
ANXIOUS TIMES

by June Spence photography by Jared Lazarus

In the same way that grim headlines seem to be today's media mainstay, anxiety disorders seem more and more like a defining impairment for this era. Managing these disorders—which are significantly more common than depression disorders—can be daunting, but Duke psychiatrists say that accurate diagnosis, circumspect prescribing, and strategic referral to behavioral therapy or specialty care can bring solace to sufferers in nerve-wracking times.

Even if you've thus far managed to avoid a personal crisis via economic downturn, domestic or foreign violence, or plain-out natural disaster, the cultural pulse of dread that dominates our times is inescapable. We're still slogging through the aftermath of the worst financial crisis since the Great Depression. Earthquakes have shattered neighboring communities and allied economies. Job losses and home foreclosures continue to ripple through the media headlines, with no clear end in sight. It seems that by the millions, Americans are facing agonizingly uncertain futures.

**Patient names have been changed.*

In times of trouble heightened anxiety is an appropriate response, one that can spark positive action. A few sleepless nights of fretting over impending layoffs may well drive someone to more mindful spending, or even to develop a new set of skills to better compete in the marketplace. Anxiety keeps humans alert to dangers both physical and social, so at its best it's a powerful tool for survival.

But for those with anxiety disorders—which affect 40 million adults in the United States, according to the Anxiety Disorders Association of America—such sensations take on a life of their own, far removed from the events that triggered them. Instead of spurring self-protective action, fear and dread become overwhelming, even incapacitating.

PERSONALITY VS. PATHOLOGY

"Imagine you're sinking in quicksand while having a heart attack, and someone has stuck a loaded gun in your mouth," says Liam*. That's how urgent and terrifying his panic attacks were when they struck. "There was an impending sense of doom. That's one of the worst things. You feel it will happen, that this is the end. My body isn't working; I'm going to die." Eventually Liam learned he had mitral valve prolapse, which is associated with panic attacks, but the severity of his anxiety had by then eclipsed its origins. "It was completely debilitating. I had no control of my nightmarish racing thoughts, and no control of my body's reaction to these thoughts."

Carrie is a cancer survivor with a long career in a volatile industry, but it wasn't until a confrontation with a supervisor four years ago that her struggle with anxiety began. "I'd wake up in the morning and have this sense of dread, and every day it got a little worse. No peace, no sleep; the thought of eating was horrible. It felt like that fight-or-flight adrenaline had kicked in and never turned off. I could feel it in my stomach, a constant fluttering. I felt like all the areas

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of my life were out of control. I'd pace back and forth, praying for it to stop. You try to maintain this normalcy, but inside you're screaming."

To Liam and Carrie, it was clear that something physical had gone terribly awry. But the forms anxiety disorders take are not always so easily recognized. In some people, the line between personality and pathology can be difficult to discern—as with Tim, whose acute social anxiety was something he'd long taken for granted. He says he'd always been "introverted and shy. I thought, 'This is who I am, this is the hand that was dealt to me,' and for the most part I tried to accept it."

A former tennis pro, Tim had felt at home out on the court, but found the frequent board meetings and presentations the job required "extremely challenging. Any time I was the center of attention, I don't think I coped very well. I didn't have any growth through repetition. I probably knew early on that the anxiety was interfering with my life, but I didn't have the strength or the will to follow up—maybe it was not even knowing how to follow up." But four years ago, as the date of his daughter's wedding approached, he began to wonder whether something could be done to help. "I just wanted to enjoy the moment and be there as her dad."

"People often think it's a question of character," says Wei Zhang, MD, PhD, director of the Anxiety and Traumatic Stress Program at Duke, which conducts research on anxiety disorders and provides adult outpatient care. "They assume they're just stressed out. Perhaps there has been some stressful event, the stock market's down, there's a death in the family, and they think they just have to tough it out. Or they think it's natural because their mom was like that—and, of course, anxiety disorder does have a genetic component."

ROOTS OF THE CRISIS

Social anxiety has been linked with a functional variation in the human serotonin transporter gene, which appears as either a short or long allele. People who carry one or two short alleles are predisposed to a stronger emotional reaction to threat and fear, which sometimes manifests as anxiety. Among humans of European ancestry, 64 percent have at least one copy of the short (or "S") allele.

But why should an allele that could bias individuals towards maladaptive emotional responses appear so frequently? "It's important to understand that the S allele is advantageous under most circumstances, largely through its positive effects on arousal and attention," says Duke neurobiologist Ahmad Hariri, PhD, who is studying variations in the serotonin transporter gene that may account for up to 10 percent of the difference in the reactivity of the amygdala—the structure in the brain that is crucial to both the formation of emotional states and the encoding of memories that have an emotional component, such as those of a traumatic event. These genetic differences may help explain why one person

A CURE—VIA CANCER

Marie says she probably struggled with anxiety for most of her life, never being fully aware of it or knowing what to call it. Then she was diagnosed with cancer, and her anxiety went into overdrive. She felt frozen by fear one minute, overloaded on adrenaline the next. "I felt so traumatized and fearful," she says. "I couldn't find a place within myself to rest and draw from my own inner reserves. It was like I was holding a huge piece of kryptonite, and I couldn't move away from it."

While under the care of Duke oncologist Andrew Berchuck, MD, Marie discovered a class on mindfulness-based stress reduction at Duke Integrative Medicine. "That was one of the first doors to open," she says. Marie later began working with psychiatrist Margaret Maytan, MD, at the Duke Comprehensive Cancer Center. Medication helped her clear her mind and opened her up to other therapies. She began practicing yoga, qigong, and meditation. She discovered the therapeutic value of making huge, colorful drawings with oil crayons. After meeting with a nutritionist, Marie adopted a "vegan plus fish" diet and her energy soared. She began taking four-mile walks in the woods near her Hillsborough home.

Marie's anxiety abated, and remarkably, she feels less anxious than before she was diagnosed. "Now I know that I had generalized anxiety before. Cancer has transformed my ability to know what stress feels like and to be active about what I need to do to help curtail it."

Maytan says that anxiety is part of the journey for every cancer patient. However, its severity and the ability of the patient to cope vary widely. "Some people become extremely anxious even when their prognosis is excellent and their treatment not so demanding. Others facing a terminal diagnosis may cope well, without the need for professional assistance."

What are the clues to how well a patient is coping? "When a patient is not sleeping, having episodes of panic, feeling out of control, or having a hard time functioning because of anxiety, think about a referral to a psychiatrist," says Maytan. "There's no need for a cancer patient's days to be filled with disabling anxiety."

reacts to a stressful situation with a debilitating depression, anxiety, or post-traumatic stress, when another does not.

"Maybe evolution favors this genetic constitution in particular environments characterized by uncertainty or volatility," suggests Duke neurobiologist Michael Platt, PhD. Platt's research group studies the social behavior of rhesus macaque monkeys, who are the only other primates with similar variation in the same gene. "Being more easily aroused might promote more risk-taking behaviors outside of the social realm, like leaping farther between trees or traveling farther," he says—behaviors that contribute to the success and survival of individuals carrying the gene.

The variation could also offer protection in certain social situations. A recent study by Platt's group showed that macaques with the short/long allele combination, like humans, become averse to risk when experiencing social anxiety. This may aid them in avoiding dangerous interactions with others. "There's a heightened vigilance in social situations," explains Platt, which could benefit a low-status monkey, "although someone high in status who is risk-averse may not take advantage of opportunities or resources available."

Identifying and understanding genetic predispositions to anxiety disorders could one day pave the way for more tailored and effective therapies. "We may be able to get to who is most at risk for these disorders

Richard D'Alli, MD

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and even to find the biological pathways where we could intervene to prevent the disorders from ever occurring," Hariri says. "To shift these trajectories before they even begin to manifest, that's the dream." However, genes are not destiny, Platt is quick to emphasize. "This is not deterministic. A lot depends on environment. A traumatic childhood experience, for example, an uncertain or deprived upbringing—that's when the short allele starts to have a bigger negative impact."

SHIFTING SYMPTOMS

If an anxiety disorder is triggered in childhood, it can present very differently than it does in adults, and its appearance shape-shifts with maturity. Duke child and adolescent psychiatrist Richard D'Alli, MD, chief of the Division of Child Development and Behavioral Health and medical director for Child and Adolescent Psychiatry Services, says identifying it is "really about adjusting your sights as a clinician to the developmental stage of the child. Anxiety might look like excessive fussiness in infancy. Toddlers may show anxiety by being inhibited or behaving in a way that is avoidant. When they get to pre-K or kindergarten, separation anxiety can be the issue, when they throw massive tantrums and may refuse to go to school or be away from their parents. In adolescents you may see the anxiety manifesting as social phobia [also called social anxiety disorder, or SAD]—isolation from friends, or not participating in the classroom out of fear so that it affects grades." Substance abuse may emerge at this stage as well, as an attempt at self-medicating.

What separates the difficulties almost all children experience from a true disorder that calls for intervention is impairment. "When we say someone is impaired, we really mean that they are in some way prevented from doing their developmentally appropriate job," observes D'Alli. "What's the job of a kindergartner? To go to school, to stay in circle time, to take naps, to eat with the other kids, to be a family member." Similarly, in adults, the threshold between distress and disorder is functional impairment, says Zhang. "It's when you could achieve more in your life without that fear and avoidance."

"The sooner any kind of medical or psychological disorder can be identified and treated, the better the long-term outcome," says D'Alli. "No one questions that about cancer. We ought not to question it in pediatric psychiatric disorders, of which anxiety is one of the most prevalent."

TRADING IN THE BENZ

The first-line drug treatment for a range of anxiety disorders is SSRIs or SNRIs (selective serotonin and norepinephrine reuptake inhibitors). While some physicians may be tempted to try benzodiazepines, lured by this older class of drug's promise of quick short-term relief from panic symptoms or insomnia, "they carry a lot of

baggage," warns Zhang. Potentially addictive, benzodiazepines also have been shown to worsen depression, which commonly co-exists with anxiety. They are emphatically not recommended for post-traumatic stress disorder (PTSD), says Zhang, because they impair the ability for cognitive restructuring, which is important in recovery from PTSD. And according to D'Alli, they're not appropriate for children: "At present there are no data to support long-term treatment of child and adolescent anxiety with benzodiazepines."

Compared to benzodiazepines, efficacy and safety are much better established for SSRIs and SNRIs, Zhang says. Still, only 50 to 60 percent of adult patients experience some symptom relief from the medication. "The rate of complete remission is even lower—about 30 to 40 percent. And remission should be the ultimate goal of treatment."

The psychotherapy approach of cognitive behavioral therapy (CBT) has also proven to be beneficial for anxiety, especially PTSD, notes Zhang. "A lot of studies bear that out. However, alone it is not always sufficient, especially when symptoms are severe. A patient unable to concentrate, for example—how much is he going to be able to absorb in CBT?" Studies have shown greater efficacy with medication and CBT combined than with either alone.

Combined therapy has also been proven effective in children. Duke researchers led by principal investigator John March, MD, took part in the Child/Adolescent Anxiety Multimodal Study (or CAMS, published in October 2008 in the *New England Journal of Medicine*), which showed dramatic improvement in children with separation anxiety, generalized anxiety, or social anxiety disorders that were treated with both sertraline (Zoloft) and CBT. Medication and therapy taken separately showed efficacy as well.

The study's authors further noted no suicidality among the participants—a reassuring finding for physicians and parents disturbed by the black-box warning that remains on SSRIs specifically because of concerns about suicidal tendencies among young patients. Nonetheless, medication need not always be the first step in treating children's anxiety, says D'Alli. "Some very good news that we have from CAMS is that CBT has just as much a chance of being effective in the treatment of pediatric anxiety as any evidence-based medicine." To increase the probability of a more robust response to treatment, a combination of SSRI with CBT is indicated. But if there are concerns about medication, it serves to start with the therapy: "There is no black box warning on therapy!"

DIAGNOSIS DILEMMAS

Anxiety disorder is significantly more widespread than depression—one third of the population will experience anxiety disorder in their lifetimes, as opposed to the one person in five who will suffer

I'd have nightmares, wake in a cold sweat, and in the morning the sense of dread was overwhelming.

major depression. However, anxiety hasn't achieved anything approaching the level of public—or professional—awareness that depression has.

This diagnosis disparity may exist because of how people with anxiety disorder commonly present. "Oftentimes patients will come in with vague somatic symptoms, such as headache, nightmares, fatigue, or irritability," notes Zhang. "Sleep disturbances are common: night waking, waking in a cold sweat or panic. Or they don't have the sense of being rested and refreshed—they may not even realize their sleep quality is not good."

Chest discomfort, muscle tension, or GI symptoms are also red flags, and even less likely to be linked to a psychiatric condition. "Anxiety disorder has a lot of overlapping symptoms with chronic fatigue, fibromyalgia, and irritable bowel syndrome. You can treat the symptoms, but if you don't treat the underlying cause, patients may still come back with those symptoms. More tests may be run, and doctor and patient are both left scratching their heads."

Anxiety and heart health—what's the connection?

Chronic anxiety doesn't just turn people's lives upside down; it also can erode their heart health over time. Anxiety—along with depressed mood—is one of two primary components of stress, a known contributor to cardiovascular disease.

The Duke Heart-Mind Center is the country's first dedicated program to study the link between emotional and cardiovascular health. Led by Duke psychiatrist Ranga Krishnan, MB ChB, dean of the Duke-NUS Graduate Medical School Singapore, Duke Heart Center director Christopher O'Connor, MD, and Duke professor of medical psychology James Blumenthal, PhD, the center is pursuing a variety of clinical trials, including:

- **REMIT**, which is assessing the impact of the drug escitalopram on stress-related myocardial ischemia
- **COPE-HF**, which is comparing the impact of coping-skills training with standard medical care in outpatients treated for heart failure.
- **ENHANCED**, which is using the Duke-developed "mental stress test" to examine the effects of stress-management strategies and exercise on cardiovascular biomarkers. During the test, participants perform stress-evoking tasks while clinicians monitor their heart rate and blood pressure and use echocardiography to detect myocardial ischemia.
- **UPBEAT**, which is studying the benefits of exercise and anti-depressant medication in cardiac patients with symptoms of depression.
- **INSPIRE**, which is a telephone-based coping skills intervention for patients with COPD.

To learn more, call Jennifer Wilson at 919-681-4367.

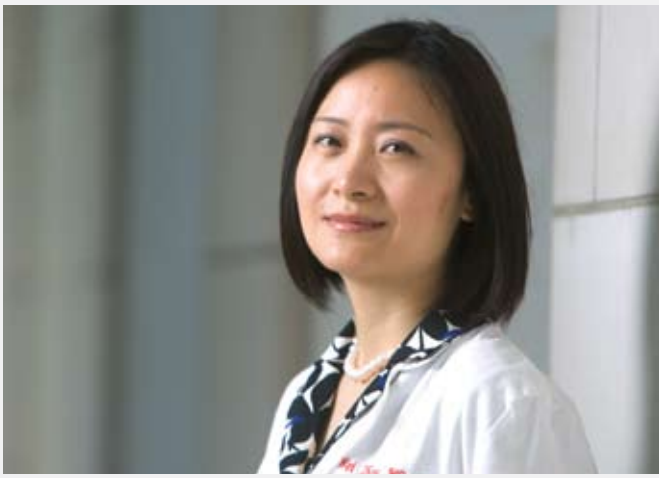
FEMININE MISTAKE?

Anxiety more prevalent in women

Betty Friedan famously wrote about a crippling malaise among 1950s housewives, dubbing it "the problem that has no name." In the twenty-first century, the malady gripping a disproportionate number of maniacally multitasking mothers/wives/professionals has been clearly identified: anxiety disorder. Women are more likely to be affected by generalized anxiety disorder, panic disorder, post-traumatic stress disorder (PTSD), and specific phobia than men—in some cases twice as likely, according to the Anxiety Disorders Association of America.

There's no single reason why women have an increased risk, according to Duke psychiatrist Wei Zhang, MD, PhD. Hormonal fluctuations put more women at risk for anxiety and depression during adolescence, pregnancy, the postpartum period, and menopause. Psychological studies suggest women engage in more cognitive avoidance—strategies to avoid threatening thoughts and emotions—than men. Social factors such as gender roles and discrimination seem to be in play as well. And there are more female victims of sexual assault and childhood sexual abuse, common triggers of PTSD.

Anxiety disorders not only affect the patient's well-being, but potentially that of her offspring. "There are studies suggesting that the children of moms with depression and anxiety have worse outcomes in their academic and social development," says Zhang, "so it's very important to recognize and treat."



Wei Zhang, MD, PhD

The Generalized Anxiety Disorder scale

Primary care physicians can use the Generalized Anxiety Disorder-7 (GAD-7) scale to quickly and effectively screen their patients for anxiety disorders. The subscale, which is the first two items of the GAD-7, can also be a good measure of core anxiety symptoms.

Over the past two weeks how often have you been bothered by the following problems?	not at all	several days	more than half the days	nearly every day
Feeling nervous, anxious, or on edge	☐ 0	☐ 1	☐ 2	☐ 3
Not being able to stop or control worrying	☐ 0	☐ 1	☐ 2	☐ 3
Worrying too much about different things	☐ 0	☐ 1	☐ 2	☐ 3
Having trouble relaxing	☐ 0	☐ 1	☐ 2	☐ 3
Being so restless that it is hard to sit still	☐ 0	☐ 1	☐ 2	☐ 3
Becoming easily annoyed or irritable	☐ 0	☐ 1	☐ 2	☐ 3
Feeling afraid as if something awful might happen	☐ 0	☐ 1	☐ 2	☐ 3

total score _____ = add columns _____ + _____ + _____

Scores of 5, 10, and 15 reflect mild, moderate, and significant anxiety.

Careful, directed questioning can help primary care physicians to identify a potential anxiety disorder—and it's possible to do so within the time constraints of the average exam. A brief but effective screening tool is the Generalized Anxiety Disorder-7 (GAD-7) and its subscale, the Generalized Anxiety Disorder-2 (GAD-2). Both perform well in screening not only for GAD, but for panic disorder, SAD, and PTSD (see box above).

"Some very simple screening questions can help you narrow down the cause," adds Zhang. "The most important thing in recognizing PTSD, for example, is identifying a history of trauma—that's the center of the issue. It's very important to ask about whether there has been a very stressful event. PTSD is oftentimes missed even among the psychiatric community; it's treated as GAD or depression, and they've missed the elephant in the room."

You try to maintain this normalcy, but inside you're screaming.

Anxiety is also often a co-morbid condition. Patients frequently have multiple anxiety disorders or experience acute anxiety alongside depression, bipolar disorder, or addiction. In these cases, tailored treatments, optimally under a specialist's care, are needed. For Liam, who struggled for years to head off his brutal panic attacks without shutting off from the world, connecting with the right specialist was key. "He saw past the anxiety and zeroed in on what no one else had recognized, that it was a part of bipolar disorder."

THE GRADUAL RECOVERY

But even then change didn't happen overnight. As his specialist gradually fine-tuned his medications, Liam worked on getting regular exercise and eating more healthily, lifestyle changes he feels helped stabilize him as well. The difference, he says, is "night and day. Now, I can do most of the things I could do before. That doesn't mean I don't ever get anxious or fear a panic attack, but it's like having a second chance at a normal life." For Carrie, a six-week medical leave allowed for intense therapy and careful medication management, which helped stabilize her enough to return to work. Within four months she was feeling more like her old self, and "today couldn't be more different," she reports. "I am more at ease with myself."

Tim's first step toward recovery was volunteering for a Duke study on SAD. He later sought treatment through the Anxiety and Traumatic Stress Program. Drug therapy has provided dramatic relief of his symptoms, he reports. "The medication offers me an opportunity to be comfortable in situations where I wouldn't otherwise be." Now a sculptor by trade, he's still often the center of attention, attending gallery openings and delivering presentations and Q&As. But unlike in his tennis years, "there's no trepidation going forward, only positive anticipation and excitement. I am seeing a different side of myself—it's illuminating."

Helping patients find their way to normal lives is what drives Zhang and her colleagues, whether that means feeling like their "old selves" or tapping into new, unprecedented selves. "In the face of trauma or stress," she observes, "people can and do overcome their fear with help. Human beings have a lot of resilience."

The Anxiety and Traumatic Stress Program at Duke is a major referral center throughout the Southeast, providing services to more than 500 adult outpatients annually. For more information, visit ***psychiatry.mc.duke.edu*** *and click on "Clinical Services," or call* ***800-MED-DUKE*** *(physicians) or* ***888-ASK-DUKE*** *(patients).*

Duke Children's provides online continuing medical education for clinicians, including CME courses on pediatric psychiatric conditions. Learn more at ***pediatrics.duke.edu*** *(click on "Education").*