nosis. 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

A. 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.

B. 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.

C. 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).

D. The disturbance does not occur exclusively during the course of a delirium.

E. 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 1 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 fac-

tors 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

A. 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.
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.
C. 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).
D. The disturbance does not occur exclusively during the course of a delirium.
E. 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:

A. 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).

B. Mixed symptoms are observable by others and represent a change from the person's usual behavior.

C. For individuals whose symptoms meet full criteria for either mania or hypomania, the diagnosis should be bipolar I or bipolar II disorder.

D. 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:

A. 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).

B. 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.

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.

A. Mood reactivity (i.e., mood brightens in response to actual or potential positive events).

B. 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.

C. 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.

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.

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").

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.

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

A. 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).

B. 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).

C. 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.

D. 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 prominent 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.