

# Generalized Anxiety Disorder (DSM-IV-TR #300.02)

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Generalized anxiety disorder (GAD), also known as “chronic anxiety neurosis,” is characterized by chronic “free-floating anxiety,” accompanied by such autonomic symptoms as tremor, tachycardia, and diaphoresis.

The lifetime prevalence of generalized anxiety disorder has been estimated at about 5%, and the female to male ratio at about 2:1. Some doubt, however, has been expressed about these figures, as it appears that in the epidemiologic surveys patients with depression may have been misdiagnosed as having generalized anxiety disorder.

## ONSET

Onset is usually in adolescence or childhood years; however, it may also first appear in early adult years. Symptoms tend to evolve gradually and insidiously.

## CLINICAL FEATURES

Commonly the patient complains of anxiety, sometimes with bitterness, and often has already consulted several other physicians in the search for relief. The patient is easily startled and jumpy, and loud noises or sudden movements may be particularly alarming. Unable to relax, the patient may spend restless hours at night waiting for sleep.

The patient often complains of a sense of shakiness and may have a fine tremor of the hands. Some patients may “shake like a leaf.” The heart may race uncomfortably, “like a bird fluttering in the chest.” They may have a lump in the throat, and cold clammy skin is evident upon a handshake.

Patients often complain of indigestion and cramping. They may have constipation or diarrhea. Frequent urination is common. Some may complain of lightheadedness and a fear that they might faint. The completion of minor tasks requires an inordinate degree of effort, and patients often complain of feeling exhausted and of being unable to concentrate.

Patients may volunteer “reasons” why they are anxious; however, on close inspection, either their concerns are unjustified or, if in fact they have an actual occasion for worry, their anxiety and other symptoms are all out of proportion to the facts. Indeed often the free-floating anxiety has “attached” itself to part of the patient’s life, or the patient, in a desperate attempt to “make sense” of this experience, has decided that this or that thing is the “cause” of the anxiety.

## COURSE

This appears to be a chronic disorder, with symptoms waxing and waning over the years or decades. Whether or not this could be an episodic illness, with long symptom-free intervals, is not clear.

## COMPLICATIONS

When symptoms are mild, they may constitute but little interference in the patient’s life. In severe cases, however, patients may be completely “paralyzed” by their anxiety and may be unable to function in almost any capacity.

## ETIOLOGY

Both family and twin studies support a genetic role in generalized anxiety disorder, and although it is not entirely clear what is inherited, several findings support the presence of abnormalities in GABAergic and noradrenergic activity. GABAergic dysfunction is suggested by the effectiveness of benzodiazepines in this disorder and by the finding of reduced benzodiazepine binding sites, not only on peripheral blood lymphocytes but also within the left temporal pole. Noradrenergic dysfunction is suggested by the similarity of the symptoms of the disorder with those seen upon infusion of noradrenergic drugs and by the presence of a reduced number of alpha-2 adrenergic receptor sites on platelets.

## DIFFERENTIAL DIAGNOSIS

An agitated depressive episode, especially during its prodrome, or an agitated dysthymia may present with a clinical picture very similar to that of generalized anxiety disorder, and these two disorders probably occasion most of the many incorrect diagnoses of generalized anxiety disorder. However, certain qualitative differences are noted between the symptomatology of depression and that of generalized anxiety disorder that may allow for the correct diagnosis. Although depressed patients may be anxious, they also experience pervasive despair, hopelessness, or melancholy—affects that are at the most only transiently present in generalized anxiety disorder. The sense of fatigue is likewise different in these disorders. Depressed patients complain of feeling drained or chronically leaden and weighted down; in contrast the patient with generalized anxiety disorder may not experience fatigue until an actual attempt is made to do something. Crying spells, which are common in depression, are not often seen in generalized anxiety disorder.

Patients with panic disorder may develop considerable anticipatory anxiety; however, here the anxiety is over the prospect of having another attack, and panic attacks are not part of the symptomatology of generalized anxiety disorder. Thus in any chronically anxious patient one must take a painstaking history in search of a panic attack.

Patients with specific phobia, social phobia, or obsessive-compulsive disorder may likewise experience considerable anxiety; however, here the symptoms are clearly in direct proportion to the patient’s proximity to the dreaded event. Such a clear and predictable correlation between symptoms and events is not seen in generalized anxiety disorder.

In hypochondriasis, anxiety may be pervasive; however, in contrast to generalized anxiety disorder, the symptoms are always intimately connected with one thing, namely the patient's apprehension that she may have an underlying serious disease.

Patients dependent on alcohol, sedative-hypnotics, or anxiolytics may repeatedly find themselves in the midst of withdrawal symptoms characterized by anxiety and autonomic symptoms. Should their substance use be secret, a diagnosis of generalized anxiety disorder might be considered. One clue would be a marked fluctuation in symptoms occurring over hours. Such a course is not seen in generalized anxiety disorder but is quite typical of an intoxication fading rapidly into withdrawal.

A variety of drugs if taken chronically may produce a constant set of side effects that may mimic generalized anxiety disorder. These include caffeine, sympathomimetics, yohimbine, and certain of the "alerting" antidepressants, such as desipramine, bupropion, and the SSRIs. Antipsychotic-induced akathisia may also at times cause some diagnostic uncertainty.

A number of general medical conditions may also cause chronic anxiety, and in most cases the diagnosis is suggested by their associated signs and symptoms. Examples include chronic obstructive pulmonary disease, congestive heart failure, Cushing's syndrome and as a sequela to cerebral infarction in the right hemisphere. Hyperthyroidism is suggested by proptosis, and in many cases by a simple handshake: in contrast to the generalized anxiety patient whose handshake is cold and clammy, the hyperthyroid patient's hand is warm and sweaty. Given, however, the subtlety of many cases of hyperthyroidism, it is appropriate in all cases to get a thyroid profile. Hypocalcemia may also present with chronic anxiety, and may or may not be accompanied by other signs and symptoms such as tetany, Chvostek's or Trousseau's sign, cataracts, calcification of the basal ganglia or a movement disorder.

## TREATMENT

Either cognitive behavior therapy or medications may be utilized, and it is not clear which is more effective. Medications include antidepressants, buspirone, benzodiazepines, hydroxyzine and propranolol.

Effective antidepressants, with their average effective doses, include venlafaxine (as the extended release preparation in a dose of ~225 mg), paroxetine (20–40 mg) and imipramine (150 mg); trazodone (250 mg) is also more effective than placebo, but probably not as effective as the other antidepressants. Given the lack of head-to-head comparisons of venlafaxine, paroxetine and imipramine, the choice among them is often made on the basis of their side-effect profile, and with this in mind, most clinicians will choose either venlafaxine or paroxetine.

Buspirone may be used in low doses of 5 mg tid; however, higher doses, in the range of 15 to 20 mg tid, are probably more effective.

Among the benzodiazepines, effective agents include diazepam (15–25 mg daily), alprazolam (1 to 4 mg) and lorazepam (1 to 4 mg). Among these, diazepam is probably

preferable, as, given its long half-life, there is a lower probability of withdrawal symptoms.

Hydroxyzine, an antihistamine similar to diphenhydramine, is more effective than placebo when given in a total daily dose of approximately 50 mg.

Propranolol, although generally ineffective against the experience of anxiety *per se*, may relieve the "peripheral" manifestations of anxiety, such as tremor and tachycardia; the effective dose ranges between 60 and 240 mg.

Choosing among these various medications is not straightforward. The antidepressants and buspirone all require weeks to become effective, and on this score the benzodiazepines are definitely preferable, as they work almost immediately. This enthusiasm for benzodiazepines, however, is tempered by the fact that after a month or so of treatment they are less effective than antidepressants for anxiety *per se*; furthermore, and most importantly, the benzodiazepines carry with them the risk of neuroadaptation and withdrawal symptomatology. Hydroxyzine, like the benzodiazepines, is immediately effective, and has the advantage of not causing neuroadaptation. Propranolol, given its relative ineffectiveness against anxiety *per se*, is generally a last choice for monotherapy.

All other things being equal, it seems preferable to start with either an antidepressant, such as venlafaxine or paroxetine, or with buspirone. Should these be ineffective, it is appropriate to consider a benzodiazepine, such as diazepam, or hydroxyzine: in patients with substance abuse, hydroxyzine should be used. Propranolol might be considered as monotherapy in cases where the "peripheral" symptoms were the most troubling to patients; in most cases, however, if it is used at all, it is employed as an adjunct to one of the other medications. In some cases, serial trials of one agent after another are justified in an attempt to find an optimum regimen. Importantly, when either switching from a benzodiazepine to another agent, or simply stopping a benzodiazepine, it is critical to gradually taper the dose to mitigate withdrawal; furthermore, one may consider "covering" the patient during this tapering with either imipramine or buspirone, as either agent will blunt the exacerbation of anxiety symptoms typically seen during a benzodiazepine taper.

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