CHPR: Many patients we see on the inpatient psych unit have both a psychiatric and a substance use diagnosis, and it can be tricky to figure out whether their psychotic symptoms reflect the drug use versus the underlying psychiatric disorder. How do you distinguish between these diagnoses?

Dr. Athanasiou: I start by looking at the type of symptoms the patient is experiencing. We typically see predominantly positive symptoms—hallucinations and delusions—with substance-induced psychosis (SIP), whereas primary psychotic illnesses, such as schizophrenia, are more likely to also present with negative symptoms, like blunted affect and lack of motivation. Next, I look at the onset of symptoms in relation to the timing of potential substance use. The presence of psychotic symptoms prior to initiation of substance use indicates the presence...
of a primary psychotic disorder, while the onset of psychotic symptoms shortly after substance use increases the likelihood of SIP.  

**CHPR: What are some ways we can determine onset accurately?**  

**Dr. Athanasiou:** You can look at the results of urine drug tests, family history of substance use or psychotic disorders, collateral information about recent drug use or prodromal symptoms, and even physical exam findings, like constricted pupils, that may indicate recent drug use. But it can still be difficult to differentiate between them, especially considering that substance use is widespread in individuals with psychiatric disorders. Also, SIP can persist for a period beyond the expected substance intoxication or withdrawal. When this occurs, it can make it particularly difficult to differentiate. The DSM qualifies this dilemma by stating that a primary psychotic illness should be considered when the symptoms persist for longer than about one month after substance use.

**CHPR: But might symptoms of SIP sometimes persist beyond a month?**  

**Dr. Athanasiou:** Yes, and this is an important question that we are still trying to understand better. There’s evidence that, for some individuals who use methamphetamines, the symptoms of psychosis can persist beyond a month (Fiorentini A et al, *Front Psychiatry* 2021;12:694863).

**CHPR: Does that mean the DSM’s one-month duration might be too restrictive?**  

**Dr. Athanasiou:** For time-limited symptoms resulting from the direct effects of a particular substance, such as methamphetamine-induced transitory psychotic symptoms, it’s still helpful to use the one-month duration as a practical means to differentiate from individuals with a primary psychotic illness. But the persistent symptoms of psychosis that occur with repeated episodes of SIP can extend beyond the one-month mark, so that timeframe does seem too restrictive.

**CHPR: Individuals who use methamphetamine and other stimulants are more likely to subsequently be diagnosed with a primary psychotic illness, even if they’ve been abstinent for several months, compared to individuals who have never used these substances, right?**  

**Dr. Athanasiou:** Correct, and we refer to this as conversion or transition rates. Several studies have shown that about 25% of individuals diagnosed with SIP will subsequently transition to a primary psychotic illness (Murrie B et al, *Schizophrenia Bull* 2020;46(3):505–516). The rates of these conversions vary for different substances, with rates being highest for cannabis, followed by stimulants.

**CHPR: How likely is it that someone can return to their premorbid functioning if they are able to remain abstinent for a lengthy period?**  

**Dr. Athanasiou:** This is an important question. For someone diagnosed with SIP, studies have shown that abstaining from substance use significantly lowers their risk of converting to a primary psychotic disorder and improves their level of functioning (Murrie et al, 2020). But several factors affect a person’s likelihood of returning to their premorbid functioning, like the type of substance used, severity of symptoms, age of onset, and family history.

**CHPR: Please elaborate on these risk factors.**  

**Dr. Athanasiou:** They shift depending on the substance, but there are some commonalities. In general, the dose or potency of the substance, and the frequency or length of time that the individual has been using, all increase the risk of converting to a primary psychotic disorder. So, for example, if you consider somebody who occasionally uses cannabis versus somebody who meets criteria for cannabis use disorder (CUD), the individual with CUD is at higher risk of subsequently developing a psychotic disorder. Also, several studies have shown that there are different risks based on the substances used—cannabis shows the highest rate of conversion to schizophrenia, followed by methamphetamines and then hallucinogens (Starzer MSK et al, *Am J Psychiatry* 2018;175(4):343–350).

**CHPR: And age of use is another risk factor.**  

**Dr. Athanasiou:** Yes, that’s an important concern. The earlier that someone starts using substances like methamphetamines or cannabis, the higher the likelihood that they’ll develop a primary psychotic disorder later in life. But the prodromal phase of primary psychotic disorders like schizophrenia often begins before adulthood—which is around the same time when cannabis use might first start—so individuals may be more likely to use cannabis during a prodromal phase. Are we seeing people who already have an underlying predisposition to psychotic illness, and then the cannabis use precipitates the onset? Or is there a shared genetic vulnerability to both CUD as well as psychotic illness? What we are likely seeing is not a causal link, but rather a strong

---

**EDITORIAL INFORMATION**

Publisher: Daniel Carlat, MD  
Editor-in-Chief: Victoria Hendrick, MD  
Deputy Editor: Talia Puzzantian, PharmD, BCPP; professor, Keck Graduate Institute School of Pharmacy, Claremont, CA  
Senior Editor: Ilana Fogelson  
Director of Digital Content: Laurie Martin  
Associate Editor: Harmony Zambrano  
Editorial Contributors: Audrey Abelleira, PharmD, BCPP; David C. Fipps, DO; Shirshendu Sinha, MBBS, MD  
Editorial Board: Timothy Botello, MD, professor emeritus, Department of Psychiatry, University of Southern California, Los Angeles General Hospital, Los Angeles, CA  
Jeff Cardenas, MD, psychiatric emergency room director, Olive View UCLA Medical Center; clinical professor, health sciences, Department of Psychiatry & Biobehavioral Sciences, UCLA David Geffen School of Medicine, Los Angeles, CA  
Michael Gitlin, MD, distinguished professor of clinical psychiatry; director, Mood Disorders Clinic, Geffen School of Medicine at UCLA in Los Angeles, CA  
Adrienne Grzenda, MD, PhD, clinical assistant professor, psychiatry & biobehavioral sciences, UCLA David Geffen School of Medicine and Olive View UCLA Medical Center, Los Angeles, CA  
Brian Holroyda, MD, chief psychiatrist, Contra Costa County Detention Health Services, Martinez, CA  
Sandra Hyams, PMHNP, psychiatric nurse practitioner, Acclaim Multi-Specialty Group, John Peter Smith Hospital, Fort Worth, TX  
Michael Strong, MD, clinical assistant professor of psychiatry, Carver College of Medicine, University of Iowa, Iowa City, IA  
All editorial content is peer reviewed by the editorial board. Dr. Carlat, Dr. Hendrick, Dr. Puzzantian, Ms. Martin, Ms. Fogelson, Ms. Zambrano, Dr. Botello, Dr. Cardenas, Dr. Gitlin, Dr. Grzenda, Dr. Holroyda, Ms. Hyams, and Dr. Strong have no financial relationships with companies related to this material.  

Carlat Publishing occasionally uses artificial intelligence (AI) tools, such as ChatGPT and Bard, in various stages of our content creation process, such as editing articles and creating preliminary drafts and outlines. In all cases, our content is extensively revised during the editorial process by human clinicians and by our board of medical experts to ensure quality and accuracy. This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists, and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

*The Carlat Hospital Psychiatry Report* (ISSN 2768-3877)  
POSTMASTER: Send address changes to The Carlat Psychiatry Report, P.O. Box 626, Newburyport, MA 03950
association between cannabis and onset of a primary psychotic illness (D’Souza DC et al, World Psychiatry 2023;22(2):231–232).

**CHPR:** If cannabis use does precipitate the onset of schizophrenia, it would be good if there were better public health messaging about this possible risk.

**Dr. Athanasiou:** Right, especially since the general population does not appreciate the relationship between cannabis and psychosis. But it’s difficult to distill the scientific evidence into a clear and concise message that resonates with our patients or the public. The evidence tells us that most people who use cannabis will not experience cannabis-induced psychosis, but for a subset of the population, cannabis can be quite risky. I make a point of talking to patients about the risk of cannabis use. For those with a primary psychotic disorder, I tell them that cannabis is likely worsening their symptoms and making it harder for their antipsychotic medications to work. For young patients at risk for a psychotic disorder—for example, patients who have a first-degree relative with schizophrenia—I emphasize that cannabis poses the most significant risk, above any other substance, for triggering a psychotic illness.

**CHPR:** It would be great if pediatricians provided psychoeducation on this point to their adolescent patients.

**Dr. Athanasiou:** I agree. Many pediatricians do, and this topic is becoming a greater public health concern now that cannabis is being legalized throughout the country and globally, because at the same time it seems that the perception of its harms may be decreasing. People are more willing now to initiate cannabis use, to use it more frequently, and to use it in higher potencies. In addition, the concentration of THC in cannabis products has been increasing in recent years. In the early 2000s the potency was less than 9%, but many of the current cannabis flower products have a potency over 20% (www.tinyurl.com/29mcf4fe). Newer formulations such as vape pens or concentrates can have even higher concentrations, upwards of 80% THC (www.tinyurl.com/ycmbv2c).

**CHPR:** Unlike cannabis and methamphetamine, the likelihood of psychosis from opioids is low, right?

**Dr. Athanasiou:** Right, but a concern now is that we are seeing many more people use both opioids and psychostimulants, especially methamphetamine. Many experts see this combination as the next phase—some people call it a “fourth wave”—of the opioid crisis.

**CHPR:** Can you say more about this next phase? What specific concerns do you have about it?

**Dr. Athanasiou:** There are several concerns about this next phase. One major issue is the potential for inadvertent exposure to hazardous opioids such as illicitly produced fentanyl. This drug poses an elevated risk of overdose fatalities due to its considerably higher potency. Also, opioids and methamphetamines each have their own set of health risks, and when they’re combined, they elevate patients’ risks of harmful outcomes, like heart attacks, strokes, seizures, and respiratory depression. While there are approved pharmacotherapies for opioid use disorders, like buprenorphine, methadone, and naltrexone, there are no approved medications for stimulant use disorders (StUD), and the behavioral therapies that have shown efficacy for StUD are not always easy to access.

**CHPR:** Do antipsychotic medications work as well for SIP as for primary psychotic illnesses?

**Dr. Athanasiou:** Several studies have looked at both first-generation and second-generation antipsychotics and have found they are efficacious in treating hallucinations and delusions related to SIP, with most of the evidence based on methamphetamines (Fluyau D et al, Front Psychiatry 2019;10:740). Although there have not been enough studies to guide us specifically on the treatment of SIP, the consensus is to approach it in the acute phase similarly to treatment approaches for primary psychotic disorders. The evidence becomes less clear for psychosis that persists beyond the acute phase, but generally clinicians will utilize treatment approaches similar to primary psychotic disorders. Some guidelines, such as from Australia, recommend using benzodiazepines before antipsychotics for cases of SIP or agitation in acute settings (www.tinyurl.com/57wstbp3). The concern stems from the cardiovascular risks—such as QT prolongation—from drugs like methamphetamine and cocaine, which can be exacerbated by antipsychotics. If benzodiazepines are not effective, then antipsychotics would be the appropriate next treatment.

**CHPR:** You referred to behavioral therapies for StUD a few moments ago. Can you say more about treatments for SIP besides antipsychotic meds?

**Dr. Athanasiou:** This is a great question because it is always important to address the substance use as well as the psychosis. Studies have shown that cessation of substance use significantly reduces the reoccurrence of psychosis, and so an integrative approach that addresses both the psychotic illness and the substance use is important. Several psychosocial treatments appear effective for substance use disorders. Therapies that incorporate cognitive behavioral therapy, such as the Matrix Model, have shown efficacy for methamphetamine use disorder, as has contingency management (Glasner-Edwards S et al, CNS Drugs 2014;28(12):1115–1126). Motivational enhancement therapy can be effective for multiple substances. Clinicians are familiar with 12-step programs from Alcoholics Anonymous, and many people find such groups are helpful. Psychoeducation is important, and we should always talk with our patients about the negative effects that substances can have on psychosis. It may also be a good
Wernicke’s Encephalopathy and Korsakoff’s Syndrome

Continued from page 1

recent memory more than remote memory—caused by thiamine deficiency and often associated with WE. A hallmark of the syndrome is confusion, where patients fabricate information to fill memory gaps. Other symptoms include behavioral changes, apathy, and changes in personality similar to those seen in frontal lobe lesions (eg, executive dysfunction, inattention, and poor planning). KS either accompanies or follows untreated WE in most cases and is considered to be irreversible. Thus, recognizing WE and initiating timely treatment are essential to preventing progression to KS.

High-risk conditions

You probably associate WE with patients suffering from alcohol use disorder, since alcohol impairs thiamine absorption and utilization. But many other conditions also raise the risk of thiamine deficiency, like restrictive eating disorders and excessive vomiting (eg, hyperemesis gravidarum or cannabis hyperemesis syndrome). A low magnesium level (<1.6 mg/dl) also increases the risk since it’s an essential cofactor for thiamine-dependent enzymes. In addition, structural (eg, malabsorptive bariatric surgeries) and functional changes (eg, gastroparesis, or delayed stomach emptying) to the gastrointestinal tract limit thiamine’s absorption. Interventions such as chemotherapy and hemodialysis also deplete thiamine stores (Donnino M et al, Ann Emerg Med 2007;50(6):715–721).

Lastly, as thiamine is stored primarily in skeletal muscle and in the heart, brain, liver, and kidneys, any related impairment or end-stage disease will reduce thiamine reserves.

Presentation conundrum

Diagnosing WE can be tricky as the classic triad of symptoms—confusion, eye movement issues (ophthalmoplegia), and lack of coordination (ataxia)—occurs in only about 10% of cases (Sinha et al, 2019). This infrequency probably contributes to the alarming statistic that approximately 85% of WE cases go undiagnosed until autopsy (Sinha et al, 2019). Since most WE cases are likely undiagnosed, we don’t have accurate estimates of its prevalence or of its morbidity and mortality rates.

How can you make sure not to miss a case of WE? Look for the most consistent characteristic of this syndrome: a change in mental status. The presentation ranges from mild neurocognitive changes, drowsiness, and apathy to more severe cognitive impairment and even coma in rare cases.

Ophthalmoplegia is the second most common symptom, with horizontal nystagmus—involuntary rapid horizontal eye movement when patients are asked to follow an object with their eyes only, without moving their head—being the most frequently observed ocular abnormality. However, you might encounter other ocular manifestations, such as strabismus (misalignment of the eyes), ptosis (droopy eyelids), or miosis (constricted pupils). Gait ataxia, the third characteristic in the classic triad, also shows a variable presentation ranging from mild abnormalities in gait to a complete inability to stand or walk.

Labs and imaging

In WE, thiamine levels will typically be low (<70 nmol/L if whole blood; <8 nmol/L if serum), but a normal serum thiamine level doesn’t rule out WE, as serum concentrations don’t always accurately reflect thiamine levels in the brain. Have a patient fast overnight before obtaining their morning thiamine level. Depending on the lab, you might not get the result for several days.

Magnetic resonance imaging (MRI) of the brain is the most important imaging tool to diagnose and prognosticate WE, and the most significant radiological feature is loss of volume of the mammillary bodies. Cerebral cortex involvement is generally an adverse prognostic indicator (Zhong C et al, Am J Neuroradiol 2005;26(9):2301–2305). Do not assume a normal MRI rules out WE, as findings can be unremarkable in early or mild cases.

Treatment

Given the acute and potentially reversible nature of WE, if suspected, initiate thiamine treatment immediately rather than waiting for lab or

Continued on page 9
**Q&A with the Expert**

**Caridad Ponce Martinez, MD, FAPA, FASAM**  
Assistant professor of psychiatry, UMass Chan Medical School, Worcester, MA.

Dr. Ponce Martinez has no financial relationships with companies related to this material.

---

**CHPR:** How can we make sure not to miss the symptoms of alcohol withdrawal among patients who are admitted to psychiatric emergency departments or inpatient units?  
**Dr. Ponce Martinez:** Make sure to ask about the patient’s pattern of alcohol use and explore whether there has been a recent reduction or cessation after chronic alcohol use. Keep in mind that a blood alcohol level of zero is not necessary for someone to experience alcohol withdrawal.

**CHPR:** So a patient may present with symptoms of alcohol withdrawal, even though they still appear intoxicated.  
**Dr. Ponce Martinez:** Among patients with chronic, heavy drinking, that’s correct.

**CHPR:** What screening tests do you use in your evaluation of alcohol withdrawal?  
**Dr. Ponce Martinez:** I like to use the Alcohol Use Disorders Identification Test (AUDIT), the AUDIT-C, or the CAGE questionnaire. A positive screening test tells me I need to do an additional evaluation to determine the risk for alcohol withdrawal (Editor’s note: For an AUDIT-C calculator, see: www.tinyurl.com/bdc8fxbd).

**CHPR:** Which patients are at particular risk for complications of alcohol withdrawal?  
**Dr. Ponce Martinez:** The patients at highest risk are those who have previously experienced severe alcohol withdrawal symptoms. Elderly patients and patients with other medical conditions or complications, like severe liver disease or seizure disorders, are also at elevated risk. So are patients who, because of their underlying psychiatric conditions, might not be able to readily communicate as their symptoms worsen.

**CHPR:** What are the typical symptoms of alcohol withdrawal?  
**Dr. Ponce Martinez:** They range from mild to severe. During mild alcohol withdrawal, patients may experience nausea, vomiting, tremulousness, diaphoresis, sensitivity to light or sound, headache, anxiety, insomnia, and restlessness. For most patients, symptoms tend to be mild or moderate, but I ask if they have ever experienced more severe symptoms: hallucinations, seizures, or delirium tremens (DTs). It’s important to identify patients who have experienced these more severe symptoms so that we can be prepared to manage them in advance. DTs is rare but can be lethal, so I watch for symptoms carefully. Historically the mortality rate of DTs was as high as 20%, although due to better medical management, it is now 1%–4% (Turner RC et al., *J Gen Intern Med* 1989;4(5):432–444). Patients sometimes mistake tremulousness with DTs, so I’ve learned to be very descriptive of what I’m referring to—alcohol withdrawal plus rapid-onset, fluctuating confusion or disorientation 72–96 hours after stopping/reducing alcohol use. I also ask whether the patient has ever needed to be admitted to a medical hospital or intensive care unit (ICU) for the management of their alcohol withdrawal symptoms. This can help me anticipate greater withdrawal symptom severity.

**CHPR:** Over what timeframe do withdrawal symptoms appear?  
**Dr. Ponce Martinez:** Mild symptoms occur as early as six hours after the last drink. Again, that is from a reduction or cessation in drinking to when they present; it does not need to be abstinence. Symptoms can take as long as 36 hours to appear, although typically you’ll see symptoms within 24 hours of the last drink. Different symptoms have different times of manifestation: Withdrawal seizures can occur six to 48 hours later; alcoholic hallucinosis, meaning hallucinations with intact sensorium, can occur 12–48 hours later; and DTs typically occurs 48–96 hours after alcohol reduction or cessation. There is some nuance in the timing of these symptoms—particularly when there are other substances of abuse or medications like benzodiazepines, barbiturates, opioids, other sedatives, or beta-adrenergic antagonists—that may mask or even worsen some of the withdrawal symptoms. Some of the cases I monitor most closely are patients who have taken benzodiazepines, since the appearance of alcohol withdrawal symptoms may be delayed.

**CHPR:** How do you distinguish the hallucinations of DTs from schizophrenia?  
**Dr. Ponce Martinez:** The hallucinations from alcohol withdrawal are transient and new in onset,
as opposed to those of a patient with schizophrenia. The hallucinations can be auditory, visual, or tactile, and range from mild perceptual distortions to frank hallucinations. Interestingly, visual hallucinations from alcohol withdrawal syndromes are often of animals (Wartenburg AA. Management of alcohol intoxication and withdrawal. In: Miller SC, Fiellin DA, Rosenthal RN, Saiz R, eds. The ASAM Principles of Addiction Medicine. 6th ed. Philadelphia, PA: Wolters Kluwer; 2019:704–722). Patients may also experience formication, or tactile hallucinations: the sensation of bugs crawling on their skin. When the hallucinations are present with delirium and autonomic instability, the patient is experiencing DTs. However, hallucinations can be present on their own, which is referred to as alcoholic hallucinosis.

**CHPR: Are there any other symptoms of withdrawal that may be confused with symptoms of other psychiatric conditions/disorders?**

**Dr. Ponce Martinez:** Mild withdrawal symptoms, including tremulousness, insomnia, and anxiety, can be confused with anxiety disorders; the timeline of these symptoms and their appearance in the context of alcohol cessation or reduction can be a helpful way to distinguish between the two. Irritability, restlessness, and insomnia could also be confused with a hypomanic state.

**CHPR: How do you monitor the progression of alcohol withdrawal symptoms?**

**Dr. Ponce Martinez:** The Clinical Institute Withdrawal Assessment–Alcohol Revised (CIWA-Ar) scale is a helpful tool. There are other scales for patients with severe symptoms who can’t communicate, but for the patients we typically see in a psychiatric unit, the CIWA-Ar scale is appropriate (Editor’s note: The CIWA-Ar scale can be found here: www.tinyurl.com/3bpets8). Of note, the CIWA-Ar requires repeat administration so you can see the trajectory of the symptoms of alcohol withdrawal. Mild symptoms, meaning a CIWA-Ar score less than 8, include headache, gastrointestinal symptoms, and tremulousness. Scores of 8–15 indicate moderate withdrawal symptoms, and scores greater than 15 indicate severe alcohol withdrawal with impending DTs. These patients need to be transferred rapidly to a medical unit or ICU.

**CHPR: Besides CIWA-Ar scores of greater than 15, what other reasons would you have to transfer someone from a psychiatric unit to a medical unit for the treatment of withdrawal?**

**Dr. Ponce Martinez:** For stand-alone psychiatric units where there is limited medical support, I would recommend caution when admitting patients who have a history of moderate to severe alcohol withdrawal, or who are experiencing withdrawal symptoms despite a high blood alcohol content, or who have risk factors for complicated alcohol withdrawal, like concomitant withdrawal from other substances. This is because psychiatric units usually lack the ability to rapidly escalate medical care if necessary, including transfer to a medical unit. Another reason to transfer patients to a medical unit is for intravenous (IV) treatment if they can’t take medications by mouth because of severe nausea and vomiting. And patients who require monitoring more frequently than every two hours are typically not appropriate for inpatient psychiatric units.

**CHPR: Would you send a patient to a medical unit if their blood alcohol level is over a certain limit?**

**Dr. Ponce Martinez:** Not necessarily, as a blood alcohol level is just one piece of information in my evaluation of a patient. But I would be concerned if a patient presented with a high blood alcohol level yet exhibited alcohol withdrawal symptoms, as this would indicate that the patient has a high tolerance and is at risk of severe withdrawal symptoms.

**CHPR: What pharmacologic protocol do you follow for the management of withdrawal?**

**Dr. Ponce Martinez:** The standard of care involves use of benzodiazepines, and I use the CIWA-Ar to guide the treatment. There are several protocols about how to administer benzodiazepines, and there is certainly a lot of personal and institutional preference for which benzodiazepines to use, but there’s no particular benefit of one benzodiazepine over another. When selecting benzodiazepines, I consider factors like liver function and age. For elderly patients, I worry about co-occurring medical conditions or other sedating medications and prefer shorter-acting agents, like lorazepam (Ativan), that can be easily titrated and are less likely to cause excessive sedation. A concern with excessive sedation is that patients will be at risk of respiratory depression and aspiration.

**CHPR: What do you do for patients who have mild or moderate symptoms and no medical complications?**

**Dr. Ponce Martinez:** For those patients, especially if they aren’t taking other sedating medications, I prefer to use longer-acting agents, like chlordiazepoxide (Librium) 50–100 mg/dose and diazepam (Valium) 10–20 mg/dose. These medications provide longer relief and require less frequent dosing. Diazepam has the added advantage of rapid-onset symptom relief and active metabolites, which can prolong the effect. And longer-acting agents are less reinforcing, which is an important consideration in patients with alcohol use disorder (AUD). But I like using lorazepam as it is one of the easiest benzodiazepines to titrate. One option for treatment for patients at moderate or severe risk for complications of alcohol withdrawal involves providing benzodiazepines on a fixed-dose regimen, for example lorazepam 2 mg every four hours or chlordiazepoxide 50 mg every six hours. It’s important to monitor the need for more medication if the fixed dose is inadequate. Therefore, lorazepam 2 mg can additionally be ordered as needed every four hours if the CIWA-Ar score is ≥8. The CIWA-Ar is repeated one hour after every dose. It’s helpful to calculate the total dose of benzodiazepines received over a 24-hour period when assessing the effectiveness of a medication regimen and considering a taper to, for example, 1 mg of lorazepam every four hours. But, if a patient has required 2 mg of lorazepam six times over the course of 24 hours, and CIWA-Ar scores have ranged between 8 and 16, these high CIWA-Ar scores indicate that a taper is not recommended at this time because the patient may actually need even higher doses of benzodiazepines.
CHPR: Do you also use symptom-triggered treatment, and can you describe this treatment approach?

Dr. Ponce Martinez: Symptom-triggered treatment involves using patients’ scores on a standardized scale to determine when to dose a benzodiazepine. We use the CIWA-Ar and prescribe a benzodiazepine if the score reaches a threshold of ≥8, then we evaluate the symptoms one hour later, again using the CIWA-Ar. Another approach is the loading-dose strategy, where we provide repeated doses of a long-acting benzodiazepine—for example, diazepam 10–20 mg hourly—until the withdrawal symptoms decrease or there are signs of oversedation, and we monitor for several hours without further medication, and the benzodiazepine level then decreases naturally. Different strategies can be used in combination. If a patient is on symptom-triggered therapy but requires dosing every hour due to persistent CIWA-Ar scores ≥8, then a fixed-dose therapy may be preferred. This would allow the withdrawal symptoms to be treated more aggressively, thereby preventing development of more severe symptoms.

CHPR: Do you use any medications besides benzodiazepines?

Dr. Ponce Martinez: Yes, phenobarbital can be used, primarily in medical units and ICUs. But even for patients with very severe withdrawal symptoms, benzodiazepines are effective. Non-benzodiazepine anticonvulsants, like carbamazepine, valproic acid, and gabapentin, are also options (Amato L et al, Cochrane Database Syst Rev 2011;6:CD008537; Wartenburg, 2019) but don’t seem to be superior to benzodiazepines. Benzodiazepines are the only medications with FDA approval for treatment of alcohol withdrawal.

CHPR: What are the advantages of using antiepileptic medications for alcohol withdrawal?

Dr. Ponce Martinez: Anticonvulsants are helpful not only because of their low abuse potential, but also because of their potential “anti-kindling effect” as the risk of seizures increases with repeated episodes of alcohol withdrawal. And anticonvulsants don’t increase cravings or heighten the risk to relapse to alcohol use, unlike benzodiazepines.

CHPR: For how long do you prescribe them?

Dr. Ponce Martinez: I continue some anticonvulsants long term. Several studies have looked at the use of gabapentin for the long-term management of alcohol withdrawal symptoms (Anton RF et al, JAMA Intern Med 2020;180(5):728–736; Ahmed S et al, Prim Care Companion CNS Disord 2019;21(4):19r02465). Gabapentin does not have FDA approval for alcohol withdrawal, but at 1200 mg daily, in divided doses three or four times daily, it helps target protracted withdrawal symptoms like insomnia, anxiety, and irritability. These symptoms can be a significant risk factor for relapse to alcohol use following an episode of detoxification.

CHPR: How long do these protracted withdrawal symptoms last?

Dr. Ponce Martinez: They can last weeks to months after cessation of alcohol use, particularly if untreated.

CHPR: What are your dosing considerations when using antiepileptic drugs?

Dr. Ponce Martinez: I aim for therapeutic blood levels, but one thing to consider with many of these medications is that they undergo hepatic metabolism, so for patients with alcohol-related liver disease, they may not be an option. Gabapentin is an exception as it’s renally excreted and is safe to use in patients with liver disease.

CHPR: What about beta blockers like propranolol for anxiety and tremor?

Dr. Ponce Martinez: While they often provide symptomatic relief, they can be problematic because they mask some of the autonomic symptoms of alcohol withdrawal and make it difficult to utilize scales like the CIWA-Ar to guide treatment.

CHPR: Do you also treat patients’ nutritional deficiencies?

Dr. Ponce Martinez: Yes, I do. Most patients who present with AUD are at risk of thiamine deficiency, which can lead to Wernicke’s encephalopathy (WE) and/or Korsakoff’s syndrome, so I provide thiamine supplementation. In the inpatient psychiatric unit, I dose it orally at a minimum of 100 mg PO daily for three days and continue the oral supplementation for several weeks. In the medical units, thiamine is administered IV or intramuscularly. This supplementation is particularly important before any administration of glucose, to avoid precipitation of WE (Editor’s note: See article on WE in this issue). Patients are likely to have folic acid, pyridoxine (vitamin B6), and other nutritional deficiencies, so I usually prescribe them a daily multivitamin.

CHPR: Once patients are past the withdrawal symptoms and ready for discharge, do you send them out with medications like naltrexone or acamprosate?

Dr. Ponce Martinez: The answer is absolutely, yes. Medications for AUD are effective and significantly underused throughout our medical system. Once patients are ready for discharge, we have an opportunity to educate them about the available treatments to help decrease cravings for alcohol and support their treatment goals with regard to AUD, whether that is reduction or cessation of use. One great option for patients with AUD is extended-release naltrexone, which we can administer prior to hospital discharge. It’s a monthly injectable medication, but patients may prefer oral naltrexone because they don’t like injections or have a hard time obtaining the injection in the community. Acamprosate is another option, at a dose of 666 mg three times daily. Off-label medications like topiramate, gabapentin, and baclofen can also be helpful in the treatment of AUD.

CHPR: Thank you for your time, Dr. Ponce Martinez.
If you work in a psychiatric unit, you probably often face the challenge of managing patients with co-occurring substance use disorders (SUDs). Benzodiazepines offer considerable benefits in the management of alcohol withdrawal symptoms and agitation, but they require a mindful approach when you’re working with patients with a history of alcohol use disorder (AUD) or other SUDs. Approximately 12.6% of the US population reported benzodiazepine use within the previous year, with misuse accounting for nearly 20% of all use (Maust DT et al, Psychiatr Serv 2019;70(2):97–106). Risk of misuse is highest for adults 18–25, and concomitant cannabis or alcohol use has been associated with a higher risk of misuse. Given the potential risks of cognitive impairment, falls, dependence, misuse, and even higher mortality rate among patients with AUD, the use of benzodiazepines warrants caution (Heikkinen M et al, Addiction 2021;116(8):1990–1998). This article provides an overview of important considerations when using benzodiazepines for patients with SUDs in psychiatric inpatient settings.

Inpatient use of benzodiazepines

Benzodiazepines rank among the most frequently misused substances, and misuse is prevalent among patients with AUD. Both benzodiazepines and alcohol act via the GABAergic system, leading to a potent combined effect that increases the likelihood of adverse outcomes, including, in severe cases, fatal overdoses. Further, exposure to benzodiazepines can trigger a return to use for patients in recovery from AUD. So, before prescribing benzodiazepines, thoroughly check the patient’s history, their substance use patterns, and any factors that might increase risk of a relapse, such as poor physical health, poor sleep, or psychosocial stressors (Sliedrecht W et al, Psychiatry Res 2019;278:97–115).

A good rule of thumb is to keep the duration of benzodiazepine use as short and the dosage as low as possible, considering that tolerance and physical dependence on benzodiazepines can develop in just one week (Vinkers CH et al, Adv Pharmacol Sci 2012;2012:416864). In the days leading up to discharge, taper the dosage gradually since abrupt discontinuation can produce a rebound of anxiety, insomnia, and irritability. Typically, a dose reduction of 25%–50% every week is well tolerated, but you can taper the dose as quickly as every two or three days in many cases. A taper is not necessary if the benzodiazepine use was sporadic during the inpatient admission.

For the medical management of alcohol withdrawal, I prefer long-acting benzodiazepines, such as chlor Diazepam (Librium) or diazepam (Valium), over short-acting agents like alprazolam (Xanax). This is because a longer half-life allows for more consistent management of withdrawal symptoms and a smoother, more tolerable experience for the patient. The pharmacokinetic profiles of chlordiazepoxide and diazepam are similar; however, both have been subject to recent drug shortages, so the choice between them will largely be guided by hospital formulary and availability. Typical symptom-triggered dosages of chlor Diazepam are 25–100 mg PO, and the range for diazepam is 5–10 mg PO, as needed every four to six hours based on severity of withdrawal symptoms. Lorazepam (Ativan), while not a long-acting benzodiazepine, is a good option for elderly patients or those with liver disease as it lacks active metabolites, with doses of 2–4 mg every four to six hours. I recommend symptom-triggered dosing as a way to minimize overall benzodiazepine exposure (for more on symptom-triggered dosing, see Q&A with Dr. Ponce Martinez this issue).

For all patients, I make sure to optimize non-benzodiazepine treatment options that they can continue to utilize once discharged. Antidepressants, such as escitalopram or venlafaxine, are first-line pharmacotherapy for anxiety disorders and are my first considerations in formulating a benzodiazepine-sparing regimen (Szuhany KL and Simon NM, JAMA 2022;328(24):2431–2445). Antipsychotics, specifically second-generation agents like olanzapine, are an effective alternative to benzodiazepines for managing agitation. These often act faster and produce a lower risk of oversedation than benzodiazepines (Amore M et al, Front Psychiatry 2021;12:628965). I also often prescribe gabapentinoids (gabapentin and pregabalin) for anxiety. When used short term, pregabalin appears as effective as lorazepam and has the added advantage of improving anxiety symptoms in cases refractory to antidepressants. The risk of withdrawal or rebound anxiety symptoms is minimal when discontinuing pregabalin following long-term use. Like pregabalin, gabapentin improves anxiety symptoms and enhances the therapeutic response to antidepressants. Gabapentin doses are 300–3600 mg per day, and pregabalin doses are 150–600 mg per day (Greenblatt H and Greenblatt DJ, Clin Pharmacol Drug Dev 2018;7(3):228–232).

Understanding a patient’s substance use history and their susceptibility to SUDs is crucial in making informed decisions about benzodiazepine use. If you need to prescribe benzodiazepines for withdrawal symptoms or acute anxiety/agitation, keep the duration short and taper the medications prior to discharge. Don’t overlook alternative medications for treating anxiety, like second generation antipsychotics, antidepressants, gabapentin, and pregabalin.
imaging results. Any patients suffering from mental status changes in the setting of high-risk conditions should also be treated immediately. Gastrointestinal thiamine absorption is often unreliable, so intravenous (IV) administration is the most effective route of administration. We recommend administering 200–500 mg IV thiamine three times daily for three to five days, followed by 100 mg oral thiamine three times daily until the patient’s altered mental status resolves. If IV administration is not an option on a psychiatric unit, do not administer by intramuscular injection as this mode of administration is ineffective for WE. Instead, temporarily transfer the patient to a medical floor for the IV thiamine. High-dose IV thiamine best facilitates diffusion across the blood-brain barrier, allowing for quick correction and preventing irreversible cognitive impairment or death (Thomson D et al, *Neuropsychol Rev* 2012;22(2):81–92). Also, check the patient’s magnesium and replenish as necessary, as thiamine activity requires adequate magnesium levels. It is critical to initiate parenteral thiamine before administering glucose. Otherwise, glucose will deplete the patient’s meager thiamine stores, risking acute precipitation of WE.

**Prevention**

A short course of high-dose IV thiamine should be a routine component in the treatment of intoxicated patients admitted to the ED as well as hospitalized patients suffering from delirium with risk factors for WE. Thiamine is inexpensive and safe, making undertreatment of WE more of a concern than overtreatment. Prophylactic and preventative measures in high-risk patients are already considered the standard of care in some populations, such as following bariatric surgery (Lin Q et al, *Front Surg* 2023;10:1016347). Prophylactic measures include 100 mg PO TID for asymptomatic outpatients, while asymptomatic inpatients can start with 100 mg IV for one day, followed by 200 mg PO daily for the rest of the hospitalization. If new WE symptoms emerge, treat with 500 mg IV for three to five days.

**Prognosis**

Prompt administration of parenteral thiamine is crucial for optimal outcomes. While ocular issues generally respond favorably to treatment and fully resolve within days to weeks, improvement in gait ataxia tends to be slower, often leaving patients with lingering disturbances. Neurocognitive recovery is a gradual process: While symptoms like apathy, drowsiness, and confusion often improve with treatment, memory and learning deficits often persist. In some cases, patients may not improve and may progress to KS.

**CARLAT VERDICT**

WE can lead to irreversible disability if not treated promptly, but you might miss it if you solely rely on the classic triad of confusion, opthalmoplegia, and ataxia. Keep a high index of suspicion if a patient presents with any of the three symptoms, especially if they belong to groups at risk for thiamine deficiency (eg, alcohol use disorders, eating disorders, or any other conditions that impair nutrient absorption). Timely administration of IV thiamine can rapidly resolve symptoms, although some patients may still progress to KS, a condition marked by irreversible memory impairment and behavioral changes.

---

**Research Updates**

**IN PSYCHIATRY**

---

**BIPOLAR DISORDER**

Sublingual Dexmedetomidine for Acute Agitation in Bipolar Disorder

Sébastien Hardy, PharmD, BCPS. Dr. Hardy has no financial relationships with companies related to this material.

**REVIEW OF:** Preskorn SH et al, *JAMA* 2022;327(8):727–736

**STUDY TYPE:** Randomized controlled trial

Acute agitation is common in patients with bipolar disorder. When we use pharmacotherapy, we typically use oral or parenteral antipsychotic medications (eg, haloperidol, olanzapine) and benzodiazepines (eg, lorazepam), but these do not always work quickly and are poorly tolerated by some patients. It would be helpful to have additional options for the management of acute agitation.

In April 2022, the FDA approved a sublingual film formulation of dexmedetomidine—an alpha2-adrenergic receptor agonist approved in intravenous form for procedural sedation and anesthesia—for the acute treatment of agitation in patients with bipolar disorder and schizophrenia. The sublingual formulation bypasses first-pass metabolism and is absorbed quickly.

This randomized, double-blind, placebo-controlled trial tested sublingual dexmedetomidine in patients with mild to moderate agitation associated with bipolar I and II disorder (n=380) across 15 clinical sites. The authors estimated baseline agitation by using the Positive and Negative Syndrome Scale–Excited Component (PEC) score, which includes five items (poor impulse control, tension, hostility, uncooperativeness, and excitement) each rated from 1 to 7. The PEC total score ranges from 5 (absence of agitation) to 35 (extremely severe). Mean...
total PEC score at baseline was 18.

Patients were randomly assigned to receive a single dose of dexmedetomidine (180 µg or 120 µg) or placebo, self-administered under supervision of a staff member. A repeat dose of 60 µg or 90 µg could be given two hours after the first dose, at the investigators’ discretion, if the change from baseline on the PEC score was less than 40% and if there were no safety concerns. All patients also were continued on their current psychiatric medications.

Dexmedetomidine was significantly more effective than placebo in reducing agitation (both dosages p<0.001 vs placebo). The onset of effect began within 20 minutes for both dosages. Response rates (defined as a decrease of 40% or more in PEC score at two hours compared to baseline) were 91% (180 µg dose), 77% (120 µg), and 46% (placebo). Unfortunately, the study did not compare dexmedetomidine with any standard agitation medications.

Dexmedetomidine produced no serious adverse events. The most common side effects were somnolence, dry mouth, hypotension, and dizziness. One patient in each dexmedetomidine group reported suicidal ideation lasting one day.

CARLAT TAKE

Sublingual dexmedetomidine appears to be a fast-acting, well-tolerated option for mild to moderate agitation in patients with bipolar disorder. The sublingual film requires self-administration, so it will not be an option for patients who are unwilling to cooperate. Until more safety data are available, minimize its use in the elderly, adolescents, and patients with comorbid health conditions.

DEPRESSION

Are Individuals With Major Depressive Symptoms More Likely to Own a Gun in the United States?

Susan L. Siegfried, MD. Dr. Siegfried has no financial relationships with companies related to this material.

Rates of gun ownership were comparable among depressed individuals (31%) and non-depressed individuals (32%), but among individuals with depressive symptoms, 36% reported they made their first gun purchase during the COVID-19 pandemic, compared to 19% of non-depressed individuals. Depressive symptoms were significantly associated with first-time purchase of a gun (odds ratio [OR] 1.8) and thoughts about purchasing a gun in the future (OR 1.5). Depressed individuals were more likely than non-depressed individuals to purchase a gun from concerns related to the COVID-19 pandemic (p<0.001) or to protect themselves against someone they knew (p=0.001).

CARLAT TAKE

Gun ownership is common in individuals with depression in the United States, especially since the COVID-19 pandemic. Be sure to ask your depressed patients if they own or plan to purchase firearms, as the risk of suicide is several times higher among people who own guns.

GENDER-AFFIRMING CARE

Initiation of Gender-Affirming Hormones and Mental Health Outcomes

Erin Conklin, MSN, CNP, PMHNP-BC. Ms. Conklin has no financial relationships with companies related to this material.

Researchers used data from the COVID States Project, an internet survey that included questions about gun ownership and gun-purchasing plans as well as the Patient Health Questionnaire (PHQ-9).

The survey included participants from all 50 states and the District of Columbia (n=24,770). They were on average 46 years old, female (65%), and White (74.0%). More than half of the sample was currently employed (57%) and living in a suburban area (58%). Of these, 28% reported at least moderate depressive symptoms as defined by a PHQ-9 score of 10 or greater.

Rates of gun ownership were comparable among depressed individuals (31%) and non-depressed individuals (32%), but among individuals with depressive symptoms, 36% reported they made their first gun purchase during the COVID-19 pandemic, compared to 19% of non-depressed individuals. Depressive symptoms were significantly associated with first-time purchase of a gun (odds ratio [OR] 1.8) and thoughts about purchasing a gun in the future (OR 1.5). Depressed individuals were more likely than non-depressed individuals to purchase a gun from concerns related to the COVID-19 pandemic (p<0.001) or to protect themselves against someone they knew (p=0.001).

Does the initiation of GAH in adolescence improve or worsen mental health outcomes in transgender youth? A recent study used data from the 2015 Transgender Survey—the largest-ever survey on transgender people in the US (n=21,715)—to answer this important question. The study compared mental health outcomes among individuals who initiated GAH with those of individuals who desired but never accessed GAH.

Notably, 78% of respondents reported wanting GAH, but only 0.6% and 1.7% reported having access to GAH in early (ages 14–15) and late (ages 16–17) adolescence,
CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com with your username and password to take the post-test. You must answer 75% of the questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be completed within a year from each issue’s publication date. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Carlat CME Institute maintains responsibility for this program and its content. The Carlat CME Institute designates this enduring material educational activity for a maximum of two (2) AMA PRA Category 1 Credits™. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/

This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives (LO) are listed on page 1.

1. What is the most consistent sign associated with Wernicke’s encephalopathy (WE) (LO #1)?
   [ ] a. Change in mental status  [ ] c. Ophthalmoplegia
   [ ] b. Transient global amnesia  [ ] d. Gait ataxia

2. According to Dr. Athanasiou, which of the following has the highest conversion rates to primary psychotic illness (LO #2)?
   [ ] a. Opioids  [ ] c. Hallucinogens
   [ ] b. Stimulants  [ ] d. Cannabis

3. Which of the following is most likely to delay the onset of delirium tremens symptoms (LO #3)?
   [ ] a. Impaired liver function due to liver damage or disease
   [ ] b. Rapid onset (less than six hours) of three or more mild to moderate alcohol withdrawal symptoms
   [ ] c. Polysubstance use of alcohol and benzodiazepines discovered during intake
   [ ] d. Presence of a comorbid condition associated with thiamine deficiency

4. According to a 2022 study on sublingual dexmedetomidine, which of the following statements is true (LO #4)?
   [ ] a. It was proven more effective than standard agitation medications
   [ ] b. It is fast acting and well tolerated
   [ ] c. It is recommended for elderly and adolescent populations
   [ ] d. Its most common side effects are nausea and asthenia

5. When administering thiamine for asymptomatic hospitalized patients with risk factors for WE, what prophylactic dose and route of administration are recommended (LO #1)?
   [ ] a. 50 mg oral  [ ] c. 200 mg intramuscular
   [ ] b. 100 mg intravenous  [ ] d. 100 mg oral

6. True or false: Symptoms of substance-induced psychosis resolve within four weeks (LO #2).
   [ ] a. True  [ ] b. False

7. Which of the following is a valid strategy for managing alcohol withdrawal symptoms using benzodiazepines in patients with a history of substance use disorders (LO #3)?
   [ ] a. Avoid use of benzodiazepines altogether in patients with a history of alcohol or substance misuse
   [ ] b. Utilize symptom-triggered dosing of benzodiazepines and discontinue use upon conclusion of treatment
   [ ] c. Opt for frequent, low doses of a short-acting benzodiazepine over a long-acting benzodiazepine
   [ ] d. Taper benzodiazepines gradually for up to two weeks following discharge

8. What did a 2022 study conclude regarding the relationship between depressive symptoms and gun ownership during the COVID-19 pandemic (LO #4)?
   [ ] a. Rates of gun ownership were significantly higher among individuals with depressive symptoms
   [ ] b. Depressive symptoms had no association with first-time gun purchases during the pandemic
   [ ] c. Non-depressed individuals were more likely to purchase a gun to protect themselves against someone they knew
   [ ] d. The overall rate of gun ownership fell during the pandemic
Research Updates
Continued from page 10
respectively. In contrast, 57% of respondents accessed GAH in adulthood.

After adjustments for potential confounders (including age, race, gender assigned at birth, sexual orientation, employment status, and previous pubertal suppression treatment), access to GAH during early or late adolescence was associated with significantly lower likelihood of past-month severe psychological distress (p<0.0001) or suicidal ideation (p=0.0007) compared with access to GAH in adulthood. Also, access to GAH in adolescence or adulthood was associated with significantly lower risk of suicidal ideation (p<0.001) compared to those who wanted but never accessed GAH.

CARLAT TAKE
Access to GAH in adolescence or adulthood is associated with improved mental health outcomes among transgender individuals, including lower rates of severe psychological distress and suicidal ideation. The results of this study support the Endocrine Society’s recommendation that transgender adolescents have access to GAH.

Learn more and search full archives online:
www.thecarlatreport.com