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Depressive Disorders: Major, Minor, and Mixed

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Synonyms

Clinical depression; Depression; Unipolar depression

Definition

The depressive disorders comprise a spectrum of clinical syndromes characterized by persistent depressed mood or sadness, loss of interest (apathy), or loss of pleasure (anhedonia). These symptoms are to be distinguished from the transient feelings of unhappiness or sadness that constitute normal reactions to the disappointments or losses experienced in everyday life. The symptoms of depressive disorders cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not due to the direct physiological effects of a substance or a general medical condition. Depression is generally differentiated from bereavement, the expectable constellation of depressive symptoms following the loss of a loved one, although depression may be diagnosed if such symptoms are sufficiently severe and pervasive or are not characteristic of a "normal" grief reaction in the individual's culture. The depressive disorders are also to be distinguished from depressive *episodes* of bipolar disorder, which is diagnosed if the individual has ever had a manic or hypomanic episode.

Role of Pharmacotherapy

Clinical Features, Etiology, and Pathogenesis

Recognition of depression as a distinct disease dates back at least as far as the Hippocratic writings of the fifth and fourth centuries B.C. Lifetime prevalence varies among diagnostic categories and according to the specific diagnostic criteria used, with risks for major depression ranging from 10 % to 25 % in women and 5 % to 12 % in men. Prevalence rates are unrelated to income, education, marital status, or ethnicity; prevalence rates across cultures show up to sevenfold differences, although female preponderance and mean age of onset tend to be consistent. Depressive disorders may have their onset at any age, but the average is in the mid-20s. Incidence and prevalence then decline through adulthood, although subsyndromal depressive symptoms begin to rise again in the seventh decade. At least 60 % of individuals with a single episode of major depression will have subsequent episodes. Major depression is associated with significantly increased mortality; up to 15 % of individuals with severe illness die by suicide.

The etiology of depressive disorders is unknown. There is a familial pattern, with major depression 1.5–3 times more common in individuals with an affected first-degree biological relative; heritability based on twin studies is 40–50 %. Neuroticism (a temperament characterized by negative

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affectivity) appears to account for a substantial part of this genetic liability. However, no single major gene locus has been shown to cause depression. Rather, genetic risk appears to involve multigenic and/or gene-environment interactions. The short allele of the serotonin transporter-linked polymorphic region (5-HTTLPR), in particular, has been most strongly implicated in gene-environment interactions leading to depression. Environmental risk factors include early-life abuse and neglect and major life stress.

The predominant theories of pathogenesis in depression have focused on monoamine neurotransmission and hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Early monoamine theories posited simple deficiencies in serotonin or norepinephrine function, but such hypotheses have been superseded by complex formulations involving a wide array of intracellular and transsynaptic signaling pathways. Similarly, while early HPA axis theories emphasized hyperactivity, more recent work suggests that derangements in this neuroendocrine system are more variable and may be linked to abnormalities in neurotrophins (such as brain-derived neurotrophic factor (BDNF)) and neurogenesis. Other theories of pathogenesis have explored the role of reduced neurotransmission in the dopamine and GABA systems, altered glutamatergic neurotransmission, impaired endogenous opioid function, abnormal circadian rhythms, hypothalamic-pituitary-thyroid (HPT) axis dysfunction, monoamine-acetylcholine imbalances, cytokine-mediated neuroimmune abnormalities, deficient neurosteroid synthesis, neuronal and glial cellular abnormalities, and dysfunction of specific brain structures and circuits.

Diagnostic Categories

Major Depressive Disorder (Major Depression)

The diagnosis of major depression requires the presence of at least five of nine key symptoms during the same 2-week period, with at least one of the symptoms being either (1) depressed mood or (2) loss of interest or pleasure. In addition to these, the other key symptoms are (3) significantly decreased or increased weight or appetite, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy (anergia), (7) feelings of worthlessness or guilt, (8) diminished concentration or indecisiveness, and (9) recurrent thoughts of death, suicidal ideation, or suicidal behavior.

Between 50 % and 70 % of individuals shows clinically significant improvement with a given antidepressant. There is no compelling evidence of differential efficacy between drugs in unselected patients, and drug selection is usually based on a consideration of side effect profiles. Selective serotonin reuptake inhibitors (SSRIs) are the most frequently used first-line drugs for major depression. This group includes fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, and vilazodone. Common side effects of these drugs are constipation, diarrhea, dizziness, headache, insomnia, nausea, somnolence, and sexual dysfunction. Other frequently used classes of antidepressants are the serotonin-norepinephrine reuptake inhibitors (SNRIs) and the norepinephrine reuptake inhibitors (NARIs). The SNRIs include venlafaxine, desvenlafaxine, milnacipran, levomilnacipran, and duloxetine, which have side effect profiles generally similar to the SSRIs. The NARIs include bupropion and reboxetine, with side effects that include dry mouth, insomnia, headache, nausea, constipation, tremor, and tachycardia; bupropion is less likely to cause sexual dysfunction than the SSRIs or SNRIs, but lowers the seizure threshold at high doses. The tricyclic antidepressants (TCAs) include amitriptyline, imipramine, clomipramine, nortriptyline, desipramine, protriptyline, trimipramine, amoxapine, and dothiepin. While the TCAs were the first class of drugs used to treat depression, they have largely been supplanted in that role by newer drugs because of their unfavorable side effect profile (anticholinergic effects, cardiovascular effects, somnolence, and tremor) and their high degree of lethality in overdose. Tetracyclic antidepressants,

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which include maprotiline, mirtazapine, and mianserin, constitute another group of less commonly used agents; maprotiline has side effects similar to the TCAs, whereas mirtazapine and mianserin are notable for causing somnolence, dry mouth, and substantial weight gain. Agomelatine, a melatonergic agonist, is a newer drug which has found some use in countries where it is available; the most likely side effect is dizziness. The nonselective monoamine oxidase inhibitors (MAOIs), which include phenelzine, tranylcypromine, and isocarboxazid, are generally considered third- or later-line drugs, as they can cause life-threatening hypertensive or hyperpyrexic reactions when inadvertently combined with foods or drugs that enhance noradrenergic or serotonergic activity. More selective MAOIs, such as the reversible inhibitor of monoamine oxidase A (RIMA) moclobemide or the transdermal formulation of the MAO-B selective selegiline, are far less likely to cause such reactions. The triazolopyridine antidepressants trazodone and its congener nefazodone are now infrequently used as primary treatments for depression; trazodone can cause severe priapism, while nefazodone has been associated with rare fatal hepatic necrosis, and both drugs cause significant somnolence. The second-generation antipsychotic quetiapine has shown efficacy in treating depression, but its use for this purpose is limited by its side effect profile, which includes somnolence, weight gain, and the risk of tardive dyskinesia.

Major depression of mild to moderate severity may be treated with psychotherapy, with or without medication; cognitive-behavioral therapy and interpersonal psychotherapy, in particular, have been supported in controlled clinical trials. Milder cases of depression may also respond to complementary and alternative medical approaches, such as light (phototherapy), exercise, and herbal or dietary supplements (e.g., St. John's wort (*Hypericum perforatum*), omega-3 fatty acids, S-adenosine-L-methionine (SAMe)). Severe and treatment-resistant cases of depression are often managed with combinations of drugs or with electroconvulsive therapy. Among newer neuromodulatory approaches, transcranial magnetic stimulation has demonstrated convincing efficacy and is now in increasing use. In contrast, vagus nerve stimulation has not gained widespread acceptance, but deep brain stimulation is under active investigation. Rarely, stereotactic ablative neurosurgery, generally involving lesions in frontolimbic circuitry, is used in intractable cases.

Major Depressive Disorder with Psychotic Features (Psychotic Depression)

This form of depression is defined by the presence of either delusions or hallucinations and is invariably severe; inpatient treatment is usually necessary because of profound functional impairment or intense suicidality. Psychotic features whose content reflects the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment are considered *mood-congruen*t; *mood-incongruent* psychotic features generally involve non-depressive persecutory delusions, thought insertion, thought broadcasting, or delusions of control. Pharmacotherapy usually involves the use of an antipsychotic in combination with an antidepressant. However, electroconvulsive therapy (ECT) is often required.

Major Depressive Disorder with Catatonia

Catatonia is diagnosed when at least two of five key symptoms are present, including (1) motoric immobility, such as catalepsy or stupor, (2) excessive purposeless motor activity (catatonic excitement), (3) extreme negativism (motiveless resistance to instructions or maintenance of a rigid posture against attempts to be moved) or mutism, (4) bizarre posturing, stereotypies, mannerisms, or grimacing, and (5) echolalia or echopraxia. Catatonic symptoms often respond acutely to benzodiazepines. However, since this syndrome generally occurs in the context of psychotic depression, treatment with an antipsychotic/antidepressant combination or ECT is usually necessary for sustained improvement.

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Major Depressive Disorder with Melancholic Features (Melancholia)

The critical feature of this syndrome is profound anhedonia or lack of reactivity (not even transient mood improvement in response to positive events). In addition, at least three of six key symptoms are present, including (1) distinct quality of mood (different from usual feelings of sadness or loss), (2) morning worsening of mood (diurnal variation), (3) early morning awakening, (4) marked psychomotor retardation or agitation, (5) significant anorexia or weight loss, and (6) excessive guilt. Episodes of melancholia are usually severe, and patients with psychotic depression are usually melancholic. As the successor to the historical syndrome of endogenous depression, melancholia was originally defined in an attempt to identify those patients who would have a better response to somatic treatment than other patients. Subsequent research has failed to establish this preferential response, but has shown that melancholic patients are less likely than other patients to respond to placebo. Pharmacotherapy involves standard antidepressant drugs. Some authorities believe that first-generation drugs (i.e., TCAs and MAOIs) are more effective. Severe cases may require ECT.

Major Depressive Disorder with Atypical Features (Atypical Depression)

This syndrome is defined by the presence of mood reactivity (mood brightening in response to positive events) in conjunction with at least two of four key symptoms, including (1) significant weight gain or appetite increase, (2) hypersomnia, (3) leaden paralysis (heavy feelings in the limbs), and (4) a long-standing pattern of interpersonal rejection sensitivity. The diagnostic criteria for atypical depression reflect early efforts to identify a group of patients who would preferentially respond to MAOIs rather than TCAs. The importance of this distinction has receded as other, safer agents have supplanted the MAOIs, and treatment of atypical depression is now usually initiated with SSRIs or other second-generation antidepressants. However, ongoing research has generally supported the existence of meaningful neurobiological differences between atypical depression and melancholia (e.g., HPA axis hypoactivity in atypical depression vs. hyperactivity in melancholia).

Major Depressive Disorder with Peripartum Onset (Postpartum Depression)

Episodes of major depression whose onset occurs during pregnancy or within 4 weeks of delivery are considered peripartum (as are similarly timed manic or mixed episodes). Such episodes used to be labeled postpartum, but it is now recognized that 50 % of such episodes actually occur prior to delivery. Diagnostic criteria are otherwise the same as for other depressive syndromes, although postpartum episodes are usually distinguished by symptom content that is focused on the infant. The mother may express excessive concern for the infant's well-being, feelings of being overwhelmed, fear of being responsible for the infant, hostility, or apathy. Psychotic symptoms may develop, in which case there may be a risk of infanticide. Postpartum depression must be distinguished from the transient mood lability ("baby blues") occurring in the first 10 days postpartum in up to 70 % of women, which may be a risk factor for a major depressive episode but usually resolves on its own. Pharmacotherapy for postpartum depression involves standard antidepressant drugs, with antipsychotics if psychotic symptoms are present. All antidepressants are secreted in breast milk, but few specific adverse events have been reported, so benefits and risks of breastfeeding must be addressed.

Major Depressive Disorder with Seasonal Pattern (Seasonal Depression, Seasonal Affective Disorder)

Episodes of major depression are considered seasonal (as are manic or mixed episodes) if (1) there has been a regular temporal relationship between the onset of the episode and a particular time of year (for depression, usually fall or winter), (2) full remissions also occur at a characteristic time of year (usually spring), (3) in the last 2 years two episodes have occurred with the seasonal pattern, but

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no nonseasonal episodes have occurred, and (4) seasonal episodes substantially outnumber nonseasonal episodes over the individual's lifetime. The diagnosis is not made if seasonal psychosocial stressors (e.g., school or work) better account for the seasonal pattern. Seasonal depression is more common at higher latitudes and in younger individuals. Pharmacotherapy usually involves SSRIs or NARIs, although light therapy appears to be equally effective and is often used.

Major Depressive Disorder with Anxious Distress

Anxious distress includes (1) feeling keyed up or tense, (2) feeling unusually restless, (3) difficulty concentrating because of worry, (4) fear that something awful will happen, and (5) feeling that one might lose control of oneself. Major depression with anxious distress is diagnosed when at least 2 of these symptoms occur during the majority of days of a major depressive episode. This syndrome is common and may be associated with a higher suicide risk, longer illness duration, and increased treatment resistance. Pharmacotherapy usually begins with SSRIs and SNRIs, as NARIs may lack efficacy, and the side effect profiles of other antidepressants often render them poorly tolerated in this population. Benzodiazepines are frequently used adjunctively, especially early in treatment. Persistent depressive disorder (dysthymia) can also be diagnosed with anxious distress.

Major Depressive Disorder with Mixed Features (Mixed Depression)

When at least three manic or hypomanic symptoms are evident nearly every day during the majority of days of a major depressive episode, mixed features are diagnosed. These symptoms include (1) elevated or expansive mood, (2) inflated self-esteem or grandiosity, (3) increased talkativeness, (4) flight of ideas or subjective racing thoughts, (5) increased energy or goal-directed activity, (6) increased or excessive involvement in activities with a high potential for painful consequences, and (7) decreased need for sleep. The symptoms must represent a change from the individual's usual demeanor, must be observable by others, and must not be attributable to the effects of a drug or substance. If symptoms meet the full criteria for mania or hypomania, bipolar I or bipolar II disorder should be diagnosed. The pharmacotherapy of this condition remains controversial. Individuals with the syndrome are at increased risk for developing a bipolar disorder, so some authorities advocate treatment with mood stabilizers rather than antidepressants. When antidepressants are used, SSRIs are most commonly employed, in part due to some evidence suggesting increased risk for mania/hypomania with other antidepressants.

Other Specified Depressive Disorder (Minor Depression)

This group of syndromes is distinguished by symptoms characteristic of a depressive disorder that cause clinically significant distress or functional impairment but do not meet full criteria for a defined depressive subtype. Examples include *recurrent brief depression* (concurrent presence of depressed mood and at least four other depressive symptoms for 2–13 days at least once a month (not associated with menses) for at least 12 consecutive months), *short-duration depression* (depressed affect and at least four other depressive symptoms for more than 4 but less than 14 days), and *depression with insufficient symptoms* (depressed affect and at least one other depressive symptom that persist for at least 2 weeks). The nosological validity of these syndromes is not well established. There is only limited support for using pharmacotherapy in the management of minor depression, and while some studies suggest SSRIs may be of benefit, an especially careful assessment of risks and benefits should be undertaken.

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Cross-References

- ▶ Antidepressants
- ▶ Antipsychotic Drugs
- ▶ Benzodiazepines
- ▶ Bipolar Disorder
- ▶ Monoamine Oxidase Inhibitors
- ▶ NARIs
- ▶ Neurogenesis
- ▶ Neurosteroids
- ▶ SNRIs
- ▶ SSRI
- ▶ Suicide

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