UTAH MEDICAID DUR REPORT
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OPIOID DEPENDENCE TREATMENT WITH
VIVITROL® (EXTENDED-RELEASE NALTREXONE)

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Contents
Introduction ........................................................................................................................................... 3
Background ........................................................................................................................................... 4
Methodology ......................................................................................................................................... 5
Vivitrol Indications & Pharmacology ................................................................................................. 5
  Table 1. Vivitrol Prescribing Information: Indications, Dosing, & Use Concerns ............................ 5
Clinical Guidelines ............................................................................................................................... 6
  Table 2. Clinical Guidelines ................................................................................................................ 7
Clinical Efficacy ................................................................................................................................... 9
Safety .................................................................................................................................................. 10
  Table 3. Selected Safety Concerns for Vivitrol ................................................................................... 11
Inappropriate Use of Vivitrol.................................................................................................................. 13
Place in Therapy & Potential Criteria for Review ................................................................................ 13
Medicaid Utilization Data ..................................................................................................................... 16
  Table 4. Total Number of Claims for Vivitrol and Buprenorphine-containing Products ............... 16
  Table 5. Total Number of Pediatric Claims for Vivitrol and Buprenorphine-containing Products .... 16
  Table 6. Total Number of Patients on Vivitrol and Buprenorphine-containing Products ............... 17
  Table 7. Number of Pediatric Patients on Vivitrol and Buprenorphine-containing Products .......... 17
  Table 8. Age at First Fill of Vivitrol between 2014 and 2017 ......................................................... 18
Medicaid Utilization Overview .............................................................................................................. 19
Summary ............................................................................................................................................... 20
Appendix A ............................................................................................................................................. 21
  Table 1. Comparison of Maintenance Treatment Options for OUD ................................................ 21
Appendix B ............................................................................................................................................. 25
  Table 1. Randomized Controlled Trials ............................................................................................ 25
  Table 2. Cochrane Systematic Reviews ............................................................................................. 29
References ............................................................................................................................................. 31
Introduction

Treatment advancement for opioid use disorder is paramount, as opioid related mortality rates overshadow recovery. Abuse of prescribed opioids is associated with many adverse sequelae including premature death, and has significant medical, societal, and criminal-justice costs. The rate of opioid-prescription deaths in Utah has increased substantially over the past two decades, and since 2002 has outnumbered deaths from heroin and cocaine combined. In 2015, the state’s overdose death rate from natural and semi-synthetic opioids was reported to be 12.7 per 100,000 population (357 total cases in 2015). Sixty-five percent of the opioid-overdose cases in Utah, during 2012 to 2014, occurred in individuals with a known substance abuse disorder. Other co-occurring circumstances included physical health (61%) and mental health (56%) disorders, alcohol dependence (16%), and suicide attempts (10%).

Preventative strategies such as the Utah Controlled Substance Database Program, which provides prescribers and pharmacists with opioid-prescription fill histories, was implemented to curb inappropriate prescribing. In Utah, the rate of prescription-opioid dispensing increased by 29% (from 686 to 889 per 1,000 population) from 2002 to 2015, a phenomenon likely influenced by the aging baby-boomer population, recognition of undertreated pain, and the large prevalence of chronic pain in the United States. To help minimize abuse risk, federal and state-level guidelines have been published to promote judicious prescribing practices. In more recent years, opioid-prescribing in Utah declined between 2014 and 2015, from 910 to 889 per 1,000 population; data from 2016 is not yet available. This reduction is perhaps related to the efforts that government and healthcare organizations are taking to curtail the detrimental trends associated with opioid addiction. In addition to prevention measures, healthcare allies will need to address the potential gap in care when it comes to treating opioid use disorder (OUD). The Surgeon General’s 2016 report highlights that “[o]nly about 10 percent of people with a substance use disorder receive any type of specialty treatment.”

Treatment of OUD, formerly known as opioid dependence, is challenging and often progresses as a series of remissions and relapses. Woody et al, explain that “[s]ustained remission occurs in a significant minority of individuals, but it usually takes 10 or more years to emerge, and many survivors have medical and psychosocial problems that permanently impair their health, chances for employment, and overall adjustment.” The most widely used pharmacotherapies for OUD are methadone and buprenorphine (BUP) products. Issues involved with these agents include physical dependence, increased diversion risk, and additive respiratory depression risk. Nonetheless, “[s]tudies have shown that they are most effective when used over an extended, but as-yet-unspecified, period of time and with counseling and other services...” Naltrexone, an opioid antagonist, used for managing OUD is not associated with physical dependence, diversion, or additive CNS depression. The oral formulation of naltrexone has been available since the 1980’s and is dosed once daily or every other day. There is a long-standing history of poor compliance and high drop-out rates with the oral regimen, “with over one quarter dropping out after a few days and almost one-half dropping out in [the] first few weeks.”

However, in cohorts compliant with oral naltrexone, positive outcomes have been demonstrated—lower relapse rates and improvements in employment, legal, and social status. These results motivated the development of extended-release naltrexone, Vivitrol®, approved for OUD in 2010. Prior to this, Vivitrol was already on the market, approved by the Federal Drug Administration (FDA) for alcohol dependence in 2006.
Background

Naltrexone is an opioid antagonist with high affinity for the mu-opioid receptor. The long-acting formulation of Vivitrol facilitates a once-a-month administration frequency. Naloxone is also an opioid antagonist, however, its rapid onset and short duration of action makes it most useful as an antidote for opioid overdose and as an abuse deterrent in combination buprenorphine/naloxone products. Other agents labeled for OUD management include the full-opioid agonist, methadone, and the partial-opioid agonist, buprenorphine. Unlike naltrexone, methadone and buprenorphine induce and/or maintain physiologic dependence and cause withdrawal upon abrupt discontinuation.

The entrance of extended-release naltrexone into the OUD-treatment landscape has expanded treatment accessibility since restrictions on the provider type and treatment setting are less stringent for naltrexone compared to other options. Naltrexone does not induce opioid-related habit forming effects; thus, the risk of diversion is null compared to that of methadone and buprenorphine containing products. Naltrexone prescriptions can be filled by retail pharmacies and issued by prescribers without a special waiver or registration number from the Drug Enforcement Agency (DEA). The controlled substances, methadone and buprenorphine, are more highly regulated and require prescribing physicians to maintain specialized certifications to authorize such prescriptions. Treatment with buprenorphine, a DEA Schedule III controlled substance, can be carried out in an office-based setting by a waivered physician (per the Drug Addiction Treatment Act of 2000); prescriptions are fillable at retail pharmacies. However, without observed-dosing oversight, buprenorphine may be diverted and has been involved in accidental exposures to children. Methadone, a DEA Schedule II controlled substance, is prescribed and dispensed for OUD only in a highly-structured opioid therapy program (OTP) that must be licensed by the United States Substance Abuse and Mental Health Services Administration (SAMHSA). OTPs may operate in a variety of venues: intensive outpatient, residential, or hospital settings.

Opioid use disorder is conceptualized as a chronic, relapsing disease that involves managing patients through the opioid withdrawal and maintenance stages, with many needing long-term treatment. A paired pharmacological- psychosocial treatment approach has improved outcomes in both the detoxification and maintenance stages. After detoxification, patients can engage in maintenance treatment with methadone, buprenorphine/naloxone, or naltrexone products for the prevention of relapse. Many factors including patient attitudes and access to care (i.e. free-time, transportation, appointment availability) are associated with the chosen treatment and retention outcome. Although utilization rates of Vivitrol have been low among U.S.-treatment programs, due to various incorporation barriers, recent studies reported patient preference rates for extended-release naltrexone (XR-NTX) as high as 32% to 52%.

The purpose of this report is to review the appropriate use of Vivitrol and factors that may affect its efficacy and safety outcomes for OUD management. The Utah Medicaid Preferred Drug List currently includes Suboxone® as the preferred agent in the substance-abuse treatment category. Bunavail®, Zubsolv®, and generic buprenorphine/naloxone are non-preferred options. Summary information for the agents indicated for OUD in the United States is included in Appendix A, Table 1.
Methodology

Relevant information from the Drug Class Review, *Opioid Dependence Treatment With Buprenorphine: November 2016*, prepared by the University of Utah’s Drug Regimen Review Center was incorporated into this report. A Cochrane Library literature search for systematic reviews was conducted. Medline (PubMed), EMBASE, UptoDate, the Agency for Healthcare Research and Quality (AHRQ), the U.S. Department of Health and Human Services website, the FDA website (including product labeling information), the SAMHSA website, and Lexicomp were searched for safety information, systematic reviews, clinical trials, and other guidelines.

Vivitrol Indications & Pharmacology

Vivitrol is labeled for the prevention of opioid-dependence relapse following detoxification and should be used as part of a comprehensive management program that includes psychosocial support. It is recommended for patients to be opioid-free for at least 7 to 10 days prior to initiation, in order to avoid precipitating a severe opioid withdrawal event. Vivitrol is available as a long-acting injectable suspension (single use vial) that must be administered intramuscularly into the gluteal muscle by a healthcare provider every 4 weeks or once monthly. Vivitrol is also approved for the treatment of alcohol dependence in patients able to abstain from alcohol in an outpatient setting prior to initiation. Selected prescribing information (PI) from the product’s package insert is outlined in Table 1.

<table>
<thead>
<tr>
<th>Dosage Form &amp; Storage</th>
<th>Vivitrol®-naltrexone: injectable powder for suspension; single use vial containing 380mg naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Refrigerate; may be unrefrigerated (not to exceed 77°F) for up to 7 days; do not freeze</td>
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</table>

<table>
<thead>
<tr>
<th>FDA Approved Indications</th>
<th>Should be used as part of a comprehensive management program that includes psychosocial support</th>
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<tbody>
<tr>
<td></td>
<td>Approved for the prevention of relapse to opioid dependence, following opioid detoxification</td>
</tr>
<tr>
<td></td>
<td>Approved for the treatment of alcohol dependence in patients able to abstain from alcohol in an outpatient setting prior to initiating therapy</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Dosage &amp; Administration for Opioid Dependence Prevention</th>
<th>Dose: Naltrexone 380 mg via intramuscular injection every 4 weeks or once a month</th>
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<tbody>
<tr>
<td></td>
<td>• Should be opioid-free 7 to 10 days prior to initiation of therapy</td>
</tr>
<tr>
<td></td>
<td>• Must be administered by a healthcare provider via intramuscular gluteal injection</td>
</tr>
<tr>
<td></td>
<td>• Package includes customized needles; Vivitrol must not be injected with any other needle. Needle lengths provided (1 1/2 &amp; 2 inches) may not be adequate in every patient</td>
</tr>
<tr>
<td></td>
<td>• Healthcare providers should consider an alternate treatment for patients whose body habitus precludes an intramuscular gluteal injection with one of the provided needles</td>
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<tr>
<th>Other Initiation Concerns</th>
<th>Switching From Oral Naltrexone</th>
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<tbody>
<tr>
<td></td>
<td>• Guidance is not provided by the manufacturer prescribing information</td>
</tr>
<tr>
<td></td>
<td>Switching from Buprenorphine, Buprenorphine/Naloxone, or Methadone</td>
</tr>
<tr>
<td></td>
<td>• Guidance is not provided by the manufacturer, however, there are case reports of some patients experiencing severe withdrawal when switching from opioid agonist to opioid antagonist therapy. Patients transitioning from buprenorphine or methadone may be vulnerable to withdrawal effects for as long as 2 weeks after switching.</td>
</tr>
<tr>
<td></td>
<td>• See Appendix A for more information on switching therapies</td>
</tr>
</tbody>
</table>

Table 1. Vivitrol Prescribing Information: Indications, Dosing, & Use Concerns
Inappropriate Use

- Not approved for the detoxification period (use methadone or buprenorphine products)

**Contraindicated** for the following patients:
- receiving opioid analgesics
- in acute opioid withdrawal
- with current physical dependences on opioids (including partial agonists)
- who failed a naloxone challenge test
- who have a positive urine screen for opioids
- with hypersensitivity to naltrexone, polylactide-co-glycolide, carboxymethyl-cellulose, or to any other components of the diluent.

The depot formulation of Vivitrol gradually releases medication from polymer microspheres. This polymer is commonly used in medical technologies such as medical sutures. Upon administration, the biphasic release system produces plasma drug-concentration peaks approximately 2 hours after injection and again in 2 to 3 days. Metabolism of naltrexone occurs through dihydrodiol dehydrogenase to produce the primary metabolite, 6β-naltrexol, which has some antagonist activity. The cytochrome P450 enzymes are not involved in naltrexone metabolism. The elimination of half-life of naltrexone and 6β-naltrexol is five to ten days. Excretion of naltrexone occurs through the urine primarily as metabolites (percentages not reported in the package insert). The therapeutic duration of action is expected to last about a month, as the approved dosing interval is every 4 weeks or per month frequency. Dose adjustments are not required for mild to moderate hepatic impairment (Group A and B Child-Pugh classifications) or for mild renal impairment (creatinine clearance 50-80 mL/min); the pharmacokinetics of Vivitrol have not been assessed for insufficiencies more severe than these aforementioned levels of impairment.

Clinical Guidelines

Treatment guidelines advocate for providing OUD maintenance pharmacotherapy following opioid detoxification. The American Society of Addiction Medicine (ASAM) treatment guideline does not specify preference for one product over another since there is limited head-to-head evidence. In contrast, the Department of Veterans Affairs and Department of Defense (VA/DoD) guideline concludes that there is strong evidence supporting opioid agonist therapy and moderate evidence supporting extended-release naltrexone (XR-NTX) for relapse prevention, therefore, methadone and buprenorphine-containing products are designated as first-line agents and XR-NTX as a second-line option for patients unwilling to take or whom have failed opioid agonist therapies, patients with contraindications, or individuals without access to preferred options. Similar preferences are stated by the World Federation of Societies of Biological Psychiatry.

Guidelines overwhelmingly suggest that treatment should be individualized. Selection of the appropriate regimen and treatment venue should be guided by the patient’s disease history and preferences, along with the provider’s assessment of the patient’s psychosocial situation, co-occurring disorders, opportunities for treatment retention, and risk of medication diversion. The ASAM guideline does not recommend a specific length of treatment regarding each agent, however, highlights that relapse rates are high for most patients; thus, long-term treatment is often needed and should be decided based on the prescriber’s assessment of the patient’s response and circumstances. A similar recommendation is made by other authors. Table 2 provides an overview of recent guidelines published for managing OUD with pharmacotherapy.
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation Excerpts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016</strong></td>
<td>“Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.”</td>
</tr>
</tbody>
</table>
| **The ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use; 2015** | • Use of other addictive drugs (i.e. marijuana, stimulants) should not be a reason to suspend opioid use disorder treatment, although, these types of patients have been shown to have poorer outcomes.  
• The use of benzodiazepines and other sedative hypnotics may be a reason to suspend agonist treatment because of safety concerns related to respiratory depression and opioid agonists  
• The venue in which treatment is provided is as important as the specific medication selected.  
  o Opioid Treatment Programs: patients may benefit from a daily supervised setting  
• The patient’s preferences, psychosocial situation, co-occurring disorders, and risk of diversion should be considered when deciding on the treatment venue and medication.  
• Addiction should be considered a bio-psycho-social-spiritual illness, for which the use of medication(s) is but only one component of overall treatment.  
  ◦ Methadone: recommended for patients who may benefit from supervised daily dosing in an OTP, or for patients for whom failed buprenorphine  
  ◦ Oral Naltrexone: poor outcomes are often observed as a result of poor medication adherence. “The oral formulation may be considered for patient in whom adherence can be supervised or enforced.” The extended release product may be more appropriate for those with adherence issues.  
  ◦ Extended-release injectable naltrexone: reduces, but does not eliminate, issues with medication adherence  

**Special Populations (refer to guidelines for additional information)**  
• Pregnant women: use methadone or buprenorphine monoproduct; If taking naltrexone prior to becoming pregnant the decision to discontinue the medication (if relapse risk is low) or to continue naltrexone are options; however, informed consent of the reviewed risks should be documented.  
• Adolescents: Although FDA approval of these agents is limited in regard to patients under age 18, the guideline advocates that practitioners should consider employing pharmacotherapy for adolescents with OUD.  
• Individuals in the Criminal Justice System: Treatment with naltrexone XR is recommended; oral naltrexone is not recommended.  
• Patients with Pain: treat mild pain with NSAIDs and moderate to severe pain with short-term use of ketorolac.  
• Surgery: Extended-release naltrexone should be discontinued 30 days prior to surgery |
### Table 2. Continued

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation Excerpts</th>
<th>Pharmacotherapy for Opioid Use Disorder</th>
</tr>
</thead>
</table>
| VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders; 2015\(^{34}\) | • The following medications are recommended, with consideration of patient preferences  
  o Buprenorphine/naloxone combination therapy  
  o Methadone in an opioid treatment program  
 • The appropriate treatment setting should be individualized with consideration of patient preferences  
 • For patients who are unwilling, have contraindications, or do not have accessibility to engage in opioid agonists therapy that have been opioid free for a sufficient period of time, a prescriber shall offer:  
  o Extended-release injectable naltrexone  
 • There is insufficient evidence to recommend for or against oral naltrexone for treatment of opioid use disorder.  
 • “While documented abstinence from alcohol is not required for therapeutic benefit with injectable naltrexone, even greater benefit may be seen in patients who achieve some duration of alcohol abstinence (e.g., two to four days) prior to the initial injection of naltrexone.”  |

**Psychosocial Interventions with or without Pharmacotherapy**

- For patients receiving office-based buprenorphine treatment, there is insufficient evidence to recommend for or against any specific psychosocial intervention. The choice of psychosocial intervention should be made considering patient preferences and provider training/competence.
- In opioid treatment program settings, patients should be offered individual counseling and/or contingency management, considering patient preferences and provider training/competence.

| National Institute on Drug Abuse: Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition; 2012)\(^{33}\) | • No single pharmacological treatment is considered appropriate for everyone. The choice depends on the type of drug and characteristics of the patient.  
  “Effective treatment attends to multiple needs of the individual, not just his or her drug abuse. To be effective, treatment must address the individual’s drug abuse and any associated medical, psychological, social, vocational, and legal problems. It is also important that treatment be appropriate to the individual’s age, gender, ethnicity, and culture.”  
  “Remaining in treatment for an adequate period of time is critical.” The appropriate duration of therapy depends on the type and degree of the patient’s problems and needs. Significantly longer than 3 months of therapy is recommended and needed for lasting positive outcomes; treatment frequently requires multiple treatment episodes (long-term process). Relapses can occur requiring treatment to be reinstated or adjusted. Programs should include strategies to engage and keep patients in treatment.  |

| The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: Opioid dependence. (2011)\(^{35}\) | • First-line medications: methadone, buprenorphine or buprenorphine/naloxone  
 • Second-line medications: naltrexone, heroin  
 • Adjunctive medications: clonidine, lofexidine  |

**Abbreviation key:**  
ASAM, American Society of Addiction Medicine; NSAIDs, non-steroidal anti-inflammatory drugs; OBOT, office-based opioid treatment; OTP, opioid treatment program; OUD, opioid use disorder;
**Clinical Efficacy**

Systematic reviews and prospective trials pertaining specifically to the Vivitrol formulation were focused on, for inclusion of this review. There have been two randomized trials evaluating the efficacy of Vivitrol. One trial, carried out in treatment sites located in Russia, compared Vivitrol against placebo. The second trial, performed in North America compared Vivitrol to treatment-as-usual. Together, these trials demonstrated a significant reduction in opioid use and craving and an increase in treatment retention and time-to-relapse. The positive effects of the drug waned after the end of active treatment, highlighting the chronicity of the disease state and the need for ongoing therapy. Other ancillary studies were performed using the data-pool from these two trials. Prospective randomized studies have not been published that directly compare Vivitrol with oral naltrexone, methadone, or buprenorphine; however, one trial is currently underway.

A Cochrane meta-analysis was identified that captured data pertaining only to the efficacy of sustained-release naltrexone (Depotrex® by Biotek Inc.), with a publication date that predated the OUD-approval of Vivitrol. Since the data applied to an unapproved formulation that has not demonstrated bioequivalence to Vivitrol, the focus of this review will be on more recent randomized studies that are directly applicable to Vivitrol treatment outcomes. There were no other meta-analyses identified that assessed the efficacy of extended release naltrexone treatment. Summary tables of the reviewed studies can be viewed in Appendix B.

**Randomized Clinical Trials Evaluating Vivitrol Efficacy:**

- **Krupitsky et al.** — The efficacy of Vivitrol for the treatment of opioid dependence was evaluated in a randomized, double-blind, 24-week trial taking place in Russia. Patients, who were voluntarily seeking treatment and had successfully completed opioid detoxification, were randomized to receive a naltrexone injection of 380 mg (n = 126) or a placebo injection (n = 124), both in combination with biweekly counseling. The primary endpoint was the percentage of confirmed abstinence during weeks 5-24; the cumulative distribution for each group over the treatment period was compared and substantial separation between groups resulted, with the XR-NTX group having a significantly higher percentage of opioid-free weeks. The median proportion of patients with confirmed abstinence was 90% for the XR-NTX arm vs. 35% for the placebo arm (p=0.0002). Significantly more patients in the XR-NTX group achieved 100% abstinence at 24 weeks (36% vs. 23%, p=0.0224). Other secondary measures comparing XR-NTX versus placebo included:
  - Median retention days were significantly higher in the XR-NTX group vs. placebo, (168 vs 96 days, p=0.0042). The percentage of patients receiving all 6 injections in the experimental group was 57.9% and 42% in the placebo group.
  - Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the XR-NTX group (p<0.0001).
  - A statistically significant decrease in craving was observed with XR-NTX treatment, with a 50% mean reduction in subjective craving compared to no change in the placebo group by week 8.

- **Lee et al.** — The efficacy of Vivitrol for the prevention of opioid-dependence relapse was evaluated in a North American population with a criminal history; the comparator was “treatment as usual” (TAU) which included counseling and referral services. Patients were
treated over 24 weeks and follow-up extended to 78 weeks. Compared to the TAU group, participants in the experimental group had a) a longer median time to relapse (10.5 vs. 5.0 weeks, \( P<0.001 \)), b) a lower rate of relapse (43% vs. 64% of participants, \( P<0.001 \)), and c) a higher rate of opioid-negative urine samples (74% vs. 56%, \( P<0.001 \)) during the first 24 weeks. During the follow-up period after treatment had been discontinued, week 52 and 78 rates of opioid-negative urine samples were similar between groups showing that treatment effect wanes once discontinued. Secondary outcomes such as self-reported cocaine, alcohol, and intravenous drug use, unsafe sex, and re-incarceration were not significantly different between treatment arms.

- **Friedmann et al.** An ancillary study was conducted based on the Lee et al. trial to assess whether baseline population characteristics (i.e. age, gender, depression, suicidal thoughts, drug abuse risk, substance use, medical, employment status, socialization, legal and family/social issues, history of abuse, and quality of life measures) have an effect on XR-NTX-efficacy outcomes. The only significant moderator of the XR-NTX-treatment effect was alcohol intoxication (occurring in the 30 days prior to randomization), which significantly increased the risk of opioid relapse (41% vs. 65%, respectively, \( P<0.04 \)).

The study by Krupitsky et al, led to the U.S. approval of the medication. Wolfe et al, pointed out that the adequacy of the safety assessment (especially for overdose risk in dropouts) and the study design with a placebo comparator, when other standard-of-care pharmacotherapies exist, should be questioned. Furthermore, Krupitsky et al, and Lee et al, did not detail the experiences of those patients who challenged naltrexone’s efficacy with opioid ingestion while under treatment. This observation would be interesting since there have been reports of patients experiencing a high or partial high upon opioid intake, challenging the naltrexone blockade, while treated with long-acting naltrexone implants.

### Safety

In general, naltrexone is a well-tolerated medication. The most common adverse events in patients treated for OUD, according to the PI, include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache, occurring at rates of 2% or more and at least twice as frequent as the rate in the placebo group. In patients treated for alcohol dependence, the most common adverse events reported in the PI include nausea, vomiting, injection site reactions, muscle cramps, dizziness, somnolence, anorexia, and decreased appetite, occurring at rates of 5% or more and at least twice as frequent as the rate in the placebo group. Adverse event information from clinical trials employing Vivitrol for OUD management can be viewed in Appendix B, Table 1.

Proper usage and risks involved with Vivitrol therapy are emphasized through the FDA’s REMS (Risk Evaluation Mitigation Strategy) program. Patient counseling tools and an injection technique guide are education materials available to healthcare providers through this program. Table 3 outlines safety concerns and special-population use recommendations for Vivitrol. Further safety information beyond the product’s labeling is discussed following the table.
Table 3. Selected Safety Concerns for Vivitrol

**Psychiatric:** Patients with co-occurring psychiatric disorders should be monitored for adverse events. Suicidal thoughts, attempted suicide, and depression have been reported.\(^{23}\)

**Hepatic Insufficiency:** Dose adjustment is not necessary for mild to moderate hepatic impairment. The pharmacokinetics were not evaluated in patients with severe hepatic impairment.

**Renal Insufficiency:** No dose adjustment is necessary for mild renal insufficiency (CrCl 50-80 mL/min); use with caution in moderate to severe renal impairment since pharmacokinetic studies have not been conducted to guide therapy decisions.

**Pregnancy:** There are no adequate RCTs assessing Vivitrol use in pregnant patients. Vivitrol should only be used if the potential benefit justifies the potential risk to the fetus.

- **Pregnancy Category C:** Naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses ≥30 mg/kg/day (11 times the human exposure based on an AUC (0-28d) comparison) and to rabbits at oral doses ≥60 mg/kg/day (2 times the human exposure based on an AUC (0-28d) comparison).
- No evidence of teratogenicity was found in rats or rabbits when naltrexone was administered at doses up to 200 mg/kg/day (175- and 14-times the human exposure based on AUC, respectively).
- Transfer of naltrexone and its active metabolite into human breast milk has been reported. The potential risk for tumorigenicity (shown for naltrexone in animal studies) and risk of adverse reactions in the nursing infant and mother should be weighed against the benefits of therapy.

**Pediatric:** The safety, efficacy, and pharmacokinetics have not been established for this population.

**Geriatric:** No patients over age 65 were included in the studies leading to the approval of Vivitrol for OUD management. The pharmacokinetics of Vivitrol have not been evaluated in the geriatric population.

**Gender:** Gender did not influence the pharmacokinetics of Vivitrol.

**Race:** The effect on the pharmacokinetics due to this potential modulator has not assessed.

### Special Populations*

**Vulnerability to Opioid Overdose:** Relapsing patients are considerably vulnerable to opioid overdose following naltrexone discontinuation, upon missing a dose, or at the end of the dosing interval. This risk is present since the patient’s physiological tolerance to opioids diminishes during naltrexone therapy, compared to their pre-treatment baseline status. Patients are at risk of fatal overdose especially if they return to using opioids at doses near their pre-treatment intake. Patients must be warned of this. Additionally, those who attempt to use high doses of opioid to overcome the blockade mitigated by naltrexone may experience a fatal overdose.

**Hypersensitivity Reactions:** Some reported cases of injection site reactions have required surgical intervention.

**Precipitation of Opioid Withdrawal:** Patients should be opioid-free for a minimum of 7-10 days, prior to initiation of therapy, to avoid precipitation of a severe opioid withdrawal episode.

**Hepatotoxicity:** Cases of hepatitis and clinically significant liver dysfunction were reported with Vivitrol treatment while in the clinical development and post-marketing periods.

**Depression and Suicidality:** Monitor patients for the development of depression or suicidal thinking.

**Pain Management:** Consider regional analgesia or non-opioid analgesics. If an opioid is used/necessary, the patient should be monitored closely by healthcare providers in a setting equipped for cardiopulmonary resuscitation.

### Contraindications

- Receiving opioid analgesics
- In acute opioid withdrawal
- With current physical dependence to opioids (including partial agonists)
- Who failed a naltrexone challenge test
- Who have a positive urine screen for opioids
- With hypersensitivity reactions to naltrexone, poly(lactide-co-glycolide), carboxymethyl-cellulose, or any other components of the diluent

### Drug Interactions

- Naltrexone antagonizes the effects opioid containing anticough, antidiarrheal, and analgesic products.

*Additional information can be found in the product’s prescribing information.

**Abbreviations:** AUC, area under the curve; CrCl, creatinine clearance; OUD, opioid use disorder; RCTs, randomized controlled trials
Pregnancy: The choice of pharmacological treatment for opioid use disorder during pregnancy is an area of contentious debate and needs further study to clarify the risks of each option. An issue with opioid maintenance therapies during pregnancy is that the baby will likely endure neonatal abstinence syndrome (NAS) upon birth and possibly developmental deficiencies. Naltrexone does not cause NAS and does not seem to induce developmental problems, however, robust studies are needed to differentiate the long-term risk of these agents.

Hepatotoxicity: Vivitrol’s prescribing information warns that cases of hepatitis and liver dysfunction were observed during the development and post-marketing phases (rates not provided). Elevated liver transaminase occurrences are further described as having contributory etiologies in many cases (e.g. pre-existing alcoholic liver disease, hepatitis B/C infection, and concomitant use of other hepatotoxic drugs).

Mitchell et al, evaluated the hepatotoxic potential of Vivitrol in a population with considerable vulnerability (Hepatitis C (HCV) rate of 88.8% and Human Immunodeficiency Virus (HIV) rate of 42%). Over the 24 week trial, there was no significant difference between treatment arms (XR-NTX vs. placebo) in the frequency of hepatic-injury enzyme elevations. The authors concluded that XR-NTX can be used safely, with monitoring, in patients with underlying mild to moderate chronic HCV and/or HIV infections.

Risk of opioid overdose: It is important to warn patients taking naltrexone about their increased vulnerability to opioid overdose as described in Table 3. The possibility of a patient attempting to overcome the antagonist action of naltrexone, by taking large opioid doses, is a topic further discussed by Kjome et al, who point out that “[n]altrexone is also believed to antagonize euphoric effects of opioid agonists more than respiratory and cardiovascular effects. This would be an issue for an individual who may try to override a naltrexone-induced antagonism with higher doses of opioids, leading to respiratory depression and death before full euphoric effects are reached.”

Risk of non-opioid drug abuse/or overdose: The concern of increased abuse or overdose from non-opioid drug abuse while in OUD treatment has been discussed. There may be a heightened potential for patients to substitute sedatives or other drugs to satisfy residual withdrawal symptoms or drug-seeking tendencies. This topic, however, must be further explored especially since some studies suggest illicit drug use decreases while under OUD treatment, in general.

Depressive Symptoms: Trends depicting the association between XR-NTX treatment and depression/suicidality have varied depending on the indication studied. In the trial by Lee et al, where patients were treated for OUD, depression and serious depression/suicidality were low overall, however, higher in the TAU group (1.3% vs. 7% with depression, and 2% vs. 4% with serious depression/suicidality, respectively). Krupitsky et al, performed a randomized controlled trial (n=306) with results also suggesting that naltrexone treatment does not increase depression, anxiety, or anhedonia. In contrast, among clinical trials assessing the efficacy and safety of Vivitrol for alcohol-dependence, some treatment groups had higher levels of depressed mood than the control groups. Overall, elevated rates of mental illness have been reported in patients with substance use disorders; thus, these patients should be monitored for worsening mood-affect regardless of the chosen treatment.
Inappropriate Use of Vivitrol

Injection Needle/Administration: Vivitrol must be injected only with the needles provided by the manufacturer within the product’s packaging. The reason for this requirement is not fully divulged in the package insert. Furthermore, the injection must be administered by a healthcare provider who shall evaluate whether the provided 1 ½ or 2 inch needle will adequately facilitate intramuscular delivery into the gluteus muscle based on the patient’s body habitus. An alternative regimen is advised if one of the provided needles will not accomplish such an injection.

Dosing Interval: The ASAM authors note that some clinicians have diverged from the indicated dosing interval of every 4 weeks/or once-a-month and have administered the medication more frequently (every 3 weeks). It is written in the guideline, “There is no objective evidence supporting the safety or efficacy of this practice, however, and the Guideline Committee did not endorse it. More research is needed on safe dosing intervals for long-acting injectable naltrexone.”23 Perhaps prescribers using the product in this manner view that it would be better to offer the patient an early re-injection opportunity as opposed to a late administration in the case where appointment or schedule restrictions prevent the patient from attending the clinic at the 4 week mark. Since there is concern that patients may be more vulnerable to opioid overdose at the end of the injection cycle, this strategy may have been employed in an effort to mitigate such risk, however, must be further studied.

Place in Therapy & Potential Criteria for Review

Vivitrol is intended for patients with OUD who have detoxified and are free of opioids or opioid-containing medications, including tramadol, buprenorphine, and methadone, for a minimum of 7–10 days. In addition, the medication is indicated for patients with alcohol use disorder who have stopped drinking. The following topics are items for consideration, as potential prescribing criteria are developed for Vivitrol.

Supportive Counseling: Efficacy of Vivitrol has been proven only when used as part of a treatment program that integrates counseling and support.

Particular Candidacy: Patients that may be more suitable candidates for Vivitrol over methadone or buprenorphine-containing products are those with the following conditions/or situations:

- Hypersensitivity to methadone or buprenorphine products
- Respiratory insufficiency, paralytic ileus (a concern particularly with methadone), or clinical conditions that could be exacerbated upon administration of methadone or buprenorphine.
- Concomitant use disorders involving alcohol, sedatives, hypnotics, or anxiolytics. Naltrexone is a safer option in this situation since methadone and buprenorphine can potentiate CNS depression in combination with these agents.
- Patients with concomitant psychiatric diagnoses that impair their ability to maintain daily attendance at a methadone treatment center; Compliance with long-acting naltrexone dosing schedules may be easier for this type of patient.
- Patients employed or seeking employment in work sectors that do not allow any kind of opioid ingestion (this may be the case in transportation, healthcare, legal, and public safety type jobs).
• Patients with severe cardiovascular disease or taking drugs that may exaggerate hypotensive effects (BUP concern) or QT-prolongation (methadone concern)
• Drug interactions involving Cytochrome P enzyme; Methadone and buprenorphine are metabolized through the cytochrome P450 enzyme pathway. Many agents interact with this pathway including alcohol, anticonvulsants, antiretrovirals, and macrolide antibiotics.
• Situations where the patient has difficulty adhering to more frequent dosing regimens of methadone/buprenorphine or where diversion is a concern.
• Patients who wish to not use any sort of opioid-treatment

Special Populations:

• **Pediatric & Geriatric Populations:** Vivitrol has yet to be shown as safe and effective in the pediatric or geriatric population for OUD management. Furthermore, the pharmacokinetics have not been established for these two populations. The ASAM (American Society of Addiction Medicine) guideline authors advise that practitioners should consider all available pharmacotherapies for the adolescent population.23

• **Incarcerated Persons:** The ASAM guideline committee, advocates in favor of naltrexone availability for incarcerated groups preparing to re-enter the community.23 During the re-entry period after imprisonment, this population is at high-risk for relapse and overdose at which time naltrexone can prevent relapse and negative outcomes. A similar trend is also described by the authors, where “...individuals leaving detoxification with no meaningful follow-up treatment, or to persons who have been detoxified in the course of medical or surgical treatment and who leave the hospital with no immediate relapse prevention follow-up therapy,” face higher rates of overdose/relapse.23

• **Pregnancy:** The American College of Obstetricians and Gynecologists (ACOG) concluded in 2012, that the available evidence “supports the use of buprenorphine as a potential first-line medication for pregnant opioid-dependent women who are new to treatment”.54 Other authors argue that methadone remains the standard treatment because of the lack of data on pregnancy outcomes after first trimester buprenorphine exposure, and the lack of data on long-term neurodevelopmental outcomes after in utero exposure.54 At this point there is a lack of data assessing the use of Vivitrol during pregnancy, so the manufacture advised use only if the benefits clearly outweigh the risks.

Accessibility: Unlike methadone and buprenorphine, naltrexone can be prescribed in any setting by any clinician with the authority to prescribe, since it is not a controlled substance. This has made treatment more accessible since non-specialty prescribers may employ this therapy. A potential barrier (e.g. difficulty procuring appointments) for Vivitrol administration by a healthcare provider may be initiated if the provider type is restricted on the state level. Nonetheless, administration by a skilled healthcare provider helps ensure that the product will be stored, administered, and employed appropriately.

Other potential barriers to OUD treatment access that could be relevant to our population and should be considered include requirements for concurrent counseling (aimed at improving adherence, but could deter patients from initiating or continuing treatment if not easily accessible) and a potentially insufficient ratio of specialized providers to beneficiaries.55,56

Initiation Challenges: Patients who are wanting Vivitrol treatment must undergo detoxification which is a significant challenge to endure for most. Those who are able to accept and accomplish this first step
have a commendable degree of motivation, however such a challenge may be off-putting for some and is perhaps reflected by the low utilization of this agent in the U.S. and state level.

*Naloxone Challenge Test*: To help ensure a patient is not physically dependent on opioids, a naloxone challenge test can be utilized prior to administering Vivitrol. The package insert highlights rare case reports where a few patients experienced withdrawal despite demonstrating a negative naloxone challenge or urine screening tests. Trials with naloxone challenge tests have used a variety of approaches—administration of >0.8 mg of naloxone intravenously, intramuscularly, or subcutaneously to assess opioid-withdrawal symptoms.

*Oral vs. Injectable Naltrexone*: Although there has not been a prospective randomized head-to-head trial to compare outcomes of oral naltrexone to Vivitrol, the oral formulation is known to have significant limitations in regard to compliance and retention.

*Potential Criteria for Discussion*: The following items may be considered while developing prior authorization criteria for the prescribing of Vivitrol:

- Diagnosis codes corresponding to FDA approved indications (e.g. opioid and/or alcohol use disorder)
- Injection frequency limits
- Clinical reason for not using alternative agents
- Documentation of ongoing participation in a program including psychosocial support
- Documentation to confirm opioid-free status prior to treatment initiation (e.g. urine screening and/or naloxone challenge test)
- Documentation that the provider regularly assesses the patient’s controlled substance history via the Utah Controlled Substance Database monitoring program
- Regular documentation of that the prescriber counsels the patient including, but not limited to, addressing opioid overdose vulnerability
- Accessibility restrictions based on provider certifications (e.g. DEA holding prescribers)
- Monitoring specifications (e.g. liver function tests)
Medicaid Utilization Data

Table 4. Total Number of Claims for Vivitrol and Buprenorphine-containing Products

<table>
<thead>
<tr>
<th>Test Type</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vivitrol Intramuscular Injection 380mg</td>
<td>134</td>
<td>28</td>
<td>78</td>
<td>15</td>
</tr>
<tr>
<td>Naltrexone Generic Tablet 50mg</td>
<td>584</td>
<td>757</td>
<td>1104</td>
<td>195</td>
</tr>
<tr>
<td>Buprenorphine HCl (Sublingual and Subdermal Formulations)</td>
<td>164</td>
<td>161</td>
<td>275</td>
<td>65</td>
</tr>
<tr>
<td>Buprenorphine HCl / Naloxone HCl (Sublingual and Buccal Formulations)</td>
<td>3676</td>
<td>3369</td>
<td>3226</td>
<td>573</td>
</tr>
</tbody>
</table>

* 2017 data is abbreviated up to March 2017
** Data is normalized to a 30-day supply and pooled from ACO and FFS payers
Abbreviations: OUD, opioid use disorder

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Table 5. Total Number of Pediatric Claims for Vivitrol and Buprenorphine-containing Products **

<table>
<thead>
<tr>
<th>Test Type</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vivitrol Intramuscular Injection 380mg</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Naltrexone Generic Tablet 50mg</td>
<td>74</td>
<td>66</td>
<td>102</td>
<td>11</td>
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<tr>
<td>Buprenorphine HCl (Sublingual and Subdermal Formulations)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Buprenorphine HCl / Naloxone HCl (Sublingual and Buccal Formulations)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* 2017 data is abbreviated up to March 2017
** Data is normalized to a 30-day supply and pooled from ACO and FFS payers; Pediatric age limit considered is less than 18 years of age
Abbreviations: OUD, opioid use disorder
Table 6. Total Number of Patients on Vivitrol and Buprenorphine-containing Products

<table>
<thead>
<tr>
<th></th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vivitrol Intramuscular Injection 380mg</td>
<td>46</td>
<td>15</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Naltrexone Generic Tablet 50mg</td>
<td>173</td>
<td>237</td>
<td>353</td>
<td>128</td>
</tr>
<tr>
<td>Buprenorphine HCl (Sublingual and Subdermal Formulations)</td>
<td>54</td>
<td>61</td>
<td>75</td>
<td>41</td>
</tr>
<tr>
<td>Buprenorphine HCl / Naloxone HCl (Sublingual and Buccal Formulations)</td>
<td>733</td>
<td>729</td>
<td>672</td>
<td>363</td>
</tr>
</tbody>
</table>

* 2017 data is abbreviated up to March 2017
** Patients from both ACO and FFS payers

Abbreviations: OUD, opioid use disorder

Total Number of Patients on Vivitrol and Buprenorphine-containing Products

![Bar chart showing the number of patients on different products from 2014 to 2017]

Table 7. Number of Pediatric Patients on Vivitrol and Buprenorphine-containing Products *

<table>
<thead>
<tr>
<th></th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vivitrol Intramuscular Injection 380MG</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Naltrexone Generic Tablet 50MG</td>
<td>13</td>
<td>13</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Buprenorphine HCl (Sublingual and Subdermal Formulations)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Buprenorphine HCl / Naloxone HCl (Sublingual and Buccal Formulations)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* 2017 data is abbreviated up to March 2017
** Patients from both ACO and FFS payers

Abbreviations: OUD, opioid use disorder
Table 8. Age at First Fill of Vivitrol between 2014 and 2017

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18-30</td>
<td>4</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>31-40</td>
<td>7</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>41-50</td>
<td>4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>51-64</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&gt;64</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>17</strong></td>
<td><strong>60</strong></td>
<td></td>
</tr>
</tbody>
</table>

Patient Gender & Age at First Vivitrol Fill (2014-2017)

![Bar chart showing the number of patients by age and gender](chart.png)

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL MEDICAID CLAIMS FOR VIVITROL (ACO + FFS)</td>
<td>255</td>
</tr>
<tr>
<td>TOTAL CLAIMS THAT WERE FFS CATEGORY</td>
<td>21 (8.2%)</td>
</tr>
<tr>
<td>TOTAL UNIQUE PATIENTS RECEIVING VIVITROL</td>
<td>77</td>
</tr>
<tr>
<td>TOTAL UNIQUE PATIENTS RECEIVING VIVITROL THAT ARE IN THE FFS CATEGORY</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>TOTAL UNIQUE PATIENTS RECEIVING AN OPIOID FILL WITHIN 30 DAYS AFTER RECEIVING A VIVITROL INJECTION</td>
<td>*An opioid fill was defined as AHFS class code 28080800 (minus buprenorphine and methadone)</td>
</tr>
<tr>
<td>TOTAL UNIQUE PATIENTS RECEIVING A BUPRENORPHINE-CONTAINING PRODUCT WITHIN 60 DAYS OF RECEIVING VIVITROL</td>
<td>5 (6.49%)</td>
</tr>
<tr>
<td>TOTAL UNIQUE PATIENTS RECEIVING A BUPRENORPHINE-CONTAINING PRODUCT MORE THAN 60 DAYS PRIOR TO RECEIVING VIVITROL</td>
<td>3 (3.9%)</td>
</tr>
<tr>
<td>TOTAL UNIQUE PATIENTS RECEIVING A BUPRENORPHINE-CONTAINING PRODUCTS AFTER RECEIVING VIVITROL</td>
<td>3 (3.9%)</td>
</tr>
</tbody>
</table>

Prescriber Specialty: Prescriber specialties related to Vivitrol prescriptions were not able to be captured since Vivitrol is administered and billed at the clinic site, as opposed to being billed through a retail pharmacy setting.

Medicaid Utilization Overview

Overall, the use of Vivitrol is low compared to other agents approved for OUD management. In 2016, a total of 23 patients received Vivitrol; this represents 2% of the 1,123 patients identified on agents that can be used for OUD treatment in an office-based setting (non-OTP venue). After further assessment of the diagnostic codes for the 2016 group taking Vivitrol, the following details were found: a) 10 of the 23 patients had a diagnosis code related to opioid dependence, b) 10 of the 23 patients had a diagnosis code related to alcohol dependence, c) two of these patients may have been taking Vivitrol to manage both opioid and alcohol co-occurring disorders, and d) the diagnostic code was unknown for two patients. Over the last three years, Vivitrol has not been used for patients under 18 years old.

Assessment to capture any prescribed opioids, filled within 30 days following a Vivitrol claim, was carried out. From 2014 to 2017, nine different occurrences were identified, involving six patients that filled an opioid (fills were for tramadol, hydrocodone or oxycodone-containing short acting products). In three of these nine cases, a patient received two opioids within the 30 day time frame. One of the six patients had a diagnosis code related to alcohol dependence, four patients had a diagnosis code related to opioid dependence, and one didn’t have either.

The frequency of Vivitrol administrations in the Medicaid population was considered. The shortest time between injections was 25 days (during the 2014 to 2017 period assessed), with the majority of refills falling between day 27 and 33, with respect to the prior fill.
Summary

Vivitrol is an opioid antagonist that is approved to prevent opioid dependence relapse and alcohol dependence. A challenging barrier to treatment initiation, however, is that patients must detoxify from opioids completely before starting this agent. This barrier is perhaps less substantial with methadone and buprenorphine-containing products which continue to provide some opioid stimulation. Agonist medications are associated with diversion if not administered in an OTP setting; there is no diversion risk with Vivitrol. Vivitrol is not known to potentiate respiratory depression as the opioid-agonist options may, especially when combined with other CNS-depressants. Nonetheless, patients must be warned of their vulnerability to opioid overdose toward the end of the dosing cycle and upon missing a dose or discontinuing Vivitrol. There are topics of uncertainty that remain to be answered by future studies: a) what is the head-to-head efficacy comparison between opioid agonists and long-acting antagonists for OUD maintenance therapy; or b) which approach is better for which patient (pregnancy, adolescents, and patients with poly-substance addictions)?

Potential prescribing criteria have been outlined for discussion, keeping in mind that naltrexone may be especially useful for patients who have contraindications or who have failed therapy with buprenorphine and methadone; patients confined to opioid-free environments; patients for whom agonist treatment is not accessible; patients wanting to be free of opioids completely; or those wanting to treat a concurrent alcohol use disorder (given the additional indication of Vivitrol).23
## Appendix A

Table 1. Comparison of Maintenance Treatment Options for OUD\textsuperscript{38,58-68}

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Buprenorphine Pill or film</th>
<th>Buprenorphine Implant</th>
<th>Extended Release Naltrexone</th>
<th>Oral Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Full Mu-opioid receptor agonist</td>
<td>Partial Mu-opioid receptor agonist</td>
<td>Full Mu-opioid receptor antagonist</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Pharmacokinetics**   | • Highly variable inter-individual pharmacokinetics  
                        • Long bi-phasic half-life with high potential for accumulation:  
                          ▶ delayed toxicity including respiratory depression  
                          ▶ may take up to 10 days to reach steady-state serum levels.  
                        • Significant first-pass metabolism, but high lipid solubility so excellent sublingual bioavailability  
                        • Both buprenorphine and naloxone are extensively metabolized by liver  
                        • Avoids first-pass metabolism, so overall therapy involves a lower total daily dose than oral-NTX, however, the steady state AUC is higher compared to oral therapy  
                        • Not metabolized by CYP enzymes, however is excreted primarily as its metabolite through the urine.  
                        • Significant first-pass metabolism  
                        • Not metabolized by CYP enzymes, however is excreted primarily as its metabolite through the urine.  
| **Controlled Substance** | Yes: CII                              | Yes: CIII                        |                       | No                           |                 |
Table 1. Comparison of Maintenance Treatment Options for OUD

<table>
<thead>
<tr>
<th>Indication</th>
<th>Methadone</th>
<th>Buprenorphine Pill or film</th>
<th>Buprenorphine Implant</th>
<th>Extended Release Naltrexone</th>
<th>Oral Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Detoxification &amp; maintenance treatment of opioid addiction, in conjunction with appropriate social and medical services. • Chronic Pain</td>
<td>Treatment of opioid dependence. (Note that buprenorphine single product buccal film; Belbuca; the transdermal patch and injections are indicated for use in pain management).</td>
<td>Maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low to moderate doses (≤8 mg/day) of a transmucosal buprenorphine-containing product for 3 months or longer with no need for supplemental dosing or adjustments.</td>
<td>Opioid dependence: For the blockade of the effects of exogenously administered opioids (for the prevention of relapse to opioid dependence, following opioid detoxification). Alcohol dependence: Treatment of alcohol dependence (in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol).</td>
<td>Alcohol dependence and for the blockade of the effects of exogenously administered opioids</td>
</tr>
<tr>
<td>Age</td>
<td>Adults (Manufacturers state that safety, efficacy, and pharmacokinetics not established in pediatric patients &lt;18 years of age) Caution in elderly</td>
<td>Zubsolv, Bunavail: ≥16 years Buprenorphine sublingual tablets: safety and efficacy have not been established in pediatric patients. Caution in elderly or debilitated patients</td>
<td>Adults: the safety and efficacy have not been established in patients &lt;16 years and studies did not include patients &gt;65 years old</td>
<td>The safety, efficacy, and pharmacokinetics have not been established in the pediatric, elderly, or perinatal populations.</td>
<td></td>
</tr>
<tr>
<td>Administration/Convenience</td>
<td>Daily dosing (with OTP oversight, which is good for compliance and minimizes diversion, however, may be difficult for patient to consistently attend) Flexible dosing: recent evidence Cochrane review &amp; other review noted greater treatment retention and lower cost associated with methadone vs buprenorphine when using flexible dosing</td>
<td>Daily dosing, but can be given every 2 to 3 days as tolerated and can be filled at a local pharmacy (vs visiting a clinic daily) Advantage: dosing flexibility Films dissolve more quickly than tablets =&gt; advantage when monitored dose ingestion is indicated; potentially enhanced patient satisfaction</td>
<td>Four implants are inserted every 6 months; must be done by a certified healthcare provider. Potential surgical complications (during insertion or removal): risk of implant migration, protrusion, expulsion, and nerve damage resulting from the procedure Advantage: verifiable dosing</td>
<td>Every 4 weeks/once a month administration IM gluteal injection by healthcare provider (alternating buttocks) Advantage: verifiable dosing</td>
<td>Daily or every other day dosing Has had historically low rates of compliance and retention</td>
</tr>
<tr>
<td>Setting</td>
<td>Methadone</td>
<td>Buprenorphine Pill or film</td>
<td>Buprenorphine Implant</td>
<td>Extended Release Naltrexone</td>
<td>Oral Naltrexone</td>
</tr>
<tr>
<td>---------</td>
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<td>----------------</td>
</tr>
<tr>
<td>Setting</td>
<td>• Limited to specially licensed OTP prescribing and dispensing; (advantage: high structure of delivery setting), until the patient receives take-home doses.</td>
<td>• Office-based or OTP setting; any pharmacy can fill the prescription</td>
<td>• Office-based or OTP setting: providers must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE REMS program</td>
<td>• Any medical setting, requires injection by healthcare provider; can be prescribed by any licensed healthcare with prescribing authority (no special training required);</td>
<td>• Any medical setting</td>
</tr>
<tr>
<td>Setting</td>
<td>• Only licensed physicians who are DEA registered and who work at an OTP can order methadone for dispensing at the certified OTP or hospital.</td>
<td>• Increased accessibility to treatment and avoiding the stigma and other negative feelings associated with going to methadone clinic; requires an X-DEA number/waiver to prescribe in and office-based setting or the physician needs to be DEA registered and work at an OTP</td>
<td>• Closed Distribution – only to healthcare providers certified in the Probuphine REMS Program can purchase the medication</td>
<td>• Can be purchased at a retail pharmacy (usually through the specialty division)</td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td>• Nicholls et al.64 mention long waiting lists for entry into methadone maintenance treatment.</td>
<td></td>
<td>• Office-based or OTP setting: providers must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE REMS program</td>
<td>• Can be purchased at a retail pharmacy (usually through the specialty division)</td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td></td>
<td></td>
<td>• Closed Distribution – only to healthcare providers certified in the Probuphine REMS Program can purchase the medication</td>
<td>• Can be purchased at a retail pharmacy (usually through the specialty division)</td>
<td></td>
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<tr>
<td>Setting</td>
<td></td>
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</tr>
<tr>
<td>Setting</td>
<td>Supervised and if compliant with treatment for 2 years, could receive a 30-day take-home dose.</td>
<td>May be lost or forgotten (if prescribed outside of an OTP)</td>
<td>Can’t be lost or forgotten vs. daily; long-acting which should improve adherence</td>
<td>Can’t be lost or forgotten vs. daily; long-acting which should improve adherence/facilitate compliance</td>
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<td>Setting</td>
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<tr>
<td>Setting</td>
<td>Usually administered in OTP unless compliant for 2 years, could receive take-home supply which could be stolen misused or abused.</td>
<td>Could be stolen/missused/abused</td>
<td>Unlikely to be stolen/missused/abused. Contains a significant amount of drug that could lead to accidental exposure or intentional misuse or abuse if implant comes out of skin</td>
<td>Unlikely: has not been associated with diversion or physical dependence</td>
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<td>Setting</td>
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<tr>
<td>Setting</td>
<td>Common Adverse Effects/Safety Concerns</td>
<td>Sedation (especially early in treatment), constipation, QT prolongation</td>
<td>Lower extremity swelling, urinary hesitancy, constipation</td>
<td>Implant-site pain, itching, and redness, headache, depression, constipation, nausea, vomiting, back pain, toothache, and oropharyngeal pain</td>
<td>Injection site reactions, nausea/vomiting, malaise, hepatic enzyme abnormalities, toothache, insomnia, dizziness, appetite suppression, headache</td>
</tr>
<tr>
<td>Setting</td>
<td>Higher overdose incidence and mortality (1 of every 3 opioid-related deaths is associated with methadone ingestion).73,74</td>
<td>Appears to have a better safety profile (pending direct comparison studies) with regard to overdose vs methadone64 or with respect to QT prolongation potential.75</td>
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<tr>
<td>Setting</td>
<td>Adherence</td>
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<td>Setting</td>
<td>Abuse Potential</td>
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<td>Setting</td>
<td>Common Adverse Effects/Safety Concerns</td>
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</table>
Table 1. Comparison of Maintenance Treatment Options for OUD\textsuperscript{38,58-68}

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Buprenorphine Pill or film</th>
<th>Buprenorphine Implant</th>
<th>Extended Release Naltrexone</th>
<th>Oral Naltrexone</th>
</tr>
</thead>
</table>
| **Warnings / Precautions** | \bullet Overdosing  
\bullet Drug-drug interactions involving CYP-enzymes  
\bullet Respiratory insufficiency or suppression especially with concurrent BZPs/alcohol/CNS depressants  
\bullet Hypersensitivity  
\bullet Cardiac conduction abnormalities  
\bullet Physical dependence; withdrawal upon abrupt discontinuation  
\bullet Liver insufficiency  
\bullet Neonatal withdrawal syndrome possible with perinatal use | \bullet Respiratory insufficiency or suppression especially with concurrent BZPs/alcohol/CNS depressants  
\bullet Hypersensitivity  
\bullet Physical dependence; withdrawal upon abrupt discontinuation  
\bullet Liver insufficiency  
\bullet Drug-drug interactions involving CYP-enzymes  
\item Anti-retrovirals: Some potential interactions, but appear to be fewer interactions vs methadone possibly due to different route of absorption (sublingual or buccal); less competitive.\textsuperscript{66,76}  
\bullet Neonatal withdrawal syndrome possible with perinatal use | \bullet Potential serious complications from insertion and removal. Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion. Incomplete insertions or infections may lead to protrusion or expulsion. \item See also pill/film applicable precautions | \bullet Precipitated withdrawal if given before opioid free washout period; may be severe enough to require hospitalization (opioid-free period of 7-10 days is recommended;  
\bullet Abstinence from opioids can be difficult for patients to achieve)  
\bullet Vulnerability to opioid overdose  
\bullet Injection site reactions/hypersensitivity  
\bullet Hepatotoxicity  
\bullet Depression and Suicidality: monitor patients  
\bullet Pain management challenges | \bullet Methadone to buprenorphine: Better tolerated when on <30-40 mg of methadone; mono-buprenorphine product is recommended \bullet Methadone to naltrexone: Must be completely withdrawn from opioids and be opioid free for at least 7 days (may take 14 days). \bullet Buprenorphine to methadone: No delay needed \bullet Buprenorphine to naltrexone: because of the long BUP half-life, it may take 7-14 days after last dose of buprenorphine to be opioid-free \bullet Converting back to sublingual tablet: On day of implant removal, resume buprenorphine treatment at previous sublingual dose\textsuperscript{77}  
\bullet Naltrexone to buprenorphine: Wait 30 days for ER naltrexone (one day for oral naltrexone) \bullet Naltrexone to methadone: Wait 30 days for ER naltrexone (one day for oral naltrexone). Use low initial dose of methadone. |

* Refer to individual package inserts for complete prescribing information on these agents  
Abbreviation key: AE, adverse effects; BUP, buprenorphine; BZPs, benzodiazepines; CNS, central nervous system; CYP, cytochrome P450; HCV, hepatitis C virus; NTX, naltrexone; OTP, opioid therapy program; OUD, opioid use disorder; RCT, randomized controlled trial; XR-NTX, extended release naltrexone
### Appendix B

#### Table 1. Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study &amp; Design</th>
<th>Title &amp; Assessment Goals</th>
<th>Patients</th>
<th>Main Results</th>
<th>Safety</th>
<th>Author’s Conclusions</th>
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</thead>
<tbody>
<tr>
<td>Friedmann, et al.; 2016&lt;sup&gt;78&lt;/sup&gt;</td>
<td>Do patient characteristics moderate the effect of extended-release naltrexone (XR-NTX) for opioid use disorder? Assessed baseline covariates, and their two-way interaction on relapse status at the 6 month follow-up</td>
<td>See Lee et al, below XR-NTX: n=153 TAU: n=155</td>
<td>Baseline covariates assessed included age, gender, depression, suicidal thoughts, drug abuse risk, substance use, medical, psychiatric and employment status, socialization, legal and family/social issues, history of abuse and quality of life measures—most did not appear to influence the effectiveness of XR-NTX. The only significant moderator of XR-NTX that emerged was alcohol intoxication occurring in the prior 30 days to randomization; this significantly increased the risk of opioid relapse (41% vs. 65%, respectively, P&lt;0.04)</td>
<td>See Lee et al, below</td>
<td>Authors’ conclusions: “XR-NTX appeared to work equally well across subgroups with diverse demographic, addiction, mental health and environmental characteristics, with the possible exception of working better among those without recent alcohol intoxication. These findings should be reassuring to practitioners increasingly using XR-NTX as medical addiction therapy in diverse and often vulnerable populations.”</td>
</tr>
<tr>
<td>Study &amp; Design</td>
<td>Title &amp; Assessment Goals</td>
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<td>Main Results</td>
<td>Safety</td>
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<td>Lee, et al.; 2016</td>
<td>Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders</td>
<td>Open-label RCT including 5 sites in North America</td>
<td>Compared a 24 week course of XR-NTX (Vivtrol) to treatment as usual care (brief counseling and referrals for community treatment programs), both combined with counseling</td>
<td>Included: community-dwelling adults under criminal justice supervision with a preference for opioid-free rather than opioid maintenance treatment Excluded: pregnancy, untreated psychiatric disorder or serious medical condition, drug or alcohol dependence requiring a level of care that would interfere with trial participation, elevated liver enzymes (3X ULN), BMI&gt;40, chronic pain diagnosis, history of hospital treated overdose in the previous 3 years</td>
<td>XR-NTX: n=153 TAU: n=155 Participants were predominantly middle-aged men Primary Endpoint - Time to an opioid-relapse event during the 24 week treatment phase (relapse defined as ≥10 days of opioid use in a 28-day period) Compared to the TAU group, participants assigned to XR-NTX during the 24 week treatment phase had: • A longer median time to relapse (10.5 vs. 5.0 weeks, P&lt;0.001; HR, 0.49; 95% CI, 0.36 to 0.68) • A lower rate of relapse (43% vs. 64% of participants, P&lt;0.001; odds ratio, 0.43; 95% CI, 0.28 to 0.65) • A higher rate of opioid-negative urine samples (74% vs. 56%, P&lt;0.001; odds ratio, 2.30; 95% CI, 1.48 to 3.54). -At week 52 and 78, rates of opioid-negative urine samples were similar between groups (no statistical difference) -61% of the patients in the XR-NTX group received the 6th injection</td>
</tr>
<tr>
<td>Study &amp; Design</td>
<td>Title &amp; Assessment Goals</td>
<td>Patients</td>
<td>Main Results</td>
<td>Safety</td>
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| *Mitchell, et al. 2012*<sup>69</sup> | Hepatic Safety of Injectable Extended-Release Naltrexone in Patients With Chronic Hepatitis C and HIV Infection. | See Krupitsky *et al.* | • Over 24 weeks, there was no significant difference between groups in the frequency of elevations in AST, ALT, and GGT (>3 x ULN).  
• Most of the elevations greater than three times the ULN occurred in patients with chronic HCV infection and improved/or returned toward baseline  
• The frequency of elevations in AST and ALT during treatment in patients with HIV infection was not significantly different compared with that in patients without HIV infection. | Authors’ conclusions: “XR-NTX can be used safely in eligible patients with opioid dependence, including those with underlying mild to moderate chronic HCV and/or HIV infections.” |
### Table 1. Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study &amp; Design</th>
<th>Title &amp; Assessment Goals</th>
<th>Patients</th>
<th>Main Results</th>
<th>Safety</th>
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<tbody>
<tr>
<td>Krupitsky, et al. 2011&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicenter randomized trial</td>
<td>Included: patients with OUD voluntarily seeking treatment, 18 years or over, who had successfully detoxified from opioids – opioid-free for at least 7 days prior to initiation</td>
<td>XR-NTX vs Placebo Primary Endpoints</td>
<td>XR-NTX was well tolerated; Two patients in each group discontinued treatment due to adverse events.</td>
<td>Authors’ conclusions: “XR-NTX represents a new treatment option that is distinct from opioid agonist maintenance treatment. XR-NTX in conjunction with psychosocial treatment might improve acceptance of opioid dependence pharmacotherapy and provide a useful treatment option for many patients.”</td>
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<tr>
<td></td>
<td>Compared a 24 week course of XR-NTX to placebo, both combined with counseling</td>
<td>Excluded: pregnancy or breastfeeding; bipolar or depressive disorder with suicidal ideation, significant medical conditions (i.e. endocarditis, renal failure, tuberculosis, hepatic failure); present dependence on non-opioid substances (i.e. alcohol, stimulants)</td>
<td>XR-NTX vs Placebo</td>
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<td>XR-NTX: n=126 Placebo: n=124</td>
<td>XR-NTX: Median proportion of weeks (from week 5 to 24) of confirmed abstinence: (90.0% vs 45.0%, p=0.0002).</td>
<td>XR-NTX vs Placebo</td>
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<td>6 injections with study drug or placebo every 4-weeks</td>
<td>Population distribution of confirmed abstinence: Significant difference with higher rates in the XR-NTX group</td>
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<td>Participants were predominantly young, white men, addicted to heroin for about 10 years, and with high rates of HIV and hepatitis C infection</td>
<td>Patients with total confirmed abstinence (measured as 100% opioid-free weeks achieved): (36% vs 23%, p=0.02)</td>
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<td>Secondary Endpoints</td>
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<td>Mean change in VAS craving score: A statistically significant decrease was observed with the XR-NTX group reporting a 50% mean reduction in subjective craving compared to no change in the placebo group by week 8</td>
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<td>Median retention: (168 days vs 96 days, p=0.0042).</td>
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<td>Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the XR-NTX group (p&lt;0.0001).</td>
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<td>Statistically different adverse event rates between the two groups resulted for: XR-NTX vs Placebo</td>
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<td>Insomnia (6% vs 1%, p=0.036)</td>
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<td>At least 1 AE (50% vs 32%, p&lt;0.01)</td>
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<td>At least 1 drug-related AE (26% vs 10%, p&lt;0.01)</td>
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</table>

**Abbreviation key:** AE, adverse effects; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; GGT, gamma-glutamyl transferase; HCV, hepatitis C virus; HR, hazard ratio; n, number of patients; N, number of studies; OUD, opioid use disorder; RCT, randomized controlled trial; TAU, treatment as usual; ULN, upper limit of normal; VAS, visual analog scale; XR-NTX, extended release naltrexone;
**Table 2. Cochrane Systematic Reviews**

<table>
<thead>
<tr>
<th>Study &amp; Design</th>
<th>Title &amp; Assessment Goals</th>
<th>Studies &amp; Participants Included</th>
<th>Main Results</th>
<th>Safety</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minozzi et al. 2011⁷⁹</td>
<td>Oral naltrexone maintenance treatment for opioid dependence</td>
<td>Types of studies: RCTs using oral NTX for opioid dependence were considered. Cross-over studies were excluded. Types of participants: Heroin addicts. Types of interventions: Experimental arm: oral-NTX in any dosage after detoxification alone or in combination with psychosocial treatment. Control arm: placebo, other pharmacological treatments, or psychosocial treatments.</td>
<td>N=13, n=1158</td>
<td>“Comparing oral naltrexone versus placebo or no pharmacological treatments, no statistically significant difference were noted for all the primary outcomes considered. The only outcome statistically significant in favour of naltrexone is reincarceration, RR 0.47 (95%CI 0.26-0.84), but results come only from two studies. Considering only studies were patients were forced to adherence a statistical significant difference in favour of naltrexone was found for retention and abstinence, RR 2.93 (95%CI 1.66-5.18). Comparing naltrexone versus psychotherapy, in the two considered outcomes, no statistically significant difference was found in the single study considered. Naltrexone was not superior to benzodiazepines and to buprenorphine for retention and abstinence and side effects. Results come from single studies.”</td>
<td>“The findings of this review suggest that oral naltrexone did not perform better than treatment with placebo or no pharmacological agent with respect to the number of participants re-incarcerated during the study period. If oral naltrexone is compared with other pharmacological treatments such as benzodiazepine and buprenorphine, no statistically significant difference was found. The percentage of people retained in treatment in the included studies is however low (28%). The conclusion of this review is that the studies conducted have not allowed an adequate evaluation of oral naltrexone treatment in the field of opioid dependence. Consequently, maintenance therapy with naltrexone cannot yet be considered a treatment which has been scientifically proved to be superior to other kinds of treatment.”</td>
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</table>
Table 2. Cochrane Systematic Reviews

<table>
<thead>
<tr>
<th>Lobmaier, et al.; 200878</th>
<th>Sustained-Release Naltrexone For Opioid Dependence</th>
<th>Types of studies</th>
<th>Only one study met inclusion for efficacy assessment (N=1): Comparators: SR-NTX depot (Depotrex®) vs. placebo (n=60; 8 week study; depot-NTX administered twice, 4 weeks apart)</th>
<th>For treatment of OUD</th>
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<tr>
<td></td>
<td>To evaluate the effectiveness of sustained-release naltrexone for opioid dependence and its adverse effects in different study populations</td>
<td>For assessment of effectiveness only RCTs using SR-NTX for opioid dependence were considered. For assessment of safety, prospective controlled and uncontrolled trials, case series and record-linkage studies were considered.</td>
<td>*NOTE: This delivery system is not bioequivalent to Vivitrol</td>
<td>• Most common adverse effects were: fatigue and administration site-related conditions.</td>
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<tr>
<td></td>
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<td>Types of participants</td>
<td>Types of interventions</td>
<td>Efficacy Results: SR-NTX depot 384mg vs placebo</td>
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<tr>
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<td>Adults or adolescents with opioid dependence.</td>
<td>Any use of sustained-release formulations (i.e. depot or implant) of naltrexone compared to any other pharmacological or psychosocial or placebo.</td>
<td>(1) Retention at week 8: No statistically significant difference between SR-NTX depot and placebo [68% vs. 39%; RR 1.75, CI 0.92 to 3.3]</td>
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<td>(2) Time to drop out: 48 vs. 27 days, statistical significant difference demonstrated between arms (WMD 21.0, CI 10.68 to 31.32)</td>
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<td>(3) Heroin craving, on visual analogue scales: &quot;Needing heroin&quot; was scored significantly lower in the naltrexone depot group compared to the placebo group</td>
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Efficacy Results:

SR-NTX depot 384mg vs placebo

(1) Retention at week 8: No statistically significant difference between SR-NTX depot and placebo [68% vs. 39%; RR 1.75, CI 0.92 to 3.3]

(2) Time to drop out: 48 vs. 27 days, statistical significant difference demonstrated between arms (WMD 21.0, CI 10.68 to 31.32)

(3) Heroin craving, on visual analogue scales: "Needing heroin" was scored significantly lower in the naltrexone depot group compared to the placebo group

For treatment of OUD

• Most common adverse effects were: fatigue and administration site-related conditions.
• The number of possibly naltrexone-related adverse effects was not significantly different between groups in any RCT.
• Depression (HAM-D scale) and severity of opioid and cocaine use (CGIS): No significant difference between treatment groups was reported on depression or severity of drug use scores.

Note: A previous Cochrane review did not find enough evidence to support oral naltrexone in the treatment of opioid dependence (Minozzi 2006)

“There is insufficient evidence to evaluate the effectiveness of sustained-release naltrexone for treatment of opioid dependence. For naltrexone injections, administration site-related adverse effects appear to be frequent, but of moderate intensity and time limited. For a harm-benefit evaluation of naltrexone implants, more data on side effects and adverse events are needed.”

Abbreviation key: BMI, body mass index; CGIC, Clinical Global Impressions Score; CI, confidence interval; HAM-D, Hamilton Depression Rating Scale; HR, hazard ratio; NTX, naltrexone; OUD, opioid use disorder; RCT, randomized controlled trial; RR, relative risk; SR-NTX, sustained-release naltrexone; TAU, treatment as usual; ULN, upper limit of normal; WMD, weighted mean difference; XR-NTX, extended release naltrexone;
References


