Hepatic Function Considerations in Patients Using Vivitrol® (naltrexone) for Alcohol Dependency

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Preceptor: Mark Schneiderhan, PharmD, BCPP – Human Development Center; Duluth, MN
Objectives

- Understand the history of Revia® and the basis for hepatic safety concern
- Understand appropriate indications for use/treatment considerations of Vivitrol® (naltrexone) long-acting injection
- Determine the role (if any) of hepatic function testing both at baseline and during treatment with Vivitrol®
- Apply current data and discuss a patient case regarding Vivitrol® use
*Presenters have no association or financial ties to either drug manufacturing company
**Case**

### Demographics
- 53 yo Caucasian male
- 5’11”, 292 lbs, BMI = 40.7

### Diagnoses
- **Schizoaffective disorder, bipolar type**
- **Alcohol use disorder** (drinking 3-4 beers/day)
- **Tobacco use disorder** (smoking 2 ppd)

### Current Medications
- Invega Sustenna 234 mg/1.5 mL IM q 4 wks
- Invega (paliperidone) XR 3 mg tablet QD pm – 3-4 days prior to next injection
- Vivitrol® XR 380 mg IM injection
- Lithium carbonate 300 mg tablet QD – not taking
- Nicotrol 10 mg inhalation cartridge – not using
Timeline

Initial evaluation at HDC
May 6, 2002

Referral to Dr. Schneiderhan for CMM
Drinking 11-14 beers/day

Discussed option of Vivitrol® with NP following visit

June 27, 2018
Vivitrol® recommended at patient visit and LFTs ordered

July 18, 2018
NP prescribes Vivitrol®

August 6, 2018
Received first Vivitrol® injection

August 29, 2018

Most recent visit
Currently drinking 3.5 beers/day

June 12, 2019
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Annual</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>3.6</td>
<td>pending</td>
<td>3.5-5 g/dL</td>
</tr>
<tr>
<td>Total protein</td>
<td>6.6</td>
<td>pending</td>
<td>4-8 g/ dL</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>64</td>
<td>pending</td>
<td>45-122 U/L</td>
</tr>
<tr>
<td>Aspartate transaminase (AST)</td>
<td>15</td>
<td>pending</td>
<td>10-40 U/L</td>
</tr>
<tr>
<td>Alanine transaminase (ALT)</td>
<td>30</td>
<td>pending</td>
<td>18-65 U/L</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.8</td>
<td>pending</td>
<td>0.2-1 mg/dL</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>0.2</td>
<td>pending</td>
<td>0-0.2 mg/dL</td>
</tr>
</tbody>
</table>
Questions to Consider

- Are baseline hepatic function tests (i.e. ALT, AST, GGT, total bilirubin) needed prior to Vivitrol® treatment initiation?
  - If so, what implications does this have on overall treatment?

- Should there be routine hepatic function monitoring in patients taking Vivitrol®?
  - If so, how frequently should monitoring occur?
Background of Hepatic Safety

- **Revia® (oral naltrexone)**
  - FDA approved for opioid dependency (1984)\(^1\)
  - FDA approved for alcohol dependency (1994)\(^1\)

- Following the New Drug Application, indications of obesity and senile dementia were explored; however high dosages 6x greater than recommended (300 mg/day) lead to hepatic injury\(^2\)

**BLACK BOX WARNING: Hepatotoxicity**

"Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses and is contraindicated in acute hepatitis or liver failure"
## Indications for Use

<table>
<thead>
<tr>
<th>Alcohol dependence (2006)</th>
<th>Opioid antagonist with highest affinity for the mu opioid receptor</th>
</tr>
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<tbody>
<tr>
<td>Opioid dependence (2010)</td>
<td>380 mg IM gluteal injection every 4 weeks</td>
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</table>

## Mechanism of Action

- Opioid antagonist with highest affinity for the mu opioid receptor

## Dosing

- 380 mg IM gluteal injection every 4 weeks

## Adverse Effects

- Injection site reactions
- Dizziness
- Fatigue
- Decreased appetite
- Nausea/vomiting

## Precautions & Contraindications

- Concomitant use of opioid analgesics
- Major depression or suicidality
# Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th><strong>Revia®</strong></th>
<th><strong>Vivitrol®</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>96% absorbed from GI tract</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; peak 2 hours post injection</td>
</tr>
<tr>
<td></td>
<td>Peak levels of both naltrexone and 6β-naltrexol within 1 hour of dose</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; peak 2-3 days post injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total exposure 3-4 fold higher</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Low protein binding (21%)</td>
<td>Low protein binding (21%)</td>
</tr>
<tr>
<td></td>
<td>Volume of distribution = 1,350 L</td>
<td>Volume of distribution = 1,350 L</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Primary metabolite = 6β-naltrexol</td>
<td>Primary metabolite = 6β-naltrexol</td>
</tr>
<tr>
<td></td>
<td>Subject to 1&lt;sup&gt;st&lt;/sup&gt; pass metabolism</td>
<td>CYP450 system not involved</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Occurs primarily via urine</td>
<td>Occurs primarily via urine</td>
</tr>
<tr>
<td></td>
<td>$T_{1/2} = 4$ hours (metabolite = 13 hours)</td>
<td>$T_{1/2} = 5-10$ days</td>
</tr>
</tbody>
</table>
Mean naltrexone concentration-time profiles following the administration of monthly IM Vivitrol® or daily PO Revia®

https://www.vivitrolhcp.com/dosing-and-administration
The Evidence

Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence: A Randomized Control Trial

- Double-blind, placebo controlled trial, 6 months
- Primary outcome: event rate of heavy drinking days
- Patients experienced a 25% and 17% greater reduction in heavy drinking rates with XR-NTX 380 mg and XR-NTX 190 mg, respectively when compared to placebo
- Statistically significant adverse effects (secondary outcome): nausea, fatigue, decreased appetite, dizziness, injection site pain
The Evidence

Hepatic Safety of Once-Monthly Injectable Extended-Release Naltrexone Administered to Actively Drinking Alcoholics

- Post-hoc analysis of randomized control trial data
- Patients with mental health diagnoses excluded*
- Measured LFTs at baseline and every 4 weeks during the 6-month treatment period
- No significant differences in AST, ALT, or bilirubin at any timepoint throughout the study
- Significantly lower GGT levels in XR-NTX 380 mg group at weeks 4, 8, 12, and 20 (p <0.05)
- Subgroup analysis → patients drinking heavily throughout treatment
  - Suggests that medication doesn’t interact with alcohol to promote hepatotoxicity
Current Guidance

- **Substance Abuse and Mental Health Services Administration (SAMHSA)**
  - Constant LFT monitoring not recommended
  - Practitioners should not delay treatment to test for liver disease first

- **Providers Clinical Support System (PCSS)**
  - Baseline LFTs unnecessary and may delay treatment
  - No evidence to support frequency of monitoring LFTs
Referral to Dr. Schneiderhan for CMM
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Discussion of Case

- Special considerations:
  - Ambivalence and somatic thoughts towards medications and side effects
    - Notice treatment delay of ~1 month
  - Mental health conditions
    - Excluded population in clinical trials

- Alcohol Consumption:
  - Prior to Vivitrol® initiation: 11-24 beers/day
  - 10 month post-Vivitrol® initiation: 3.5 beers/day

- PHQ-9 Assessment:
  - Prior to Vivitrol® initiation: 24 Severe depression
  - 10 month post-Vivitrol® initiation: 18 Moderately severe
Practice Question #1

1. Where did the concern of hepatotoxicity arise from that led to naltrexone’s black box warning?
   a) Safety data from the clinical trials of Revia®
   b) Studies exploring alternate indications in which doses 6x greater than the FDA recommended dose were used
   c) Case reports of hepatotoxicity in the post-market phase of Vivitrol®
   d) There isn’t a black box warning for naltrexone
1. Where did the concern of hepatotoxicity arise from that led to naltrexone’s black box warning?

a) Safety data from the clinical trials of Revia®

b) Studies exploring alternate indications in which doses 6x greater than the FDA recommended dose were used

c) Case reports of hepatotoxicity in the post-market phase of Vivitrol®

d) There isn’t a black box warning for naltrexone
2. Which of the following is NOT an important consideration when initiating Vivitrol® extended-release IM injection for the treatment of alcohol dependency?

a) Achieving an opioid-free period of at least 7-10 days
b) Potential for injection site reactions
c) Drug interactions (other than opioids)
d) Monitoring for worsening depression/suicidality
2. Which of the following is NOT an important consideration when initiating Vivitrol® extended-release IM injection for the treatment of alcohol dependency?

a) Achieving an opioid-free period of at least 7-10 days
b) Potential for injection site reactions
c) Drug interactions (other than opioids)
d) Monitoring for worsening depression/suicidality
Practice Question #3

3. Based on current literature, which of the following is the best recommendation regarding LFT monitoring in patients using Vivitrol® for the treatment of alcohol dependency?

a) Baseline LFTs should be ordered prior to initiation; no evidence supports routine monitoring of LFTs thereafter

b) Baseline LFTs should be ordered prior to initiation; LFTs should be monitored annually thereafter

c) Baseline LFTs are unnecessary and may delay treatment; LFTs should be monitored annually following treatment initiation

d) Baseline LFTs are unnecessary and may delay treatment; no evidence supports routine monitoring of LFTs
Answer to Practice Question #3

3. Based on current literature, which of the following is the best recommendation regarding LFT monitoring in patients using Vivitrol® for the treatment of alcohol dependency?

a) Baseline LFTs should be ordered prior to initiation; no evidence supports routine monitoring of LFTs thereafter

b) Baseline LFTs should be ordered prior to initiation; LFTs should be monitored annually thereafter

c) Baseline LFTs are unnecessary and may delay treatment; LFTs should be monitored annually following treatment initiation

d) Baseline LFTs are unnecessary and may delay treatment; no evidence supports routine monitoring of LFTs
Vivitrol® XR 380 mg IM injection can be beneficial for the treatment of alcohol dependence.

Liver function testing at baseline and during treatment with Vivitrol® is unnecessary, as no significant rises in LFTs have been reported following initiation of therapy. This even applies to individuals who continue to actively drink.

Significant adverse effects include nausea, fatigue, decreased appetite, dizziness, and injection site reactions.

Patients should NOT be actively taking opioid analgesic medications.

Patients with major depression/suicidality should be closely monitored for worsening symptoms.
References