

Depression

(See also *Harrison's Principles of Internal Medicine*, 17th Edition, Chapter 386)

Definition

- A clinical mood disorder associated with depressed mood or loss of interest and other symptoms that prevent a patient from leading a normal life
- Depressive disorders usually begin in early adulthood and recur episodically over a lifetime.
- Major depression
 - Depressed mood on a daily basis for a minimum duration of 2 weeks
- Dysthymic disorder
 - A pattern of chronic (at least 2 years), ongoing, mild depressive symptoms
- Minor depression
 - Experience of at least 2 depressive symptoms for 2 weeks but does not meet the criteria for major depression
- Seasonal affective disorder
 - Seasonal pattern of depression

Epidemiology

- Unipolar depressive disorders
 - Twice as common in women as in men; incidence increases with age in both sexes
 - Major depression
 - Fourth among all diseases in terms of disability-adjusted life years in the Global Burden of Disease Study (conducted by World Health Organization)
 - Projected to rank second by year 2020
 - Approximately 15% of the population experiences a major depressive episode at some point in life.
 - 6–8% of all outpatients in primary care settings satisfy diagnostic criteria for the disorder.
 - Dysthymic disorder
 - Affects ~5% of primary care patients
 - Seasonal affective disorder
 - More common in women
 - Prevalence increases with distance from the equator.
- Depression associated with medical illness
 - Cardiac disorders
 - 20–30% manifest a depressive disorder.
 - A higher percentage experience depressive symptomatology when self-reporting scales are used.
 - Cancer
 - Mean prevalence of depression is 25%.
 - Neurologic disorders
 - Depression occurs frequently in stroke and neurodegenerative diseases.

- Diabetes mellitus
 - Prevalence varies from 8–27%.
 - Severity of mood state correlates with the level of hyperglycemia and presence of complications.
- HIV/AIDS
 - Lifetime prevalence estimated at 22–45%

Risk Factors

- Family history
 - More frequent in families of bipolar individuals
- Female sex
- Medications
 - Antihypertensive drugs; especially β -adrenergic blockers and calcium-channel blockers
 - Antiarrhythmic agents
 - Glucocorticoids
 - Antimicrobials
 - Systemic analgesics
 - Antiparkinsonian medications
 - Anticonvulsants
- Medical illnesses
- Stressors/negative life events
 - Death of a relative
 - Assault
 - Severe marital or relationship problems
- Alcohol or substance abuse
- Past episodes of depression
 - 50–60% of patients who have a first episode have at least 1 or 2 recurrences.

Etiology

- Genetic factors
 - Monozygotic twins have a higher concordance rate (46%) than dizygotic twins (20%); little evidence for any effect of a shared family environment.
 - May influence the sensitivity of individuals to stressful events
- Neurotransmitter abnormalities
 - Decreased noradrenaline and serotonin levels in the brain
- Possible neuroendocrine abnormalities
 - Increased cortisol and corticotropin-releasing hormone secretion
 - Increase in adrenal size
 - Decreased inhibitory response of glucocorticoids to dexamethasone
 - Blunted response of thyroid-stimulating hormone (TSH) level to infusion of thyroid-releasing hormone
 - Upregulation of proinflammatory cytokines (major depression)
- Defect in regulation of biologic rhythms
 - Diurnal variations in symptom severity
 - Alterations in circadian rhythmicity of neurochemical and neurohumoral factors

- Major depression
 - Decrease in rapid eye movement (REM) sleep onset (REM latency), increase in REM density, decrease in stage IV delta slow-wave sleep

Associated Conditions

- Medical illnesses
 - Cardiac disorders
 - Cancer
 - Neurologic disorders, particularly cerebrovascular disorders, Parkinson's disease, dementia, multiple sclerosis, and traumatic brain injury
 - Diabetes mellitus
 - Hypothyroidism/hyperthyroidism
 - HIV/AIDS
 - Hepatitis C
 - Chronic fatigue syndrome
 - Fibromyalgia
- Substance abuse

Symptoms & Signs

- Major depression
 - Five (or more) of the following symptoms are present during most of the day, nearly every day, in the same 2-week period. At least 1 of the symptoms is either depressed mood or loss of interest or pleasure:
 - Depressed mood
 - Sadness, indifference, apathy, or irritability
 - Diminished interest or pleasure in almost all or all activities
 - Significant weight loss or weight gain (e.g., a change of >5% of body weight in a month) or decrease or increase in appetite
 - Insomnia or hypersomnia; early-morning awakening
 - Psychomotor agitation or retardation
 - Fatigue or loss of energy
 - Feelings of worthlessness or excessive or inappropriate guilt (may be delusional)
 - Diminished ability to think or concentrate, or indecisiveness
 - Recurrent thoughts of death (not just fear of dying); recurrent suicidal ideation without specific plan; suicide attempt or specific plan for committing suicide
 - The symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
 - The symptoms are not due to the direct physiologic effects of a substance or general medical condition.
- Dysthymic disorder
 - Does not appear to be episodic
 - Not clearly associated with either psychosocial dysfunction or change from usual experience in life
 - Ongoing (at least 2 years) mild depressive symptoms
 - Less severe and less disabling than major depression
 - Major depression vs. dysthymic disorder sometimes difficult to separate
 - Can occur together; "double depression"

- Minor depression
 - At least 2 depressive symptoms for 2 weeks; does not meet full criteria for major depression
 - Associated with significant morbidity and disability
- Seasonal affective disorder
 - Onset and remission of episodes at predictable times of the year
 - Symptoms
 - Anergy
 - Fatigue
 - Weight gain
 - Hypersomnia
 - Episodic carbohydrate craving
 - Potential improvement by altering light exposure

Differential Diagnosis

- A general medical condition
 - Cancer
 - Extreme cachexia may be misinterpreted as part of the symptoms of depression.
 - Hypothyroidism
 - Features of depression, most commonly depressed mood and memory impairment
 - Subclinical hypothyroidism can also produce symptoms of depression and cognitive difficulty.
 - Symptoms respond to thyroid replacement.
 - Hyperthyroid states
 - May also present with depression especially in geriatric populations
 - Chronic disorders of uncertain etiology
 - Chronic fatigue syndrome and fibromyalgia are strongly associated with depression and anxiety.
- Mood-incongruent delusions or hallucinations
- Direct physiologic effects of a substance (e.g., a drug of abuse, a medication)
 - When feasible, change medication to aid in decision about causal relationship between pharmacologic therapy and mood change.
- Bereavement

Diagnostic Approach

- Major depressive episode suspected
 - Determine if it is unipolar or bipolar depression.
 - Determine if it is secondary to general medical illness or substance abuse (10–15% of cases).
 - Symptoms in cases of associated disease may be due to:
 - Psychological stress of coping with disease
 - Disease process itself
 - Medications used to treat disease
 - Assess the risk of suicide.
 - Approximately 4–5% of all depressed patients will commit suicide; most will have sought help from a physician within 1 month of death.

- Use direct questioning; patients are reluctant to verbalize without prompting.
 - Probe in an empathic and hopeful manner.
 - Be sensitive to denial and possible minimization of distress.
- If patient has specific plans or significant risk factors (e.g., a past history of suicide attempts, profound hopelessness, concurrent medical illness, substance abuse, social isolation), refer to a mental health specialist for immediate care.
- Presence of anxiety, panic, or agitation significantly increases near-term suicidal risk.
- Validated questionnaires exist to screen patients for mental disorders.
 - Inventories that require only 10 minutes to complete
 - Link patient responses to formal diagnostic criteria of anxiety, mood, somatoform, and eating disorders and to alcohol abuse or dependence
 - Prime MD (and a self-report form, the Patient Health Questionnaire)
 - Symptom-Driven Diagnostic System for Primary Care

Laboratory Tests

- Laboratory tests are generally not helpful in the evaluation or diagnosis of depression.
- TSH level may be useful in determining presence of thyroid disease.

Imaging

- No imaging studies are indicated in the evaluation and treatment of depression.

Diagnostic Procedures

- No diagnostic procedures are indicated in the evaluation and treatment of depression.

Treatment Approach

- Coordinate short-term symptom remission with long-term maintenance strategies to prevent recurrence.
- Most effective intervention is combined medication and psychotherapy.
- If treatment regimen is unsuccessful:
 - Select alternative drug, or
 - Use combinations of antidepressants, and/or adjunctive treatment
 - Consider referral to mental health specialist

Specific Treatments

General approach to medications

- Determine if there is a history of good response in patient or first-degree relative.
 - If not available, evaluate characteristics and match to a drug.
 - Consider:
 - Health status
 - Side effects
 - Convenience
 - Cost
 - Patient preference

- Drug interaction risk
 - Suicide potential
 - Medication compliance history
- Suicidal ideation: Choose a drug with low toxicity if taken in overdose.
 - Selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressant drugs are distinctly safer.
 - Tricyclic antidepressants (TCA): Prescribe only a 10-day supply for patients with suicide risk.
- 60–70% respond to any drug chosen if given in a sufficient dose for 6–8 weeks
- Begin new medication at one-third to one-half target dose if drug is a TCA, bupropion, venlafaxine, or mirtazapine.
- Initiate full dose as tolerated if an SSRI.
- If patient experiences side effects, evaluate possibility of tolerance.
 - Consider temporary decrease in dose or adjunctive treatment.
- If unacceptable side effects continue:
 - Taper drug over 1 week and initiate new drug
 - Consider potential drug interactions
- Evaluate response after 6 weeks at target dose.
 - If inadequate, increase dose in stepwise fashion as tolerated.
- If inadequate response at maximal dose:
 - Consider tapering and switching to new drug
 - If TCA, obtain plasma level to guide treatment

Antidepressants

- SSRIs
 - Fluoxetine
 - Usual daily dose: 10–80 mg
 - Has very long half-life
 - Sertraline
 - Usual daily dose: 50–200 mg
 - Paroxetine
 - Usual daily dose: 20–60 mg
 - Fluvoxamine
 - Usual daily dose: 100–300 mg
 - Citalopram
 - Usual daily dose: 20–60 mg
 - No inhibitory effects on the P450 system
 - Escitalopram
 - Usual daily dose: 10–30 mg
 - Most specific of currently available SSRIs; appears to have no specific inhibitory effects on the P450 system
 - Duloxetine
 - Usual daily dose: 40–60 mg (may be divided bid)
 - Most with once-daily dosing, usually in a.m.
 - Side effects: headache, nausea and other GI effects, jitteriness, insomnia, sexual dysfunction, akathisia (during the first week of treatment; rare), effect on plasma levels of other medications (except sertraline), angina due to vasospasm (rare)
 - Serotonin syndrome when multiple serotonin medications are combined
 - Myoclonus
 - Agitation
 - Abdominal cramping
 - Hyperpyrexia

- Hypertension
 - Potentially death
- Potential drug interactions
 - Monoamine oxidase inhibitors (MAOIs)
 - Serotonin syndrome—absolute contraindication
 - Serotonergic agonists (e.g., tryptophan, fenfluramine)
 - Potential serotonin syndrome
 - Drugs metabolized by P450 isoenzymes
 - TCAs, other SSRIs, antipsychotics, beta blockers, codeine, terfenadine, astemizole, triazolobenzodiazepines, calcium-channel blockers, 1C antiarrhythmics, carbamazepine
 - Drugs that are bound tightly to plasma proteins (e.g., warfarin)
 - Increased bleeding secondary to displacement
 - Drugs that inhibit the metabolism of SSRIs by P450 isoenzymes (e.g., quinidine)
 - Increased SSRI side effects
- TCAs
 - Amitriptyline
 - Usual daily dose: 150–300 mg
 - Most patients require daily dose of 150–200 mg to achieve therapeutic blood level of 150–300 ng/mL and satisfactory remission.
 - Some patients show a partial effect at lower doses.
 - Nortriptyline
 - Usual daily dose: 50–200 mg
 - Best tolerated, especially by elderly
 - Imipramine
 - Usual daily dose: 150–300 mg
 - Most patients require daily dose of 150–200 mg to achieve a therapeutic blood level of 150–300 ng/mL and satisfactory remission.
 - Some patients show a partial effect at lower doses.
 - Desipramine
 - Usual daily dose: 150–300 mg
 - Greatest risk of lethal overdose
 - Doxepin
 - Usual daily dose: 150–300 mg
 - Clomipramine
 - Usual daily dose: 150–300 mg
 - Once-daily dosing, usually qhs
 - Generic equivalents make TCAs relatively inexpensive.
 - Geriatric patients may require a low starting dose and slow escalation.
 - Side effects: anticholinergic (dry mouth, tachycardia, constipation, urinary retention, blurred vision), sweating, tremor, postural hypotension, cardiac toxicity due to conduction block or arrhythmias (uncommon at therapeutic levels), sedation, weight gain
 - Contraindicated in patients with serious cardiovascular risk factors
 - Blood levels of most TCAs available
 - With several tricyclics (particularly nortriptyline, imipramine, and desipramine), there is a well-defined relationship among dose, plasma level, and therapeutic response.
 - Significant ethnic differences in drug metabolism
 - Hispanic, Asian, and African-American patients generally require lower doses than Caucasians to achieve a comparable blood level.
 - Potentially lethal in overdose (lethal dose = 2 g)

- Mixed norepinephrine/serotonin reuptake inhibitors
 - Venlafaxine
 - Usual daily dose: 75–375 mg
 - Bid-tid dosing (extended-release available)
 - Side effects: nausea, dizziness, dry mouth, headaches, increased blood pressure, anxiety, insomnia
 - Lower potential for drug interactions than SSRIs
 - Contraindicated with MAOIs
 - Mirtazapine
 - Usual daily dose: 15–45 mg
 - Once-daily dosing
 - Side effects: somnolence, weight gain, neutropenia (rare)
- Mixed-action drugs
 - Bupropion
 - Usual daily dose: 250–450 mg
 - TID dosing; sustained-release also available
 - Exceptionally short half-life, requiring frequent dosing
 - Side effects: jitteriness, flushing, seizures in at-risk patients, anorexia, tachycardia, psychosis
 - Fewer sexual side effects than SSRIs or TCAs
 - Trazodone
 - Usual daily dose: 200–600 mg
 - Side effects: sedation, dry mouth, ventricular irritability, postural hypotension, priapism (rare)
 - Useful in low doses for sleep; sedating effects with no anticholinergic side effects
 - Nefazodone
 - Usual daily dose: 300–600 mg
 - Once-daily dosing; steady state within 4–5 days
 - Side effects: sedation, headache, dry mouth, nausea, constipation
 - No effect on REM sleep, unlike other antidepressants
 - May inhibit one or more cytochrome P450 enzymes
 - Amoxapine
 - Usual daily dose: 200–600 mg
 - Side effects: sexual dysfunction
 - Extrapyramidal symptoms possible
 - Risk of tardive dyskinesia with long-term use
- MAOIs
 - Phenelzine
 - Usual daily dose: 45–90 mg
 - Tranylcypromine
 - Usual daily dose: 20–50 mg
 - Isocarboxazid
 - Usual daily dose: 20–60 mg
 - May be more effective in patients with atypical features or treatment-refractory depression
 - Side effects: insomnia, hypotension, anorgasmia, weight gain, hypertensive crisis, tyramine cheese reaction
 - Lethal reactions with SSRIs
 - Do not use concomitantly with TCA—possible hyperadrenergic effects
 - Hypertensive crisis following intake of tyramine-containing food or sympathomimetic drugs
 - Serious reactions with narcotics

Management of antidepressant side effects

- Nausea, loss of appetite
 - Usually short lived and dose related
 - Consider temporary dose reduction or administration with food and antacids
- Diarrhea
 - Famotidine 20–40 mg/day
- Constipation
 - Wait for tolerance
 - Diet change
 - Stool softener
 - Exercise
 - Avoid laxatives
- Sexual dysfunction
 - Consider dose reduction; drug holiday
- Anorgasmia/impotence; impaired ejaculation
 - Bethanechol 10–20 mg 2 hours before activity or 25 mg tid, or
 - Buspirone 10 mg tid, or
 - Cyproheptadine 4–8 mg 2 hours before activity, or
 - Bupropion 100 mg bid, or
 - Amantadine 100 mg bid/tid
- Orthostasis
 - Tolerance unlikely
 - Increase fluid intake
 - Use calf exercises/support hose
 - Fludrocortisone 0.025 mg/day
- Anticholinergic
 - Wait for tolerance
- Dry mouth, eyes
 - Maintain good oral hygiene
 - Use artificial tears
 - Sugar-free gum
- Tremor/jitteriness
 - Antiparkinsonian drugs not effective
 - Use dose reduction/slow increase
 - Lorazepam 0.5 mg bid, or
 - Propranolol, 10–20 mg bid
- Insomnia
 - Schedule all doses for the morning
 - Trazodone 50–100 mg qhs
- Sedation
 - Caffeine
 - Schedule all dosing for bedtime
 - Bupropion 75–100 mg in afternoon
- Headache
 - Evaluate diet, stress, other drugs
 - Try dose reduction
 - Amitriptyline 50 mg/day
- Weight gain
 - Decrease carbohydrates
 - Exercise
 - Consider fluoxetine

- Loss of therapeutic benefit over time
 - Potentially related to tolerance
 - Increase dose or drug holiday
 - Add amantadine 100 mg bid; buspirone 10 mg tid; or pindolol 2.5 mg bid

Other treatments

- Electroconvulsive therapy
 - At least as effective as medication
 - Reserved for treatment-resistant cases and delusional depressions
- Transcranial magnetic stimulation
 - Investigational treatment of depression
 - Shown to have efficacy in several controlled trials
- Cognitive-behavioral and interpersonal therapies
 - Give patients time to describe their experience, outlook, and the impact of depression.
 - Occasional empathic silence may be as helpful for the treatment alliance as verbal reassurance.
 - Effective in improving psychological and social adjustment
- Vagus nerve stimulator
 - Currently investigational

Depression in general medical illness

- Cardiac
 - SSRIs
 - First-line drugs for patients at risk for TCA-related complications
 - Appear not to induce electrocardiogram changes or adverse cardiac events
 - May interfere with hepatic metabolism of anticoagulants causing increased anticoagulation
 - TCAs
 - Contraindicated in bundle branch block
 - TCA-induced tachycardia—a concern in congestive heart failure
- Cancer
 - Antidepressant medication improves quality of life and mood.
 - Psychotherapeutic approaches, particularly group therapy
 - May have some effect on short-term depression, anxiety, and pain symptoms
- Neurologic disorders
 - TCA and SSRI agents, stimulant compounds, and MAOIs are effective against depression.
- Diabetes mellitus
 - Treatment is complicated by effects of antidepressive agents on glycemic control.
 - MAOIs can induce hypoglycemia and weight gain.
 - TCAs can produce hyperglycemia and carbohydrate craving.
 - SSRIs may reduce fasting plasma glucose; easier to use than MAOIs and may improve dietary and medication compliance.
- Hypothyroidism/hyperthyroidism
 - Improvement in mood usually follows normalization of thyroid function.
 - Adjunctive antidepressant medication is sometimes required.
- Chronic fatigue syndrome and fibromyalgia
 - Patients may partially benefit from antidepressant treatment, usually at lower-than-normal dosing.

Monitoring

- Evaluate response to treatment after ~2 months.
 - Three-quarters of patients show improvement by this time.
 - If remission is inadequate, question patient about compliance.
 - Consider medication dose increase if side effects are not troublesome.
 - If unsuccessful, refer to a mental health specialist.
- Approximately 40% of primary care patients with depression drop out of treatment and discontinue medication if no symptomatic improvement occurs within a month.
 - Additional support is necessary to improve outcome.
 - Increase intensity and frequency of visits during the first 4–6 weeks of treatment.
 - Provide supplemental educational materials about:
 - Depression
 - Benefits and side effects of medications
 - Stress reduction
 - How alcohol may exacerbate depressive symptoms and impair drug response
 - Obtain psychiatric consultation as indicated.
- Refer all patients with serious suicidality and/or severe depression and those refractory to treatment for psychiatric evaluation.

Complications

- In major depression, symptoms may cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Suicide
 - Question patients directly and initiate urgent/emergent referral if patient is suicidal.

Prognosis

- Unipolar depressive disorders
 - Pattern of recurrence and clinical progression in a developing episode is variable.
 - Nature of attacks may be similar over time.
 - Severe depressive episode may progress to a psychotic state in a minority of patients.
 - Dysthymic disorder
 - May respond to antidepressant treatment
 - Minor depression
 - Responds to pharmacologic treatment
 - Remission
 - Continue drug treatment for at least 6–9 months to prevent relapse.
 - After 2 or more episodes of depression, consider indefinite maintenance treatment.

Prevention

- Initial episode of a depressive disorder is not typically preventable.
- Recurrence of depression many times can be prevented by combination of:
 - Medication compliance
 - Balanced diet
 - Regular exercise
 - Maintaining a regular sleep pattern

- Avoiding drugs and alcohol
- Seeking treatment immediately when symptoms recur

ICD-9-CM

- 311 Depressive disorder, not elsewhere classified

See Also

- Alcoholism
- Anxiety, Including Obsessive-Compulsive Disorder
- Approach to Weight Loss
- Bipolar Disorder
- Chronic Fatigue Syndrome
- Fibromyalgia
- Health Care Screening and Disease Prevention
- Hypothyroidism
- Somatoform Disorders

Internet Sites

- Professionals
 - Health Information
National Institute of Mental Health
 - Depression
ClinicalTrials.gov
- Patients
 - Depression
National Institute of Mental Health
 - Depression
MedlinePlus
 - Homepage
National Mental Health Association

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PEARLS

- Major depression is a common disease and often has a lifelong relapsing course.
- Assessment of suicide by direct questioning is an essential part of the evaluation of depression; if present, emergent referral to a psychiatrist is needed.
- The most effective treatment for depression is medication combined with psychotherapy.
- SSRIs are widely used due to ease of daily administration and relatively low side-effect profile; specific medication choice is tailored to the individual patient.
- Depression is common in general medical illnesses including cardiac, neurologic, and oncologic conditions.