



Official reprint from UpToDate®

www.uptodate.com © 2023 UpToDate, Inc. and/or its affiliates. All Rights Reserved.

Wolters Kluwer

Unipolar depression in adults: Course of illness

AUTHOR: William Coryell, MD**SECTION EDITOR:** Peter P Roy-Byrne, MD**DEPUTY EDITORS:** Sara Swenson, MD, 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: **Dec 15, 2021**.

INTRODUCTION

Major depressive disorder (unipolar major depression) and persistent depressive disorder (dysthymia) represent depressive syndromes that are distinguished by the type and number of symptoms that occur as well as their duration. Depressive symptoms can include depressed mood, loss of interest or pleasure in most or all 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 [1]. The World Health Organization estimated that major depressive disorder was the 11th greatest cause of disability and mortality in the world among 291 diseases and causes of injuries [2].

Preliminary studies suggest that course of illness may be associated with structural brain changes. As an example, a one-year prospective magnetic imaging study followed patients with treatment-resistant unipolar major depression (n = 26) who were treated with pharmacotherapy, and found that remission was associated with subtle increases in hippocampal volume and cortical thickness, whereas nonremission was associated with decreased volume and thickness [3].

This topic reviews the course of illness in patients with major depressive disorder and persistent depressive disorder (dysthymia). The course of illness in psychotic depression and minor depression is discussed separately, as is the epidemiology, clinical features, diagnosis, and treatment of depression:

- (See ["Unipolar major depression with psychotic features: Maintenance treatment and course of illness"](#), section on 'Course of illness'.)
 - (See ["Unipolar minor depression in adults: Epidemiology, clinical presentation, and diagnosis"](#), section on 'Course of illness'.)
 - (See ["Unipolar depression in adults: Epidemiology"](#).)
 - (See ["Unipolar depression in adults: Assessment and diagnosis"](#).)
 - (See ["Unipolar major depression in adults: Choosing initial treatment"](#).)
 - (See ["Unipolar depression in adults: Choosing treatment for resistant depression"](#).)
 - (See ["Diagnosis and management of late-life unipolar depression"](#).)
-

DEFINITIONS

Major depressive disorder (unipolar major depression) and persistent depressive disorder (dysthymia) are defined in the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition (DSM-5) [1]:

- **Major depressive disorder** is diagnosed in patients who have suffered at least one major depressive episode ([table 1](#)). An episode is a period lasting at least two weeks, with five or more of the following nine symptoms: depressed mood, loss of interest or pleasure in most or all 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.
- **Persistent depressive disorder (dysthymia)** is diagnosed in patients with depressed mood for at least two years that is accompanied by at least two of the following symptoms: decreased or increased appetite, insomnia or hypersomnia, low energy, poor self-esteem, poor concentration, and hopelessness ([table 2](#)).

Additional information about the clinical presentation and diagnosis of major depressive disorder and persistent depressive disorder (dysthymia) is discussed separately. (See ["Unipolar depression in adults: Assessment and diagnosis"](#).)

The term recovery is used to indicate the resolution of a depressive episode [4]. Although different definitions of recovery exist, many long-term observational studies require at least two consecutive months with no more than one or two mild symptoms of depression and no impairment of psychosocial functioning.

STUDY SETTING

The setting of a study can affect the observed course of illness for depressed patients. Individuals who are identified in the community surveys may have a more benign course than patients at tertiary care facilities; in either case, the individuals or patients may not be receiving treatment [5,6]. In addition, patients seen in routine clinical practice often differ from patients who are followed after they complete randomized trials. Patients who participate in trials are usually recruited through advertisements, are willing to risk assignment to placebo, and meet extensive exclusion criteria that are typically used in industry-sponsored trials; thus, these patients may have less suicidality, psychosis, comorbidity, and functional impairment [7-9].

MAJOR DEPRESSIVE DISORDER

The course of illness for major depressive disorder (unipolar major depression) is heterogeneous, which may reflect that the disorder represents a variety of illnesses that differ in their pathogenesis, clinical presentation, and treatment response [10-12]. Patients may experience a single major depressive episode, follow a highly recurrent course with full resolution of symptoms between episodes, or spend much of their lives struggling with persistent, fluctuating symptoms. Depressive episodes can range in intensity from states that produce limited impairment and are little noticed by others, to catatonic or psychotic conditions that render the patient incapable of self-care.

Although the large majority of major depressive episodes eventually end [5,13-15], some patients are ill for much of their lives due to recurrences and/or lengthy episodes. A 12-year, prospective observational study of 431 patients with major depressive disorder, who sought treatment at study intake, found that they were depressed for 59 percent (mean average) of the follow-up time [6]. In a six-year, prospective observational study of 903 patients with major depressive disorder, most of whom were treated in primary care settings, symptoms were present for 50 to 100 percent of the follow-up time in 36 percent of the patients [16].

Recovery — The median time to recovery from a major depressive episode in prospective observational studies is approximately 20 weeks [13,14]. This finding is consistent in treated patients with multiple recurrent episodes (up to five), and for individuals in the community who have not sought treatment.

Prospective observational studies have found that the probability of recovery from major depression progressively decreases as the duration of the episode increases [13,14]. This decreasing rate of recovery is graphically illustrated ([figure 1](#) and [figure 2](#)).

Major depressive episodes may remit quickly. Prospective observational studies have found that episodes (some of which were untreated) often remitted soon after onset (eg, ≤ 8 weeks), in a reproducible manner across different patient populations ([figure 2](#) and [figure 1](#)) [13,14]. In addition, remission of depressive episodes that occurs during treatment that is started soon after onset of the episode often appears to be the result of a placebo effect [17,18]. Thus, for mild to moderate depression with recent onset and no suicidality or psychosis, reassurance and watchful waiting with short-term follow-up (eg, two weeks) may be a reasonable alternative to antidepressant treatment. (See "[Unipolar depression in adults and initial treatment: General principles and prognosis](#)", section on 'Patient engagement and retention in treatment'.)

There are several risk factors for a longer time to recovery from major depression, which have been identified in at least two separate prospective observational studies that included at least two years of follow-up and were not confined to a particular age or diagnostic subgroup:

- Longer episode duration at baseline [19-21]
- Greater baseline symptom severity [22-25]
- Psychotic features (ie, delusions and/or hallucinations) [26-28]
- Higher levels of anxiety [22,29-32]
- Pre-existing comorbid disorders [21,23,25], including personality disorders [19,22,33-35]
- High levels of neuroticism [35-39]
- Poorer psychosocial functioning [22,32,40-44]
- Childhood maltreatment [32,43,45,46]

Recurrence — Major depressive disorder is highly recurrent [5,47-49]:

- In a prospective study of individuals in the Dutch general population who had recovered from an episode of major depression (n = 687), the cumulative rate of recurrence at [50]:
 - 5 years was 13 percent
 - 10 years was 23 percent
 - 20 years was 42 percent
- In a prospective study of 318 patients who recovered from a major depressive episode and were assessed semi-annually or annually for up to 10 years, 64 percent suffered at least one subsequent episode [51]. The median time to recurrence for the first the recurrent episode was approximately 3 years and for subsequent episodes was 1 to 1.5 years.

The risk of recurrence appears to be greatest in the first few months after recovery from a major depressive episode. Thereafter, the probability of recurrence progressively decreases as

the duration of recovery (wellness) increases. As an example, a prospective study found that among 318 patients who recovered from a major depressive episode, approximately [51]:

- 20 percent suffered a recurrence in months 1 through 6 after recovery
- 19 percent in months 7 through 12 after recovery
- 15 percent in months 13 through 18
- 13 percent in months 19 through 24
- 11 percent in months 25 through 30
- 9 percent in months 31 through 36

Clinical factors that may be associated with recurrence of major depression include:

- Prior history of recurrence – This is the most consistently identified risk factor [33,50-61]. As an example, a prospective study of 318 patients found that each recurrence increased the risk of a subsequent recurrence by 16 percent [51].
- Residual depressive symptoms – This is another potent risk factor [53,56,58,59,61-64]. As an example, a prospective study of 322 patients found that the median time to recurrence was four times shorter for patients with one or two mild symptoms during the recovery period than for patients with no symptoms (32 versus 135 weeks) [65,66].
- Childhood maltreatment – A meta-analysis of seven epidemiologic studies (10,191 depressed individuals) found that recurrent depressive episodes were twice as likely among individuals who were mistreated during childhood (physical or sexual abuse, neglect, or family conflict or violence) compared with individuals who were not [45]. A subsequent study of 687 euthymic individuals with a lifetime history of unipolar major depression found that time to recurrence was shorter among individuals with negative youth experiences [50].
- Other factors such as:
 - Greater severity (intensity) of the preceding depressive episode [19,50,53,67,68]
 - Younger age at time of assessment [50,53,67,69]
 - Younger age of onset of major depressive disorder [54,70]
 - Comorbid personality disorder [33,35,71]
 - Poorer psychosocial functioning [44,50]
 - Feeling that life circumstances are beyond one's control (ie, low mastery) [60]

- Emotional dysregulation and repeated exposure to adversity [61,72]

Treatment-resistant depression — Relapse appears to be greater in patients with major depression who require more than one course of treatment to remit, compared with patients who remit after the initial course of treatment [73]. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which prospectively administered up to four sequential trials of pharmacotherapy to patients who presented with unipolar major depression, more than 1500 patients remitted and were followed for up to one year [74]. The rate of relapse after each treatment step was as follows:

- Remission occurred with initial treatment – 34 percent relapsed
- Remission occurred with step two – 47 percent
- Remission occurred with step three – 43 percent
- Remission occurred with step four – 50 percent

The difference in relapse following remission after initial treatment and after step two was statistically significant.

It is not clear if all-cause mortality or suicide is greater in treatment-resistant depression, compared with the general population of patients with depression [73,75]. Mortality in depression is discussed elsewhere in this topic. (See '[Mortality](#)' below.)

Long-term course of illness — For any individual patient who suffers more than one episode of major depression, time to recovery and time to recurrence are inconsistent across multiple episodes [14,51,76]. However, long-term prospective studies of patients with major depression, receiving various levels of treatment or none at all, have found that course of illness remains the same for the cohort over time, including [13,14,77,78]:

- Mean time to recovery from an episode of major depression
- Probability of recurrence
- Amount of time ill with major depression

As an example, a study prospectively followed 220 patients with major depressive disorder for 20 years, and examined the proportion of weeks ill with major depression [79]. The 20 years of follow-up were grouped into five-year periods to determine whether the proportion of weeks ill with depression changed over time, and patients were divided into three groups according to their age at study intake (mean age 25, 36, and 55 years). The amount of time ill with depression did not change as patients moved from their third decade of life to their fifth decade, from their fourth to their sixth decade, or their sixth to their eighth decade of life ([figure 3](#)).

Clinical features that are present during the initial episode of unipolar major depression may be associated with a greater lifetime burden of depressive symptoms. As an example, a retrospective, multinational, community-based study of individuals ($n > 8000$) found that early age of onset, suicidal ideation and behavior, severe dysphoria, and anxiety during the first lifetime episode of unipolar major depression were associated with a greater persistence and severity of subsequent depressive symptoms [80].

Clinicians may conclude that the course of illness tends to worsen in major depression (eg, episodes appear to progressively become longer or more frequent) when in fact it does not, because patients who experience more symptoms are more likely to continue visiting clinicians than patients who remain euthymic for long periods [81].

Functioning — Although psychosocial functioning typically improves in patients who recover from a major depressive episode [82], functional recovery often takes longer than syndromal recovery [83]. As an example, a prospective study of patients with recurrent unipolar depression ($n > 1000$) found that on average, functional recovery lagged behind syndromal recovery by approximately one year [84]. The delay in functional recovery was attributed primarily to subsyndromal symptoms, and the persistence of these symptoms speaks to the need for continuation treatment.

Additional information about functional impairment in unipolar depression is discussed separately. (See "[Unipolar depression in adults: Clinical features](#)", section on '[Functional impairment](#)'.)

Quality of life — Depression is associated with impaired quality of life, which refers to subjective satisfaction with one's physical, psychological, and social functioning. Quality of life may remain impaired despite resolution of the depressive syndrome. As an example, the STAR*D study prospectively administered [citalopram](#) to patients with unipolar major depression who were followed for up to 12 months [85]. Quality of life was impaired in nearly all patients at study intake. Among patients who remitted ($n > 800$), quality of life remained impaired in more than 30 percent, and was severely impaired in 9 percent.

PERSISTENT DEPRESSIVE DISORDER (DYSTHYMIA)

The diagnostic criteria for persistent depressive disorder (dysthymia) in the DSM-5 [1] are nearly identical to the criteria for dysthymic disorder in DSM-IV-TR [86]. The primary difference is that persistent depressive disorder also subsumes patients who were labelled as chronic unipolar major depression in DSM-IV-TR (which categorized chronic major depression as a subset of

unipolar major depression). DSM-5 consolidated dysthymic disorder and chronic major depression into persistent depressive disorder (dysthymia) because there was little difference between dysthymic disorder and chronic major depression with regard to demographics, symptom patterns, treatment response, and family history [87-90]. However, much of the literature is based upon the diagnoses used prior to DSM-5.

Additional information about the clinical features and diagnosis of depressive disorders is discussed separately. (See '[Definitions](#)' above and "[Unipolar depression in adults: Assessment and diagnosis](#)".)

Dysthymic disorder — In follow-up studies of dysthymic disorder, most episodes resolved but recurrence was common [91]:

- A prospective study of 82 patients with dysthymic disorder followed for up to 10 years found that approximately 74 percent recovered; the median time from study entry to recovery was approximately four years [92].
- A prospective study of 53 patients who recovered from dysthymic disorder and were followed for a median of eight years found that 55 percent suffered a recurrence [92].

Also, patients with dysthymic disorder recovered more slowly than patients with nonchronic major depression [91]. In an observational study of 49 patients followed prospectively for six months, recovery occurred in fewer patients with dysthymic disorder compared with unipolar major depression (25 versus 63 percent) [93].

Observational studies of dysthymic disorder found that patients usually had exacerbations that met criteria for a major depressive episode, a phenomenon labelled “double depression” [94]. As an example, two studies of dysthymic disorder (190 and 87 patients) found that most patients also met criteria for major depression (62 and 59 percent of patients) [92,95]. Underlying dysthymia also seemed to worsen the course of major depression; studies found that among patients who recovered from major depressive episodes superimposed upon dysthymic disorder, time to relapse of another major depressive episode was shorter than that experienced by patients who recovered from major depression not superimposed upon dysthymic disorder [94,96]. (In DSM-5, the formal diagnosis for double depression is persistent depressive disorder with intermittent major depressive episodes [1].)

In studies of dysthymic disorder, predictors of poor outcome included:

- Family history of dysthymic disorder or chronic major depression [92,97]
- High neuroticism scores [97]

- Comorbid anxiety disorder [98,99]

Chronic major depression — In DSM-IV-TR, patients who met full criteria for an episode of major depression continuously for two years were diagnosed with chronic major depression [86]. In DSM-5, these patients are given the diagnosis persistent depressive disorder with persistent major depressive episode [1].

Prospective observational studies found that the probability of recovery from an episode of chronic major depression was less than the rate of recovery from shorter episodes [100]. Nevertheless, patients with chronic major depression recovered [100,101]:

- A prospective observational study, at a tertiary medical center, of 35 patients with major depression who were continuously ill for five years found that during the following five years, recovery occurred in 38 percent [102].
- A nationally representative community survey in the United States identified individuals with chronic major depression (n = 504) and found that after three years of follow-up, only 12 percent continued to meet criteria for major depression [46].

Thus, clinicians should encourage patients to continue treatment and efforts to manage their illness despite persistent symptoms [103].

Clinical factors at baseline that were associated with a shorter time to recovery from chronic major depression in prospective studies included a high level of psychosocial functioning, less severe depressive symptoms, absence of psychiatric comorbidity, and absence of psychosis [100].

MINOR DEPRESSION

Course of illness in minor depression is discussed separately. (See "[Unipolar minor depression in adults: Epidemiology, clinical presentation, and diagnosis](#)", section on 'Course of illness'.)

MORBIDITY

Depression may adversely affect the overall health of patients [104]. Depression is associated with coronary heart disease, diabetes mellitus, Parkinson disease, stroke, and with worse outcomes in comorbid general medical illnesses [105-111]. In addition, depression in later life may be an independent risk for subsequent cognitive decline [112-114] and possibly dementia

[115]. (See "[Mild cognitive impairment: Epidemiology, pathology, and clinical assessment](#)", section on '[Neuropsychiatric symptoms](#)'.)

MORTALITY

All-cause — All-cause mortality is approximately 50 to 100 percent greater in depressed individuals, compared with nondepressed individuals [116-121]. As an example:

- A meta-analysis of 293 studies from 35 countries (n >100,000 depressed individuals and >1,600,000 nondepressed individuals) found that the risk of mortality was 52 percent greater in depressed individuals; heterogeneity across studies was high [122].
- A subsequent meta-analysis of 43 studies (sample size not provided) found that the risk of mortality was 71 percent greater in depressed individuals; heterogeneity across studies was high [123].
- A subsequent national registry study identified more than 900,000 individuals who died, including more than 78,000 with a lifetime diagnosis of unipolar depression [124]. All-cause mortality was two times greater in people with depression, compared with the general population. Assuming onset of depression at age 30, life expectancy in depressed individuals was roughly 11 years shorter.

In addition, a retrospective study of military veterans with a history of depression (n >700,000) or without depression (n >4,000,000) found that the mean age of death was 71 versus 76 years [125]. Major depression and less severe (minor) depression are each associated with excess mortality. (See "[Unipolar minor depression in adults: Epidemiology, clinical presentation, and diagnosis](#)", section on '[All-cause mortality](#)'.)

The excess mortality that is observed in depression is greater for men than women. A meta-analysis of 13 prospective observational studies (n >5500 depressed men and women) found that the risk of death was twice as great in depressed men than in depressed women [126]. In two community registry studies, life expectancy for depressed males was 11 and 15 years shorter compared to the general population, and for depressed females was 7 and 13 years shorter [127,128].

For some patients with depression plus a general medical disease, it appears that the mortality risk of depression is not fully explained by the comorbid medical illness [129-131]:

- A community survey and mortality database of 61,349 individuals found that depressive disorders were associated with an increased mortality that was only partly explained by

somatic symptoms or illnesses (hazard ratio 1.5, 95% CI 1.4-1.7) [132].

- A meta-analysis of 25 observational studies (9417 patients) showed that mortality rates were 25 percent higher in cancer patients with depressive symptoms compared with nondepressed cancer patients (risk ratio 1.25, 95% CI 1.12-1.40), and 39 percent higher in cancer patients diagnosed with major or minor depression (risk ratio 1.39, 95% CI 1.10-1.89) [133].
- In a prospective study of 4873 women, mortality was higher for women with depression plus diabetes mellitus (relative risk 3.1, 95% CI 2.7-3.6) than diabetes alone (relative risk 1.7, 95% CI 1.5-1.9) [134].

Treatment-resistant depression is associated with increased mortality from accidents and suicides [135]. By contrast, continuity of care for major depression with the same psychiatrist is associated with decreased all-cause mortality [136].

One aspect that is typically not addressed in studies of depression and mortality is whether the increased risk for death varies according to lifetime extent of depressive morbidity.

Suicide — Major depression greatly increases the risk of suicide [137]. In a prospective study that followed 186 patients with major depressive disorder for up to 38 years, the incidence of suicide was 27 times greater than that for the general population [117]. In addition, increased suicide rates in adolescents and young adults from 2000 to 2017 [138] mirrored increases in the point prevalence of major depressive disorder in this age group over the same period [139].

Many risk factors for suicide have been identified. In a meta-analysis of results from 28 articles (n >12,000 suicides, 3,000,000 controls), the risk factor that was most strongly associated with suicide was prior history of suicide attempt (odds ratio 5, 95% CI 3-7) [140]. Other risk factors included male sex, family history of psychiatric disorder, more severe depression, hopelessness, and comorbidity. As an example, traumatic brain injury is associated with an increased risk of suicide [141,142].

Additional information about suicide is discussed separately. (See "[Suicidal ideation and behavior in adults](#)".)

Homicide — Mortality due to homicide is elevated in patients with depressive syndromes. A retrospective study of Swedish national registries compared the risk of homicidal death among individuals with a lifetime history of unipolar depression and no history of substance use, to the risk among individuals with no history of mental disorders [143]. After controlling for

sociodemographic factors, the risk of death due to homicide among depressed patients was 2.6-fold higher (hazard ratio 3, 95% CI 2-4). However, the absolute risk was small.

Accidental death — Depressed patients may be at increased risk of dying from accidents (eg, motor vehicle accidents, falls, or accidental poisoning). In a Swedish national registry study, which compared depressed patients (n >200,000) with the general population (n >6.9 million) and controlled for sociodemographic factors and substance use disorders, accidental deaths were two fold greater among depressed patients [144].

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 depressive disorder (unipolar major depression) ([table 1](#)) and persistent depressive disorder (dysthymia) ([table 2](#)) represent depressive syndromes that are distinguished by the type and number of symptoms that occur as well as their duration. (See '[Definitions](#)' above and "[Unipolar depression in adults: Assessment and diagnosis](#)".)
- Patients who are initially and correctly diagnosed with major depressive disorder may eventually change diagnosis to bipolar disorder or schizophrenia. (See "[Unipolar depression in adults: Assessment and diagnosis](#)", section on '[Diagnostic stability](#)'.)
- The median time to recovery from a major depressive episode is approximately 20 weeks. However, episodes may remit quickly. Thus, for mild to moderate depression with recent onset and no suicidality or psychosis, reassurance and watchful waiting with short-term follow-up (eg, two weeks) may be a reasonable alternative to antidepressant treatment. Possible risk factors for a longer time to recovery include: longer episode duration at baseline, greater baseline symptom severity, psychotic features, higher levels of anxiety, pre-existing comorbid disorders, high levels of neuroticism, poorer psychosocial functioning, and a history of childhood maltreatment. (See '[Recovery](#)' above.)
- Among patients with major depressive disorder, recurrent episodes occur in approximately 50 percent. The risk of recurrence appears to be greatest in the first few months after recovery from a major depressive episode and thereafter progressively decreases as the duration of recovery (wellness) increases. Factors that may be associated

with recurrence include prior history of recurrence, residual depressive symptoms, childhood maltreatment, symptom severity of the preceding depressive episode, younger age at time of assessment, younger age of onset of major depressive disorder, and comorbid personality disorder. (See '[Recurrence](#)' above.)

- For any individual patient who suffers more than one episode of major depression, time to recovery and time to recurrence are inconsistent across multiple episodes. However, for groups of patients, course of illness remains the same for the cohort over time, including mean time to recovery from an episode of major depression, probability of recurrence, and amount of time ill with major depression. (See '[Long-term course of illness](#)' above.)
- Depression is associated with poor psychosocial and physical functioning. (See '[Functioning](#)' above.)
- Although most episodes of dysthymia resolve, recurrences are common. Most patients with dysthymia have exacerbations that meet criteria for a major depressive episode. (See '[Persistent depressive disorder \(dysthymia\)](#)' above.)
- Depression is associated with coronary heart disease, diabetes mellitus, and stroke, and with worse outcomes in comorbid general medical illnesses. (See '[Morbidity](#)' above.)
- Depression is associated with increased all-cause mortality, completed suicide, homicidal death, and accidental death. (See '[Mortality](#)' above.)

Use of UpToDate is subject to the [Terms of Use](#).

Topic 14693 Version 35.0

→