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XR Naltrexone What You Need to Know

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Disclosures

- No Conflict of Interest with respect to this talk on naltrexone and XR-naltrexone
- No business relationship with Alkermes
- Office Based Addiction Medicine Private Practice where I use naltrexone, Vivitrol, along with the full spectrum of addiction pharmacotherapy for patients
- Clinical Research and Abuse Liability Consultant at Jazz Pharmaceuticals

Naltrexone

- Non-addictive opiate blocker (antagonist)
- FDA Approved Formulations
  - Oral tablet (Revia®, generics)
  - XR depot injection (Vivitrol®)
- Non-FDA Approved Formulations
  - implantable pellets – made by compounding pharmacies – I have no experience with these

Uses for naltrexone

- In US, Vivitrol® FDA approved to treat alcohol dependence for people who are able to abstain from alcohol
- In US, Vivitrol® FDA approved to prevent relapse to opioid dependence for people who have completed opioid detoxification
- In US, REVIA ® is FDA approved for treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids.
- In Europe, oral naltrexone is used to help people with alcohol dependence to reduce alcohol consumption and stop drinking (Sinclair Method)
- Oral naltrexone shown effective in reducing sugar and carb cravings.
- In US, Contrave® (naltrexone/bupropion) is FDA approved for weight management as part of reduced calorie diet and exercise plan.

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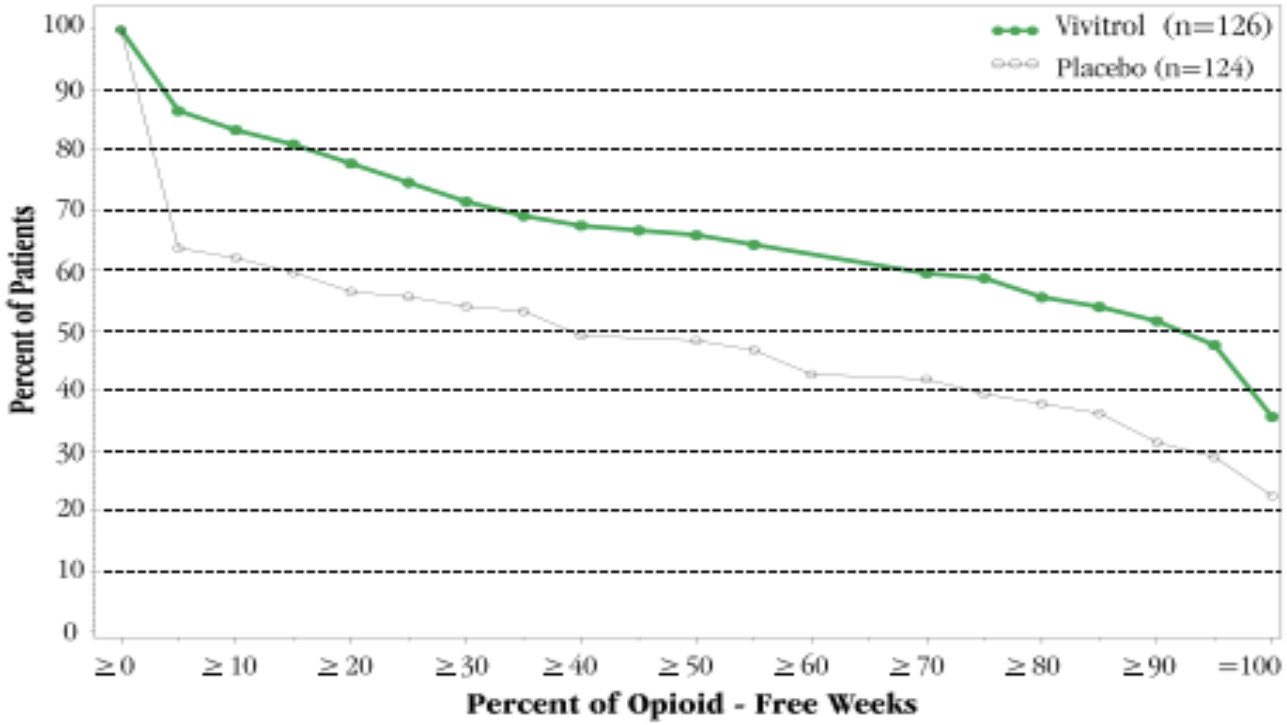
Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the VIVITROL group from Week 5 to Week 24.

Figure 1: Subjects Sustaining Varying Percentages of Opioid-Free Weeks



Before starting XR-naltrexone

- Always discuss all options for opiate and/or alcohol dependence
  - Other medication options
  - Treatment that doesn't involve medication

- Naltrexone is not a stand alone treatment
  - Individual therapy
  - Group therapy
  - Community support group

Before starting XR-naltrexone

Opiate Dependence

- Opiate free prior to 1st dose of oral naltrexone or XR-naltrexone
- No methadone or buprenorphine 7-10 days
- May require medical detox (outpatient vs. inpatient)
- Consider switch long acting to short acting opioid to facilitate transition
- Consider ultra-low dose naltrexone initiation (requires clinical experience)

Advise opiate dependent patient

- Transitioning from Rx opiates to naltrexone will result in temporary withdrawal symptoms
- Switching from buprenorphine or methadone to XR-naltrexone may cause precipitated withdrawal for up to 2 weeks
- We will work to diminish the severity of withdrawal
- Naltrexone will block an opiate's effect to a point – beyond which overdose is still possible
- Opiate tolerance will reduce after naltrexone
- There have been cases of overdose/death when opiates were used towards end of dosing interval or after missing a dose of XR-naltrexone.

Advise alcohol dependent patient

- No alcohol at the time of 1st dose oral or XR-naltrexone
- Naltrexone does NOT diminish adverse effects of alcohol
- Naltrexone does NOT alter/lower BAL if you drink alcohol
- Your thinking, memory, balance, coordination, reflexes are still impaired if you drink alcohol while taking naltrexone
- Do not drink and drive. Do not drink and operate machinery.

Side effects oral naltrexone

- Nausea
- Nausea
- Nausea
- Nausea
- Nausea
- Nausea
- Nausea
- Dizziness, Abdominal cramping, joint or muscle pain/stiffness, Anxiety, Restlessness, Trouble sleeping, fatigue, headache

Most side effects resolve after a few days.

Adverse effects of Vivitrol

- Adverse effects of oral naltrexone plus:
  - Injection site reaction
    - Pain
    - Tenderness
    - Swelling
    - Redness
    - Bruising
    - Itching
    - Hardness/ Scarring
    - Necrosis (tissue death – may require surgery)

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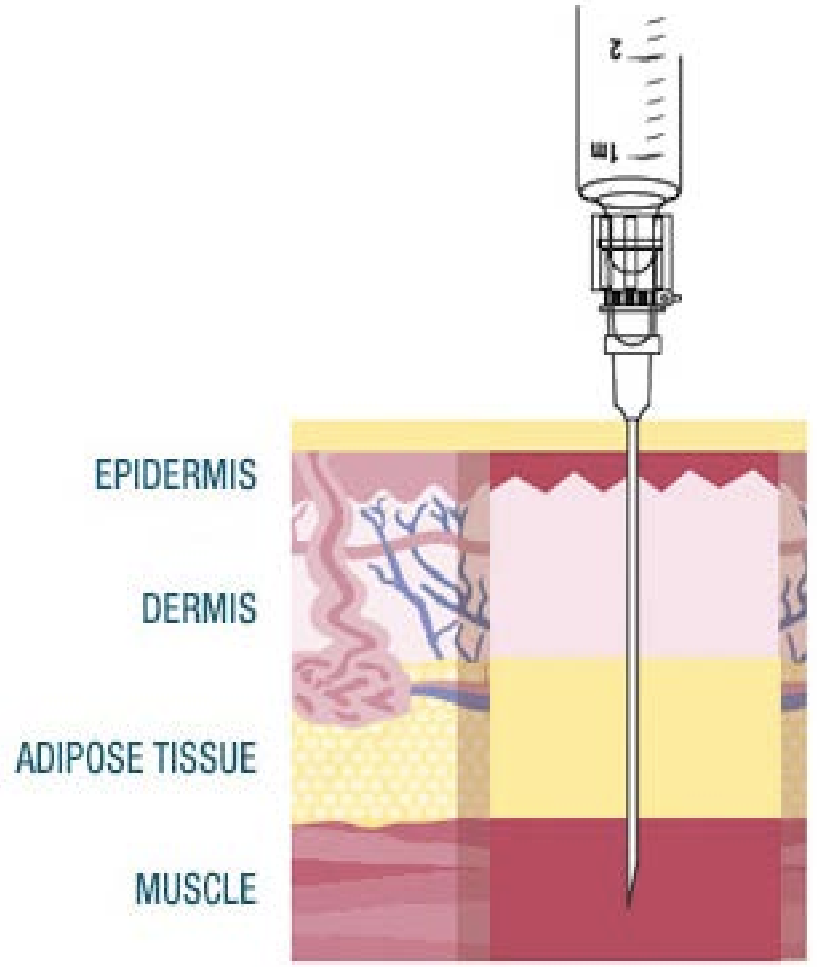
VIVITROL must not be given

- **intravenously**
- **subcutaneously**
- **or into adipose tissue**

Inadvertent subcutaneous injection of VIVITROL may increase the likelihood of severe injection site reactions

Gluteal intramuscular injection of VIVITROL



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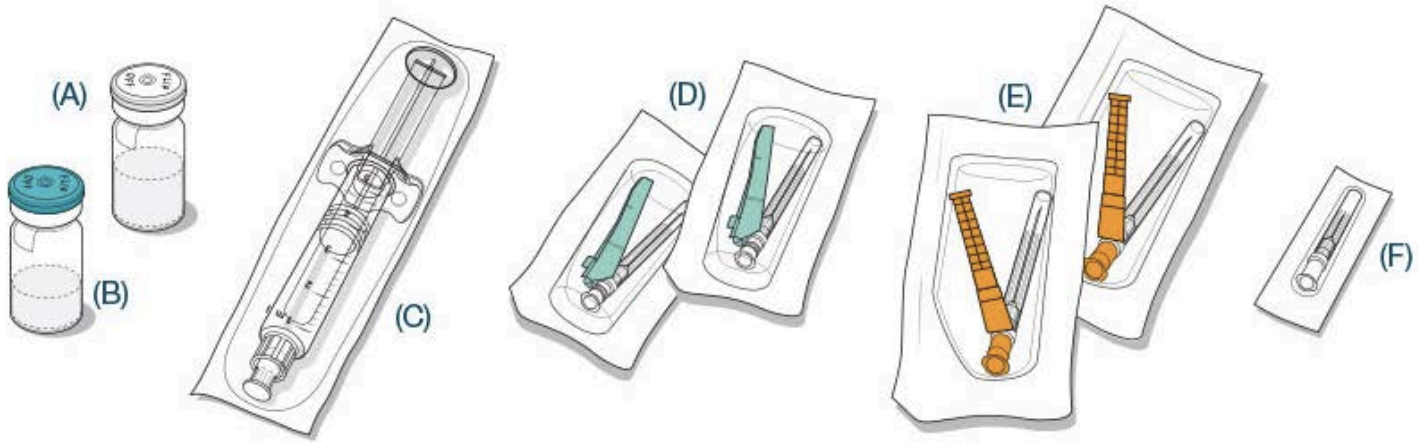
Vivitrol Kit

Each carton of VIVITROL includes:



One - Package Insert/Directions for Use

One - Medication Guide

(A) One - Diluent for the Suspension of VIVITROL Microspheres

(B) One - Vial Containing VIVITROL Microspheres

(C) One - Prepackaged Syringe

(D) Two - TERUMO® 1.5-inch 20G Administration Needles with Aqua Needle Protection Device [one spare]

(E) Two - NEEDLE-PRO® 2-inch 20G Administration Needles with Orange Needle Protection Device [one spare]

(F) One - TERUMO® 1-inch 20G Preparation Needle [Not for Administration]

Administering Vivitrol

- Remove package from refrigerator about 45 min prior to injection. Allow contents to warm to room temperature. (IMPORTANT)
- Prepare patient for injection (prone position, drape, clean injection site –upper outer gluteal location - with alcohol x 3)
- Open kit, remove and tap Vivitrol vial few times on hard surface until microsphere powder freely shifts
- Pop open tops of Vivitrol powder and diluent, wipe tops with alcohol and allow to air dry while prepping syringe
- Kit comes with 3 needle sizes (1”, 1.5”, 2”). Use 1” need to aspirate diluent into the syringe, then inject diluent using same syringe/needle into Vivitrol vial. You will have to shake the vial vigorously to mix suspension. Then aspirate suspension from vial back into same syringe.
- Remove and discard 1” needle, and replace with 2” needle to administer Vivitrol deep IM. If patient is obese and 2” needle is not enough to administer deep IM, don’t do administer it.
- Immediately insert the needle deep IM into injection site, aspirate for blood. If negative, administer 4ml of Vivitrol suspension by smoothly advancing plunger to inject.

Vivitrol injection site reactions

- VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe.
- Injection site reactions not improving may require prompt medical attention, including, in some cases, surgical intervention.
- Select proper needle size for patient body habitus, and use **only** the needles provided in the carton.
- Patients should be informed that any concerning injection site reactions should be brought to the attention of their healthcare provider.

Vivitrol injection site reactions

- Vivitrol injection may be followed by pain, tenderness, swelling, erythema, bruising, or pruritis
- Some ISRs can be very severe
- In clinical trials, 1 patient developed induration that persisted and enlarged after 4 weeks, subsequently developed necrotic tissue, required surgical excision.
- Post-marketing surveillance, more ISRs reported: induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis, some needing surgical debridement.
- Reported cases were primarily in female patients
- Inadvertent subcutaneous injection may increase likelihood of ISR. ONLY USE NEEDLES provided in Vivitrol kit.

Vivitrol AE in opiate dependent people

Adverse events (occurring in ≥2% of patients treated with VIVITROL and at least twice as frequently with VIVITROL than placebo) were:

- Hepatic enzyme abnormalities
- Injection site pain
- Nasopharyngitis
- Insomnia
- Toothache

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AE in >2% of Opioid Dependent People on Vivitrol

	VIVITROL 380 mg with psychosocial support (n=126)	Placebo with psychosocial support (n=124)
Alanine aminotransferase increased	13%	6%
Aspartate aminotransferase increased	10%	2%
Gamma-glutamyltransferase increased	7%	3%
Nasopharyngitis	7%	2%
Insomnia	6%	1%
Influenza	5%	4%
Hypertension	5%	3%
Injection site pain	5%	1%
Toothache	4%	2%
Headache	3%	2%

Naltrexone and Liver Injury

- Oral naltrexone and Vivitrol is not indicated with acute hepatitis or liver failure
- Naltrexone is metabolized in the liver.
  - Pharmacokinetics of Vivitrol not altered in mild to moderate hepatic impairment (Child-Pugh A & B class)
  - Dose adjustment of Vivitrol is not required in mold or moderate hepatic impairment
- In excessive doses, oral naltrexone itself can cause liver injury
- It can also cause liver injury in people who develop liver disease from other causes.
- Hepatitis and clinically significant liver dysfunction have been observed with VIVITROL
- I check Comprehensive Metabolic Panel with liver function tests at baseline.
- Depending on the clinical situation, I usually re-check at 3 months and every 6 months thereafter.

Naltrexone and Depression

- Blocking endogenous opiates may aggravate clinical depression or unmask a subclinical depression.
- Always assess for depression at baseline
- From my clinical experience, most patients actually feel significantly improved mood when they stop using and stabilize in recovery.
- But some patients may need some mood support.
- If there is depression at baseline, I will offer depression treatment (medication, psychotherapy, adjuvant therapy) along with naltrexone and monitor closely.
- Vivitrol should always be part of a comprehensive treatment plan that includes psychosocial support

Naltrexone and Depression

Adverse Events of a Suicidal Nature in Opiate Dependent Patients

24-week Placebo Controlled Study of Vivitrol in Russia (n=250)

- No reported adverse events involving depressed mood or suicidal thinking in either Vivitrol or Placebo group

Open Label, Long Term Safety Study in US

- 5% of patients on Vivitrol (n=101)
- 10% of patients on oral naltrexone (n=20)

Naltrexone and Pain Management

- Do not use oral naltrexone or VIVITROL if opioid analgesia is necessary

WHAT IF YOU'RE ALREADY ON NALTREXONE AND YOU NEED TO HAVE SURGERY?

- If planned surgery, then stop naltrexone
- When? Depends on pharmacokinetics...

Pharmacokinetics of REVIA (oral naltrexone)

- Oral absorption ranges between 5% - 40%
- Elimination half-life of naltrexone = 4 hours
- Elimination half-life of 6-β-naltrexol = 13 hours
- Naltrexone is out of your system in 1 day
- 6-β-naltrexol is out of your system in 3 days

Vivitrol pharmacokinetics

VIVITROL is designed to continuously release naltrexone for 28 days or 1 month.

What happens after a single Vivitrol IM injection?

- Initial transient peak plasma level at 2 hours
- Second plama peak approximately 2-3 days later
- Plasma concentrations slowly decline starting 14 days
- Plasma level still measurable for more than 1 month

Vivitrol pharmacokinetics

Total naltrexone exposure is 3 to 4-fold higher following VIVITROL 380 mg IM vs. oral naltrexone 50 mg/day for 28 days

Steady state is reached at the end of the dosing interval following the first injection.

As with oral naltrexone, there is minimal naltrexone accumulation with Vivitrol

Vivitrol Pharmacokinetics

How long will the XR-naltrexone (VIVITROL) stay in my system?

- Elimination of naltrexone and metabolites occurs primarily via urine
- Elimination half life of naltrexone following VIVITROL administration is 5-10 days (depends on erosion of the polymer matrix)
- With normal kidney function, VIVITROL (naltrexone) washed out at 50 days

Pain Management on Vivitrol

So what do you do for the opiate dependent patient on Vivitrol who needs emergency surgery?

Vivitrol and Pain Management

When Reversal of VIVITROL Blockade Is Required for Pain Management: For VIVITROL patients in emergency situations, suggestions for pain management include regional analgesia or use of non-opioid analgesics.

If opioid therapy is required to reverse the VIVITROL blockade, patients should be closely monitored by trained personnel in a setting staffed and equipped for CPR.

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Conclusions

- Both IR naltrexone and XR naltrexone (Vivitrol) are effective tools in the addiction medicine toolbox
- Appropriate patient selection and education is critical to successful outcomes with either modality
- Treatment initiation can be complicated
- Either modality should be part of a comprehensive treatment program including psychosocial support (individual/group therapy, community support group) and adjuvant therapy (nutrition, exercise, meditation)
- Ongoing regular medical monitoring is requisite

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