# Managing patients with comorbid OPIOID and ALCOHOL use disorders

## Consider the type and severity of withdrawal symptoms, patients' goals, and other factors

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When left untreated, opioid use disorder (OUD) is a debilitating and potentially lethal illness. Despite the availability of safe and effective medications for OUD, the prevalence of opioid use and overdose deaths has been increasing every year.[1] An additional challenge in OUD treatment is the high prevalence of comorbid alcohol use disorder (AUD).[2-6] A Clinical Trials Network survey from the National Institute on Drug Abuse found 38% of persons seeking treatment for OUD also had AUD.[7] Other analyses have found alcohol was involved in approximately one-fifth of opioid-related deaths.[8] Research also reveals that comorbid OUD and AUD contributes to poor treatment outcomes, more medical comorbidities, and a high risk of death (including overdose death).[4,9] There is no standard of care for this particular patient population.[3] This article reviews the evidence and summarizes practical considerations regarding the clinical management of patients with comorbid OUD and AUD.

To illustrate the various decision points, we will follow 2 hypothetical patients through various stages of treatment (***Figure, page 23***), from their presentation in the emergency department (ED) or outpatient clinic, through their hospital admission (if needed), and into their outpatient follow-up treatment.

CASE REPORTS

Ms. A and Ms. B present to the ED for evaluation of nausea, vomiting, sweating, anxiety, and tremor. Both patients describe their most recent use of both alcohol and opioids approximately 12 hours ago, and each has been attempting to stop using both substances at home.

continued

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**Comorbid OUD and AUD**

**Clinical Point**

**Overlapping features of alcohol withdrawal and opioid withdrawal include nausea, vomiting, diarrhea, sweating, anxiety, and tremor**

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## Decision-making in the emergency setting

In the ED, a few important decisions need to be made regarding treatment:

- Are the presenting symptoms primarily due to alcohol withdrawal syndrome (AWS), opioid withdrawal syndrome (OWS), or both?
- Does the patient require inpatient medical withdrawal management (detoxification) based on the history and severity of the withdrawal symptoms?
- What are the patient's treatment goals for their AUD and OUD?
- Is maintenance medication for OUD indicated? If so, which medication is most appropriate?

In the ED, the presentation of individuals affected by both OUD and AUD can be challenging because OWS shares overlapping features with AWS, including nausea, vomiting, diarrhea, sweating, anxiety, and tremor. However, although acute OWS is typically very uncomfortable, it is rarely lethal. On the other hand, severe AWS may result in delirium, seizures, and death,[10] which makes it essential to recognize and treat appropriately.

Both Ms. A and Ms. B should be medically evaluated and treated by an emergency medicine physician in conjunction with psychiatric (or addiction medicine) consultation. The ED assessment of a patient presenting with both AUD and OUD should include vital signs monitoring; physical examination; blood work including comprehensive metabolic panel, serum magnesium, and phosphorus; complete blood count; pregnancy test for women of reproductive age; urine drug screen (UDS); urinalysis; and serum ethanol level. Of note, sympathetic hyperactivity is found in both alcohol and opioid withdrawal, and patients with alcohol withdrawal may also have hypokalemia, a condition associated with an increased risk of arrhythmia. Furthermore, a prolonged QTc would affect clinical decision-making about medications for OUD (ie, methadone) and withdrawal management (ie, ondansetron, trazodone, and hydroxyzine). Therefore, an electrocardiogram should be conducted, where appropriate.

Initial treatment of AWS includes vitamin supplementation (thiamine, folic acid, and multivitamins) and benzodiazepine administration (symptom-triggered and/or scheduled taper). It may also include IV fluid resuscitation, analgesics for pain, ondansetron for nausea and vomiting, and other electrolyte repletion as indicated by the laboratory results.[11] Additional measures for patients in opioid withdrawal should include alpha-2 agonists such as clonidine or lofexidine for adrenergic symptoms, antiemetics, antidiarrheals, muscle relaxants, anxiolytics such as hydroxyzine, and sleep medications such as trazodone.[12]

The next decision is whether the patient needs to be admitted for inpatient treatment. This decision is based primarily on the risk assessment and severity of AWS, including a compelling history of complicated AWS such as seizures or delirium tremens as well as consideration of the complexity and severity of any comorbid medical or psychiatric conditions. Other indications for medical withdrawal management include a history of unsuccessful ambulatory withdrawal management and pregnancy. For severe AWS, a scheduled benzodiazepine taper in addition to the symptom-triggered protocol should be considered.[13-15] A psychiatric evaluation may be obtained in the ED, as long as the patient is sober enough to meaningfully participate in the psychiatric interview. Wherever possible, psychiatric interviews should be supplemented by collateral information.

**CASE REPORTS CONTINUED**

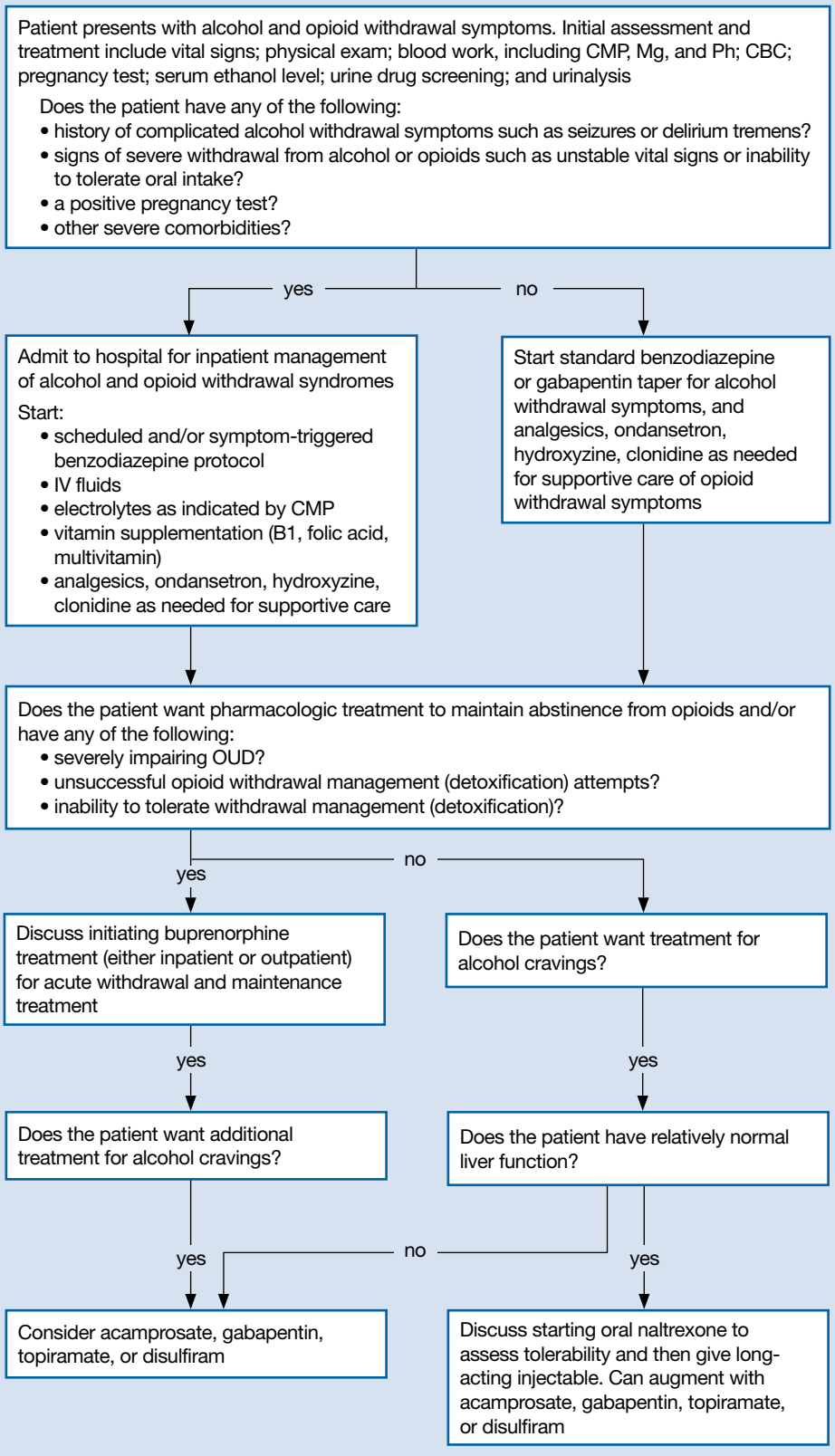
Ms. A admits to a 5-year history of alcohol and opioid use that meets the criteria for severe AUD and severe OUD. She has previously required inpatient treatment for seizures related to AWS. Laboratory results are notable for a serum ethanol level of 380 mg/dL, UDS positive for opioids, and a negative pregnancy test.

## Disposition of patients in alcohol and opioid withdrawal

Given Ms. A's history of seizures while withdrawing from alcohol, she is appropriate for hospital admission for medically managed withdrawal observation. As previously mentioned, there is clinical overlap between AWS

Figure

## Treating patients with comorbid AUD and OUD




AUD: alcohol use disorder; CBC: complete blood count; CMP: comprehensive metabolic panel; Mg: serum magnesium; OUD: opioid use disorder; Ph: phosphorous

### Clinical Point

**Acute opioid withdrawal is rarely lethal, but severe alcohol withdrawal may result in delirium, seizures, and death**

**Comorbid OUD and AUD**

**Clinical Point**

**Buprenorphine or methadone should be prescribed with caution to patients with uncontrolled alcohol use disorder**

and OWS, and differentiating between the 2 syndromes is essential and may be lifesaving. Whereas anxiety, agitation, diaphoresis, tachycardia, hypertension, and insomnia can be seen in both opioid and alcohol withdrawal, OWS-specific symptoms include mydriasis, lacrimation, rhinorrhea, bone or joint aches, yawning, and piloerection. AWS may present with visual or tactile hallucinations, delirium, and grand mal seizures.[15]

The details of inpatient management are beyond the scope of this article; however, both patients should be started on thiamine, folic acid, and a multivitamin. For patients in alcohol withdrawal with a history of poor diet who appear malnourished or have a history of malabsorption (such as gastric bypass surgery), thiamine 100 mg/d IV should be given for 3 to 5 days to prevent Wernicke encephalopathy.[16] Where there is any concern the patient may be exhibiting signs of Wernicke-Korsakoff Syndrome (impaired cognition, evident malnourishment, ataxia, or eye movement abnormalities), high-dose thiamine IV should be given presumptively as follows: 500 mg IV 3 times a day for 3 days, 250 mg/d IV for 5 days, and then oral supplementation 100 mg/d for at least 30 days.[17]

In summary, on presentation to the ED, both patients should be medically stabilized and started on benzodiazepines for alcohol withdrawal. The risk assessment and the severity of the AWS often determines the level of care.

**CASE REPORTS CONTINUED**

On hospital Day 2, Ms. A tells the consulting psychiatrist she would like to start medications to treat her substance use disorders. She has a long history of failed attempts to achieve abstinence from opioids, so she and the psychiatrist agree to initiate a trial of buprenorphine/naloxone for her OUD, 4 mg/1 mg to 8 mg/2 mg for Day 1. Although buprenorphine/naloxone seems to help her alcohol cravings somewhat, she requests additional help. She experiences migraine headaches, which is in part why she began using opioid medications. Via joint decision making with her psychiatrist, she agrees to a trial of topiramate, with a slow titration schedule starting at 25 mg/d.

## Management decisions: Buprenorphine for OUD

The next issue is to determine the appropriate treatment for the patient's OUD. Although treating OWS is important in improving the patient's health, decreasing their discomfort, and facilitating their participation in a psychosocial treatment program,[18] current evidence suggests that opioid withdrawal management alone without medication for OUD rarely leads to long-term recovery.[19,20] Some research suggests that the risk of accidental opioid overdose immediately following acute withdrawal management may actually be increased due to decreased tolerance in these patients.[12,21,22]

Three medications have the most evidence for OUD treatment: buprenorphine, methadone, and naltrexone.[15] The decision to use buprenorphine, methadone, or naltrexone depends on a variety of factors, including the severity of the OUD, patient history of prior treatment successes and failures, comorbid medical and psychiatric conditions, and patient preference.[4] Treatment with buprenorphine or methadone is preferred over naltrexone for patients who do not want to or cannot tolerate the physical and emotional discomfort of the opioid withdrawal process, who experience moderate to severe OUD, who have a history of failed abstinence-based treatment, or who have more severe physiological tolerance/dependence.[12] Buprenorphine is a mu opioid receptor partial agonist that has been shown to reduce opioid cravings,[23] provide moderate pain relief,[24] and ameliorate OWS.[12] It does not typically result in significant respiratory depression, which is the biggest safety concern for opioid use.[12] Buprenorphine may also treat comorbid AUD at higher doses; however, the data are inconclusive.[25,26] Buprenorphine should be prescribed with caution to patients with comorbid, uncontrolled AUD, due to the risk of respiratory depression when combined with alcohol. Patients who continue to drink alcohol but are able to abstain from opioids may consider starting an AUD-specific medication. Pharmacologic options are discussed in more detail in the next section.

For patients who have higher physiological dependence or more severe OUD,

methadone may be a reasonable alternative to buprenorphine. Methadone, a mu-opioid receptor agonist, ameliorates OWS, reduces opioid cravings, and reduces the euphoric effects of opioid ingestion if the patient relapses. However, methadone can only be dispensed for the treatment of OUD by a federally-certified treatment program governed by restrictive and federally mandated guidelines. Compared to buprenorphine, methadone is more dangerous in overdose, has more drug interactions, and is more commonly diverted for recreational use.[27] Furthermore, methadone should be prescribed with caution to patients with comorbid, uncontrolled AUD, because both alcohol and methadone can result in respiratory depression.

By contrast, the first-line treatment for individuals experiencing moderate to severe AUD is typically naltrexone.[28] Naltrexone is contraindicated in Ms. A because she has a severe OUD and is unlikely to tolerate the opioid withdrawal process. Research suggests that the use of naltrexone for OUD should be limited to patients who have a mild disorder or who show low physiological dependence.[29] Alternatively, acamprosate, disulfiram, topiramate, or gabapentin should be considered for Ms. A.[4,28,30] Because each of these medications have specific strengths and weaknesses, medication selection should be based on individual patient factors such as comorbid psychiatric and medical conditions and/or patient preference.[28]

## Management decisions: AUD augmentation strategies

Naltrexone is contraindicated for patients who are receiving opioids, including opioid agonist therapy for OUD. Therefore, clinicians need to consider other options for these individuals. There are several medications with good evidence, including acamprosate, disulfiram, topiramate, and gabapentin. Acamprosate and disulfiram are FDA-approved for AUD; the latter 2 have been used off-label.

Acamprosate is a glutamate receptor modulator that reduces alcohol cravings and is recommended for patients who have achieved and wish to maintain abstinence. It can be used in patients with liver disease, because it is not hepatically metabolized.[30] Topiramate is also used to reduce alcohol cravings. It antagonizes glutamate at alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) and kainite receptors, facilitates gamma-aminobutyric acid (GABA) function, and reduces the extracellular release of dopamine in the mesocorticolimbic regions of the brain.[30] Topiramate is a reasonable option for patients with a seizure disorder, a history of migraine headaches,[30] or who are overweight or obese and wish to lose weight.[31] In a nonrandomized study, topiramate reduced alcohol intake and cravings more than naltrexone.[32]

Disulfiram is another second-line therapy for AUD. It is best used under close supervision because it does not reduce alcohol cravings but makes ingesting alcohol extremely aversive by preventing the breakdown of the alcohol metabolite acetaldehyde, and in doing so causes a cluster of unpleasant symptoms, including sweating, palpitations, flushing, nausea/vomiting, and increased sympathetic tone.[28] Disulfiram only works if it is taken daily, and it requires a high degree of motivation and/or daily supervision at home or in the clinic.[33] It is not recommended to be used as a first-line treatment based on its potential toxicity, adverse effects, and mixed findings on its efficacy. In addition, it should not be given to medically vulnerable/fragile individuals.

Lastly, gabapentin, a voltage-gated calcium channel modulator, may also be used as a second-line agent for AUD. Patients who have started alcohol withdrawal management with gabapentin may wish to continue treatment to assist with craving suppression.[30] It is also a good choice for patients who have comorbid diabetic neuropathy or other neuropathic pain conditions, anxiety, or insomnia.[30,34] Of note, there have been reports of gabapentin misuse.

**CASE REPORTS CONTINUED**

Ms. B presents to the ED with a 5-year history of moderate AUD and a 2-year history of mild OUD. She denies a history of severe or complicated AWS. Her laboratory results are sig-

**Clinical Point**

**Naltrexone targets both AUD and OUD but is contraindicated in patients who are receiving opioid agonists for OUD**

Comorbid OUD and AUD

## Related Resources

- Chaney L, Mathia C, Cole T. Transitioning patients with opioid use disorder from methadone to buprenorphine. Current Psychiatry. 2022;21(12):23-24,28. doi:10.12788/cp.0305
- Eatmon CV, Trent K. Pharmacotherapy for alcohol use disorder in patients with hepatic impairment. Current Psychiatry. 2021;20(12):25-28. doi:10.12788/cp.0068

**Drug Brand Names**

Acamprosate • Campral
Buprenorphine/naloxone • Suboxone, Zubsolv
Clonidine • Catapres
Disulfiram • Antabuse
Gabapentin • Neurontin
Hydroxyzine • Vistaril
Lofexidine • Lucemyra
Methadone • Methadose, Dolophine
Naloxone • Narcan
Naltrexone • ReVia, Vivitrol
Ondansetron • Zofran
Topiramate • Topamax
Trazodone • Desyrel, Oleptro

**Clinical Point**

**Options for patients with AUD who can't take naltrexone include acamprosate, disulfiram, topiramate, and gabapentin**

nificant for a serum ethanol level of 250 mg/dL, UDS positive for opioids, and a negative pregnancy test.

### Management decisions: Naltrexone for OUD

In contrast to Ms. A, Ms. B is likely able to complete the opioid withdrawal management process. It is reasonable to treat her uncomplicated, moderate alcohol withdrawal as an outpatient with gabapentin or a benzodiazepine taper. Had her AUD been as severe as Ms. A's, or if she were unsuccessful with ambulatory withdrawal treatment attempts, Ms. B would also be a candidate for inpatient medical treatment for alcohol withdrawal regardless of the severity of her OUD. Ongoing pharmacotherapy for her AUD after withdrawal management is the same as previously outlined. After Ms. B completes the taper (typically 1 week after the ED visit), she should follow up for initiation of pharmacotherapy for AUD. Ms. B is an ideal candidate for naltrexone, which targets both AUD and OUD.

Naltrexone is a semi-synthetic competitive antagonist at mu-opioid receptors and a partial agonist at kappa receptors; it has little to no activity at delta receptors. Naltrexone has been shown to reduce alcohol cravings and diminish the euphoric effects of alcohol by reducing endogenous opioid release and receptor activation.[35] Thus, even when patients do use alcohol while taking naltrexone, the amount of alcohol they use is typically substantially reduced.[36] In fact, at a standard dose of 50 mg/d, 95% of mu-opioid receptors are occupied and are shown to yield approximately 40% alcohol abstinence rates at 1 year.[36]

Once Ms. B has completed withdrawal management from both alcohol and opioids, she should have a trial period of oral naltrexone to prove tolerability, and then transition to the long-acting injectable (LAI) formulation. Patients able to complete withdrawal management from opioids and transition to LAI naltrexone have been shown to have equivalent rates of successful abstinence from opioids compared to buprenorphine.[37] Though Ms. B could opt to try buprenorphine to treat her mild OUD, naltrexone would be the preferred option because it has 3 advantages:

- it blocks the mu-opioid receptor, which prevents euphoria if an illicit substance is used
- it does not cause physiologic dependence or withdrawal syndrome if/when stopped
- if it is not effective, it is easy to switch to buprenorphine.

Lastly, all patients with OUD should be prescribed a rescue naloxone kit, in accordance with harm-reduction guidelines. Naloxone, a potent opioid receptor antagonist, is used to prevent or reverse respiratory depression in opioid overdose. Naloxone rescue kits include intranasal naloxone, which makes it easy for nonclinician bystanders to administer while waiting for

## Bottom Line

Patients with comorbid opioid use disorder (OUD) and alcohol use disorder (AUD) often pose significant management challenges when they present in withdrawal. This article reviews the evidence and summarizes practical considerations regarding the clinical management of patients with comorbid OUD and AUD.

emergency transport.[38] Most states allow naloxone kits to be prescribed to individuals who have a concern for overdose among friends, family, or others in the community. The wide distribution and easy availability of naloxone rescue kits have been essential in decreasing overdose deaths among patients who misuse opioids.[39]

## Take-home points

Patients with both OUD and AUD are relatively common and often pose significant management challenges when they present to the clinic or the ED in withdrawal. Because severe AWS can be life-threatening, hospitalization should be considered. OWS is often accompanied by intense cravings that can lead to relapse and the risk of accidental opioid overdose/death. As soon as patients are able to engage in a discussion about their treatment options, clinicians need to clarify the patient's goals and priorities. In medications for OUD, the decision of whether to use buprenorphine, naltrexone, or methadone is guided by the severity of the OUD, the patient's past treatment experience (illicit as well as prescribed), and patient preference. If the OUD is mild or if the patient prefers to avoid opioid agonist medications and can tolerate the opioid withdrawal process, both the AUD and OUD can be treated with naltrexone, preferably with the LAI formulation. Other AUD medications and outpatient psychotherapy may be used to augment treatment outcomes. For patients with a moderate to severe OUD, buprenorphine (preferably with immediate initiation) or methadone therapy should be offered. Patients with comorbid OUD and AUD who are treated with opioid agonists should be offered medication for AUD other than naltrexone, as outlined above. All patients with substance use disorders would benefit from psychosocial interventions, including group and individual therapy as well as community sober support groups.

### Clinical Point

**All patients with opioid use disorder should be prescribed a rescue naloxone kit to use in the event of an opioid overdose**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continued

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**Comorbid OUD and AUD**

## Clinical Point

**Patients with AUD and OUD would benefit from psychotherapy and community support groups**


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