After substance withdrawal, underlying psychiatric symptoms emerge

Prompt identification and treatment can ease suffering

When treating patients who abuse substances, it is important to watch for underlying clinical conditions that have been suppressed, relieved, or muted by alcohol or drugs. Many of these conditions can be mistaken for signs of withdrawal, drug-seeking, or new conditions arising from loss of euphoria from the drug. Prompt recognition of these disorders and use of appropriate non-addictive treatments can prevent “against medical advice” discharges, relapses, and unneeded suffering in many cases.

Because the brain is the target organ, these conditions are either neurologic or psychiatric in nosology. Although psychiatric clinicians might not be familiar with neurologic conditions, quick recognition and treatment is necessary.

Restless legs syndrome and periodic limb movements of sleep

Restless legs syndrome (RLS) has 2 key components: paresthesia and akathisia. Although primarily involving the lower extremities, involvement also can include the upper extremities, torso, and head.

Paresthesia differs from typical neuropathies in that it usually is not painful; rather, patients describe an odd sensation using terms such as ticklish, “creepy-crawly,” and other uncomfortable sensations.

Akathisia is a motor restlessness and need to move. The patient might feel momentary relief by moving or rubbing the extremities, only to have the paresthesia return quickly followed by the akathisia. Generally, reclining...
Withdrawal-emergent syndromes

When a patient withdraws from benzodiazepines or narcotics, restless legs syndrome can emerge

Clinical Point

When a patient withdraws from benzodiazepines or narcotics, restless legs syndrome can emerge.

**Table 1**

<table>
<thead>
<tr>
<th>Medication and dosing</th>
<th>Mechanism of action</th>
<th>Common side effects</th>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin, 100 to 900 mg, 3 times a day</td>
<td>Unknown in RLS</td>
<td>Dizziness, sedation, edema</td>
<td>Severe renal impairment</td>
</tr>
<tr>
<td>Ropinirole, 0.25 to 4 mg, gradually titrated</td>
<td>D2, D3 agonist</td>
<td>Sedation, hallucinations, disinhibition</td>
<td>Severe renal impairment</td>
</tr>
<tr>
<td>Pramipexole, 0.125 to 0.5 mg</td>
<td>D2, D3 agonist</td>
<td>Sedation, hallucinations, disinhibition</td>
<td>Severe renal impairment</td>
</tr>
</tbody>
</table>

PLMS: periodic limb movements of sleep; RLS: restless leg syndrome

is the most prominent position that produces symptoms, but they can occur while sitting.

The cause of RLS is an abnormality of central dopamine or iron, or both, in the substantia nigra; iron is a cofactor in dopamine synthesis. All RLS patients should have a serum ferritin level drawn and if <50 μg/dL, be treated with iron supplementation. Dopamine agonists, such as ropinirole, pramipexole, and carbidopa/levodopa, are effective (Table 1); other useful agents include benzodiazepines such as clonazepam and opioids such as hydrocodone.

When a patient withdraws from benzodiazepines or narcotics, RLS can emerge and cause suffering until it is diagnosed and treated. Typical myalgia in opioid withdrawal can confound the diagnosis. The immediate-release (IR) and extended-release (ER) formulations of gabapentin often are a good choice when treating benzodiazepine or narcotic withdrawal. The side effect profile of gabapentin is relatively benign, with somnolence often reported by non-substance abusers, but it is unlikely that addicts, who have grown tolerant to more potent agents such as benzodiazepines and opioids such as hydrocodone.

Periodic limb movements of sleep (PLMS) essentially is akathisia during sleep, and occurs in most patients with RLS. The patient feels tired in the morning because of lack of deep stage-N3 sleep. Because of the inverse relationship between serotonin and dopamine, most selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors can exacerbate RLS and PLMS. Other culprits include antipsychotics, antiemetics, and antihistamines. The differential diagnosis includes withdrawal from opioids and attention-deficit/hyperactivity disorder (ADHD), which may be comorbid with RLS. There are many causes of secondary RLS including renal failure, pregnancy, varicose veins, and neuropathy.

**Tremor**

Benign familial, or essential, tremor is a fine intention tremor that can be suppressed by alcohol or benzodiazepines. After detoxification from either of these substances, persistent tremor can re-emerge; often, it is benign,
although cerebellar and parkinsonian tremors must be ruled out. Essential tremor can be treated with gabapentin or beta blockers such as propranolol or metoprolol (Table 2).

### Anxiety and panic disorder

Social anxiety often presents in addiction treatment centers in the context of group therapy, speaking in 12-step meetings, and having the patient describe his (her) autobiography and history of addiction. Because social anxiety disorder is the third most common psychiatric disorder after simple phobia and major depressive disorder, it is not surprising that it emerges after withdrawal. Patients with social anxiety disorder might self-medicate with alcohol or drugs, especially benzodiazepines (Box, page 30).

Residential treatment presents an excellent environment for desensitization to fears of public speaking; early recognition is key. Apprehension about group therapy, presenting a substance abuse history, or speaking at a 12-step meeting can lead to premature or “against medical advice” discharge.

Panic disorder commonly is comorbid with substance abuse. Many patients will arrive at treatment with a prescription for benzodiazepines. Because the risk of cross-addiction is high among recovering addicts, benzodiazepines should be avoided. Treating underlying anxiety is crucial for fostering sobriety.

Generalized anxiety disorder is common among patients with an addiction, and can lead to relapse if not addressed. Use of non-addictive medications and cognitive therapy is useful in addressing this condition.

A quandary might arise in states where medical marijuana is legal, because Cannabis can be prescribed for anxiety disorders and posttraumatic stress disorder (PTSD). Promoting abstinence from all substances can present a challenge in patients with anxiety disorders who live in these states.

Medications for anxiety and panic disorder include gabapentin, buspirone, hydroxyzine, beta blockers, and atypical antipsychotics (Table 2). Only buspirone and hydroxyzine are FDA-approved for anxiety; buspirone monotherapy generally is ineffective for panic disorder.

Explaining to patients how anxiety arises, such as how classical conditioning leads to specific phobias, can be therapeutic. Describing Klein’s false suffocation alarm theory of panic attacks can illustrate the importance of practicing slow, deep breathing to prevent hyperventilation. Also, relabeling a panic attack with self-talk statements such as “I know what this is. It’s just a panic attack” can be helpful. Smartphone apps are available to help patients cope with anxiety and acute panic.

### Mood disorders

Many patients with bipolar disorder experience substance abuse at some point; estimates are that up to 57% of patients have a...
Withdrawal-emergent syndromes

Persons with a mood disorder are at high risk of substance abuse because of genetic factors; patients also might self-medicate their mood symptoms. After alcohol or drugs are withdrawn, mood disorders can emerge or resurge. Often, patients enter treatment taking antidepressants and mood stabilizers and usually haven’t been truthful with their treatment provider about their substance abuse. Care must be taken to ascertain whether mood symptoms are secondary to substance abuse. Asking “What’s the longest period of abstinence you’ve had in 2 years and how did you feel emotionally?” often will help you identify a secondary mood disorder. For example, a response of “6 months and I felt really depressed the entire time” would indicate a primary depressive disorder.

Because CNS depressants, such as alcohol and benzodiazepines, can exacerbate a mood disorder, consider continuing or resuming a mood stabilizer or antidepressant during substance abuse treatment. When meeting a new patient, perform an independent evaluation, because substance use can mimic bipolar and depressive disorders. Careful assessment of suicidal ideation is necessary for all patients.

Clinical Point
Consider continuing or resuming a mood stabilizer or antidepressant during substance abuse treatment.

Mr. Y, age 30, presents with benzodiazepine and opioid dependence and a 5-year history of panic attacks and chronic social anxiety. He is considering leaving residential treatment because he has to speak in front of groups. He coped with his symptoms by drinking, which led to 2 episodes of pancreatitis; 5 years ago he started abusing opioids.

Mr. Y completed detoxification 4 years earlier, then was prescribed buprenorphine/naloxone, 16 mg/d, and diazepam, 5 mg/d, but he took more diazepam than indicated. He says he is depressed because “I’m not the person I was.” He had been treated with doxepin, sertraline, paroxetine, and escitalopram without significant benefit, although alprazolam and diazepam did help anxiety.

Mr. Y is given a diagnosis of opioid use disorder, sedative use disorder, panic disorder with agoraphobia, social anxiety disorder, and major depression, recurrent, moderate. He is prescribed gabapentin, 300 mg, 3 times a day, and started in cognitive-behavioral therapy and desensitization techniques for his social anxiety.

Two days later Mr. Y still is anxious and not sleeping. Restless legs syndrome and probable periodic leg movements of sleep are diagnosed—uncovered after opioid withdrawal. Ropinirole, 0.25 mg, is added and gabapentin is increased to 600 mg, 3 times a day.

Two days later, Mr. Y is slightly improved but “scared to death” to present at group therapy. The treatment team starts atenolol, hoping it will help Mr. Y’s performance anxiety; gabapentin and ropinirole are increased to 900 mg, 3 times a day, and 0.5 mg, respectively.

Within 3 days, Mr. Y improves and his anxiety diminishes. He responds well to atenolol but feels some ebbing between doses. Mr. Y is smiling, sleeping better, and says he didn’t think he had “a chance for sobriety” if the high anxiety and panic didn’t resolve.

Atenolol is switched to extended-release metoprolol, 100 mg/d. Two days later, Mr. Y reports fewer side effects with metoprolol, including less postural hypotension—but also less benefit for his anxiety. Dosage is increased to 200 mg/d. He continues to do well and, close to the time of discharge, requests a dosage increase of metoprolol to 300 mg/d. Three months later he is sober and panic-free, without further episodes of restless legs symptoms.

Self-medicating panic and social anxiety with alcohol

Box

Sleep disorders

Insomnia—as a primary or secondary disorder—is common among patients with a substance use disorder. Insomnia always needs to be addressed. Not sleeping well interferes with cognition and energy and makes depression and bipolar disorder worse. Some experts recommend “waiting out” the insomnia, hoping that sobriety will resolve it—but it might not.

Initial insomnia can be treated with melatonin, 3 to 6 mg at bedtime or earlier in the evening. Melatonin acts by regulating circadian rhythms, but can cause increased dreaming and nightmares; therefore, it should be avoided in patients who struggle with nightmares. Trazodone, 50 to 150 mg at bedtime, is an inexpensive sleep aid for initial insomnia and doesn’t cause weight gain, which many drugs with antihistaminic properties can. Prazosin, 1 to 2 mg initially, for nightmares in PTSD is effective.
Antipsychotics might be necessary if nothing else works; quetiapine is effective for sleep and the ER form is FDA-approved as an add-on agent in major depression. Low-dose doxepin (≤10 mg) is effective for middle insomnia. At these low dosages, troublesome side effects of tricyclic antidepressants can be avoided.

As many as 40% of adults with ADHD have a delayed sleep-phase disorder. Ask your patient if she is a “night owl,” how chronic the condition is, and when her best sleep occurs. Morning light and evening melatonin can help, but often are insufficient. Many patients present with undiagnosed or untreated sleep apnea, which can cause excessive daytime sleepiness. Referral to a sleep center is prudent; use of the Epworth Sleepiness Scale is a quick way to assess excessive daytime sleepiness.

ADHD
ADHD commonly is comorbid with a substance use disorder. Patients might present with an earlier diagnosis, including treatment. Several drugs of abuse can alleviate ADHD symptoms, including amphetamines, opioids, cocaine, and Cannabis; self-medicating is common. Because opioids increase dopamine release, a report of improved work and school performance while taking opioids early in addiction can be a clue to an ADHD diagnosis.

Explaining ADHD as a syndrome of “interest-based attention” helps. If a residential treatment program uses reading and writing assignments, a patient with ADHD might struggle and will need extra help and time and a quiet place to do assignments. A non-addictive medication, such as atomoxetine, can help, but has an antidepressant-like delay of 3 to 5 weeks until onset of symptom relief. Using a long-acting stimulant can be effective and quick, with an effect size 3 to 4 times higher than atomoxetine; such agents should be avoided in patients who abuse amphetamines.

Studies show that treating ADHD, even with stimulants, neither helps nor hurts outcomes in substance abuse

Chronic pain
Many substance abuse patients began taking opioids for acute, then chronic, pain before their use escalated to addiction. These are challenging patients; often, they are referred for treatment without true addiction.

Keep in mind that dependence is not addiction. Pseudo-addiction is a condition in which pain is undertreated and the patient takes more medication to obtain relief, calls for early refills, and displays drug-seeking behavior but is not using drugs to achieve euphoria. A thorough history and physical and referrals to specialists such as orthopedic surgeons and pain specialists are necessary. Explaining opioid-induced hyperalgesia is important to help the patient understand that (1) pain can be made worse by increasing the dosage of an opioid because of supersensitivity and (2) many patients who are weaned off these drugs will experience a decrease or complete relief of pain.

Gabapentin, duloxetine, or amitriptyline can be beneficial for chronic pain, as well as mindfulness techniques, physical therapy, and complementary and alternative medicine. Pregabalin can produce euphoria and often should be avoided.

A medication guide for recovery
Paul Earley, MD, former medical director at Talbott Recovery in Atlanta, Georgia, publishes an online guide that classifies medications into categories:
Withdrawal-emergent syndromes

Gabapentin, duloxetine, or amitriptyline can be beneficial for chronic pain; pregabalin can produce euphoria and should be avoided

Clinical Point


Bottom Line

When patients withdraw from drugs or alcohol, neurologic or psychiatric symptoms, such as akathisia, tremor, insomnia, pain, anxiety, depression, and inattention, often emerge. The challenge for clinicians is to determine if the symptoms are caused by an underlying disorder that was masked by the effects of drugs or alcohol or by withdrawal. Prompt recognition and treatment with either agents with low potential for abuse or psychotherapy are essential.