Subject: Vivitrol (naltrexone for extended-release injectable suspension)	Original Effective Date: 6/23/14
Policy Number: MCP-177	Revision Date(s):
Review Date(s): 12/16/15; 9/15/2016; 6/22/2017	

DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION STATEMENTS

This policy addresses the use of the injectable (intramuscular), long-acting form of naltrexone (Vivitrol®) for the treatment of alcohol or opiate dependence.

- The covered FDA-approved indications are conditions that are considered medically necessary; however it is not inclusive of all conditions which may be approved by the Medical Reviewer. At the discretion of the Medical Director and on a case-by-case basis, Molina Healthcare may consider authorization of the biologic therapies addressed in this policy for members with exceptional circumstances and for members with severe disease who may fall outside of the defined criteria.

- Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

- Vivitrol is marketed as providing increased compliance as compared to the oral formulation of naltrexone. However, there are no trials to substantiate the claim that increased compliance leads to better outcomes through either increased rates of abstinence or increased time to a first heavy drinking day. A heavy drinking day is defined as 5 or more standard drinks consumed on a given day for males and 4 or more standard drinks consumed on a given day for females. The monthly injection method of administration addresses non-compliance with the oral medication regimen and reduces first-pass hepatic metabolism as compared to oral naltrexone.

- Naltrexone extended-release injectable suspension offers an alternative to oral naltrexone in the treatment of alcohol dependence. The formulation offers pharmacokinetic advantages over the oral formulation that allow it to be dosed once a month versus daily; however, studies have not been conducted to establish a clinical advantage of the injectable formulation over the oral. The new formulation may be associated with better compliance, but the efficacy associated with the use of this agent does not appear to be any better than the oral formulation.

FDA INDICATIONS

Alcohol dependence: It is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment.

Patients should not be actively drinking at the time of initial administration and treatment with Vivitrol should be part of a comprehensive management program that includes psychosocial support.

Opioid dependence: For the prevention of relapse to opioid dependence following opioid detoxification.

Available as: 380mg per vial suspension (extended release) for injection. Supplied with diluent, prepackaged syringe (5 mL), and appropriate needles

Approved by the FDA:
1984: Naltrexone approved for the adjuvant treatment of patients dependent on opiate agonists.
1995: Naltrexone for the treatment of alcoholism was granted January 1995.

April 2006: Vivitrol approved as a once-monthly intramuscular naltrexone formulation used to help control cravings for alcohol
October 2010: Vivitrol approved for the prevention of relapse to opioid dependence after opioid detoxification.

RECOMMENDATIONS/COVERAGE CRITERIA

Injectable naltrexone (Vivitrol®) may be authorized for the treatment of alcohol dependence for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Board certified addiction medicine specialist

2. Diagnosis/Indication [ALL]

- ❒ Member meets ONE of the following diagnosis based on criteria in **DSM-IV-TR** (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised) OR by **DSM-5** (Diagnostic and Statistical Manual of Mental Disorders, fifth edition[4]): [ONE]
  - ➢ *Refer to Appendix 1 for DSM-IV-TR criteria*

  - ❍ Alcohol Dependence/Alcohol Use Disorder (AUD) and member has the ability to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol®

  - ❍ Opioid Dependence/Opioid Use Disorder (OUD) and Vivitrol® is being prescribed following opioid detoxification for the prevention of relapse to opioid dependence

NOTE: Vivitrol (naltrexone) will not be authorized for indications other than alcohol or opioid dependence

3. Age/Gender/Other restrictions [ALL]

- ❑ 18 years of age or older
  - ➢ *Vivitrol (naltrexone) has not been studied in children younger than 18 years old.*[a-d]

- ❒ The following conditions are **NOT** applicable: [ALL]

  - ❍ Member does **NOT** require prescribed opioid medications for treatment of a medical condition (i.e. for pain management, cough suppressant, etc.)

  - ❍ Member is **NOT** in acute opioid withdrawal

- ❒ Opioid-free (including buprenorphine and methadone) for a minimum of 7-10 days[a-d] as evidenced by pharmacy claims
  - ➢ *Patients must be free of all opioid-containing medications, including medications used to treat opioid dependence for a minimum of 7 – 10 days, at the time of initial Vivitrol (naltrexone) administration.*
  - ➢ *To prevent occurrence of an acute abstinence syndrome (withdrawal) in patients dependent on opioids or exacerbation of a preexisting subclinical abstinence syndrome, patients must be opioid free for a minimum of 7 to 10 days before starting naltrexone treatment.*

- ❒ A recent **urine** drug screen that is negative for alcohol, opioids, and illicit drugs. Lab must be dated within 14 days of the request. **Submitted with initial authorization request and 3 times a year as a follow up. NOTE:** Qualitative urine drug screen is only required if the result is positive.

- ❒ Clinical Opiate Withdrawal Scale (COWS) with a score of 5 or more. COWS must be completed 7 days prior to this request. Available at: http://www.naabt.org/documents/cows_induction_flow_sheet.pdf
  - ➢ *Although the COWS is directed at opioid dependence, it helps prompt the clinician to look for opioid use, even when it isn't the focus of treatment. This prevents the clinician from precipitating opioid withdrawal in members that may be getting a vivitrol injection for alcohol dependence.*[E]

- ❒ Member does **NOT** have Acute hepatitis, Active liver disease (AST or ALT > 3 times the upper limit of normal), Severe hepatic impairment (Child-Pugh class C) as evidenced by **liver function studies**

- ❒ **FOR ALCOHOL DEPENDENCE/AUD ONLY** [ALL]

  - ❍ Member has had ONE or more of the following occurrences related to alcoholism within the past 6 months:
    - Emergency Room visits
    - Hospital Admissions
    - Services for alcohol or drug related illness, injury or detoxification

  - ❍ Abstained from drinking alcohol for at least 7 days in an outpatient setting, community setting prior to the first planned dose of Vivitrol (naltrexone) **NOTE:** Abstinence during treatment in a residential setting, or during incarceration, does not meet this criterion

- ❒ **OPIOID DEPENDENCE/OPIOID USE DISORDER (OUD) ONLY** [ALL]

  - ❍ Member has been opioid free for at least 7 days
    NOTE: Member must not currently be receiving opioid analgesics or in acute opioid withdrawal

  - ❍ Successfully completed an opioid detoxification program

4. Step/Conservative Therapy/Other condition Requirements [ALL]

❒ FOR ALCOHOL DEPENDENCE/AUD ONLY: [ONE]

❍ Inadequate clinical response **(for at least the three months)**, intolerance or contraindication to a therapeutic dose of ORAL anti-alcoholic agents **[acamprosate or disulfiram (Antabuse®)] or oral naltrexone (Revia®).** Documentation required.

❍ Member requires injectable therapy due to clinical condition. Prescriber to submit clinical rationale and documentation. [MEDICAL DIRECTOR REVIEW REQUIRED]

- ➢ *Depot preparations of naltrexone may improve adherence by reducing the frequency of medication administration from daily to monthly and by achieving a steady therapeutic level of medication, thus avoiding peak effects that can exacerbate adverse events.*[6,11]

❍ Recently enrolled with Molina Healthcare and has already stabilized on Vivitrol (naltrexone) for **at least the three months.** Documentation required.

❒ FOR OPIOID DEPENDENCE/OUD ONLY: [ONE]

❍ Inadequate clinical response **(for at least the three months),** intolerance or contraindication to a therapeutic dose of **ORAL agents for the treatment of opioid dependency [buprenorphine, methadone] AND oral naltrexone (Revia®).** Documentation required.

- ➢ *Some occupations (which may include workers involved with public safety, transport of hazardous materials, and medical professionals) do not allow workers to use methadone and, in some cases, buprenorphine. Opioid antagonists do not generally face such restrictions.*[8,10]

❍ Member requires injectable therapy due to clinical condition. Prescriber to submit clinical rationale and documentation. [MEDICAL DIRECTOR REVIEW REQUIRED]

- ➢ *For patients who are highly motivated and/or under circumstances where administration can be supervised, treatment with oral naltrexone (an opioid antagonist) is feasible, but not recommended. Oral naltrexone has been found to be effective only when adherence is enforced.*[6]

❍ Recently enrolled with Molina Healthcare and has already stabilized on Vivitrol (naltrexone) for **at least the three months.** Documentation required.

❒ Recent comprehensive History and Physical examination, specifically for the purposes of obtaining medical clearance to begin treatment with Vivitrol (naltrexone) [ALL: A AND B]

A. Member does **NOT** have hepatic or renal dysfunction, specifically: [DOCUMENTATION REQUIRED]

❍ Acute hepatitis, severe hepatic impairment (Child-Pugh class C) or hepatic failure, or active liver disease (AST or ALT > 3 times the upper limit of normal)

- ➢ *No dosage adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh class A or B). The pharmacokinetics of injectable naltrexone has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C).*

❍ Moderate to severe renal impairment (estimated or measured CrCl less than 50 ml/min)

B. Physician provided statement of clearance for member to begin Vivitrol injections

- ❒ Active participation in a comprehensive management program which provides psychosocial support, including: [ALL]
    - ❍ An initial evaluation or scheduled appointment with a licensed Drug & Alcohol Provider to determine the recommended level of care
    - ❍ Referral to or enrollment in formal behavioral health counseling and/or substance abuse counseling that is consistent with the level of care recommended at the initial evaluation. Initial treatment must be performed by a licensed Drug & Alcohol Provider or a behavioral health provider.
        - ➢ *Medications for alcohol use disorders do not replace counseling. Treatment with naltrexone for extended-release injectable suspension can be one part of a comprehensive management program that includes psychosocial support and participating in 12-Step or other mutual-help group programs.*

- ❒ **Patient Readiness**
  Member has been counseled on, and agrees to comply, with the following: [ALL]
    - ❍ On the prescribed regimen and plan of treatment that includes at least monthly visits with the administering physician
    - ❍ Actively participate in a comprehensive substance abuse treatment program for alcohol/opioid dependence that includes a psychosocial support system during the entire course of therapy.

5. Contraindications/Exclusions to Vivitrol (naltrexone) therapy [ANY]
Request will NOT be authorized ANY of the following conditions apply [ANY]

- ❑ Non-FDA approved indications
- ❑ Hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent or any ingredient in the formulation
- ❑ Pregnancy or breastfeeding
- ❑ Member requires opioid medications (including tramadol and tapentadol) for therapeutic reasons
- ❑ Current physiologic opioid dependence or current use of opioid analgesics
- ❑ Acute opiate withdrawal
- ❑ Failure of the Naloxone Challenge Test
- ❑ Positive urine screen for opioids
- ❑ Acute hepatitis, Active liver disease (AST or ALT > 3 times the upper limit of normal), Severe hepatic impairment (Child-Pugh class C)
    - ➢ *No dosage adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh class A or B). The pharmacokinetics of injectable naltrexone have not been evaluated in patients with severe hepatic impairment (Child-Pugh class C).*
- ❑ Moderate to severe renal impairment (estimated or measured CrCl less than 50 ml/min)
    - ➢ *Mild renal insufficiency (creatinine clearance of 50–80 mL/min) had little or no influence on injectable naltrexone pharmacokinetics and no dosage adjustment is necessary. Injectable naltrexone pharmacokinetics have not been evaluated in subjects with moderate and severe renal insufficiency.*[a]

6. Labs/Reports/Documentation required [ALL]
All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.
NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

7. Recommended Dosing Regimen [ALL]
Dosage prescribed is within the FDA-approved labeling based on member's confirmed diagnosis:

- ❒ The recommended dose of naltrexone is 380 mg delivered intramuscularly (IM) every 4 weeks or once a month. The injection should be administered by a health care provider as an IM gluteal injection, alternating buttocks, using the carton components provided. Naltrexone must not be administered intravenously (IV) or subcutaneously.

8. Authorization Limit [ALL]

- ❑ Quantity limit: One vial per 28 days of Vivitrol (naltrexone) 380 mg strength. Each IM injection (no more than 380mg/injection) must be given by a physician or nurse once every 4 weeks
- ❒ Initial authorization may be authorized **up to 3 months** (3 injections per authorization period)
- ❒ Re-authorization for continuation of treatment is required **every 3 months** to determine continued need for Vivitrol (3 injections per authorization period)
- ❑ TOTAL DURATION OF TREATMENT: Treatment is limited to 24 weeks; extensions to be determined on case-by-case basis by a Molina Medical Director

  NOTE: *The optimal duration of pharmacotherapy is not known. Controlled studies have been conducted for up to 6 months; some patients have been treated with injectable naltrexone therapy longer. Experts recommend at least six months of medication with an additional six months of follow-up.*[6]

CONSIDERATIONS

- **Re-initiation of treatment in patients who previously discontinued:** There are no data to specifically address reinitiation of treatment.
- **Switching from oral naltrexone for alcohol dependence:** There is limited information, no systematically collected data that specifically address the switch from oral naltrexone to naltrexone injection

9. Route of Administration [ALL]

- ❑ Medication is considered to be **administered in the provider's office** until information from the manufacturer, scientific literature, practice standards, or governing State or Federal agency indicates that self-administration by a patient or caregiver is safe and acceptable.
  - *Vivitrol (naltrexone) is administered as an intramuscular gluteal injection and should only be administered with the administration needle provided with the product (1.5 inch, 20 gauge). Vivitrol (naltrexone) should not be administered intravenously, subcutaneously, or inadvertently into fatty tissue.*
- ❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

CONTINUATION OF THERAPY

Continuation of therapy with Vivitrol (naltrexone) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❑ Member continues to meet ALL initial coverage criteria **AND** no 'Exclusions/Discontinuations' criteria are applicable
- ❑ Vivitrol continues to be prescribed for its FDA approved indication: [ONE]
  - ❍ Documentation submitted indicates that Vivitrol continues to be prescribed for its FDA approved indication for the treatment of alcohol dependence in patients who are able to abstain from alcohol.
  - ❍ For the prevention of relapse to opioid dependence following opioid detoxification

2. Compliance [ALL]

- ❑ Adherence to plan of treatment and MONTHLY injections as prescribed and verified by Prescriber

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence has not been demonstrated

3. Labs/Reports/Documentation required [ALL]

Demonstrated efficacy to Vivitrol (naltrexone) treatment as documented by the following (efficacy endpoints used in clinical trials): [ALL]

- ❑ A clinical rationale for continued treatment for the prevention of relapse
- ❑ Improvement in opioid and/or alcohol dependence evidenced by a decrease or cessation of use/abuse of alcohol and/or opioids
- ❑ Active participation in at least monthly formal behavioral health counseling, substance abuse counseling, or an addiction recovery program as determined appropriate for individual patient by the Prescriber. If member is not on continued counseling program, Prescriber to submit documentation of reason counseling has been discontinued for this member.
- ❒ A recent **urine** drug screen that is negative for alcohol, opioids, and illicit drugs. Lab must be dated within 14 days of the request. **Submitted with initial authorization request and 3 times a year as a follow up. NOTE:** Qualitative urine drug screen is only required if the result is positive.
- ❑ Treatment plan and rationale of a continued medical need for Vivitrol (naltrexone)
- ❑ Documentation that the member is complying with a treatment plan that includes relapse prevention[B1]

  Reference: TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. (2005). HHS. Publication No. (SMA) 08-4214.

4. Discontinuation of Treatment [ANY]

Request will **NOT** be authorized if ANY of the following conditions apply [ANY]

- ❑ For alcohol dependence/AUD: No clinically significant reduction in alcohol use within 3 months
- ❑ For opioid dependence/OUD: No clinically significant reduction in opioid use within 3 months
- ❑ Adverse side effects or any medical reason to discontinue Vivitrol (naltrexone)
- ❑ Member is able to use the oral form of naltrexone
- ❑ Vivitrol is no longer a necessary part of member's overall substance abuse treatment plan either because of: [ANY]
  - ❍ Member's successful abstinence from alcohol
  - ❍ Vivitrol has not been effective for the treatment goal of abstinence
- ❑ Contraindications/Exclusions to Vivitrol (naltrexone) therapy [ANY]
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent or any ingredient in the formulation
  - ❍ Pregnancy or breastfeeding
  - ❍ Member requires opioid medications (including tramadol and tapentadol) for therapeutic reasons
  - ❍ Current physiologic opioid dependence or current use of opioid analgesics
  - ❍ Acute opiate withdrawal
  - ❍ Failure of the Naloxone Challenge Test
  - ❍ Positive urine screen for opioids
  - ❍ Acute hepatitis, active liver disease (AST or ALT > 3 times baseline or 5 times the upper limit of normal), severe hepatic impairment (Child-Pugh class C)
  - ❍ Moderate to severe renal impairment (estimated or measured CrCl less than 50 ml/min)

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

5. Recommended Dosing Regimen [ALL]
Dosage prescribed is within the FDA-approved labeling based on member's confirmed diagnosis:

- ❒ The recommended dose of naltrexone is 380 mg delivered intramuscularly (IM) every 4 weeks or once a month. The injection should be administered by a health care provider as an IM gluteal injection, alternating buttocks, using the carton components provided. Naltrexone must not be administered intravenously (IV) or subcutaneously.

6. Authorization Limit [ALL]

- ❑ Quantity limit: One vial per 28 days of Vivitrol 380 mg strength. Each IM injection (no more than 380mg/injection) must be given by a physician or nurse once every 4 weeks
- ❒ Initial authorization may be authorized **up to 3 months** (3 injections per authorization period)
- ❒ Re-authorization for continuation of treatment is required **every 3 months** to determine continued need for Vivitrol (3 injections per authorization period)
- ❑ TOTAL DURATION OF TREATMENT: Treatment is limited to 24 weeks; extensions to be determined on case-by-case basis by a Molina Medical Director
  NOTE: *The optimal duration of pharmacotherapy is not known. Controlled studies have been conducted for up to 6 months; some patients have been treated with injectable naltrexone therapy longer. Experts recommend at least six months of medication with an additional six months of follow-up.*[6]

CONSIDERATIONS

- ➢ **Re-initiation of treatment in patients who previously discontinued:** There are no data to specifically address reinitiation of treatment.
- ➢ **Switching from oral naltrexone for alcohol dependence:** There is limited information, no systematically collected data that specifically address the switch from oral naltrexone to naltrexone injection

10. Route of Administration [ALL]

- ❑ Medication must be **administered in the provider's office** (by the prescriber or the designated licensed health care professional of the prescriber agrees) until information from the manufacturer, scientific literature, practice standards, or governing State or Federal agency indicates that self-administration by a patient or caregiver is safe and acceptable.
- ❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

COVERAGE EXCLUSIONS

All other uses that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

SUMMARY

Naltrexone extended-release injectable suspension is a microsphere formulation of naltrexone for suspension intended only for intramuscular (IM) administration. The microspheres are approximately 100 micrometers in size and are produced using a polylactide-coglycolide (PLG) polymer. PLG is a biodegradable medical polymer that slowly hydrolyzes into lactic and glycolic acids following injection. The lactic and glycolic acids are then metabolized to carbon dioxide and water.

Naltrexone is an opioid antagonist. Its highest affinity is for the mμ opioid receptor. Its precise mechanism of action in alcohol dependence is not known; however, the effects are believed to involve blockade of the endogenous opioid system. Naltrexone is not associated with tolerance or dependence; however, it can precipitate withdrawal symptoms in those who are physically opioid dependent. Moreover, due to its antagonistic effects on mu receptors, in can interfere with the effects of endogenous opioid peptides. The precise mechanism by which naltrexone acts to reduce alcohol consumption, in dependent individuals, is not well characterized; however it is believed that its action on opioid receptors plays an important role in this effect.

The precise mechanism of the opiate antagonist effects of naltrexone is not known. However, naltrexone reportedly shares the actions of naloxone and is thought to act as a competitive antagonist at mc, k, and d receptors in the CNS; the drug appears to have the highest affinity for the m receptor. The drug may displace opiates from opiate-occupied receptor sites by competitive binding at the receptors, and displacement of naltrexone from these receptors by opiates is also reportedly possible.

In 1994, the FDA had approved *oral* naltrexone for treating alcohol use disorders, based on multiple clinical studies that found the medication was generally safe and significantly reduced alcohol craving, alcohol consumption, and relapse.

The U.S. Food & Drug Administration (FDA) approved extended-release injectable naltrexone (Vivitrol) for use in treatment of alcohol dependence (2006) and for use in treatment of opioid dependence (2010). Naltrexone is an opioid antagonist that binds to the opioid receptors, blocking the euphoric effects of exogenous opioids in those who are opioid dependent. The neurobiological mechanism by which it reduces alcohol consumption in alcohol dependent individuals is not entirely understood, but clinical data suggests that there is involvement of the endogenous opioid system.

ALCOHOL DEPENDENCY

There are two drugs FDA-approved, in addition to Vivitrol and oral naltrexone, for treatment of alcohol dependence.

1) Naltrexone (Depade®, Revia®, Duramed Pharmaceuticals Inc., Pomona, New York)
   The FDA approved naltrexone in 1984 for the adjuvant treatment of patients dependent on opiate agonists. FDA approval of naltrexone for the treatment of alcoholism was granted January 1995.

   The FDA approved Vivitrol, a once-monthly intramuscular naltrexone formulation used to help control cravings for alcohol in April 2006, and then in October 2010, the FDA approved Vivitrol for the prevention of relapse to opioid dependence after opioid detoxification.

2) Acamprosate (Campral®, Forest Pharmaceutical, Inc., St. Louis, MO)
   Acamprosate received approval in 2004 as an adjunct to psychosocial support for the maintenance of abstinence in alcohol-dependent patients. Acamprosate is a synthetic compound that is structurally similar to the amino acid neurotransmitter gamma (γ)-aminobutyric acid (GABA) and that acts both on GABA (agonizing effect) and glutamate

(antagonizing effect) receptors. Although the precise mechanism of action of acamprosate in the maintenance of abstinence is not known, the current predominating theory focuses on its antagonizing properties at the N-methyl-D-aspartate (NMDA) receptor of the glutamate system. That is, because alcohol inhibits glutamate, chronic drinking may lead to compensatory changes in the glutamate system. When alcohol is no longer present, such as during abstinence after chronic excessive drinking, a hyperglutamatergic state may occur, and this state has been associated with alcohol craving. Similar to disulfiram, acamprosate is taken orally daily.

3) Disulfiram (Antabuse®, Duramed Pharmaceuticals Inc., Pomona, NY)
An aversion therapy that has been available since 1951, blocks the metabolism of alcohol, which causes an accumulation of acetaldehyde and symptoms such as nausea and vomiting. This drug is taken orally once daily but requires strict patient adherence to be effective. Although disulfiram can decrease drinking days when taken in a supervised fashion, there is little evidence that it affects abstinence, presumably due to poor patient compliance.

❖ **Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A Randomized Controlled Trial Garbutt et al. (2005)[2,B]**

Naltrexone extended-release injectable suspension was assessed in a 24-week placebo-controlled, multicenter, double-blind, randomized study enrolling 624 outpatients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria for alcohol dependence.[B]

Injections of placebo (209 patients), naltrexone 190 mg extended-release (210 patients), or naltrexone 380 mg extended-release (205 patients) were administered IM every 4 weeks. Oral naltrexone was not administered prior to the initial or subsequent injections. Low-intensity psychosocial support was provided to all subjects. A total of 6 injections were administered to 401 patients (64%), while 463 patients (74%) received 4 injections.

The primary study end point was the rate of heavy drinking days in the intent-to-treat population. Patients treated with naltrexone 380 mg extended-release injection had a greater reduction in days of heavy drinking (defined as self-report of 5 or more standard drinks consumed on a given day for male patients and 4 or more drinks for female patients) compared with those treated with placebo.

Heavy drinking days were reduced 25% in the naltrexone 380 mg group ($P = 0.03$) and 17% in the naltrexone 190 mg group ($P = 0.07$) compared with placebo. Greater reductions in heavy drinking days were observed in those abstinent at study entry and in men. During the study, complete abstinence was maintained in 7% of patients in the 380 mg group, 6% in the 190 mg group, and 5% in the placebo group. The 53 patients who abstained completely from drinking during the week prior to the first dose of medication and were treated with naltrexone 380 mg extended-release injection had greater reductions in the number of drinking days and the number of heavy drinking days compared with those treated with placebo. In this subgroup, patients treated with naltrexone were also more likely than placebo-treated patients to maintain complete abstinence throughout treatment (41% vs 35% in the 190 mg group and 17% in the placebo group; differences not statistically significant).

❖ **Naltrexone Depot for Treatment of Alcohol Dependence: A Multicenter, Randomized, Placebo-Controlled Clinical Trial[3,B]**
Naltrexone extended-release injectable suspension was also assessed in a 3-month randomized, double-blind, placebo-controlled study enrolling 315 alcohol-dependent subjects.

Patients received naltrexone (158 patients) or placebo (157 patients) monthly for 3 months. The naltrexone dose was 300 mg (two 150 mg injections) for the first dose and 150 mg for the subsequent doses. All patients also received 5 sessions of manual-guided motivational enhancement therapy. The time to first drinking day, percentage of patients with no heavy drinking throughout the study, and gamma-glutamyl transpeptidase levels all favored the naltrexone. The median time to first heavy drinking day was 11 days in the naltrexone group compared with 6 days in the placebo group ($P = 0.05$). The mean number of heavy drinking days was 22.4 in the naltrexone group compared with 25.3 in

the placebo group ($P = 0.29$). The median time to first drinking day was 5 days in the naltrexone group compared with 3 days in the placebo group ($P = 0.003$). Abstinence was maintained in 18% of the naltrexone-treated patients compared with 10% of the placebo recipients ($P = 0.048$).

The primary efficacy was based on patients' self-report. No secondary method to ensure the accuracy of the self-reporting results. The primary goal of abstinence can't be fully demonstrated in a short term study. The study was not a direct comparison to oral naltrexone.

- **Cochrane Review**

A 2010 systematic review from the Cochrane Collaboration evaluated the effectiveness and tolerability of opioid antagonists in the treatment of alcohol dependence.[9]

All double-blind RCTs comparing naltrexone or nalmefene with placebo or active control were included. Primary outcomes included: return to heavy drinking, return to any drinking, and drinking days. A literature search through January 2010 identified 50 studies (n=7,793) to be included in the evidence synthesis; 47 of which were included in the meta-analysis. Only 4 of the RCTs evaluated the injectable ER formulation of naltrexone. These trials showed that injectable naltrexone appears effective, but not all outcomes were statistically significant. Injectable naltrexone was administered at four-week intervals at doses between 150 mg and 400 mg.

Analysis of injectable naltrexone showed reduced risk of any drinking after detoxification to 92% of the placebo group (RR 0.92, 95% CI 0.84-1.0), the percentage of drinking days by about 9% (mean difference [MD] -8.54, 95% CI -15.77 to -1.31), and the percentage of heavy drinking days by about 3% (MD -3.05, 95% CI -8.46 o 2.35). Injectable naltrexone caused significantly more daytime sleepiness, decreased appetite, dizziness, fatigue, and vomiting than placebo. Early withdrawals due to side effects were more frequent in the injectable naltrexone group than the placebo group (RR 1.57, 95% CI 0.92 to 2.69).

Conclusion: The authors concluded that the treatment effects of injectable naltrexone are comparable in magnitude to oral naltrexone. However, statistical significance was missed. Other than a more pronounced sedative effect, the tolerability appears comparable to oral naltrexone.

- **Hayes**

A Hayes Technology Brief was available for Vivitrol® (Injectable Naltrexone) (Alkermes Inc.) for Outpatient Treatment of Alcohol Dependence at the time of this writing in April 2014. However, this report was archived on Mar 19, 2013; due to being 'Outdated.'

OPIOID DEPENDENCE

The Vivitrol labeled indication was expanded to include prevention of relapse to opioid dependence following opioid detoxification by FDA approval on October 12, 2010.

- There is limited head to head evidence evaluating extended-release naltrexone injection.

- Injectable, sustained-release naltrexone for the treatment of **opioid dependence:** a randomized, placebo-controlled trial.

  Comer et al (2006) reported on the safety and efficacy of a sustained-release depot formulation of naltrexone in treating opioid dependence.[1] Injectable naltrexone (opioid antagonist) was addressed in a feasibility study by Comer and colleagues (2006). The study (n=60) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 8-week clinical trial. Participants received an initial inpatient detoxification then oral naltrexone for three consecutive days to ensure participants were willing and able to tolerate the effects of injectable naltrexone. Participants were then randomized into groups receiving placebo, 192 mg or 384 mg naltrexone twice at 4 week intervals. The groups had physical evaluations twice weekly for treatment response and adverse events. Psychosocial evaluations were conducted twice during the study period. The highest percentage of negative urine samples occurred in the 384 mg group followed by the 192 mg group. Heroin craving was high in all 3 groups at the study's onset. Those who received either dose of naltrexone reported needing heroin less than the placebo group (p less than .001). The authors noted that opioid dependents pose a greater risk for Vivitrol adverse events than alcoholic individuals in that opioid abuse can involve injectable routes of administration increasing the chance of HIV and compromised immunity. They also acknowledged that larger studies with more diverse populations are needed.

- **Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicenter randomized trial**[7]

  The efficacy of naltrexone extended-release injectable suspension in the treatment of opioid dependence was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of opioid-dependent (DSM-IV) outpatients, who were completing or had recently completed detoxification.[4] A total of 250 eligible patients were randomized to receive naltrexone 380 mg (n = 126) or placebo (n = 124), both in combination with drug counseling. The primary endpoint was confirmed abstinence, calculated by each patient's rate of opioid-free weeks. All missing urine drug test results were imputed as positive for opioid use. Results demonstrated opioid-free weeks from week 5 to 24 weeks were significantly different between treatment groups (P = 0.0002), with a median of 90% opioid-free urines in the extended-release naltrexone group and 35% in the placebo group. In addition, significantly more naltrexone -treated patients achieved complete abstinence from Week 5 to Week 24 vs. placebo-treated patients (36% vs. 23%, respectively; P = 0.0224).[4] Overall, 51% of the naltrexone -treated patients and 65% of the placebo-treated patients did not complete the 24 weeks of treatment and 13% of naltrexone-treated patients compared to 36% of placebo-treated patients dropped out of the study before week 5.

  - Double-blind, placebo-controlled, randomized, 24-week trial of patients with opioid dependence disorder
  - Randomized trial with high dropout rate (54.4%)
  - 250 patients ≥ 18 years old with opioid dependence and who had ≤ 30 days of inpatient detoxification and ≥ 7 days off all opioids were randomized to naltrexone extended-release 380 mg vs. placebo intramuscularly once per month for 24 weeks
  - All patients received 12 biweekly counseling sessions
  - Compared naltrexone extended-release vs. placebo
    - Number of subjects completing treatment 53.2% vs. 37.9% (p = 0.0171)
    - Confirmed total abstinence in 35.7% vs. 22.6% (p = 0.0224, NNT 8)
    - Median proportion of weeks of confirmed abstinence 90% vs. 35% (p = 0.0002)
    - Median proportion of self-reported opioid free days over 24 weeks 99.2% vs. 60.4% (p = 0.0004)
    - ≥ 1 drug-related adverse event in 26% vs. 10% (p = 0.001, NNH 6)
  - Conclusions

- The study was not a direct comparison to oral naltrexone
- Naltrexone extended-release intramuscularly once monthly associated with reduced opioid use in patients with opioid dependence after detoxification
- For the treatment of opioid dependence, there is moderate level evidence that when compared to placebo, naltrexone extended-release injectable suspension is associated with reduced opioid use after detoxification and improves confirmed total abstinence in 35.7% vs. 22.6% (p = 0.0224, NNT 8) of patients when studied for 24 weeks, in combination with drug counseling.4

❖ A Cochrane review found no significant differences between oral naltrexone and placebo in preventing relapse in opioid addicts after detoxification.[8]

DEFINITIONS

- **Naloxone challenge** is a test to see whether a patient is at risk of precipitated opioid withdrawal before being given naltrexone. A naloxone challenge should be done selectively and with great care (e.g., by or in close consultation with a physician experienced in management of opioid withdrawal) since patients can rapidly experience serious opioid withdrawal.
  - Give 0.2 to 0.4 mg of naloxone subcutaneously or intravenously; if patient is physiologically dependent on opioids, precipitated withdrawal usually begins within minutes.
  - Patients with low levels of opioid use may require up to a total dose of 0.8 mg of naloxone to precipitate withdrawal, given in increments of 0.2 mg every 30 minutes.
  - Symptoms usually peak within 30 minutes and subside in 3 to 4 hours.

APPENDIX

APPENDIX 1: Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is published by the American Psychiatric Association and provides a common language and standard criteria for the classification of mental disorders. It is used in the United States and in varying degrees around the world, by clinicians, researchers, psychiatric drug regulation agencies, health insurance companies, pharmaceutical companies and policy makers.

Alcohol abuse

- Maladaptive pattern of alcohol use leading to significant impairment or distress
- Not meeting criteria for alcohol dependence
- One or more of the following within 12 months:
  - recurrent drinking resulting in failure to fulfill major role obligations
  - recurrent drinking in situations in which it is physically hazardous
  - recurrent alcohol-related legal problems
  - continued alcohol use despite persistent or recurrent social or interpersonal problems caused or exacerbated by alcohol

Alcohol Dependence

- Maladaptive pattern of alcohol use leading to significant impairment or distress
- 3 or more of the following within 12 months
  - need for significantly increased amounts of alcohol to achieve intoxication or desired effect, or significantly diminished effect with continued use of the same amount of alcohol
  - alcohol withdrawal syndrome, or use of substances to relieve or avoid withdrawal symptoms
  - persistent desire or unsuccessful efforts to cut down or control drinking
  - drinking more or longer than intended
  - giving up or reducing activities due to drinking
  - considerable time spent in activities to obtain alcohol, drink, or recover from alcohol effects
  - continued drinking despite knowledge of having persistent or recurrent physical or psychological problems exacerbated by alcohol use
  - considered physical dependence (in addition to psychological dependence) if evidence of tolerance or withdrawal

APPENDIX 2: Medications that are FDA approved for treating adults with alcohol-use disorders

Generic Drug Name	Mechanism	Dosing
Acamprosate	Thought to antagonize glutamatergic N-methyl-D-aspartate (NMDA) receptors and agonize gamma-aminobutyric acid (GABA) type A receptors	666 mg 3 times per day
Disulfiram	Inhibits aldehyde dehydrogenase (ALDH2), causing accumulation of acetaldehyde during alcohol consumption, which produces highly unpleasant symptoms	250 to 500 mg per day
Naltrexone	Opioid antagonist; competitively binds to opioid receptors and may block the effects of endogenous opioids	Oral: 50 to 100 mg per day Intramuscular injection: 380 mg per month

APPENDIX 3: Clinical Opiate Withdrawal Scale (COWS)

Clinical Opiate Withdrawal Scale (COWS)

Flow-sheet for measuring symptoms over a period of time during buprenorphine induction

For each item, write in the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ **Date:** _____

Buprenorphine induction:

Enter scores at time zero, 30min after first dose, 2 h after first dose, etc.
Times: _____ _____ _____ _____

Resting Pulse Rate: (record beats per minute) *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120				
Sweating: *over past ½ hour not accounted for by room temperature or patient activity* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face				
Restlessness *Observation during assessmen*t 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds				
Pupil size 0 pupils pinned or normal size for room light				

1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible				
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort				
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks				
GI Upset: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting				
Tremor *observation of outstretched hands* 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching				
Yawning *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute				
Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult				
Gooseflesh skin 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection				
Total scores **with observer's initials**				

Score

5-12 = mild;
13-24 = moderate;
25-36 = moderately severe;
more than 36 = severe withdrawal

CODING INFORMATION

CPT	Description
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS	**Description**
J2315	Injection, naltrexone, depot form, 1 mg
ICD-9	**Description [For dates of service *prior* to 10/01/2015]**
303.9	Other and unspecified alcohol dependence
303.90	Other and unspecified alcohol dependence, continuous
303.91	Other and unspecified alcohol dependence, episodic
ICD - 10	**Description [For dates of service *on or after* 10/01/2015]**
F10.1	alcohol abuse
F10.9	alcohol use, unspecified
F10.20	Alcohol dependence, uncomplicated
ICD-9	**Description[For dates of service *prior to* 10/01/2015]**
304.0	Opioid type dependence
304.00	Opioid type dependence, unspecified
304.01	Opioid type dependence, continuous
304.02	Opioid type dependence, episodic
ICD-10	**Description [For dates of service *on or after* 10/01/2015]**
F11.20	Opioid dependence, uncomplicated

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