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Class Update: Substance Use Disorders

Date of Review: September 2016 **Date of Last Review:** January 2015

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Increases in misuse and abuse of opioids and subsequent increases in accidental opioid-related deaths have caught the attention of policy makers in the United States (U.S.) and in Oregon. On July 22, 2016, the Comprehensive Addiction and Recovery Act (CARA) was enacted which authorizes the federal government to strengthen opioid prevention and treatment programs and improve community access to naloxone. Improved practices in opioid prescribing will likely lead to decreased prescribing of opioids but it may be at the expense of increased illicit opioid use (i.e., heroin, synthetic fentanyl, prescription opioids) for persons dependent on or addicted to opioids. Illicit opioid use is a major cause of mortality from acute causes (e.g., overdose, traffic accidents) and transmission of blood-borne infections like HIV and Hepatitis C due to injection drug use. A review of new published data and updated clinical practice guidelines for management of substance use disorders will help inform whether current Oregon Health Plan (OHP) policies remain appropriate to access to these medications.

Research Questions:
1. Is there new evidence for differences in efficacy between drug therapies for alcohol use disorder or opioid use disorder?
2. Is there new evidence for differences in harms between drug therapies for alcohol use disorder or opioid use disorder?
3. Are there subpopulations based on demographics (i.e., adolescents, elderly, women, criminal justice offenders) or practice settings (i.e., rehabilitation/addiction center, clinics, private physician offices or patient self-administration) in which a drug for alcohol use disorder or opioid use disorder may be more effective or less harmful than other drugs?

Conclusions:
- Treatment for opioid use disorder was last reviewed by the Pharmacy and Therapeutics Committee in January 2015 and treatment for alcohol use disorder was last reviewed in July 2014. Since then, two high quality systematic reviews from the Agency for Healthcare Research and Quality (AHRQ) and the Cochrane Collaboration, and one high quality clinical practice guideline from the Veterans Affairs and Department of Defense (VA/DoD) were especially informative.

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Alcohol Use Disorder

- There is high quality evidence for use of acamprosate and oral naltrexone to decrease alcohol consumption in patients with alcohol use disorder when used concurrently with psychosocial interventions; however, there is insufficient evidence to support their use based on an improvement in clinically relevant health outcomes (i.e., morbidity or mortality) alone.
    - The number needed to treat [NNT] to prevent one person from returning to *any* drinking is 12 persons (95% Confidence Interval [CI], 8 to 26; 16 trials; n=4847) for acamprosate and 20 persons (95% CI, 11 to 500; 16 trials; n=2347) for oral naltrexone 50 mg daily.[1]
    - Oral naltrexone is associated with statistically significant improvement in prevention of returning to *heavy* drinking (NNT 12; 95% CI, 8 to 26; 19 trials; n=2875) but acamprosate is not associated with an improvement.[1]
- There is no statistically significant association with return to *any* drinking or return to *heavy* drinking with extended-release injectable naltrexone; however, there was a statistically significant association with reduction in *heavy* drinking days (weighted mean difference [WMD] -4.6%; 95% CI, -8.5% to -0.56%; 2 trials; n=926), although it is unclear if this difference is clinically meaningful.[1]
- There is insufficient evidence to adequately support an association between disulfiram use and preventing return to *any* drinking or improvement in other alcohol consumption outcomes.[1] However, blinded studies may be incapable of distinguishing a difference between disulfiram and control groups due to high attrition and fear for disulfiram-ethanol reactions. Blinded studies may be incompatible for disulfiram research; when data from open-labeled studies are pooled, there is moderate quality evidence that disulfiram is safe and efficacious for treatment of alcohol use disorder in supervised settings.[2]
- There is low quality evidence that suggests off-label use of topiramate may be useful in decreasing alcohol consumption.[1]
- There is high quality evidence of no difference between acamprosate and oral naltrexone in return to *any* drinking (RD 0.02; 95% CI, -0.03 to 0.08); return to *heavy* drinking (RD 0.01; 95% CI, -0.05 to 0.06); or percent of drinking days (WMD -2.98%; 95% CI, -13.4 to 7.5%).[1] There is insufficient evidence to compare extended-release injectable naltrexone or disulfiram with other drugs for treatment of alcohol use disorder.
- There is insufficient evidence to demonstrate differences in harms for medications used to treat alcohol use disorder.
- The updated clinical practice guideline from the Veterans Affairs and Department of Defense (VA/DoD) for the management of substance abuse disorders strongly recommends that treatment choice between acamprosate, disulfiram, naltrexone (oral or extended-release injection) or topiramate be individualized based on specific needs and patient preferences.[3] In all cases, strong psychosocial interventions are needed to successfully treat patients with alcohol use disorder.[3]

Opioid Use Disorder

- Moderate quality evidence from 2 trials demonstrates no difference between methadone and buprenorphine maintenance treatment in terms of self-reported opioid use (risk ratio [RR] 0.37; 95% CI, 0.08 to 1.63) or positive opioid urine drug screens (RR 0.81; 95% CI, 0.56 to 1.18).[4] Low quality evidence from 3 trials demonstrates no difference in treatment retention between methadone and buprenorphine maintenance treatment programs (RR 0.69; 95% CI, 0.39 to 1.22).[4]
- Maintenance treatment with buprenorphine is more effective than detoxification treatment alone or psychosocial treatment alone, based on low quality evidence that assessed self-reported opioid use in the last 30 days (RR 0.54; 95% CI, 0.31 to 0.93), urine drug screens (RR 0.63; 95% CI, 0.43 to 0.91), and treatment retention (RR 0.33; 95% CI, 0.23 to 0.47).[4]
- There is moderate quality evidence from 2 trials of no difference in rates of adverse events between methadone and buprenorphine maintenance treatment (RR 1.10; 95% CI, 0.64 to 1.91).[4]
- For patients with a diagnosis of opioid use disorder, the VA/DoD strongly recommends buprenorphine/naloxone or methadone in an Opioid Treatment Program depending on specific patient needs or preferences.[3] Alternatively, buprenorphine without naloxone is strongly recommended to be used in

patients who are pregnant, and extended-release injectable naloxone is recommended as an option for patients for whom buprenorphine/naloxone or methadone is contraindicated, unacceptable, or unavailable, and who have established opioid abstinence for a sufficient period of time. In all cases, strong psychosocial interventions are needed to successfully treat patients with opioid use disorder.[3]

Sub-groups

- There is insufficient evidence to confirm which treatments for alcohol or opioid use disorders are more or less effective or safe in older or younger subgroups, by gender, racial or ethnic minorities, smokers or nonsmokers, or those with certain coexisting conditions.[1] However, the VA/DoD strongly recommend that sublingual buprenorphine (without naloxone) be reserved for pregnant patients when used to treat opioid use disorder.[3]
- When compared to non-pharmacological treatment, there is low quality evidence that opioid agonist treatment (methadone or buprenorphine) and naltrexone may not be effective reducing illicit drug use in criminal justice offenders.[6] However, there is moderate quality evidence that naltrexone treatment reduces criminal activity as evidenced by decreased re-incarceration rates.[6]
- There is moderate quality evidence that disulfiram is more effective in supervised settings.[2] Otherwise, there is insufficient evidence to know with certainty whether buprenorphine products are more effective or safer when given in designated Opioid Treatment Programs or in private physician offices, or whether daily supplies should be administered or multi-day supplies may be administered. Methadone is restricted to designated Opioid Treatment Programs.

Recommendations:

- Continue to require clinical prior authorization (PA) criteria for all buprenorphine products and the naltrexone extended-release injection product based on recommended amendments in Appendix 4.
- Remove buprenorphine sublingual tablets from the OHP fee-for-service Preferred Drug List (PDL) and restrict use to pregnant females as required by clinical PA criteria in Appendix 4.
- After review of comparative drug costs in the executive session, no other changes to the OHP PDL were made.

Previous Conclusions:

- New evidence is still insufficient to determine if there is any difference in efficacy/effectiveness or safety between different opioid dependence treatments, including different buprenorphine formulations.
- New evidence is insufficient to determine if a specific subpopulation may benefit more with a specific drug or formulation approved for opioid dependence.

Previous Recommendations:

- No further review or research needed at this time.

Background:

Substance Use Disorders (SUD) can develop in individuals who use alcohol, opioids, or other addicting drugs in harmful quantities.[3] About 9% of adults in the U.S. have a non-tobacco SUD, and about 25% of all Americans will develop a non-tobacco SUD over the course of a lifetime.[3] Excessive alcohol use and illicit drug use, including illicit prescription drug use, costs $223.5 billion and $193.5 billion, respectively, each year in the U.S. according to the latest available estimates from the Centers for Disease Control and Prevention (CDC) and U.S. Department of Justice.[3] Excessive alcohol use in the U.S. results in about 88,000 premature deaths each year from acute (e.g., alcohol poisoning, motor vehicle accidents) and chronic causes (e.g., liver disease, hypertension, heart disease, stroke, pancreatitis).[3]

Illicit opioid use (heroin or prescription opioids) is also a major cause of mortality from acute causes (e.g., overdose, traffic accidents) and transmission of blood-borne infections like HIV and Hepatitis C due to injection drug use. An estimated 400,000 persons have used heroin in the past month in the U.S. and 4 million persons have reported nonmedical use of prescription pain relievers.[7] Worldwide, opioid use disorder has resulted in 11 million life-years lost from health problems, disabilities, and early death from opioid-related conditions.[7] When tobacco use is included, SUDs are the leading actual cause of death in the U.S.[3]

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) specifically recognizes SUDs related to substances such as tobacco, alcohol, opioids, cannabis, sedatives, anxiolytics, and 5 other substances.[8] According to the DSM-V, SUDs are associated with a pattern of inappropriate substance use that adversely affects one's personal or professional life or results in noticeable distress.[8] In persons with SUDs, there is an underlying change in the way the brain functions that may persist beyond detoxification that can result in repeated relapses and intense cravings when exposed to different drug-related stimuli.[8] These addictive substances alter brain circuitry involved in complex functions like motivation and decision-making and alter natural reward mechanisms for essential substances like food and water.[3] Pleasure normally experienced with stimuli such as food or social interactions are diminished with repeated use of addicting substances.[3]

Over 16 million adults in the U.S. had a diagnosis of alcohol use disorder in 2014 (10.6 million males and 5.7 million females).[9] In adolescents aged 12-17 years, it was estimated that 679,000 had alcohol use disorder which was fairly equally diagnosed between boys and girls.[9] Unfortunately, only 1 in 10 patients are treated for alcohol use disorder and treatment options remain underutilized despite their potential to improve health outcomes.[1] Treatments for alcohol use disorder include a combination of cognitive behavioral therapy, motivational enhancement therapy, 12-step programs (e.g., Alcoholic Anonymous), and pharmacotherapy. Pharmacotherapy options for patients with alcohol use disorder include oral options like disulfiram, acamprosate, and naltrexone, as well as extended-release injectable naltrexone. All of these treatments have been approved by the U.S. Food and Drug Administration (FDA) for treatment of alcohol dependence in patients who are able to abstain from alcohol. Outcomes studied have been primarily limited to reduction in alcohol consumption: return to any drinking, return to heavy drinking, drinking days, heavy drinking days (≥4 drinks per day for women; ≥5 for men), or drinks per drinking day. Off-label use of topiramate and gabapentin for alcohol use disorder has also shown some benefit, whereas drugs like baclofen, buspirone, antidepressants, and antipsychotics have not consistently shown benefit.[3]

Opioid analgesics have been used for decades to manage pain, but they can also produce feelings of euphoria, tranquility and sedation that lead to substantial misuse and abuse of these drugs. A person will build tolerance to regular use of opioids, including heroin, which can result in the desire for higher and higher doses to achieve the intended effect but at the expense of serious adverse events such as respiratory suppression and death. With the recent dramatic increase in misuse of prescription opioids and ease of accessibility of opioids, including heroin, it is imperative that physicians understand how to diagnose and navigate treatment strategies with their patients. From 2007 to 2014, the number of private insurance claim lines with an opioid dependence diagnosis increased 3,203%, with most of the claims associated with persons between 19-35 years of age.[10] On July 22, 2016, the Comprehensive Addiction and Recovery Act (CARA) was enacted which authorizes the federal government to strengthen opioid prevention and treatment programs, and improve community access to naloxone.[11]

Medically supervised treatment of long-acting opioid agonists for acute withdrawal symptoms (i.e., detoxification) can improve a patient's health and facilitate participation in a rehabilitation program.[7] However, detoxification alone is not helpful to produce long-term recovery and may increase a patient's risk for overdose due to lost tolerance for opioids.[7] The most effective approach is to relieve symptoms of detoxification with methadone or buprenorphine and then gradually reduce the dose to allow the patient to adjust to the absence of an opioid.[7] However, only licensed addiction-treatment programs and physicians who have completed specific training for opioid drugs can administer opioids to treat opioid use disorder. Some non-opioid medications, such as the centrally-acting

α-2 agonist clonidine, are also used off-label to manage the autonomic over-activity associated with opioid withdrawal. Loperamide, prochlorperazine and nonsteroidal anti-inflammatory drugs (NSAIDs) can also be used in combination to manage other withdrawal symptoms.

Opioid maintenance treatment, with methadone or buprenorphine/naloxone most commonly utilized, reduces withdrawal and cravings and has long been used in the treatment of heroin or prescription opioid dependence for rehabilitation purposes.[7] Oral and extended-release injectable naltrexone formulations are also approved by the FDA for opioid dependence in patients who can abstain from opioids. The regular dosing of a long-acting opioid lessens the sense of euphoria or intoxication that is usually associated with each illicit drug dose and has demonstrated reduction in illicit opioid use, mortality, criminal activity, HIV risk behavior and seroconversion, as well as improved physical and mental health and social functioning.[4] Concurrent psychosocial support is essential to address some of the psychological and social problems that can be associated with opioid use disorder.[4]

Methadone is a mu-opioid agonist and an N-methyl-D-aspartate (NMDA) antagonist given as a single daily dose for opioid dependence in approved Opioid Treatment Programs (i.e., 'methadone clinics'). Previous data show that methadone has strong evidence that demonstrates effectiveness in reducing mortality and substance use, improving physical and mental health outcomes, reducing criminal activity and reducing risk for HIV and risk behaviors.[4] However, methadone is not without harms. Adverse effects may include prolonged QT interval which rarely result in Torsade de pointes, and respiratory depression associated with titrating the drug. Opioid Treatment Programs have strict guidelines for dosing, supervised treatment and associated services. The optimal dosage of methadone for retention in treatment is at least 60 mg daily but many patients will require higher doses.[7]

Buprenorphine is a partial opioid agonist and has lower intrinsic activity at the opioid receptor, but due to its very high affinity for the receptor, buprenorphine possesses antagonist properties that block the effects of other opioids. Buprenorphine has a favorable safety profile compared to methadone due to its limited effects on the respiratory system and also has evidence for reduced mortality similar to methadone.[4] Unlike methadone which is 100% bioavailable as an oral formulation, buprenorphine has poor bioavailability and must be developed in formulations that are not swallowed orally (e.g., sublingual, buccal, transdermal, etc.). For treatment of opioid-dependence (and not pain), a buprenorphine sublingual formulation is available and buprenorphine/naloxone buccal and sublingual formulations are available. Buprenorphine and naloxone are usually formulated in 4:1 to discourage injection of the drug. The low dose of naloxone does not precipitate withdrawal symptoms unless it is injected. These products (C-III) are not as highly controlled as methadone (C-II) and can be provided by physicians who have received a waiver from the Substance Abuse and Mental Health Services Administration (SAMSHA), have completed 8 hours of buprenorphine training, and have a special Drug Enforcement Administration (DEA) number.[7] Previously, these physicians were limited to caring for 30 patients at a time, but that number was increased to 275 patients in July 2016.[7]

There are no guidelines that specify when to refer a patient to an Opioid Treatment Program for methadone or buprenorphine maintenance treatment. Both drugs have demonstrated improvement in clinical outcomes in multiple randomized clinical trials (RCTs). High-quality evidence supports the use of medication-assisted treatment using methadone or buprenorphine/naloxone over psychosocial treatment alone to improve outcomes.[7] Choice of drug typically comes down to individual clinician and patient preferences. Methadone can be dispensed in Opioid Treatment Programs only, whereas buprenorphine can also be prescribed by physicians in office-based settings, including primary care, outpatient specialty SUD treatment facilities, and mental health clinics. Considerations include cost; concomitant medical (e.g., heart disease) and psychiatric conditions; the availability of methadone clinics; the availability of physicians trained in administering buprenorphine; and the risk of diversion when determining which option is most appropriate. For example, an office-based treatment program may not be suitable for patients with a concurrent substance abuse disorder (e.g., alcohol, sedatives, anxiolytics) or even patients who regularly use sedative-hypnotics like benzodiazepines.[5] Buprenorphine is more expensive than methadone, and the private office charges for buprenorphine might exceed the usual

costs of a methadone clinic.[7] However, buprenorphine may be safer than methadone during induction and early stabilization phases of treatment. Buprenorphine can also be administered in physician offices which can improve access to opioid maintenance treatment.[7]

Evidence from one RCT also shows that extended-release injectable opioid antagonist naloxone can be successfully used to treat opioid use disorder.[7] The long-acting formulation can be given in both general healthcare and specialty substance use disorder treatment settings. There is insufficient evidence at this time to recommend oral naltrexone because it requires a highly motivated patient to be successful and it has not consistently demonstrated superiority to control groups at treatment retention or in opioid consumption.[3] Patients who initiate naltrexone treatment must be free of opioid dependence (e.g., >7 days without acute withdrawal symptoms), which should be confirmed based on an opioid-free urine sample and a naloxone challenge (intramuscular or intravenous administration of 0.8 to 1.6 mg of naloxone; or alternatively, 50 mg or oral naloxone with no subsequent withdrawal symptoms).[7]

Clinically important outcomes for studies that assess efficacy of substance use disorders can include: treatment retention/completion; illicit substance use or any alcohol consumption; risk behaviors (injecting, sexual, polysubstance use, overdoses, hospital admissions); quality of life as assessed by validated scales (e.g., WHO Quality of Life scale), employment, physical health as assessed by validated scales (e.g., 36-item Short Form), adverse effects and aberrant opioid-related behaviors (e.g., multiple prescribers, lost medications, or unauthorized dose increases).[4]

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

<u>Alcohol Use Disorder</u>

The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review on the efficacy of various medications used for the treatment of alcohol use disorder.[1] Eligible studies were double-blind RCTs that enrolled adults with alcohol use disorder that evaluated an FDA-approved medication or off-label medication (i.e., baclofen, buspirone, citalopram, fluoxetine, sertraline, topiramate, quetiapine, and others) for at least 12 weeks against placebo or another medication in an outpatient setting.[1] Studies were required to assess one of the following outcomes: 1) consumption – return to any drinking, return to heavy drinking, drinking days, heavy drinking days (≥4 drinks per day for women; ≥5 for men), drinks per drinking day; 2) health outcomes – accidents (i.e., motor vehicle crashes), injuries, quality of life, function, and mortality; or 3) adverse effects.[1] Adequacy of randomization, allocation concealment, similarity of groups and baseline, blinding, attrition, validity and reliability of measures, whether intention-to-treat analysis was used, and methods of handling missing data were considered in assessment of the risk of bias of the studies.[1] Meta-analyses of RCTs were conducted using random-effects models.[1] Weighted mean differences

(WMD) with 95% CIs were used for continuous outcomes.[1] Risk differences (RD) with 95% CI were conducted for binary outcomes.[1] Studies with high or unclear risk of bias were excluded from the main analaysis but were included in sensitivity analyses.[1] The I^2 statistic was calculated to assess for statistical heterogeneity.[1] Publication bias was assessed when possible (≥10 studies in a meta-analysis) by examination of funnel plots. Strength of evidence was graded as high, moderate, low or insufficient based on 4 key domains: risk of bias, consistency, directness and precision.[1] A total of 123 studies were included.[1] Most studies assessed acamprosate (27 studies; n=7519), naltrexone (53 studies, n=9140) or both.[1] Treatment duration ranged from 12 to 52 weeks.[1] In most cases, psychosocial interventions were also given to participants.[1] Most studies enrolled patients after detoxification or required a period of sobriety before randomization.[1]

Both acamprosate and oral naltrexone improve alcohol consumption outcomes.[1] The NNT to prevent one person from returning to any drinking is 12 persons (95% CI, 8 to 26; 16 trials; n=4847) for acamprosate and 20 persons (95% CI, 11 to 500; 16 trials; n=2347) for oral naltrexone 50 mg daily.[1] Acamprosate was not associated with an improvement in return to heavy drinking but oral naltrexone is associated with statistically significant improvement (NNT 12; 95% CI, 8 to 26; 19 trials; n=2875).[1] There was no statistically significant association with return to any drinking or return to heavy drinking with extended-release injectable naltrexone; however, there was a statistically significant association with reduction in heavy drinking days (WMD -4.6%; 95% CI, -8.5% to -0.56%; 2 trials; n=926).[1] There is insufficient evidence for disulfiram to adequately support an association with preventing return to any drinking or improvement in other alcohol consumption outcomes.[1] However, the largest disulfiram trial to date (n=605) did report fewer drinking days for patients who returned to drinking.[1] Meta-analyses of head-to-head RCTs that compared acamprosate with oral naltrexone did not find a statistically significant difference between these 2 medications in return to any drinking (RD 0.02; 95% CI, -0.03 to 0.08); return to heavy drinking (RD 0.01; 95% CI, -0.05 to 0.06) or percent of drinking days (WMD -2.98%; 95% CI, -13.4 to 7.5%).[1] There was insufficient evidence to support most medications used off label for alcohol use disorder.[1] The exceptions are topiramate and valproic acid.[1] Topiramate is associated with fewer drinking days (WMD -6.5%; 95% CI, -12.0% to -1.0%; 2 trials; n=541), heavy drinking days (WMD -9.0%; 95% CI, -15.3% to -2.7%; 3 trials; n=691) and drinks per drinking day (WMD -1.0; 95% CI, -1.6 to -0.48; 3 trials; n=691).[1] Valproic acid demonstrated some efficacy in consumption outcomes in patients with bipolar disorder.[1] Trials primarily focused on consumption outcomes; very few trials reported health outcomes and those that did were not powered to assess health outcomes.[1] There was also insufficient evidence to make fair estimations of potential adverse events with these agents due to inadequate precision.[1] In general, adverse events occurred more often in active treatment groups than placebo, but differences were not statistically significant.[1] In head-to-head trials of naltrexone and acamprosate, no statistically significant differences in withdrawal due to adverse events were observed.[1] Compared with placebo, patients treated with acamprosate had a higher risk of anxiety (number needed to harm [NNH] 7); diarrhea (NNH 11) and vomiting (NNH 42); patients treated with naltrexone had a higher risk for dizziness (NNH 16) and vomiting (NNH 24).[1]

Overall, acamprosate and oral naltrexone (50 mg/day) have the best evidence for treatment alcohol use disorder when used concurrently with psychosocial interventions; however, evidence is limited to alcohol consumption outcomes, including evidence for alcohol abstinence but health outcomes are still lacking.[1] A summary of the evidence extracted from the AHRQ report is summarized in **Table 1**. The mean age of participants was generally in the 40s.[1] There is insufficient evidence to confirm which treatments are more or less effective or safe in older or younger subgroups, different sex groups, racial or ethnic minorities, smokers or nonsmokers, and those with certain coexisting conditions.[1] Most trials of acamprosate were conducted in Europe while most trials of naltrexone were conducted in the U.S.[1] The few U.S.-based acamprosate trials did not find the drug to be efficacious, which may be related to the sources that the patients were recruited from (inpatient treatment programs vs. advertisements).[1] Overall, most trials were conducted in specialized outpatient treatment settings and very little evidence from primary care settings is available.[1]

Table 1. Summary of Findings and Strength of Evidence for the Efficacy of Medications use to Treat Alcohol Use Disorder Versus Placebo (*Agency for Healthcare Research and Quality*).[1]

Medication	Outcome	N (studies)	N (subjects)	Finding	Effect Size (95% CI)	NNT	SOE
Acamprosate vs. Placebo	Return to any drinking	16	4,847	Reduced by acamprosate	RD -0.09 (-0.14 to -0.04)	12	Moderate
	Return to heavy drinking	7	2,496	No difference	RD -0.01 (-0.04 to 0.03)	NA	Moderate
	Percentage of drinking days	13	4,485	Reduced by acamprosate	WMD -8.8 (-12.8 to -4.8)	NA	Moderate
Disulfiram vs Placebo	Return to any drinking	2	492	No difference	RD -0.04 (-0.11 to 0.03)	NA	Low
Naltrexone 50 mg oral vs. Placebo	Return to any drinking	16	2,347	Reduced by naltrexone	RD -0.05 (-0.10 to -0.00)	20	Moderate
	Return to heavy drinking	19	2,875	Reduced by naltrexone	RD -0.09 (-0.13 to -0.04)	12	Moderate
	Percentage of drinking days	15	1,992	Reduced by naltrexone	WMD -5.4 (-7.5 to -3.2)	NA	Moderate
	Percentage of heavy drinking days	6	521	Reduced by naltrexone	WND -4.1 (-7.6 to -0.61)	NA	Moderate
Naltrexone injection vs. Placebo	Return to any drinking	2	939	No difference	RD -0.04 (-0.10 to 0.03)	NA	Low
	Return to heavy drinking	2	615	No difference	RD -0.01 (-0.14 to 0.13)	NA	Low
	Percentage of heavy drinking days	2	926	Reduced by naltrexone	WMD -4.6 (-8.5 to -0.56)	NA	Low
Topiramate vs. Placebo	Percentage of drinking days	2	521	Reduced by topiramate	WMD -8.5 (-15.9 to -1.1)	NA	Moderate
	Percentage of heavy drinking days	2	521	Reduced by topiramate	WMD -11.5 (-18.3 to -4.8)	NA	Moderate
	Number of drinks per drinking day	2	521	Reduced by topiramate	WMD -1.1 (-1.7 to -0.4)	NA	Moderate
Other drugs	The evidence is insufficient to determine the efficacy of other medications because of inconsistency, imprecision, or lack of sufficient studies in the literature (e.g., amitriptyline, aripiprazole, atomoxetine, baclofen, buspirone, citalopram, desipramine, fluoxetine, fluvoxamine, gabapentin, imipramine, olanzapine, ondansetron, paroxetine, quetiapine, varenicline, viloxazine).						

Abbreviations: CI = confidence interval; N = number; NA = not applicable; NNT = number needed to treat; RD = risk difference; SOE = strength of evidence; WMD = weighted mean difference.

Disulfiram appears to be successful for alcohol use disorder in patients who are compliant or supervised in real-world settings, but the efficacy of disulfiram in clinical trials has been conflicting which has led to controversy around use of the drug based on poorly designed trials. A systematic review with meta-analysis was conducted to determine whether disulfiram treatment is more effective in open-label studies rather than in blinded trials because of the negative psychological impact participants may have in blinded trials because of fear of the disulfiram-ethanol reaction (DER).[2] The hypothesis was that blinded trials would not show a difference in efficacy between disulfiram and control groups because fear of DER would dissuade compliance in all groups.[2] All controlled trials that evaluated use of disulfiram in patients with alcohol use disorder were eligible for inclusion.[2] These studies included both blind and open-label designs, both supervised and unsupervised.[2] The methodological quality of the studies was analyzed according to the Cochrane Collaboration's tool for assessing risk of bias.[2] Efficacy outcomes were analyzed using a random-effects model, due to high heterogeneity in the studies, and by calculating the Hedge's *g* effect-size for each trial with the uncertainty of each result expressed by their 95% CIs.[2] An effect size of 0.2 to 0.3 is thought to be a 'small' treatment effect, about 0.5 a 'medium' treatment effect, and 0.8 to infinity a 'large' treatment effect.[2] Publication bias was assessed using funnel plots and heterogeneity was assessed by calculating the I^2 value (range 0% to 100%, with 0%-40% considered unimportant heterogeneity).[2] The primary endpoint of the meta-analysis was the combined effect-size at the end of treatment for the primary outcomes studied. Primary outcomes included: total abstinence; proportion of abstinent days to treatment days; mean days of alcohol use; no relapse; time to first heavy drinking day; or 3 or more weeks of consecutive abstinence.

Overall, 23 studies were eligible for inclusion in the meta-analysis.[2] The studies were published between 1973 and 2010; most were from the U.S. (10) study durations of 8 to 52 weeks.[2] Most participants in the studies were males and 2 studies evaluated adolescents.[2] In addition, 6 of the studies evaluated a population of cocaine abusers who also had an alcohol use disorder.[2] The results of the meta-analysis found significant success rate for disulfiram compared to controls (g=0.58; 95% CI, 0.35 to 0.82; I^2=72%).[2] A funnel plot analysis indicated possible publication bias but the summary effect size remained significant after correcting for missing studies (g=0.53 to g-0.63; p<0.001).[2] A subgroup analysis that compared blinded RCTs to open-label RCTs found that open-label RCTs found a significant superiority of disulfiram versus controls (g=0.70; 95% CI, 0.46 to 0.93; I^2=65%) whereas the blinded RCTs found no efficacy with disulfiram compared to controls (g=0.01; 95% CI, -0.29 to 0.32; I^2=43%).[2] When blinded trials were excluded, the funnel plot showed symmetry which demonstrated that there was no publication bias among those types of studies.[2] A subgroup analysis by supervision categories found disulfiram to be significantly superior to controls when medication compliance was supervised (g=0.82; 95% CI, 0.59 to 1.05; I2=46%) but not when treatment was unsupervised (g=0.26; 95% CI, -0.02 to 0.53).[2] No publication bias was found when studies were broken down by supervision categories.[2] In another subgroup analysis by control group, disulfiram was statistically significantly superior to naltrexone (g=0.77; 95% CI, 0.52 to 1.02; I^2=26%) and to acamprosate (g=0.76; 95% CI, 0.04 to 1.48; I^2=81%).[2] In terms of safety, disulfiram was associated with an increased risk for adverse events compared to controls (RR 1.40; 95% CI, 1.01 to 1.94).[2] Out of studies that reported adverse events totaling 962 participants, 8 subjects reported a serious adverse event that required hospitalization but most continued the disulfiram study after discharge.[2] A total of 13 deaths were reported (disulfiram groups = 6; control groups = 6; unspecified = 6).[2] The authors concluded that blinded studies were incapable of distinguishing a difference between treatment groups and thus are incompatible with disulfiram research.[2] Open-labeled trials in supervised settings have shown disulfiram to be safe and efficacious comparted to other abstinence supportive pharmacological treatments (naltrexone, acamprosate, topiramate) or to no disulfiram for alcohol use disorder.[2]

Opioid Use Disorder

The efficacy and safety of maintenance opioid agonist therapy for the treatment of pharmaceutical opioid dependence was recently evaluated in a systematic review by the Cochrane Collaboration.[4] All RCTs that evaluated at least 30 days of full opioid agonist maintenance treatment (i.e., methadone) against another full opioid agonist or partial opioid agonist (buprenorphine) for opioid use disorder were eligible for inclusion.[4] In addition, RCTs that evaluated full or partial opioid agonist maintenance therapy for opioid use disorder versus placebo, psychosocial treatment only (without opioid agonist treatment), or detoxification only were also eligible for inclusion.[4] Eligible RCTs had to enroll patients who were primarily dependent on prescription opioids rather than heroin.[4] The primary outcomes studied were 1) illicit opioid use; 2) illicit opioid use at end of treatment; and 3) retention. Overall, 6 RCTs met inclusion criteria (n=607).[4] Three studies compared methadone with buprenorphine and 3 studies compared buprenorphine to either buprenorphine taper or brief intervention and referral to treatment.[4] The mean duration of the studies was 105 days.[4] The mean age of participants was 31.6 years and 77% were male.[4] Five of the trials took place in the U.S. but the evidence was somewhat limited by their open-label design and small sample sizes (53 to 204 participants).[4] There was enough consistency in the way the trials collected and reported primary outcomes to pool data on key outcome measures.[4] Moderate quality evidence from 2 trials demonstrates no difference between methadone and buprenorphine maintenance treatment in terms of self-reported opioid use (risk ratio [RR] 0.37; 95% CI, 0.08 to 1.63) or positive opioid urine drug screens (RR 0.81; 95% CI, 0.56 to 1.18).[4] Low quality evidence from 3 trials demonstrates no difference in treatment retention between methadone and buprenorphine maintenance treatment programs (RR 0.69; 95% CI, 0.39 to 1.22).[4] In addition, there is moderate quality evidence from 2 trials of no difference in rates of adverse events between methadone and buprenorphine maintenance treatment (RR 1.10; 95% CI, 0.64 to 1.91).[4] Buprenorphine maintenance treatment may be superior to detoxification treatment alone or psychosocial treatment alone in terms of self-reported opioid use in the last 30 days (RR 0.54; 95% CI, 0.31 to 0.93) and positive opioid urine drug screens (RR 0.63; 95% CI, 0.43 to 0.91) based on low quality evidence.[4] In addition, buprenorphine maintenance treatment is superior to detoxification treatment alone or psychosocial treatment alone in terms of treatment retention (RR 0.33; 95% CI, 0.23 to 0.47) and adverse events (RR 0.19; 95% CI, 0.06 to 0.57) based on moderate quality evidence.[4] Overall, the authors concluded that

there is low to moderate quality evidence to support the use of methadone or buprenorphine maintenance therapy for opioid dependence but further research may change the overall findings from this review.[4]

The effectiveness of pharmacological interventions for illicit drug-using (abuse or dependence) offenders (i.e., subject to the criminal system) in reducing drug use, criminal activity, or both, was recently evaluated in a systematic review by the Cochrane Collaboration.[6] The systematic review was conducted because trials in the criminal justice setting are largely lacking, and continuity of care is critical for the treatment of individuals who transition between prison and the community.[6] All RCTs that assessed the efficacy of any pharmacological intervention that is designed to reduce, eliminate or prevent relapse of drug use or criminal activity, or both, in drug-using offenders were eligible for inclusion.[6] Control interventions could be no treatment, minimal treatment, waiting list, treatment as usual, or other treatment (pharmacological or psychosocial).[6] Where studies reported a number of different follow-up periods, the longest time reported was used to provide the most conservative estimate of effectiveness.[6] Alcohol and tobacco use was excluded from drug use outcomes data.[6] Fourteen (n=2647) trials lasting between 6 months and 4 years met inclusion criteria but most studies had small sample sizes.[6] Thirteen studies used methadone as an intervention and most trials were conducted in prison.[6] In general, the trials included evaluated methadone, buprenorphine, or naltrexone compared to no intervention, other non-pharmacological treatments (e.g., counselling) or other pharmacological drugs.[6] The methodological quality of the included trials was mostly unclear as methods were generally poorly described.[6] According to the investigators, the biggest threats to risk of bias were open label study designs (performance and detection bias) and incomplete outcome data (attrition bias).[6] Heterogeneity between studies prevented the ability to pool some data; however, 11 studies were included in the meta-analysis.[6] When compared to non-pharmacological treatment, there was low quality evidence that opioid agonist treatment (methadone or buprenorphine) was not effective at reducing drug use based on objective dichotomous data (i.e., hair and urine analysis) (RR 0.72; 95% CI, 0.51 to 1.00; n=237), self-reported subjective dichotomous data (yes/no) (RR 0.61; 95% CI, 0.31 to 1.18; n=317) or self-reported continuous data (SMD -0.62; 95% CI, -0.85 to -0.39; n=510).[6] No statistically significant differences in individual treatments were found between methadone and buprenorphine in self-reported dichotomous data of drug use (yes/no) (RR 1.04; 95% CI, 0.69 to 1.55; n=370) or continuous data of drug use (amount of drug use) (MD 0.70; 95% CI, -5.33 to 6.73; n=81) or in criminal activity (RR 1.25; 95% CI, 0.83 to 1.88).[6] There was also low quality evidence that naltrexone was not effective at reducing drug use (RR 0.69; 95% CI, 0.28 to 1.70; n=63) but there was moderate quality evidence that naltrexone treatment reduced criminal activity as evidenced by re-incarceration (RR 0.40; 95% CI, 0.21 to 0.74; n=114).[6] In a separate systematic review that looked specifically at female drug-using offenders, the only trial identified used buprenorphine which did not significantly reduce self-reported drug use compared to placebo in this population (RR 0.58; 95% CI, 0.25 to 1.35; n=36).[12] Low retention rates after prison release significantly limit adequate follow-up of all trials in these systematic reviews.

New Guidelines:

<u>VA/DoD Clinical Practice Guideline for the Management of Substance Abuse Disorders</u>[3]

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-based Practice Work Group facilitates the development of clinical practice guideline for the VA and DoD populations. In December 2015, the VA/DoD published an update of their clinical practice guideline for the evaluation, treatment and management of substance abuse disorders.[3] The guideline workgroup used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence base and assign a grade for the strength of each recommendation.[3] For example, a strong recommendation indicates the workgroup was highly confident based on evidence that benefits related to the recommendation outweigh risks.[3] The VA/DoD emphasizes that medical management for substance abuse disorders is a shared decision-making process that must provide strategies to increase medication adherence, as well as monitoring of substance use and its consequences.[3] Management of substance use disorders must also support abstinence through education and referral to support groups.[3]

Alcohol Use Disorder

The VA/DoD recommend all patients in general medical and mental healthcare settings be screened for unhealthy alcohol use every year using the 3-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire or the Single-item Alcohol Screening Questionnaire (SASQ) [*strong recommendation*].[3] A single initial intervention regarding alcohol-related risks and advice to abstain or drink within the established limits is recommended for patients without documented alcohol use disorder that screen positive for unhealthy alcohol use by the nationally established age and gender-specific limits for daily and weekly consumption in Table 2 [*strong recommendation*].[3]

Table 2. Nationally Established Age- and Gender-specific limits for Daily and Weekly Alcohol Consumption.[3]

- Men aged ≤65 y: ≤4 standard drinks per day and ≤14 per week
- Men aged >65 y and all women: ≤3 standard drinks per day and ≤7 per week
- Patients with contraindications including potential drug-drug interactions: 0 drinks per day

For patients with substance use disorders, there is insufficient evidence to recommend for or against using a standardized assessment that would determine initial intensity and setting of substance use disorder care rather than the clinical judgment of trained providers.[3]

In addition to offering one or more recognized non-pharmacological interventions (Behavioral Couples Therapy for alcohol use disorder; Cognitive Behavioral Therapy for substance abuse disorders; Community Reinforcement Approach; Motivational Enhancement Therapy; and/or 12-step Facilitation), any of the following specific pharmacotherapy options is recommended for moderate-severe alcohol use disorder based on RCTs and several systematic reviews/meta-analyses [*strong recommendation*][3]:

- Acamprosate
- Disulfiram
- Naltrexone (oral or extended-release)
- Topiramate

In the absence of contraindications, there is insufficient evidence to recommend routine use of one of the recommended medications over another; thus, treatment choice should be individualized based on specific needs and patient preferences.[3]

For management of moderate to severe alcohol withdrawal, a benzodiazepine is recommended with adequate monitoring [*strong recommendation*].[3] Pharmacotherapy strategies for managing alcohol withdrawal should include a predetermined fixed medication (i.e., given in advance of the emergence of anticipated withdrawal) with a tapering schedule and an additional medication available as needed; alternatively, treatment may be only given when signs or symptoms of withdrawal occur (e.g., as needed dosing) [*strong recommendation*].[3] Non-benzodiazepine alternatives such as carbamazepine, gabapentin, or valproic acid are recommended for managing mild to moderate alcohol withdrawal in patients from whom risks of benzodiazepines outweigh benefits (e.g., inadequate monitoring available, abuse liability, or allergy/adverse reactions) [weak recommendation].[3] The VA/DoD strongly recommend against the use of alcohol to manage medically supervised withdrawal.[3]

Opioid Use Disorder

For patients with a diagnosis of opioid use disorder, the VA/DoD recommends any of the following specific medications considering patient preferences [*strong recommendation*][3]:

- Buprenorphine/naloxone
- Methadone in an Opioid Treatment Program

Specific recommendations for treatment of opioid use disorder are also recommended[3]:
- Buprenorphine alone without naloxone in pregnant women for whom buprenorphine is indicated [*weak recommendation*]
- The method of buprenorphine treatment (i.e., Opioid Treatment Program or office-based) should be individualized for the patient [strong recommendation]
- Extended-release injectable naloxone is an option for patients for whom opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued and who have established abstinence for a sufficient period of time [*strong recommendation*]
- There is insufficient evidence to recommend for or against oral naltrexone for the treatment of opioid use disorder
- Addiction-focused Medical Management alone or in conjunction with another psychosocial intervention is recommended at initiation of office-based buprenorphine [*strong recommendation*][3]

The VA/DoD do not recommend withdrawal management unless patients are stabilized from opioid use disorder because it substantially increases risk for relapse and overdose [*strong recommendation*].[3] In such cases, administration of long-term opioid agonists (methadone, buprenorphine) is preferred over short tapers because it is more effective and less harmful.[3] A taper of opioids using methadone or buprenorphine can be used if medically supervised in patients that 1) require abstinence from opioids; 2) wish to receive non-opioid agonist treatment (extended-release naloxone injection); 3) have minimal symptoms of opioid dependency; or 4) are in a profession that does not permit opioid agonist treatment [*strong recommendation*].[3] Clonidine may be used for withdrawal management as a second-line agent in patients with opioid use disorder who may have contraindications to methadone or buprenorphine [*strong recommendation*].[3]

The VA/DoD do not have specific pharmacotherapy recommendations for or against management of cannabis use disorder, cocaine use disorder or methamphetamine use disorder because of insufficient evidence.[3]

New Safety Alerts:
None identified.

New Formulations or Indications:
PROBUPHINE (buprenorphine) [C-III] implant device for subdermal use was approved by the FDA in May 2016.[13] The device is not available in retail pharmacies and must be inserted and removed by the certified prescriber.[13] The implants can only be obtained through a restricted Risk Evaluation and Mitigation Strategy (REMS) program that requires specialized training for physicians on insertion and removal techniques, as well as the risks for accidental overdose, misuse and abuse of opioids.[13] Certification for use of PROBUPHINE, which must be renewed every 12 months, must be achieved before use of the device.[13]

The approved indication is for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability of no more than 8 mg daily of a sublingual (SL) or buccal buprenorphine-containing product.[13] Treatment should accompany counseling and other psychosocial support.[13] Four implants are inserted subdermally in the upper arm for 6 months and are removed by the end of the sixth month.[13]

The efficacy of the implant is based on evidence from one double-blind, double-dummy, 6-month RCT (n=173) that compared the 4 simultaneous 80 mg buprenorphine implants with sublingual buprenorphine in adults who met DSM-IV-TR criteria for opioid dependence.[14] All patients in the trial were clinically stable on at least 6 months on SL buprenorphine at 8 mg per day or less.[14] Patients randomized to the SL buprenorphine group remained on their pre-enrollment dose (75% were taking 8 mg daily). Patients are eligible for the implant based on the enrollment in the clinical trial and manufacturer prescribing information[13]:

- no reported illicit opioid use
- no reports of significant withdrawal symptoms
- low to no desire/need to use illicit opioids
- no hospitalizations (addiction or mental health issues), emergency room visits, or crisis interventions in the past 90 days
- stable living environment, participation in a structured activity/job that contributes to the community, consistent participation in recommended cognitive behavioral therapy/peer support program
- consistent compliance with clinic visit requirements

The 4 implants contained 80 mg of buprenorphine each and yield similar plasma concentrations at a range (0.5-1.0 ng/mL) comparable to 8 mg per day or less of SL buprenorphine.[14] The primary efficacy end point was the difference in proportion of responders, defined as participants with at least *4 of 6 months* without evidence of illicit opioid use (based on urine test and self-report composites) by treatment group.[14] A total of 81/84 (96.4%) of patients in the implant group responded to therapy versus 78/89 (87.6%) patients in the SL group.[14] The difference was 8.8% (1-sided 97.5% CI, 0.009 to infinity; p<0.001 for noninferiority; p=0.03 for superiority) for the primary endpoint (NNT = 12).[14] In a sensitivity analysis for all randomized participants, with all missing urine samples imputed as positive for opioids and no illicit opioid use for all 6 months, 70/87 (80.5%) patients in the implant group and 60/90 (66.7%) in the SL buprenorphine group remained opioid-free, resulting in a proportion difference of 13.8% (1-sided 97.5% CI, 0.010 to infinity; p<0.001 for noninferiority; p=0.03 for superiority).[14] Drug-related adverse events were consistent with the known safety profile of buprenorphine and the subdermal implantation procedures (local site adverse events).[14]

Randomized Controlled Trials:

A total of 108 citations were manually reviewed from the literature search. After manual review, most citations were excluded because of wrong study design (i.e., observational), lack of control group, hospital setting, or outcome studied (i.e., non-clinical). The remaining trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 3: Description of Randomized Comparative Clinical Trials.

Alcohol Use Disorder				
Study	Comparison	Population	Primary Outcome	Results
O'Malley, et al.[15] DB, PC, PG, RCT 8 weeks N=128	1. Naltrexone 25 mg/d + naltrexone 25 mg PRN once per day (≥2 hrs prior to drinking situations). Max 50 mg/day. 2. Placebo targeted + placebo daily	Ages 18-25 years reporting ≥4 heavy drinking days (≥4 drinks/women or ≥5 drinks/men) in past 4 weeks.	Outcome 1: % days abstinent (PDA) Outcome 2 % heavy drinking days (PHDD) Self-reported drinking by web-based diary	PDA: 1. 56.6% (SD 22.52) 2. 62.5% (SD 15.57) LSMD -2.55; 95% CI, -8.46 to 3.36) PHDD: 1. 21.6% (SD 16.05) 2. 22.9% (SD 13.20) LSMD -1.44; 95% CI, -6.60 to 3.71)

Opioid Use Disorder				
D'Onofrio, et al.[16] SC, OL, RCT 30 days N=329	1. Referral to addiction services 2. Referral to addiction services + Brief Negotiation Interview (BNI) 3. Referral to addiction services + BNI + 3-day supply of buprenorphine (8 mg day 1, 16 mg days 2 and 3) to bridge until first clinic visit.	Ages ≥18 years reporting to ED with DSM-IV criteria for opioid dependence and positive UDS for opioids nonmedical prescription opioid or heroin use in past 30 days	Engagement in treatment (enrollment and receiving formal addiction treatment	1. 38/102 (37%; 95% CI, 28 to 47%) 2. 50/111 (45%; 95% CI, 36 to 54%) 3. 89/114 (78%; 95% CI, 70 to 85%; p<0.001 vs. other 2 comparisons)
Lee, et al.[17] MC, OL, RCT 6 months	1. VIVITROL (naltrexone ER) inj once per month 2. Usual care (brief counseling, referral to addiction services)	Criminal justice offenders ages 18-60 years with opioid dependence per DSM-IV criteria but currently opioid free per UDS and willing to try opioid-free treatment	Time to an opioid-relapse event during the 6-month treatment phase (defined as ≥10 days opioid use in a 28-day period)	Time to first relapse: 1. 10.5 weeks 2. 5.0 weeks (HR 0.49; 95% CI, 0.36 to 0.68) Total participants with relapse: 1. 66 (43%) 2. 99 (64%) (OR 0.43; 95% CI, 0.28 to 0.65)

Abbreviations: CO = cross-over; DB = double-blind; ED = emergency department; ER = extended-release; LSMD = least squares mean difference; MC = multi-centered; MD = mean difference; MME = morphine milligram equivalents; NRS = numerical rating scale (range 0-10); OL = open label; PC = placebo-controlled; PG = parallel group; RCT = randomized clinical trial; SC = single center; SD = standard deviation.

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET DR	ACAMPROSATE CALCIUM	ACAMPROSATE CALCIUM	Y
SUBLINGUAL	FILM	SUBOXONE	BUPRENORPHINE HCL/NALOXONE HCL	Y
SUBLINGUAL	TAB SUBL	BUPRENORPHINE HCL	BUPRENORPHINE HCL	Y
SUBLINGUAL	TAB SUBL	BUPRENORPHINE-NALOXONE	BUPRENORPHINE HCL/NALOXONE HCL	Y
SUBLINGUAL	TAB SUBL	ZUBSOLV	BUPRENORPHINE HCL/NALOXONE HCL	Y
ORAL	TABLET	NALTREXONE HCL	NALTREXONE HCL	Y
BUCCAL	FILM	BUNAVAIL	BUPRENORPHINE HCL/NALOXONE HCL	N
ORAL	TABLET	ANTABUSE	DISULFIRAM	N
ORAL	TABLET	DISULFIRAM	DISULFIRAM	N
INTRAMUSC	SUS ER REC	VIVITROL	NALTREXONE MICROSPHERES	N

Appendix 2: Abstracts of Clinical Trials

O'Malley, et al.
Reduction of Alcohol Drinking in Young Adults by Naltrexone: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial of Efficacy and Safety. *J Clin Psychiatry* (2015).

Objective: Naltrexone, an opioid antagonist, may facilitate reduction in drinking among young adults. We compared the efficacy and safety of naltrexone administered daily plus targeted dosing with placebo to reduce drinking in heavy drinking young adults.
Methods: Randomized, double-blind, placebo-controlled study, outpatient research center, March 2008-January 2012. Participants were ages 18-25, reporting ≥4 heavy drinking days in the prior 4 weeks. Interventions included naltrexone 25 mg daily plus 25 mg targeted (at most daily) in anticipation of drinking (n=61) or daily/targeted placebo (n=67). All received a personalized feedback session and brief counseling every other week. Primary outcomes were percent days heavy drinking (PHDD) and percent days abstinent (PDA) over the 8-week treatment period. Secondary outcomes included drinks/drinking day and percent days with estimated blood alcohol levels ≥0.08 g/dL.
Results: Of 140 randomized, 128 began treatment, comprising the evaluable sample. During treatment, PHDD (Naltrexone M=21.60, SD=16.05; Placebo M=22.90, SD=13.20) (p=0.58) and PDA (Naltrexone M=56.60, SD=22.52; Placebo M=62.50, SD=15.75) (p=0.39) did not differ by group. Naltrexone significantly reduced drinks per drinking day (Naltrexone M=4.90, SD=2.28; Placebo M=5.90, SD=2.51) (p=0.009) and percentage of drinking days with estimated BAC ≥0.08 g/dL (Naltrexone M=35.36, SD=28.40; Placebo M=45.74, SD=26.80) (p=0.042). There were no serious adverse events. Sleepiness was more common with naltrexone.
Conclusions: Naltrexone did not reduce frequency of drinking or heavy drinking days, but reduced secondary measures of drinking intensity. While effects were modest, the risk-benefit ratio favors offering naltrexone to help young adult heavy drinkers reduce their drinking.

D'Onofrio, et al.
Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial. *JAMA* (2015).

IMPORTANCE: Opioid-dependent patients often use the emergency department (ED) for medical care.
OBJECTIVE: To test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention); and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine).
DESIGN, SETTING, AND PARTICIPANTS: A randomized clinical trial involving 329 opioid-dependent patients who were treated at an urban teaching hospital ED from April 7, 2009, through June 25, 2013.
INTERVENTIONS: After screening, 104 patients were randomized to the referral group, 111 to the brief intervention group, and 114 to the buprenorphine treatment group.
MAIN OUTCOMES AND MEASURES: Enrollment in and receiving addiction treatment 30 days after randomization was the primary outcome. Self-reported days of illicit opioid use, urine testing for illicit opioids, human immunodeficiency virus (HIV) risk, and use of addiction treatment services were the secondary outcomes.
RESULTS: Seventy-eight percent of patients in the buprenorphine group (89 of 114 [95%CI, 70%-85%]) vs 37%in the referral group (38 of 102 [95% CI, 28%-47%]) and 45%in the brief intervention group (50 of 111 [95% CI, 36%-54%]) were engaged in addiction treatment on the 30th day after randomization (p< 0.001). The buprenorphine group reduced the number of days of illicit opioid use per week from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) versus a reduction

from 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) in the referral group and from 5.6 days (95% CI, 5.3-5.9) to 2.4 days (95% CI, 1.8-3.0) in the brief intervention group (p<0.001 for both time and intervention effects; p=0.02 for the interaction effect). The rates of urine samples that tested negative for opioids did not differ statistically across groups, with 53.8% (95% CI, 42%-65%) in the referral group, 42.9% (95% CI, 31%-55%) in the brief intervention group, and 57.6% (95% CI, 47%-68%) in the buprenorphine group (p=0.17). There were no statistically significant differences in HIV risk across groups (p=0.66). Eleven percent of patients in the buprenorphine group (95% CI, 6%-19%) used inpatient addiction treatment services, whereas 37% in the referral group (95% CI, 27%-48%) and 35% in the brief intervention group (95% CI, 25%-37%) used inpatient addiction treatment services (p< .001).
CONCLUSIONS AND RELEVANCE: Among opioid-dependent patients, ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of urine samples that tested positive for opioids or of HIV risk. These findings require replication in other centers before widespread adoption.

Lee, et al.
Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. *N Engl J Med* (2016).

BACKGROUND: Extended-release naltrexone, a sustained-release monthly injectable formulation of the full mu-opioid receptor antagonist, is effective for the prevention of relapse to opioid dependence. Data supporting its effectiveness in U.S. criminal justice populations are limited.
METHODS: In this five-site, open-label, randomized trial, we compared a 24-week course of extended-release naltrexone (Vivitrol) with usual treatment, consisting of brief counseling and referrals for community treatment programs, for the prevention of opioid relapse among adult criminal justice offenders (i.e., persons involved in the U.S. criminal justice system) who had a history of opioid dependence and a preference for opioid-free rather than opioid maintenance treatments and who were abstinent from opioids at the time of randomization. The primary outcome was the time to an opioid-relapse event, which was defined as 10 or more days of opioid use in a 28-day period as assessed by self-report or by testing of urine samples obtained every 2 weeks; a positive or missing sample was computed as 5 days of opioid use. Post-treatment follow-up occurred at weeks 27, 52, and 78.
RESULTS: A total of 153 participants were assigned to extended-release naltrexone and 155 to usual treatment. During the 24-week treatment phase, participants assigned to extended-release naltrexone had a longer median time to relapse than did those assigned to usual treatment (10.5 vs. 5.0 weeks, P<0.001; hazard ratio, 0.49; 95% confidence interval [CI], 0.36 to 0.68), a lower rate of relapse (43% vs. 64% of participants, P<0.001; odds ratio, 0.43; 95% CI, 0.28 to 0.65), and a higher rate of opioid-negative urine samples (74% vs. 56%, P<0.001; odds ratio, 2.30; 95% CI, 1.48 to 3.54). At week 78 (approximately 1 year after the end of the treatment phase), rates of opioid-negative urine samples were equal (46% in each group, P = 0.91). The rates of other prespecified secondary outcome measures — self-reported cocaine, alcohol, and intravenous drug use, unsafe sex, and reincarceration — were not significantly lower with extended-release naltrexone than with usual treatment. Over the total 78 weeks observed, there were no overdose events in the extended-release naltrexone group and seven in the usual-treatment group (p= 0.02).
CONCLUSIONS: In this trial involving criminal justice offenders, extended-release naltrexone was associated with a rate of opioid relapse that was lower than that with usual treatment. Opioid-use prevention effects waned after treatment discontinuation.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 2 2016

1 exp Buprenorphine, Naloxone Drug Combination/ or exp Buprenorphine/ 3133
2 exp Naltrexone/ 4363
3 exp Prescription Drug Misuse/ or exp Opioid-Related Disorders/ or exp Substance-Related Disorders/ 134079
4 1 or 2 7341
5 3 and 4 3247
6 limit 5 to (english language and humans and yr="2015 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 77

Ovid MEDLINE(R) without Revisions 1996 to July Week 2 2016

1 acamprosate.mp. 641
2 exp Disulfiram/ 760
3 exp Naltrexone/ 4363
4 exp Alcoholism/ 27319
5 exp Substance-Related Disorders/ 133713
6 exp Alcohol Deterrents/ 1461
7 1 or 2 1308
8 4 or 5 or 6 134283
9 7 and 8 1247
10 limit 9 to (english language and humans and yr="2014 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 31

Buprenorphine and Buprenorphine/Naloxone Products

Goals:
- Encourage use of buprenorphine products on the Preferred Drug List.
- Restrict use of buprenorphine products under this PA to management of opioid use disorder.
- Restrict use of oral transmucosal buprenorphine monotherapy products (without naloxone) to pregnant patients or females actively trying to conceive.

Length of Authorization:
Up to 6 months

Requires PA:
- Buprenorphine sublingual tablets
- Buprenorphine/naloxone buccal film (Bunavail), sublingual film (Suboxone) and sublingual tablets (Zubsolv)
- Buprenorphine (Probuphine) subdermal implants

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system(s)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Buprenorphine therapy must be part of a comprehensive treatment program that includes psychosocial support.
4. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 6 months that the patient has not been prescribed any opioid analgesics from other prescribers?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the requested medication a preferred agent?	**Yes:** Go to #7	**No:** Go to #6
6. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #7
7. Is the request for the buprenorphine implant system (Probuphine)?	**Yes:** Go to #8	**No:** Go to #9
8. Has the patient been *clinically stable* on 8 mg daily or less of Suboxone or Subutex (or equivalent, see Table 1) for at least 6 months? Note: see Table 1 for definition of clinical stability and for equivalent dosing of other buprenorphine products.	**Yes:** if <u>all</u> criteria in Table 1 met, approve 4 implants for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., more than 24 mg/day or 48 mg every other day)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is the prescribed product a buprenorphine monotherapy product (i.e., without naloxone)	**Yes:** Go to #11	**No:** Go to #13
11. Is the patient pregnant or a female actively trying to conceive?	**Yes:** Go to #13	**No:** Go to #12
12. Does the patient have a contraindication or intolerance to buprenorphine/naloxone combination products that prevents successful management of opioid use disorder?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. What is the patients' pharmacy-of-choice? Document pharmacy name and NPI or address in PA record. Lock patient into their pharmacy-of-choice for 6 months.	Inform prescriber patient will be locked into a single pharmacy for all prescriptions. Go to #14	
14. What is the expected length of treatment?	Document length of therapy: _____ Approve for anticipated length of treatment or 6 months, whichever is shorter.	

Table 1. Criteria for Approved Use of Probuphine (buprenorphine implant).[1]

PROBUPHINE implants are only for use in patients who meet ALL of the following criteria:
• Patients should not be tapered to a lower dose for the sole purpose of transitioning to PROBUPHINE • Stable transmucosal buprenorphine dose (of 8 mg per day or less of a sublingual Subutex or Suboxone sublingual tablet or its transmucosal buprenorphine product equivalent) for 3 months or longer without any need for supplemental dosing or adjustments: o Examples of acceptable daily doses of transmucosal buprenorphine include: ▪ Subutex (buprenorphine) sublingual tablet (generic equivalent) 8 mg or less ▪ Suboxone (buprenorphine and naloxone) sublingual tablet (generic equivalent) 8 mg/2 mg or less ▪ Bunavail (buprenorphine and naloxone) buccal film 4.2 mg/0.7 mg or less ▪ Zubsolv (buprenorphine and naloxone) sublingual tablets 5.7 mg/1.4 mg or less

Consider the following factors in determining clinical stability and suitability for PROBUPHINE treatment: • no reported illicit opioid use • low to no desire/need to use illicit opioids • no reports of significant withdrawal symptoms • stable living environment • participation in a structured activity/job that contributes to the community • consistent participation in recommended cognitive behavioral therapy/peer support program • stability of living environment • participation in a structured activity/job
Reference: PROBUPHINE (buprenorphine implant for subdermal administration) [Prescribing Information]. Princeton, MJ: Braeburn Pharmaceuticals, Inc., May 2016.

P&T Review: *9/16 (AG); 1/15 (AG); 9/09; 5/09*
Implementation: *TBD; 9/1/13; 1/1/10*

Naltrexone Extended Release Inj. (Vivitrol®)

Goal(s):

- Promote safe and cost effective therapy for the treatment of alcohol and opioid dependence.

Length of Authorization:

Up to 6 months

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Does the patient have a diagnosis of alcohol dependence (DSM-IV-TR) or alcohol use disorder (DSM-V)?	**Yes:** Go to #4	**No:** Go to #5
4. Has the requesting prescriber provided documentation and/or confirmation of abstinence from alcohol as assessed by the provider or by objective testing?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Patients must have demonstrated alcohol abstinence prior to administration.
5. Does the patient have a diagnosis of opioid dependence (DSM-IV-TR) or opioid use disorder (DSM-V)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 6 months that the patient has not been prescribed any opioid analgesics from other prescribers?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the patient physiologically free of opioid dependence for ≥7 days, as confirmed by: a. Negative urine drug screen for opioids (including heroin) and their metabolites; and b. Negative naloxone challenge test (0.8 to 1.6 mg of IM/IV naloxone; or alternatively, 50 mg or oral naloxone with no subsequent withdrawal symptoms)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
8. Has the patient tried and failed first-line oral opioid agonists (buprenorphine/naloxone or methadone) if for the treatment of opioid dependency; or is the patient unable to take oral therapy or requires injectable therapy due to poor adherence?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system(s)?	**Yes:** Approve one 380 mg injection every 4 weeks for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness. Naltrexone extended-release injection therapy must be part of a comprehensive treatment program that includes psychosocial support.

P&T Review: 9/16 (AG); 1/15 (AG); 5/14; 11/13
Implementation: 1/1/14