosis

Because chronically irritable children and adolescents typically present with complex histories, the diagnosis of disruptive mood dysregulation disorder must be made while considering the presence or absence of multiple other conditions. Despite the need to consider many other syndromes, differentiation of disruptive mood dysregulation disorder from bipolar disorder and oppositional defiant disorder requires particularly careful assessment.

Bipolar disorders

The central feature differentiating disruptive mood dysregulation disorder and bipolar disorders in children involves the longitudinal course of the core symptoms. In children, as in adults, bipolar I disorder and bipolar II disorder manifest as an episodic illness with discrete episodes of mood perturbation that can be differentiated from the child's typical presentation. The mood perturbation that occurs during a manic episode is distinctly different from the child's usual mood. In addition, during a manic episode, the change in mood must be accompanied by the onset, or worsening, of associated cognitive, behavioral, and physical symptoms (e.g., distractibility, increased goal-directed activity), which are also present to a degree that is distinctly different from the child's usual baseline. Thus, in the case of a manic episode, parents (and, depending on developmental level, children) should be able to identify a distinct time period during which the child's mood and behavior were markedly different from usual. In contrast, the irritability of disruptive mood dysregulation disorder is persistent and is present over many months; while it may wax and wane to a certain degree, severe irritability is characteristic of the child with disruptive mood dysregulation disorder. Thus, while bipolar disorders are episodic conditions, disruptive mood dysregulation disorder is not. In fact, the diagnosis of disruptive mood dysregulation disorder cannot be assigned to a child who has ever experienced a full-duration hypomanic or manic episode (irritable or euphoric) or who has ever had a manic or hypomanic episode lasting more than 1 day. Another central differentiating feature between bipolar disorders and disruptive mood dysregulation disorder is the presence of elevated or expansive mood and grandiosity. These symptoms are common features of mania but are not characteristic of disruptive mood dysregulation disorder.

Oppositional defiant disorder

While symptoms of oppositional defiant disorder typically do occur in children with disruptive mood dysregulation disorder, mood symptoms of disruptive mood dysregulation disorder are relatively rare in children with oppositional defiant disorder. The key features that warrant the diagnosis of disruptive mood dysregulation disorder in children whose symptoms also meet criteria for oppositional defiant disorder are the presence of severe and frequently recurrent outbursts and a persistent disruption in mood between outbursts. In addition, the diagnosis of disruptive mood dysregulation disorder requires severe impairment in at least one setting (i.e., home, school, or among peers) and mild to moderate impairment in a second setting. For this reason, while most children whose symptoms meet criteria for disruptive mood dysregulation disorder will also have a presentation that meets criteria for oppositional defiant disorder, the reverse is not the case. That is, in only approximately 15% of individuals with oppositional defiant disorder would criteria for disruptive mood dysregulation disorder be met? Moreover, even for children in whom criteria for both disorders are met, only the diagnosis of disruptive mood dysregulation disorder should be made. Finally, both the prominent mood symptoms in disruptive mood dysregulation disorder and the high risk for depressive and anxiety disorders in follow-up studies justify placement of disruptive mood dysregulation disorder among the depressive disorders in DSM-5. (Oppositional defiant disorder is included in the chapter “Disruptive, Impulse-Control, and Conduct Disorders.”) This reflects the more prominent mood component among individuals with disruptive mood dysregulation disorder, as compared with individuals with oppositional defiant disorder. Nevertheless, it also should be noted that disruptive mood dysregulation disorder appears to carry a high risk for behavioral problems as well as mood problems.

Attention-deficit/hyperactivity disorder, major depressive disorder, anxiety disorders, and autism spectrum disorder

Unlike children diagnosed with bipolar disorder or oppositional defiant disorder, a child whose symptoms meet criteria for disruptive mood dysregulation disorder also can receive a comorbid diagnosis of ADHD, major depressive disorder, and/or anxiety disorder. However, children whose irritability is present only in the context of a major depressive episode or persistent depressive disorder (dysthymia) should receive one of those diagnoses rather than disruptive mood dysregulation disorder. Children with disruptive mood dysregulation disorder may have symptoms that also meet criteria for an anxiety disorder and can receive both diagnoses, but children whose irritability is manifest only in the context of exacerbation of an anxiety disorder should receive the relevant anxiety disorder diagnosis rather than disruptive mood dysregulation disorder. In addition, children with autism spectrum disorders frequently present with temper outbursts when, for example, their routines are disturbed. In that instance, the temper outbursts would be considered secondary to the autism spectrum disorder, and the child should not receive the diagnosis of disruptive mood dysregulation disorder.

Intermittent explosive disorder

Children with symptoms suggestive of intermittent explosive disorder present with instances of severe temper outbursts, much like children with disruptive mood dysregulation disorder. However, unlike disruptive mood dysregulation disorder, intermittent explosive disorder does not require persistent disruption in mood between outbursts. In addition, intermittent explosive disorder requires only 3 months of active symptoms, in contrast to the 12-month requirement for disruptive mood dysregulation disorder. Thus, these two diagnoses should not be made in the same child. For children with outbursts and intercurrent, persistent irritability, only the diagnosis of disruptive mood dysregulation disorder should be made.

Comorbidity

Rates of comorbidity in disruptive mood dysregulation disorder are extremely high. It is rare to find individuals whose symptoms meet criteria for disruptive mood dysregulation disorder alone. Comorbidity between disruptive mood dysregulation disorder and other DSM-defined syndromes appears higher than for many other pediatric mental illnesses; the strongest overlap is with oppositional defiant disorder. Not only is the overall rate of comorbidity high in disruptive mood dysregulation disorder, but also the range of comorbid illnesses appears particularly diverse. These children typically present to the clinic with a wide range of disruptive behavior, mood, anxiety, and even autism spectrum symptoms and diagnoses. However, children with disruptive mood dysregulation disorder should not have symptoms that meet criteria for bipolar disorder, as in that context, only the bipolar disorder diagnosis should be made. If children have symptoms that meet criteria for oppositional defiant disorder or intermittent explosive disorder *and* disruptive mood dysregulation disorder, only the diagnosis of disruptive mood dysregulation disorder should be assigned. Also, as noted earlier, the diagnosis of disruptive mood dysregulation disorder should not be assigned if the symptoms occur only in an anxiety-provoking context, when the routines of a child with autism spectrum disorder or obsessive-compulsive disorder are disturbed, or in the context of a major depressive episode.

Major Depressive Disorder

Diagnostic Criteria

1. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
    - **Note:** Do not include symptoms that are clearly attributable to another medical condition.
    1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, and hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
    2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
    3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
    4. Insomnia or hypersomnia nearly every day.
    5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
    6. Fatigue or loss of energy nearly every day.
    7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
    8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
    9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
2. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
3. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A–C represent a major depressive episode.
Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.
In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in MDE. In grief, self-esteem is generally preserved, whereas in MDE feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about "joining" the deceased, whereas in MDE such thoughts are focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression.

4. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
5. There has never been a manic episode or a hypomanic episode.

- **Note:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Coding and Recording Procedures

- The diagnostic code for major depressive disorder is based on whether this is a single or recurrent episode, current severity, presence of psychotic features, and remission status. Current severity and psychotic features are only indicated if full criteria are currently met for a major depressive episode. Remission specifiers are only indicated if the full criteria are not currently met for a major depressive episode. Codes are as follows:

Severity/course specifier	Single episode	Recurrent episode*
Mild (p. 188)	**296.21 (F32.0)**	**296.31 (F33.0)**
Moderate (p. 188)	**296.22 (F32.1)**	**296.32 (F33.1)**
Severe (p. 188)	**296.23 (F32.2)**	**296.33 (F33.2)**
With psychotic features (p. 186)**	**296.24 (F32.3)**	**296.34 (F33.3)**
In partial remission (p. 188)	**296.25 (F32.4)**	**296.35 (F33.41)**
In full remission (p. 188)	**296.26 (F32.5)**	**296.36 (F33.42)**
Unspecified	**296.20 (F32.9)**	**296.30 (F33.9)**
*For an episode to be considered recurrent, there must be an interval of at least 2 consecutive months between separate episodes in which criteria are not met for a major depressive episode. The definitions of specifiers are found on the indicated pages. **If psychotic features are present, code the "with psychotic features" specifier irrespective of episode severity.		

- In recording the name of a diagnosis, terms should be listed in the following order: major depressive disorder, single or recurrent episode, severity/psychotic/remission specifiers, followed by as many of the following specifiers without codes that apply to the current episode.

Specify:

- **With anxious distress** (p. 184)
- **With mixed features** (pp. 184–185)
- **With melancholic features** (p. 185)
- **With atypical features** (pp. 185–186)
- **With mood-congruent psychotic features** (p. 186)
- **With mood-incongruent psychotic features** (p. 186)
- **With catatonia** (p. 186). **Coding note:** Use additional code 293.89 (F06.1).
- **With peripartum onset** (pp. 186–187)
- **With seasonal pattern** (recurrent episode only) (pp. 187–188)

Diagnostic Features

The criterion symptoms for major depressive disorder must be present nearly every day to be considered present, with the exception of weight change and suicidal ideation. Depressed mood must be present for most of the day, in addition to being present nearly every day. Often insomnia or fatigue is the presenting complaint, and failure to probe for accompanying depressive symptoms will result in underdiagnosis. Sadness may be denied at first but may be elicited through interview or inferred from facial expression and demeanor. With individuals who focus on a somatic complaint, clinicians should determine whether the distress from that complaint is associated with specific depressive symptoms. Fatigue and sleep disturbance are present in a high proportion of cases; psychomotor disturbances are much less common but are indicative of greater overall severity, as is the presence of delusional or near-delusional guilt.

The essential feature of a major depressive episode is a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities (Criterion A). In children and adolescents, the mood may be irritable rather than sad. The individual must also experience at least four additional symptoms drawn from a list that includes changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation or suicide plans or attempts. To count toward a major depressive episode, a symptom must either be newly present or must have clearly worsened compared with the person's pre-episode status. The symptoms must persist for most of the day, nearly every day, for at least 2 consecutive weeks. The episode must be accompanied by clinically significant distress or impairment in social, occupational, or

other important areas of functioning. For some individuals with milder episodes, functioning may appear to be normal but requires markedly increased effort.

The mood in a major depressive episode is often described by the person as depressed, sad, hopeless, discouraged, or “down in the dumps” (Criterion A1). In some cases, sadness may be denied at first but may subsequently be elicited by interview (e.g., by pointing out that the individual looks as if he or she is about to cry). In some individuals who complain of feeling “blah,” having no feelings, or feeling anxious, the presence of a depressed mood can be inferred from the person’s facial expression and demeanor. Some individuals emphasize somatic complaints (e.g., bodily aches and pains) rather than reporting feelings of sadness. Many individuals report or exhibit increased irritability (e.g., persistent anger, a tendency to respond to events with angry outbursts or blaming others, an exaggerated sense of frustration over minor matters). In children and adolescents, an irritable or cranky mood may develop rather than a sad or dejected mood. This presentation should be differentiated from a pattern of irritability when frustrated.

Loss of interest or pleasure is nearly always present, at least to some degree. Individuals may report feeling less interested in hobbies, “not caring anymore,” or not feeling any enjoyment in activities that were previously considered pleasurable (Criterion A2). Family members often notice social withdrawal or neglect of pleasurable avocations (e.g., a formerly avid golfer no longer plays, a child who used to enjoy soccer finds excuses not to practice). In some individuals, there is a significant reduction from previous levels of sexual interest or desire.

Appetite change may involve either a reduction or increase. Some depressed individuals report that they have to force themselves to eat. Others may eat more and may crave specific foods (e.g., sweets or other carbohydrates). When appetite changes are severe (in either direction), there may be a significant loss or gain in weight, or, in children, a failure to make expected weight gains may be noted (Criterion A3).

Sleep disturbance may take the form of either difficulty sleeping or sleeping excessively (Criterion A4). When insomnia is present, it typically takes the form of middle insomnia (i.e., waking up during the night and then having difficulty returning to sleep) or terminal insomnia (i.e., waking too early and being unable to return to sleep). Initial insomnia (i.e., difficulty falling asleep) may also occur. Individuals who present with oversleeping (hypersomnia) may experience prolonged sleep episodes at night or increased daytime sleep. Sometimes the reason that the individual seeks treatment is for the disturbed sleep.

Psychomotor changes include agitation (e.g., the inability to sit still, pacing, hand-wringing; or pulling or rubbing of the skin, clothing, or other objects) or retardation (e.g., slowed speech, thinking, and body movements; increased pauses before answering; speech that is decreased in volume, inflection, amount, or variety of content, or muteness) (Criterion A5). The psychomotor agitation or retardation must be severe enough to be observable by others and not represent merely subjective feelings.

Decreased energy, tiredness, and fatigue are common (Criterion A6). A person may report sustained fatigue without physical exertion. Even the smallest tasks seem to require substantial effort. The efficiency with which tasks are accomplished may be reduced. For example, an individual may complain that washing and dressing in the morning are exhausting and take twice as long as usual.

The sense of worthlessness or guilt associated with a major depressive episode may include unrealistic negative evaluations of one’s worth or guilty preoccupations or ruminations over minor past failings (Criterion A7). Such individuals often misinterpret neutral or trivial day-to-day events as evidence of personal defects and have an exaggerated sense of responsibility for untoward events. The sense of worthlessness or guilt may be of delusional proportions (e.g., an individual who is convinced that he or she is personally responsible for world poverty). Blaming oneself for being sick and for failing to meet occupational or interpersonal responsibilities as a result of the depression is very common and, unless delusional, is not considered sufficient to meet this criterion.

Many individuals report impaired ability to think, concentrate, or make even minor decisions (Criterion A8). They may appear easily distracted or complain of memory difficulties. Those engaged in cognitively demanding pursuits are often unable to function. In children, a precipitous drop in grades may reflect poor concentration. In elderly individuals, memory difficulties may be the chief complaint and may be mistaken for early signs of a dementia (“pseudodementia”). When the major depressive episode is successfully treated, the memory problems often fully abate. However, in some individuals, particularly elderly persons, a major depressive episode may sometimes be the initial presentation of an irreversible dementia.

Thoughts of death, suicidal ideation, or suicide attempts (Criterion A9) are common. They may range from a passive wish not to awaken in the morning or a belief that others would be better off if the individual were dead, to transient but recurrent thoughts of committing suicide, to a specific suicide plan. More severely suicidal individuals may have put their affairs in order (e.g., updated wills, settled debts), acquired needed materials (e.g., a rope or a gun), and chosen a location and time to accomplish the suicide. Motivations for suicide may include a desire to give up in the face of perceived insurmountable obstacles, an intense wish to end what is perceived as an unending and excruciatingly painful emotional state, an inability to foresee any enjoyment in life, or the wish to not be a burden to others. The resolution of such thinking may be a more meaningful measure of diminished suicide risk than denial of further plans for suicide.

The evaluation of the symptoms of a major depressive episode is especially difficult when they occur in an individual who also has a general medical condition (e.g., cancer, stroke, myocardial infarction, diabetes, pregnancy). Some of the criterion signs and symptoms of a major depressive episode are identical to those of general medical conditions (e.g., weight loss with untreated diabetes; fatigue with cancer; hypersomnia early in pregnancy; insomnia later in pregnancy or the postpartum). Such symptoms count toward a major depressive diagnosis except when they are clearly and fully attributable to a general medical condition. Non-vegetative symptoms of dysphoria, anhedonia, guilt or worthlessness, impaired concentration or indecision, and suicidal thoughts should be assessed with particular care in such cases. Definitions of major depressive episodes that have been modified to include only these non-vegetative symptoms appear to identify nearly the same individuals as do the full criteria.

Associated Features Supporting Diagnosis

Major depressive disorder is associated with high mortality, much of which is accounted for by suicide; however, it is not the only cause. For example, depressed individuals admitted to nursing homes have a markedly increased likelihood of death in the first year. Individuals frequently present with tearfulness, irritability, brooding, obsessive rumination, anxiety, phobias, and excessive worry over physical health, and complaints of pain (e.g., headaches; joint, abdominal, or other pains). In children, separation anxiety may occur.

Although an extensive literature exists describing neuroanatomical, neuroendocrinological, and neurophysiological correlates of major depressive disorder, no laboratory test has yielded results of sufficient sensitivity and specificity to be used as a diagnostic tool for this disorder. Until recently, hypothalamic-pituitary-adrenal axis hyperactivity had been the most extensively investigated abnormality associated with major depressive episodes, and it appears to be associated with melancholia, psychotic features, and risks for eventual suicide. Molecular studies have also implicated peripheral factors, including genetic variants in neurotrophic factors and pro-inflammatory cytokines. Additionally, functional magnetic resonance imaging studies provide evidence for functional abnormalities in specific neural systems supporting emotion processing, reward seeking, and emotion regulation in adults with major depression.

Prevalence

Twelve-month prevalence of major depressive disorder in the United States is approximately 7%, with marked differences by age group such that the prevalence in 18- to 29-year-old individuals is threefold higher than the prevalence in individuals' age 60 years or older. Females experience 1.5- to 3-fold higher rates than males beginning in early adolescence.

Development and Course

Major depressive disorder may first appear at any age, but the likelihood of onset increases markedly with puberty. In the United States, incidence appears to peak in the 20s; however, first onset in late life is not uncommon.

The course of major depressive disorder is quite variable, such that some individuals rarely, if ever, experience remission (a period of 2 or more months with no symptoms, or only one or two symptoms to no more than a mild degree), while others experience many years with few or no symptoms between discrete episodes. It is important to distinguish individuals who present for treatment during an exacerbation of a chronic depressive illness from those whose symptoms developed recently. Chronicity of depressive symptoms substantially increases the likelihood of underlying personality, anxiety, and substance use disorders and decreases the likelihood that treatment will be followed by full symptom resolution. It is therefore useful to ask individuals presenting with depressive symptoms

to identify the last period of at least 2 months during which they were entirely free of depressive symptoms.

Recovery typically begins within 3 months of onset for two in five individuals with major depression and within 1 year for four in five individuals. Recency of onset is a strong determinant of the likelihood of near-term recovery, and many individuals who have been depressed only for several months can be expected to recover spontaneously. Features associated with lower recovery rates, other than current episode duration, include psychotic features, prominent anxiety, personality disorders, and symptom severity.

The risk of recurrence becomes progressively lower over time as the duration of remission increases. The risk is higher in individuals whose preceding episode was severe, in younger individuals, and in individuals who have already experienced multiple episodes. The persistence of even mild depressive symptoms during remission is a powerful predictor of recurrence.

Many bipolar illnesses begin with one or more depressive episodes, and a substantial proportion of individuals who initially appear to have major depressive disorder will prove, in time, to instead have a bipolar disorder. This is more likely in individuals with onset of the illness in adolescence, those with psychotic features, and those with a family history of bipolar illness. The presence of a “with mixed features” specifier also increases the risk for future manic or hypomanic diagnosis. Major depressive disorder, particularly with psychotic features, may also transition into schizophrenia, a change that is much more frequent than the reverse.

Despite consistent differences between genders in prevalence rates for depressive disorders, there appear to be no clear differences by gender in phenomenology, course, or treatment response. Similarly, there are no clear effects of current age on the course or treatment response of major depressive disorder. Some symptom differences exist, though, such that hypersomnia and hyperphagia are more likely in younger individuals, and melancholic symptoms, particularly psychomotor disturbances, are more common in older individuals. The likelihood of suicide attempts lessens in middle and late life, although the risk of completed suicide does not. Depressions with earlier ages at onset are more familial and more likely to involve personality disturbances. The course of major depressive disorder within individuals does not generally change with aging. Mean times to recovery appear to be stable over long periods, and the likelihood of being in an episode does not generally increase or decrease with time.

Risk and Prognostic Factors

Temperamental

Neuroticism (negative affectivity) is a well-established risk factor for the onset of major depressive disorder, and high levels appear to render individuals more likely to develop depressive episodes in response to stressful life events.

Environmental

Adverse childhood experiences, particularly when there are multiple experiences of diverse types, constitute a set of potent risk factors for major depressive disorder. Stressful life events are well recognized as precipitants of major depressive episodes, but the presence or absence of adverse life events near the onset of episodes does not appear to provide a useful guide to prognosis or treatment selection.

Genetic and physiological

First-degree family members of individuals with major depressive disorder have a risk for major depressive disorder two- to fourfold higher than that of the general population. Relative risks appear to be higher for early-onset and recurrent forms. Heritability is approximately 40%, and the personality trait neuroticism accounts for a substantial portion of this genetic liability.

Course modifiers

Essentially all major non-mood disorders increase the risk of an individual developing depression. Major depressive episodes that develop against the background of another disorder often follow a more refractory course. Substance use, anxiety, and borderline personality disorders are among the most common of these, and the presenting depressive symptoms may obscure and delay their recognition. However, sustained clinical improvement in depressive symptoms may depend on the appropriate treatment of underlying illnesses. Chronic or disabling medical conditions also increase risks for major depressive episodes. Such prevalent illnesses as diabetes, morbid obesity, and cardiovascular disease

are often complicated by depressive episodes, and these episodes are more likely to become chronic than are depressive episodes in medically healthy individuals.

Culture-Related Diagnostic Issues

Surveys of major depressive disorder across diverse cultures have shown sevenfold differences in 12-month prevalence rates but much more consistency in female-to-male ratio, mean ages at onset, and the degree to which presence of the disorder raises the likelihood of comorbid substance abuse. While these findings suggest substantial cultural differences in the expression of major depressive disorder, they do not permit simple linkages between particular cultures and the likelihood of specific symptoms. Rather, clinicians should be aware that in most countries the majority of cases of depression go unrecognized in primary care settings and that in many cultures, somatic symptoms are very likely to constitute the presenting complaint. Among the Criterion A symptoms, insomnia and loss of energy are the most uniformly reported.

Gender-Related Diagnostic Issues

Although the most reproducible finding in the epidemiology of major depressive disorder has been a higher prevalence in females, there are no clear differences between genders in symptoms, course, treatment response, or functional consequences. In women, the risk for suicide attempts is higher, and the risk for suicide completion is lower. The disparity in suicide rate by gender is not as great among those with depressive disorders as it is in the population as a whole.

Suicide Risk

The possibility of suicidal behavior exists at all times during major depressive episodes. The most consistently described risk factor is a past history of suicide attempts or threats, but it should be remembered that most completed suicides are not preceded by unsuccessful attempts. Other features associated with an increased risk for completed suicide include male sex, being single or living alone, and having prominent feelings of hopelessness. The presence of borderline personality disorder markedly increases risk for future suicide attempts.

Functional Consequences of Major Depressive Disorder

Many of the functional consequences of major depressive disorder derive from individual symptoms. Impairment can be very mild, such that many of those who interact with the affected individual are unaware of depressive symptoms. Impairment may, however, range to complete incapacity such that the depressed individual is unable to attend to basic self-care needs or is mute or catatonic. Among individuals seen in general medical settings, those with major depressive disorder have more pain and physical illness and greater decreases in physical, social, and role functioning.

Differential Diagnosis

Manic episodes with irritable mood or mixed episodes

Major depressive episodes with prominent irritable mood may be difficult to distinguish from manic episodes with irritable mood or from mixed episodes. This distinction requires a careful clinical evaluation of the presence of manic symptoms.

Mood disorder due to another medical condition

A major depressive episode is the appropriate diagnosis if the mood disturbance is not judged, based on individual history, physical examination, and laboratory findings, to be the direct pathophysiological consequence of a specific medical condition (e.g., multiple sclerosis, stroke, hypothyroidism).

Substance/medication-induced depressive or bipolar disorder

This disorder is distinguished from major depressive disorder by the fact that a substance (e.g., a drug of abuse, a medication, a toxin) appears to be etiologically related to the mood disturbance. For example, depressed mood that occurs only in the context of withdrawal from cocaine would be diagnosed as cocaine-induced depressive disorder.

Attention-deficit/hyperactivity disorder

Distractibility and low frustration tolerance can occur in both attention-deficit/ hyperactivity disorder and a major depressive episode; if the criteria are met for both, attention-deficit/hyperactivity disorder may be diagnosed in addition to the mood disorder. However, the clinician must be cautious not to overdiagnose a major depressive episode in children with attention-deficit/hyperactivity disorder whose disturbance in mood is characterized by irritability rather than by sadness or loss of interest.

Adjustment disorder with depressed mood
A major depressive episode that occurs in response to a psychosocial stressor is distinguished from adjustment disorder with depressed mood by the fact that the full criteria for a major depressive episode are not met in adjustment disorder.

Sadness
Finally, periods of sadness are inherent aspects of the human experience. These periods should not be diagnosed as a major depressive episode unless criteria are met for severity (i.e., five out of nine symptoms), duration (i.e., most of the day, nearly every day for at least 2 weeks), and clinically significant distress or impairment. The diagnosis other specified depressive disorder may be appropriate for presentations of depressed mood with clinically significant impairment that do not meet criteria for duration or severity.

Comorbidity

Other disorders with which major depressive disorder frequently co-occurs are substance-related disorders, panic disorder, obsessive-compulsive disorder, anorexia nervosa, bulimia nervosa, and borderline personality disorder.

Persistent Depressive Disorder (Dysthymia)

Diagnostic Criteria

300.4 (F34.1)
This disorder represents a consolidation of DSM-IV-defined chronic major depressive disorder and dysthymic disorder.

1. Depressed mood for most of the day, for more days than not, as indicated by either subjective account or observation by others, for at least 2 years.
   Note: In children and adolescents, mood can be irritable and duration must be at least 1 year.
2. Presence, while depressed, of two (or more) of the following:
   1. Poor appetite or overeating.
   2. Insomnia or hypersomnia.
   3. Low energy or fatigue.
   4. Low self-esteem.
   5. Poor concentration or difficulty making decisions.
   6. Feelings of hopelessness.
3. During the 2-year period (1 year for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 months at a time.
4. Criteria for a major depressive disorder may be continuously present for 2 years.
5. There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder.
6. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
7. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g. hypothyroidism).
8. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: Because the criteria for a major depressive episode include four symptoms that are absent from the symptom list for persistent depressive disorder (dysthymia), a very limited number of individuals will have depressive symptoms that have persisted longer than 2 years but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder or unspecified depressive disorder is warranted.
Specify if:

- **With anxious distress** (p. 184)
- **With mixed features** (pp. 184–185)
- **With melancholic features** (p. 185)
- **With atypical features** (pp. 185–186)
- **With mood-congruent psychotic features** (p. 186)
- **With mood-incongruent psychotic features** (p. 186)
- **With peripartum onset** (pp. 186–187)

Specify if:

- **In partial remission** (p. 188)
- **In full remission** (p. 188)

Specify if:

- **Early onset:** If onset is before age 21 years.
- **Late onset:** If onset is at age 21 years or older.

Specify if (for most recent 2 years of persistent depressive disorder):

- **With pure dysthymic syndrome:** Full criteria for a major depressive episode have not been met in at least the preceding 2 years.
- **With persistent major depressive episode:** Full criteria for a major depressive episode have been met throughout the preceding 2-year period.
- **With intermittent major depressive episodes, with current episode:** Full criteria for a major depressive episode are currently met, but there have been periods of at least 8 weeks in at least the preceding 2 years with symptoms below the threshold for a full major depressive episode.
- **With intermittent major depressive episodes, without current episode:** Full criteria for a major depressive episode are not currently met, but there has been one or more major depressive episodes in at least the preceding 2 years.

Specify current severity:

- **Mild** (p. 188)
- **Moderate** (p. 188)
- **Severe** (p. 188)

Diagnostic Features

The essential feature of persistent depressive disorder (dysthymia) is a depressed mood that occurs for most of the day, for more days than not, for at least 2 years, or at least 1 year for children and adolescents (Criterion A). This disorder represents a consolidation of DSM-IV-defined chronic major depressive disorder and dysthymic disorder. Major depression may precede persistent depressive disorder, and major depressive episodes may occur during persistent depressive disorder. Individuals whose symptoms meet major depressive disorder criteria for 2 years should be given a diagnosis of persistent depressive disorder as well as major depressive disorder.

Individuals with persistent depressive disorder describe their mood as sad or “down in the dumps.” During periods of depressed mood, at least two of the six symptoms from Criterion B are present. Because these symptoms have become a part of the individual’s day-to-day experience, particularly in the case of early onset (e.g., “I’ve always been this way”), they may not be reported unless the individual is directly prompted. During the 2-year period (1 year for children or adolescents), any symptom-free intervals last no longer than 2 months (Criterion C).

Prevalence

Persistent depressive disorder is effectively an amalgam of DSM-IV dysthymic disorder and chronic major depressive episode. The 12-month prevalence in the United States is approximately 0.5% for persistent depressive disorder and 1.5% for chronic major depressive disorder.

Development and Course

Persistent depressive disorder often has an early and insidious onset (i.e., in childhood, adolescence, or early adult life) and, by definition, a chronic course. Among individuals with both persistent depressive disorder and borderline personality disorder, the covariance of the corresponding features over time suggests the operation of a common mechanism. Early onset (i.e., before age 21 years) is associated with a higher likelihood of comorbid personality disorders and substance use disorders.

When symptoms rise to the level of a major depressive episode, they are likely to subsequently revert to a lower level. However, depressive symptoms are much less likely to resolve in a given period of time in the context of persistent depressive disorder than they are in a major depressive episode.

Risk and Prognostic Factors

Temperamental

Factors predictive of poorer long-term outcome include higher levels of neuroticism (negative affectivity), greater symptom severity, poorer global functioning, and presence of anxiety disorders or conduct disorder.

Environmental
Childhood risk factors include parental loss or separation.

Genetic and physiological
There are no clear differences in illness development, course, or family history between DSM-IV dysthymic disorder and chronic major depressive disorder. Earlier findings pertaining to either disorder are therefore likely to apply to persistent depressive disorder. It is thus likely that individuals with persistent depressive disorder will have a higher proportion of first-degree relatives with persistent depressive disorder than do individuals with major depressive disorder, and more depressive disorders in general.

A number of brain regions (e.g., prefrontal cortex, anterior cingulate, amygdala, and hippocampus) have been implicated in persistent depressive disorder. Possible polysomnographic abnormalities exist as well.

Functional Consequences of Persistent Depressive Disorder

The degree to which persistent depressive disorder impacts social and occupational functioning is likely to vary widely, but effects can be as great as or greater than those of major depressive disorder.

Differential Diagnosis

Major depressive disorder
If there is a depressed mood plus two or more symptoms meeting criteria for a persistent depressive episode for 2 years or more, then the diagnosis of persistent depressive disorder is made. The diagnosis depends on the 2-year duration, which distinguishes it from episodes of depression that do not last 2 years. If the symptom criteria are sufficient for a diagnosis of a major depressive episode at any time during this period, then the diagnosis of major depression should be noted, but it is coded not as a separate diagnosis but rather as a specifier with the diagnosis of persistent depressive disorder. If the individual's symptoms currently meet full criteria for a major depressive episode, then the specifier of "with intermittent major depressive episodes, with current episode" would be made. If the major depressive episode has persisted for at least a 2-year duration and remains present, then the specifier "with persistent major depressive episode" is used. When full major depressive episode criteria are not currently met but there has been at least one previous episode of major depression in the context of at least 2 years of persistent depressive symptoms, then the specifier of "with intermittent major depressive episodes, without current episode" is used. If the individual has not experienced an episode of major depression in the last 2 years, then the specifier "with pure dysthymic syndrome" is used.

Psychotic disorders
Depressive symptoms are a common associated feature of chronic psychotic disorders (e.g., schizoaffective disorder, schizophrenia, delusional disorder). A separate diagnosis of persistent depressive disorder is not made if the symptoms occur only during the course of the psychotic disorder (including residual phases).

Depressive or bipolar and related disorder due to another medical condition
Persistent depressive disorder must be distinguished from a depressive or bipolar and related disorder due to another medical condition. The diagnosis is depressive or bipolar and related disorder due to another medical condition if the mood disturbance is judged, based on history, physical examination, or laboratory findings, to be attributable to the direct pathophysiological effects of a specific, usually chronic, medical condition (e.g., multiple sclerosis). If it is judged that the depressive symptoms are not attributable to the physiological effects of another medical condition, then the primary mental disorder (e.g., persistent depressive disorder) is recorded, and the medical condition is noted as a concomitant medical condition (e.g., diabetes mellitus).

Substance/medication-induced depressive or bipolar disorder
A substance/medication-induced depressive or bipolar and related disorder is distinguished from persistent depressive disorder when a substance (e.g., a drug of abuse, a medication, a toxin) is judged to be etiologically related to the mood disturbance.

Personality disorders
Often, there is evidence of a coexisting personality disturbance. When an individual's presentation meets the criteria for both persistent depressive disorder and a personality disorder, both diagnoses are given.

Comorbidity

In comparison to individuals with major depressive disorder, those with persistent depressive disorder are at higher risk for psychiatric comorbidity in general, and for anxiety disorders and substance use disorders in particular. Early-onset persistent depressive disorder is strongly associated with DSM-IV Cluster B and C personality disorders.

Premenstrual Dysphoric Disorder

Diagnostic Criteria

625.4 (N94.3)

1. In the majority of menstrual cycles, at least five symptoms must be present in the final week before the onset of menses, start to *improve* within a few days after the onset of menses, and become *minimal* or absent in the week postmenses.
2. One (or more) of the following symptoms must be present:
    1. Marked affective lability (e.g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection).
    2. Marked irritability or anger or increased interpersonal conflicts.
    3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts.
    4. Marked anxiety, tension, and/or feelings of being keyed up or on edge.
3. One (or more) of the following symptoms must additionally be present, to reach a total of *five* symptoms when combined with symptoms from Criterion B above.
    1. Decreased interest in usual activities (e.g., work, school, friends, and hobbies).
    2. Subjective difficulty in concentration.
    3. Lethargy, easy fatigability, or marked lack of energy.
    4. Marked change in appetite; overeating; or specific food cravings.
    5. Hypersomnia or insomnia.
    6. A sense of being overwhelmed or out of control.
    7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of “bloating,” or weight gain.

    Note: The symptoms in Criteria A–C must have been met for most menstrual cycles that occurred in the preceding year.
4. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).
5. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).
6. Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles. (**Note:** The diagnosis may be made provisionally prior to this confirmation.)
7. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).

Recording Procedures

If symptoms have not been confirmed by prospective daily ratings of at least two symptomatic cycles, “provisional” should be noted after the name of the diagnosis (i.e., “premenstrual dysphoric disorder, provisional”).

Diagnostic Features

The essential features of premenstrual dysphoric disorder are the expression of mood lability, irritability, dysphoria, and anxiety symptoms that occur repeatedly during the premenstrual phase of the cycle and remit around the onset of menses or shortly thereafter. These symptoms may be accompanied by behavioral and physical symptoms. Symptoms must have occurred in most of the menstrual cycles during the past year and must have an adverse effect on work or social functioning. The intensity and/or expressivity of the accompanying symptoms may be closely related to social and cultural background characteristics of the affected female, family perspectives, and more specific factors such as religious beliefs, social tolerance, and female gender role issues.

Typically, symptoms peak around the time of the onset of menses. Although it is not uncommon for symptoms to linger into the first few days of menses, the individual must have a symptom-free period in the follicular phase after the menstrual period begins. While the core symptoms include mood and anxiety symptoms, behavioral and somatic symptoms commonly also occur. However, the presence of physical and/or behavioral symptoms in the absence of mood and/or anxious symptoms is not sufficient for a diagnosis. Symptoms are of comparable severity (but not duration) to those of another

mental disorder, such as a major depressive episode or generalized anxiety disorder. In order to confirm a provisional diagnosis, daily prospective symptom ratings are required for at least two symptomatic cycles.

Associated Features Supporting Diagnosis

Delusions and hallucinations have been described in the late luteal phase of the menstrual cycle but are rare. The premenstrual phase has been considered by some to be a risk period for suicide.

Prevalence

Twelve-month prevalence of premenstrual dysphoric disorder is between 1.8% and 5.8% of menstruating women. Estimates are substantially inflated if they are based on retrospective reports rather than prospective daily ratings. However, estimated prevalence based on a daily record of symptoms for 1–2 months may be less representative, as individuals with the most severe symptoms may be unable to sustain the rating process. The most rigorous estimate of premenstrual dysphoric disorder is 1.8% for women whose symptoms meet the full criteria without functional impairment and 1.3% for women whose symptoms meet the current criteria with functional impairment and without co-occurring symptoms from another mental disorder.

Development and Course

Onset of premenstrual dysphoric disorder can occur at any point after menarche. Incidence of new cases over a 40-month follow-up period is 2.5% (95% confidence interval = 1.7–3.7). Anecdotally, many individuals, as they approach menopause, report that symptoms worsen. Symptoms cease after menopause, although cyclical hormone replacement can trigger the re-expression of symptoms.

Risk and Prognostic Factors

Environmental

Environmental factors associated with the expression of premenstrual dysphoric disorder include stress, history of interpersonal trauma, seasonal changes, and sociocultural aspects of female sexual behavior in general, and female gender role in particular.

Genetic and physiological

Heritability of premenstrual dysphoric disorder is unknown. However, for premenstrual symptoms, estimates for heritability range between 30% and 80%, with the most stable component of premenstrual symptoms estimated to be about 50% heritable.

Course modifiers

Women who use oral contraceptives may have fewer premenstrual complaints than do women who do not use oral contraceptives.

Culture-Related Diagnostic Issues

Premenstrual dysphoric disorder is not a culture-bound syndrome and has been observed in individuals in the United States, Europe, India, and Asia. It is unclear as to whether rates differ by race. Nevertheless, frequency, intensity, and expressivity of symptoms and help-seeking patterns may be significantly influenced by cultural factors.

Diagnostic Markers

As indicated earlier, the diagnosis of premenstrual dysphoric disorder is appropriately confirmed by 2 months of prospective symptom ratings. A number of scales, including the Daily Rating of Severity of Problems and the Visual Analogue Scales for Premenstrual Mood Symptoms, have undergone validation and are commonly used in clinical trials for premenstrual dysphoric disorder. The Premenstrual Tension Syndrome Rating Scale has a self-report and an observer version, both of which have been validated and used widely to measure illness severity in women who have premenstrual dysphoric disorder.

Functional Consequences of Premenstrual Dysphoric Disorder

Symptoms must be associated with clinically meaningful distress and/or an obvious and marked impairment in the ability to function socially or occupationally in the week prior to menses. Impairment in social functioning may be manifested by marital discord and problems with children, other family members, or friends. Chronic marital or job problems should not be confused with dysfunction that occurs only in association with premenstrual dysphoric disorder.

Differential Diagnosis

Premenstrual syndrome
Premenstrual syndrome differs from premenstrual dysphoric disorder in that a minimum of five symptoms is not required, and there is no stipulation of affective symptoms for individuals who have premenstrual syndrome. This condition may be more common than premenstrual dysphoric disorder, although the estimated prevalence of premenstrual syndrome varies. While premenstrual syndrome shares the feature of symptom expression during the premenstrual phase of the menstrual cycle, it is generally considered to be less severe than premenstrual dysphoric disorder. The presence of physical or behavioral symptoms in the premenstruum, without the required affective symptoms, likely meets criteria for premenstrual syndrome and not for premenstrual dysphoric disorder.

Dysmenorrhea
Dysmenorrhea is a syndrome of painful menses, but this is distinct from a syndrome characterized by affective changes. Moreover, symptoms of dysmenorrhea begin with the onset of menses, whereas symptoms of premenstrual dysphoric disorder, by definition, begin before the onset of menses, even if they linger into the first few days of menses.

Bipolar disorder, major depressive disorder, and persistent depressive disorder (dysthymia)
Many women with (either naturally occurring or substance/medication-induced) bipolar or major depressive disorder or persistent depressive disorder believe that they have premenstrual dysphoric disorder. However, when they chart symptoms, they realize that the symptoms do not follow a premenstrual pattern. Women with another mental disorder may experience chronic symptoms or intermittent symptoms that are unrelated to menstrual cycle phase. However, because the onset of menses constitutes a memorable event, they may report that symptoms occur only during the premenstruum or that symptoms worsen premenstrually. This is one of the rationales for the requirement that symptoms be confirmed by daily prospective ratings. The process of differential diagnosis, particularly if the clinician relies on retrospective symptoms only, is made more difficult because of the overlap between symptoms of premenstrual dysphoric disorder and some other diagnoses. The overlap of symptoms is particularly salient for differentiating premenstrual dysphoric disorder from major depressive episodes, persistent depressive disorder, bipolar disorders, and borderline personality disorder. However, the rate of personality disorders is no higher in individuals with premenstrual dysphoric disorder than in those without the disorder.

Use of hormonal treatments
Some women who present with moderate to severe premenstrual symptoms may be using hormonal treatments, including hormonal contraceptives. If such symptoms occur after initiation of exogenous hormone use, the symptoms may be due to the use of hormones rather than to the underlying condition of premenstrual dysphoric disorder. If the woman stops hormones and the symptoms disappear, this is consistent with substance/medication-induced depressive disorder.

Comorbidity

A major depressive episode is the most frequently reported previous disorder in individuals presenting with premenstrual dysphoric disorder. A wide range of medical (e.g., migraine, asthma, allergies, seizure disorders) or other mental disorders (e.g., depressive and bipolar disorders, anxiety disorders, bulimia nervosa, substance use disorders) may worsen in the premenstrual phase; however, the absence of a symptom-free period during the postmenstrual interval obviates a diagnosis of premenstrual dysphoric disorder. These conditions are better considered premenstrual exacerbation of a current mental or medical disorder. Although the diagnosis of premenstrual dysphoric disorder should not be assigned in situations in which an individual only experiences a premenstrual exacerbation of another mental or physical disorder, it can be considered in addition to the diagnosis of another mental or physical disorder if the individual experiences symptoms and changes in level of functioning that are characteristic of premenstrual dysphoric disorder and markedly different from the symptoms experienced as part of the ongoing disorder.

Substance/Medication-Induced Depressive Disorder

Diagnostic Criteria

1. A prominent and persistent disturbance in mood that predominates in the clinical picture and is characterized by depressed mood or markedly diminished interest or pleasure in all, or almost all, activities.
2. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

3. The disturbance is not better explained by a depressive disorder that is not substance/medication-induced. Such evidence of an independent depressive disorder could include the following:
    - The symptoms preceded the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced depressive disorder (e.g., a history of recurrent non-substance/medication-related episodes).
4. The disturbance does not occur exclusively during the course of a delirium.
5. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

- **Coding note:** The ICD-9-CM and ICD-10-CM codes for the [specific substance/medication]-induced depressive disorders are indicated in the table below. Note that the ICD-10-CM code depends on whether or not there is a comorbid substance use disorder present for the same class of substance. If a mild substance use disorder is comorbid with the substance-induced depressive disorder, the 4th position character is “1,” and the clinician should record “mild [substance] use disorder” before the substance-induced depressive disorder (e.g., “mild cocaine use disorder with cocaine-induced depressive disorder”). If a moderate or severe substance use disorder is comorbid with the substance-induced depressive disorder, the 4th position character is “2,” and the clinician should record “moderate [substance] use disorder” or “severe [substance] use disorder,” depending on the severity of the comorbid substance use disorder. If there is no comorbid substance use disorder (e.g., after a one-time heavy use of the substance), then the 4th position character is “9,” and the clinician should record only the substance-induced depressive disorder.

		ICD-10-CM		
	ICD-9-CM	With use disorder, mild	With use disorder, moderate or severe	Without use disorder
Alcohol	**291.89**	**F10.14**	**F10.24**	**F10.94**
Phencyclidine	**292.84**	**F16.14**	**F16.24**	**F16.94**
Other hallucinogen	**292.84**	**F16.14**	**F16.24**	**F16.94**
Inhalant	**292.84**	**F18.14**	**F18.24**	**F18.94**
Opioid	**292.84**	**F11.14**	**F11.24**	**F11.94**
Sedative, hypnotic, or anxiolytic	**292.84**	**F13.14**	**F13.24**	**F13.94**
Amphetamine (or other stimulant)	**292.84**	**F15.14**	**F15.24**	**F15.94**
Cocaine	**292.84**	**F14.14**	**F14.24**	**F14.94**
Other (or unknown) substance	**292.84**	**F19.14**	**F19.24**	**F19.94**

Specify if (see Table in the chapter “Substance-Related and Addictive Disorders” for diagnoses associated with substance class):

- **With onset during intoxication:** If criteria are met for intoxication with the substance and the symptoms develop during intoxication.
- **With onset during withdrawal:** If criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.

Recording Procedures

ICD-9-CM

The name of the substance/medication-induced depressive disorder begins with the specific substance (e.g., cocaine, dexamethasone) that is presumed to be causing the depressive symptoms. The diagnostic code is selected from the table included in the criteria set, which is based on the drug class.

For substances that do not fit into any of the classes (e.g., dexamethasone), the code for “other substance” should be used; and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category “unknown substance” should be used.

The name of the disorder is followed by the specification of onset (i.e., onset during intoxication, onset during withdrawal). Unlike the recording procedures for ICD-10-CM, which combine the substance-induced disorder and substance use disorder into a single code, for ICD-9-CM a separate diagnostic code is given for the substance use disorder. For example, in the case of depressive symptoms occurring during withdrawal in a man with a severe cocaine use disorder, the diagnosis is 292.84 cocaine-induced depressive disorder, with onset during withdrawal. An additional diagnosis of 304.20 severe cocaine use disorder is also given. When more than one substance is judged to play a significant role in the development of depressive mood symptoms, each should be listed separately (e.g., 292.84 methylphenidate-induced depressive disorder, with onset during withdrawal; 292.84 dexamethasone-induced depressive disorder, with onset during intoxication).

ICD-10-CM

The name of the substance/medication-induced depressive disorder begins with the specific substance (e.g., cocaine, dexamethasone) that is presumed to be causing the depressive symptoms. The diagnostic code is selected from the table included in the criteria set, which is based on the drug class and presence or absence of a comorbid substance use disorder. For substances that do not fit into any of the classes (e.g., dexamethasone), the code for “other substance” should be used; and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category “unknown substance” should be used.

When recording the name of the disorder, the comorbid substance use disorder (if any) is listed first, followed by the word “with,” followed by the name of the substance-induced depressive disorder, followed by the specification of onset (i.e., onset during intoxication, onset during withdrawal). For example, in the case of depressive symptoms occurring during withdrawal in a man with a severe cocaine use disorder, the diagnosis is F14.24 severe cocaine use disorder with cocaine-induced depressive disorder, with onset during withdrawal. A separate diagnosis of the comorbid severe cocaine use disorder is not given. If the substance-induced depressive disorder occurs without a comorbid substance use disorder (e.g., after a one-time heavy use of the substance), no accompanying substance use disorder is noted (e.g., F16.94 phencyclidine-induced depressive disorder, with onset during intoxication). When more than one substance is judged to play a significant role in the development of depressive mood symptoms, each should be listed separately (e.g., F15.24 severe methylphenidate use disorder with methylphenidate-induced depressive disorder, with onset during withdrawal; F19.94 dexamethasone-induced depressive disorder, with onset during intoxication).

Diagnostic Features

The diagnostic features of substance/medication-induced depressive disorder include the symptoms of a depressive disorder, such as major depressive disorder; however, the depressive symptoms are associated with the ingestion, injection, or inhalation of a substance (e.g., drug of abuse, toxin, psychotropic medication, other medication), and the depressive symptoms persist beyond the expected length of physiological effects, intoxication, or withdrawal period. As evidenced by clinical history, physical examination, or laboratory findings, the relevant depressive disorder should have developed during or within 1 month after use of a substance that is capable of producing the depressive disorder (Criterion B1). In addition, the diagnosis is not better explained by an independent depressive disorder. Evidence of an independent depressive disorder includes the depressive disorder preceded the onset of ingestion or withdrawal from the substance; the depressive disorder persists beyond a substantial period of time after the cessation of substance use; or other evidence suggests the existence of an independent non-substance/medication-induced depressive disorder (Criterion C). This diagnosis should not be made when symptoms occur exclusively during the course of a delirium (Criterion D). The depressive disorder associated with the substance use, intoxication, or withdrawal must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning to qualify for this diagnosis (Criterion E).

Some medications (e.g., stimulants, steroids, l-dopa, antibiotics, central nervous system drugs, dermatological agents, chemotherapeutic drugs, immunological agents) can induce depressive mood disturbances. Clinical judgment is essential to determine whether the medication is truly associated with inducing the depressive disorder or whether a primary depressive disorder happened to have its onset while the person was receiving the treatment. For example, a depressive episode that developed within the first several weeks of beginning alpha-methyldopa (an antihypertensive agent) in an individual with no history of major depressive disorder would qualify for the diagnosis of medication-induced depressive disorder. In some cases, a previously established condition (e.g., major depressive

disorder, recurrent) can recur while the individual is coincidentally taking a medication that has the capacity to cause depressive symptoms (e.g., l-dopa, oral contraceptives). In such cases, the clinician must make a judgment as to whether the medication is causative in this particular situation.

A substance/medication-induced depressive disorder is distinguished from a primary depressive disorder by considering the onset, course, and other factors associated with the substance use. There must be evidence from the history, physical examination, or laboratory findings of substance use, abuse, intoxication, or withdrawal prior to the onset of the depressive disorder. The withdrawal state for some substances can be relatively protracted, and thus intense depressive symptoms can last for a long period after the cessation of substance use.

Prevalence

In a nationally representative U.S. adult population, the lifetime prevalence of substance/medication-induced depressive disorder is 0.26%.

Development and Course

A depressive disorder associated with the use of substance (i.e., alcohol, illicit drugs, or a prescribed treatment for a mental disorder or another medical condition) must have its onset while the individual is using the substance or during withdrawal, if there is a withdrawal syndrome associated with the substance. Most often, the depressive disorder has its onset within the first few weeks or 1 month of use of the substance. Once the substance is discontinued, the depressive symptoms usually remit within days to several weeks, depending on the half-life of the substance/medication and the presence of a withdrawal syndrome. If symptoms persist 4 weeks beyond the expected time course of withdrawal of a particular substance/medication, other causes for the depressive mood symptoms should be considered.

Although there are a few prospective controlled trials examining the association of depressive symptoms with use of a medication, most reports are from postmarketing surveillance studies, retrospective observational studies, or case reports, making evidence of causality difficult to determine. Substances implicated in medication-induced depressive disorder, with varying degrees of evidence, include antiviral agents (efavirenz), cardiovascular agents (clonidine, guanethidine, methyldopa, reserpine), retinoic acid derivatives (isotretinoin), antidepressants, anticonvulsants, anti-migraine agents (triptans), antipsychotics, hormonal agents (corticosteroids, oral contraceptives, gonadotropin-releasing hormone agonists, tamoxifen), smoking cessation agents (varenicline), and immunological agents (interferon). However, other potential substances continue to emerge as new compounds are synthesized. A history of such substance use may help increase diagnostic certainty.

Risk and Prognostic Factors

Temperamental

Factors that appear to increase the risk of substance/medication-induced depressive disorder can be conceptualized as pertaining to the specific type of drug or to a group of individuals with underlying alcohol or drug use disorders. Risk factors common to all drugs include history of major depressive disorder, history of drug-induced depression, and psychosocial stressors.

Environmental

There are also risks factors pertaining to a specific type of medication (e.g., increased immune activation prior to treatment for hepatitis C associated with interferon-alfa-induced depression); high doses (greater than 80 mg/day prednisone-equivalents) of corticosteroids or high plasma concentrations of efavirenz; and high estrogen/progesterone content in oral contraceptives.

Course modifiers

In a representative U.S. adult population, compared with individuals with major depressive disorder who did not have a substance use disorder, individuals with substance-induced depressive disorder were more likely to be male, to be black, to have at most a high school diploma, to lack insurance, and to have lower family income. They were also more likely to report higher family history of substance use disorders and antisocial behavior, higher 12-month history of stressful life events, and a greater number of DSM-IV major depressive disorder criteria. They were more likely to report feelings of worthlessness, insomnia/hypersomnia, and thoughts of death and suicide attempts, but less likely to report depressed mood and parental loss by death before age 18 years.

Diagnostic Markers

Determination of the substance of use can sometimes be made through laboratory assays of the suspected substance in the blood or urine to corroborate the diagnosis.

Suicide Risk

Drug-induced or treatment-emergent suicidality represents a marked change in thoughts and behavior from the person's baseline, is usually temporally associated with initiation of a substance, and must be distinguished from the underlying primary mental disorders.

In regard to the treatment-emergent suicidality associated with antidepressants, a U.S. Food and Drug Administration (FDA) advisory committee considered meta-analyses of 99,839 participants enrolled in 372 randomized clinical trials of antidepressants in trials for mental disorders. The analyses showed that when the data were pooled across all adult age groups, there was no perceptible increased risk of suicidal behavior or ideation. However, in age-stratified analyses, the risk for patients ages 18–24 years was elevated, albeit not significantly (odds ratio [OR] = 1.55; 95% confidence interval [CI] = 0.91–2.70). The FDA meta-analyses reveal an absolute risk of suicide in patients taking investigational antidepressants of 0.01%. In conclusion, suicide is clearly an extremely rare treatment-emergent phenomenon, but the outcome of suicide was serious enough to prompt the FDA to issue an expanded black-box warning in 2007 regarding the importance of careful monitoring of treatment-emergent suicidal ideation in patients receiving antidepressants.

Differential Diagnosis

Substance intoxication and withdrawal

Depressive symptoms occur commonly in substance intoxication and substance withdrawal, and the diagnosis of the substance-specific intoxication or withdrawal will usually suffice to categorize the symptom presentation. A diagnosis of substance-induced depressive disorder should be made instead of a diagnosis of substance intoxication or substance withdrawal when the mood symptoms are sufficiently severe to warrant independent clinical attention. For example, dysphoric mood is a characteristic feature of cocaine withdrawal. Substance/medication-induced depressive disorder should be diagnosed instead of cocaine withdrawal only if the mood disturbance is substantially more intense or longer lasting than what is usually encountered with cocaine withdrawal and is sufficiently severe to be a separate focus of attention and treatment.

Primary depressive disorder

A substance/medication-induced depressive disorder is distinguished from a primary depressive disorder by the fact that a substance is judged to be etiologically related to the symptoms, as described earlier (see section "Development and Course" for this disorder).

Depressive disorder due to another medical condition

Because individuals with other medical conditions often take medications for those conditions, the clinician must consider the possibility that the mood symptoms are caused by the physiological consequences of the medical condition rather than the medication, in which case depressive disorder due to another medical condition is diagnosed. The history often provides the primary basis for such a judgment. At times, a change in the treatment for the other medical condition (e.g., medication substitution or discontinuation) may be needed to determine empirically whether the medication is the causative agent. If the clinician has ascertained that the disturbance is a function of both another medical condition and substance use or withdrawal, both diagnoses (i.e., depressive disorder due to another medical condition and substance/medication-induced depressive disorder) may be given. When there is insufficient evidence to determine whether the depressive symptoms are associated with substance (including a medication) ingestion or withdrawal or with another medical condition or are primary (i.e., not a function of either a substance or another medical condition), a diagnosis of other specified depressive disorder or unspecified depressive disorder would be indicated.

Comorbidity

Compared with individuals with major depressive disorder and no comorbid substance use disorder, those with substance/medication-induced depressive disorder have higher rates of comorbidity with any DSM-IV mental disorder; are more likely to have specific DSM-IV disorders of pathological gambling and paranoid, histrionic, and antisocial personality disorders; and are less likely to have persistent depressive disorder (dysthymia). Compared with individuals with major depressive disorder and a comorbid substance use disorder, individuals with substance/medication-induced depressive disorder are more likely to have alcohol use disorder, any other substance use disorder, and histrionic personality disorder; however, they are less likely to have persistent depressive disorder.

Depressive Disorder Due to Another Medical Condition

Diagnostic Criteria

1. A prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all, or almost all, activities that predominates in the clinical picture.
2. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.
3. The disturbance is not better explained by another mental disorder (e.g., adjustment disorder, with depressed mood, in which the stressor is a serious medical condition).
4. The disturbance does not occur exclusively during the course of a delirium.
5. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Coding note: The ICD-9-CM code for depressive disorder due to another medical condition is **293.83,** which is assigned regardless of the specifier. The ICD-10-CM code depends on the specifier (see below).

Specify if:

- **(F06.31) With depressive features:** Full criteria are not met for a major depressive episode.
- **(F06.32) With major depressive–like episode:** Full criteria are met (except Criterion C) for a major depressive episode.
- **(F06.34) With mixed features**: Symptoms of mania or hypomania are also present but do not predominate in the clinical picture.
- **Coding note:** Include the name of the other medical condition in the name of the mental disorder (e.g., 293.83 [F06.31] depressive disorder due to hypothyroidism, with depressive features). The other medical condition should also be coded and listed separately immediately before the depressive disorder due to the medical condition (e.g., 244.9 [E03.9] hypothyroidism; 293.83 [F06.31] depressive disorder due to hypothyroidism, with depressive features).

Diagnostic Features

The essential feature of depressive disorder due to another medical condition is a prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all, or almost all, activities that predominates in the clinical picture (Criterion A) and that is thought to be related to the direct physiological effects of another medical condition (Criterion B). In determining whether the mood disturbance is due to a general medical condition, the clinician must first establish the presence of a general medical condition. Further, the clinician must establish that the mood disturbance is etiologically related to the general medical condition through a physiological mechanism. A careful and comprehensive assessment of multiple factors is necessary to make this judgment. Although there are no infallible guidelines for determining whether the relationship between the mood disturbance and the general medical condition is etiological, several considerations provide some guidance in this area. One consideration is the presence of a temporal association between the onset, exacerbation, or remission of the general medical condition and that of the mood disturbance. A second consideration is the presence of features that are atypical of primary Mood Disorders (e.g., atypical age at onset or course or absence of family history). Evidence from the literature that suggests that there can be a direct association between the general medical condition in question and the development of mood symptoms can provide a useful context in the assessment of a particular situation.

Associated Features Supporting Diagnosis

Etiology (i.e., a causal relationship to another medical condition based on best clinical evidence) is the key variable in depressive disorder due to another medical condition. The listing of the medical conditions that are said to be able to induce major depression is never complete, and the clinician's best judgment is the essence of this diagnosis.

There are clear associations, as well as some neuroanatomical correlates, of depression with stroke, Huntington's disease, Parkinson's disease, and traumatic brain injury. Among the neuroendocrine conditions most closely associated with depression are Cushing's disease and hypothyroidism. There are numerous other conditions thought to be associated with depression, such as multiple sclerosis. However, the literature's support for a causal association is greater with some conditions, such as Parkinson's disease and Huntington's disease, than with others, for which the differential diagnosis may be adjustment disorder, with depressed mood.

Development and Course

Following stroke, the onset of depression appears to be very acute, occurring within 1 day or a few days of the cerebrovascular accident (CVA) in the largest case series. However, in some cases, onset of the depression is weeks to months following the CVA. In the largest series, the duration of the major depressive episode following stroke was 9–11 months on average. Similarly, in Huntington's disease the depressive state comes quite early in the course of the illness. With Parkinson's disease and Huntington's disease, it often precedes the major motor impairments and cognitive impairments associated with each condition. This is more prominently the case for Huntington's disease, in which depression is considered to be the first neuropsychiatric symptom. There is some observational evidence that depression is less common as the dementia of Huntington's disease progresses.

Risk and Prognostic Factors

The risk of acute onset of a major depressive disorder following a CVA (within 1 day to a week of the event) appears to be strongly correlated with lesion location, with greatest risk associated with left frontal strokes and least risk apparently associated with right frontal lesions in those individuals who present within days of the stroke. The association with frontal regions and laterality is not observed in depressive states that occur in the 2–6 months following stroke.

Gender-Related Diagnostic Issues

Gender differences pertain to those associated with the medical condition (e.g., systemic lupus erythematosus is more common in females; stroke is somewhat more common in middle-age males compared with females).

Diagnostic Markers

Diagnostic markers pertain to those associated with the medical condition (e.g., steroid levels in blood or urine to help corroborate the diagnosis of Cushing's disease, which can be associated with manic or depressive syndromes).

Suicide Risk

There are no epidemiological studies that provide evidence to differentiate the risk of suicide from a major depressive episode due to another medical condition compared with the risk from a major depressive episode in general. There are case reports of suicides in association with major depressive episodes associated with another medical condition. There is a clear association between serious medical illnesses and suicide, particularly shortly after onset or diagnosis of the illness. Thus, it would be prudent to assume that the risk of suicide for major depressive episodes associated with medical conditions is not less than that for other forms of major depressive episode, and might even be greater.

Functional Consequences of Depressive Disorder Due to Another Medical Condition

Functional consequences pertain to those associated with the medical condition. In general, it is believed, but not established, that a major depressive episode induced by Cushing's disease will not recur if the Cushing's disease is cured or arrested. However, it is also suggested, but not established, that mood syndromes, including depressive and manic/hypomanic ones, may be episodic (i.e., recurring) in some individuals with static brain injuries and other central nervous system diseases.

Differential Diagnosis

Depressive disorders not due to another medical condition

Determination of whether a medical condition accompanying a depressive disorder is causing the disorder depends on a) the absence of an episode(s) of depressive episodes prior to the onset of the medical condition, b) the probability that the associated medical condition has a potential to promote or cause a depressive disorder, and c) a course of the depressive symptoms shortly after the onset or worsening of the medical condition, especially if the depressive symptoms remit near the time that the medical disorder is effectively treated or remits.

Medication-induced depressive disorder

An important caveat is that some medical conditions are treated with medications (e.g., steroids or alpha-interferon) that can induce depressive or manic symptoms. In these cases, clinical judgment, based on all the evidence in hand, is the best way to try to separate the most likely and/or the most

important of two etiological factors (i.e., association with the medical condition vs. a substance-induced syndrome).

Adjustment disorders
It is important to differentiate a depressive episode from an adjustment disorder, as the onset of the medical condition is in itself a life stressor that could bring on either an adjustment disorder or an episode of major depression. The major differentiating elements are the pervasiveness the depressive picture and the number and quality of the depressive symptoms that the patient reports or demonstrates on the mental status examination. The differential diagnosis of the associated medical conditions is relevant but largely beyond the scope of the present manual.

Comorbidity

Conditions comorbid with depressive disorder due to another medical condition are those associated with the medical conditions of etiological relevance. It has been noted that delirium can occur before or along with depressive symptoms in individuals with a variety of medical conditions, such as Cushing's disease. The association of anxiety symptoms, usually generalized symptoms, is common in depressive disorders, regardless of cause.

Other Specified Depressive Disorder

311 (F32.8)
This category applies to presentations in which symptoms characteristic of a depressive disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the depressive disorders diagnostic class. The other specified depressive disorder category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for any specific depressive disorder. This is done by recording "other specified depressive disorder" followed by the specific reason (e.g., "short-duration depressive episode").
Examples of presentations that can be specified using the "other specified" designation include the following:

1. **Recurrent brief depression:** Concurrent presence of depressed mood and at least four other symptoms of depression for 2–13 days at least once per month (not associated with the menstrual cycle) for at least 12 consecutive months in an individual whose presentation has never met criteria for any other depressive or bipolar disorder and does not currently meet active or residual criteria for any psychotic disorder.
2. **Short-duration depressive episode (4–13 days):** Depressed affect and at least four of the other eight symptoms of a major depressive episode associated with clinically significant distress or impairment that persists for more than 4 days, but less than 14 days, in an individual whose presentation has never met criteria for any other depressive or bipolar disorder, does not currently meet active or residual criteria for any psychotic disorder, and does not meet criteria for recurrent brief depression.
3. **Depressive episode with insufficient symptoms:** Depressed affect and at least one of the other eight symptoms of a major depressive episode associated with clinically significant distress or impairment that persist for at least 2 weeks in an individual whose presentation has never met criteria for any other depressive or bipolar disorder, does not currently meet active or residual criteria for any psychotic disorder, and does not meet criteria for mixed anxiety and depressive disorder symptoms.

Unspecified Depressive Disorder

311 (F32.9)
This category applies to presentations in which symptoms characteristic of a depressive disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the depressive disorders diagnostic class. The unspecified depressive disorder category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for a specific depressive disorder, and includes presentations for which there is insufficient information to make a more specific diagnosis (e.g., in emergency room settings).

Specifiers for Depressive Disorders

Specify if:

- **With anxious distress:** Anxious distress is defined as the presence of at least two of the following symptoms during the majority of days of a major depressive episode or persistent depressive disorder (dysthymia):
    1. Feeling keyed up or tense.
    2. Feeling unusually restless.
    3. Difficulty concentrating because of worry.
    4. Fear that something awful may happen.
    5. Feeling that the individual might lose control of himself or herself.

  Specify current severity:

    - **Mild:** Two symptoms.
    - **Moderate:** Three symptoms.
    - **Moderate-severe:** Four or five symptoms.
    - **Severe:** Four or five symptoms and with motor agitation.
    - **Note:** Anxious distress has been noted as a prominent feature of both bipolar and major depressive disorder in both primary care and specialty mental health settings. High levels of anxiety have been associated with higher suicide risk, longer duration of illness, and greater likelihood of treatment nonresponse. As a result, it is clinically useful to specify accurately the presence and severity levels of anxious distress for treatment planning and monitoring of response to treatment.
    -
    - **With mixed features:**

    1. At least three of the following manic/hypomanic symptoms are present nearly every day during the majority of days of a major depressive episode:
        1. Elevated, expansive mood.
        2. Inflated self-esteem or grandiosity.
        3. More talkative than usual or pressure to keep talking.
        4. Flight of ideas or subjective experience that thoughts are racing.
        5. Increase in energy or goal-directed activity (either socially, at work or school, or sexually).
        6. Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, foolish business investments).
        7. Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia).
    2. Mixed symptoms are observable by others and represent a change from the person's usual behavior.
    3. For individuals whose symptoms meet full criteria for either mania or hypomania, the diagnosis should be bipolar I or bipolar II disorder.
    4. The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication or other treatment).

    - **Note:** Mixed features associated with a major depressive episode have been found to be a significant risk factor for the development of bipolar I or bipolar II disorder. As a result, it is clinically useful to note the presence of this specifier for treatment planning and monitoring of response to treatment.
    -
    - **With melancholic features:**

    1. One of the following is present during the most severe period of the current episode:
        1. Loss of pleasure in all, or almost all, activities.
        2. Lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens).
    2. Three (or more) of the following:
        1. A distinct quality of depressed mood characterized by profound despondency, despair, and/or moroseness or by so-called empty mood.
        2. Depression that is regularly worse in the morning.
        3. Early-morning awakening (i.e., at least 2 hours before usual awakening).
        4. Marked psychomotor agitation or retardation.
        5. Significant anorexia or weight loss.
        6. Excessive or inappropriate guilt.

    - **Note:** The specifier "with melancholic features" is applied if these features are present at the most severe stage of the episode. There is a near-complete absence of the capacity for pleasure, not merely a diminution. A guideline for evaluating the lack of reactivity of mood is that even highly desired events are not associated with marked

brightening of mood. Either mood does not brighten at all, or it brightens only partially (e.g., up to 20%–40% of normal for only minutes at a time). The “distinct quality” of mood that is characteristic of the “with melancholic features” specifier is experienced as qualitatively different from that during a nonmelancholic depressive episode. A depressed mood that is described as merely more severe, longer lasting, or present without a reason is not considered distinct in quality. Psychomotor changes are nearly always present and are observable by others. Melancholic features exhibit only a modest tendency to repeat across episodes in the same individual. They are more frequent in inpatients, as opposed to outpatients; are less likely to occur in milder than in more severe major depressive episodes; and are more likely to occur in those with psychotic features.

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  - **With atypical features:** This specifier can be applied when these features predominate during the majority of days of the current or most recent major depressive episode or persistent depressive disorder.
    1. Mood reactivity (i.e., mood brightens in response to actual or potential positive events).
    2. Two (or more) of the following:
       1. Significant weight gain or increase in appetite.
       2. Hypersomnia.
       3. Leaden paralysis (i.e., heavy, leaden feelings in arms or legs).
       4. A long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment.
    3. Criteria are not met for “with melancholic features” or “with catatonia” during the same episode.
  - **Note:** “Atypical depression” has historical significance (i.e., atypical in contradistinction to the more classical agitated, “endogenous” presentations of depression that were the norm when depression was rarely diagnosed in outpatients and almost never in adolescents or younger adults) and today does not connote an uncommon or unusual clinical presentation as the term might imply. Mood reactivity is the capacity to be cheered up when presented with positive events (e.g., a visit from children, compliments from others). Mood may become euthymic (not sad) even for extended periods of time if the external circumstances remain favorable. Increased appetite may be manifested by an obvious increase in food intake or by weight gain. Hypersomnia may include either an extended period of nighttime sleep or daytime napping that totals at least 10 hours of sleep per day (or at least 2 hours more than when not depressed). Leaden paralysis is defined as feeling heavy, leaden, or weighted down, usually in the arms or legs. This sensation is generally present for at least an hour a day but often lasts for many hours at a time. Unlike the other atypical features, pathological sensitivity to perceived interpersonal rejection is a trait that has an early onset and persists throughout most of adult life. Rejection sensitivity occurs both when the person is and is not depressed, though it may be exacerbated during depressive periods.
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  - **With psychotic features:** Delusions and/or hallucinations are present.
  - **With mood-congruent psychotic features:** The content of all delusions and hallucinations is consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment.
  - **With mood-incongruent psychotic features:** The content of the delusions or hallucinations does not involve typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment, or the content is a mixture of mood-incongruent and mood-congruent themes.
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  - **With catatonia:** The catatonia specifier can apply to an episode of depression if catatonic features are present during most of the episode. See criteria for catatonia associated with a mental disorder (for a description of catatonia, see the chapter “Schizophrenia Spectrum and Other Psychotic Disorders”).
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  - **With peripartum onset:** This specifier can be applied to the current or, if full criteria are not currently met for a major depressive episode, most recent episode of major depression if onset of mood symptoms occurs during pregnancy or in the 4 weeks following delivery.

- **Note:** Mood episodes can have their onset either during pregnancy or postpartum. Although the estimates differ according to the period of follow-up after delivery, between 3% and 6% of women will experience the onset of a major depressive episode during pregnancy or in the weeks or months following delivery. Fifty percent of "postpartum" major depressive episodes actually begin prior to delivery. Thus, these episodes are referred to collectively as *peripartum* episodes. Women with peripartum major depressive episodes often have severe anxiety and even panic attacks. Prospective studies have demonstrated that mood and anxiety symptoms during pregnancy, as well as the "baby blues," increase the risk for a postpartum major depressive episode. Peripartum-onset mood episodes can present either with or without psychotic features. Infanticide is most often associated with postpartum psychotic episodes that are characterized by command hallucinations to kill the infant or delusions that the infant is possessed, but psychotic symptoms can also occur in severe postpartum mood episodes without such specific delusions or hallucinations. Postpartum mood (major depressive or manic) episodes with psychotic features appear to occur in from 1 in 500 to 1 in 1,000 deliveries and may be more common in primiparous women. The risk of postpartum episodes with psychotic features is particularly increased for women with prior postpartum mood episodes but is also elevated for those with a prior history of a depressive or bipolar disorder (especially bipolar I disorder) and those with a family history of bipolar disorders. Once a woman has had a postpartum episode with psychotic features, the risk of recurrence with each subsequent delivery is between 30% and 50%. Postpartum episodes must be differentiated from delirium occurring in the postpartum period, which is distinguished by a fluctuating level of awareness or attention. The postpartum period is unique with respect to the degree of neuroendocrine alterations and psychosocial adjustments, the potential impact of breast-feeding on treatment planning, and the long-term implications of a history of postpartum mood disorder on subsequent family planning.

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  - **With seasonal pattern:** This specifier applies to recurrent major depressive disorder.

1. There has been a regular temporal relationship between the onset of major depressive episodes in major depressive disorder and a particular time of the year (e.g., in the fall or winter).
   - **Note:** Do not include cases in which there is an obvious effect of seasonally related psychosocial stressors (e.g., regularly being unemployed every winter).
2. Full remissions (or a change from major depression to mania or hypomania) also occur at a characteristic time of the year (e.g., depression disappears in the spring).
3. In the last 2 years, two major depressive episodes have occurred that demonstrate the temporal seasonal relationships defined above and no nonseasonal major depressive episodes have occurred during that same period.
4. Seasonal major depressive episodes (as described above) substantially outnumber the nonseasonal major depressive episodes that may have occurred over the individual's lifetime.

- **Note:** The specifier "with seasonal pattern" can be applied to the pattern of major depressive episodes in major depressive disorder, recurrent. The essential feature is the onset and remission of major depressive episodes at characteristic times of the year. In most cases, the episodes begin in fall or winter and remit in spring. Less commonly, there may be recurrent summer depressive episodes. This pattern of onset and remission of episodes must have occurred during at least a 2-year period, without any nonseasonal episodes occurring during this period. In addition, the seasonal depressive episodes must substantially outnumber any nonseasonal depressive episodes over the individual's lifetime. This specifier does not apply to those situations in which the pattern is better explained by seasonally linked psychosocial stressors (e.g., seasonal unemployment or school schedule). Major depressive episodes that occur in a seasonal pattern are often characterized by loss of energy, hypersomnia, overeating, weight gain, and a craving for carbohydrates. It is unclear whether a seasonal pattern is more likely in recurrent major depressive disorder or in bipolar disorders. However, within the bipolar disorders group, a seasonal pattern appears to be more likely in bipolar II disorder than in bipolar I disorder. In some individuals, the onset of manic or hypomanic episodes may also be linked to a particular season. The prevalence of winter-type seasonal pattern appears to vary with latitude, age, and sex. Prevalence increases with higher

latitudes. Age is also a strong predictor of seasonality, with younger persons at higher risk for winter depressive episodes.

Specify if:

- **In partial remission:** Symptoms of the immediately previous major depressive episode are present, but full criteria are not met, or there is a period lasting less than 2 months without any significant symptoms of a major depressive episode following the end of such an episode.
- **In full remission:** During the past 2 months, no significant signs or symptoms of the disturbance were present.

Specify current severity:

- Severity is based on the number of criterion symptoms, the severity of those symptoms, and the degree of functional disability.
- **Mild:** Few, if any, symptoms in excess of those required to make the diagnosis are present, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning.
- **Moderate:** The number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for “mild” and “severe.”
- **Severe:** The number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of the symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning.