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Generalized Anxiety Disorder: Diagnosis, Neurobiology, and Treatment

By Philip T. Ninan, MD

Case Report

LJ is a 47-year-old divorced male who presented with a chief complaint of anxiety. He described anxiety as being nervous and not being able to turn his mind off. He was worrying uncontrollably about his upcoming marriage, having to sell his house, the impact of a move on his children, and how his children would get along with his stepchildren. He was irritable with his fiancée. He was also worried about being unproductive at work and an upcoming review with implications for his finances over the next several years. He reported difficulty falling asleep and disturbed sleep, and not feeling rested in the morning. He had considerable difficulty paying attention and staying focused on even simple tasks. As a result he had difficulty functioning at work and did not go to work for a few days because he felt so overwhelmed. He was isolating himself socially. He described wanting to stay at home and crawl into a safe place. Physically, he felt he had little energy. He had nonexertional, nonradiating chest pains, increased perspiration, and facial flushing. He also described gastrointestinal distress, a feeling of tightness in his stomach, which was reduced with food. These symptoms had become an issue during the previous year as he struggled with his decision to remarry.

He reported anxiety dating back to his childhood. He had tremendous anxiety, crying every day and stomach upset going to school in first grade and subsequently at the beginning of every school year. These symptoms would last for 1 to 2 weeks. They would also occur when he was faced with a new situation such as going to a new school, a new job, or starting a new project. He also described similar experiences when he was responsible for making a major decision, and also when faced with deadlines.

He also reports periods when the excessive anxiety developed into depressive symptoms. The first was when he was a sophomore in high school, and it lasted for 2 years. He had decreased self-esteem but not to the degree that he felt hopeless or worthless. He was still able to maintain good grades, but he retreat-

Dr. Ninan is professor of psychiatry and behavioral sciences, and director of the Mood and Anxiety Disorders Program, at Emory University School of Medicine in Atlanta, GA.

ed to becoming very dependent on his mother. His sleep was not disturbed, but he had increased appetite without weight gain. He had suicidal ideation but no plans, intention, or attempts. His second episode began when he was a freshman in college and it lasted for about 6 months. He remembers questioning his religious beliefs and being very troubled. His third episode occurred 5 years previously when he went through a nasty divorce that lasted 2 years. He had a lot of anxiety as well as sadness, fatigue, difficulty with concentration and memory, and negative effects on his work.

He reported one panic attack in his life. He was very stressed at work and had not slept well the night before. He took a day off and felt better. He denied symptoms of hypomania, psychosis, obsessive-compulsive disorder (OCD), or eating disorder. He had not been abused or exposed to potentially life-threatening trauma.

He drank alcohol excessively for a brief time in his 20s but did not get into any trouble. He denied blackouts and legal or relationship difficulties as a result of his drinking. Currently he has an occasional glass of wine before dinner. He had no experience with street drugs. He avoided caffeine.

Family History

His mother overused alcohol and might have had an episode of depression when she was a young adult. His father was very logical and risk-aversive and had increasing anxiety with age, though never to the degree of impairment or requiring treatment. He had a brother, 2 years younger, who developed depression under major stressful events, received some treatment (details unknown), and had done well since.

Social and Developmental History

The patient grew up in what he described as an ideal setting. Professionally, he was a successful lawyer who was doing well financially.

Treatment History

He was treated by a psychiatrist in high school and received psychotherapy and also an unknown antidepressant for 1 to 2 years. He had no side effects but also did not believe he received any benefit from either treatment. When he had his depression in college, he received psychotherapy from a psychologist. About 14 years ago he started therapy with a psychologist to talk about job-related stresses, and it evolved into marital therapy. About 12 years ago he was prescribed alprazolam by his internist and has been on alprazolam off and

on since then. He found it worked moderately well, particularly in helping him sleep at night. Initially he would take 0.25–0.5 mg, averaging four to five doses a week, but would also go up to 3 weeks without it. He denied any history suggestive of withdrawal symptoms.

About 5 years previously, he started under the care of a psychiatrist focusing on medication management. He was treated sequentially with fluoxetine, paroxetine, venlafaxine, sertraline, and bupropion. He finally settled on 100 mg of sertraline and took it for 4 years, describing it as moderately helpful. He had some sexual side effects, mainly difficulty achieving an orgasm, and so was started on 15 mg of buspirone, which helped partially. He stayed on that combination until he forgot it when he went on a Christmas vacation and therefore discontinued it. He had some transient lightheadedness.

He was off medications for about 3 months beyond an occasional alprazolam until 2 weeks prior to his evaluation, when he started himself back on buspirone. He increased the dose to 30 mg/day in divided doses with only a mild degree of diarrhea, and transient dizziness about half an hour after each dose.

Medical History

He had had a recent physical exam including a cardiac stress test that was normal. He had low back problems for which he was recently prescribed clonazepam 1 mg/day, which he took for a month before discovering that it was similar to alprazolam and therefore discontinued it. He was prone to stress-related shingles (mild) and allergic skin reactions. He has no known medication allergies.

Mental Status Examination

The patient was a well-dressed male who looked his stated age. Behaviorally he was comfortable in the interview and was able to give a good history and describe his experiences well. He had a full range of affect. He reported a moderate degree of anxiety but no current sadness. There was no evidence of a thought disorder or perceptual alterations. He was not suicidal. He was of above-average intelligence. He had very good insight into his condition. His sensorium was clear and his attention and memory were unimpaired on testing.

Diagnosis

Axis I:	Generalized anxiety disorder (GAD) Major depressive disorder, unipolar, multiple episodes, currently in remission.
Axis II:	None

Axis III: None
Axis IV: Moderate, primarily focusing on relationship issues.
Axis V: Currently 55. Highest in the previous year (78).

Discussion of the Diagnosis

The history of the generalized anxiety disorder (GAD) diagnosis in psychiatry is interesting. Theoretical perspectives have regularly influenced diagnostic classification and GAD is no exception. Psychodynamic concepts perceived anxiety as a core symptom leading to general psychopathology, but focused on underlying defensive processes and motivational drives while de-emphasizing manifest symptoms. The *Diagnostic and Statistical Manual of Mental Disorders*, Second Edition (*DSM-II)* diagnosis of "anxiety neurosis" was split in the *DSM-III* into GAD and panic disorder characterized by panic attacks. This division was strongly influenced by the available literature suggesting panic disorder responded to antidepressant treatments such as imipramine, while GAD was responsive to anxiolytic agents such as the benzodiazepines. Treatment response has had a significant influence on our nomenclature. Thus the modern age of psychopharmacology had neuroleptics for the psychoses, mood stabilizers for bipolar disorder, antidepressants for the depressive disorders, and anxiolytics for the anxiety disorders. However, with advances in clinical psychopharmacology, the diagnostic distinctions have muddied, as in the case of GAD, which is now known to respond to antidepressants as well.

GAD in *DSM-III* required 1 month of symptoms of generalized and persistent anxiety with motor tension, autonomic hyperactivity, apprehensive expectation, and excessive vigilance. *DSM-III-R* changed the "generalized and persistent anxiety" to "unrealistic worry" as necessary for the diagnosis and increased the length of time symptoms had to be present to 6 months. *DSM-IV* has focused on the cognitive aspects of anxiety and required difficulty controlling the worry as a requirement for the diagnosis of GAD. To differentiate the worry in GAD from obsessions seen in OCD, the term "unrealistic" was discarded. The distinction from hypochondriacal somatic concerns was spelled out by differentiating it from concerns of having a serious illness. The distinction between worry and ruminations seen in depression are that the content of worry is about potential catastrophic outcome, while ruminations focus on negative expectations, particularly about the self, such as low self-esteem, guilt, etc.

DSM-IV criteria for GAD has six requirements. The first two require excessive anxiety and its cognitive component, worry, for at

least 6 months, as well as the worry being uncontrollable. LJ described feeling anxious and worried, such that he could not turn his mind off from his worrisome thoughts. He described his worry as spinning his wheels unproductively, leaving him unable to focus on his responsibilities such as his work.

GAD in *DSM-IV* also requires at least three of six associated symptoms, including restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance. At least some of the symptoms have to be present for more days than not during the previous 6 months. Associated symptoms that LJ had included fatigue, difficulty concentrating, irritability, and sleep disturbance.

The associated symptom criteria for GAD are also seen in major depression, except for muscle tension, which seems to be unique for patients with GAD. The fundamental difference is that depressed patients have sadness as the dominant emotional experience as compared to anxiety in GAD. However, many patients have both sadness and anxiety and have difficulty deciding which is more prominent. Given this overlap, clinicians may find it difficult to differentiate the two if the major depression is less severe and not marked by vegetative symptoms or suicidality. Since there is a significant overlap of symptoms between GAD and major depressive disorder (MDD), the comorbid diagnosis of GAD with MDD should be given only when the symptoms of GAD persist outside of the MDD episode. However, this raises the argument that GAD may be considered a subsyndromal version of MDD in some patients. Thus patients with MDD who have responded partially to treatment may not meet criteria for MDD any more but now meet GAD criteria. Since dysthymia is a diagnosis requiring lesser intensity of symptoms than MDD, though of longer duration (2 years), the distinction of GAD and dysthymia may also be difficult.

In differentiating the worry in GAD from other disorders, *DSM-IV* spells out that the content of the worry is about everyday issues and not senseless or ego-alien as in obsessions. The focus of the worry is not anticipatory anxiety of panic attacks as in panic disorder, phobic situations such as in social or specific phobias, weight issues as in eating disorders, physical illness as in somatization disorders, or a potentially life-threatening traumatic experience such as in posttraumatic stress disorder (PTSD).

DSM-IV also requires marked distress or impairment in functioning for the diagnosis of GAD. Additionally, the GAD symptoms are not the result of direct physiological effects of substance abuse/dependence or a general medical condition.

Course of Treatment and Illness

LJ was educated about current perspectives and knowledge on GAD. He was given educational material to read. The relationship of the emotion of anxiety to uncontrollable worry was emphasized. His tendency to experience pathological anxiety from his early years and his tendency to respond to novelty, change, and challenges with an exaggerated anxiety response were noted. A treatment plan was developed.

From the point of view of psychotherapy, he had a long-term relationship with his psychotherapist that he found comforting. The therapy was largely based on psychodynamic principles, but was also flexible and at times directive. His therapist was contacted and she agreed to continue to explore his ambivalence towards the wedding scheduled in 5 weeks. In addition, because controlled trials have documented the benefits of cognitive behavior therapy in GAD, he was referred to a cognitive behavior therapist with the agreement of his current therapist who did not feel qualified to provide that. However, because of time constraints, LJ did not have an appointment with a cognitive behavior therapist for 3 months.

Pharmacologically, he was already on buspirone, was tolerating it, and had some confidence in it. The lack of sexual side effects was important under the circumstances. So the mutually agreed-upon strategy was to increase the dose and evaluate its efficacy. The dose was built up to 60 mg in divided doses during the next 2 weeks with only minor, transient dizziness as a side effect.

He was given permission to continue the benzodiazepine on an as-needed basis and document the frequency of its use. He was switched to clonazepam because of its longer length of action. However, he found that during the day if his anxiety was intense, alprazolam had a faster onset of action. He was educated about the use of benzodiazepines sublingually if he needed immediate effects.

With this strategy, he reported only a mild degree of benefits during the next several weeks, though it was impossible to assess how symptomatic he would have been without any pharmacological intervention. He went ahead with the wedding, with a tremendous amount of anxiety, though he enjoyed the honeymoon with minimal anxiety. On his return, he had considerable difficulty functioning at work and worried whether he had made the right choice in going ahead with the wedding. At this point he was considered to have had an adequate trial of buspirone and was started on venlafaxine (extended release) and buspirone discontinued during the next 2 weeks. The dose of ven-

lafaxine (extended release) was gradually increased to 187.5 mg/day over 6 weeks, the titration being slowed because of side effects. Venlafaxine (extended release) was initially taken in divided doses and subsequently as a single dose. Side effects included some urinary hesitation and dry mouth, gastrointestinal distress with reduced hunger, blurring of vision, and transient sexual side effects on one occasion.

About a month after starting venlafaxine (extended release), he reported about a 50–60% improvement globally. His anxiety level was considerably diminished but he continued to worry and had difficulty with sustained attention. He enjoyed a weekend getaway with his wife and was encouraged by that experience. After 2 months on venlafaxine (extended release), he reported that he was close to l00% better in terms of his anxiety. He was able to handle his work as well as his home situation quite well. He discontinued his benzodiazepine use without difficulty because he didn't feel the need for it. Side effects of venlafaxine (extended release) were blurring of vision that was greater on one side, some decreased libido, and occasional difficulty reaching a climax. The dose of venlafaxine (extended release) was reduced to 150 mg and it helped with the sexual side effects.

Discussion

The experience of anxiety in humans is almost universal, with GAD being a pathologic extension in intensity and chronicity (more than 6 months) and beyond the control of the individual. GAD is thus a categorical label for one end of the spectrum of the experience of anxiety. "Trait" anxiety is a temperament marked by chronic experiences of anxiety that is less intense than seen in GAD. Typically, the anxiety in GAD is persistent for years or decades, often beginning early in life, with fluctuations in its intensity, not unlike the patient under discussion. The manifestations of anxiety change with developmental stages and the challenges they entail.

GAD is a common anxiety disorder. The National Comorbidity Survey of the general US population reported the 1-year prevalence of GAD of 3% and the lifetime prevalence of 5.1%. GAD is more common in women than in men.

Early studies examining the genetic aspects of GAD found the familial aggregation of GAD was separate from panic disorder. Studies of identical and nonidentical twins by Kendler and colleagues reported that roughly 30% of the liability for the development of GAD came from genetic sources. A recent follow-up study by the same group found that GAD and MDD shared the same genetic factors, the difference being distinct environmental risk factors.

Neurobiology of GAD

Emotions provide color and fullness to our conscious existence. There may be a few primary emotions just like there are three primary colors, which in varying combinations allow us to perceive millions of colors. When emotions become intense, they become the focus of attention and drive cognitive patterns and behavior.

Neurobiologically emotions are the result of "motivational" circuits becoming activated, with the subjective component being the experience of feelings. These motivational circuits have been evolutionarily conserved because of value to the survival of the species. Fear triggered by physical threat may be considered a primary emotion. As we evolved into social animals, a component of fear branched into the experience of anxiety, which focuses more on social threats with the potential for embarrassment and humiliation. There is considerable overlap between the neuroanatomical circuits that mediate fear and anxiety, but also distinct differences. This makes sense as behaviorally, pathological anxiety can be controlled without the experience of fear being affected.

Fear and anxiety are protective systems that trigger a series of typical species responses that include a set of defensive behaviors, autonomic arousal, hypoalgesia, potentiation of somatic reflexes, and activation of the hypothalamic pituitary adrenal (or "stress") axis. A critical anatomical structure central to emotions is the amygdala, an almond-shaped structure considered part of the limbic system. The amygdala and its connections have a central role in emotions, particularly fear and anxiety. Damage to the amygdala limits the capacity of animals and humans to associate emotions with experiences. The output of the amygdala, through its central nucleus, can potentially explain the repertoire of emotional and somatic experiences described in pathological anxiety. The amygdala can store memories, emotional memories, which is different from the storage of facts, called declarative memories. Emotional memories connect emotional experiences based on associations that might be specific cues or contextually driven. Such memories may leave an emotional tone for the individual.

Pathologic anxiety, such as seen in GAD, may be the result of dynamic activation of neurocircuits critically involving specific amygdaloid nuclei. Excessive activation in these neurocircuits as a result of negative life experiences, cognitive precepts, or excessive somatic preoccupations may be associated with the experience of anxiety. The amygdala is reciprocally connected with prefrontal areas important in complex executive functions, including cognitive processes such as

working memory and language. Cognitive mechanisms can influence the threshold for activation of the amygdaloid circuits, thus allowing for cognitive control of emotional responses. The functions of the prefrontal cortex include extinction of conditioned fear encoded in the amygdala, control of mood shifts based on internal or external cues, and modulation of autonomic and neuroendocrine functions.

Comorbidity Associated With GAD

The anxiety in GAD may be viewed as a basic symptom seen in many conditions including the other anxiety disorders as well as in major depression. GAD thus lacks a unique and pathognomonic profile of anxiety often seen in the other disorders. Anxiety symptoms can be cued to the anticipation of panic attacks in panic disorder, social or performance situations in social phobia, obsessions in OCD, or intrusive recollections of the trauma that led to the development of PTSD. In addition, the majority of patients with major depression experience symptoms of anxiety at the emotional, cognitive, or somatic level. The presence of anxiety increases the severity of depression as well as the potential for suicidality.

GAD is often comorbid with other anxiety disorders as well as mood disorders, substance abuse/dependence, or general medical conditions. Comorbidity results in a greater degree of symptoms, functional impairment, use of general medical services, and a poorer response to treatment. This is particularly true of comorbid MDD.

Given the symptomatic overlap of anxiety in these anxiety and mood disorders, it is not surprising that diagnostic comorbidity is the rule in GAD. Thus, only a quarter of patients with GAD are free of other psychiatric comorbidity clinically. Epidemiologic samples indicate a lifetime comorbidity of 90%, with two thirds having a current comorbid diagnosis.

A model for placing the relationship of the anxiety such as seen in GAD and major depression in perspective would be to use the analogy of hypertension and coronary artery disease. Blood pressure is universally human, as is tension at an emotional level. Above certain thresholds, they are both considered pathologic, ie, hypertension and pathologic anxiety. There are different forms of hypertension (eg, postural, continuous, malignant) just as there are different anxiety disorders (GAD, panic disorder, etc.). Etiologies for both hypertension and the various anxiety disorders involve genetic/environmental interactions. Hypertension is considered a risk factor for the development of coronary artery disease. Similarly, anxiety disorders like GAD can be considered a risk factor for the development of major depression.

Changing behavior (eg, diet, exercise, weight reduction) is an effective treatment for hypertension. Similarly, changes in behavior (eg, those initiated by cognitive behavioral techniques) can effectively reverse symptoms in GAD. Pharmacologic treatments can block and/or suppress symptomatic expressions of hypertension as well as in GAD.

An important implication of such an analogy is that successful treatment to achieve remission (as against simply an end point of a 50% reduction in symptoms, which defines response in clinical trials) requires addressing not only the symptoms in GAD, but also its comorbidities. The achievement of remission with treatment in GAD reduces the risk of complications like major depression and increases the ability of the individual to return to the fully premorbid functional state and function without limitations.

Pharmacological Treatment of GAD

Benzodiazepines are widely prescribed for the treatment of anxiety, including GAD. Their popularity is due to their rapid benefit in reducing symptoms of anxiety (though a delay of 1–3 weeks exists for achieving syndromal benefit in the anxiety disorders), ease of use, and wide margin of safety when used for short courses of therapy.

Specific binding sites for benzodiazepines are present in varying concentrations in different regions of the brain. Benzodiazepine receptors are structurally and functionally coupled to GABA-A receptors and the associated chloride-ion channels in postsynaptic nerve cell membranes. GABA-A receptors mediate an important inhibitory neurotransmission system in the brain. Benzodiazepines relieve anxiety by potentiating the inhibitory effects of GABA at the GABA-A receptor. Activation of the benzodiazepine receptors in the presence of GABA increases the frequency with which the chloride-ion channels open, allowing chloride ions to flow into the neuronal cells. The result is a negatively charged, hyperpolarized membrane, which makes depolarization by excitatory neurotransmitters less likely. The benzodiazepine-GABA-A receptor has close interactions with serotonin, norepinephrine, dopamine, and other neurotransmitters, which thus influence the activity of each other.

All benzodiazepines appear to be equally effective anxiolytics in groups of people, though individual variations exist; thus, the choice of a benzodiazepine depends largely on its pharmacokinetic properties and patient factors. The dosing requirements for benzodiazepines also vary between patients. The most common side effects of benzodiazepine therapy are sedation and drowsiness. These effects are dose-related and tend to subside after a few weeks of treatment. The initial sedation

might be useful for anxious patients with insomnia. With continued use, tolerance often develops for the sedative effects, but not the anxiolytic effects. Difficulty with concentration and memory, as well as impairment of psychomotor skills (making driving potentially dangerous), are other common adverse effects of benzodiazepine treatment.

Another medication used in the treatment of GAD is buspirone, the only azaspirone marketed in the United States. It is pharmacologically and clinically different from the benzodiazepines, lacking their anticonvulsant, muscle-relaxant, hypnotic, motor-impairment, and dependence effects. Although the precise mechanism of action of buspirone is not yet fully understood, it acts as a partial agonist of the serotonin type 1A receptor and does not interact with the benzodiazepine-GABA-chloride receptor complex. In addition to affecting serotonergic function, buspirone increases release of norepinephrine and dopamine.

Buspirone appears to have a preferential effect for the psychic symptoms of anxiety, irritability, and aggression but does not appear to suppress panic attacks. The anxiolytic effects of buspirone may not be felt for several weeks. Buspirone is generally well tolerated, and any adverse reactions that occur are usually mild. The most common side effects are dizziness, light-headedness, or fuzziness that occurs about 30 minutes after the drug is taken. Usually fewer than 10% of patients discontinue buspirone in clinical trials because of adverse effects.

Antidepressants have undergone renewed interest since the introduction of newer agents that are safer, have fewer side effects, and produce robust efficacy. They have the advantage of treating comorbid major depression. There is some evidence for the efficacy of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) in GAD. However, the largest series of studies with antidepressants use venlafaxine. Venlafaxine blocks the neuronal reuptake of both serotonin and, at higher doses, norepinephrine. Venlafaxine in its extended-release form has shown to be efficacious in the treatment of GAD diagnosed by *DSM-IV* criteria in several studies. These studies uniformly indicated significant benefit for venlafaxine (extended release) acutely as well as maintenance lasting for 6 months.

The patient presented provides a good example of the advantages of antidepressant treatment of GAD, and the potential to achieve remission. Given the long-term nature of LJ's struggles with anxiety and its potential to develop into major depression, the recommendation would be to continue medications indefinitely. Another option would be to deliver cognitive behavior therapy, which could potentially allow him to gradually discontinue pharmacological treatment.

Conclusion

Generalized anxiety disorder is a common disorder whose impact has been historically underappreciated. It is associated with significant distress, impairment, chronicity, comorbidity, and costly use of medical services. Advances in treatment give the clinician several options in the pharmacological and psychotherapeutic management of GAD today, such that remission of illness can be the goal.

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