

Anxiety in a Headache Patient

In headache patients, anxiety may increase pain while pain may fuel anxiety.



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Caitlin is a 27-year-old woman with a history of migraines and anxiety. She began having separation anxiety at age 5. The patient can remember hanging onto her mother's leg "for dear life" on the first day of kindergarten. Later, at 9 years of age, symptoms of obsessive-compulsive disorder (OCD) began; these included intrusive thoughts, an aversion to germs, and the compulsion to touch everything "equally on both sides." These symptoms waxed and waned over time. By age 15, Caitlin suffered from generalized anxiety disorder (GAD), with intense worrying and feeling "keyed up." The anxiety would, at times, trigger a migraine. Additionally, when Caitlin's headaches were worse, her anxiety also increased.

Over the years, Caitlin found yoga, Pilates, and exercise to be helpful in managing her anxiety. She also noted that cognitive-behavioral psychotherapy was very useful. Biofeedback was "not for her," but she was able to use breathing techniques to calm herself down. As far as medications, she was prescribed fluoxetine (Prozac) and later switched to escitalopram (Lexapro). The selective serotonin reuptake inhibitor (SSRI) helped her anxiety, but not the migraines. She did take alprazolam (Xanax) for acute, severe anxiety.

She was switched to serotonin norepinephrine reuptake inhibitors (SNRIs), starting with duloxetine (Cymbalta) and then desvenlafaxine (Pristiq). These agents helped to treat the anxiety and, to a lesser extent, the migraines. A course of gabapentin did not help the anxiety or the headaches. Caitlin feels that with therapy and medications, she remains anxious but is significantly improved.

Caitlin's history is fairly typical; anxiety may change over time, both in form and in severity. The search for effective medications may take time, as there is no accurate predictor of who will do well with what medication.

What Is Anxiety?

Anxiety is a necessary and universal emotion. With anxiety that originates from a real or perceived threat of danger, one experiences an increase in heart rate, blood pressure, diaphoresis, and other physical accompaniments to anxiety. At times, anxiety comes across as excessive worrying, and this leads to avoidant behavior. Hypervigilance is an excessive focusing of one's attention on a possible danger or perceived danger.

When we think of anxiety, it is usually revolving around a problem or threat in the future. Fear, on the other hand, can be a very intense emotional reaction to a danger or threat that is in the present. We react to immediate dangers with the "fight-or-flight" response. Fear and anxiety, to some extent, are crucial for our existence. Fear allows us to escape from imminent threats; anxiety allows us to prepare for future problems. Anxiety, at least in low or moderate amounts, helps motivate many people to achieve. When someone crosses from moderate to high anxiety, it usually will interfere with the ability to perform.

The triggers for fear and anxiety may be internal or external. With internal triggers, one may have panic attacks that accelerate, feeding on themselves, in part because the associated tachycardia can convey the message that a serious physical problem is imminent. External triggers involve situations that may trigger phobias, or severe anxiety. These may include social situations, crowded or closed-in spaces, tests or other performances, etc. This leads to avoidant behavior, as anxious patients will tend to avoid those situations.

Types of Anxiety

Separation Anxiety Disorder

Patients with separation anxiety disorder have a fear of leaving a close relationship, such as the parent or home situation. Separation anxiety begins in childhood, and may or may not continue later on in life. It may manifest itself for the first time in kindergarten, with the child hanging onto the mother. Approximately 5% of the adult population has had the symptoms of separation anxiety. Separation anxiety may morph into a panic disorder or GAD.

Panic Disorder

Panic attacks occur with a number of physical symptoms that may include feelings of choking, trembling, diaphoresis, racing heart, shortness of breath, chest pain, fears of losing control or dying, numbness, chills or flushing, dizziness, lightheadedness, or fainting. Panic attacks usually reach their peak quickly, and last minutes to 1 or 2 hours. While they may be triggered by situations such as having to speak in public, they often occur without any obvious external trigger. Panic attacks may occur with agoraphobia, which involves a fear of situations where escape is not easy. These include public places and crowds, public transportation, highway driving, being on a bridge, or in an elevator or other enclosed space, being far from home or alone, or being stuck at a party. Agoraphobia such as this may occur without panic disorder.

Generalized Anxiety Disorder

GAD involves excessive worrying, which may be about school, work, family, health, finances, or the outside world. With GAD, most people worry on a daily basis, not just occasionally. To diagnose GAD, the worrying must have been present for at least 6 months. People with GAD don't worry about just one facet of life, but many things. The worry becomes completely out of proportion to the significance of the problems. They also feel the physical aspects of anxiety, such as feeling "keyed up," having concentration problems, insomnia, irritability, anger, or fatigue. Approximately 5% to 6% of the population suffers from GAD. It is more common in women than in men.

Social Anxiety Disorder

Social anxiety disorder, also known as SAD, is common during adolescence, particularly with the onset

of dating, parties, and other social events. It may persist into the adult years. Public speaking is difficult for those with SAD, and this and other triggers can lead to avoidant behavior. Approximately 12% of the population experiences SAD at some point.

Obsessive-compulsive Disorder

OCD often has an onset in early adolescence. The obsessions are intrusive, and distressing thoughts become focused on one or more concerns: germs or other contaminants, a need to have things arranged perfectly, a fear of hurting someone close, somatic (body) obsessions, hoarding, or sexual or religious obsessions. Compulsions are actions that reduce the person's anxiety somewhat, and are triggered by the obsessions. Compulsions can take the form of obsessive checking (particularly things like locks or a stove), repeated cleaning routines, repetition of words, prayers or actions, counting, or arranging objects over and over. As with most anxiety symptoms, OCD may wax and wane over time.

Post-traumatic Stress Disorder

This occurs following one or repeated traumas, such as abuse of various types, a serious accident, combat, being in a fire, etc. Symptoms of post-traumatic stress disorder (PTSD) include reliving the trauma through flashbacks or nightmares, and subsequent avoidance of certain situations. PTSD may lead to feeling detached, or having amnesia for certain parts of the trauma. Hypervigilance may occur, with increased arousal and insomnia, concentration problems, anger, and a marked startle response. Approximately 6% to 7% of the population has had PTSD.

The Limbic System

A propensity to anxiety is a physical, inherited illness, as is migraine. It is not psychological! By viewing certain key structures in the brain, such as the amygdala, one can almost predict who has anxiety. Even at age 5, in a child with separation anxiety, the amygdala is larger than normal and fires more often. Anxiety could almost be termed "the overactive amygdala syndrome."

The amygdala is part of the larger limbic system, which includes the thalamus, hippocampus, hypothalamus, along with the anterior cingulate gyrus and the orbitofrontal cortex. The amygdala warns of incoming dangers, after processing multiple incoming sensory inputs. Amygdala connections are vast, with direct connections to:

1. The hypothalamus, triggering fight-or-flight responses
2. The locus ceruleus (in the pons), increasing the output of norepinephrine, with a resulting rise in blood pressure, heightened response to fear, and level of alertness
3. Various other structures, such as the periaqueductal gray matter, modulating aspects of our fear response. The amygdala regulates the tone of our emotions, and is hyperreactive in anxious patients

The hypothalamus initiates our fear response; when it overreacts, the resultant anxiety is out of proportion to the actual threat. The hypothalamus may trigger an overproduction of corticotrophin release factor, adding to the anxiety response. The thalamus is our integrating relay station, with a vital direct connection to the amygdala. The thalamus controls many brain functions, and its amygdala connection initiates our stress response. The thalamus plays

a vital role in regulating sleep and eating patterns, which often are disrupted in anxious patients. The hippocampus is crucial for memory, and it holds the memories that trigger the fear response. The hippocampus is important in the development of PTSD by holding onto the traumatic memories.

Treatments of Anxiety In Pain Patients

Non-pharmaceutical Approaches

Pharmacotherapy is important in treating anxiety, but it is by no means the only treatment. For those with severe pain and psychologic comorbidities, “it takes a village” to treat a patient, which may include psychotherapists, yoga or Pilates instructors, biofeedback specialists, etc.

Taking medicine alone is considered passive coping and is not sufficient for those with severe anxiety. People are best off when they exercise regularly, and learn relaxation techniques, whether they are based in yoga, Pilates, tai chi, deep breathing, biofeedback, or meditation. We need to promote this “active coping” as a vital component of treating chronic pain and anxiety. The addition of psychotherapy, primarily cognitive/behavioral, is also important. It is vital to locate an excellent therapist, and for the patient to stick with that therapist for at least 4 to 6 months. While short-term therapy is better than no therapy, we believe that the ideal time frame is 1 or more years. It takes some time to integrate the ideas of therapy into our lives. Self-help books, while somewhat useful, do not replace a great therapist; neither does talking to a close friend or relative. A great therapist can be life-changing.

Medications for Anxiety

Benzodiazepines

Benzodiazepines are a well-recognized treatment for anxiety, and

are best used for acute anxiety, or a panic attack. Alprazolam is the most effective benzodiazepine for panic attacks, and is best used on an “as needed” basis. The lowest effective dose should be used; usual doses are 0.25 mg to 1 mg (start with ½ or 1 of the 0.25 mg tablets) as needed. Alprazolam should be limited and the patient closely monitored for overuse. Limited quantities should be prescribed.

At times, in a minority of patients, daily benzodiazepines are warranted. The usual situation is when the patient cannot tolerate non-addicting approaches, such as the antidepressants. For insomnia, the occasional patient will only do well with a benzodiazepine, such as clonazepam (Klonopin). Diazepam (Valium) has anti-anxiety and muscle-relaxant properties. Patients must be warned of the dangers of overuse and of combining these agents with alcohol or opioids, as well as the difficulty patients may encounter on withdrawal. For some highly anxious patients, the only medication tolerated is a benzodiazepine.

Antidepressants: Tricyclics

The older tricyclic antidepressants (TCAs) are more useful for certain types of pain (particularly headaches) than are the SSRIs or SNRIs. We will often use a TCA in anxious pain patients in an attempt to treat both their anxiety and migraine in order to minimize medication use. The prototype tricyclic is amitriptyline (Elavil). Amitriptyline is inexpensive, and is useful for chronic daily headache, migraine, neuropathy, fibromyalgia, etc. We recommend that clinicians start with very low doses of amitriptyline, taken at night, 5 mg (½ of a 10 mg tablet), slowly increasing to 20 or 25 mg per day. Doses may be increased to 100 mg (or more), but

side effects may limit its usefulness. These include sedation, dry mouth, constipation, dizziness, weight gain, and urinary retention. Other TCAs include nortriptyline, a milder form of amitriptyline; doxepin, which has fewer side effects and is helpful for insomnia; and protriptyline (Vivactil). Protriptyline is one of the few TCAs that does not cause weight gain, but anticholinergic effects limit its use.

Antidepressants: SSRIs and SNRIs

Because of the potential for adverse events, the newer SSRIs and SNRIs are often favored over the older TCAs. The major SSRIs differ somewhat in their side effect profile. Some patients do extremely well with one SSRI, but not with another. The most common side effects include nausea, spaciness, drowsiness or fatigue, dry mouth, anxiety, insomnia, decreased libido, impotence, asthenia, sweating, constipation, tremor, diarrhea, and anorexia. In addition, weight gain may be a major problem. In fact, weight gain and sexual side effects are the most common reason to discontinue an SSRI. Any of the SSRIs can decrease motivation.

Since many of the adverse events are dose related, one key to minimizing side effects is to begin with low doses—“start low and go slow” (Table 1, page 30). Minimizing the dose can, for instance, decrease the sedation or sexual side effects. Compliance is enhanced when the SSRIs are slowly titrated. The initial anxiety seen with SSRIs often abates if low enough doses are used.

At times, we will use a combination of older TCAs (usually at night) and SSRIs in the morning. One of the SNRIs, duloxetine, has several pain and GAD indications, making it a useful tool for treating the comorbid migraine patient. Table 2 (page 32) highlights the more effective

Table 1. Keys to Using Antidepressants in Comorbid Anxiety and Pain Patients

- Start with very low doses. This minimizes sedation and anxiety and increases compliance. If the patient is bipolar, SSRIs are best avoided.
- If patients are warned about the initial anxiety that may occur with SSRIs, they are more likely to be compliant and stay on the medication.
- For most headache patients, lower doses are utilized than for severe depression.
- If one SSRI does not help or causes side effects, it is often worthwhile to try another. Patients have widely differing responses to these medications.
- Slowly withdraw patients in order to avoid withdrawal syndrome.
- If the headaches are exacerbated, discontinue the SSRI.
- Paroxetine (Paxil), fluoxetine (Prozac), and duloxetine (Cymbalta) have more drug interactions than the others. These are all cytochrome P450 2D6 inhibitors.

SSRIs, selective serotonin reuptake inhibitors

SSRIs and SNRIs for mood and headaches listed below.

The Major SSRIs

These are more effective for moods than for headaches.

Fluoxetine (Prozac, generic) is available in 10, 20, and 40 mg pulvules; 10 mg scored tablets; or liquid (20 mg/5 mL). Prozac Weekly is a once per week capsule, equal to 20 mg daily. Fluoxetine is the prototype SSRI, having been used in tens of millions of people. Fluoxetine is a long-acting SSRI with a well-established track record. Its elimination half-life is 4 to 6 days, but the active metabolite, norfluoxetine, has an elimination half-life of 4 to 16 days. The long half-life is generally an advantage in avoiding the SSRI withdrawal

syndrome. It is important to start with low doses of SSRIs; 5 or 10 mg of fluoxetine is a good starting point. Many patients report initial anxiety (or even panic) from SSRIs, and if they are on a low enough dose, they are less likely to discontinue the medication. Patients can begin with ½ a tablet of 10 mg fluoxetine. Over 4 to 10 days, the dose may be raised to 10 or 20 mg. The effective dose for migraine or tension headache varies widely, from 5 mg per day to 60 mg (or more). Formal studies on fluoxetine for headache prevention have yielded mediocre results. Most patients are on 20 mg daily. Milder tension-type headache often responds to low doses (10 or 20 mg). As is true with TCAs, lower doses of SSRIs are used for headache

than for major depression. In some patients, SSRIs actually exacerbate headaches. Fluoxetine is an inhibitor of the cytochrome P450 (CYP450) 2D6 system, and to a lesser extent, CYP450 3A4.

Sertraline (Zoloft, generic) is available in 25, 50, and 100 mg scored tablets. Sertraline is somewhat shorter-acting; elimination half-life is 26 hours of the parent drug and 62 to 104 hours of the active metabolite. Because the half-life is shorter than with fluoxetine, patients are occasionally able to stop sertraline for 1 or 2 days and alleviate the sexual side effects. However, with the shorter half-life, withdrawal syndrome is occasionally seen with sertraline. I usually start with 25 mg, or ½ of a 25 mg tablet, and slowly increase; the average antidepressant dose is 75 to 150 mg, but the usual headache dose is approximately 50 mg. While many patients are on 100 mg or more for headaches, most patients are maintained on lower doses. The cost of the 50 mg and 100 mg tablets is approximately the same. In higher doses, sertraline is a CYP450 2D6 and 3A4 inhibitor.

Paroxetine (Paxil, generic) is available in 10, 20, 30, and 40 mg tablets. Paxil CR (controlled release) is available in 12.5 and 25 mg doses. The elimination half-life is 21 hours, with no active metabolite. Paroxetine is generally very well tolerated. I usually begin with ½ of a 10 mg tablet and slowly increase to 10 or 20 mg; many patients need 30 to 60 mg for depression. Another option is starting with 12.5 mg CR and titrate as needed to 25 mg CR. It is important to stop paroxetine slowly in order to minimize withdrawal. Paroxetine (SSRI) withdrawal consists of one to several days (and occasionally longer) of flu-like symptoms, malaise, dizziness, and asthenia. This

often goes unreported to the physician. Managing the withdrawal can be difficult; at times, the addition of fluoxetine may help in weaning off of the short-acting SSRI. Paroxetine is a potent inhibitor of the CYP450 2D6 system and, to a lesser extent, 3A4.

Citalopram (Celexa, generic) is available in 20 and 40 mg tablets, which are scored. The mean terminal half-life is about 35 hours. Citalopram has a clean profile with regard to CYP450 enzymes. It has been an outstanding antidepressant with a very good track record, and is well tolerated. Side effects are similar to the other SSRIs. As always, we start with low doses, half of a 20 mg tablet for 4 to 6 days, then progress to 20 mg per day. Withdrawal symptoms have been unusual with citalopram. Its use has mostly given way to escitalopram, but, due to its lower cost, citalopram is useful.

Vilazodone (Viibryd) is a newer SSRI with a dual mechanism of action. Vilazodone is well tolerated, and patients may have fewer problems with weight gain and sexual side effects. It is available in 10, 20, and 40 mg tablets. We start with ½ or one of a 10 mg tablet, and slowly increase to 20 or 40 mg.

Escitalopram (Lexapro) is a newer, more selective version of citalopram and has been fairly well tolerated. It is metabolized primarily by the liver. Escitalopram has a favorable side effect profile, but side effects are similar to the other SSRIs. Escitalopram is available in 10 and 20 mg tablets. We start with ½ of the 10 mg tablet for 4 to 6 days, and then increase to 10 mg daily. Withdrawal symptoms are relatively unusual with escitalopram; it is fairly clean as far as drug interactions. Escitalopram has risen to be one of the most prescribed antidepressants in the United States.

The Major SNRIs

Venlafaxine (Effexor XR) and **Desvenlafaxine** (Pristiq) are major SNRIs. The long-acting venlafaxine is available in 37.5, 75, and 150 mg doses. Venlafaxine has been an outstanding antidepressant because of efficacy and tolerability. A generic is available, but does not consistently work as well. Desvenlafaxine is a newer form of venlafaxine, which is very well tolerated. It is available in 50 and 100 mg doses, and is usually started at 50 mg; the final dose ranges from 50 to 100 mg per day.

Basically, venlafaxine and desvenlafaxine are SSRIs at low doses; at higher doses, levels of norepinephrine, rather than dopamine, are affected. They are very well tolerated, with less weight gain and sexual side effects than some of the other antidepressants. Venlafaxine has few interactions with CYP450 enzymes, rendering it a fairly clean medication. We usually begin with 37.5 mg and progress to 75 mg, with a typical dose in headache patients being 75 mg or 150 mg. Effexor XR is particularly well tolerated. It is very useful in headache patients who have concurrent anxiety and depression. Sustained elevation in blood pressure may occur at higher doses, particularly 250 mg or more per day. The lower doses have not increased blood pressure. While headache is a potential side effect of venlafaxine and desvenlafaxine, it has been no more so than the rate of placebo in studies. Nausea, constipation, somnolence, dry mouth, dizziness, insomnia, and agitation are seen more than in placebo. However, if doses remain low, venlafaxine and desvenlafaxine are well tolerated. While venlafaxine and desvenlafaxine are less effective than TCAs for pain or headache, their efficacy in anxiety and depression, and their

tolerability, render them extremely useful medications.

Duloxetine (Cymbalta) has three FDA pain indications, and is a very effective antidepressant. Duloxetine increases both serotonin and norepinephrine. It is available in 20, 30, and 60 mg capsules. Duloxetine may be helpful for headache, as well as for anxiety/depression. The usual dose is 60 mg daily for depression; starting dose is 20 or 30 mg, increasing over several days to weeks. Side effects include, among others, nausea, dry mouth, anxiety, fatigue, lethargy, sexual effects, and weight gain. Use with caution in patients with glaucoma. Duloxetine is a moderate CYP450 2D6 inhibitor. It has been much more effective for moods (including anxiety and depression) than for pain.

Miscellaneous Medications

In addition to antidepressants and benzodiazepines, various other medications are useful on occasion.

For those migraine patients on the bipolar spectrum, antipsychotic medications, such as quetiapine (Seroquel) and aripiprazole (Abilify), are often used. These two medications can be particularly helpful for the management of anxiety and depression.

Certain anticonvulsant agents may be of benefit. Gabapentin increases the neurotransmitter γ -aminobutyric acid (GABA), which calms the brain. Gabapentin may decrease certain types of pain, and some patients find it helpful for anxiety or insomnia. Pregabalin (Lyrica) is a newer form of gabapentin, and may be beneficial.

Muscle relaxants are useful in some anxious patients. Preference is given to the non-addicting muscle relaxants, such as cyclobenzaprine. These may be helpful for associated insomnia.

Table 2. Major SSRIs and SNRIs for Anxiety in Pain Patients

Drug Name (Brand)	Formulation	Usual Dosage	Comments
SSRIs			
Citalopram (Celexa, generic)	Oral tablet	½ of a 20 mg tablet/d for 4-6 d (initial dose); may go up to 40 mg/d	Effective and well tolerated antidepressant. Mean terminal half-life is ≈35 h; has a clean drug–drug interaction profile (ie, cytochrome P450 enzymes). Side effect profile similar to other SSRIs.
Escitalopram (Lexapro)	Oral tablet	½ of a 10 mg tablet/d for 4-6 d (initial dose); limit to 30 mg/d	Well tolerated with a favorable side effect profile similar to other SSRIs. Fairly clean drug–drug interaction profile.
Fluoxetine (Prozac, others)	Oral tablet, oral pulvule, oral liquid	5 or 10 mg/d for 4-10 d (initial dose); limit to 80 mg/d	Well-established, long-acting SSRI; half-life is 4-6 d—an advantage in avoiding SSRI withdrawal syndrome. Important to start with low doses so patients are less likely to discontinue the medication.
Paroxetine (Paxil, generic)	Oral tablet and oral CR tablet	Oral tablet: ½ of a 10 mg tablet/d (initial dose); limit to 30 mg/d Oral CR tablet: 12.5 mg tablet/d (initial dose); limit to 25 mg/d	Well tolerated with no active metabolite and a shorter half-life of 21 h. Discontinue slowly to minimize withdrawal symptoms, which can include flu-like symptoms, malaise, dizziness, and asthenia. Adding fluoxetine may help wean patient off.
Sertraline (Zoloft, generic)	Oral tablet	½ of a 25 mg tablet/d (initial dose) Average dose for antidepressant: 75 to 150 mg/d Average dose for headache: 50 mg/d	Shorter half-life (26 h). Patients can usually stop sertraline for 1-2 d and alleviate sexual side effects. Due to short half-life, withdrawal syndrome is occasionally seen.
Vilazodone (Viibryd)	Oral tablet	5 or 10 mg tablet/d (initial dose); up to 40 mg/d	Newer SSRI with dual mechanism of action. Is well tolerated, and may have lower incidence of weight gain and sexual side effects.

Table 2. Major SSRIs and SNRIs for Anxiety in Pain Patients

Drug Name (Brand)	Formulation	Usual Dosage	Comments
SNRIs			
Desvenlafaxine (Pristiq)	Oral capsule	50 mg capsule/d (initial dose); up to 100 mg/d	Highly effective and tolerable antidepressant. Useful in headache patients who have concurrent anxiety/depression. Side effects include nausea, constipation, somnolence, dry mouth, dizziness, insomnia, and agitation. At lower doses, is classified as an SSRI.
Duloxetine (Cymbalta)	Oral capsule	20 or 30 mg capsule/d (initial dose); 60 mg/d is usual dose for depression	Very effective antidepressant and has 3 FDA pain indications. May benefit both headache and anxiety/depression. Side effects include nausea, dry mouth, anxiety, fatigue, lethargy, sexual effects, and weight gain. Use with caution in patients with glaucoma.
Venlafaxine (Effexor XR, generic)	Oral capsule	37.5 mg capsule/d (initial dose); 75 or 150 mg/d is usual dose for depression	Highly effective and tolerable antidepressant. Useful in headache patients who have concurrent anxiety/depression. Side effects include nausea, constipation, somnolence, dry mouth, dizziness, insomnia, and agitation. At lower doses, is classified as an SSRI.

CR, controlled release; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors

Conclusion

Anxiety is commonly encountered in pain and headache patients. Like migraine, anxiety is an inherited physical condition. In headache patients, pain may fuel anxiety, and anxiety may increase the pain. With medications, the antidepressants remain the mainstay of preventive treatment; the benzodiazepines are used sparingly. A variety of non-medicine approaches should

also be used in treatment, such as psychotherapy, yoga, exercise, etc. For quality of life, it is crucial to treat anxiety and other psychiatric comorbidities in addition to treating the pain. ■

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