Medscape

Depression

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OVERVIEW

Practice Essentials

Major depressive disorder has significant potential morbidity and mortality, contributing to suicide, incidence and adverse outcomes of medical illness, disruption in interpersonal relationships, substance abuse, and lost work time. During 2009–2012, 7.6% of Americans aged 12 and over had depression (moderate or severe depressive symptoms in the past 2 weeks). Depression was more prevalent among females and persons aged 40–59. [204] With appropriate treatment, 70-80% of individuals with major depressive disorder can achieve a significant reduction in symptoms.

Signs and symptoms

Most patients with major depressive disorder present with a normal appearance. In patients with more severe symptoms, a decline in grooming and hygiene may be observed, as well as a change in weight. Patients may also show the following:

- Psychomotor retardation
- Flattening or loss of reactivity in the patient's affect (ie, emotional expression)
- Psychomotor agitation or restlessness

Major depressive disorder

Among the criteria for a major depressive disorder, at least 5 of the following symptoms have to have been present during the same 2-week period (and at least 1 of the symptoms must be diminished interest/pleasure or depressed mood) [1] :

- Depressed mood: For children and adolescents, this can also be an irritable mood
- Diminished interest or loss of pleasure in almost all activities (anhedonia)
- Significant weight change or appetite disturbance: For children, this can be failure to achieve expected weight gain
- Sleep disturbance (insomnia or hypersomnia)
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness
- Diminished ability to think or concentrate; indecisiveness

- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

See Clinical Presentation for more detail.

Diagnosis

Screening instruments

Self-report screening instruments for depression include the following:

- Patient Health Questionnaire-9 (PHQ-9): A 9-item depression scale; each item is scored from 0-3, providing a 0-27 severity score.
- Beck Depression Inventory (BDI) or the Beck Depression Inventory-II (BDI-II): 21-question symptom-rating scales providing a 0-63 severity score.
- BDI for primary care: A 7-question scale adapted from the BDI.
- Zung Self-Rating Depression Scale: A 20-item survey.
- Center for Epidemiologic Studies-Depression Scale (CES-D): A 20-item instrument that allows patients to evaluate their feelings, behavior, and outlook from the previous week.

In contrast to the above self-report scales, the Hamilton Depression Rating Scale (HDRS) is performed by a trained professional, not the patient. The HDRS has 17 or 21 items, scored from 0-2 or 0-4; a total score of 0-7 is considered normal, while scores of 20 or higher indicate moderately severe depression.

The Geriatric Depression Scale (GDS), although developed for older adults, has also been validated in younger adults. The GDS contains 30 items; a short-form GDS has 15 items.

Laboratory studies

No diagnostic laboratory tests are available to diagnose major depressive disorder, but focused laboratory studies may be useful to exclude potential medical illnesses that may present as major depressive disorder.

See Workup for more detail.

Management

In all patient populations, the combination of medication and psychotherapy generally provides the quickest and most sustained response. [2, 3]

Pharmacotherapy

Drugs used for treatment of depression include the following:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin/norepinephrine reuptake inhibitors (SNRIs)
- Atypical antidepressants
- Tricyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)

- St. John's wort (*Hypericum perforatum*)

Psychotherapy

There are a number of evidence-based psychotherapeutic treatments for adults with major depressive disorder. The following have been deemed to have strong research support by Division 12 of the American Psychological Association: [4, 222]

- Behavior Therapy/Behavioral Activation
- Cognitive Therapy
- Cognitive Behavioral Analysis System of Psychotherapy
- Interpersonal psychotherapy (IPT)
- Problem-solving therapy (PST)
- Self-Management/Self-Control Therapy

Evidence-based psychotherapeutic treatments for children and adolescents with major depressive disorder include the following: [5]

- Interpersonal psychotherapy (IPT)
- Cognitive-behavioral therapy (CBT)
- Behavior therapy (BT)

Many of these treatments incorporate a parent/family component when working with children or adolescents.

In mild cases, psychosocial interventions are often recommended as first-line treatments. The American Psychiatric Association (APA) guideline supports this approach but notes that combining psychotherapy with antidepressant medication may be more appropriate for patients with moderate to severe major depressive disorder. [6]

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is a highly effective treatment for depression. The indications for ECT include the following:

- Need for a rapid antidepressant response
- Failure of drug therapies
- History of good response to ECT
- Patient preference
- High risk of suicide
- High risk of medical morbidity and mortality

Stimulation techniques

Transcranial magnetic stimulation (TMS) is approved by the FDA for treatment-resistant major depression.

Vagus nerve stimulation (VNS) has been approved by the FDA for use in adult patients who have failed to respond to at least 4 adequate medication and/or ECT treatment regimens. The stimulation device requires surgical implantation.

See Treatment and Medication for more detail.

Background

As many as two thirds of people with depression do not realize that they have a treatable illness and therefore do not seek professional help. In addition, persistent ignorance and misperceptions of the disease by the public, including many health providers, as a personal weakness or failing that can be willed or wished away leads to painful stigmatization and avoidance of the diagnosis by many of those affected.

In the primary care setting, where many of these patients first seek treatment, the presenting complaints often can be somatic, such as fatigue, headache, abdominal distress, or sleep problems. (See Presentation.)

The American Psychiatric Association's *Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* [1] classifies the depressive disorders as disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, and depressive disorder due to another medical condition. In addition, depressive disorders may be further categorized by specifiers that include peripartum onset, seasonal pattern, melancholic features, mood-congruent or mood-incongruent psychotic features, anxious distress, and catatonia. The common feature of the depressive disorders is the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. What differs among them are issues of duration, timing, or presumed etiology. [1]

The differential diagnosis for depression includes other psychiatric disorders, CNS diseases, endocrine disorders, drug-related conditions, infectious and inflammatory diseases, and sleep-related disorders. (See DDx.)

Depression screening tests can be used to screen for depression and bipolar disorder. The most widely used is the Patient Health Questionnaire-9 (PHQ-9). It is important to understand that the results obtained from the use of any depression rating scales are imperfect in any population, especially the geriatric population. (See Workup.)

Many effective treatments are available for major depressive disorder, including psychotherapy (e.g., cognitive-behavioral therapy, interpersonal psychotherapy, behavior therapy), used either alone or in combination with medication. However, the combined approach provides some patients with the quickest and most sustained response. Uncomplicated depression that is not severe typically responds equally well to psychotherapy or an antidepressant. (See Treatment.)

There is evidence to support the use of all antidepressants approved by the FDA for use in major depression, although predicting what an individual patient's response to a particular agent will be is difficult. Assuming adherence to the treatment regimen and lack of drug or disease-state interactions, treatment for 2-12 weeks at a therapeutic-dose level is usually needed to achieve a clinical response. The choice of medication should be guided by anticipated safety and tolerability, physician familiarity, and personal and family history of previous treatments. (See Medications.)

This article focuses on major depressive disorder in adults. For information on depression in children and adolescents, see the Medscape Reference article Pediatric Depression. For information on depression in bipolar disorder, see Bipolar Affective Disorder.

Pathophysiology

The underlying pathophysiology of major depressive disorder has not been clearly defined. Current evidence points to a complex interaction between neurotransmitter availability and receptor regulation and sensitivity underlying the affective symptoms.

Clinical and preclinical trials suggest a disturbance in central nervous system serotonin (5-HT) activity as an important factor. Other neurotransmitters implicated include norepinephrine (NE), dopamine (DA), glutamate, and brain-derived neurotrophic factor (BDNF). [7] However, drugs that produce only an acute rise in neurotransmitter availability, such as cocaine or amphetamines, do not have the efficacy over time that antidepressants do.

The role of CNS 5-HT activity in the pathophysiology of major depressive disorder is suggested by the therapeutic efficacy of selective serotonin reuptake inhibitors (SSRIs). In addition, studies have shown that an acute, transient relapse of depressive symptoms can be produced in research subjects in remission using tryptophan depletion, which causes a temporary reduction in CNS 5-HT levels. However, the effect of SSRIs on 5HT reuptake is immediate, but the antidepressant effect requires exposure of several weeks' duration. Also, some antidepressants have no effect on 5HT (eg, desipramine), and the antidepressant tianeptine enhances 5HT uptake. All this, together with preclinical research findings, implies a role for neuronal receptor regulation, intracellular signaling, and gene expression over time, in addition to enhanced neurotransmitter availability.

Seasonal affective disorder is a form of major depressive disorder that typically arises during the fall and winter and resolves during the spring and summer. Studies suggest that seasonal affective disorder is also mediated by alterations in CNS levels of 5-HT and appears to be triggered by alterations in circadian rhythm and sunlight exposure.

Vascular lesions may contribute to depression by disrupting the neural networks involved in emotion regulation—in particular, frontostriatal pathways that link the dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate, and dorsal cingulate. [8] Other components of limbic circuitry, in particular the hippocampus and amygdala, have been implicated in depression.

Brain structures

Functional neuroimaging studies support the hypothesis that the depressed state is associated with decreased metabolic activity in neocortical structures and increased metabolic activity in limbic structures. [9] Serotonergic neurons implicated in affective disorders are found in the dorsal raphe nucleus, the limbic system, and the left prefrontal cortex.

A meta-analysis comparing brain structures in patients with major depression, in healthy controls, and in patients with bipolar disorder demonstrated associations between depression and increased lateral ventricle size, larger cerebrospinal fluid volume, and smaller volumes of the basal ganglia, thalamus, hippocampus, frontal lobe, orbitofrontal cortex, and gyrus rectus. Patients experiencing a depressive episode had smaller hippocampal volume than those in remission. [10]

In one study, positron emission tomographic (PET) images showed abnormally diminished activity in an area of the prefrontal cortex in patients with unipolar depression and bipolar depression. This region is related to emotional response and has widespread connections with other areas of the brain, including the areas that appear to be responsible for the regulation of DA, noradrenaline (locus ceruleus), and 5-HT (raphe nuclei). [11]

Both functional and structural abnormalities were found in the same brain region during a major depressive episode. Sacher et al found increases in glucose metabolism in the right subgenual and pregenual anterior cingulate cortices and decreased gray matter volumes in the amygdala, dorsal frontomedian cortex, and right paracingulate cortex. [11]

Aging

An integrative model of late-onset depression posits that age-related brain changes and disease-related changes (eg, cerebrovascular disease), coupled with physiologic vulnerabilities (eg, genetic risk factors, personal history of depression) and psychosocial adversity, lead to disruptions in the functional circuitry of emotion regulation—namely, hypometabolism of cortical structures and hypermetabolism of limbic structures. [8]

Endocrine changes in depression are evident across the life span, but some are unique to aging. Women with a previous history of depression are at higher risk of developing depression during menopause, although estrogen replacement does not relieve depression; low testosterone levels have been associated with depression in older men.

Etiology

The specific cause of major depressive disorder is not known. As with most psychiatric disorders, major depressive disorder appears to be a multifactorial and heterogeneous group of disorders involving both genetic and environmental factors.

Evidence from family and twin studies indicates that with depression that develops in early childhood, the transmission from parents to children appears to be related more to psychosocial influences than to genetics. [12] Adolescent-onset and adult-onset depression, while more heritable than prepubertal depression, likewise reflect an interaction between genes and environmental stressors.

Genetics

Genetic factors play an important role in the development of major depression. Evidence from twin studies suggests that major depression has a concordance of 40-50%. First-degree relatives of depressed individuals are about 3 times as likely to develop depression as the general population; however, depression can occur in people without family histories of depression, as well. [13]

Two susceptibility loci have been identified in which no specific gene of interest has been definitively identified. The MDD1 locus is located at 12q22-q23.2 and is most strongly linked to major depression in males. [14] The MDD2 locus is located at 15q25.2-q26.2 and has been associated with early onset or recurrent episodes of depression. [15]

Although multiple genes are likely to influence the susceptibility to depression, those involved in the serotonin system are a focus of investigation, especially because many antidepressant medications work by influencing serotonin. [16] The *SLC6A4* gene, which is located at 17q11.2, encodes a serotonin transporter (also known as 5-hydroxytryptamine transporter) that is responsible for actively clearing serotonin from the synaptic space.

A polymorphism in the promoter region of the *SLC6A4* gene consists of a 44bp insertion or deletion involving repeat elements. These polymorphisms are referred to as either a long allele or a short allele. Caspi et al found that persons who were homozygous or heterozygous for the short allele had more depressive symptoms and suicidality in association with stressful life events than those patients who were homozygous for the long allele. [17]

Other studies also suggest that genes controlling either the production or utilization of serotonin play an important role in the pathogenesis of depression. The *TPH2* gene encodes tryptophan hydroxylase, which is the rate-limiting enzyme in the synthesis of serotonin. An in vitro study of a *TPH2* polymorphism, R441H, found an approximately 80% loss in serotonin production.

The clinical significance of this polymorphism remains uncertain, however. Zhang et al found that the allele was more common in a cohort of patients with major depression than in a control

population, [18] but a later study by Garriock et al did not find any patients with the R441H mutation in a cohort with major depression, a control group, or a group with bipolar disorder. [19]

The *HTR3A* and *HTR3B* regions, which encode serotonin receptors and are located at chromosome 11q23.2, are also known to be associated with major depression in both European and Japanese populations. Yamada e al surveyed 29 polymorphisms located within the *HTR3A* and *HTR3B* genes and found a single-nucleotide polymorphism that was associated with depression in females. [20]

A study of genes in the hypothalamic-pituitary-adrenal axis found that in patients with major depression, homozygosity for the T allele in the *FKBP5* gene was associated with a quicker response to antidepressants than heterozygosity or homozygosity for the C allele in that location. However, homozygosity for the T allele was also associated with an increased recurrence of depressive episodes. [21]

Studies such as those reported by Akiskal and Weller [22] and Weissman et al [23] suggest a genetic component in the etiology of depressive disorders. Individuals with a family history of affective disorders, panic disorder, or alcohol dependence carry a higher risk for major depressive disorder.

Children and adolescents

Nobile et al found that human platelet 5-HT uptake is differentially influenced in children and adolescents with and without depression by a common genetic variant of the promoter region of the serotonin transporter gene (*5-HTTLPR*). Depressed persons had a lower rate of serotonin uptake and a lower serotonin dissociation constant [24]

Birmaher et al found that before the onset of affective illness, children who were at high risk for depression, on the basis of family history, had the same pattern of neuroendocrine response to infusion of a serotonergic precursor (5-hydroxy-L-tryptophan) challenge as did children with major depression. Compared with low-risk children, high-risk children and depressed children secreted significantly less cortisol and, in girls, more prolactin. [25] These findings could constitute the identification of a trait marker for depression in children.

Late-onset depression

Some evidence suggests that late-onset depression (after age 60 years) is an etiologically and clinically distinct syndrome [26] and that genetic factors likely play less of a role in late-onset depression than in early-onset depression. A family history of depression is less common among patients with late-onset depression than in younger adults with depression. However, although findings have been inconsistent, certain genetic markers have been found to be associated with late-onset depression. Such markers include polymorphisms of apolipoprotein E, *BDNF*, and 5-HT transporter genes. Interestingly, these markers have also been associated with cognitive impairment, hippocampal volume, and antidepressant response, respectively.

Genetic influences on antidepressant drug response

Genetics also play a significant part in the response to pharmacologic treatment of major depression. A study of the drug transporter gene *ABCB1* (which encodes a transporter glycoprotein and functions as an active efflux pump for a number of drugs across the blood-brain barrier) found an association between 2 single-nucleotide polymorphisms and achievement of remission with citalopram, paroxetine, amitriptyline, and venlafaxine. Also, in a mouse model lacking the gene homologous to the human *ABCB1* gene, the mice had significantly higher concentrations of citalopram, venlafaxine, or desvenlafaxine after 11 days of subcutaneous administration of the drugs, despite drug plasma concentrations that were identical to those in mice lacking this mutation. [27]

Approximately 40% of patients who are treated with a selective serotonin reuptake inhibitor (SSRI) will either discontinue treatment or switch medications because of an adverse effect of the medication. In one study, an increased risk for sexual dysfunction from SSRIs was found to be associated with alleles in the *5HT2A* and *GHB3* genes. [28]

A study of response to treatment with citalopram identified a significant association between treatment outcome and a marker in *HTR2A*, which is located at chromosome 13q14.2 and encodes the serotonin 2A receptor. The A allele (a single-nucleotide polymorphism in an intron of this gene) reduced the likelihood of nonresponse to citalopram in whites but not in the African-American population. An AA genotype resulted in a 16-18% reduction in absolute risk of being a nonresponder. [29]

Stressors

Although major depressive disorder can arise without any precipitating stressors, stress and interpersonal losses certainly increase risk. For example, loss of a parent before the age of 10 years increases the risk of later depression. Cognitive-behavioral models of depression posit that negative cognitions and underlying all-or-nothing schemata contribute to and perpetuate depressed mood. [26]

Chronic pain, medical illness, and psychosocial stress can also play a role in major depressive disorder. Older adults may find medical illness psychologically distressing, and these illnesses may lead to increased disability, decreased independence, and disruption of social networks. [30] Chronic aversive symptoms such as pain associated with chronic medical illness may disrupt sleep and other biorhythms leading to depression.

Other psychosocial risk factors for depression in late life include the following [31] :

- Impaired social supports
- Caregiver burden
- Loneliness
- Bereavement
- Negative life events

Cognitive-behavioral models of depression suggest that the presence of negative life events in addition to one’s perception of or reaction to those events may impact the development and maintenance of depressive symptoms. Cognitive models of depression posit that negative cognitions and underlying all-or-nothing schemata contribute to and perpetuate depressed mood. [26] More specifically, cognitive vulnerability-stress models suggest that, in the face of negative life events, individuals who have a tendency to make negative attributions about the causes of those events, about themselves, and about future consequences (in line with the hopelessness theory of depression) may be more likely to develop depression. [32] This has been suggested as potentially contributing to gender differences in rates of depression following puberty (e.g., Hyde, Mezulis, and Abramson [33]). Behavioral models suggest that depression may result from deficits in response-contingent positive reinforcement andinadequate social skills [34] or reliance upon escape and avoidance behaviors, [35] such that avoidance behaviors in response to negative life events and corresponding negative emotions may lead to worsened depression. [36]

In addition, neurochemical hypotheses point to the deleterious effects of cortisol and other stress-related substances on the neuronal substrate of mood in the CNS.

Exposure to certain pharmacologic agents increases the risk of depression, such as reserpine, beta-blockers, and steroids such as cortisol. Abused substances can also increase risk of major depressive disorder, such as cocaine, amphetamine, narcotics, and alcohol. With agents of abuse, however, it is unclear whether depression is a consequence or facilitator.

Risk-factor interactions

Researchers are currently investigating the relationship between genetic vulnerability, environmental stressors, and brain structural abnormalities in the development of depression. In an MRI genetic study, Frodl et al found that patients with major depression who carried the S allele of *5-HTTLPR* and had a history of childhood emotional neglect had smaller hippocampal volumes than patients who had only one of those factors. They concluded that structural hippocampal brain changes resulting from stress may be part of the risk for developing depression and that these changes are more pronounced in individuals with the S-allele. [37]

Conflicting evidence exists regarding the interaction between the functional serotonin transporter promoter (5-HTTLPR) and stress in the development of depression. A 2011 meta-analysis suggested that 5-HTTLPR moderates the relationship between stress and depression. [38] Earlier, smaller meta-analyses had concluded that the evidence did not support the presence of the interaction.

Neuroendocrine abnormalities and neurodegenerative diseases

Possible abnormalities of the neurotransmitter systems remain under investigation. Compared with control subjects, depressed prepubertal children had lower cortisol secretion during the first 4 hours of sleep, according to De Bellis et al. Nocturnal secretion of adrenocorticotropin, growth hormone, and prolactin did not differ between the 2 groups. [39]

Potential biological risk factors have been identified for depression in the elderly. Neurodegenerative diseases (especially Alzheimerdisease and Parkinsondisease), stroke, multiple sclerosis, seizure disorders, cancer, macular degeneration, and chronic pain have been associated with higher rates of depression. [40] Alternatively, a large, longitudinal study found that depression that starts early in life increases the risk for Alzheimer's disease (AD). Researchers used data from the Prospective Population Study of Women in Gothenburg Sweden, which began in 1968. The study sample included 800 women (mean age, 46 years), born between 1914 and 1930, who were followed up with in 1974, 1980, 1992, 2000, 2009, and 2012. Data show those women who experienced the onset of depression before age 20 years were three times more likely to develop AD (adjusted HR, 3.41; 95% CI, 1.78 - 6.54). [205]

Parent-child relations

The parent-child relation model conceptualizes depression as the result of poor parent-child interaction. Adults with depression report low paternal involvement and high maternal overprotection during early childhood. Troubled relationships with parents, siblings, and peers are common in children and adolescents with affective illness.

Affective illness in a parent may be a factor in child abuse and/or neglect that promotes affective illness in the child. Childhood abuse and neglect, as well as a cumulative load of stressors over a lifetime, have been associated with both early-adult and late-onset depression.

Hammen et al reported a significant temporal association between depression diagnoses in mother and child. [41] They found that children with substantial stress exposure who also had symptomatic mothers were significantly more depressed than children who were exposed to comparable levels of stress only.

Mothers' remission from depression, regardless of timing, has a consistently favorable influence on their children. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Child study, all children whose mothers experienced remission from depression showed improvement in mood and behavior in the following year; children whose mothers recovered from depression within the first 3 months of treatment showed not only improved mood and behavior but significant improvement in functioning, as well. [42]

Vascular depression

The vascular depression hypothesis posits that cerebrovascular disease may cause or contribute to late-life depression. Various lines of evidence support this hypothesis, including the following [43] :

- Higher incidence of depression following a left-sided stroke
- Higher prevalence of ischemic white-matter changes in older adults with depression than those without
- Bidirectional association between depression and coronary artery disease and depression and diabetes
- Higher rates of depression among patients with vasculardementia than those with Alzheimer disease

Epidemiology

United States statistics

During 2009–2012, 7.6% of Americans aged 12 and over had depression (defined as having moderate or severe depressive symptoms in the past 2 weeks). Depression was more prevalent among females than males and among adults aged 40–59 than those of other age groups. Rates of any depressive symptoms were lower among non-Hispanic white persons than among Hispanic and non-Hispanic black persons. Once poverty was taken into account, however, rates of depression did not differ significantly by race or Hispanic origin. [204]

In 2015, an estimated 16.1 million adults aged 18 or older in the United States had at least one major depressive episode in the past year. This number represented 6.7% of all U.S. adults. [46]

International statistics

Internationally reported adult prevalence rates of depression generally mirror those of the United States, and estimates of 1-month prevalence of depression in community-dwelling elderly are relatively consistent (eg, England, 2.9%; The Netherlands, 2.0%; Sweden, 5.6%; Nigeria, 1.6%). However, sparse data are available on the international incidence of major depression in children and adolescents.

Helgason examined the entire Icelandic birth cohort of 1895-97 with periodic follow-up until cohort individuals reached age 74-76 years. The lifetime estimates of risk for any affective disorder were 14.8% for females and 9.8% for males. [47] The WorldHealthOrganization(WHO) collaborative study on the assessment of depressive disorders found considerable similarity in depressive symptomatology across cultures in Canada, Iran, Japan, and Switzerland. [48]

The Stirling County Study, which began shortly after World War II, offered a 40-year perspective of the prevalence and incidence of psychiatric disorders in an adult population in Atlantic Canada, in which the overall prevalence of depression remained stable at 5% across 3 separate samples in

1952, 1970, and 1992. In the 2000 sample, however, the prevalence had shifted from older to younger persons, and the female-to-male ratio had increased. [49]

Copeland et al found widely ranging prevalences for depression in elderly persons in 9 European populations. The prevalence for females was higher than that for males, and there was no constant association between prevalence and age. Meta-analysis revealed an overall prevalence of 12.3% and frequencies of 14.1% for females and 8.6% for males. [50]

Children and adolescents

The incidence of depression was 0.9% in preschool-aged children, 1.9% in school-aged children, and 4.7% in adolescents in a study by Kashani and Sherman. [51] In another study, more than 22% of female high school students and more than 11% of male high school students reported 1 current or lifetime episode of unipolar depression. The percentage of male students with 2 or more episodes of unipolar depression was 4.9%; it was 1.6% in female students. [52]

Garrison et al reported a 1-year incidence of major depression of 3.3% in adolescents aged 11-16 years. [53] Their epidemiologic study was conducted between 1987 and 1989 in a single school district in the southeastern United States.

In prepubertal children, boys and girls are affected equally. Hankin et al found that the most critical time for sex differences in depression to emerge is from age 15-18 years. [54] During this period, the increase in overall rates of depression and onset of new cases of depression peak.

Hispanic youths in Los Angeles county (aged 12-17 years) reported more symptoms of depression, independent of socioeconomic status, when compared with white, black, or Asian American adolescents, using the Children's Depression Inventory (CDI). [55] This study also found significant effects of social class on depression. As income decreased, the average prevalence of depression increased.

Elderly persons

Although rates of depression in women and men are highest in those aged 25-44 years, the incidence of clinically significant depressive symptoms increases with advancing age, especially when associated with medical illness or institutionalization. However, the depression might not meet criteria for major depression because of somewhat atypical features of depression in elderly persons. For instance, there is a higher prevalence of dysthymic disorder in aging and medically ill populations.

Prognosis

Major depressive disorder has significant potential morbidity and mortality, contributing as it does to suicide, incidence and adverse outcomes of medical illness, disruption in interpersonal relationships, substance abuse, and lost work time. With appropriate treatment, 70-80% of individuals with major depressive disorder can achieve a significant reduction in symptoms, although as many as 50% of patients may not respond to the initial treatment trial.

Twenty percent of individuals with major depressive disorder untreated at 1 year will continue to meet criteria for the diagnosis, whereas an additional 40% will have a partial remission. Pretreatment irritability and psychotic symptoms may be associated with poorer outcomes. Partial remission and/or a history of prior chronic major depressive episodes are risk factors for recurrent episodes and treatment resistance.

A study of first-episode psychotic depression by Tohen et al found that most patients achieved syndromal remission (86%) and recovery (84%); however, only 35% recovered functionally. Earlier

syndromal recovery was associated with subacute onset, lower initial depression scores, and lack of mood-incongruent psychotic features. Within 2 years, almost half the patients experienced new episodes. In 41% of patients, the diagnosis was changed, usually to bipolar or schizoaffective disorders. [56]

Recurrence of early depression

According to the AmericanAcademyofChildandAdolescentPsychiatry(AACAP) practice parameters for depressive disorders in childhood and adolescence, a history of a previous depressive episode, subsyndromal symptoms of depression, dysthymia, and anxiety disorders increase the risk for future depression. [57] In a study of an epidemiologic sample of 776 adolescents by Pine and associates, symptoms of majordepressioninadolescencestrongly predicted episodes of major depression in adulthood. [58]

Late-onset depression

The prognosis for patients with late-onset depression is felt to be poorer than that for younger patients, and it appears to be dependent on physical disability or illness and lack of social support. Of particular importance is the increasing risk of death by suicide, particularly among elderly men. The length of a depressive episode in the aging population is approximately 18 months, whereas in people 20–55 years of age, the length of an episode is 18 to 24 weeks.

In older patients, depression is frequently comorbid with chronic medical conditions and can lead to worsening medical outcomes, including mortality. [26] For example, coronary artery disease is a risk factor for the development of depression, and depression is an independent risk factor for the development of coronary disease. Patients with both conditions are more likely to die than those with coronary artery disease alone. Both behavioral and physiologic explanations are likely for these associations. [59]

Millard suggested the "rule of thirds" concerning the prognosis of late-onset depression, which states that regardless of treatment, approximately one third of patients will manifest remission, another one third will remain symptomatic in the same condition, and the remaining one third will worsen. [60] In fact, research has shown that approximately 60% of patients with late-onset depression will have at least 1 recurrence, and up to 40% of these patients will have chronic or continuously recurrent depression. [61]

Late-onset depression has been reported to double the risk of developing mildcognitiveimpairment [62] and the likelihood that the mild impairment will develop into dementia. [63] The Diabetes and Aging Study showed that when depression is comorbid with type 2 diabetes, it increases the risk of all-cause dementia by about 2-fold compared with diabetes alone. [64] A 40-month study of 2977 middle-aged and older adults with long-standing type 2 diabetes found depression at baseline to be associated with accelerated cognitive decline. [65, 66]

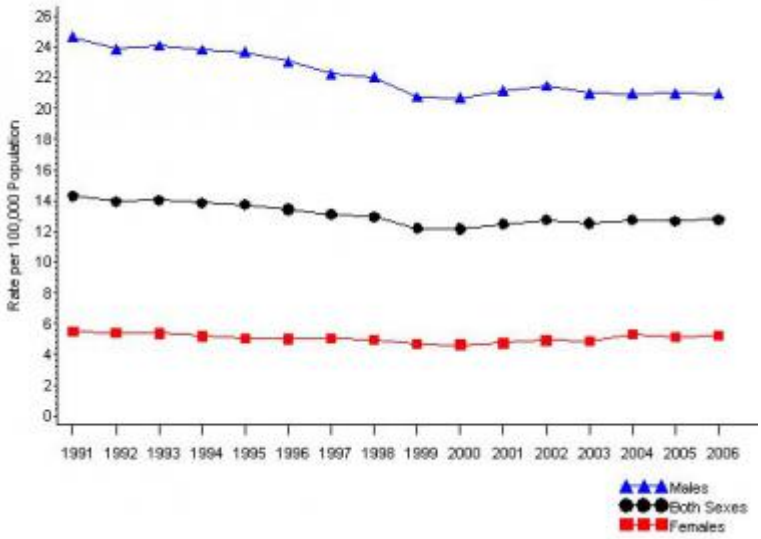
Compared with participants without a depression history, those with late-life depression reportedly have increased all-cause dementia risk; however, early-life depression had no association with dementia risk. [67] Treating depression has been suggested to possibly stunt progression to mild cognitive impairment and then to dementia, although there has been little evaluation of this hypothesis to date.

Suicide

Depression plays a role in more than one half of all suicide attempts, whereas the lifetime risk of suicide among patients with untreated depressive disorder is nearly 20%. [68] According to Centers for Disease Control and Prevention (CDC) data, suicide was the 10th leading cause of death in the

United States in 2009, accounting for 36,909 deaths; it was the second leading cause of death in people 25-34 years of age, the third leading cause in people aged 10-24 years, and the fourth leading cause at ages 35-54. [69]

However, despite these data and the fact that depression is more often diagnosed in women, the highest suicide rate is in men older than 75 years (see the graph below); more men than women die from suicide by a factor of 4.5:1. White men complete more than 78% of all suicides, and 56% of suicide deaths in males involve firearms. Poisoning is the predominant method among females. Attempted suicide is more frequent in women.



From 1991-2006, the suicide rate was consistently higher among males. Suicide rates declined among both sexes from 1991-2000; the rate among males decreased from 24.64 to 20.67 suicides per 100,000 and 5.48 to 4.62 suicides per 100,000 among females. From 2000-2006, however, the suicide rates gradually increased among females. Note: All rates are age-adjusted to the standard 2000 population. Rates based on less than 20 deaths are statistically unreliable. Source: Centers for Disease Control and Prevention. National suicide statistics at a glance: Trends in suicide rates among persons ages 10 years and older, by sex, United States, 1991-2006. Available at: http://www.cdc.gov/violenceprevention/suicide/statistics/trends01.html. Accessed: May 5, 2010.

In addition to older age and male sex, risk factors for suicide include the following [70, 71] :

- Diagnosis of major depression
- Previous history of suicide attempts
- Depressive symptoms with agitation or distress
- Burden of medical disease and the presence of a current serious medical condition (although this risk may be mediated by a diagnosis of depression)
- Recent stressful life events, especially family discord
- Lack of social support
- Being widowed or divorced
- The presence of a gun in the home
- Unexplained weight loss
- High levels of anxiety
- Lack of a reason not to commit suicide

- Presence of a specific plan that can be carried out
- Rehearsal of the plan

The relationship between use of antidepressants and risk of suicide varies with patient age. Treatment with antidepressants has been associated with increased suicidality in children, adolescents, and young adults 18 to 24 years of age. There is no evidence of increased risk for adults older than 24 years of age; for adults 65 years of age or older, the risk is actually decreased. [72]

Suicide rates among Native Americans and Alaskan Natives between ages 15 and 34 years are almost twice the national average for this age range. Hispanic females make significantly more suicide attempts than their male or non-Hispanic counterparts.

In one study, there were strong correlations of suicide rates with indicators of access to health care in the United States. [73] Multivariate analysis of state-by-state statistics showed that the state rate of federal aid for mental health was the strongest indicator, followed by the rate of uninsured persons and population density of psychiatrists and physicians and by population density. These researchers concluded that the findings support the view that clinical intervention is a crucial element in the prevention of suicide.

In 2005, 1.4% of all deaths worldwide were attributed to suicide. The actual number is unknown, as underreporting is predictably significant in many regions of the world. Suicide is estimated to be the eighth leading cause of death in all age ranges. In Eastern Europe, 10 countries report more than 27 suicides per 100,000 persons. Latin America and Muslim countries report the lowest rates, with fewer than 6.5 cases per 100,000 persons. Suicide rates increased from 1955-2009 in most countries but have decreased from 1990-2009.

Patient Education

Education plays an important role in the successful treatment of major depressive disorder. Over the long term, patients may also become aware of signs of relapse and may seek treatment early. Patients should be aware of the rationale behind the choice of treatment, potential adverse effects, and expected results. The involvement of the patient in the treatment plan can enhance medication compliance and referral to counseling.

Family members also need education about the nature of depression and may benefit from supportive interactions. Engaging family can be a critical component of a treatment plan, especially for pediatric and late-onset depression. Family members are helpful informants, can ensure medication compliance, and can encourage patients to change behaviors that perpetuate depression (eg, inactivity).

The following Web sites are valuable resources for patient and family education:

- National Institute of Mental Health: Depression
- MedlinePlus: Depression
- FamilyDoctor.org: Depression
- DepressionandBipolarSupportAlliance(DBSA)
- FamiliesforDepressionAwareness

Helpful Web sites specifically for late-onset depression include the following:

- MedlinePlus: Depression-elderly

- National Institute of Mental Health: OlderAdults:Depressionand Suicide Facts
- University of Maryland Medical Center: Depression-elderly

Clinical Presentation