Naltrexone Treatment for Alcohol Use Disorder

Elliott Brady, MD, MPH
Vittoria Boni, MD
Family Physicians
Family Medicine Residency Program
Penn Medicine Lancaster General Health

Jon Lepley, DO, FAOAAM
Medical Director of Addiction Medicine
Lancaster General Health Physicians


Brady


Boni


Lepley

CASE VIGNETTE

A 38-year-old man presents to his primary care provider to establish care. He is obese and mildly hypertensive, with a BMI of 32 and blood pressure measuring 142/86. He does not smoke cigarettes or use illicit drugs but reports consuming a six-pack of beer four days per week. Sometimes he drinks even more heavily, leading to arguments with his spouse and a hangover the next day.

He occasionally misses work after a very heavy drinking day. He has tried to quit drinking but usually only manages to abstain for a few weeks before returning to his previous pattern. He has not consumed alcohol for the past five days but reports routinely feeling the urge to purchase alcohol on his way home from work. He does not display any symptoms of clinical depression. He is not interested in behavioral counseling but is willing to consider medication to help him cut back on his alcohol use.

BACKGROUND

Excess alcohol consumption is associated with short-term and long-term health consequences. The impairing effects of alcohol predispose individuals to being involved in motor vehicle accidents, perpetrate intimate partner violence, and undertake risky sexual behaviors that can result in unintended pregnancy or sexually transmitted diseases. Over time, heavy consumption of alcohol is associated with many chronic health problems, including obesity, hypertension, sleep apnea, and gastrointestinal cancers.[1]

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines heavy alcohol consumption as more than four drinks per day or more than 14 drinks per week for men, and more than three drinks per day or more than seven drinks per week for women.[2] The rationale for these differences is based on variation in biological factors between sexes, and these recommendations are based on sex assigned at birth rather than gender identity.

Although excess alcohol consumption is associated with health risks, alcohol use disorder (AUD) is not defined by how much alcohol is consumed. The essential features of AUD are a compulsion to drink alcohol, impaired control over alcohol use, and negative consequences that result from alcohol consumption. A diagnosis of AUD is made by clinical interview. Diagnostic criteria are defined in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (see Table 1 on page 106).[3]

Naltrexone is one of three medications approved by the Food and Drug Administration (FDA) to treat AUD. The other two medications are acamprosate and disulfiram. The recommended dosing of acamprosate involves taking six capsules daily; its utility is limited by difficulty adhering to this regimen. Disulfiram causes a severe aversive reaction in the face of alcohol consumption, and these adverse effects, poor adherence, and lack of published effectiveness limit its use.[4] As a result, naltrexone is generally considered the mainstay of treatment.

PATHOPHYSIOLOGY

Alcohol exerts an influence on four critical neurotransmitter systems in the brain. These are gamma-aminobutyric acid (GABA), glutamate, dopamine, and endogenous opioids (endorphins). GABA is an inhibitory neurotransmitter that suppresses neuronal excitability throughout the central nervous system. Glutamate is the most abundant excitatory neurotransmitter in the brain and plays a crucial role in shaping learning and memory.[5] Dopamine and endorphins exert influence within the ventral tegmental area (VTA) and nucleus accumbens (NAc) — brain regions involved in reward, pleasure, and assignment of salience to environmental cues.

Alcohol's influence over these neurotransmitters is dose dependent. Relatively low doses of alcohol can stimulate glutamate, dopamine, and endogenous opioid activity in the VTA and NAc. This may produce a sensation of arousal and increased energy.[6] These effects may be responsible for the reinforcement of alcohol use despite negative consequences in people who develop an AUD. Naltrexone exerts blockade at opioid receptors within the VTA and NAc (see Fig. 1) to reduce or eliminate the reinforcing effects of alcohol.[7]

At higher doses, alcohol mimics the effects of GABA and suppresses the excitatory neurotransmitter glutamate.[8] The effect on GABA accounts for alcohol's potential to cause somnolence and impaired motor function during intoxication. Abrupt cessation of alcohol after prolonged heavy consumption is associated with a surge in glutamate activity causing neurologic excitation associated with an alcohol withdrawal syndrome.[9] Naltrexone attenuates the opioid-mediated release of GABA in the VTA (see Fig. 1) but does not offset the impairing effects of alcohol or prevent or treat alcohol withdrawal.

Functional neuroimaging studies demonstrate differential effects in these neurochemical pathways among people with AUD compared to social drinkers.[10,11] Individuals with AUD will crave alcohol during periods of abstinence due to increased recruitment of stress peptides in the extended amygdala and experience a powerful reinforcing effect through dopaminergic pathways in the NAc.[12] This contributes to an inability to control their use, heavy consumption, and development of tolerance. The pattern of alcohol use that emerges results in short-term impairment, long-term physical health problems, and adverse psychosocial consequences. These observable features that define AUD are rooted in neurobiology gone awry and validate the conceptualization of AUD as a brain disease.

SCOPE OF THE PROBLEM

In a 2021 national survey, 29.5 million people in the United States over 12 years of age had AUD in the past year.[13] This equates to 10.6% of the adult and adolescent population. Alcohol is the most common substance implicated in substance use disorders, with affected individuals outnumbering those affected by marijuana, cocaine, heroin, hallucinogenic agents, inhalants, methamphetamine, and prescription drugs combined.[13] People aged 18 to 25 years are most likely to have an AUD, encompassing 15% of people in this demographic.

The environmental factors associated with the COVID-19 pandemic have contributed to a remarkable surge in the prevalence of AUD. Over the first two decades of the 21st century, the United States saw a gradual decline in the prevalence of AUD from 7.7% in 2002 to 5.3% in 2019.[14] The alarming spike in 2021 to more than 10% of the population with AUD

Table 1. Alcohol Use Disorder Diagnostic Criteria[3]

1	Alcohol is often taken in larger amounts or over a longer period than was intended.
2	There is a persistent desire or are unsuccessful efforts to cut down or control alcohol use.
3	A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4	Craving, or a strong desire or urge to use alcohol.
5	Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6	Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7	Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8	Recurrent alcohol use in situations in which it is physically hazardous.
9	Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10	Tolerance, as defined by either of the following: a) a need for markedly increased amounts of alcohol to achieve intoxication or desired effect; b) a markedly diminished effect with continued use of the same amount of alcohol.
11	Withdrawal, as manifested by either of the following: a) the characteristic withdrawal syndrome for alcohol; b) alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

— Mild: The presence of 2-3 symptoms. — Moderate: The presence of 4-5 symptoms. — Severe: The presence of 6 or more symptoms. —

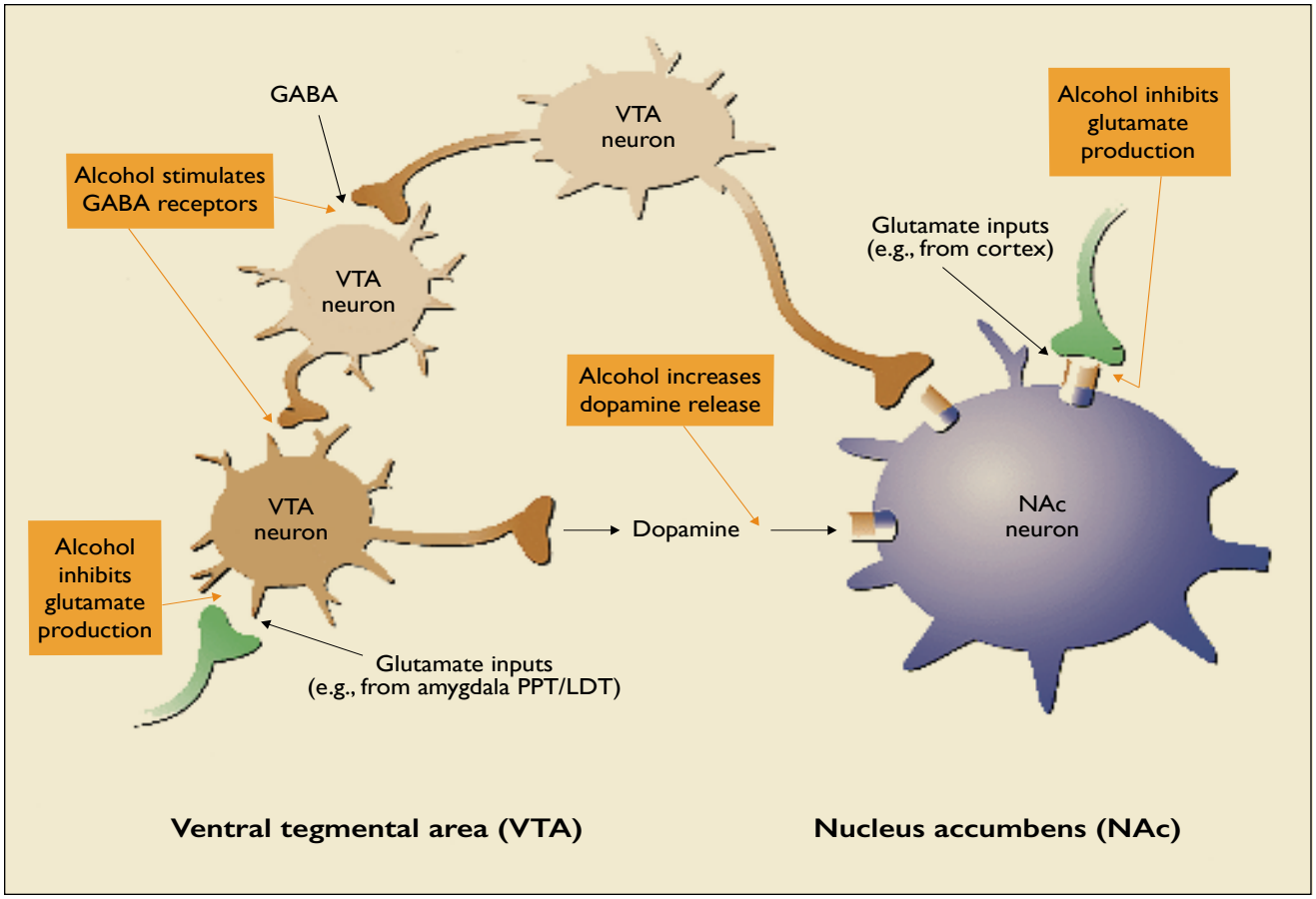

Fig. 1. Neurobiological pathways in alcohol use disorder.

may partly be explained by differences in data collection and a shift toward greater utilization of web-based surveys post-pandemic.[13] However, the COVID-19 pandemic and associated social isolation contributed to a secondary public health crisis around substance-related morbidity and mortality.

For the first time in 60 years, estimated life expectancy in the United States is in a state of decline.[15] Currently, alcohol contributes to nearly 15% of deaths among people aged 20 to 49 years and 20% of deaths that occur in people under 20 years of age.[16] Alcohol-related mortality increased by more than 20% in 2020 and 2021,[17] and alcohol has been implicated in 20% of substance overdose deaths in Lancaster County since the beginning of the COVID-19 pandemic.[18]

Despite this profound impact, AUD is often undiagnosed and inadequately treated. Fewer than 10% of people with AUD receive any treatment. Among the minority who receive treatment, effective medications are grossly underutilized, with just 1.6% of individuals with AUD reporting receipt of medication for their problem.[14]

EVIDENCE FOR EFFICACY OF NALTREXONE

Naltrexone is a semi-synthetic opioid with close structural similarity to oxymorphone, though it does not exert any agonist activity at the mu-opioid receptor. Instead, it is a competitive antagonist at mu-opioid receptors in the central nervous system. When treating AUD, this blockade may diminish dopaminergic effects that would otherwise reinforce alcohol consumption.[19] Additionally, naltrexone has been shown to reduce cravings for alcohol when alcohol-dependent individuals are exposed to environmental cues.[20]

Peak serum levels of naltrexone occur relatively quickly, about 60 minutes after oral administration, undergoing first-pass metabolism independent of cytochrome P450 enzymes, yielding its active metabolite 6-beta-naltrexol.[21] The elimination half-life of naltrexone and its active metabolite is 4 and 13 hours, respectively.[22]

Naltrexone was approved by the FDA to treat AUD in 1984 on the strength of animal models that demonstrated its efficacy.[23] Subsequent placebo-controlled trials showed that the medication reduces

alcohol cravings, supports alcohol abstinence, and reduces heavy drinking.[24,25]

While one multi-site trial involving 627 male Veterans Affairs patients characterized as "older, heavier drinkers, with long duration of alcoholism" failed to show evidence of long-term benefit from naltrexone 50 mg daily combined with psychosocial interventions,[26] the COMBINE study enrolled 1,383 patients among 11 academic sites and studied the effect of naltrexone 100 mg per day among individuals with less severe alcohol problems. In this trial, even without additional behavioral interventions, naltrexone reduced heavy drinking and improved rates of alcohol abstinence compared to placebo.[27] Systematic reviews further validate that naltrexone reduces heavy drinking and increases abstinence rates.[28,29]

Hepatotoxicity has historically been ascribed to naltrexone, but randomized controlled trials support that naltrexone is not hepatotoxic at therapeutic doses.[30,31] An expert panel convened by the Substance Abuse and Mental Health Services Administration (SAMHSA) in 2016 concluded that naltrexone treatment should not be delayed while awaiting results of liver function testing, and frequent testing in the absence of clinical findings such as jaundice, abdominal pain, nausea, or vomiting is unwarranted.[32] The safety and efficacy of naltrexone in individuals with a severe hepatic impairment such as cirrhosis are unknown, and caution in this population is warranted.

Concerns about medication adherence among people with AUD, paired with the relatively short half-life of naltrexone, have led to the development of a naltrexone 380 mg extended-release injectable formulation.[33] This is commonly known as naltrexone XR or its brand name Vivitrol®. Randomized controlled trials validate that naltrexone XR is superior to placebo in supporting a goal of abstinence and reducing heavy drinking.[33,34]

No prospective, double-blind, randomized controlled trials compare naltrexone XR to oral naltrexone when treating AUD. The superiority of one product over the other remains uncertain. The choice of naltrexone formulation can be individualized based on cost, patient preference, and ability to adhere to an oral formulation.

CLINICAL CONSIDERATIONS WHEN PRESCRIBING NALTREXONE

Naltrexone therapy is most effective when initiated after at least four days of abstinence from alcohol.[6,34] Individuals who consume alcohol daily for extended periods may develop alcohol withdrawal syndrome (AWS) when they attempt to abstain from alcohol. Untreated AWS can progress to seizures and delirium tremens, with a reported mortality rate of 1% to 5%.[35]

Clinicians should inquire about symptoms when their patient attempts to abstain from alcohol. Table 2 displays the Short Alcohol Withdrawal Scale,[36] which describes symptoms of AWS using lay terms. Patients who report these symptoms within 6 to 24 hours of abstinence from alcohol should receive medication treatment for AWS before beginning naltrexone treatment.

Ambulatory treatment of AWS by an experienced clinician may be considered for uncomplicated patients with mild-to-moderate symptoms.[37,38] Patients with a history of complicated withdrawal, seizures, delirium tremens, or co-occurring psychiatric disorders should be referred to a residential treatment setting for withdrawal management.[38] Patients using multiple substances also may be better served in a specialized residential treatment setting for substance withdrawal before naltrexone initiation.

Table 2. Short Alcohol Withdrawal Scale (SAWS)

Item	None (0)	Mild (1)	Moderate (2)	Severe (3)
Anxious				
Feeling confused				
Restless				
Miserable				
Problems with memory				
Tremors (shakes)				
Heart pounding				
Sleep disturbance				
Sweating				

The patients fill in the SAWS by ticking the appropriate boxes showing how they have been feeling for each of the 10 symptoms in the previous 24 hours. Each item is scored on a four-point scale: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. The scores are summed up to give a total score. Total scores suggest severity of withdrawal: mild withdrawal <12 points; moderate-to-severe withdrawal ≥12 points.

Adapted from Elholm et al.[36]

Naltrexone can precipitate withdrawal if administered to an individual with physiologic opioid dependence and can hinder the effectiveness of opioid analgesics. Therefore, naltrexone is contraindicated in patients who require long-term opioid therapy for chronic pain or opioid agonist treatment for opioid use disorder. Patients should abstain from all opioids for at least seven days before receiving naltrexone treatment. Patients who regularly used opioids before the period of abstinence should also undergo urine toxicology testing before starting naltrexone, as some opioids may linger and exert clinically significant effects beyond this seven-day window.[39]

Naltrexone should be initiated at 25 mg daily for the first week of treatment and then increased to 50 mg daily. Common adverse effects are nausea, vomiting, abdominal discomfort, headache, and fatigue; lower starting doses may minimize these effects.[6] Patients may continue taking naltrexone even if they return to drinking alcohol because naltrexone will not cause a disulfiram-like reaction in the face of alcohol consumption. Patients who continue to drink heavily despite adherence to naltrexone may increase their dose to 100 mg daily. Individuals who cannot adhere to a daily medication or do not display improvement with oral naltrexone may be candidates for monthly injections of naltrexone XR.

Because of the potential to hinder the effectiveness of opioids prescribed for pain, oral naltrexone should be discontinued at least three days before an elective surgery, and naltrexone XR should not be administered within six weeks of an elective surgery. Acute emergency pain management in a patient receiving naltrexone XR is a complex problem potentially requiring expertise from Pain Management and Anesthesiology. Patients receiving naltrexone XR should consider a medical alert card or bracelet to notify health care providers of their use of this medication in emergency or trauma settings.

Naltrexone may be more effective when combined with psychosocial interventions, though there is a consensus that no single counseling modality works best for every patient. Project MATCH was an ambitious NIAAA-sponsored study that sought to identify the best therapeutic modality for AUD based on individual patient characteristics.[40]

The study showed that cognitive behavioral therapy (CBT), motivation enhancement therapy (MET), and twelve-step facilitation (TSF) were equally effective at reducing alcohol consumption.[41] The only significant correlation revealed that patients with low psychiatric severity displayed more abstinent days with TSF compared to CBT,[41] and patients with high anger traits fared better with MET.[42]

A secondary analysis of Project MATCH data revealed low correlation between treatment attendance and effect size.[43] Many patients had good outcomes without receiving these interventions. Therefore, patients can be referred to adjunctive behavioral therapies, but medication should not be withheld when these interventions are declined or unavailable.

KEY TAKEAWAYS

Patients should abstain from all opioids for at least seven days before receiving naltrexone treatment.

Patients may continue taking naltrexone even if they return to drinking alcohol because naltrexone will not cause a disulfiram-like reaction in the face of alcohol consumption. Patients who continue to drink heavily despite adherence to naltrexone may increase their dose to 100 mg daily.

Patients should be advised to abstain from alcohol but to continue taking naltrexone and attend follow-up appointments if they fail to achieve that goal. Abstinence from alcohol is ideal, but a good clinical response may be defined by a substantial reduction in alcohol use to an amount that falls within limits defined by NIAAA.

Patients should be reassessed within one month of initiating treatment or changing the dose or formulation. Patients should be evaluated every three to six months after a good clinical response is achieved. The optimal duration of naltrexone treatment is unknown. Patients may consider medication discontinuation with close follow-up if they achieve a good clinical response over at least four months of treatment.[6]

CASE VIGNETTE CONCLUSION

The patient in the case vignette meets the criteria for a moderate AUD. He may find it reassuring to learn that this is a common medical problem with a basis in neurobiology and that effective treatments exist. He has abstained from alcohol for at least four days

without displaying a need for treatment of AWS. He does not use opioids or other illicit drugs, and there is no clinical suspicion of severe hepatic impairment. He is a good candidate for naltrexone treatment.

Naltrexone can be prescribed at a dose of 25 mg for the first six days and then increased to 50 mg daily. Clinicians should recommend baseline labs that include liver function testing, but medication should not be delayed or withheld pending these results. He should be reevaluated within one month of beginning the medication. If he fails to achieve a good clinical response, clinicians should inquire about medication adherence and consider increasing his dose to 100 mg daily or changing to naltrexone XR monthly injections.

After achieving a good clinical response, naltrexone should be continued for at least four months. The patient's need for treatment of hypertension and obesity should be reevaluated in the context of the elimination of unhealthy alcohol use as a contributing factor. If his relationship problems and absenteeism at work do not resolve, he should be encouraged to reconsider his stance against behavioral counseling and offered a referral to behavioral health for care coordination.

He may choose to discontinue naltrexone treatment after several months of abstinence or well-controlled alcohol use that falls within NIAAA guidelines. As with all patients, routine screening for problem alcohol use should be incorporated into future annual health surveillance, and naltrexone treatment can be reinstituted when indicated.

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Elliott Brady, MD, MPH
Family Medicine Residency Program
Penn Medicine Lancaster General Health
540 N. Duke St.
Lancaster, PA 17602
717-544-4950
Elliott.Brady@pennmedicine.upenn.edu

Vittoria Boni, MD
Family Medicine Residency Program
Penn Medicine Lancaster General Health
540 N. Duke St.
Lancaster, PA 17602
717-544-4950
Vittoria.Boni@pennmedicine.upenn.edu

Jon Lepley, DO, FAOAAM
Addiction Medicine
Lancaster General Health Physicians
609 N. Cherry St.
Lancaster, PA 17602
717-544-2120
Jon.Lepley@pennmedicine.upenn.edu