

# Medications for Addiction Treatment: An Opportunity for Prescribing Clinicians to Facilitate Remission from Alcohol and Opioid Use Disorders

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## ABSTRACT

Substance use disorders are a leading cause of morbidity and mortality in the United States. Medications for the treatment of substance use disorders are effective yet underutilized. This article reviews recent literature examining medications used for the treatment of alcohol and opioid use disorders. The neurobehavioral rationale for medication treatment and the most common ways medications work in the treatment of substance use disorders are discussed. Finally, the medications and the evidence behind their effectiveness are briefly reviewed. Physicians and other prescribing clinicians should take an active role in facilitating remission and recovery from substance use disorders by prescribing these effective medications with brief medical management counseling.

**KEYWORDS:** Substance use disorders, addiction, addiction treatment, medication

## INTRODUCTION

Substance use disorders are common cause of morbidity and mortality,<sup>1</sup> and costly to society.<sup>2</sup> Medications are effective tools in the contemporary treatment of alcohol and opioid use disorders. Despite their effectiveness, these medications are greatly underutilized, particularly for alcohol use disorders.<sup>3</sup> This article reviews the rationale for the use of medications in addiction treatment and the currently available options for clinical use.

### Neurobehavioral Rationale for Medications in Addiction Treatment

People typically misuse substances initially to activate the brain's reward centers to make themselves feel good. Abusable substances produce euphoria or other pleasurable sensations rapidly and reliably, the ideal situation for operant conditioning. With chronic use, behavioral conditioning from the reinforcing effects of these substances produce long-lasting, quasi-permanent changes in the limbic and cortical systems that manage drives, reward and motivation, learning and memory, judgment, emotion and impulse control. These neurophysiological changes preserve memory of the euphoria and a basic drive to re-experience it, leading to the learned compulsive use behavior, loss of control,

craving, and use despite adverse consequences that characterize addictive disorders. The rapid onset and short-acting nature of most substances of abuse means that dosing, and the often-antisocial behaviors associated with drug procurement, must occur multiple times per day. In addition, many substances (e.g., opioids) produce dysphoria, craving and other adverse withdrawal symptoms when the substance is absent, a form of negative reinforcement for drug cessation. Over time, the development of tolerance means that larger doses, more potent compounds or more bioavailable routes of administration (i.e., injection) must be employed to stave off withdrawal and achieve euphoria. For example, chronic opioid users commonly reach a point where they are no longer getting high and only use to prevent withdrawal and "feel normal" – a common impetus to seek treatment.

### How Medications Work In Addiction Treatment

Contemporary medication addiction treatment (MAT) generally works in one or more ways. MAT:

- (1) Attenuates the euphoria reward, helping to extinguish drug use and associated antisocial/dysfunctional behaviors;
- (2) Reduces withdrawal symptoms and thereby the negative conditioning that deters cessation of drug use; or
- (3) Produces aversive symptoms with use of the substance (i.e., punishment).

Commonly heard concerns about "substituting one addiction for another" arise from a misunderstanding of the behavioral definition of addiction. Although some medications (e.g., long-acting opioids like methadone or buprenorphine) do maintain physical dependence (i.e., tolerance and withdrawal on cessation), it should not be confused with the behavioral disorder of addiction. Most contemporary addiction medications work by attenuating the reinforcing (i.e., addicting) effects of substances. Pure antagonists like naltrexone block the positive reinforcement from euphoria, but do not address the dysphoria and other symptoms of withdrawal. The substitution of long-acting oral agonist medication like methadone reduces both the positive reinforcing euphoria of short-acting opioids like heroin or oxycodone, and withdrawal, thereby mitigating the negative reinforcement of drug use associated with its cessation. Buprenorphine works similarly, blocking the positive reinforcement and preventing withdrawal's negative reinforcement. The impact of these medications is to decrease and ultimately

**Table 1.** FDA-Approved Medications for Alcohol Use Disorders

	Action	Precautions	Adverse Reactions and Common Side Effects	Adult Dosage
<b>Oral naltrexone</b>	Blocks opioid receptors; reduces reward in response to alcohol use	Must be opioid-free 7 to 10 days. If opioid analgesia needed, larger doses required and respiratory depression deeper and prolonged. Monitor liver function.	Precipitates severe withdrawal if concurrently taking opioids; hepatotoxicity at supratherapeutic doses. Nausea, vomiting, and somnolence.	50 mg PO daily.
<b>Naltrexone depot injection</b>	Same as oral naltrexone but effects last 30 days.	Same as oral naltrexone.	Same as oral naltrexone, plus site reaction and greater somnolence.	380 mg gluteal IM injection monthly.
<b>Acamprosate</b>	Mechanism unknown but believed to reduce glutamatergic hyperexcitability.	Evaluate renal function. Moderate Kidney Disease (adjust dose for CrCl 30-50 mL/min).	Mild diarrhea.	666 mg PO TID. If creatinine clearance 30-50 mL/min: 333 mg PO TID.
<b>Disulfiram</b>	Inhibits intermediate metabolism of alcohol which can cause flushing, nausea, dizziness, and tachycardia if patient uses alcohol.	Monitor liver function. Warn patient to avoid alcohol in diet, OTC medications, toiletries. Psychosis or severe myocardial disease relatively contraindications	Disulfiram-alcohol reaction, hepatotoxicity.	250 mg PO daily (range 125 mg to 500 mg)

extinguish the compulsive and dysfunctional behaviors characteristic of addiction. Disulfiram, described below for alcohol use disorders, is the only currently available pharmacotherapy that works through punishment upon use of alcohol.

**Medications For Alcohol Use Disorder**

*Oral Naltrexone*

Naltrexone is an antagonist of the  $\mu$ -opioid receptor. Opioid receptors are believed to mediate some of the rewarding effects of alcohol. By blocking the effects of endogenous opioids released by alcohol use, naltrexone is believed to reduce the rewarding effects of alcohol use. Naltrexone is generally well tolerated. Potential side effects include nausea, vomiting, somnolence and reversible elevations of liver transaminases.

The efficacy of naltrexone for alcohol use disorders has been examined in multiple large meta-analyses. The most recent meta-analyses found that naltrexone, particularly at a daily dose of 50 mg, was associated with improvements in multiple alcohol consumption outcomes, including return to any drinking, return to heavy drinking, and the number of drinking days.<sup>4</sup> The number needed to treat (NNT) to prevent one person from returning to any drinking or heavy drinking was 12, though it is important to note that most studies evaluated were short-term in duration (12 weeks). Only one long-term trial (12 months or greater) exists for naltrexone and it found no difference between naltrexone and placebo.<sup>5</sup> There is convincing evidence that the effectiveness of naltrexone is dependent on genetic factors<sup>6</sup> and adherence.<sup>7</sup>

*Naltrexone Depot Injection*

Because good adherence to oral naltrexone has been associated with improved effectiveness in treating alcohol dependent patients, an extended-release injectable form of naltrexone was developed. The rationale for this formulation was that a monthly injection would increase adherence to the medication compared to daily oral administration. Aside from a greater sedating effect and injection site reactions, the side effect profile of injectable naltrexone is comparable to oral naltrexone.

A recent meta-analysis found that injectable naltrexone was associated with a reduction in the number of heavy drinking days but was not associated with reductions in return to any drinking or heavy drinking.<sup>4</sup> In one study, among patients sober four or more days prior to the injection, injectable naltrexone tripled continuous abstinence.<sup>8</sup>

*Acamprosate*

Acamprosate’s mechanism of action is poorly understood, but it is believed to reduce the glutamatergic hyperexcitability that occurs during protracted alcohol withdrawal. By reducing this hyperexcitability, acamprosate may attenuate symptoms of protracted withdrawal such as anxiety and insomnia that negatively reinforce alcohol use. Acamprosate is generally well tolerated. The most common side effect associated with acamprosate is mild, transient diarrhea.

The efficacy of acamprosate has been examined in numerous clinical trials. A recent meta-analysis found that acamprosate was associated with improvement in the return to any drinking with a NNT of 12.<sup>4</sup> Another meta-analysis

of 22 randomized, placebo-controlled trials found that acamprosate increased abstinence days by 10% and complete abstinence almost two-fold.<sup>9</sup> Of note, earlier European trials of acamprosate showed efficacy in maintaining abstinence but subsequent trials conducted in the United States did not show a significant effect.<sup>10</sup>

**Disulfiram**

Disulfiram is used as an aversive agent and a deterrent to alcohol use. Disulfiram inhibits the enzyme aldehyde dehydrogenase. When taken with alcohol, disulfiram causes an elevation of serum acetaldehyde concentration. This buildup of acetaldehyde produces an adverse reaction characterized by flushing, increased heart rate and hypotension and may lead to nausea, vomiting, and dizziness. Disulfiram is relatively contraindicated in those with psychosis and those with severe myocardial disease. It can interact with alcohol found in everyday products like perfume and aerosols, and can cause hepatotoxicity in rare cases.

Randomized placebo-controlled clinical trials suggest that oral disulfiram has limited efficacy for alcohol use disorders. A recent meta-analysis of four well-controlled trials of disulfiram found no overall reduction in alcohol use.<sup>4</sup> Disulfiram might be more effective when medication is administered in a supervised manner. A systematic review of 11 randomized trials found improved short-term abstinence among alcohol dependent patients for whom administration of disulfiram was supervised.<sup>11</sup>

**Other Alcohol Pharmacotherapies**

Other medications have some evidence to support their off-label use for the treatment of alcohol use-disorders.

Topiramate, an anti-convulsant with GABA-ergic properties, has been found to reduce alcohol consumption in a small number of randomized clinical trials.<sup>4</sup> The opioid receptor antagonist nalmefene reduced alcohol use in a few clinical trials and may have less risk of hepatotoxicity than oral naltrexone.<sup>12</sup>

**Medications For Opioid Use Disorder**

**Methadone**

Methadone is a  $\mu$ -opioid receptor agonist with excellent oral bioavailability and a long half-life. Methadone maintenance treatment, or the daily administration of methadone to those with opioid use disorders, can reduce opioid craving, prevent symptoms of opioid withdrawal and reduce the effects of shorter-acting opioids such as heroin through cross-tolerance. These actions free patients from the need to seek illicit opioids and help normalize daily functioning. The use of methadone to treat opioid addiction is highly regulated and limited to licensed opioid treatment programs. Methadone is generally well tolerated, though overdose can occur, especially when taken in combination with sedative-hypnotics. Methadone has been linked with QTc interval prolongation but recommendations for regular screening with electrocardiogram at time of methadone initiation have been controversial.<sup>13</sup> Constipation and sweating are common side effects.

Multiple randomized clinical trials over 30 years have demonstrated that methadone maintenance treatment is highly effective in retaining patients in treatment and reducing opioid use.<sup>14</sup> Recent meta-analyses of observational studies affirm that methadone maintenance decreases mortality<sup>15</sup> and HIV transmission.<sup>16</sup> Doses of 60-100 mg/day of

**Table 2.** FDA-Approved Medications for Opioid Use Disorders

	Action	Precautions	Adverse Reactions and Common Side Effects	Adult Dosage
<b>Methadone</b>	Full opioid agonist. Long half-life allow for daily dosing which reduces need to seek illicit opioids.	Can be lethal in overdose. Has been linked with QTc interval prolongation.	Constipation and sweating.	Starting dose no more than 30 mg depending on patient tolerance to opioids. Maintenance doses of $\geq$ 60 mg daily more effective.
<b>Buprenorphine</b>	Partial opioid agonist which reduces need to seek illicit opioids. Most common formulation includes naloxone which discourages injection.	Should be opioid-free 12-24 hours prior to induction, maybe longer if using long-acting opioids. Monitor liver function.	Constipation, dizziness, nausea and vomiting	Start 4mg/1mg of sublingual buprenorphine/naloxone, total of 8 mg/2 mg in first day. Typical maintenance dose between 16-24 mg daily.
<b>Naltrexone depot injection</b>	Blocks opioid receptors and effects of opioids.	Must be opioid-free 7 to 10 days. If opioid analgesia needed, larger doses required and respiratory depression deeper and prolonged. Monitor liver function.	Precipitates severe withdrawal if concurrently taking opioids; hepatotoxicity at supratherapeutic doses. Nausea, vomiting, and somnolence, site reaction.	380 mg gluteal IM injection monthly.

methadone are more effective than lower doses in increasing treatment retention and decreasing opioid use.<sup>17</sup> Because the risk of relapse after methadone discontinuation is high, long-term treatment is necessary for many patients.

Federal law restricts the use of methadone to licensed opioid treatment programs for the treatment of opioid use disorders. Such programs are required to provide addiction counseling and directly supervise dosing such that, for example, weekly take-home dosing cannot occur among stable patients for the first nine months.

### *Buprenorphine*

Buprenorphine, a partial  $\mu$ -opioid receptor agonist, is approved for opioid maintenance treatment in office-based settings. The most common formulation is taken sublingually and includes naloxone, an opioid receptor antagonist with poor bioavailability when taken orally or sublingually. This formulation was designed to discourage misuse via injection. Buprenorphine has a long duration of action due to its high opioid receptor affinity and slow dissociation from the receptor. Buprenorphine's partial agonist properties block euphoria from other opioids, reduce craving and prevent withdrawal, while the ceiling on its agonist properties reduces the risk of respiratory depression. Because it is a partial agonist and has strong opioid receptor affinity, buprenorphine may precipitate opioid withdrawal symptoms if taken too soon after ingestion of other opioids. Possible side effects include constipation, dizziness, nausea and vomiting. It has also been linked to rare cases of hepatitis.

In randomized clinical trials buprenorphine maintenance treatment is as effective as methadone in reducing opioid use.<sup>18</sup> However, buprenorphine may be less effective than methadone in retaining patients in long-term treatment, particularly in studies that utilized dosing protocols that closely reflect clinical practice.

In order to prescribe office-based buprenorphine, physicians must have completed an approved 8-hour course and requested an amended controlled substance license from the federal Drug Enforcement Administration. Buprenorphine prescribers are limited to 30 active buprenorphine patients in the first year and 100 patients thereafter. Counseling services must be available, but are not required.

### *Naltrexone Depot Injection*

Naltrexone is a long-acting opioid antagonist that produces a dose-dependent blockage of all opiate effects. When administered orally, it effectively improves treatment retention and abstinence in patients with opioid use disorders only when adherence can be assured.<sup>19</sup> Extended-release injectable naltrexone was developed to improve adherence.

Two randomized clinical trials of injectable naltrexone for the treatment of opioid use disorders demonstrated improvement in treatment retention and the number of negative urine drug tests for opioids.<sup>20,21</sup> An ongoing effectiveness trial is testing injectable naltrexone against treatment

as usual in a group of recently released parolees with an opioid use disorder and early findings are similarly promising.<sup>22</sup>

### **Medication Management Counseling**

Much evidence suggests that pharmacotherapy and office-based medication management counseling by a doctor or nurse in generalist settings is as effective as more extensive counseling interventions.<sup>23</sup> For opioid use disorders, medications even without counseling can have substantial benefits.<sup>24</sup> Medical management counseling includes direct advice to stop substance use; monitoring and feedback of improvements in medical conditions and other consequences to enhance motivation; regular visits to monitor and encourage adherence to the pharmacotherapy; and recommending participation in mutual help groups.<sup>25</sup>

## **DISCUSSION**

A growing number of medications for alcohol and opioid use disorders have been found to be effective in reducing substance use and in some cases, mortality related to substance use. Additionally, several of these medications have been found to be cost-effective.<sup>26,27</sup> Despite these findings, medication treatments for addiction continue to be underutilized. Physicians and other prescribing clinicians can take an active role in facilitating remission and recovery among their recovering patients by prescribing these effective medications and delivering brief medical management counseling.

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