Unipolar depression: Pathogenesis

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INTRODUCTION

Unipolar depression is a major public health problem associated with increased functional disability and mortality. The illness likely represents a group of heterogeneous disorders that are phenotypically similar [1]. Efforts to understand the pathogenesis of depression, as well as its neurobiology, are intended to discern these different diseases or subtypes.

This topic reviews the pathogenesis of unipolar depression. The neurobiology, clinical features, assessment, diagnosis, and treatment of unipolar depression are discussed separately:

- (See "Unipolar depression: Neurobiology".)
- (See "Unipolar depression in adults: Clinical features".)
- (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".)

DEFINITIONS OF DEPRESSION

The term "depression" can be used in multiple ways, which can be confusing; depression may refer to a [2,3]:

- 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 normal or a symptom of a psychopathological syndrome or a general medical disorder.

- 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 identifies 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.

PATHOGENESIS

Unipolar depression likely represents a group of heterogeneous disorders that are phenotypically similar [1]. Depression can thus be considered the final common pathway of different disease processes that occur across a biopsychosocial continuum. Efforts to understand the pathogenesis of depression are intended to discern these different diseases or subtypes.

The pathogenesis of major depression appears to involve three broad sets of risk factors, which often co-occur [4]:

- Internalizing (emotional) factors
  - Genetics
  - Neuroticism
  - Low self-esteem
  - Early-onset anxiety disorder
  - Past history of major depression
- Externalizing (behavioral) factors
  - Genetics
  - Substance misuse
  - Conduct disorder
- Adversity factors

- Trauma during childhood or adulthood
- Stressful life events in past year
- Parental loss
- Low parental warmth
- History of divorce
- Marital problems
- Low social support
- Low education

Parental-related adversity may be specifically due to parental mental illness, substance abuse, and criminality [5].

Genetics — Unipolar major depression is likely due to genetic effects as well as environmental influences specific to the individual. (See "Unipolar depression: Genetics".)

Preterm birth — A national registry study found an association between preterm birth and increased risk of hospitalization in adulthood for depressive disorder, which occurred in a monotonic manner [6]. Compared to adults with term births:

- Adults born at 32 to 36 weeks were 30 percent more likely to have depressive disorder (hazard ratio 1.3, 95% CI 1.1-1.7).
- Adults born at less than 32 weeks gestation were three times more likely to have depressive disorder (hazard ratio 2.9, 95% CI 1.8-4.6).

Low birth weight — Low birth weight (<2500 g) is weakly associated with depression in adulthood [7]. As an example, a meta-analysis of 14 prospective and retrospective studies (n >30,000 births) found that low birth weight modestly increases the odds of depression later in life (odds ratio 1.4, 95% CI 1.2-1.6) [8].

Childhood adversity — Early life adversity may predispose individuals to unipolar major depression by altering sensitivity to stress and response to negative stimuli [5,9]. Preclinical studies suggest early life stress causes sustained hyperactivity of corticotropin-releasing factor cells in the hypothalamus, which leads to increased stress responses. (See "Unipolar depression: Neurobiology", section on 'Hypothalamic-pituitary-adrenal axis'.)

The association between childhood adversity and adult depression is well established [10]. As an example, a meta-analysis of 17 studies (n >21,000 individuals) found that depressive syndromes were more likely to occur in adults who were exposed to parental divorce during childhood, compared with adults who were not exposed (odds ratio 1.6, 95% CI 1.3-1.9) [11].

Other types of childhood adversities are also associated with adult depression. Two national registry studies (one with a cohort of roughly 500,000 individuals and the second with nearly 1,000,000 individuals) identified young adults who were either exposed to childhood adversities or not, and compared the incidence of depressive disorders in the two groups [12,13]. Both studies found that exposure to at least one adversity was common (30 and 50 percent of the cohort). After adjusting for potential confounding factors, the analyses found that each of the following childhood adversities was associated with an increased risk of depressive disorders in young adulthood. Depending upon the study and particular adversity, the risk of a depression diagnosis was increased by 10 percent (parental incarceration) to 58 percent (parental psychiatric disorder):

- Child welfare intervention
- Housing instability
- Public assistance for household
- Parental criminality/incarceration
- Parental death (unnatural cause)
- Parental disability
- Parental general medical illness
- Parental psychiatric disorder/substance abuse

One of the studies estimated that nearly 20 percent of all cases of depressive disorders were attributable to childhood adversity [12].

Youth are frequently exposed to multiple childhood adversities, and with each additional adversity the risk of depression in young adulthood increases in a dose-response manner [13]. In one study, as the total number of childhood adversities increased, the risk of adult depression increased as follows [12]:

- One adversity – hazard ratio 1.54 (95% CI 1.49-1.59)
- Two adversities – hazard ratio 1.98 (95%CI 1.89-2.07)
- Three adversities – hazard ratio 2.42 (95% CI 2.26-2.59)
- Four or more adversities – hazard ratio 3.05 (95% CI 2.83-3.29)

Thus, the risk of depression increased by approximately 50 percent in young adults who suffered one childhood adversity and by 300 percent in young adults with four or more adversities.

Childhood maltreatment — Many adults with depressive syndromes report a history of childhood maltreatment, including abuse or neglect. In a series of meta-analyses based upon

118 studies of adults with depression (sample size not reported), the prevalence of childhood maltreatment was as follows [14]:

- Any childhood maltreatment – 46 percent
- Sexual abuse – 25 percent
- Physical abuse – 28 percent
- Emotional abuse – 37 percent
- Physical neglect – 36 percent
- Emotional neglect – 43 percent

Nearly 20 percent of the adults with depressive syndromes reported multiple types of childhood maltreatment.

Multiple studies indicate that childhood maltreatment is associated with an increased risk of depressive syndromes in adulthood [15]. As an example, a series of meta-analyses based upon 83 studies (sample size not reported) found that depression was three to four times more likely to occur in adults with childhood maltreatment than adults without maltreatment [14]:

- Any childhood maltreatment – odds ratio 2.8 (95% CI 2.4-3.4)
- Sexual abuse – odds ratio 2.7 (95% CI 2.4-3.0)
- Physical abuse – odds ratio 2.7 (95% CI 2.3-3.1)
- Emotional abuse – odds ratio 3.7 (95% CI 2.9-4.8)
- Physical neglect – odds ratio 2.5 (95% CI 1.6-3.7)
- Emotional neglect – odds ratio 3.5 (95% CI 2.5-5.0)

In addition, onset of depression in adults occurred four years earlier in those with childhood maltreatment than those without maltreatment (mean age 23 versus 27 years) and childhood maltreatment was associated with increased severity of adult depression.

Early menarche — Early puberty in girls is a consistently observed antecedent of adolescent depression and appears to be associated with depression in adult women as well. A prospective, nationally representative survey of adolescent girls in the United States followed subjects for approximately 14 years; after adjusting for potential confounding factors (eg, age, father absence, and household income), the analyses found that depressive syndromes were more common in adult women with an early age at menarche (eg, age 9 years), primarily due to persistence of adolescent depression into adulthood [16]. The mean age of onset of menarche is typically 12 years.

Stressful life events — Stressful life events increase the likelihood of suffering an episode of major depression. As an example, a meta-analysis of 102 studies (sample size not reported)

found that the risk of depressive syndromes was greater in individuals who were sexually assaulted, compared with individuals who were not assaulted, and the risk was moderate to large [17].

After a stressful event occurs, it is not clear how long individuals are at risk for an episode of depression. One study found that the risk persists for many years, whereas another study found a much smaller window of risk:

- A prospective study of a nationally representative sample (n >1000) in the United States followed individuals for 25 years [18]. After controlling for potential confounding factors (eg, baseline sociodemographic variables, depressive symptoms, and general medical health), the analyses showed that stressful life events at baseline were modestly associated with major depression at follow-up (odds ratio 1.41, 95% CI 1.03-1.93).

- A study of twin pairs (using prospective and retrospective data) found that vulnerability to major depression after stressful life events lasted for only one month [19]. In addition, the results found that over time, the association between stressful life events and depression grew weaker, such that onset of episodes was frequently independent of stressful events. The study also found that major depression did not predispose individuals to future stressful events.

The association between intimate partner violence and incident depressive syndromes is discussed separately. (See "Intimate partner violence: Epidemiology and health consequences", section on 'Psychological'.)

Social factors — Social factors such as isolation, poor social support, criticism from family members, job strain, and depression in one's friends and neighbors may lead to depression onset or perpetuate depressive episodes [20-24].

Onset of major depression is more likely to occur in individuals who view their social support as poor. Social support refers to assistance that is provided by others and can take many forms, including emotional (eg, consolation, empathy, or encouragement) and instrumental (eg, help with groceries) [25]. A review of 36 general population studies (sample size not reported) found that social support and depression were inversely related in 33 (92 percent) of the studies, and a meta-analysis showed that the risk of depressive syndromes was modestly greater in individuals with poor social support than those with good support (odds ratio 1.35, 95% CI 1.32-1.39) [25].

Family members may contribute to onset and persistence of depression through negative, critical comments and emotional over-involvement ("expressed emotion" or social strain)

[22,26,27]. In a prospective study of 268 college males, poor sibling relationships (but not poor parental relationships) prior to age 20 predicted occurrence of major depression by age 50 [28].

Job strain, defined as work that involves both high demands and low control, is associated with an increased risk of unipolar depression:

- A meta-analysis of six prospective studies (n >27,000 individuals) found that clinically diagnosed depression was more likely to occur in adults with job strain than those with no job strain (relative risk 1.8, 95% CI 1.5-2.1) [29].
- A meta-analysis included individual-level data from 14 cohorts with more than 120,000 individuals [29]. After adjusting for potential confounding factors (eg, age, sex, socioeconomic status, and baseline depressive symptoms), the analysis found that the risk of inpatient or outpatient treated depression was modestly greater in those with job strain than those without job strain (relative risk 1.27, 95% CI 1.04-1.55).

Social networks — Unipolar depression may spread through social networks. Participants in the Framingham Heart Study (n >12,000), a socially interconnected group, were evaluated for depressive syndromes three times over 18 years [24]. Participants identified their spouses, siblings, neighbors, friends, and coworkers, many of whom also participated in the study. Subjects were more likely to be depressed by a factor of:

- 93 percent if a person they were directly connected to was depressed
- 43 percent if a person at two degrees of separation (eg, friend of a friend) was depressed
- 37 percent if a person at three degrees of separation (eg, friend of a friend of a friend) was depressed

The effect disappeared at four degrees of separation. Female friends were especially influential in the spread of depression from one person to another.

Another study found that among adults (n = 558) who were variably affected by a devastating disaster (fires), depressive syndromes subsequently occurred in 39 percent [30]. The risk of depression was greater for individuals with:

- Fewer social connections to others
- Social connections to others with depression
- Connections to others who had moved away

Psychologic factors — Psychologic factors that predispose individuals to depression include the following:

- Maladaptive beliefs and dysfunctional attitudes – Cognitive psychology has demonstrated the presence of distorted and negative thoughts in individuals vulnerable to depression, with further worsening of cognitive distortions in the depressed state [31,32].

- Psychodynamic perspectives have focused upon the role of early life losses (see 'Childhood adversity' above), self-esteem, and difficulties in managing acute losses (real, imagined, or threatened) and interpersonal relationships [33-35].

- Personality traits – Personality psychology has demonstrated the importance of personality traits in the onset and course of depression [36]. As an example, neuroticism, which is the tendency to experience negative emotions such as anger, anxiety, frustration, and sadness, is associated with major depression [4]. However, individuals who exhibit high levels of neuroticism may be protected from episodes of unipolar major depression if they also score high on the personality traits of extraversion (sociability and energetic) plus conscientiousness (organized and self-disciplined) [37].

- Learned behaviors – Behavioral psychology has noted the importance of learned behaviors, with family or other environmental responses (often inadvertently) reinforcing depressive cognitions and behaviors [38].

Psychotic experiences — Temporally primary psychotic experiences may be associated with subsequent onset of major depression. A coordinated set of community surveys in 18 countries retrospectively assessed age of onset of psychotic experiences (hallucinations or delusions) and mental disorders, and found that first onset of unipolar major depression was more likely to occur in individuals with prior psychotic experiences, compared to others with no history of psychotic experiences [39]. In some cases, it appears that reality testing was not fully impaired during the psychotic experiences, such that individuals recognized that the perceptual abnormalities and unusual thought content were a product of their own minds [40].

Secondary depression — General medical disorders and use of medications and drugs of abuse can lead to subsequent onset of depressive syndromes.

General medical disorders — Unipolar depressive syndromes secondary to general medical disorders are common. The association between medical disorders and depression may be due to the disease process of the medical disorder (eg, hypothyroidism or hypercortisolism) or due to impaired functioning and disability that arises from the general medical disorder. Several general medical disorders are associated with unipolar depression [41]:

- Neurologic disorders – Cerebrovascular disease, dementia, epilepsies, multiple sclerosis, Parkinson disease, and traumatic brain injury. As an example, a national registry study identified depressed patients (n >24,000), and after adjusting for potential confounds (eg, age, sex, family history of psychiatric disorders, fractures not involving the skull or spine, and epilepsy), found that hospital contact for a head injury was associated with an increased risk of depression (incidence rate ratio 1.46, 95% CI 1.40-1.51), compared with no head injury [42]. Head injury between the ages of 11 to 15 years was the strongest predictor of subsequently developing depression. Other predictors of unipolar major depression secondary to traumatic brain injury include preinjury depression and postinjury unemployment [43].

- Infectious disorders – HIV/AIDS and neurosyphilis.

- Cardiac disease – Cardiomyopathy, heart failure, and ischemic heart disease.

- Endocrinopathies – There is conflicting evidence concerning the strength of the association between hypothyroidism and unipolar depression [44,45]. A meta-analysis of 25 studies including 348,000 individuals with hypothyroidism found an association between hypothyroidism (overt, subclinical, or autoimmune) and clinical depression (odds ratio 1.3, 95% CI 1.08-1.57). However, while overt hypothyroidism was more strongly associated with depression than subclinical hypothyroidism (odds ratio 1.77 versus odds ratio 1.13), the association for autoimmune hypothyroidism was not statistically significant (odds ratio 1.24, 95% CI 0.89-1.74). Additionally, in subgroup analysis, the association was confirmed in female but not male individuals.

  Other endocrinopathies associated with unipolar depression include diabetes mellitus [46] and parathyroid disorders [47].

- Inflammatory disorders – Collagen-vascular diseases, inflammatory bowel disease, and chronic liver disorders. (See "Unipolar depression: Neurobiology", section on 'Inflammation'.)

- Neoplastic disorders – Central nervous system tumors and paraneoplastic syndromes.

- Nutritional disorders – Dietary patterns [48,49], vitamin deficiencies, and trace mineral deficiencies [50]. As an example, vitamin D deficiency appears to be associated with depression [51-53]. A meta-analysis of three prospective observational studies (n >8000 individuals not depressed at baseline and followed for up to six years) found an increased risk of depression with low vitamin D (hazard ratio 2.2, 95% CI 1.4-3.5) [54].

- Somatic pain [55].
- Dermatologic disorders – A meta-analysis of 10 studies (n >180,000 individuals) found that the risk of depression was two times greater in people with eczema than those without eczema (relative risk 2.0, 95% CI 1.8-2.3) [56].

Additional information about general medical disorders is discussed in separate topics.

Medications — Medications that are associated with depressive syndromes include [57-59]:

- Glucocorticoids (see "Major adverse effects of systemic glucocorticoids", section on 'Neuropsychiatric effects')
- Interferons

Although studies have linked other medications to depression (eg, opioid analgesics and varenicline) [60-62], much of the literature is problematic. Single drug-induced symptoms (eg, anorexia, fatigue, insomnia, or sedation) may have been misinterpreted as a depressive syndrome, pre-existing depression misattributed to the drug, and depressive syndromes may have been the result of the disease for which the drug was prescribed [41,59].

As an example, depression has commonly been cited as a side effect of beta blockers, based upon observational studies [63]. However, a meta-analysis of 13 randomized trials (n >15,000 patients with heart failure) compared beta blockers with placebo and found that depression occurred less often in patients who received beta blockers [64]. Additional information about depression as a spurious side effect of beta blocker therapy is discussed separately. (See "Major side effects of beta blockers", section on 'Depression, fatigue, sexual dysfunction'.)

Drugs of abuse — Alcohol, cocaine, and other drugs of abuse are associated with unipolar depression. As an example, a retrospective study identified 156 monozygotic twin pairs reared together who were discordant for frequent lifetime use of cannabis (≥100 times) [65]. After adjusting for potential confounding factors, the analyses found that unipolar major depression was twice as likely to occur in the twin who used cannabis frequently, compared with the identical twin who used cannabis less frequently (odds ratio 2.0, 95% CI 1.1-3.5).

NEUROBIOLOGY

Multiple lines of evidence demonstrate that unipolar depression is associated with altered brain structure and function. (See "Unipolar depression: Neurobiology".)

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

- The pathogenesis of major depression appears to involve three broad sets of risk factors, including internalizing factors (emotional), externalizing factors (behavioral), and adversity factors. (See 'Pathogenesis' above.)
- Unipolar major depression is likely due to genetic effects as well as environmental influences specific to the individual. (See "Unipolar depression: Genetics".)
- Early life adversity may predispose individuals to unipolar major depression by altering sensitivity to stress and response to negative stimuli. The association between childhood adversity (eg, maltreatment) and adult depression is well established. (See 'Childhood adversity' above.)
- Stressful life events (eg, sexual assault) increase the likelihood of suffering an episode of major depression. However, after a stressful event occurs, it is not clear how long individuals are at risk for an episode of depression. (See 'Stressful life events' above.)
- Social factors such as poor social support, criticism from family members, job strain, and depression in one's friends and neighbors may lead to depression onset. (See 'Social factors' above.)
- Psychologic factors that predispose individuals to depression include maladaptive beliefs, dysfunctional attitudes, and psychotic experiences. (See 'Psychologic factors' above.)
- Depression can occur secondary to general medical illnesses and use of medications and drugs of abuse. (See 'Secondary depression' above.)
- Unipolar depression is associated with altered brain structure and function. (See "Unipolar depression: Neurobiology".)

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