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Unipolar depression in adults: Assessment and diagnosis

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INTRODUCTION

The assessment and diagnosis of unipolar depressive disorders are based upon clinical interviews and examinations [1]. Although depressive disorders are not diagnosed by laboratory tests, focused tests are often warranted to rule out other medical conditions that can cause or contribute to depressive episodes.

Most adults with clinically significant unipolar depression visit a primary care clinician rather than a psychiatrist [2-4], and 50 percent of patients are not screened or assessed for depression by their health care providers [5]. In addition, multiple studies suggest that the diagnosis is missed in at least 50 percent of depressed primary care patients [6,7]. However, these findings should be interpreted with recognition of the primary care approach to diagnosis over several office visits, the complexity of diagnosing depression in the context of chronic general medical illnesses, and that depressed patients who present to primary care practices may be less severely ill than patients who present to psychiatric practices.

This topic reviews the assessment and diagnosis of depression in adults. The clinical features, epidemiology, neurobiology, treatment, and prognosis of depression in adults are discussed separately, as are the clinical features and diagnosis of depression in pediatric and older adult patients:

- (See "Unipolar depression in adults: Clinical features".)
- (See "Unipolar depression in adults: Epidemiology".)
- (See "Unipolar major depression in adults: Choosing initial treatment".)

- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Diagnosis and management of late-life unipolar depression".)

DEFINITIONS OF DEPRESSION

The term “depression” can be used in multiple ways, which can be confusing; depression may refer to a [8,9]:

- Mood state, as indicated by feelings of sadness, despair, anxiety, emptiness, discouragement, or hopelessness; having no feelings; or appearing tearful. Depressed (dysphoric) mood may be a normal and, at times, adaptive response to loss, disappointment, or perceived failure. In addition, depressed mood may be a symptom of a psychopathological syndrome or another medical disorder (algorithm 1).

- Syndrome, which is a constellation of symptoms and signs that may include depressed mood. Depressive syndromes that are typically encountered include major depression, minor depression, or dysthymia (persistent depressive disorder).

- Mental disorder that is a distinct clinical condition. As an example, the syndrome of major depression can occur in several disorders, such as unipolar major depression (also called “major depressive disorder”), bipolar disorder, schizophrenia, substance/medication-induced depressive disorder, and depressive disorder due to another (general) medical condition.

ASSESSMENT

Unipolar depressive disorders are defined by syndromic criteria, so diagnosis depends upon the clinical history and examination. Most symptom severity scales used in depression screening do not provide a diagnosis, and regardless, a clinical interview is necessary to clarify which depressive disorder is present and to address the differential diagnosis.

History of present illness — History is the most important component of the evaluation. The history should be obtained from the patient and may often involve others such as family members or other clinicians [1]. Issues of patient confidentiality and consent must be recognized when sources other than the patient are considered.

Depressive symptoms and their context — The interview should:

- Establish the presence of depressive symptoms [8]:
  - Depressed mood most of the day
  - Loss of interest or pleasure in most or all activities
  - Insomnia or hypersomnia
  - Significant weight loss or weight gain (eg, 5 percent within a month) or decrease or increase in appetite nearly every day
  - Psychomotor retardation or agitation nearly every day that is observable by others
  - Fatigue or low energy
  - Decreased ability to concentrate, think, or make decisions
  - Thoughts of worthlessness or excessive or inappropriate guilt
  - Recurrent thoughts of death or suicidal ideation, or a suicide attempt

  Depressed mood that occurs most of the day, more days than not, and is persistent (eg, lasts for at least two weeks), can occur in several disorders (algorithm 1).

  Note that psychomotor retardation (eg, slowed speech or movements, or decreased speech output) or agitation (eg, restlessness, handwringing, inability to sit still, or pulling on clothing or skin) must be observed on examination [8]. In older adults, and in younger persons at risk for major or mild neurocognitive disorder or delirium because of general medical/neurologic illness, it is important to ask about neurocognitive symptoms (eg, attention, concentration, and memory). (See "Unipolar depression in adults: Clinical features", section on 'Symptoms'.)

- Determine the chronology of the current depressive symptoms and any prior history of depressive episodes and their course and treatment.
- Determine the impact of the depressive episode upon occupational and interpersonal functioning.
- Elicit alleviating or aggravating factors, including stressful life events and social or occupational circumstances.

- Address comorbidity. (See "Unipolar depression in adults: Clinical features", section on 'Comorbidity'.)
  - Psychiatric (eg, anxiety disorders and substance use disorders)
  - General medical
- Include questions about a past history of mania (table 1) or hypomania (table 2). Bipolar disorder often presents initially with depression rather than mania or hypomania, and multiple episodes of bipolar depression may occur prior to the first lifetime episode of mania/hypomania. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Unipolar major depression'.)

It is useful to distinguish unipolar major depression that has lasted less than two years from depressive syndromes (including major depression) that have lasted two or more years (ie, persistent depressive disorder [dysthymia]). Clinicians can ask, “During the last two years, have you had a period of two or more consecutive months when you had none of the problems you just described?” Recall of such a period can be followed by questions about specific symptoms, because these follow-up questions often reveal that the symptom-free interval was less than two months. Two months with no symptoms or the near absence of symptoms is generally regarded as defining remission from the depressive episode. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Continuation and maintenance treatment'.)

Suicide risk — All depressed patients must be queried specifically about suicidal ideation and behavior. Any positive or equivocal response should prompt clinicians to:

- Ask about the specific nature of the ideation, intent, plans, available means (eg, firearms), and actions.
- Assess the patient for risk factors for suicide, including prior history of suicide attempts, comorbid psychiatric and general medical illnesses, and family history of suicidal behavior.
- Develop a safety plan for further evaluation and treatment that depends upon the level of risk and may range from continued primary care follow-up alone to outpatient psychiatric or emergency room psychiatric evaluation.

In addition, if the clinical history or patient presentation suggest that the patients is at risk for violence directed towards others, clinicians should ask about homicidal ideation and behavior.

Additional information about suicidal ideation and behavior, including patient evaluation, risk factors, and management, is discussed separately. (See "Suicidal ideation and behavior in adults".)

General medical illness — Given the potential for general medical conditions (spanning all organ systems) and drugs to cause or contribute to depressive episodes, the assessment should address all current and significant past general medical illnesses [1]. Medication use and a review of systems are also part of an assessment of potential contributors to the depressive condition.

In some studies, the evaluation of patients with general medical disorders for major depression has focused upon the five mood and cognitive symptoms of depression. (See 'Unipolar major depression' below.)

Family history — A family history may confer increased risk for particular disorders or suicide; thus, the patient should be asked about a family history of depression, suicide, psychosis (eg, delusions and hallucinations), and bipolar disorder. A family history of bipolar disorder suggests the possibility that the patient's current depressive episode may represent bipolar depression. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Unipolar major depression'.)

Social history — The evaluation includes interpersonal, occupational, or financial stressors and the context for the clinical presentation (which may impact treatment); in addition, the social history may identify possible sources of support that may be enlisted for treatment. Assessment of family functioning is often useful in understanding the context of the presenting disorder and possible need for family therapy. (See "Unipolar depression in adults: Family and couples therapy", section on 'Assessment'.)

Mental status examination — The mental status examination supplements the history by observing the presence of depressive signs, including alterations in mood and affect, cognition (eg, attention, concentration, and memory), psychomotor activity, ruminative thought processes, speech, and suicidal thoughts. (See "The mental status examination in adults".)

Physical examination — Although the benefit of screening physical examinations in depression has not been demonstrated, we suggest a physical examination for new onset depression (especially if the psychosocial context or precipitant is not clear), severe depression (particularly patients with melancholic or psychotic features), or treatment-resistant depression, as well as patients who have or at risk for chronic medical conditions. More detailed physical examination should be pursued as guided by the history and review of systems.

Laboratory evaluation — For patients with depressive symptoms in the absence of general medical symptoms or findings on examination, the utility of screening laboratory tests has not been demonstrated. Nevertheless, we suggest focused tests for new onset depression (especially if the psychosocial context or precipitant is not clear), severe depression (particularly patients with melancholic or psychotic features), or treatment-resistant depression [10]. Commonly performed screening laboratory tests include complete blood count, serum chemistry panels, urinalysis, thyroid stimulating hormone, rapid plasma reagin, human chorionic gonadotropin (pregnancy), and urine toxicology screen for drugs of abuse.

Additional laboratory evaluations should be pursued as guided by the medical history, review of systems, and physical examination. More extensive testing (eg, vitamin B12, folate, and electrocardiogram) is often indicated for patients who have chronic medical conditions, or are at increased risk for medical illnesses, including older adult or institutionalized patients, and patients with self-neglect or substance use disorders.

Neuroimaging studies are typically reserved for patients whose evaluation suggests an increased likelihood of structural brain disease [10]. These include focal neurologic signs on physical examination or persistent cognitive impairment. However, it is reasonable to obtain neuroimaging in older depressed patients, especially patients with new onset depression in later life.

Preliminary studies have examined the utility of diagnosing unipolar major depression on the basis of biomarkers [11], but use of these tests is not standard practice, because little evidence supports their use in lieu of history and interview-derived data. As an example:

- One study reported that a highly sensitive and specific panel of blood tests can differentiate patients with major depression from individuals without major depression [12]; however, the study methods were problematic [13,14]. At the beginning of the study, patients with major depression were already diagnosed as such with clinical interviews, so it is not clear that the tests provided any benefit. In addition, the study excluded many types of patients who present with depression, including patients with substance use disorders, other medical problems (eg, rheumatoid arthritis), or a history of bipolar disorder, as well as patients taking commonly used drugs (eg, nonsteroidal anti-inflammatory drugs or antidepressants).

- A review of 14 studies found that biomarkers (eg, markers of inflammation) may perhaps be greater in patients with melancholic depression than nonmelancholic depression [15]. However, the studies often evaluated different markers, study samples were relatively small, and most of the positive results have not been replicated.

Screening for depression — Screening for depression is discussed separately. (See "Screening for depression in adults".)

Diagnostic instruments — Structured and semi-structured, interviewer-administered, diagnostic instruments, such as the Structured Clinical Interview for DSM-5 [16], are available for diagnosing unipolar depressive disorders but are rarely used in routine clinical practice. A structured instrument enables the interviewer to clarify ambiguous or contradictory responses, and may help differentiate the diagnosis of unipolar major depression (major depressive disorder) from bipolar depression. However, structured instruments are labor intensive and generally reserved for specialized evaluation, treatment, or research settings.

DIAGNOSTIC CRITERIA AND CLASSIFICATION

Nosology of depressive disorders — Multiple taxonomies are available for diagnosing depressive disorders. We recommend diagnosing unipolar depressive disorders according to the criteria in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [8]. In DSM-5, the depressive disorders that can be diagnosed include:

- Unipolar major depression (major depressive disorder) (table 3)
- Persistent depressive disorder (dysthymia) (table 4)
- Disruptive mood dysregulation disorder
- Premenstrual dysphoric disorder
- Substance/medication induced depressive disorder
- Depressive disorder due to another medical condition
- Other specified depressive disorder (eg, minor depression)
- Unspecified depressive disorder

Each of the disorders is characterized by dysphoria (sad or irritable mood) [8] (algorithm 1).

As with other psychiatric disorders defined by syndromes, each depressive disorder likely represents an etiologically heterogeneous group of conditions, with similar clinical manifestations, that are not currently distinguishable and that do not yet have differentially targeted treatments.

A reasonable alternative to DSM-5 for diagnosing depressive disorders is the World Health Organization's International Classification of Diseases-10th Revision (ICD-10) [17]. For major depression, the two sets of criteria are largely the same, whereas for other disorders such as dysthymia, the criteria differ substantially. ICD-10 mentions premenstrual tension syndrome

(called premenstrual dysphoric disorder in DSM-5) as a diagnosis but provides no diagnostic criteria. Disruptive mood dysregulation disorder is not included in ICD-10.

Use of explicit criteria sets for diagnosing depression may help avoid overdiagnosing depressive syndromes on the basis of a few symptoms, which may be better attributed to another (general) medical illness or may represent nondiagnosable ("subthreshold") depressive symptoms, for which the evidence base regarding treatment is lacking. Meta-analyses estimate that among primary care patients who are diagnosed with depression, the rate of false positives is 15 to 20 percent [6,7]; these findings should be interpreted with recognition of the time pressures imposed upon primary care clinicians.

Reliability of diagnosis — Test-retest reliability of diagnosis, which measures concordance of diagnoses across assessments conducted at two different time points, is substantial for unipolar depression. A meta-analysis of 35 test-retest reliability studies (sample size not reported) examined agreement between repeated assessments performed by either the same rater or different raters, and found that reliability was good [18]. However, heterogeneity across studies was very large.

Unipolar major depression

When to suspect the disorder — In primary care or general medical settings, the presence of unipolar major depression is suggested by the following clues [8,19]:

- Depressed mood and/or loss of interest or pleasure in most or all activities
- Feelings of helplessness and/or hopelessness
- Irritability
- Anxiety
- Obsessive rumination
- Phobias
- Excessive concern about physical health
- Complaints of pain (eg, headaches or abdominal pain)
- Presence of risk factors such as family history of major depression, and stressful life events

Diagnostic criteria — Unipolar major depression (major depressive disorder) is characterized by a history of one or more major depressive episodes (table 3) and no history of mania (table 1) or hypomania (table 2) [8]. A major depressive episode manifests with five or more of the following nine symptoms for at least two consecutive weeks; at least one symptom must be either depressed mood or loss of interest or pleasure:

- Depressed mood most of the day, nearly every day
- Loss of interest or pleasure in most or all activities, nearly every day
- Insomnia or hypersomnia nearly every day
- Significant weight loss or weight gain (eg, 5 percent within a month) or decrease or increase in appetite nearly every day
- Psychomotor retardation or agitation nearly every day that is observable by others
- Fatigue or low energy, nearly every day
- Decreased ability to concentrate, think, or make decisions, nearly every day
- Thoughts of worthlessness or excessive or inappropriate guilt, nearly every day
- Recurrent thoughts of death or suicidal ideation, or a suicide attempt

In addition, the symptoms cause significant distress or psychosocial impairment, and are not the direct result of a substance or general medical condition. Bereavement does not exclude the diagnosis of a major depressive episode.

None of the nine symptoms of unipolar major depression is pathognomonic for the disorder, and each symptom can occur in other psychiatric illnesses as well as general medical disorders [19]. In addition, episodes of major depression can vary within a patient or across patients because the combination of symptoms in one episode differ from the combination in another episode.

DSM-5 criteria for major depression appear to perform similarly across different languages, ethnicities, and cultures. A study examined DSM-IV criteria for major depression (which are similar to DSM-5) in China, The Netherlands, United Kingdom, and United States, using female patients with recurrent depression from clinical settings and individuals from community samples (total n >7000) [20]. The analyses indicated that the criteria measured the same underlying construct between the Chinese and Western samples, and among the different Western samples.

One study found that inter-rater reliability (degree to which two or more clinicians agree) in diagnosing unipolar major depression according to DSM-5 criteria was only fair (ie, questionable), which may have been due to comorbidity [21]. However, prior experience with the same criteria suggests that the reliability can be very good when clinicians are trained to apply the diagnostic criteria [21].

In some studies, the diagnosis of major depression in patients with general medical disorders has focused upon the five mood and cognitive symptoms of depression, that is, dysphoria, anhedonia, worthlessness or excessive guilt, impaired concentration and decision-making, and suicidal ideation and behavior [8]. Less emphasis was placed upon the four somatic symptoms of depression (ie, anorexia, insomnia, fatigue, and psychomotor activity), because these may be attributable to general medical conditions (eg, cancer or myocardial infarction). Support for this approach includes multiple observational studies [22,23], including two (n = 2510 and 1594 psychiatric outpatients) that diagnosed major depression in patients who had three out of the five mood and cognitive symptoms, at least one of which was low mood or loss of interest [24,25]. Approximately 95 percent of patients who endorsed five or more of the nine symptoms (ie, the standard definition of major depression) also endorsed three of the five mood and cognitive symptoms.

Diagnostic stability — Patients who are initially and correctly diagnosed with unipolar major depression (major depressive disorder) may eventually manifest new or modified symptoms warranting a change in diagnosis.

Patients with bipolar disorder often suffer one or more episodes of major depression and initially receive a diagnosis of major depressive disorder, prior to their first manic or hypomanic syndrome. As an example, a meta-analysis identified five longitudinal studies with adults and adolescents (total n >3000) who were diagnosed with major depressive disorder; the mean length of follow-up across the studies ranged from 12 to 18 years [26]. Bipolar disorder was eventually diagnosed in 23 percent. The probability of switching diagnoses was greatest in the first five years of follow-up and was higher in patients with the following characteristics:

- Younger age of onset of their first lifetime major depressive episode
- Family history of bipolar disorder
- During major depressive episodes:
    - Psychosis (eg, delusions and/or hallucinations)

- Subthreshold hypomanic symptoms such as decreased need for sleep, unusually high energy, or increased goal directed activity

In addition, treatment resistance in patients with major depressive disorder and the presence of comorbid attention deficit hyperactivity disorder or substance use disorders are associated with diagnostic conversion to bipolar disorder [27,28].

Additional information about distinguishing unipolar depression and bipolar depression, which differ in treatment, is discussed separately. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Unipolar major depression'.)

Studies in psychiatric settings suggest that at least 5 and up to 30 percent of patients initially diagnosed with major depressive disorder eventually develop symptoms warranting a change in diagnosis to a schizophrenia-spectrum disorder [29-34]. However, it is likely that the development of schizophrenia occurs at much lower rates in most primary care and other nonpsychiatric care settings. In addition, repeated diagnostic examinations find that the change from major depressive disorder to schizophrenia occurs more frequently than the reverse [30,33,34].

Depressive episode subtypes (specifiers) — DSM-5 specifies several subtypes of depressive episodes [8]. However, it is not clear whether most of these subtypes are useful for choosing a specific treatment. Older studies showed that melancholia, a more severe form of major depression, is less likely than nonmelancholic depression to respond to psychotherapy [35]. By contrast, a more recent meta-analysis of individual patient data from four randomized trials compared cognitive-behavioral therapy with an antidepressant drug in patients with unipolar major depression (total n = 805), and found that the depressive subtypes were not associated with a better response to a one treatment modality over the other modality [36]. In addition, the presence of atypical features or melancholic features did not predict outcome for patients who received a particular treatment modality; however, patients with more severe forms of melancholia would be unlikely to participate in such clinical trials.

The diagnostic criteria for depressive episode subtypes are as follows:

- **Anxious distress** – Anxious distress is characterized by the presence of two or more of the following symptoms during most days of the depressive episode [8]:
  - Tension
  - Restlessness
  - Impaired concentration due to worry
  - Fear that something awful may happen

- Fear of losing self-control

Additional information about anxious depression is discussed separately. (See "Unipolar depression in adults: Clinical features", section on 'Anxious'.)

- **Atypical features** – Atypical features are characterized by at least three of the following symptoms during the depressive episode; at least one of the symptoms is mood reactivity to pleasurable stimuli [8]:
  - Reactive to pleasurable stimuli (ie, feels better in response to positive events).
  - Increased appetite or weight gain.
  - Hypersomnia (eg, sleeping at least 10 hours per day, or at least two hours more than usual when not depressed).
  - Heavy or leaden feelings in limbs.
  - Longstanding pattern of interpersonal rejection sensitivity (ie, feeling deep anxiety, humiliation, or anger at the slightest rebuff from others), which is not limited to mood episodes, and which causes social or occupational conflicts.

  Additional information about atypical depression is discussed separately. (See "Unipolar depression in adults: Clinical features", section on 'Atypical'.)

- **Catatonia** – Catatonic features are characterized by prominent psychomotor disturbances (either increased or decreased activity), which occur during most of the depressive episode. (See "Catatonia in adults: Epidemiology, clinical features, assessment, and diagnosis".)

- **Melancholic features** – Melancholic features are characterized by at least four of the following symptoms during a depressive episode; at least one of the symptoms is either loss of pleasure or lack of reactivity to pleasurable stimuli [8]:
  - Loss of pleasure in most activities
  - Unreactive to usually pleasurable stimuli (ie, does not feel better in response to positive events)
  - Depressed mood marked by profound despondency, despair, or gloominess
  - Early morning awakening (eg, two hours before usual hour of awakening)
  - Psychomotor retardation or agitation
  - Anorexia or weight loss

- Excessive guilt

Additional information about melancholic depression is discussed separately. (See "Unipolar depression in adults: Clinical features", section on 'Melancholic features'.)

- **Mixed features** – Unipolar major depression and persistent depressive disorder (dysthymia) can be accompanied by subthreshold (not meeting full criteria) symptoms of hypomania or mania, and are referred to as major depression with mixed features and persistent depressive disorder with mixed features. Depressive episodes with mixed features are characterized by full criteria for the depressive episode and at least three of the following symptoms during most days of the episode [8]:
  - Elevated or expansive mood.
  - Inflated self-esteem or grandiosity.
  - More talkative than usual or pressured speech (an increased amount of speech that is accelerated and difficult to interrupt; the patient may continue talking even if no one is listening).
  - Flight of ideas (abrupt changes from one topic to another that are based upon understandable associations) or racing thoughts.
  - Increased energy or goal-directed activity.
  - Decreased need for sleep – Sleeping less than usual and still feeling rested and energetic. Decreased need for sleep differs from insomnia, which is marked by difficulty falling or staying asleep, and poor sleep quality. (See "Risk factors, comorbidities, and consequences of insomnia in adults".)
  - Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, buying sprees or sexual indiscretions).

  If full criteria for hypomania (table 2) or mania (table 1) are met, the diagnosis is bipolar disorder, hypomania with mixed features, or bipolar disorder, mania with mixed features, rather than unipolar depression with mixed features [8,37]. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

  Additional information about mixed features is discussed separately. (See "Unipolar depression in adults: Clinical features", section on 'Mixed features'.)

- **Peripartum onset** – Peripartum onset refers to onset of mood episodes during pregnancy or within four weeks of childbirth. (See "Unipolar major depression during pregnancy: Epidemiology, clinical features, assessment, and diagnosis" and "Postpartum unipolar major depression: Epidemiology, clinical features, assessment, and diagnosis".)

- **Psychotic features** – Psychotic features include delusions (false, fixed beliefs) and hallucinations (false sensory perceptions), which can occur at any time during a depressive episode. (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis".)

- **Seasonal pattern** – Seasonal pattern refers to a regular temporal relationship between the onset of major depressive episodes and a particular time of year, for the past two years. Remission also occurs at a specific time of year. As an example, episodes may begin in winter and remit in summer. In addition, the lifetime number of seasonal episodes substantially outnumbers the nonseasonal episodes. Additional information about recurring major depression with seasonal onset and remission is discussed separately. (See "Seasonal affective disorder: Epidemiology, clinical features, assessment, and diagnosis".)

Persistent depressive disorder (dysthymia) — The DSM-5 diagnostic criteria for persistent depressive disorder (dysthymia) (table 4) [8] are nearly identical to the criteria for dysthymic disorder in DSM-IV-TR [38]. The primary difference is that persistent depressive disorder also subsumes patients with unipolar major depression that lasts at least two years (which was called “chronic unipolar major depression” in DSM-IV-TR). DSM-5 consolidated dysthymic disorder and chronic major depression into persistent depressive disorder because there was little difference between dysthymic disorder and chronic major depression with regard to demographics, symptom patterns, treatment response, and family history [39-42].

Persistent depressive disorder manifests with three or more of the following symptoms for at least two consecutive years; at least one symptom must be depressed mood [8]:

- Depressed mood most of the day, more days than not
- Decreased or increased appetite
- Insomnia or hypersomnia
- Low energy or fatigue
- Low self esteem
- Impaired concentration or decision making
- Hopelessness

Thus, symptoms are not as numerous as in major depression. Symptom-free periods during the course of persistent depressive disorder can occur but may not exceed two consecutive months during the two-year (or longer) timeframe.

Persistent depressive disorder causes significant distress or psychosocial impairment [8]. The effect upon social and occupational functioning varies, but can exceed that of major depression.

DSM-5 uses terms to describe whether the episode of persistent depressive disorder is a pure dysthymic syndrome or a persistent major depressive episode, or includes intermittent major depressive episodes (table 4) [8]. In addition, DSM-5 specifies several subtypes for episodes of persistent depressive disorder, including anxious distress, atypical features, melancholic features, mixed features, psychotic features, and peripartum onset. The diagnostic criteria for these subtypes are discussed elsewhere in this topic. (See 'Depressive episode subtypes (specifiers)' above.)

Disruptive mood dysregulation disorder — The diagnosis of disruptive mood dysregulation disorder is discussed separately in the context of pediatric patients. (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Disruptive mood dysregulation disorder'.)

Premenstrual dysphoric disorder — Premenstrual dysphoric disorder is marked by emotional and behavioral symptoms that repeatedly occur during the week before onset of menses and remit with onset of menses or a few days thereafter, and which interfere with some aspect of the patient's life. (See "Clinical manifestations and diagnosis of premenstrual syndrome and premenstrual dysphoric disorder".)

Substance/medication induced depressive disorder — Substance/medication-induced depressive disorder consists of a mood disturbance that is characterized by a persistently depressed or irritable mood, or diminished interest or pleasure in most activities [8]. The mood disturbance develops during or soon after using substances for recreational purposes or using prescribed medications; the substances/medications are judged to be capable of causing the mood disturbance. In addition, the disturbance causes significant distress or impairs psychosocial functioning.

Substance/medication-induced depressive disorder is not diagnosed in the following situations:

- The mood disturbance precedes onset of substance intoxication or withdrawal, or exposure to medications

- The disturbance persists for a long period of time (eg, one month) after cessation of acute intoxication or withdrawal
- There is a prior history of recurrent depressive episodes
- The disturbance occurs solely during an episode of delirium (see "Diagnosis of delirium and confusional states")

Depressive syndromes may be caused by intoxication or withdrawal from a wide range of substances that are encountered in substance-related and addictive disorders, including alcohol, amphetamines, cannabis, cocaine, and stimulants [1].

Substance/medication-induced depressive disorder is often referred to as “secondary depression.” Information about depressive syndromes that are secondary to prescribed medications is discussed separately. (See "Unipolar depression: Pathogenesis", section on 'Secondary depression'.)

Depressive disorder due to another medical condition — Depressive disorder due to another medical condition consists of a mood disturbance that is characterized by a persistently depressed or irritable mood, or diminished interest or pleasure in most activities [8]. Findings from the history, physical examination, or laboratory tests indicate that the disturbance is caused by another medical condition (eg, adrenal insufficiency, Huntington disease, hypercortisolism, hypothyroidism, mononucleosis, multiple sclerosis, obstructive sleep apnea, Parkinson disease, stroke, systemic lupus erythematosus, traumatic brain injury, or vitamin B12 insufficiency). In addition, the disturbance results in significant distress or impairs psychosocial functioning. Onset of the mood disturbance generally occurs during the first month of the onset of the other medical condition. In some cases, depressive syndromes represent a prodrome or early manifestation of the other medical condition [43]. Depression that results from the treatment of chronic illnesses, such as corticosteroids or interferon, is diagnosed as substance/medication-induced depressive disorder. (See 'Substance/medication induced depressive disorder' above.)

While clinicians should always remain vigilant for the presence of other medical illnesses causing or contributing to a depressive episode, the following circumstances raise the possibility of an otherwise clinically occult medical condition contributing to the depressive presentation:

- Severe new-onset depression, including melancholia and psychotic depression

- New-onset depression in an older adult, or in a younger adult with significant chronic or acute medical conditions
- New-onset or recurrent depression that is not readily understood in the context of the patient's psychosocial stressors and circumstances
- Depression that has not responded to treatment attempts
- Depression with significant coexisting anxiety or neurocognitive impairment

Depressive syndromes may be caused by a wide range of general medical or neurologic illnesses (table 5); these depressive episodes are often referred to as secondary depression. (See "Unipolar depression: Pathogenesis", section on 'Secondary depression'.)

Depressive disorder due to another medical condition is not diagnosed if the mood disturbance clearly precedes onset of the medical condition or occurs solely during an episode of delirium. (See "Diagnosis of delirium and confusional states".)

Other specified depressive disorder — Other specified depressive disorder applies to patients with depressive symptoms that cause significant distress or impair psychosocial functioning but do not meet the full criteria for a specific depressive disorder [8]. Clinicians record the diagnosis "other specified depressive disorder," followed by the reason that the presentation does not meet full criteria for a specific depressive disorder. As an example, "other specified depressive disorder, recurrent brief depression" is diagnosed in patients who present with recurrent periods lasting for less than two weeks that are characterized by depressed or irritable mood and at least four other depressive symptoms.

Minor depression — Minor depressive episodes (table 6) consist of depressed mood plus one to three other symptoms of major depression, last for a minimum of two weeks, and cause clinically significant impairment or distress. In DSM-5, minor depression is classified as "other specified depressive disorder, depressive episode with insufficient symptoms" [8]. The clinical features and diagnosis of minor depression are discussed separately (as is the management and treatment). (See "Unipolar minor depression in adults: Epidemiology, clinical presentation, and diagnosis" and "Unipolar minor depression in adults: Management".)

Unspecified depressive disorder — Unspecified depressive disorder applies to patients with depressive symptoms that cause significant distress or impair psychosocial functioning but do not meet the full criteria for a specific depressive disorder [8]. This diagnosis is used when clinicians decide to not specify the reason that the presenting syndrome does not meet the full

criteria for a specific depressive disorder and can include situations in which there is insufficient information to make a more specific diagnosis (eg, in the emergency department).

DIFFERENTIAL DIAGNOSIS

Symptoms of unipolar depression in adults can overlap with symptoms of other psychiatric and general medical disorders. As an example, clinically significant and persistent (eg, two weeks) depressed mood can occur in multiple psychiatric and medical disorders (algorithm 1). Unipolar depression needs to be distinguished from these other disorders to prevent inappropriate treatment.

The differential diagnosis of unipolar depression in children and adolescents is discussed separately. (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Differential diagnosis'.)

Other medical illnesses — Many general medical illnesses, affecting most organ systems, can give rise to depressive symptoms or syndromes [44]. Thus, a physical examination and laboratory tests are often indicated for patients presenting with depressive symptoms to rule out another medical illness. (See 'Physical examination' above and 'Laboratory evaluation' above.)

Patients with a general medical illness may present with a persistently depressed or irritable mood, or diminished interest or pleasure in most activities, which results in significant distress or impairs psychosocial functioning. The diagnosis in these cases is depressive disorder due to another medical condition. (See 'Depressive disorder due to another medical condition' above.)

Patients using medications prescribed for another medical illness may also present with a persistently depressed or irritable mood, or diminished interest or pleasure in most activities, which results in significant distress or impairs psychosocial functioning. The diagnosis in these cases is substance/medication induced depressive disorder. (See 'Substance/medication induced depressive disorder' above.)

Sadness — Periods of sadness and irritability (dysphoria) in the absence of other symptoms do not warrant the diagnosis of a depressive disorder. As an example, the diagnosis of unipolar major depression (table 3) requires not only that the dysphoria occurs for most of the day for nearly every day for at least two weeks, but that the dysphoria is accompanied by at least four other depressive symptoms as well as significant distress or psychosocial impairment. Sadness and irritability are generally a normal, adaptive part of the human condition, particularly in response to loss, disappointment, or perceived failure.

Burnout — Burnout is a work-related condition that is characterized by emotional exhaustion, dissatisfaction with one's accomplishments, and depersonalization (detachment from one's job) [45,46]. The condition can occur in the context of chronic job-related stress, including medical practice.

Physician burnout appears to undermine career engagement and patient care [47]. As an example, a meta-analysis included 170 observational studies (n >230,000 physicians) and found that physicians with burnout were more than three times as likely to be dissatisfied with their career (odds ratio 3.8, 95% CI 3.2-4.4), regret their career choice (odds ratio 3.5, 95% CI 2.4-5.0), and to have thoughts or intentions to leave their job (odds ratio 3.1, 95% CI 2.3-4.2) [48]. In addition, physicians with burnout were twice as likely to be involved in patient safety incidents (odds ratio 2.0, 95% CI 1.7-2.5), have low professionalism (odds ratio 2.3, 95% CI 2.0-2.7), and to receive low patient satisfaction ratings (odds ratio 2.2, 95% CI 1.4-3.6). However, heterogeneity across studies was substantial.

Job-stress can also lead to unipolar major depression, and symptoms that may be observed in both burnout and unipolar major depression include dysphoria, fatigue, and suicidal ideation. Distinguishing burnout from unipolar major depression is based primarily upon determining whether the individual meets diagnostic criteria for unipolar major depression (table 3), because burnout is not a single standardized syndrome and is often poorly defined [49].

Adjustment disorder with depressed mood — Adjustment disorder with depressed mood and depressive disorders such as unipolar major depression can both present with dysphoria that occurs in the context of psychosocial stressors. However, adjustment disorder is diagnosed only if symptoms do not meet criteria for another specific disorder (eg, major depression or another depressive disorder).

Adjustment disorder with depressed mood is classified in the category trauma- and stressor-related disorders, and is marked by depressed mood that occurs in response to an identifiable psychosocial stressor (eg, marital conflicts, job loss, academic failure, or persistent painful illness with progressive disability) [8]. The stressor may be a single event or there may be multiple stressors, and a stressor may be recurrent or continuous.

The diagnostic criteria for adjustment disorder with depressed mood are as follows [8]:

- Low mood, tearfulness, or feelings of hopelessness that occur in response to an identifiable stressor within three months of onset of the stressor.
- Symptoms are clinically significant as evidenced by at least one of the following:

- Significant distress that exceeds what would be expected given the nature of the stressor
- Impaired social or occupational functioning

- The syndrome does not meet criteria for another psychiatric disorder (eg, unipolar major depression)
- The syndrome does not represent an exacerbation of a preexisting psychiatric disorder
- The syndrome does not represent bereavement
- After the stressor and its consequences have ended, the syndrome resolves within six months

Attention deficit hyperactivity disorder — Impaired concentration, inattention, and fidgeting can occur in both attention deficit hyperactivity disorder (ADHD) and depressive disorders [8]. However, these symptoms become prominent in depressive disorders only during active mood episodes, whereas the symptoms are pervasive in ADHD. In addition, depressive disorders are characterized by symptoms such as sleep and appetite disturbance and suicidality, which are not present in ADHD. (See "Attention deficit hyperactivity disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)

ADHD can also be comorbid with depressive disorders. (See "Unipolar depression in adults: Clinical features", section on 'Psychiatric'.)

Bipolar disorder — Bipolar disorder is often underdiagnosed in patients who present with depressive syndromes, and it is critical to ask about a history of mania (table 1) or hypomania (table 2), which define bipolar disorder and affect treatment of the depressive episode [1]. However, clinicians should also avoid overdiagnosing bipolar disorder in patients with unipolar depression; overdiagnosis of bipolar depression may be more likely in depressed patients who are more severely ill (eg, have higher rates of comorbidity, chronicity, and functional impairment) [50]. The differential diagnosis of unipolar major depression and bipolar major depression is discussed separately. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Unipolar major depression'.)

Borderline personality disorder — Symptoms that are common to borderline personality disorder and unipolar major depression include dysphoria and recurrent suicidal ideation [8]. However, borderline personality disorder is characterized by mood states that fluctuate within a single day, whereas major depression is marked by dysphoria that is present most of the day,

nearly every day, for at least two weeks. (Other personality disorders, such as antisocial, histrionic, and narcissistic, can also include fluctuating mood states.)

In addition, borderline personality disorder can include identity disturbance, frantic efforts to avoid abandonment, and chronic feelings of emptiness, which are not features of major depression [8]. Conversely, major depression can include insomnia or hypersomnia, weight loss or weight gain, and low energy, which are not features of borderline personality disorder.

Complicated grief — Complicated grief is a form of acute grief that is abnormally intense, prolonged, and disabling. Although several symptoms such as sadness, insomnia, and social withdrawal can occur in both complicated grief and major depression, complicated grief is a unique and recognizable disorder that can be distinguished from depression. (See "Prolonged grief disorder in adults: Epidemiology, clinical features, assessment, and diagnosis", section on 'Unipolar major depression'.)

Delirium — Delirium and unipolar depression can both manifest difficulty with attention or concentration, poor sleep, and psychomotor retardation or agitation. However, delirium is marked by decreased level of alertness and consciousness, significant impairment of other neurocognitive functions, and marked fluctuation of symptoms, which are not characteristic of depression. (See "Diagnosis of delirium and confusional states".)

Schizophrenia and schizoaffective disorder — Unipolar major depression with psychotic features, schizophrenia, and schizoaffective disorder can all present with delusions and hallucinations. However, in unipolar psychotic depression, delusions and hallucinations occur only during an episode of major depression [8]. By contrast, in schizophrenia and schizoaffective disorder, psychotic symptoms can and do occur in the absence of major depression. The clinical features and diagnosis of unipolar major depression with psychotic features, schizophrenia (table 7), and schizoaffective disorder are discussed separately, as is the assessment of depression in patients with schizophrenia. (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis" and "Schizophrenia in adults: Clinical features, assessment, and diagnosis" and "Depression in schizophrenia".)

WHEN TO REFER

The decision to refer patients to a mental health specialist will depend on many factors: the primary care clinician's own level of expertise and confidence in assessing, diagnosing, and treating depression; the availability of mental health specialty resources; and patient/family

preference. In general, the following clinical factors should lead to psychiatric referral sooner rather than later:

- Patients for whom the diagnosis of depression or its comorbidities is uncertain
- Depression that endangers the life of the patient (ie, suicidality or inability to care for self) or others (aggressivity or inability to care for dependent others)
- Severe, psychotic, and catatonic depression
- Depression that occurs in the context of bipolar disorder, schizoaffective disorder, or schizophrenia

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Depression in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Depression in children and adolescents (Beyond the Basics)")

SUMMARY

- **Terminology** – Depression can refer to a mood state, syndrome, or specific clinical disorder. Depressed mood may be a normal and adaptive response to loss; in addition, depressed mood may be a symptom of a psychopathological syndrome or disorder, or another medical disorder (algorithm 1). (See 'Definitions of depression' above.)

- **Assessment** – The assessment of patients who are being evaluated for a depressive disorder includes the history of present illness, current and past medical illness, family history, social history, mental status examination, physical examination, and focused laboratory tests. The history must address suicidal ideation and behavior. (See 'Assessment' above.)

  Although there is no evidence to support screening physical examinations and routine laboratory testing in the diagnosis of depression, an exam and a complete blood count, serum chemistry panels, urinalysis, thyroid stimulating hormone, rapid plasma reagin, human chorionic gonadotropin (pregnancy), and urine toxicology screen for drugs of abuse may be helpful when underlying medical conditions are suspected. (See 'Physical examination' above and 'Laboratory evaluation' above.)

  Several screening instruments are available to facilitate assessments for depression. (See "Screening for depression in adults".)

- **Nosology** – Depressive disorders include unipolar major depression, persistent depressive disorder (dysthymia), disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, and depressive disorder due to another medical condition. (See 'Nosology of depressive disorders' above.)

- **Unipolar major depression** – Episodes of unipolar major depression (table 3) require the presence of at least five depressive symptoms, including depressed mood or loss of interest, for a minimum of two consecutive weeks. (See 'Unipolar major depression' above and "Unipolar depression in adults: Clinical features", section on 'Symptoms'.)

- **Persistent depressive disorder** – Persistent depressive disorder (dysthymia) (table 4) is diagnosed in patients with three or more depressive symptoms for at least two consecutive years; at least one symptom must be depressed mood. (See 'Persistent depressive disorder (dysthymia)' above.)

- **Subtypes** – Subtypes of unipolar major depression and persistent depressive disorder include anxious, atypical, catatonia, melancholia, mixed features, peripartum, psychotic, and seasonal. (See 'Depressive episode subtypes (specifiers)' above.)

- **Differential diagnosis** – The differential diagnosis of unipolar depressive disorders includes general medical disorders, sadness, burnout, adjustment disorder with depressed mood, attention hyperactivity disorder, bipolar disorder, borderline personality disorder, complicated grief, delirium, schizophrenia, and schizoaffective disorder. (See 'Differential diagnosis' above.)

- **Referral** – Referral to a mental health specialist is indicated for patients in whom the diagnosis of depression or its comorbidities is uncertain; patients with severe depression, depression unresponsive to initial treatment, and psychotic or catatonic depression; or depression that is part of bipolar disorder, schizoaffective disorder, or schizophrenia. (See 'When to refer' above.)

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