Chapter 5
Psychological Comorbidities

Anxiety in a Headache Patient

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 h. 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 do not 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, 5–6% of the population suffers from GAD. It is more common in women than in men.

**Social Anxiety Disorder**

Social anxiety disorder 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 Social anxiety disorder, and this and other triggers can lead to avoidant behavior. Approximately 12% of the population experiences Social anxiety disorder 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.

**Posttraumatic 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 posttraumatic 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, 6–7% 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
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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**

**Nonpharmaceutical 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 4–6 months. While short-term therapy is better than no therapy, we believe that the ideal timeframe 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 0.25–1 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 nonaddicting approaches, such as the antidepressants. For insomnia, the occasional patient will only do well with a benzodiazepine, such as clonazepam (Klonopin). Diazepam (Valium) has antianxiety 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 5.1). 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 5.2 highlights the SSRIs and SNRIs. 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.
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**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 4–6 days, but the active metabolite, norfluoxetine, has an elimination half-life of 4–16 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 4–10 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. 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, 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 h, with no active metabolite. Paroxetine is generally very well tolerated.

**Sertraline** (Zoloft, generic) is available in 25, 50, and 100 mg scored tablets. Sertraline is somewhat shorter acting; elimination half-life is 26 h of the parent drug and 62–104 h 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 75–150 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 and 100 mg tablets is approximately the same.

**Table 5.1** Keys to using antidepressants in comorbid anxiety and pain patients

<table>
<thead>
<tr>
<th>Key</th>
<th>Description</th>
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<tbody>
<tr>
<td>Start with very low doses. This minimizes sedation and anxiety and increases compliance. If the patient is bipolar, SSRIs are best avoided.</td>
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<tr>
<td>If patients are warned about the initial anxiety that may occur with SSRIs</td>
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<tr>
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<tr>
<td><strong>Paroxetine</strong> (Paxil), fluoxetine (Prozac), and duloxetine (Cymbalta) have more drug interactions than the others. These are all cytochrome P450 2D6 inhibitors</td>
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SSRIs selective serotonin reuptake inhibitors
I usually begin with ½ of a 10-mg tablet and slowly increase to 10 or 20 mg; many patients need 30–60 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 h. 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 4–6 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 4–6 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 USA.

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 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 Food and Drug Administration (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
Anxiety in a Headache Patient

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.

Newer Antidepressants

Fetzima and Brintellix are relatively new; Fetzima is unusual in that it has more norepinephrine activity than the typical SNRI (more norepi than serotonin); this may be useful for avoiding fatigue and weight gain, but it may be more activating (norepi is activating, serotonin more calming). Brintellix has unusual 5HT-7 properties; the jury is out as to the place both of these newer medications will have in treating anxiety.

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 nonaddicting muscle relaxants, such as cyclobenzaprine. These may be helpful for associated insomnia.

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 nonmedicine 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. Note this is an update of an article originally published in PPM, Vol. 12, May, 2012.
Psychological Comorbidities

Attention-Deficit Hyperactivity Disorder and Patients with Pain

A growing number of patients with chronic pain are presenting with attention-deficit hyperactivity disorder (ADHD). Clinicians need to understand how the disorder is diagnosed in adults, as well as how to balance various medications required to treat both ADHD and pain.

Along with anxiety and depression, ADHD is a common comorbidity among patients with chronic pain. Although most commonly diagnosed in childhood, ADHD is seen in approximately 4.7% of adults [7].

ADHD has become a well-recognized and validated syndrome, known for the havoc it can create in patients’ lives. The public is increasingly aware of ADHD, and more of our patients arrive at the clinic with that diagnosis. The current criteria relate primarily to children and adolescents and are not entirely applicable to an adult population. Because more patients carry the diagnosis and are on ADHD medications (primarily stimulants), it is important for pain physicians to be aware of the consequences of the disorder. In addition, it is helpful to be aware of interactions between ADHD and pain medications.

**Diagnosis of ADHD in Adults**

The diagnosis of ADHD includes the patient’s history along with corroborating evidence: educational records and history, family or significant other’s input, and so forth. In my experience, most patients who carry the diagnosis of ADHD from childhood have been correctly diagnosed; although there is occasional overdiagnosis of ADHD, underdiagnosis remains more prevalent.

The standard criteria for the diagnosis of ADHD require that the symptoms have lasted for at least 6 months [4]. One objective test that we have found useful is the Adult Self-Report Scale (ASRS) [14], which is an 18-item questionnaire. The first nine questions relate to attention, the remaining nine to hyperactivity. Using the first nine questions gives the clinician an easy screen for ADHD and requires only minutes to administer. The attention portion of the ASRS gives a score of 0–36, with 36 being the most severe. This scale or similar ones, along with the clinical and educational histories, helps to determine the diagnosis.

An important question to ask the patient is, “How difficult is it for you to do boring tasks?” People with ADHD have great difficulty with boring material. To aid the diagnosis, I often have the patient read books or other materials on adult ADHD so that they can provide better-informed input into the diagnosis.

The three primary features of ADHD (attention, hyperactivity, and impulsivity) do change over time. As patients approach adulthood, hyperactivity often decreases, whereas impulsivity may cause more problems for adults than for children. There-
fore, using hyperactivity as a measure of ADHD may not be valid in adulthood; many children and adolescents “lose” the “H” (hyperactive) portion of ADHD and present as the inattentive type.

ADHD adversely affects adults in their family and work life; these are not addressed by the current criteria. The age of onset is usually by age 7 but not always. Some patients have a somewhat older age of onset for ADHD symptoms.

In children, parents’ and teachers’ input is crucial. In adults, we often utilize the patient’s recall for assessment in addition to asking someone who knows the person well. There are pitfalls in assessing adults; for example, we must not compare the patient with a high-functioning, high-IQ peer group, but rather with normal or average people. In addition, particularly in college students, the desire to excel on examinations or improve scores does not qualify them to be diagnosed as having ADHD.

Mood disorders may cause an attention/concentration problem in adults, leading to an inappropriate diagnosis of ADHD. However, most patients with ADHD do have associated psychiatric comorbidities, such as anxiety or depression. Many who fit on the bipolar spectrum can have concurrent ADHD. It is important to assess for all of these conditions.

**ADHD and Impairment**

Adult patients with ADHD are often impaired in several categories. They may have done poorly in school, leading to problems with their work and career. Home life is adversely affected, with problems accomplishing daily responsibilities. Relationships are negatively affected by ADHD, and family life often falls apart as a result. The severity of childhood/teen ADHD is an accurate predictor of impairment as an adult. Young children who are constantly restless and cannot wait their turn in line, for example, often show more impairment as young adults. ADHD increases the likelihood of driving accidents and also of drug or alcohol abuse. It is probably not true that ADHD allows one to excel in certain areas; the evidence speaks more for impairment than for any positive outcome for those with ADHD, particularly if it is not treated.

The associated psychiatric comorbidities add to impairment, particularly if they are not treated. These include anxiety, depression, bipolar depression, and substance abuse.

The evidence is strong for treating ADHD. Compared with treated patients, untreated ADHD greatly increases the risk, at age 20–25, for drug abuse, accidents, joblessness, and jail. The clinical stakes for under-recognizing and undertreating ADHD are enormous. If impulsivity does not improve by the early 20s, it is a poor prognostic indicator for how the patient will do over time.
**ADHD and the Patient With Pain**

ADHD complicates the lives of patients with pain. The patient struggles with functional impairment due to pain, and ADHD adds to this dysfunction. Education often suffers because of pain; students take longer to complete their degree, and the addition of the negative impact of ADHD can make completion impossible. Family life is adversely affected, as spouses may tire of the burden of pain complaints, along with the various ADHD symptoms. Chronic pain often leads to joblessness or underperforming at work; ADHD only accentuates this problem. In a patient with chronic pain and ADHD and, for instance, anxiety and depression, we commonly encounter a person who is underfunctioning in a number of areas.

**ADHD Medications**

The “first-line” medications for ADHD are stimulants [13,24, 25]. The most commonly used stimulants include methylphenidate (Concerta, Ritalin, Ritalin LA, Focalin, and others: generics available), dextroamphetamine (Dexedrine, others: generics available), amphetamine and dextroamphetamine (Adderall, Adderall XR: generic available for these), and lisdexamfetamine (Vyvanse). The longer-acting forms are Adderall XR, Vyvanse, Ritalin LA, Focalin XR, Daytrana, and Concerta. Side effects of these agents include, among others, anxiety, insomnia, tachycardia, and, occasionally, increased headache. The stimulants have mild analgesic effects and in some may be an adjunct for the pain. In addition, some patients with depression find that the stimulants act as an adjunct for the depression, whereas in others they may actually exacerbate depression. Fatigue is a common comorbidity encountered in patients with pain, and stimulants may help patients’ energy level during the day. In addition, the anorexiant effects are beneficial for some patients with pain, as obesity and weight gain are commonly encountered among these patients.

The stimulants may improve attention, energy level, pain, and depression as well as decrease appetite. However, many patients cannot tolerate them because of adverse effects. In addition, patients with pain are usually on various medications, with possible interactions. For instance, patients with pain often are taking antidepressants, with resulting tachycardia when combined with stimulants. When patients with pain are utilizing daily opioids, adding a stimulant contributes another potentially addicting medication. Fortunately, addiction to stimulants among adults with ADHD is uncommon.

When stimulants are not appropriate or not tolerated, there are various “second-line” medications for ADHD. The $\alpha_2$-adrenergic agonists (guanfacine ER [Intuniv], clonidine [Kapvay]) are primarily utilized in children and adolescents. Various antidepressants have been successfully used for ADHD. These include the older tricyclics (desipramine, nortriptyline) as well as bupropion. These may be appropriate with concurrent anxiety or depression. Atomoxetine (Strattera), an
SNRI, is used as a second-line medication for ADHD and is very similar to the tricyclic desipramine, which also increases norepinephrine. Although these medications are not as effective as the stimulants, they offer several benefits. These include the advantage of not being addictive, and, when used as once-daily medications, they are longer acting.

**Nonmedication Treatments**

In addition to medications, we often refer patients to psychotherapy. Although therapy does not improve attention itself, the patient benefits in a number of ways. These include help with associated anxiety/depression, family life, relationships, organization, and work life. A good therapist who is acquainted with pain and ADHD can play a crucial role in improving functioning and quality of life.

It is important to work on sleep issues and diet. In addition, as with almost all patients, we supplement with at least 2000 units of vitamin D$_3$. We stress the role of exercise, advising patients to try to build up to 20–30 min daily on average.

**Conclusion**

ADHD is commonly encountered, seen in $4.7\%$ of adults. The various symptoms complicate the lives of patients with pain. The clinical stakes for not recognizing ADHD are enormous; patients often underperform at work, have poor family relationships, and are at increased risk for substance abuse. Treatment with medications, primarily stimulants, improves quality of life and functioning. In addition, psychotherapy plays a role, as does stressing the role of sleep, nutrition, and exercise. Note this is an update of an article originally published in *Practical Pain Management*, Vol. 11, November 2011.

**Personality Disorders and the Bipolar Spectrum: Recognition and Management in a Pain Clinic Setting**

**Introduction**

Patients with moderate-to-severe personality disorders (PD) may wreak havoc on an unsuspecting medical office. It is increasingly important to recognize, limit and manage those with aggressive types of PD. Likewise, it is crucial to recognize those who fit the bipolar spectrum. In particular, the mild end of the spectrum is often missed. The clinical stakes for missing bipolar are enormous, as these patients...
tend to bounce from antidepressant to antidepressant, with predictably poor results. This chapter delves into recognition and management of patients whose pain treatment is complicated by psychological concerns.

**Personality Disorders at a Clinic**

Consider the following scenario: a 28-year-old man, “Bill” presents to the pain clinic with severe low back pain. He seems angry on the first visit, and is very demanding with the front office staff. Bill is mistrustful of physicians, and openly states to the doctor, “I will go back to work when you give the right amount of drugs that help.” Bill is upset with his last two health providers.

Over the next few months, the clinic bends over backwards for Bill, even though he can be abusive to the staff. Bill overuses opioids, and is manipulative. He always has a sense of entitlement. When he calls, stating, “I want to talk to Dr. Smith NOW, put me through!” the staff, out of fear, jumps, and does as he asks. The physician finds himself in a subservient position, trying to appease the patient and end the confrontations.

Bill laughs at the idea of seeing a psychotherapist, but after 9 months of treatment, Bill is suddenly blaming everything on the physician and clinic: his pain, his obesity, his sexual dysfunction. Bill threatens to sue, and reports the doctor to the state regulatory office. What happened here?

Bill will be later diagnosed as a paranoid PD. The clinic did not recognize him as such, and failed to set limits on Bill’s behavior. The disruptions in the business of the clinic, the increased stress on the staff, and the monopolization of the doctor’s time cannot be recovered. In the following, we discuss the features of PDs that should help with identification. Better management of the problem starts with recognition.

Approximately, 10–12% of people have features of a PD [15]. There are a number of PDs, and some are more dangerous and difficult than others. In general, characteristics of PDs include lack of insight, poor response to psychotherapy or other therapeutic interventions, difficulty with attachments and trust, a sense of entitlement, and the creation of chaos and distress in family, friends, and coworkers. Comorbid substance abuse is common.

PDs range from mild to very severe. Patients with PDs may take on different roles: victim, rescuer, or persecutor. When they turn persecutor, they can be dangerous to the person they have set their sights on. Seeing a therapist for a long period of time, perhaps 5–7 years, helps to some degree. However, goals and expectations must be limited. The plasticity of the brain is important, as some people can improve naturally over time. The following section describes some of the more severe PD types. However, many people do not fit neatly into any of these categories, but have features of two or three PDs.
Paranoid Personality Disorder This type tends to be nontrusting, suspicious, and sees the world as dangerous. They may seem secretive and reluctant to confide in others. In relationships, they view themselves as being constantly mistreated. They doubt the loyalty of everybody around them, and believe they are being exploited or harmed. These patients bear severe grudges against others. Often, they become angry easily and have a sense of entitlement. Paranoid personalities can become violent and dangerous, as most spree killers are paranoid personalities. Several notorious world leaders, such as Joseph Stalin and Saddam Hussein, were most likely paranoid personalities [16].

Antisocial Personality Disorder These people generally have no regard for the rights of others. In demeanor, they tend to be irritable and impulsive. They are exploitative, see themselves as better or superior, and can be very opportunistic in getting what they want. Antisocials are deceitful, may steal from people around them, and often have trouble with the law. They frequently engage in fraudulent activities and make very good scam artists. For example, one may take on the role of financial savior for a church, and end up stealing everything. They generally have no remorse. Conduct disorder in a child often morphs into antisocial PD. Examples include Tony Soprano on the TV show, and, in real life, the mafia’s “Dapper Don,” John Gotti [16].

Borderline Personality Disorder (BPD) This type of personality shows instability of mood, poor self-image, and pervasive abandonment fears. There is an identity disturbance and major boundary issues. Borderlines usually demonstrate impulsiveness, and very quick shifts from depression to anxiety to irritability. There are usually chronic feelings of emptiness or severe loneliness, plus anger and temper and even suicidal behavior. Under stress, they can become somewhat paranoid. Coexisting problems with drug abuse or other addictive behaviors may occur. There are often sleep disorders with severe insomnia. Severe borderlines will react with high drama and create chaos for everybody around them. They tend to have a split view, which is, they see people as wonderful or terrible, with nothing in between. Examples include Adolph Hitler, Marilyn Monroe, and Glenn Close’s character Alex, in the movie, “Fatal Attraction.” Borderline personality can vary from mild to severe, and become better or worse over time. Suicide becomes more likely as patients age into their upper twenties and thirties[16]. Suicide is also more common within a week of discharge from a psychiatric unit.

Narcissistic Personality Disorder This is less common, and is typified by a personality that sees itself as above others. The personality is grandiose, has a lack of empathy, and feels and acts self-important. There is a deep sense of entitlement. They may be very vain and constantly require admiration. They are envious, arrogant, exploitative, and can be very angry. Examples might include General George Patton, Nicole Kidman’s character in the movie, “To Die For,” Michael Douglas’ character, Gordon Gekko, in the movie, “Wall Street [16].”
There are a number of other PDs that are not as dangerous for the people around them or for health-care providers. Even though PD characteristics may seem extreme, they are often overlooked, and health-care clinics may react by treating these patients in a dysfunctional manner. The problem begins with not recognizing the PD.

Pain and Personality Disorders

One previous study on BPD concluded that BPD comorbidity with migraine is associated with increased disability from the headaches [23]. In addition, among those with BPD, there was an increase in medication overuse headache, and headaches were more pervasive. There was a higher degree of depression among those with BPD, more unscheduled visits for acute headache treatment, and a lesser chance of adequate response of headache medications. Those with BPD were more severely affected by headaches, and more inclined to be refractory to treatment [23].

Another study indicated that the incidence of BPD was increased in migraineurs [12]. My recent study of 1000 migraineurs indicated that 5.5% of patients had a moderate or severe PD [21]. There is ample evidence that transformed migraine is associated with more prevalent psychopathology, including PD, than is episodic migraine. BPD itself is the mental health equivalent of chronic pain. In my experience, the two most important prognostic indicators for those with PD are impulsivity and substance abuse.

Treatment for those with PD necessitates a caring, but stern, approach. Limits must be set on physician contact, including telephone calls. No abuse of staff should be tolerated. Referral to other health-care providers, particularly mental health professionals, should be suggested. Psychotherapists and psychiatrists who are experienced with this population are vital if the patient is to be adequately managed. Many of the PD patients do not do well with traditional, insight-oriented therapy treatment, but are better managed long-term with dialectical behavioral approach. For a therapy to be beneficial, it must be consistent and long term. A psychoeducational approach may also help. Unfortunately, many PD patients will not continue in therapy, even with encouragement and support. Our therapeutic goals for the PD patient are relatively modest.

It is easy to become drawn into the drama surrounding patients with PDs, particularly those with BPD. The patient with BPD may grant his doctor power, but then subvert the therapy. An example of this would be, “Doctor, you are the greatest, only you can help me. These headaches ruin my life, … and I know that nothing is going to work!” Some physicians are able to manage these patients without becoming involved in the drama and countertransference, but most do not do well with these patients. If there are signs of a dangerous PD from the first visit or phone call to the clinic, with abuse and anger showing at times, it is better to refer the patient than to become enmeshed in the relationship.
There are risks inherent in caring for those with certain PDs. As compared to the general population, those with BPD are at increased risk for suicide, particularly as they progress into middle age. Identifiable risk factors for suicide among BPD patients include repeated hospitalizations (five or more), a recent psychiatric hospitalization, and, among adolescents, birth trauma [16]. Certain types of PD (paranoid, narcissistic, antisocial, and borderline) are more likely to become angry and vengeful with their health-care providers, resorting to lawsuits or letters to the departments of regulation. Violence may also be a threat. A PD patient often enters as a victim, then rapidly flips into the role of persecutor. Their anger becomes intently focused, creating a stressful environment for health-care workers. Setting limits and keeping careful documentation are important in these situations.

It does take a village to help a patient with a PD, just as it does to adequately treat those with severe pain. It is important to recruit others, such as mental health providers, physical therapists, biofeedback therapists, etc., to aid in the treatment. Medications, though limited, may be beneficial for the impulsivity, aggression, self-mutilation, anxiety and depression components of PD [16]. While there are no specific medications indicated for those with PD, the Axis I symptoms are more amenable to pharmacotherapy. Antidepressants, mood stabilizers, and antipsychotics may ameliorate symptoms. Some of these medications may also lessen headache pain as well. PD patients with severe, chronic pain present additional challenges for treatment. It is important to limit and closely monitor addicting medications. Particularly with BPD, opioids and benzodiazepines are best avoided. The diagnosis of a moderate or severe PD alters both our goal and approach.

**Bipolar Disorder**

The clinical spectrum of bipolar disorder is an evolving concept. The milder end of the spectrum often is misdiagnosed as “regular” depression. For example, the important hypomanic reaction to an antidepressant has not been included in the DSM in helping to determine bipolarity [3]. Some authors feel DSM has an inherent bias toward diagnosing PDs, rather than bipolar disorders. These biases lead to bipolar disorders being missed or underdiagnosed. The name, “bipolar,” is unfair and misleading; the stigma inhibits the diagnosis. We need books and materials aimed at patients with symptoms at the milder end. When we label people with the term “bipolar,” (or worse, “manic-depressive”) and then prescribe “antipsychotic” drugs, it is no wonder patients resist the diagnosis.

Mania is better recognized than is hypomania (with milder bipolar features.) Symptoms of mania include euphoric mood, distractibility, flight of ideas, grandiosity, thoughtlessness or risk taking, and excessive involvement in pleasurable activities (i.e., sex, spending, gambling). Also, pressured speech, an increase in activities, excited (or irritable) energetic mood, and insomnia are indicators [2]. It is the milder end of the bipolar spectrum that tends to be missed. Look for those with persistently
agitated personalities, with frequent depression or excessive energy, and those with a strong bipolar or depressive family history. They may not remember a clear hypomanic or manic episode. To aid the diagnosis, it is vital to speak with a close family member; some 40% of hypomanias are missed if one simply talks to the patient. Mild bipolar signs include: early depression (as early as the teens), severe bouts of depression, quick onset depression, bipolar reactions to certain meds (complaints of being up all night, mind racing, etc.), agitation and anger, very high anxiety, poor response to medication, and moody personality. Sleep disorders are commonly seen. Cycles of brooding, irritable pessimism may be a manifestation of hypomania. Cyclical depression, for no clear reason, is common for bipolar depression, and may be accompanied by high anxiety. Depression is the primary problem with bipolar; it is much more pervasive than are the highs of hypomania. Left untreated, patients with bipolar often self-medicate.

As an example, consider “Jane,” a 44-year-old woman with a history of depression since age 16. Her mom was depressed and an alcoholic; Jane’s uncle committed suicide. In addition to the depression, Jane suffers from fibromyalgia. She tends to be irritable and angry, and self-medicates with prescription opioids and alcohol. Jane saw her family physician, who prescribed fluoxetine for her symptoms. After the first dose she was, “up all night and felt crazy, like my mind was going 95 miles an hour.” So, instead of fluoxetine, sertraline was prescribed, and the same response occurred. Jane also had similar hypomania from pseudoephedrine and corticosteroids. She finally was diagnosed as bipolar II, and was placed on lamotrigine, but then developed a rash. Quetiapine was tried, but Jane seemed overly sedated. Eventually, small doses of lithium improved Jane’s moodiness by 50%, without the extreme side effects.

The therapeutic implications for not recognizing bipolarity are substantial. Patients such as Jane, when undiagnosed, are often given a number of antidepressants, with predictable hypomanic results. The TCAs appear to have the highest propensity towards triggering mania, followed by the SSRIs. Any antidepressant can provoke hypomania (or full mania) in someone who is bipolar. The best results seem to come from a combination of mood stabilizers with antidepressants, although the role of antidepressants remains controversial. The diagnosis is a crucial step, but treatment for the bipolar patient is not always easy or successful. While psychotherapy usually is helpful, many patients are reluctant to go for therapy, often due to time or money constraints.

Comorbidity of migraine with anxiety and depression is well established, both in clinically based studies and in epidemiologic samples from community populations [19]. The physiologic overlap between migraine and depression is considerable. Antidepressants or mood stabilizers help both conditions. In the vast majority of migraine patients who suffer from depression, anxiety is a complicating factor. The anxiety disorder often precedes the age of onset of migraine, with depression following afterward. It is possible that poorly controlled migraines may fuel the onset of depression, or that depression may, at times, increase headache. However, it is more likely that shared environmental and genetic factors link migraine and depression.
The relationship between bipolar illness and migraine has not been as well studied as depression and migraine. However, in several studies, bipolar I and bipolar II were found to be increased in migraineurs \[8\]. I previously assessed 1000 consecutive migraineurs. The results were as follows: bipolar I: 2.1%; bipolar II: 2.4%; cyclothymic disorder: 1.3% bipolar disorder not otherwise specified: 2.8%; and total bipolar spectrum: 8.6% \[22\].

Other recent studies have confirmed that at least 7% of headache patients fit into the bipolar spectrum, and 30–50% of bipolar patients have migraines \[17, 18\].

Once the bipolar diagnosis is established or suspected, mood stabilizers often are very helpful for both moods and headaches. Divalproex sodium is effective for mania, hypomania, depression associated with bipolar disorder, and for headache prevention. It has been extremely well studied for these conditions and has become one of the primary migraine and chronic daily headache preventives. Lithium carbonate is underutilized; it should be used more often. One or more of the newer antiepileptics may prove to be helpful for bipolar disorders and migraine. Carbamazepine has some utility as a mood stabilizer, but not for migraine prophylaxis. Oxcarbazepine is a milder form of carbamazepine, and may be useful. Oxcarbazepine is now available in a longer-acting form, Oxtellar.

Lamotrigine is becoming one of the most commonly used mood stabilizers. It is one of the few effective medications for bipolar depression \[10\]. Doses must be slowly titrated, due to the one out of 2000–5000 occurrences of toxic epidermal necrolysis, or Stevens Johnson Syndrome.

The atypical antipsychotics are also used for bipolar symptoms \[9\]. When a mood stabilizer is effective, the underlying agitation, anger, or depression improves. Quetiapine has reasonable efficacy data. As a class, the atypicals do carry the risk of metabolic syndrome. Aripiprazole has been effective for many patients, with less sedation and metabolic issues than most of the other atypicals.

Unfortunately, the medications discussed are more effective for the manic and hypomanic symptoms. The depression often goes untreated. Bipolar patients spend the majority of their time in depression, and we need better medications for their benefit. Many patients need two to four different medications; an effective combination might be lamotrigine, lithium, and an antidepressant. Rational polypharmacy is an improvement over monotherapy in treating the various bipolar symptoms. It often takes months or years to reach the “right” balance of medications for any one individual who fits the bipolar spectrum.

**Conclusion**

For patient care, it has become increasingly important to recognize those patients whose psychiatric problems complicate their treatment in a pain clinic. Patients with a PD are more likely to abuse drugs, file lawsuits, or abuse the staff. With PD, setting limits is vital.
For those patients with bipolar symptoms, missing the diagnosis leads to poor outcomes with medication. Instead of mood stabilizers, antidepressants tend to be wrongly utilized, usually with discouraging results for the patient. Recognition that the patient fits the bipolar spectrum is the major key.

Treating patients with chronic pain is challenging enough; for those pain patients who also have psychological comorbidities, it is vital that the psychopathology be attended to, as well as the pain. Note this is an updated version of an article that originally appeared in *Practical Pain Management*, Vol. 8, April, 2008.

**Suggested Reading**