ANXIETY DISORDERS

Generalized Anxiety Disorder

GAD

DSM-5-TR 300.02 | ICD-10-CM F41.1

Persistent, difficult-to-control worry across multiple life domains with physical tension and vigilance for six months or more.

LIFETIME PREVALENCE	TYPICAL ONSET	SEX RATIO	COURSE
~5-9% (US adults)	Median age 30; insidious	2:1 female:male	Chronic, waxing and waning

CLINICAL PICTURE

- Free-floating worry shifts across health, finances, work, and family; patients describe the content as realistic but the intensity as excessive.
- Somatic complaints dominate the visit: muscle tension, headaches, GI distress, fatigue, and initial insomnia bring most patients to primary care first.
- Reassurance-seeking, over-preparation, list-making, and checking on loved ones function as safety behaviors that keep the worry cycle running.
- Restlessness, irritability, and impaired concentration are frequently misread as ADHD, occupational burnout, or an irritable depressive episode.
- Onset is insidious; patients commonly report having been worriers for as long as they can remember, with no clear index episode to anchor.
- Functional impact accrues through indecision and procrastination rather than dramatic incapacity, which delays help-seeking by a decade on average.

DIAGNOSTIC CRITERIA AT A GLANCE

- Excessive anxiety and worry about several domains, present more days than not for at least six months, that the person finds difficult to control.
- Adults need at least three of six associated symptoms: restlessness, fatigability, concentration difficulty, irritability, muscle tension, disturbed sleep.
- Children and adolescents meet the symptom threshold with only one of those six associated features rather than three.
- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Not attributable to a substance, medication, or medical condition, and not better explained by panic, social anxiety, OCD, or illness anxiety.

NEUROBIOLOGY & PHYSIOLOGY

- Deficient prefrontal top-down regulation of an overactive amygdala; ventromedial prefrontal cortex and anterior cingulate show weak inhibitory control on fMRI.
- GABAergic hypofunction at benzodiazepine binding sites, together with serotonergic and noradrenergic dysregulation, underlies both symptoms and drug response.
- Excess glutamatergic tone and alpha-2-delta calcium channel signaling account for **pregabalin** efficacy in European anxiety trials.
- Heritability approximates **30-40%** and is largely shared with major depression and trait neuroticism; no single locus carries a large effect.
- Chronic HPA axis activation and elevated inflammatory markers such as IL-6 and CRP link GAD to hypertension, irritable bowel, and coronary risk.
- Reduced heart rate variability and blunted vagal tone are reproducible autonomic findings that track with cumulative worry duration.

PSYCHOLOGICAL MECHANISMS

- Intolerance of uncertainty is the core cognitive vulnerability; worry is deployed as an illusory problem-solving strategy for unresolvable ambiguity.
- Positive beliefs about worry (it prepares me, it prevents bad outcomes) coexist with negative meta-worry that worry itself is uncontrollable and harmful.
- Worry is verbal-linguistic activity that suppresses somatic arousal, negatively reinforcing avoidance of full emotional processing (contrast avoidance model).
- Anxious or overprotective parenting and low perceived control in childhood predict adult worry; preoccupied insecure attachment is overrepresented.
- Perfectionism and inflated responsibility drive over-preparation, so good outcomes get attributed to worry rather than competence, sustaining the loop.

DIFFERENTIAL & COMORBIDITY

- Rule out hyperthyroidism, arrhythmia, pheochromocytoma, and caffeine, stimulant, or bronchodilator effects before anchoring on a primary anxiety diagnosis.
- Distinguish from panic disorder (episodic surges), social anxiety (evaluation-focused), OCD (ego-dystonic intrusions), and illness anxiety (health-specific).
- Comorbidity is the rule: **major depression** in roughly 60% lifetime, plus other anxiety disorders and alcohol or sedative misuse.
- Suicide risk rises with comorbid depression and with alcohol or benzodiazepine use; screen at every visit rather than assuming low lethality.
- New-onset worry in an older adult warrants cognitive screening, since early dementia and hypoactive delirium can present as agitated worry.

Treatment EVIDENCE-BASED MANAGEMENT

PHARMACOLOGIC

- First-line SSRIs are **escitalopram 10-20 mg/day** or **sertraline 50-200 mg/day**; start at half dose and expect 4-6 weeks to full anxiolysis.
- SNRIs **venlafaxine XR 75-225 mg/day** and **duloxetine 60-120 mg/day** are equally first-line; monitor blood pressure and discontinuation symptoms.
- **Buspirone 15-60 mg/day** in divided doses is a non-sedating augmentation option with no abuse liability but a two-week onset.
- Benzodiazepines only as a short bridge under 2-4 weeks; tolerance, falls, cognitive dulling, and dependence outweigh any chronic benefit.
- **Pregabalin 150-600 mg/day** and low-dose **quetiapine** have trial support but carry sedation, weight gain, and metabolic burden; keep them second-line.

PSYCHOTHERAPY

- **CBT** combining worry exposure, cognitive restructuring, and stimulus control over **12-16 sessions** carries the strongest evidence base.
- Applied relaxation and progressive muscle relaxation target the tension component and match CBT outcomes in several head-to-head trials.
- Intolerance-of-uncertainty therapy and **metacognitive therapy** directly target worry beliefs and yield large effect sizes in randomized trials.
- **Acceptance and commitment therapy** and mindfulness-based stress reduction reduce worry through decentering rather than through content change.
- Therapy plus medication is preferred for severe or comorbid presentations, and therapy alone lowers relapse risk after treatment ends.

ADJUNCT & SUPPORTIVE

- Track severity with the **GAD-7**, where a score of 10 or higher signals clinically significant anxiety, plus the Penn State Worry Questionnaire.
- Aerobic exercise three to five times weekly, caffeine held under 250 mg/day, and consistent sleep-wake timing produce measurable worry reduction.
- Sleep restriction and stimulus control for comorbid insomnia often cut daytime worry more efficiently than another round of dose escalation.
- Digital **CBT** programs and guided self-help are effective for mild-to-moderate GAD and extend access where specialist waitlists are long.
- Plan the taper early: continue effective pharmacotherapy at least **12 months** after remission, then discontinue slowly to limit relapse.

CLINICAL PEARLS

- Worry that hops topics but never resolves signals GAD, not the individual crisis of the week.
- Ask what worry accomplishes; positive beliefs about worry predict poor CBT response if unaddressed.
- A GAD-7 of 10 or higher warrants active treatment rather than watchful waiting and reassurance.

References

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NOTE

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