Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis

AUTHOR: Anthony J Rothschild, MD
SECTION EDITOR: Peter P Roy-Byrne, MD
DEPUTY EDITOR: David Solomon, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Oct 03, 2023.**

INTRODUCTION

Unipolar major depression with psychotic features is a severe subtype of unipolar major depression (major depressive disorder) [1]. The psychotic symptoms are delusions and/or hallucinations that are frequently consistent with depressive themes of guilt and worthlessness [2]. Psychotic depression and nonpsychotic depression differ in their diagnosis, treatment, and prognosis.

This topic reviews the epidemiology, pathogenesis, clinical features, assessment, and diagnosis of unipolar major depression with psychotic features. Treatment and prognosis are discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment" and "Unipolar major depression with psychotic features: Maintenance treatment and course of illness".)

EPIDEMIOLOGY

The lifetime prevalence rate of unipolar major depression with psychotic features varies depending upon the setting.

General population — Large, nationally representative surveys of the general adult population in European countries estimate that both the point and lifetime prevalence of unipolar major depression with psychotic features is 0.4 to 0.5 percent [3,4]. The mean age of onset of unipolar major depression among individuals with psychotic depression is 29 years [1].

Studies of risk factors have found that unipolar psychotic depression is [1,3-7]:

- More common in females than males
- Associated with unemployment, and receiving public assistance or disability payments
- Associated with a parental history of bipolar disorder

Some community surveys have found that the prevalence of psychotic depression is greater in individuals aged 60 years and over than it is in younger adults [8,9], but other surveys have not [3,5].

Patients with unipolar major depression — Many patients with unipolar major depression are psychotic. A pooled analysis of 43 studies found that among all patients with depression, psychotic depression was present in 28 percent [4]. Among patients who were hospitalized for depression (n = 22 studies), the median proportion with psychotic features was 42 percent.

PATHOGENESIS

The pathogenesis of unipolar major depression with psychotic features is unknown. Studies have identified neurobiologic abnormalities, but it is not clear if these findings represent etiologic causes or sequelae because the studies investigated patients after they developed the disorder.

Neurobiologic correlates — The neurobiology of psychotic major depression includes dysregulation of the hypothalamic-pituitary-adrenal axis [10]. A meta-analysis of 14 randomized trials (984 unipolar or bipolar patients with psychotic or nonpsychotic depression) found that nonsuppression of cortisol following a dose of dexamethasone (dexamethasone suppression test) occurred in significantly more patients with psychotic depression than nonpsychotic depression (64 versus 41 percent) [11]. Other studies have found that urine cortisol levels were significantly higher in unipolar psychotic depression than nonpsychotic depression [12]. Increased hypothalamic-pituitary-adrenal axis activity in unipolar psychotic depression is also suggested by elevated adrenocorticotrophic responses to dexamethasone plus corticotropin-releasing hormone [13]. Hypothalamic-pituitary-adrenal axis hyperactivity may possibly be related to all-cause mortality in patients with unipolar psychotic depression [14]. Mortality in

psychotic depression is discussed separately. (See "Unipolar major depression with psychotic features: Maintenance treatment and course of illness", section on 'Mortality'.)

Other neurobiologic correlates found in patients with unipolar psychotic depression include significantly decreased plasma levels of dopamine-beta-hydroxylase (the enzyme that converts dopamine to norepinephrine) [15], increased volume of cerebral ventricles [16], decreased amygdala volume [17], structural and functional abnormalities in the subgenual cingulate cortex [18], and elevated levels of micro-RNAs 126-3p and 106a-5p [19]. Regional cerebral blood flow [20] and rapid eye movement activity [21] may also be abnormal in unipolar psychotic depression. In addition, different neural circuits may be involved in the cognitive impairment observed in psychotic depression and in nonpsychotic depression [22,23].

CLINICAL FEATURES

Unipolar major depression with psychotic features is characterized by an episode of unipolar major depression that includes delusions and/or hallucinations [2].

Unipolar major depression — An episode of major depression is a period lasting at least two weeks, with five or more of the following symptoms: depressed mood, loss of interest or pleasure in most activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (table 1). The episode of major depression is unipolar if the patient has no history of mania (table 2) or hypomania (table 3) [2].

The symptoms of major depression in unipolar psychotic depression are more numerous than they are in unipolar nonpsychotic depression [5]. Psychotic depression is also marked by depressive symptoms that are more severe/intense, including [4,7,10,24-27]:

- Suicidal ideation
- Hopelessness
- Cognitive impairment (attention, concentration, learning, memory, executive functioning, and psychomotor speed)
- Insomnia
- Guilt
- Somatic complaints and hypochondriasis
- Psychomotor agitation or retardation
- Impulsivity

Evidence regarding severity of depression includes a meta-analysis of 15 studies (number of patients not reported), which compared the intensity of depressive symptoms in patients with psychotic depression and nonpsychotic depression [4]. Depressive symptoms were more intense in psychotic depression, and the clinical difference was moderate.

Psychotic features — Psychotic features that can occur during unipolar major depressive episodes consist of [2,10,28,29]:

- Delusions – False, fixed beliefs
- Hallucinations – False sensory perceptions, usually auditory

Psychotic features are often missed. The symptoms may be subtle or intermittent, and patients frequently conceal their psychosis because they are suspicious of others and fear being labeled "crazy" [30,31]. In addition, the delusions are often plausible (eg, "I've committed a crime," "My neighbors are harassing me," or "I have cancer"). Thus, the clinician may identify the symptom of guilt or persecution, but may not recognize that the symptom is a delusion. In particular, distinguishing between delusional and nondelusional guilt can be difficult and may require repeated interviews [10].

The content of psychotic features is typically mood-congruent (ie, consistent with depressive themes of worthlessness, guilt, deserved punishment, nihilism [impending disaster], and hopelessness) [2,32]. Mood-incongruent psychotic features are not directly related to depressive themes; examples include thought insertion (eg, "My cousin is sticking thoughts in my head"), thought broadcasting (eg, "I am broadcasting my thoughts over the internet"), and delusions of control. It is not known if mood-congruent and mood-incongruent psychotic features are related to treatment outcome or prognosis.

Suicidality — Unipolar major depression with psychotic features is often accompanied by suicide attempts or suicidal ideation [10]. Among patients who are currently suffering from psychotic depression, suicide attempts will occur in roughly 20 to 25 percent:

- A randomized trial of 183 patients with unipolar psychotic depression found that 21 percent had attempted suicide during the current episode and another 39 percent had suicidal ideation [33]

- A community survey of 114 individuals with unipolar psychotic depression found that 27 percent had attempted suicide during the current episode [1]

Suicide attempts and suicidal ideation in patients with unipolar psychotic depression are associated with [19,33,34]:

- Male gender
- Past suicide attempt
- Greater severity/intensity of depressive symptoms
- Delusions of guilt

A review found that during acute episodes of depression, completed suicide, suicide attempts, and suicidal ideation occur more often in psychotic unipolar depression than nonpsychotic unipolar depression [35]. As an example, a retrospective study included inpatients with unipolar major depression who either committed suicide (n = 14) or did not (n = 28); the relative risk of committing suicide during hospitalization was five times greater among patients with psychotic depression than nonpsychotic depression (relative risk 5) [36].

After the acute depressive episode has resolved, it is not clear if the rate of completed suicide differs between psychotic depression and nonpsychotic depression, due to conflicting results across observational studies:

- A review of eight studies of unipolar depression concluded that after the acute episode has resolved, the rate of completed suicide does not differ between psychotic depression and nonpsychotic depression, presumably due to patients having received treatment [35]. In the largest study, which used national registries to identify patients hospitalized for either severe psychotic unipolar depression (n >12,000) or severe nonpsychotic unipolar depression (n >26,000), death by suicide during follow-up occurred in 2 percent of each group [37].

- By contrast, in a meta-analysis that included nine studies of patients with unipolar major depression (n >33,000), the lifetime risk of completed suicide was greater in patients with psychotic depression than those with nonpsychotic depression (odds ratio 1.21, 95% CI 1.04-1.40) [38]. In another meta-analysis from the same research group, the lifetime risk of suicide attempts was also greater in patients with unipolar psychotic depression than those with unipolar nonpsychotic depression [39].

Patients with unipolar major depression (psychotic or nonpsychotic) are at increased risk of committing suicide compared with the general population. (See "Unipolar depression in adults: Course of illness", section on 'Suicide'.)

Additional information about suicidal ideation and behavior is discussed separately. (See "Suicidal ideation and behavior in adults".)

Comorbid anxiety — Comorbid anxiety disorders occur frequently in unipolar psychotic depression. A study of 259 patients with psychotic depression found that 36 percent had a

concurrent anxiety disorder such as [40]:

- Posttraumatic stress disorder
- Panic disorder
- Generalized anxiety disorder
- Social phobia
- Specific phobia

Comorbid anxiety disorders appear to be significantly more prevalent in unipolar psychotic depression than nonpsychotic depression [1].

Course of illness — Course of illness appears to be poorer in psychotic depression than nonpsychotic depression:

- **Remission** – A meta-analysis of seven studies (number of patients not reported) found that there was a trend for a lower rate of remission in patients with psychotic depression than patients with nonpsychotic depression (relative risk 0.82, 95% CI 0.67-1.00) [4].

  In a subsequent retrospective study of patients with unipolar major depression (n = 1410, including 154 with psychotic features), resistance to treatment occurred more than twice as often in psychotic depression than nonpsychotic depression (80 versus 36 percent of patients) [7].

- **Relapse** – A review concluded that the rate of relapse was greater in psychotic depression than nonpsychotic depression. As an example, a five-year prospective study found that relapse occurred in more patients with psychotic depression (n = 29) than nonpsychotic depression (n = 18) (69 versus 44 percent) [4].

ASSESSMENT

The initial clinical evaluation of patients with a possible diagnosis of unipolar psychotic depression includes a psychiatric history and mental status examination, with emphasis upon depressive and psychotic symptoms [10,41-43]. The clinician should also obtain a general medical history, physical examination, and laboratory tests that are guided by the history and examination. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Assessment'.)

Major depression with psychotic features may be mistaken for nonpsychotic depression because the delusions and hallucinations are subtle, plausible, intermittent, or concealed by the patient [30,31]. Clinicians can address this problem by [10]:

- Interviewing a family member or friend along with the patient. Family meetings for assessment and treatment of patients with major depression are discussed separately. (See "Unipolar depression in adults: Family and couples therapy".)

- Asking the patient about “strange or irrational worries” rather than “psychosis,” because the word “psychotic” may be frightening or pejorative.

DIAGNOSIS

The word “depression” is used in different ways that have distinct diagnostic meanings [2]. Major depression (table 1) is a syndrome that can occur as part of unipolar major depressive disorder, or as part of bipolar disorder if the patient has a history of mania (table 2) or hypomania (table 3). An episode of major depression is a period lasting at least two weeks, with five or more of the following symptoms: depressed mood, loss of interest or pleasure in most activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide. The clinical manifestations and diagnosis of major depression, unipolar major depressive disorder, and bipolar disorder are discussed further. (See "Unipolar depression in adults: Assessment and diagnosis" and "Bipolar disorder in adults: Clinical features", section on 'Clinical presentation' and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

According to the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition, Text Revision (DSM-5-TR), unipolar major depression with psychotic features is diagnosed when an episode of unipolar major depression includes delusions or hallucinations [2]. The delusions and/or hallucinations are classified as either mood-congruent or mood-incongruent. The congruency of psychotic features and mood are discussed separately. (See 'Psychotic features' above.)

The World Health Organization’s International Classification of Diseases – 10th Revision (ICD-10) includes the diagnosis “severe depressive episode with psychotic symptoms” for patients with unipolar major depression and delusions or hallucinations [44]. Severe depressive episode with psychotic symptoms is also diagnosed if unipolar major depression is accompanied by psychomotor retardation that has progressed to stupor, with little or no spontaneous movement or response to external stimuli.

Diagnostic stability — Among patients who are initially and correctly given the diagnosis of unipolar major depression with psychotic features, the diagnosis eventually changes to bipolar

disorder in roughly 5 to 20 percent, and to schizoaffective disorder in about 10 percent:

- A national registry study identified patients diagnosed with unipolar psychotic depression (n >8500), and found that subsequent conversion to bipolar disorder occurred in 7 percent [45]. Recurrent depression and early age of onset of psychotic depression were associated with conversion. In the general population of depressed patients, younger age of onset and psychotic features are each associated with diagnostic conversion to bipolar disorder. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Diagnostic stability'.)

- In an observational study of 107 patients who were hospitalized for their first lifetime episode of psychotic depression and then followed prospectively for a mean of four years, the diagnosis changed to bipolar disorder in 19 percent and to schizoaffective disorder in 11 percent [46].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of unipolar major depression with psychotic features includes:

- Unipolar major depression without psychotic features
- Schizophrenia and schizoaffective disorder
- Bipolar major depression with psychotic features

The correct diagnosis is essential for treatment [31,47].

Unipolar major depression without psychotic features — Unipolar major depression is present in both unipolar major depression with psychotic features and unipolar major depression without psychotic features. Psychotic depression is distinguished by the presence of delusions and hallucinations [2]. In addition, psychotic depression is characterized by more numerous and severe symptoms of major depression, compared with nonpsychotic depression [5,10,25]. Suicidal ideation, suicide attempts, and comorbid anxiety disorders are also more common in psychotic depression [1,48]. (See 'Unipolar major depression' above and 'Psychotic features' above and 'Suicidality' above and 'Comorbid anxiety' above.)

The clinical features and diagnosis of major depression are discussed separately. (See "Unipolar depression in adults: Assessment and diagnosis".)

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 [2]. 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 schizophrenia and schizoaffective disorder are discussed separately, as is the assessment and management of depression in patients with schizophrenia. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis" and "Depression in schizophrenia".)

Bipolar major depression with psychotic features — Episodes of major depression with (or without) psychotic features can occur in both unipolar major depressive disorder and bipolar disorder. Bipolar psychotic depression is diagnosed if the patient has a prior history of mania, mixed mania, or hypomania; otherwise, the episode of psychotic major depression is unipolar [2]. The clinical manifestations and diagnosis of major depression, unipolar major depressive disorder, and bipolar disorder are discussed separately. (See 'Diagnosis' above and "Unipolar depression in adults: Assessment and diagnosis" and "Bipolar disorder in adults: Clinical features", section on 'Psychosis' and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

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".)

SUMMARY

- **Major depression is a syndrome** – Major depression is a syndrome that can occur as part of unipolar major depressive disorder, or as part of bipolar disorder if the patient has a history of mania, mixed mania, or hypomania. (See 'Unipolar major depression' above and 'Diagnosis' above and "Unipolar depression in adults: Assessment and diagnosis" and "Bipolar disorder in adults: Clinical features", section on 'Clinical presentation' and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

- **Prevalence** – The estimated lifetime prevalence of unipolar major depression with psychotic features in the general adult population is 0.4 to 0.5 percent. Among individuals with unipolar major depression, approximately 28 percent have psychotic features. (See 'Epidemiology' above.)

- **Pathogenesis** – The pathogenesis of unipolar major depression with psychotic features is unknown. Neurobiologic correlates include hyperactivity of the hypothalamic-pituitary-

adrenal axis. (See 'Pathogenesis' above.)

- **Clinical features** – The symptoms of major depression in unipolar psychotic depression are more numerous and severe than they are in unipolar nonpsychotic depression. In addition, suicidal ideation, suicide attempts, and comorbid anxiety disorders are more common in unipolar psychotic depression. The psychotic features are typically consistent with depressive themes of guilt, worthlessness, and hopelessness. (See 'Clinical features' above.)

- **Assessment** – The initial clinical evaluation of patients presenting with depressive and psychotic symptoms includes a psychiatric and general medical history, mental status and physical examination, and laboratory tests guided by the symptoms, history, and findings on the physical examination. A family meeting may help reveal delusions and hallucinations that are subtle, plausible, intermittent, or concealed by the patient. (See 'Assessment' above.)

- **Diagnosis** – Unipolar major depression with psychotic features is characterized by an episode of unipolar major depression (table 1) that includes delusions and/or hallucinations. An episode of major depression is a period lasting at least two weeks, with five or more of the following symptoms: depressed mood, loss of interest or pleasure in most activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide. (See 'Diagnosis' above.)

- **Differential diagnosis** – The differential diagnosis of unipolar major depression with psychotic features includes unipolar major depression without psychotic features, schizophrenia, schizoaffective disorder, and bipolar psychotic depression. (See 'Differential diagnosis' above.)

Topic 14686 Version 19.0

→