Opioid Use Disorder Protocol utilizing Naltrexone-based Therapy
v3 Approved 01/26/2022

PURPOSE

This protocol specifies the criteria and procedures for pharmacists to initiate the dispensing and administration of naltrexone for the treatment of individuals with opioid use disorder.

PHARMACIST EDUCATION AND TRAINING

Prior to initiating the dispensing and administration of naltrexone under this protocol, pharmacist(s) must have received education and training in opioid use disorder and naltrexone therapy, including a review of the most current American Society of Addiction Medicine's (ASAM) National Practice Guideline for the treatment of opioid use disorder, from a provider accredited by the Accreditation Council for Pharmacy Education, or by a comparable provider approved by the Kentucky Board of Pharmacy.

Provider of Training: _____

Date of Training Completed: _____

CRITERIA

Pharmacist(s) authorized to initiate the dispensing and administration of naltrexone will follow the most current ASAM The National Practice Guideline for the use of medications in the treatment of opioid use disorder.

Inclusion criteria:

Any individual, 18 years or older, who has been diagnosed with an opioid use disorder and has met the following criteria:

- Documentation of opioid use disorder and baseline medical screening exam, including evaluation of hepatic function within the past 14 days
- Is adequately withdrawn from opioids as verified by point-of-care urine drug screen
- Has no signs or symptoms of withdrawal as verified by Clinical Opiate Withdrawal Scale (COWS) {Appendix 1}
- Is able to provide informed consent to receive treatment

Exclusion criteria:

- Individuals who are known to be pregnant are not eligible to receive therapies under this protocol and should be referred to their primary care or Ob/Gyn provider
- Individuals who have known contraindications (severe allergic reaction to naltrexone or any component of the extended-release injectable naltrexone formulation).
- Individuals with known acute hepatitis or liver failure or liver function tests >3 times the upper limits of normal (ULN)
- Individuals testing positive for opioids via point-of-care urine drug screen

MEDICATIONS

This protocol authorizes pharmacists to initiate the dispensing and administration of the following medications as referenced in the manufacturer's product information

1) Extended-release injectable naltrexone (Vivitrol□)
2) Oral naltrexone (ReVia, Depade) to be used solely in case of an initial withdrawal challenge

PROCEDURES FOR INITIATION OF THERAPIES

Naltrexone will be initiated only in carefully selected individuals based on relevant medical and social history and consideration of contraindications and precautions of therapy as outline in the pharmacologic product guide and identified through assessment and screening[1]

Relevant Medical and Social History

- Past medical history, including an active diagnosis of opioid use disorder
- Current medications
- Allergies and hypersensitivities
- Previous experiences with medicationfor opioid use disorder
- Any previous, ongoing, or planned psychosocial treatment or support services utilization

Contraindications and Precautions

- Known hypersensitivity to naltrexone or components of the naltrexone diluent
- Pregnancy
- Current chronic use of/treatment with opioid analgesics for chronic pain syndromes
- Current opioid dependence, including partial agonists
- Known acute hepatitis or liver failure or liver function tests >3x ULN
- Positive urine drug screen for opioids
- Positive opioid withdrawal assessment as indicated by COWS score of 5 or greater
    - Injection will not be provided to individuals with positive opioid withdrawal assessment. (Opioid withdrawal assessment will be repeated in 24 hours).
- Any individual who, at the discretion of the pharmacist has taken and failed the oral naltrexone challenge test as evidence by a change in COWS score of 2 or more
- Known moderate to severe renal impairment
- Known history of thrombocytopenia or coagulation disorders

Assessment and Screening

- Individual confirmation of absence of opioid use for 7-10 days
- Negative urine drug screen for opioids
- Negative urine pregnancy test in individuals who have the potential to get pregnant
- No signs or symptoms of opioid withdrawal per COWS score

If the pharmacist, in their clinical judgment, determines that it is uncertain whether the patient is no longer physically dependent on opioids they may perform an oral naltrexone challenge assessment as follows:

- Naltrexone 25mg oral x1 (1/2 of a 50mg tablet) --- with observation for 60 minutes for signs and symptoms of opioid withdrawal
    - Prior to and following the 60-minute observation period the pharmacist will

[1] Available at: https://ww/w.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s015lbl.pdf

complete a COWS assessment

- If any signs or symptoms of opioid withdrawal are present or if pulse and/or blood pressure increases, evaluation should be performed again in 24 hours before therapy can be initiated

If all inclusion assessment criteria are met, pharmacists will provide required education, obtain consent for treatment and administer long-acting injectable naltrexone (Vivitrol) 380mg IM according to the manufacturer's product information.[2] Individuals receiving therapy will be monitored for adverse reactions for a period of 15 minutes. In the unlikely event of serious or life-threatening allergic reaction, pharmacists will implement the attached anaphylaxis protocol (Appendix 2).

PROCEDURES FOR MONITORING AND CONTINUATION OR ADJUSTMENT OF THERAPIES

Subsequent naltrexone will be dispensed and administered every 28 days (+/- 2 days) only in individuals who confirm absence of opioid use for 7-5 days and provide a negative urine drug screen for opioids. Individuals outside of 30 days since last injection will also require an opioid withdrawal assessment. Individuals who have the potential to get pregnant must also have anegative urine pregnancy test.

Follow up monitoring and evaluation shall occur at a minimum at every 28 days (+/- 2 days) with each injection to determine effectiveness, adverse effects, and individual progress with therapy, including any participation in psychosocial treatment. If follow-up monitoring and evaluation indicates therapy continuation is warranted, naltrexone will be dispensed and administered every 28 days (+/- 2 days). Treatment periods longer than 12 months of continuous therapy are not authorized under this protocol without explicit approval from the authorizing prescriber.

Should follow-up evaluation and monitoring indicate continued therapy with extended-release injectable naltrexone is warranted, all procedures as outlined for initiation of therapies, including education, documentation, and notification, will be followed.

PATIENT EDUCATION REQUIREMENTS

Individuals receiving extended-release injectable naltrexone under the protocol will receive education regarding:

1) Benefits, including the mechanism of action of naltrexone
2) Alternatives to naltrexone
3) Requirement of opioid free period for at least 7-10 days to avoid precipitation of severe opioid withdrawal
4) Risk of precipitated withdrawal if under reporting last opioid use/current dependence
5) Risk of opioid overdose at the end of duration of effect time period, if a dose is missed, if treatment is discontinued, or in attempt to overcome blockade
6) Warnings and adverse effects possible with use of naltrexone
7) Expectation to carry and/or wear documentation of naltrexone treatment
8) Importance of psychosocial treatment in conjunction with naltrexone treatment
9) Use of rescue naloxone for emergency treatment of opiate overdose
   **naloxone rescue medication will be offered under pharmacist naloxone protocol ifindividual does not have naloxone available*

[2] Available at: https://ww/w.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s015lbl.pdf

A written medication guide (Appendix 3) will be provided to each individual at initiation of therapy.

DOCUMENTATION

Pharmacists will document via prescription record each person who receives naltrexone under this protocol, including:

(a) Documentation as required in 201 KAR 2:170 for the dispensing of prescription medication
(b) Documentation that the individual receiving naltrexone was provided with the required education pursuant to this protocol
(c) Documentation of informed consent to receive treatment
(d) Documentation of the history and assessment, care plan implemented, and follow-up evaluation and monitoring, including individual confirmation of continued opioid free period and negative urine drug screen; and if applicable, negative urine pregnancy test and/or results of oral naltrexone challenge, including COWS assessment

NOTIFICATION

Pharmacist(s) shall provide notification of the medications dispensed and administered under the protocol to the identified care provider within two (2) business days. Any individual affirmatively stating that they do not have a primary care provider will be referred for a medical evaluation prior to initiating therapies under this protocol.

Pharmacist(s) shall provide notification if medication is ceased by the individual, or if administration is not warranted under conditions of the protocol, to the primary care provider within two (2) business days.

[If directed by the authorizing prescriber] the pharmacist shall provide written notification via fax or other secure electronic means to the authorizing prescriber of persons receiving naltrexone therapy under this protocol within 7 days of initiating dispensing.

TERMS

This protocol is effective as of the date all parties execute the document. It shall remain in effect for a period of one year and shall automatically renew for successive one year periods unless otherwise terminated by any party, with or without cause. Any termination without cause shall require prior notice to all parties of no less than sixty days.

SIGNATURES

_____ _____

Prescriber Name Date

_____

Prescriber Signature

_____ _____

Pharmacist Name Date

Pharmacist Signature

APPENDIX 1
Clinical Opiate Withdrawal Scale (COWS)

For each item, circle 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 and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/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	**GI Upset:** *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 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	**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
Restlessness *Observation during assessment* 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	**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
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	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
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	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
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	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

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

Appendix 2
Addendum for Management of Adverse Reactions to Naltrexone

*Adapted from immunize.org

All medications have the potential to cause an adverse reaction. In order to minimize adverse reactions, individuals must be carefully screened for precautions and contraindications before the medication is administered. Even with careful screening, reactions may occur. These reactions can vary from trivial and inconvenient (e.g. soreness, itching) to severe and life threatening (e.g. anaphylaxis). If reactions occur, the pharmacists must be prepared with procedures for their management.

Anaphylactic Reactions

Signs and symptoms of anaphylactic reaction include:

- the sudden or gradual onset of generalized itching, erythema (redness), or urticaria (hives);
- angioedema (swelling of the lips, face, or throat);
- bronchospasm (wheezing);
- shortness of breath;
- shock;
- abdominal cramping; or
- cardiovascular collapse.

The following procedures should be used to manage **anaphylactic reactions** following administration:

(1) If itching and swelling are confined to the injection site, observe closely for at least 30 minutes, watching for the development of generalized symptoms.

(2) If symptoms are generalized, activate the emergency medical system (e.g., call 911) immediately.

(a) Administer diphenhydramine for hives or generalized itching, either orally or by intramuscular injection.

- The standard dose is 1-2 mg/kg every 4-6 hours, or 50 to 100 mg maximum single dose for adults. Do not attempt to give oral medications to an individual who is not fully alert and able to swallow safely.

(3) Place individual in a recumbent position and elevate legs.

(4) The first-line therapy in anaphylaxis is epinephrine. There are no contraindications to epinephrine in the setting of anaphylaxis.

(a) Administer aqueous epinephrine 1:1000 dilution intramuscularly, 0.01mL/kg/dose (adult dose ranges from 0.3mL to 0.5mL, with a maximum single dose of 0.5mL), as indicated:

Weight (lbs)	Weight (kg)	Dose
45-88 lb	21-40 kg	0.3mg (or mL)
89-110 lbs	41-50 kg	0.45mg (or mL)
>110 lbs	>51 kg	0.5mg (or mL)

Prefilled devices (i.e., EpiPen or similar autoinjector):Weight > 66 lbs or 30 kg – EpiPen 0.30mg

The site of injection can be gently massaged to facilitate absorption.

(b) If EMS has not arrived and symptoms are still present, the dose of epinephrine may be repeated every 5 to 15 minutes for up to 3doses, depending on the individual's response.

For all adverse reactions the following procedures should be used:

- Monitor the individual closely and check vital signs (blood pressure, pulse, andrespirations) every 2 to 5 minutes.
- Stay with individual until EMS arrives.
- If necessary, perform cardiopulmonary resuscitation (CPR) and maintain airway.
- Keep individual in supine position unless he or she is having breathingdifficulty.If breathing is difficult, individual's head may be elevated, provided blood pressure is adequate to prevent loss of consciousness. If blood pressure is low,elevate legs.
- Notify the authorizing prescriber and, if applicable the primary care provider assoon as possible.

Appendix 3: Vivitrol Medication Guide

VIVITROL® (viv-i-trol)
(naltrexone for extended-release injectable suspension)
Read this Medication Guide before you start receiving VIVITROL injections and each time you receive an injection. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about VIVITROL? VIVITROL can cause serious side effects, including:

1. **Risk of opioid overdose.**

You can accidentally overdose in two ways.

- VIVITROL blocks the effects of opioids, such as heroin or opioid pain medicines. **Do not** take large amounts of opioids, including opioid-containing medicines, such as heroin or prescription pain pills, to try to overcome the opioid-blocking effects of VIVITROL. This can lead to serious injury, coma, or death.
- After you receive a dose of VIVITROL, its blocking effect slowly decreases and completely goes away over time. If you have used opioid street drugs or opioid-containing medicines in the past, using opioids in amounts that you used before treatment with VIVITROL can lead to overdose and death. You may also be more sensitive to the effects of **lower** amounts of opioids:
  - after you have gone through detoxification
  - when your next VIVITROL dose is due
  - if you miss a dose of VIVITROL
  - after you stop VIVITROL treatment

It is important that you tell your family and the people closest to you of this increased sensitivity to opioids and the risk of overdose.

You or someone close to you should call 911 or get emergency medical help right away if you:

- have trouble breathing
- become very drowsy with slowed breathing
- have slow, shallow breathing (little chest movement with breathing)
- feel faint, very dizzy, confused, or have unusual symptoms

Talk to your healthcare provider about naloxone, a medicine that is available to patients for the emergency treatment of an opioid overdose.
Call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered.

2. **Severe reactions at the site of the injection (injection site reactions).** Some people on VIVITROL have had severe injection site reactions, including tissue death (necrosis). Some of these injection site reactions have required surgery. VIVITROL must be injected by a healthcare provider. Call your healthcare provider right away if you notice any of the following at any of your injection sites:
   - intense pain
   - the area feels hard
   - large area of swelling
   - lumps
   - blisters
   - an open wound

- a dark scab

Tell your healthcare provider about any reaction at an injection site that concerns you, gets worse over time, or does not get better by two weeks after the injection.

3. **Sudden opioid withdrawal.**

Anyone who receives a VIVITROL injection must not use any type of opioid (must be opioid-free) including street drugs, prescription pain medicines, cough, cold, or diarrhea medicines that contain opioids, or opioid dependence treatments, buprenorphine or methadone, **for at least 7 to 14 days** before starting VIVITROL. Using opioids in the 7 to 14 days before you start receiving VIVITROL may cause you to suddenly have symptoms of opioid withdrawal when you get the VIVITROL injection.

Sudden opioid withdrawal can be severe, and you may need to go to the hospital.
You must be opioid-free before receiving VIVITROL unless your healthcare provider decides that you don't need to go through detox first. Instead, your doctor may decide to give your VIVITROL injection in a medical facility that can treat you for sudden opioid withdrawal.

4. **Liver damage or hepatitis.** Naltrexone, the active ingredient in VIVITROL, can cause liver damage or hepatitis.

Tell your healthcare provider if you have any of the following symptoms of liver problems during treatment with VIVITROL:

- stomach area pain lasting more than a few days
- dark urine
- yellowing of the whites of your eyes
- tiredness

Your healthcare provider may need to stop treating you with VIVITROL if you get signs or symptoms of a serious liver problem.

What is VIVITROL?
VIVITROL is a prescription injectable medicine used to:

- treat alcohol dependence. You should stop drinking before starting VIVITROL.
- prevent relapse to opioid dependence, **after** opioid detoxification.

This means that if you take opioids or opioid-containing medicines, you must stop taking them before you start receiving VIVITROL. To be effective, treatment with VIVITROL must be used with other alcohol or drug recovery programs such as counseling. VIVITROL may not work for everyone. It is not known if VIVITROL is safe and effective in children.

Who should not receive VIVITROL? Do not receive VIVITROL if you:

- are using or have a physical dependence on opioid-containing medicines or opioid street drugs. To see whether you have a physical dependence on opioid-containing medicines or opioid street drugs, your healthcare provider may give you a small injection of a medicine called naloxone. This is called a naloxone challenge test. **If you get symptoms of opioid withdrawal after the naloxone challenge test, do not start treatment with VIVITROL at that time.** Your healthcare provider may repeat the test after you have stopped using opioids to see whether it is safe to start VIVITROL.

- are having opioid withdrawal symptoms. Opioid withdrawal symptoms may happen when you have been taking opioid-containing medicines or opioid street drugs regularly and then stop.

Symptoms of opioid withdrawal may include: anxiety, sleeplessness, yawning, fever, sweating, teary eyes, runny nose, goose bumps, shakiness, hot or cold flushes, muscle aches, muscle twitches, restlessness, nausea and vomiting, diarrhea, or stomach cramps.**"** Tell your healthcare provider if you have any of these symptoms before taking VIVITROL.

- are allergic to naltrexone or any of the ingredients in VIVITROL or the liquid used to mix VIVITROL (diluent). See the end of this Medication Guide for a complete list of ingredients in VIVITROL and the diluent.

What should I tell my healthcare provider before receiving VIVITROL? Before you receive VIVITROL, tell your healthcare provider if you:

- have liver problems
- use or abuse street (illegal) drugs
- have hemophilia or other bleeding problems
- have kidney problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if VIVITROL will harm your unborn baby.
- are breastfeeding. It is not known if VIVITROL passes into your milk, and if it can harm your baby. Naltrexone, the active ingredient in VIVITROL, is the same active ingredient in tablets taken by mouth that contain naltrexone. Naltrexone from tablets passes into breast milk. Talk to your healthcare provider about whether you will breastfeed or take VIVITROL. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
Especially tell your healthcare provider if you take any opioid-containing medicines for pain, cough or colds, or diarrhea.

If you are being treated for alcohol dependence but also use or are addicted to opioid-containing medicines or opioid street drugs, it is important that you tell your healthcare provider before starting VIVITROL to avoid having sudden opioid withdrawal symptoms when you start VIVITROL treatment.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How will I receive VIVITROL?

- VIVITROL is injected by a healthcare provider, about 1 time each month.
- VIVITROL must be injected by a healthcare provider. Do not attempt to inject yourself with VIVITROL. Serious reactions, some that may require hospitalization, might happen.
- VIVITROL is given as an injection into a muscle in your buttocks using a special needle that comes with VIVITROL.
- After VIVITROL is injected, it lasts for a month and it cannot be removed from the body.
- If you miss your appointment for your VIVITROL injection, schedule another appointment as soon as possible.
- Whenever you need medical treatment, be sure to tell the treating healthcare provider that you are receiving VIVITROL injections and mention when you got your last dose. This is

important because VIVITROL can also block the effects of opioid-containing medicines that might be prescribed for you for pain, cough or colds, or diarrhea.
- Carry written information with you at all times to alert healthcare providers that you are taking VIVITROL, so that they can treat you properly in an emergency. Ask your healthcare provider how you can get a wallet card to carry with you.

What should I avoid while receiving VIVITROL?
Do not drive a car, operate machinery, or do other dangerous activities until you know how VIVITROL affects you. VIVITROL may make you feel dizzy and sleepy. **See "What are the possible side effects of VIVITROL?"**

What are the possible side effects of VIVITROL? VIVITROL can cause serious side effects, including:
- **Depressed mood.** Sometimes this leads to suicide, or suicidal thoughts, and suicidal behavior. Tell your family members and people closest to you that you are taking VIVITROL.

You, a family member, or the people closest to you should call your healthcare provider right away if you become depressed or have any of the following symptoms of depression, especially if they are new, worse, or worry you:
- You feel sad or have crying spells.
- You are no longer interested in seeing your friends or doing things you used to enjoy.
- You are sleeping a lot more **or** a lot less than usual.
- You feel hopeless or helpless.
- You are more irritable, angry, or aggressive than usual.
- You are more or less hungry than usual or notice a big change in your body weight.
- You have trouble paying attention.
- You feel tired or sleepy all the time.
- You have thoughts about hurting yourself or ending your life.

- **Pneumonia.** Some people receiving VIVITROL treatment have had a certain type of pneumonia that is caused by an allergic reaction. If this happens to you, you may need to be treated in the hospital. Tell your healthcare provider right away if you have any of these symptoms during treatment with VIVITROL:
  - shortness of breath or wheezing
  - coughing that does not go away
- **Serious allergic reactions**. Serious allergic reactions can happen during or soon after an injection of VIVITROL. Tell your healthcare provider or get medical help right away if you have any of these symptoms of a serious allergic reaction.
  - skin rash
  - swelling of your face, eyes, mouth, or tongue
  - trouble breathing or wheezing
  - chest pain
  - feeling dizzy or faint

Common side effects of VIVITROL may include:

- nausea. Nausea may happen after your first VIVITROL injection and usually improves within a few days. Nausea is less likely with future injections of VIVITROL.
- sleepiness
- headache
- dizziness
- vomiting
- decreased appetite
- painful joints
- muscle cramps
- cold symptoms
- trouble sleeping
- toothache

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the side effects of VIVITROL. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA- 1088.

General information about VIVITROL
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about VIVITROL. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about VIVITROL that is written for health professionals.
For more information about VIVITROL call 1-800-848-4876, Option #1 or go to www.vivitrol.com.

What are the ingredients in VIVITROL?
Active ingredient: naltrexone
Inactive ingredients: polylactide-co-glycolide (PLG)
Diluent ingredients: carboxymethylcellulose sodium, polysorbate 20, sodium chloride, sodium hydroxide and hydrochloric acid as pH adjusters, in water for injection.
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