

UNDERSTANDING GENERALIZED ANXIETY DISORDER

Abstract:

Generalized anxiety disorder is diagnosed in individuals who are fearful and who worry excessively. Unlike most people who can control anxious thoughts and who can realize when their worry is excessive, people with generalized anxiety disorder struggle with mental and physical responses to situations or irrational thoughts to an extent of being disabled or immobilized. With medication and cognitive behavioral therapy, people with generalized anxiety disorder can begin to improve how they function socially, at work, and in school. Rather than avoid situations, individuals with generalized anxiety disorder can begin to improve their thought processes and anxious responses by becoming engaged in treatment and practicing new ways of thinking as well as through medication adherence.

Learning Objectives:

1. Describe the difference between anxiety and generalized anxiety disorder.
2. Explain the causes and risk factors for generalized anxiety disorder.
3. Identify the treatments and patient care for a patient with generalized anxiety disorder.

Introduction

Generalized anxiety disorder is one the most commonly diagnosed mental disorders, it affects millions of Americans and usually develops gradually often during adolescence and young adulthood. Symptoms typically include excessive worry and fear and a lack of control over situations. People with generalized anxiety disorder have difficulty focusing and concentrating, sleeping, feeling moody or irritable, and will experience uncomfortable physical symptoms. Psychotherapy, pharmacotherapy, or a combination of the two have been shown to be effective in decreasing anxiety and helping people return to a normal level of functioning.

Diagnosis of an Anxiety Disorder

Anxiety is defined as uneasiness or worry and is a normal part of life. Everyone has anxiety from time to time and anxiety is important for survival. It helps a person anticipate and avoid danger.

There are varied anxiety disorder diagnoses that need to be differentiated. A generalized anxiety disorder (GAD), for example, is different from anxiety or simple day-to-day worry. GAD is considered a serious mental disorder and someone who has generalized anxiety disorder is fearful and worried, and these feelings are overwhelming.

Fear is a normal response to a real and immediate threat. Anxiety is an anticipation of danger, but a person with GAD tends to be fearful and lives in continuous anticipation of danger that is irrational. A person with GAD will be worried and fearful when there is objectively nothing to worry about. Generalized anxiety disorder is long-lasting and intense, and it can significantly interfere with day-to-day activities. Clinicians need to differentiate between a person who is showing anxiety over a real threat and a person with a generalized anxiety disorder who has a mental disorder.

Epidemiology of Generalized Anxiety Disorder

Generalized anxiety disorder is a common mental disorder. At any one time, approximately 5%-12% of the population has a generalized anxiety disorder. It is twice as common in women as it is in men and it is especially prevalent in the elderly and in people who have chronic pain or a chronic medical illness. Generalized anxiety disorder is strongly associated with other anxiety disorders, major depression, and substance use disorders.

Generalized anxiety disorder is just one of many anxiety disorders. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) lists 12 types of anxiety disorders such as separation anxiety disorder and substance or medication-induced anxiety disorder. These disorders share many similar features, but the other anxiety disorders are caused by or related to specific situations that cause signs and symptoms.

Definition of GAD

Generalized anxiety disorder differs from normal anxiety in four important ways:

1. cause
2. duration
3. intensity
4. impairment

Cause

Someone who has generalized anxiety disorder certainly may have real, objective causes for feeling anxious. There may be explained causes such as a history of trauma or environmental stressors coinciding with a chronic state of anxiety. These need to be considered and differentiated from an anxious state with no real basis.

An important characteristic of GAD is anxiety that is unrelated to specific, identifiable stressors. People who have GAD worry, even when there appears to be nothing to worry about.

Duration

The fear and worries of someone who has generalized anxiety disorder are long-lasting. A person with GAD will have fears and worries that happen day after day, and week after week.

Intensity

Generalized anxiety disorder is also characterized by feelings of fear and worry that are very intense, feelings that are far stronger than what most of us ever experience with typical, day-to-day anxiety.

Impairment

The personal life, occupational life, and social activities of an individual who has generalized anxiety disorder are significantly impaired by the level of anxiety that is experienced. These people are so consumed by chronic worry that everyday functioning can become impossible. They will often have physical symptoms related to anxious thoughts, such as difficulty catching their breath and digestive issues. The American Psychological Association's diagnostic criteria for generalized anxiety disorder are listed in Table 1.

TABLE 1: DIAGNOSTIC CRITERIA FOR GAD

1. The patient has excessive anxiety and worry (defined as apprehensive expectation) that occurs more often than not for at least six months, and the anxiety and worry involve different aspects of the patient's life.
2. The individual finds it difficult to control worry.

3. The anxiety and worry are associated with three (or more) of the following six symptoms, and at least some of these have been present more often than not. For children, only one symptom is necessary for the diagnosis.
 1. Restlessness, feeling keyed up
 2. Easily fatigued
 3. Difficulty concentrating or mind going blank
 4. Irritability
 5. Muscle tension
 6. Difficulty falling asleep, staying asleep, or sleep that is not satisfying
4. The patient has clinically significant impairment in social, occupational, or other important areas of functioning, caused by anxiety or physical symptoms.
5. The signs and symptoms cannot be attributed to drug use, medication, or a medical condition.

The DSM-5 manual states that the criteria for diagnosing GAD include:

1. A disturbance that is not better explained by another mental disorder, for example, anxiety or worry about having panic attacks in panic disorder.
2. The fear of negative evaluation in social situations causes extreme fear is an anxiety disorder or social phobia.
3. Obsessive-compulsive disorder is characterized by unreasonable excessive thoughts and fears(obsessions) that lead to repetitive behaviors (compulsions).
4. The fear of losing, being away from, or being separated from a person or attachment figure is separation anxiety disorder.
5. Reminders or triggers of past terrifying, traumatic events either experienced or witnessed that may include flashbacks, nightmares, and uncontrollable thoughts about the event is posttraumatic stress disorder.

6. An eating disorder characterized by an abnormally low body weight, an intense fear of gaining weight, and a distorted perception of weight is anorexia nervosa.
7. Significant focus on physical symptoms, such as pain, weakness, or shortness of breath, to a level that results in major distress and/or problems functioning is somatic symptom disorder.
8. The inability to stop thinking about one or more perceived defects or flaws in physical appearance, a flaw that appears minor or can't be seen by others. This is body dysmorphic disorder.
9. Illness anxiety disorder, sometimes called hypochondriasis or health anxiety, is worrying excessively that you are or may become seriously ill. You may have no physical symptoms.
10. Delusional disorder symptoms revolve around false beliefs or inaccurate interpretations of real-life situations that cause anxiety. These interpretations persist even when the person encounters evidence that disproves the belief.

The diagnostic criteria for generalized anxiety disorder and for other mental disorders outlined in DSM-5 are specific, and this is for a good reason. There can be similarities that overlap in their clinical presentations, and making an accurate diagnosis ensures the patient receives the proper treatment. Other mental disorders described in DSM-5 that could be mistaken for generalized anxiety disorder are adjustment disorder, dysthymia, hypochondriasis, major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, and social anxiety disorder which have been mentioned above.

GAD Signs, Symptoms, and Co-occurring Conditions

Other signs and symptoms that frequently occur in patients who have generalized anxiety disorder include multiple physical responses to feeling chronically anxious. These tend to be nonspecific symptoms, and are listed below.

1. back pain
2. diarrhea
3. difficulty relaxing
4. dizziness
5. dry mouth
6. headache
7. muscle tension
8. nausea
9. palpitations
10. shortness of breath

These nonspecific symptoms may be found in many mental disorders and physical illnesses that can cause such symptoms as dizziness and palpitations, however, the diagnosis of generalized anxiety disorder is made using the criteria listed in Table 1. The presence of nonspecific symptoms in a situation for which they have no obvious cause can alert a provider to the possibility of generalized anxiety disorder.

People who have generalized anxiety disorder are at risk for other serious mental disorders; major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social phobia, specific phobias, and substance use disorders. GAD typically has a gradual onset and it usually begins when someone approaches the age of late 20s or early 30s, but as mentioned earlier children and the elderly are susceptible to this condition, as well. The earlier in life GAD starts the worse it tends to be and the higher the risk that someone will have another serious mental disorder. Generalized anxiety disorder is most often a chronic problem; the signs and symptoms of GAD will come and go but seldom resolve completely. A complete, lasting remission of GAD is rare.

Prognosis of Generalized Anxiety Disorder

Generalized anxiety disorder can significantly impair someone's ability to function. This disorder can affect every aspect of life, and the emotional, financial, professional, and consequences of having GAD can be severe. Generalized anxiety disorder has also been associated with poor health, particularly cardiovascular health.

Studies have shown that people who have generalized anxiety disorder are more likely than the general population to have high blood pressure and heart disease.

Causes of Generalized Anxiety Disorder

Generalized anxiety disorder is caused by a combination of genetic and biological, psychological, and environmental factors.

Genetic and Biological

There is some evidence that susceptibility to generalized anxiety disorder can be inherited but it is unclear how much genetics affects the risk of developing this disorder. Biological factors such as abnormal processing of serotonin (a neurotransmitter that regulates emotions and mood) and changes in specific brain structures have been investigated as possible causes of generalized anxiety disorder. However, as with genetics, there is no conclusive evidence for their role in its development.

Psychological

People with generalized anxiety disorder often have psychological attitudes that predispose them to fear and worry. They fixate and give an inordinate amount of attention to ordinary situations that are uncertain or mildly threatening, and given information about a problem they will interpret it in the worst way. In essence, people with GAD always expect trouble, they tend to see the glass as half empty, and other people would describe them as pessimists.

Environmental

An inherited susceptibility to generalized anxiety disorder and innate personality traits can explain this disorder to some degree but outside influences are also important. People who have generalized anxiety disorder worry a lot but in many cases, experience has taught them to do so. Compared to individuals who do not have this disorder, someone who has generalized anxiety disorder has had many more traumatic life experiences, especially during childhood. Specific factors that increase someone's risk of developing generalized anxiety disorder are listed in Table 2.

TABLE 2: RISK FACTORS FOR GENERALIZED ANXIETY DISORDERS

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| <ol style="list-style-type: none">1. Chronic mental disorders such as depression or a phobia2. Chronic physical illness3. Family history of generalized anxiety disorder4. Female sex5. Loss of a parent or loved one6. Poor emotional support during childhood7. Poverty8. Recent life trauma or adverse event |
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Screening for Generalized Anxiety Disorder

Generalized anxiety disorder may not always be obvious and as mentioned earlier, many of the diagnostic criteria for this disorder are nonspecific signs and symptoms. Screening tests that are quick and easy to use can determine if someone has or possibly carries generalized anxiety and if that person needs a formal evaluation.

There are many screening tests that can be used for detecting anxiety. The generalized anxiety disorder seven-item scale (GAD-7), the Hospital Anxiety and Depression Scale (HADS), the Metacognitions Questionnaire, the Penn State Worry Questionnaire, and the Worry

Domain Questionnaire are several of the more commonly used tests. The GAD-7 in particular is sensitive, specific, and can be completed quickly; it is illustrated below.

GAD-7

The GAD-7 will ask the patient: During the past two weeks how often have you been bothered by the following problems?

1. Feeling nervous, anxious, or on edge.
2. Not being able to stop or control worrying.
3. Worrying too much about different things.
4. Trouble relaxing.
5. Being so restless it is difficult to sit still.
6. Becoming easily annoyed or irritable.
7. Feeling afraid as if something awful might happen.

For those seven questions the respondent can check the following options:

1. Not at all (0)
2. Several days (1)
3. More than half the days (2)
4. Nearly every day (3)

The scores for the answers are 0, 1, 2, and 3, respectively. A score of 5 indicates a mild degree of anxiety. A score of 10 indicates moderate anxiety, and a score of 15 indicates severe anxiety.

The last part of the GAD-7 includes the following question. "If you checked off any problems in the seven-item questionnaire, how difficult have these problems made it for you to do your work, take care of things at home, or get along with people?" The respondent can answer:

1. Not difficult at all
2. Somewhat difficult
3. Very difficult
4. Extremely difficult

If the respondent has a score of 10 or more, a formal evaluation should be done for the presence of generalized anxiety disorder. If there are clear indications that someone may have generalized anxiety disorder, a GAD-7 score of 10 or more, or observed or self-reported signs and symptoms of generalized anxiety disorder, that individual should be formally evaluated for its presence. This should begin with a basic medical examination and depending on the circumstances, it may be prudent to perform laboratory testing, including a toxicology analysis, 12-lead ECG, and other diagnostic tests.

A complete health history should be taken and this should include asking the patient about the following concerns:

1. The patient's use of alcohol, illicit drugs, and tobacco.
2. Family history of psychiatric illness.
3. Recent and past traumatic events.

The patient's level of impairment should be carefully documented.

Therapy for Generalized Anxiety Disorder

Patients who have generalized anxiety disorder can be effectively treated with cognitive behavioral therapy, pharmacotherapy with an antidepressant, or a combination of the two. Determining which of these three approaches to use will depend on the patient's condition, cost of treatment, patient preference, and the availability of therapy. Cognitive behavioral therapy may not be available in the area where the patient resides. Taken along with antidepressant medication, cognitive behavioral therapy appears to be effective but direct comparison of one treatment to the other has not been fully explored.

Cognitive Behavioral Therapy

The psychotherapy of choice for treating patients who have generalized anxiety disorder is cognitive behavioral therapy. The word cognitive means *of or related to the act of thinking*, and cognitive behavioral therapy is designed to use the active process of thinking to help change the thought processes and behaviors that characterize generalized anxiety disorder. When it is reduced to basic terms, cognitive behavioral therapy can be described in the following way: *Patients are taught to observe and then act: What am I worried about, how do these worries influence my behavior, and how can I change my behavior so that I feel better?*

Cognitive behavioral therapy is effective for patients diagnosed with generalized anxiety disorder because GAD is essentially a disorder of perception. People who have generalized anxiety disorder have persistent, unrealistic, and maladaptive patterns of thinking and emotional responses, and these are the direct cause of the damaging behaviors and impaired functioning of generalized anxiety disorder. Examples of these harmful thinking processes are listed below.

Attentional Bias:

In any given situation someone who has generalized anxiety disorder will notice and focus on the bad and threatening aspects and give less attention to the positive.

Catastrophizing:

Catastrophizing could best be described as an expectation that the only outcome of a stressful situation that will happen is the worst possible one and the feeling that this terrible outcome will happen. An example would be a person who is going to take a test and thinks that

they will fail, and because of failing the test the rest of the person's life is expected to be ruined and that no one will like the person.

Low Tolerance for Uncertainty:

People who have generalized anxiety disorder have a poor tolerance for uncertainty and the unknown, and they are easily upset by uncertainty and the unknown. This is not surprising given that attentional bias and catastrophizing are so common for these people.

Poor Self-confidence:

Lack of self-confidence is a huge obstacle to addressing and dealing with stress, and it is very common in people who have generalized anxiety disorder.

Misinterpretation:

The person with GAD is hyper-focused on what is missing from life. The analogy of the glass being half full or half empty is used to describe someone with generalized anxiety disorder who usually interprets information and situations in the worst way. For the person with GAD, the glass will always be half empty.

Overestimating:

The tendency of people who have generalized anxiety disorder is to overestimate the difficulties and dangers of a problem. They look at a challenging issue and they are convinced there is no hope.

Underestimating:

People who have generalized anxiety disorder may also underestimate their ability to meet challenges and solve problems. They feel overwhelmed when anything goes wrong.

These thinking processes are the driving force behind the behaviors that are the direct cause of impaired emotional, social, and professional functioning. For easier understanding, this can be reduced to a simple formula:



Cognitive Behavioral Therapy (CBT) Process

Cognitive behavioral therapy is designed to interrupt unhealthy, maladaptive thinking processes and give the patient control over his or her life. The therapist works with the patient to examine thought processes, list the behaviors that result from these processes, and teach behavioral and cognitive coping skills. The information here is an outline of the basic structure of cognitive behavioral therapy; the theory behind this form of therapy and the content of cognitive behavioral therapy sessions are much more complex.

Patients are scheduled for 10-15 sessions that last for 60 minutes. During these sessions, the therapist will focus on many issues. Some of the most important pertain to the patient's basic information, self-monitoring, cognitive restructuring, alternate explanations, problem-solving skills, and exposure.

Information:

The therapist will provide the patient with basic information about the process of generalized anxiety disorder, such as maladaptive thinking patterns that lead to harmful behaviors, and cause life impairments. The patient is encouraged to see that a large part of

generalized anxiety is the individual thought processes and emotional reactions that are at the root of the disorder.

Self-monitoring:

Self-monitoring is one of the most important parts of cognitive behavioral therapy. A patient is required to keep track of episodes of anxiety and worry, to record how and when they happened, and to record the emotional response. A method of self-monitoring provides the patient with objective information the patient can use to make practical life changes.

Cognitive Restructuring:

Cognitive Restructuring is a technical term for developing new attitudes and ways of thinking. The therapist will discuss a specific situation and point out how unrealistic and harmful thinking processes such as attentional bias, catastrophizing, and misinterpretation have transformed relatively benign circumstances into moments of paralyzing anxiety. The therapist will help the patient recognize episodes of faulty thinking and how to change those types of thought patterns.

Alternate Explanations:

A patient who has generalized anxiety disorder is sure that a bad outcome will occur, even if there is little or no objective evidence to support this view. For example, a patient may be certain that even a relatively minor mistake made at work would result in becoming unpopular with work peers, job loss, and possibly financial ruin, and eventual breakup of the family.

There is no objective evidence that any of the patient's fears are true and the therapist will offer the patient alternate explanations, and encourage the patient to focus on alternative explanations rather than faulty ways of thinking.

Problem Solving Skills:

For many people who have generalized anxiety disorder there are anxiety-inducing situations that repeatedly occur all of the time. This is frustrating but it also allows the patient to learn problem-solving skills that work for the particular circumstances that are causing difficulties.

Exposure:

Cognitive behavioral therapists may recommend that patients deliberately expose themselves to the situations that provoke the most anxiety, almost as a form of practice for when those situations arise.

Some patients may need more than 10-15 sessions and there is some evidence that monthly follow-up sessions can be helpful. If the patient is not responding to the therapy it may be that another mental disorder exists that needs to be treated and that there have been no practical, concrete changes in the patient's life situation. The patient may need to be treated with cognitive behavioral therapy and medications.

Cognitive behavioral therapy works best if the patient is motivated and is willing to work hard and take personal responsibility for progress made. If someone is more comfortable with a traditional caregiver-patient relationship in which the patient is a passive recipient of treatments, cognitive behavioral therapy may not be the best choice.

Pharmacotherapy for GAD

The two primary classes of antidepressant drugs that are used to treat patients who have generalized anxiety disorder are the selective serotonin reuptake inhibitors (SSRIs) and the serotonin- norepinephrine reuptake inhibitors (SNRIs). Serotonin and norepinephrine are neurotransmitters, and neurotransmitters are the primary way that

nerve impulses from certain areas of the brain are transmitted to other areas of the brain and to the peripheral organs.

Selective Serotonin Reuptake Inhibitors

Serotonin is a neurotransmitter that is found in the part of the brain that controls appetite, emotions, mood, and sex. The selective serotonin reuptake inhibitors (SSRIs) work by inhibiting the reuptake of serotonin. Serotonin is released from nerve endings, stimulates a specific area of the brain, produces a certain effect (perhaps sexual arousal or an elevation in mood), and serotonin is then returned back to the nerve endings. The SSRIs inhibit the reuptake of serotonin back into the nerve endings, increasing the amount of available serotonin.

The theory of SSRIs and their effect on anxiety is that with more circulating serotonin in the area of the brain that controls emotions and mood is consistently stimulated and the patient may be less anxious.

There are many SSRIs and there is no evidence that indicates any particular SSRI is more effective than any other drug in this class. The patient is started on the lowest dose that can be prescribed and this can be gradually increased as needed. Using amounts that are higher than the recommended maximum will not be useful and should not be done.

Norepinephrine is found in many areas of the body and its primary action is as a stimulant. Norepinephrine increases heart rate and blood pressure, increases blood flow to the brain and muscles, and increases blood sugar levels. As with all other neurotransmitters, norepinephrine is released from a nerve ending, binds to a receptor on an organ or tissue, produces a specific effect, and is then returned to the nerve ending. The last part of that process is the reuptake and the SNRIs prevent the reuptake of both norepinephrine and serotonin, increasing the available levels of both.

Studies have shown that the SSRIs are 60%-70% effective for this patient population. The specific SSRI that is used does not appear to be important. They all appear to be equally effective and there is very little clinical data that directly compare them, so the choice of which one to use depends on the medical clinician's experience and how well the patient tolerates the drug. Paroxetine, sertraline, citalopram, escitalopram, fluoxetine, and fluvoxamine have all been used for treating generalized anxiety disorder. All of the SSRIs are prescribed with reported benefits and risks, which the provider should inform patients about prior to starting treatment.

TABLE 3: SSRIS AVAILABLE IN THE UNITED STATES

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| <ol style="list-style-type: none">1. Citalopram (Celexa)2. Escitalopram (Lexapro)3. Fluoxetine (Prozac)4. Fluvoxamine (Luvox)5. Paroxetine (Paxil)6. Sertraline (Zoloft)7. Vilazodone (Viibryd)8. Vortioxetine (Brintellix) |
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The SSRIs have fewer and more tolerable side effects than the other first-generation antidepressants but as with any drug they can produce unpleasant signs and symptoms. Some of these side effects such as headache, sedation, and fatigue may be mild but some are serious enough that patients may discontinue taking the SSRI. Two side effects of the SSRIs that are common and quite distressing for patients are weight gain and decreased libido and other sexual side effects. Approximately 25% of all people who take an SSRI will gain some weight and this can be as much as 50 pounds. A decreased libido and other sexual side effects such as difficulty attaining orgasm are less common. Everyone reacts differently to the SSRIs so if a patient cannot tolerate one SSRI then it should be stopped and another antidepressant or mood stabilizer tried.

There have been reports that the use of SSRIs has increased the risk of suicide, especially when these drugs are prescribed for children, adolescents, and young adults who have major depressive disorder. The prescribing information for each SSRI has a warning that states, that when an SSRI is used for these patient populations the benefits and risks must be carefully examined, and the patients, must be closely observed for suicidal ideation or behaviors.

Serotonin-Norepinephrine Reuptake Inhibitors

The Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) and the SSRIs seem to be equally effective for treating patients who have generalized anxiety disorder. The SNRIs also appear to be tolerated as well as the SSRIs, so the choice of which to use can be made between the health provider and the patient. Table 4 lists the available SNRIs, and most of the clinical experience is with duloxetine and venlafaxine.

TABLE 4: SNRIS AVAILABLE IN THE UNITED STATES

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| <ol style="list-style-type: none">1. Duloxetine (Cymbalta)2. Desvenlafaxine (Pristiq)3. Levomilnacipran(Fetzima)4. Milnacipran (Savella)5. Venlafaxine (Effexor) |
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Serotonin and norepinephrine are hormones and neurotransmitters, which pass messages between nerve cells in the brain. Serotonin is the key hormone that stabilizes mood, while norepinephrine influences emotions, alertness, and energy.

Common side effects of the SNRIs are constipation, diaphoresis, diarrhea, dizziness, insomnia, nausea, and sedation. Venlafaxine can increase blood pressure and this should be monitored during therapy with the drug.

Research has found that SSRIs may lead to faster and more significant improvements in anxiety symptoms. However, SNRIs may have fewer side effects and they may cause less “restlessness,” which could be an important consideration for those with anxiety.

SSRI and SNRI Therapy

A clinical response to an SSRI or an SNRI is usually seen within four to six weeks from the starting point of therapy. At that point, the dose should be increased slowly if the response is unsatisfactory and in order to reach proper treatment. Medication increases should be every one to two weeks for each increase until the maximum recommended dose has been reached. If drug therapy with an SSRI or SNRI is successful it should be continued for at least 12 months in order to prevent a relapse.

Therapy with an SSRI or an SNRI should never be abruptly stopped. The dose of these drugs *must* be slowly decreased and tapered, usually over a period of two to four weeks. If SSRI or SNRI therapy is quickly terminated or is tapered too quickly patients can suffer from discontinuation syndrome. The discontinuation syndrome causes a wide range of nonspecific symptoms such as dizziness, fatigue, headache, and nausea, and although the syndrome is usually mild and only lasts one to two weeks it can be severe and have a longer duration.

Drug interactions between the SSRIs and SNRIs, especially other antidepressants, can cause serious harm. The concurrent use of two medications that have an effect on serotonin reuptake or on serotonin metabolism, for example, can lead to an excess of this neurotransmitter and a potentially fatal condition called *serotonin syndrome*.

Serotonin syndrome, also called serotonin toxicity, is a potentially serious drug reaction. It's believed to occur when too much serotonin builds up in your body. Serotonin syndrome can occur if you take too much medication that boosts serotonin levels.

Serotonin is a neurotransmitter, which is a chemical that helps regulate:

1. digestion
2. blood flow
3. body temperature
4. breathing

You may have symptoms within minutes or hours of starting a new medication or having the dosage of an existing medication increased. The symptoms may include:

1. tremors
2. agitation
3. anxiety
4. restlessness
5. disorientation
6. sweating
7. hyperthermia
8. a rapid heart rate
9. nausea
10. vomiting
11. muscle rigidity
12. dilated pupils
13. twitching, jerking, or muscle spasms
14. a dry mouth and throat
15. flushed skin
16. increased bowel sounds or diarrhea
17. shivering
18. roving eye movements
19. a stretching upward of both big toes on stimulation, known as Babinski sign

In more severe cases, symptoms may include the following and could progress to a life-threatening event.

1. loss of consciousness
2. unresponsiveness
3. coma
4. seizures

Benzodiazepines

Benzodiazepines deserve special mention for the treatment of anxiety. One of the primary labeled uses of these drugs is to treat anxiety, and benzodiazepines such as diazepam (Valium) are popularly perceived as the drug of choice for the treatment of anxiety. Benzodiazepines have been shown to be effective for this purpose, but they do have limitations as a treatment for anxiety.

The Food and Drug Administration (FDA) labeled use for benzodiazepines specifically notes that the benzodiazepines are for short-term use in patients who have anxiety, but the standard course of drug therapy for generalized anxiety disorder is 12 months. The benzodiazepines are also well known to be addictive so they must be used cautiously in patients who have a history of substance use. Many patients can develop a tolerance to the benzodiazepines, making the same dose less effective over time. And the benzodiazepines must be tapered slowly; abruptly stopping the use of a benzodiazepine can cause a serious, even life-threatening withdrawal syndrome. Despite these cautions, the benzodiazepines do have a place for treating generalized anxiety disorder.

Benzodiazepines that are commonly used in the treatment of anxiety are listed below in Table 5. The generic name of the drug appears first followed by the name brand in parentheses.

TABLE 5: BENZODIAZEPINES FOR THE TREATMENT OF ANXIETY

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| <ol style="list-style-type: none">1. alprazolam (Xanax)2. clonazepam (Klonopin)3. chlordiazepoxide (Librium) |
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4. diazepam (Valium)
5. lorazepam (Ativan)

Unlike the SSRIs and SNRIs, the benzodiazepines have a rapid onset of action, minutes to hours after use, so they can be helpful during an acute anxiety attack. And, because of this rapid onset of action, they can be used with an SSRI or an SNRI during the several-week period that it takes for these medications to have a clinical effect.

Other Medications to Treat Anxiety

Finding the correct medications for someone who has generalized anxiety disorder can be a difficult, trial and error process. If the SSRIs or the SNRIs, and the benzodiazepine class of drugs such as Valium and Klonopin, are not effective there are several other classes of drugs that can be used. Other medications that have been successfully used to treat generalized anxiety disorder include:

1. antihistamine-hydroxyzine (Vistaril)
2. antipsychotics-olanzapine (Zyprexa), and risperidone (Risperdal)
3. anxiolytic-buspirone (Buspar)
4. pregabalin (Lyrica)
5. tricyclic antidepressants (TCAs) such as imipramine (Tofranil)
6. lamotrigine (Lamictal) an anticonvulsant medication used to treat anxious depression

There have also been off-label benefits with the use of certain antihypertensive medications such as propranolol (Inderal) which is often prescribed for performance anxiety and panic to alleviate uncomfortable physical responses like fast heart rate. As in the case study below, other unintended and novel treatment outcomes for patients with generalized anxiety disorder found to be resistant to standard therapy have been reported.

Case Study: Ketamine in Treatment-Resistant GAD

The following case studies were obtained from a PubMed search and discuss the novel use of ketamine in a case of treatment-resistant generalized anxiety disorder.

The authors reported on a 34-year-old woman who was diagnosed with panic disorder according to DSM-5 criteria and with co-occurring social anxiety and major depressive disorder. The patient had experienced a long-standing inability to leave the home by herself, was afraid to use public transportation, and she avoided having to go into shopping centers. Because of her anxiety, she had limited herself from having to perform certain public tasks, such as avoiding learning to drive a car and working outside the home.

The patient reportedly would suffer from panic attacks every week, she worried excessively about harming other people through her actions, and there were increasing reports of suicidal ideation. The authors stated that her depression was treated with a combination of a SSRI escitalopram up to 30 mg daily, and an anticonvulsant mood stabilizer lamotrigine up to 400 mg daily. At one point during her treatment, she required electroconvulsive therapy (ECT).

Anxiety was specifically treated with the benzodiazepine lorazepam and more than 30 sessions of cognitive-behavioral therapy. While the patient's mood and suicidal ideation improved, the anxiety remained treatment-resistant and she showed a poor response. The patient continued to predominantly remain at home and was too fearful to leave.

The authors reported that the patient later returned to the emergency department with a complaint of severe neck pain. A magnetic resonance image (MRI) revealed that she had 2 herniated discs. The emergency department provider administered a single infusion of ketamine for pain. Four days before the ketamine infusion, a 7-item Generalized Anxiety Disorder scale score was 6 and her GAD

score fell to 1 a week after the ketamine infusion, although she noticed a reduction in anxiety almost immediately after the ketamine infusion. The patient continued to notice improvement in anxiety for 10 weeks, was free of panic attacks and could engage in social activities more than before the infusion. She reportedly went to a department store alone several times weekly, started a business with a friend, volunteered at a local market, and used public transportation independently. Other outpatient treatments for depression were stopped and she remained in this improved state until she was involved in a minor car accident sometime later.

Discussion

This case involved minimal response in a female patient to prolonged and intensive multiple types of treatment for anxiety. The patient had a sudden and dramatic improvement after an incidental infusion of ketamine for pain that the authors believe led to significant and prolonged improvement of severe anxiety. The patient was diagnosed with treatment-resistant (refractory) anxiety and panic disorder and was fearful of social settings. The patient could now begin to participate in activities typically avoided due to generalized anxiety disorder that was alleviated with the incidental use of ketamine. More research is needed to better understand the benefit of ketamine in treatment-resistant generalized anxiety disorder.

Summary

Generalized anxiety disorder is one of the most commonly diagnosed mental health disorders, affecting millions of Americans. A significant percentage of the population has generalized anxiety disorder. It is more common in women than in men and it is especially prevalent in the elderly and in people who have chronic pain or other medical illness.

Generalized anxiety disorder is not the same as the normal, day-to-day fear or anxiety that everyone experiences. Signs and symptoms that are diagnostic of generalized anxiety disorder include restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and disrupted sleep. Generalized anxiety disorder is associated with an increased risk for major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social phobia, specific phobias, and substance use disorders.

The cause or causes of generalized anxiety disorder are not known, but the pathogenesis is most likely a combination of biological, environmental, genetic, and personality factors. The disorder itself is essentially a disorder of perception, and includes persistent, maladaptive patterns of thinking and emotional responses that result in damaging behaviors and impaired functioning of generalized anxiety disorder.

Other drugs that can be used to treat a patient who has generalized anxiety disorder have been mentioned. Cognitive behavioral therapy is also used often alongside medications and trains patients to rely on alternate explanations and problem-solving skills, and the therapist may use controlled exposure to the anxiety-inducing situations as part of treatment.