

Generalized anxiety disorder

TERMINOLOGY

CLINICAL CLARIFICATION

- Generalized anxiety disorder is a common illness characterized by unfocused worry and anxiety, frequently without an immediate cause, occurring on most days for a duration of 6 months or longer, which may be heightened by situational triggers^{1,2}
 - Manifests physically as increased muscle tension and autonomic hyperactivity²
 - Negatively affects the individual's psychosocial functioning on a near-daily basis²

DIAGNOSIS

CLINICAL PRESENTATION

- History
 - Hallmark of generalized anxiety disorder is excessive worrying and apprehensive expectation of a wide range of normal events and activities, such as:²
 - Work or school responsibilities and interactions
 - Family health and finances
 - Common psychological symptoms related to generalized anxiety disorder include:³
 - Being nervous and unable to relax, with poor or disturbed sleep²
 - Worrying about trivial or minor matters, with no control over worrying
 - Extreme restlessness and inability to concentrate²
 - Irritability
 - Fear of the worst happening and feeling scared in general
 - Feeling that objects are unreal (derealization) or that the self is “not really here” (depersonalization)¹
 - Sensation of losing control, “going crazy,” or passing out¹
 - Fear of death¹
 - Muscle tension and fatigability are highly correlated with generalized anxiety disorder²
 - Common physical symptoms related to anxiety include the following, ranked in order of clinical significance:⁴
 - Palpitations
 - Dyspepsia or abdominal discomfort
 - Dizziness
 - Unsteady gait
 - Dyspnea
 - Feeling hot and/or experiencing diaphoresis, regardless of ambient temperature
 - Feeling faint, hands trembling, and face flushing
 - Paresthesia marked by numbness and tingling
 - Choking sensation
 - Other common physical symptoms include:²
 - Nausea
 - Diarrhea
 - Cold extremities
 - Xerostomia
 - Bruxism
 - Headache
 - Symptoms are typically more severe in younger adults²
- Physical examination
 - Signs related to general emotional well-being include nervousness, irritability, and heightened vigilance²
 - Physical signs include:²
 - Visible tremor
 - Cold hands
 - Tachycardia
 - Tachypnea

CAUSES AND RISK FACTORS

- Causes
 - Exact cause is unknown
 - Onset of pure generalized anxiety disorder is often associated with stress arising from emotional loss and dangerous situations⁵
 - Includes the loss of a close relative or long-term separation from a partner

Generalized anxiety disorder

- Childhood adversity has a 32.4% association with anxiety disorders⁶
- Risk factors and/or associations
 - Age
 - Increasing prevalence with age, peaking in middle age²
 - Onset of symptoms after the age of 35 years is suggestive of generalized anxiety disorder⁷
 - Onset rarely occurs before adolescence; prevalence in the adolescent population is 0.9% in the United States²
 - Prevalence among adults (2.9% in the United States) is 3 times greater than in adolescents⁷
 - Sex
 - Twice as common in women as in men⁸
 - Genetics
 - Twin studies have demonstrated that there is a moderate genetic risk of generalized anxiety disorder, estimated to be between 15% and 20%,⁹ but may be as high as one-third²
 - Ethnicity/race
 - White populations are more likely to be affected than those of African, Asian, or Hispanic ethnicity¹⁰
 - Other risk factors/associations
 - Self-medication
 - Likely to contribute to increased use of alcohol and other drugs in patients with generalized anxiety disorder
 - Use of alcohol and other drugs to treat symptoms of generalized anxiety disorder is estimated to be present in 35% of patients with this disorder⁹
 - Coexisting anxiety disorders¹¹
 - Social phobia is the most prevalent (16%-59%), followed by phobias of other types (eg, specific places, situations, or objects; 16%-46%)
 - Individuals from developed countries²
 - More likely to experience generalized anxiety disorder
 - Behavioral inhibition and neuroticism are associated with generalized anxiety disorder²

DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
 - Diagnosis is based on patient history and physical examination findings; DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, version 5) criteria must be met for a diagnosis of generalized anxiety disorder²
 - Excessive use of alcohol, caffeine, or other stimulants must be ruled out as a cause of symptoms
 - GAD-7 scale³ and Beck Anxiety Inventory⁴ are alternative diagnostic tools that have proven efficacy in diagnosis, especially the GAD-7
 - GAD-7 assesses symptoms over the past 2 weeks instead of 6 months (per DSM-5²) using 7 criteria, operating on the assumption that severe symptoms are typically chronic³
 - Beck Anxiety Inventory contains 21 items comprising somatic, affective, and cognitive symptoms related specifically to anxiety disorders⁴
 - Comprehensive clinical interview is used to assess for the following DSM-5 criteria:²
 - Excessive anxiety and worry (apprehensive expectation) about various events or activities, such as work or school performance, occurring more days than not, lasting 6 months or longer
 - Patient has difficulty controlling this worry
 - Anxiety and worry occur in conjunction with at least 3 (only 1 required in children) of the following symptoms, with at least some symptoms having been present for more days than not for the past 6 months:
 - Restlessness
 - Fatigability
 - Compromised ability to concentrate
 - Crankiness/irritability
 - Increased muscle tension
 - Poor sleep quality, including trouble falling asleep, difficulty staying asleep, or restlessness
 - Patient's symptoms lead to clinical distress and engender negative effects on work, school, or everyday life
 - Another medical condition or substance abuse is not the cause
 - Different mental disorder has not given rise to the patient's symptoms
 - Maintain a high index of suspicion for medical conditions that could cause the symptoms; laboratory testing is generally deferred, but CBC, thyroid function tests, basic chemistry panel, urine drug screening, and ECG should be obtained as indicated by the clinical presentation and medical history¹²
- Functional testing
 - GAD-7³
 - Consists of 7 criteria, namely:
 - Feeling nervous, anxious, or on edge

Generalized anxiety disorder

- Not being able to stop or control worrying
- Worrying too much about different things
- Trouble relaxing
- Being so restless that it is hard to sit still
- Becoming easily annoyed or irritable
- Feeling afraid as if something awful might happen
- Subjects rate how often they have been bothered by each symptom in the last 2 weeks, with responses being 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day); total score ranges from 0 to 21
- Threshold score of 8 maximizes sensitivity and 15 maximizes specificity³
- Threshold of 10 is optimal for high sensitivity and specificity³
- Interpretation¹³
 - 10: moderate anxiety
 - 15: indicates severe anxiety
- Beck Anxiety Inventory⁴
 - Comprises 21 criteria, specifically:
 - Numbness or tingling
 - Feeling hot
 - Wobbliness in legs
 - Unable to relax
 - Fear of the worst happening
 - Dizzy or lightheaded
 - Heart pounding or racing
 - Unsteady
 - Terrified
 - Nervous
 - Feelings of choking
 - Hands trembling
 - Shaky
 - Fear of losing control
 - Difficulty breathing
 - Fear of dying
 - Scared
 - Indigestion or discomfort in abdomen
 - Faint
 - Face flushed
 - Sweating (not due to heat)
 - Subjects are asked to rate how much each symptom has affected them over the past week on a 4-point scale ranging from 0 (not at all) to 3 (severely—I could barely stand it); total score ranges from 0 to 63
 - Interpretation¹⁴
 - 0 to 9: normal
 - 10 to 18: mild to moderate anxiety
 - 19 to 29: moderate to severe anxiety
 - 30 to 63: severe anxiety

- Procedures

DIFFERENTIAL DIAGNOSIS

- Most common
 - Anxiety due to thyroid disorder
 - Characterized by unusually high¹⁵ or low¹⁶ levels of thyroxine due to dysfunction or removal of the thyroid gland
 - Anxiety and/or depression symptoms (eg, being more irritable, sad, emotionally sensitive, or anxious)¹⁷
 - Differentiating features are as follows:¹⁸
 - Hypothyroidism can also present with fatigue, dry skin, constipation, vocal changes, and prolonged ankle jerk reflex¹⁸
 - Hyperthyroidism can also present with hypertension, tachycardia, warm and moist skin, and brisk ankle jerk reflex¹⁵
 - DSM-5 diagnostic criteria:
 - Evidence from history, physical examination, or laboratory findings that disturbance is a direct pathophysiologic consequence of another medical condition

Generalized anxiety disorder

- Disturbance is not better explained by another mental disorder
- Disturbance does not occur exclusively during the course of a delirium
- Disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- Diagnosis can be confirmed by the following laboratory findings:
 - Hypothyroidism
 - TSH level is elevated to more than 10 mIU/L in primary hypothyroidism¹⁶
 - Low serum levels of total or free thyroxine¹⁷
 - Hyperthyroidism
 - TSH level is suppressed¹⁵
 - High serum levels of total or free thyroxine
- Illness anxiety disorder^{19,20}
 - Preoccupation with the possibility of having or acquiring serious illness based on misinterpretations of benign or minor physical sensations; previously known as hypochondriasis
 - Some psychological and physical symptoms of anxiety are also present
 - Subject of anxiety differs, as the patient focuses mainly on their body and general health to the exclusion of work, finances, or family matters
 - Diagnosis can be confirmed by DSM-5 criteria:
 - Preoccupation with having or acquiring a serious illness for at least 6 months
 - Frequent visits to the clinic or maladaptive avoidance
- Social anxiety disorder (social phobia)^{21,22}
 - Phobic anxiety disorder with concerns about social situations involving unfamiliar people or possible scrutiny
 - Psychological and physical symptoms of anxiety are present in certain social situations
 - Anxiety is specific to social situations
 - Characterized by early onset; typically appears by 11 years of age in 50% of individuals and 20 years of age in 80% of individuals²²
 - Diagnosis can be confirmed by DSM-5 criteria:
 - Extreme fear or anxiety related to meeting strangers, speaking in public, or being observed in social situations
 - Social phobia must last for at least 6 months and cause clinically significant impairment in social interactions
- Panic disorder²³
 - Marked by recurrent panic attacks or extreme but brief episodes of anxiety, at intervals ranging from 24 hours to several months; may coexist with generalized anxiety disorder
 - Physical signs and symptoms of anxiety (eg, sweating, palpitations, dizziness, tachycardia) are present during a panic attack
 - Intense fear or discomfort of an attack reaches its peak within minutes, unlike the constantly elevated anxiety of generalized anxiety disorder
 - History of childhood trauma or abuse is more likely in patients with panic disorder than in those with generalized anxiety disorder
 - Diagnosis can be confirmed by DSM-5 criteria:
 - Extreme panic or anxiety reaching its peak within minutes, manifesting more than 4 somatic symptoms of anxiety
 - At least 1 panic attack preceded by more than 1 month of apprehensive expectation of a similar episode
- Major depressive disorder^{24,25}
 - Sadness, lethargy, and apathy lasting at least 2 weeks, with reduced interest and pleasure in normal activities; may coexist with generalized anxiety disorder
 - Irritability, fatigue, poor sleep, and digestive symptoms are typically present, as with generalized anxiety disorder
 - Diagnosis can be confirmed by DSM-5 criteria:
 - Depressed mood for most days over 2 weeks along with at least 2 characteristic symptoms
 - Anhedonia
 - Weight loss or gain (unintentional)
 - Insomnia or hypersomnia
 - Psychomotor agitation or retardation
 - Fatigue
 - Feelings of worthlessness or inappropriate guilt
 - Diminished ability to concentrate or indecisiveness
 - Suicidal ideation or attempt
- Obsessive-compulsive disorder²⁶
 - Characterized by continually recurring thoughts or images (obsessions) that increase anxiety and repetitive or ritualistic actions (compulsions) performed to alleviate that anxiety

Generalized anxiety disorder

- Excessive worrying and some symptoms of anxiety can be present
- Differentiated by repetitive rituals and behaviors (eg, hand-washing, mental acts of ordering or checking) performed to alleviate anxiety
 - Anxiety relates more to imagined or fantastic events
- Diagnosis can be confirmed by DSM-5 criteria:
 - Obsessive thoughts and compulsive behaviors take up at least 1 hour of the day
 - Patient suffers from clinically significant impairment in an occupational or social setting
- Posttraumatic stress disorder²⁷
 - Psychological disturbance or anhedonic/dysphoric mental state caused by experiencing a serious traumatic event
 - Heightened anxiety is typically present, along with its mental and physical symptoms
 - Main distinguishing criterion is the association of anxiety with a specific event, not with normal daily functioning, and the presence of flashbacks, dreams, and dissociative states relating to that event
 - Diagnosis can be confirmed by DSM-5 criteria:
 - Adults and children older than 6 years
 - Traumatic experience, such as grave injury, sexual violence, or threat of death, or such an event affecting a close friend or relative
 - Repeated exposure to circumstances surrounding such events, as with first responders or emergency department personnel
 - Psychological disturbance lasting longer than 1 month, including invasive memories, dreams, flashbacks, avoidance of stimuli associated with such events, irritability, anxiety, and insomnia
 - Patient suffers from clinically significant impairment in an occupational or social setting
 - Children younger than 6 years, specific criteria include:
 - Witnessing traumatic events, especially those affecting a primary caregiver
 - Constriction of play, social withdrawal, and emphasis on expression of negative emotions such as fear, guilt, and shame
- Drug withdrawal²⁸
 - Withdrawal symptoms caused by cessation of sedative use (eg, alcohol, benzodiazepines) or opioid use
 - Initial symptoms and signs of withdrawal include heightened anxiety, as well as irritability, nausea, agitation, diaphoresis, and tachycardia from sedative or opioid use
 - Short-term episodic nature of anxiety symptoms, compared to the chronic nature of generalized anxiety disorder symptoms
 - In case of withdrawal from benzodiazepines, signs and symptoms begin 2 to 10 days after last use²⁸
 - Alcohol withdrawal may be accompanied by seizures and delirium; symptoms typically peak 72 hours after the last ingestion of alcohol (without medication)²⁸
 - Opioid withdrawal is associated with anxiety and panic symptoms, with onset typically 4 to 6 hours after last use of a shorter-acting opioid (eg, heroin, oxycodone) or 1 to 2 days after last use of an opioid with a longer half-life (eg, methadone, buprenorphine)²⁹
 - Diagnosis can be confirmed by patient history and observation
- Substance intoxication²
 - Anxiety and panic may be present with intoxication from a variety of substances, such as stimulants (including caffeine), alcohol, inhalants, cannabis, and phencyclidine
 - Typical history would relate anxiety to intoxication with these substances, which would typically be absent with abstinence
 - Diagnosis primarily made from patient history and clinical signs

TREATMENT

GOALS

- Alleviate anxiety in the short term and support normal day-to-day functioning
- Improve quality of life and prevent relapse in the long term

DISPOSITION

- Admission criteria
 - Admit patients reporting acute suicidal ideation or intent
 - Consider admission in patients with comorbid conditions, such as significant substance abuse with toxicity or withdrawal of sedative-hypnotics (including alcohol)
- Recommendations for specialist referral
 - Refer patients to a psychiatrist, psychologist, or appropriately trained mental health therapist for psychotherapy
 - Psychiatric referral is necessary for patients with suicidal ideation or complex coexisting illnesses

Generalized anxiety disorder

- Psychiatric evaluation, if not already accomplished, is recommended after 2 failed medication trials (ie, 2 different drugs with no response despite reaching target dose)⁷

TREATMENT OPTIONS

- Owing to the chronicity of generalized anxiety disorder, long-term therapy is anticipated²
 - Includes psychotherapy, drug therapy, and patient education (eg, self-help Internet sites) regarding disease and healthy lifestyle recommendations
- Psychotherapy is often recommended over drug treatment as initial therapy for generalized anxiety disorder because relapse is common after therapeutic medications are withdrawn, lasting beyond the period of withdrawal symptoms following their discontinuation¹
 - Cognitive behavioral therapy is the treatment of choice, with proven efficacy in reducing anxiety symptoms in the short term³⁰
 - Best choice of treatment at diagnosis, at 6-month follow-up, and for relapse¹
- However, drug treatment is commonly prescribed in the primary care setting in the United States because of better resource availability¹ and patient preference to psychotherapy¹²
 - Acute pharmacologic treatment alleviates anxiety symptoms in the short term, with or without psychotherapy; chosen to minimize adverse effects
 - Benzodiazepines (eg, diazepam, lorazepam) have a noticeable effect in 15 to 60 minutes, although they are associated with a greater risk of dependence after long-term use¹
 - More likely to lead to requests for long-term prescription than antidepressants
 - Stronger anxiolytic effect in the first 2 weeks of drug treatment¹
 - Often used initially in combination with an antidepressant (eg, selective serotonin reuptake inhibitor), tapering off after several (4-5) weeks as the antidepressant becomes effective at reducing anxiety; benzodiazepine taper takes 2 to 4 weeks¹
 - Antidepressants, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine, duloxetine), or tricyclic antidepressants (eg, imipramine), take up to 4 weeks to act, but significant improvement may be noted in as little as 2 weeks¹
 - Selective serotonin reuptake inhibitors show fewer adverse effects (eg, nausea, feeling faint, anorexia) than serotonin-norepinephrine reuptake inhibitors or tricyclic antidepressants (eg, dry mouth, sedation, postural hypotension, hampered micturition)
 - Sedation may be a desired effect to mitigate extreme insomnia and restlessness in some patients, in which case a tricyclic antidepressant may be chosen
 - Typically, tricyclic antidepressants are reserved for those patients with generalized anxiety disorder not responsive to selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors
 - Withdrawal effects may occur after drug regimen is complete; gradual tapering of the dose is recommended
 - Buspirone typically acts within 72 hours, followed by a mild dysphoric adverse effect; does not lead to dependence¹
 - Do not use as monotherapy when depression is concurrent with anxiety⁷
 - Long-term pharmacologic treatment, advised in conjunction with psychotherapy⁹
 - Selective serotonin reuptake inhibitors are the best choice, with fewer adverse effects and lower risk of long-term dependence; escitalopram or paroxetine are frequently chosen
 - For refractory cases in the absence of significant improvement with first line drugs; augmentation with other drugs has demonstrated some success¹
 - Augmentation is typically provided by a psychiatrist
 - Drugs used in combination with antidepressants have included olanzapine,³¹ risperidone,¹ trifluoperazine, and pregabalin³²
 - However, a systematic review of augmentation reported a small reduction in symptom severity, with no difference between medication and placebo on functional impairment³³
- Drug therapy
 - Selective serotonin reuptake inhibitors
 - Escitalopram¹
 - Escitalopram Oral tablet; Adults: 10 mg PO once daily initially. May increase to 20 mg/day PO after at least 1 week.
 - Escitalopram Oral tablet; Geriatric Adults: In general, the recommended initial and maximum dose in geriatric patients is 10 mg/day PO.
 - Paroxetine
 - Paroxetine Hydrochloride Oral tablet; Adults: 20 mg PO once daily initially, usually in the morning. May titrate by 10 mg/day at weekly intervals if needed and tolerated. Usual effective dose: 20 mg PO once daily. Max: 50 mg/day PO. DEBILITATED ADULTS: 10 mg PO once daily initially, with a maximum of 40 mg/day. When discontinuing, taper the dose if possible.

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- Paroxetine Hydrochloride Oral tablet; Geriatric Adults: 10 mg PO once daily initially, usually in the morning. May titrate by 10 mg/day at weekly intervals if needed and tolerated. Usual effective adult dose: 20 mg/day PO. Max: 40 mg/day PO. When discontinuing, taper the dose if possible.
- Fluoxetine
 - Fluoxetine Hydrochloride Oral tablet [Depression/Mood Disorders]; Adolescents and Children 7 years and older: Limited data; not FDA-approved. 10 mg/day PO initially, followed by titration. Limited data suggest that 20 mg/day PO may be an effective dose. Further study is needed.
 - Fluoxetine Hydrochloride Oral tablet [Depression/Mood Disorders]; Adolescents and Children 7 years and older: Limited data; not FDA-approved. 10 mg/day PO initially, followed by titration. Limited data suggest that 20 mg/day PO may be an effective dose. Further study is needed.
- Sertraline
 - Sertraline Hydrochloride Oral tablet; Children and Adolescents 7 years and older: 25 mg/day PO initially, followed by flexible dosing titration based upon response and tolerability, up to 200 mg/day. Periodically reassess to determine need for continued treatment. Evaluation of the long-term safety and efficacy of sertraline in the treatment of childhood GAD is needed.
 - Sertraline Hydrochloride Oral tablet; Adults: 25 mg PO once daily initially. After 1 week, increase to 50 mg once daily. If necessary, increase by 50 mg/day at intervals of not less than 1 week up to 200 mg/day.
 - Sertraline Hydrochloride Oral tablet; Geriatrics: See adult dosage. Per OBRA, tapering attempts or documentation of medical necessity are required in residents of long-term care facilities.
- Serotonin-norepinephrine reuptake inhibitors
 - Venlafaxine¹
 - Venlafaxine Hydrochloride Oral tablet, extended-release; Adults: Initially, 75 mg PO once daily. Alternatively, 37.5 mg PO once daily can be given for 4 to 7 days to allow for tolerability before increasing to 75 mg PO once daily. If needed, may increase further by 75 mg/day at intervals of no less than every 4 days. Max: 225 mg PO once daily.
 - Venlafaxine Hydrochloride Oral tablet, extended-release; Geriatric Adults: Initially, 75 mg PO once daily. Alternatively, 37.5 mg PO once daily can be given for 4 to 7 days to allow for tolerability before increasing to 75 mg PO once daily. If needed, may increase further by 75 mg/day at intervals of no less than every 4 days. Max: 225 mg PO once daily. The federal Omnibus Budget Reconciliation Act (OBRA) regulates the use of antidepressants in residents of long-term care facilities. When the drug is being used to manage behavior, stabilize mood, or treat psychiatric disorders, the facility should attempt periodic tapering of the medication or provide documentation of medical necessity in accordance with OBRA guidelines.
 - Duloxetine
 - Duloxetine Oral capsule, gastro-resistant pellets; Children and Adolescents 7 years and older: 30 mg PO once daily for 2 weeks, initially. Then, may consider an increase to 60 mg PO once daily. Recommended range: 30 to 60 mg/day PO. Some patients may benefit from more than 60 mg/day. Increases above 60 mg/day should occur in increments of 30 mg/day. Max: 120 mg/day PO.
 - Duloxetine Oral capsule, gastro-resistant pellets; Adults: Initially, 60 mg PO once daily. Some patients may benefit from 30 mg once daily for 1 week, then 60 mg once daily. Maintenance treatment range: 60 to 120 mg once daily. Max: 120 mg/day.
 - Duloxetine Oral capsule, gastro-resistant pellets; Geriatric Adults: See adult dosage. Per OBRA, tapering attempts or documentation of medical necessity are required in residents of long-term care facilities.
- Benzodiazepines¹
 - Diazepam
 - Diazepam Oral solution; Infants 6 months and older, Children, and Adolescents: Initially, 1 to 2.5 mg PO 3 to 4 times per day. The dose may be increased as needed and tolerated.
 - Diazepam Oral tablet; Adults: 2 to 10 mg PO 2 to 4 times per day depending upon the severity of the symptoms. Use lower initial adult doses for the debilitated adult patient. Maximum daily dosage has not been defined, but commonly implied limit is 40 mg/day in divided doses for ambulatory use.
 - Diazepam Oral tablet; Geriatric Adults: 2 to 2.5 mg PO 1 to 2 times per day, increasing the dose according to response and patient tolerability. A maximum daily dosage has not been defined, but commonly the adult limits are 40 mg/day in divided doses for ambulatory use. Do not exceed federal Omnibus Budget Reconciliation Act (OBRA) dose of 5 mg/day in residents of skilled nursing facilities without documentation of necessity.
 - Lorazepam
 - Lorazepam Oral tablet; Adults: Initially, 2 to 3 mg/day PO given in 2 to 3 divided doses. In debilitated adults give 1 to 2 mg/day PO in 2 to 3 divided doses initially. Increase gradually as needed and tolerated. Usual dosage: 2 to 6 mg/day PO. Range: 1 to 10 mg/day PO. When a higher dosage is needed, the evening dose should be increased before the daytime doses.

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- Lorazepam Oral tablet; Geriatric Adults: Initially, 1 to 2 mg/day PO given in 2 to 3 divided doses, then increase gradually as needed and tolerated. The usual dosage is 2 to 6 mg/day PO. Use smallest effective dose in order to reduce the risk of ataxia or oversedation. Do not exceed federal Omnibus Budget Reconciliation Act (OBRA) dose of 2 mg/day PO in residents of skilled nursing facilities without documentation of necessity.
- Alprazolam
 - Alprazolam Oral tablet; Children† and Adolescents† 7 years and older: Definitive dosage not established. In a study of children 7 to 16 years old (n = 13), 0.005 mg/kg/dose PO or 0.125 mg/dose PO were given 3 times per day initially for situational anxiety. Doses were increased in 0.125 mg to 0.25 mg increments. Max: 0.02 mg/kg/dose PO or 0.06 mg/kg/day PO. In another study (n = 30), initial doses were 0.25 mg PO per day for children 40 kg or less and 0.5 mg PO per day if more than 40 kg. Doses were titrated at 2-day intervals to a maximum of 0.04 mg/kg/day. Required doses ranged from 0.5 mg to 3.5 mg/day with a mean dose of 1.6 mg/day.
 - Alprazolam Oral tablet; Adults: 0.25 mg to 0.5 mg PO 3 times daily (Max: 4 mg/day PO). Increase doses at 3 to 4 day intervals. Taper dose to discontinue, decrease daily dose by no more than 0.5 mg every 3 days.
 - Alprazolam Oral tablet; Geriatric Adults: Initially, 0.25 mg PO 2 or 3 times daily. Lower initial doses may be appropriate in some patients. If needed, increase dose gradually (Max: 4 mg/day PO). Do not exceed federal Omnibus Budget Reconciliation Act (OBRA) dose of 0.75 mg/day PO in residents of skilled nursing facilities without documentation of necessity. To discontinue, decrease daily dose by no more than 0.5 mg every 3 days.
- Azapirones
 - Buspirone³⁴
 - Buspirone Hydrochloride Oral tablet; Children† and Adolescents† 6 years and older: Initially, 2.5 mg to 5 mg PO twice daily depending on the child's age, then increased as needed by no more than 5 mg/day every 7 days. Usual average maintenance dose is 15 to 30 mg/day PO, given in 2 to 3 divided doses. Max: 60 mg/day PO.
 - Buspirone Hydrochloride Oral tablet; Adults: 7.5 mg PO twice daily initially, then increase if needed by 5 mg/day every 2 to 3 days. Usual maintenance dose: 15 to 30 mg/day given in 2 to 3 divided doses. Max: 60 mg/day PO.
 - Buspirone Hydrochloride Oral tablet; Geriatric Adults: 5 mg PO twice daily initially, then increase as needed by 5 mg/day every 2 to 3 days. Usual maintenance dose: 15 to 30 mg/day given in 2 to 3 divided doses. Max: 60 mg/day.
- Tricyclic antidepressants
 - Imipramine¹
 - Imipramine Hydrochloride Oral tablet; Adults: Initially, 10 mg PO once daily at bedtime. Titrate by 10 mg PO every 2 to 4 days as tolerated. Average target range is 50 to 200 mg/day. Max: 300 mg/day.⁹
- Nondrug and supportive care
 - All patients and their family are directed to self-help Internet sites for education on generalized anxiety disorder (eg, Anxiety and Depression Association of America³⁵)³⁶
 - Educate patients on lifestyle changes that may help reduce symptoms
 - Improving quality and quantity of sleep
 - Regular exercise
 - Exercise has been shown to have significant ability to reduce anxiety symptoms and is encouraged³⁷
 - Minimizing caffeine and alcohol intake
 - Avoidance of nicotine and other drugs
 - Psychotherapy
 - Cognitive behavioral therapy
 - Multiple types of psychotherapy have been applied to the treatment of generalized anxiety disorder, with evidence strongest for the efficacy of cognitive behavioral therapy⁹
 - Recommended for all patients, although use may be guided by resource availability, patient finances, or patient preference
 - Teaches patients to substitute positive thoughts for anxiety-provoking ones¹
 - Brief description:³⁸
 - Present a cognitive model of anxiety to the patient and train in self-monitoring and identification of cues that contribute to interpretations of threat
 - Inform patients that therapy focuses on learning different, less anxiety-provoking ways of viewing the self, the world, and the future
 - Use standard cognitive therapy procedures, such as outlining cognitive predictions, interpretations, beliefs, and assumptions that lead to threatening perceptions; emphasize Socratic method (ie, stimulate critical thinking by the asking and answering of questions)
 - Focus discussions on multiple alternative perspectives for any given situation of daily living; homework emphasizes frequent applications of alternative perspectives and behavioral tasks
 - Reduction in intolerance of uncertainty is an important predictor of outcome
 - Therapy can be delivered in 6 to 12 sessions at weekly intervals³⁸

Generalized anxiety disorder

- Comorbidities
 - Major depressive disorder is the most common coexisting psychiatric illness in patients with generalized anxiety disorder, coexisting in nearly two-thirds of cases⁷
 - Occurs more often in women than in men²
 - Combination of these disorders is termed *cothymia*¹
 - Antidepressants are the preferred drug treatment, in combination with cognitive behavioral therapy
 - Panic disorder¹
 - Occurs in 25% to 50% of patients with generalized anxiety disorder^{11,7}
 - Combination of buspirone with cognitive behavioral therapy is more effective than psychotherapy alone
- Special populations
 - Children
 - Preferably, treat with cognitive behavioral therapy; medications such as antidepressants are often avoided over concern for adverse effects¹
 - However, the combination of cognitive behavioral therapy and sertraline has demonstrated efficacy in children between the ages of 7 and 17 years³⁹
 - Pregnant women
 - In the perinatal period, generalized anxiety may be exacerbated, requiring pharmacotherapy in addition to psychotherapy⁷
 - Prescribe half the usual drug (typically buspirone) dose for pregnant women, as benzodiazepines may have teratogenic effects⁷
 - 1 of the goals of therapy in these patients is to prevent premature birth or miscarriage due to anxiety

MONITORING

- When initiating drug therapy, see patients every 2 to 4 weeks; frequency is decreased to every 3 to 4 months during maintenance therapy⁷
 - If medication is effective, continue course for 6 to 12 months and then slowly taper off⁴⁰
- Following taper, 6-month follow-up is necessary¹
 - Optional continued follow-up every 6 months for a period of 5 years or longer is recommended since rates of relapse are high⁴⁰

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Generalized anxiety disorder affects quality of life⁴¹
 - Patients with anxiety disorders perceive impairments in their physical well-being, social relationships, occupation, and home and family life
- If untreated, generalized anxiety disorder can lead to alcohol and other drug abuse, as patient self-medicates to control symptoms
- Patients have increased odds of 2.32 for suicidal ideation and an odds ratio of 3.64 for suicide attempts, as demonstrated by longitudinal analysis⁴²

PROGNOSIS

- Majority of patients are susceptible to a relapse of generalized anxiety disorder 6 to 12 years after initial diagnosis⁴³
 - Patients who improve the most initially also have the best long-term outcome¹
- Rate of full remission is 27% at 3 years and 38% at 5 years postdiagnosis⁴⁰
- Rates of partial remission are 37% at 3 years and 47% at 5 years postdiagnosis⁴⁰

SCREENING AND PREVENTION

SCREENING

PREVENTION

SYNOPSIS

KEY POINTS

- Generalized anxiety disorder is a mental disorder characterized by continuous and uncontrolled worrying without a significant cause
 - Symptoms are present on most days for at least 6 months to confirm the diagnosis²
- Psychiatric symptoms include excessive worrying, nervousness, restlessness, inability to relax, and fear of worst-case scenarios

Generalized anxiety disorder

- Associated physical signs and symptoms include tachycardia, dyspepsia, tremor, dizziness, hyperhidrosis, and cold extremities
- Patients with generalized anxiety disorder typically perceive impairments in their physical well-being, social relationships, occupation, and home and family life; they have an increased risk of alcohol and other drug abuse, as well as suicide attempts
- DSM-5 criteria represent the gold standard for diagnosis²
- Cognitive behavioral therapy is the preferred treatment at both initial diagnosis and relapse, along with patient education and recommendations for a healthy lifestyle
- Supplementary drug treatment typically includes benzodiazepines or buspirone for immediate effect, followed by longer-term antidepressant therapy; supplemental medication (eg, antipsychotics) is added for refractory cases, usually under the care of a psychiatrist
- Most patients are prone to relapse 6 to 12 years after initial diagnosis,⁴³ with half in partial remission 5 years after initial diagnosis and treatment⁴⁰

URGENT ACTION

- Question all patients regarding active suicidal ideation, and if it is discovered, immediately refer to psychiatrist⁹

PITFALLS

- Generalized anxiety disorder often coexists with major depressive disorder and panic disorder; maintain a high index of suspicion during diagnosis¹¹
- Consider possible suicidal ideation in patients presenting with generalized anxiety disorder⁴²

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