The case of Brutus – Starting XR-Naltrexone

September 26, 2018 VIP Chat

Noon-12:30 MST

Adam Gordon, Discussant

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Vulnerable Veteran – Innovative PACT (VIP) & VIP Chats

- **VIP Goal:**
  - The VISN 19 VIP (Vulnerable Veteran – Innovative PACT) Initiative's over-arching goal is to **improve the health of veterans who are particularly vulnerable due to medical disease and/or their social determinants in primary care environments**
  - Veterans served by this Initiative include those with unhealthy alcohol and drug use, co-occurring pain and/or addiction disorders, social determinants of health including homelessness, and those who frequently use health care services
- **VIP "Chat" Goal:**

  To provide education, mentorship, and foster a learning collaborative to improve the knowledge and skills of health care providers in VISN 19
- The chats are generally scheduled for the **4th Wednesday of each month**
- All health care providers are welcome to join! – ***FUN***!
- Please note this presentation is ***recorded and archived***
  - VIP sharepoint site (VA only): www.tinyurl.com/vip-initiative

Disclosures and Acknowledgements

- I have no personal fiduciary conflicts of interest
- I work full time for the Salt Lake City VA Health Care System and the University of Utah
- The views expressed in this presentation are solely my own and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government or any other university or organization

- The VIP Initiative and these “chats” are sponsored by VA’s Veteran Integrated Service Network 19 (VISN 19) and the VA Salt Lake City Health Care System

AGENDA

- Introduction and Case (10 minutes)
- “Bite Sized Teach” (BST or “Beast Mode”) (15 minutes)
- Discussion (5 minutes)
  - Extended discussion (optional) (30 minutes)

youtu.be/dJ_8QmHlNPw.medicine.emory.edu/education/academy-of-medical-educators/bst-mode.html

TODAY's GOALs

- Be able to identify patients who may be appropriate for use of naltrexone in the treatment of opioid use disorder
- Understand the pitfalls and successes of the use of naltrexone for the treatment of patients with opioid use disorder and how to start it

CASE: Brutus

- Brutus is a 34 year old male Veteran who presents to your primary care clinic
- He is new to you
- He has a history of lower back pain
- Two years ago - received a prescription of Percocet
- He readily admits that he has misused the Percocet:

"I used the medications to feel 'good', but not for my back pain – they just made me feel normal. I really don't think I need them for the back pain. I sometimes take them just to take them. I really don't have any withdraw or problems, but they are like candy to me."

CASE: Brutus

- He further relates:

  “Doc, I think I want to come off the Percocet. I am sometimes popping pills at work. My boss caught me the other day and I don’t want to lose my job.

  I take these pills so sporadically. Its not a daily thing.

  I heard there was a shot I could get to help me not take these pills.

  Can you give it to me?”

CASE: Brutus history

- **Past Medical History:**
  - Nicotine use disorder – he smokes ½ pack per day
- **Social history:**
  - Was in the Marines
  - Married with 5 children
  - Works in construction
- **Family history:**
  - Children, family, and extended family alive and well

CASE: Brutus Medications/Studies

- **Allergies:**
  - None
- **Medications:**
  - Percocet 1 tablet every 6 hours PRN for pain
- **Labs/Studies:**
  - Urine drug screen:
    - Morphine **negative**
    - Cocaine **negative**
    - Amphetamine **negative**
    - 6-AM **negative**
    - Marijuana **negative**
    - Oxycodone **Positive**

CASE: Brutus conundrums

- You diagnose the patient with mild opioid use disorder
- You contemplate starting XR-Naltrexone, but wonder:
  - Is this patient appropriate for this treatment?
  - How do you actually start him on this medication?
    - Won’t he go through withdrawal?

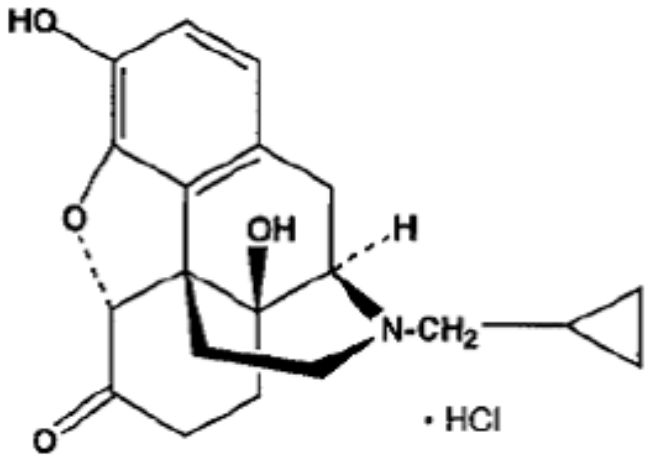
TODAY's GOALs

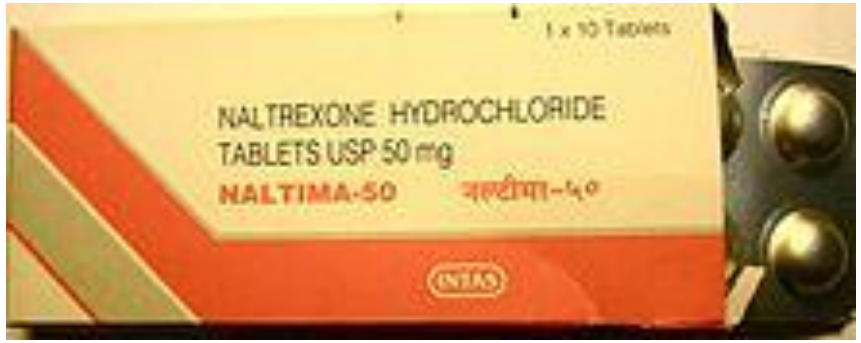
- Be able to identify patients who may be appropriate for use of naltrexone in the treatment of opioid use disorder
- Understand the pitfalls and successes of the use of naltrexone for the treatment of patients with opioid use disorder and how to start it

Naltrexone for opioid use disorder

- Oral naltrexone approved in 1984
- Injectable naltrexone approved in October 2010
  - Allows steady state of medication for 4 weeks
  - Improves compliance
  - Preferred

Oral Naltrexone





www.medscape.org/viewarticle/552196

Oral Naltrexone

- Naltrexone hydrochloride tablets are an opioid antagonist
  - is a synthetic congener of oxymorphone with no opioid agonist properties
  - Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group.
- It is a white, crystalline compound
  - Naltrexone is available in scored film-coated tablets containing 50 mg of naltrexone hydrochloride

Naltrexone for OUD: Advantages

- Able to be prescribed by any provider
  - No waiver required! (BUP)
  - No program required! (BUP or Methadone)
- No special training required
- Able to be prescribed by non-physicians
- Not an addictive substance
  - No abuse potential
- Cheap: oral
- Reduce admissions, ER visits, other costs

Comer SD 2006; Baser O 2011

Oral Naltrexone for Opioid Use Disorder

- Treatment should be initiated with an initial dose of 25 mg of naltrexone
  - If no withdrawal signs occur, the patient may be started on 50 mg a day thereafter
- A dose of 50 mg once a day will produce adequate clinical blockade of the actions of parenterally administered opioids
- As with many non-agonist treatments for addiction, Naltrexone is of proven value only when given as part of a comprehensive plan

Oral Naltrexone – Reported Side Effects

- Blurred vision or eye problems
- Tachycardia
- Mood changes
- hallucinations
- Confusion
- Nausea
- stomach pain
- low fever
- loss of appetite
- dark urine
- clay-colored stools
- jaundice

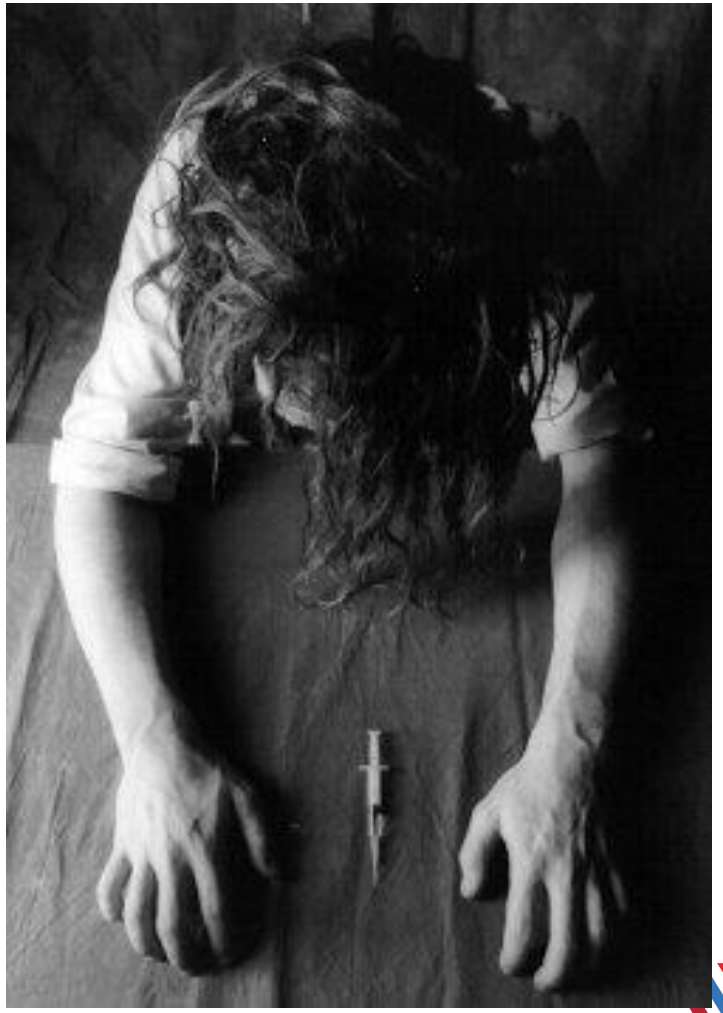
CONTRAINDICATION:

Current or recent use (in the last 7 to 14 days) of any opioid

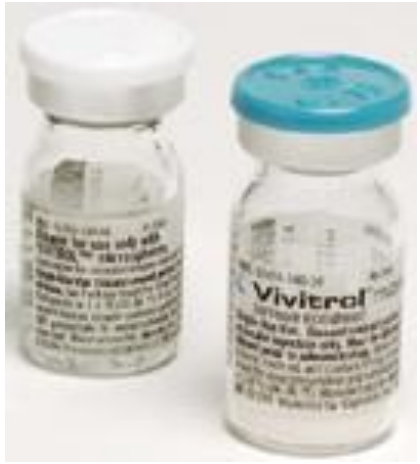
- why?

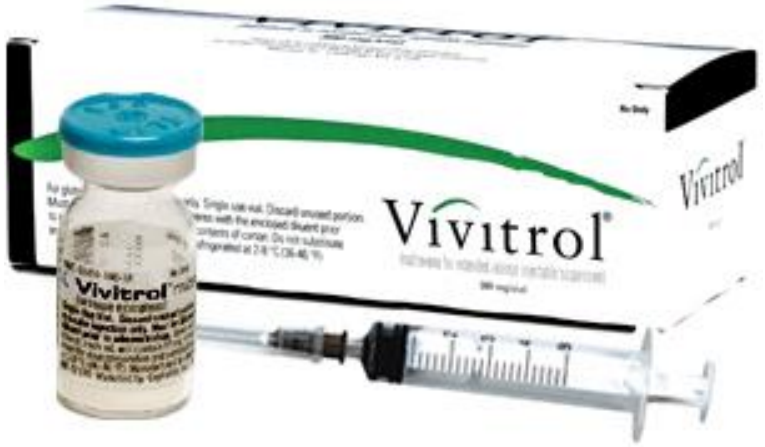
Opioid Withdrawal Syndrome

- Severe flu-like symptoms including shaking chills
- Anxiety
- Hyperactivity
- Drooling
- Lacrimation/tearing
- Rhinorrhea
- Nausea and Vomiting
- Anorexia
- Diarrhea
- Myalgias and Muscle spasms



Injectable Naltrexone





www.medscape.org/viewarticle/552196

Evidence for injectable naltrexone

ORIGINAL ARTICLE

Injectable, Sustained-Release Naltrexone for the Treatment of Opioid Dependence

A Randomized, Placebo-Controlled Trial

Sandra D. Comer, PhD; Maria A. Sullivan, MD, PhD; Elmer Yu, MD; Jami L. Rothenberg, PhD; Herbert D. Kleber, MD; Kyle Kampman, MD; Charles Dackis, MD; Charles P. O'Brien, MD

- RCT, double blind, placebo controlled
  - Placebo, 192mg or 384 mg of depot naltrexone (1 &5)
  - 2x weekly relapse prevention therapy, UDS
- 60 patients with heroin, physical dependence
- Main outcome: retention in treatment, % opioid free urine

Comer SD 2006

Evidence for injectable naltrexone

- Retention in treatment was dose related
  - 39% (placebo)
  - 60% and 68% (192mg and 385mg)
- Time to drop out (and UDS) had a significant main effect of dose
  - 27, 36, 48 days
- Well tolerated

Comer SD 2006

Evidence for injectable naltrexone

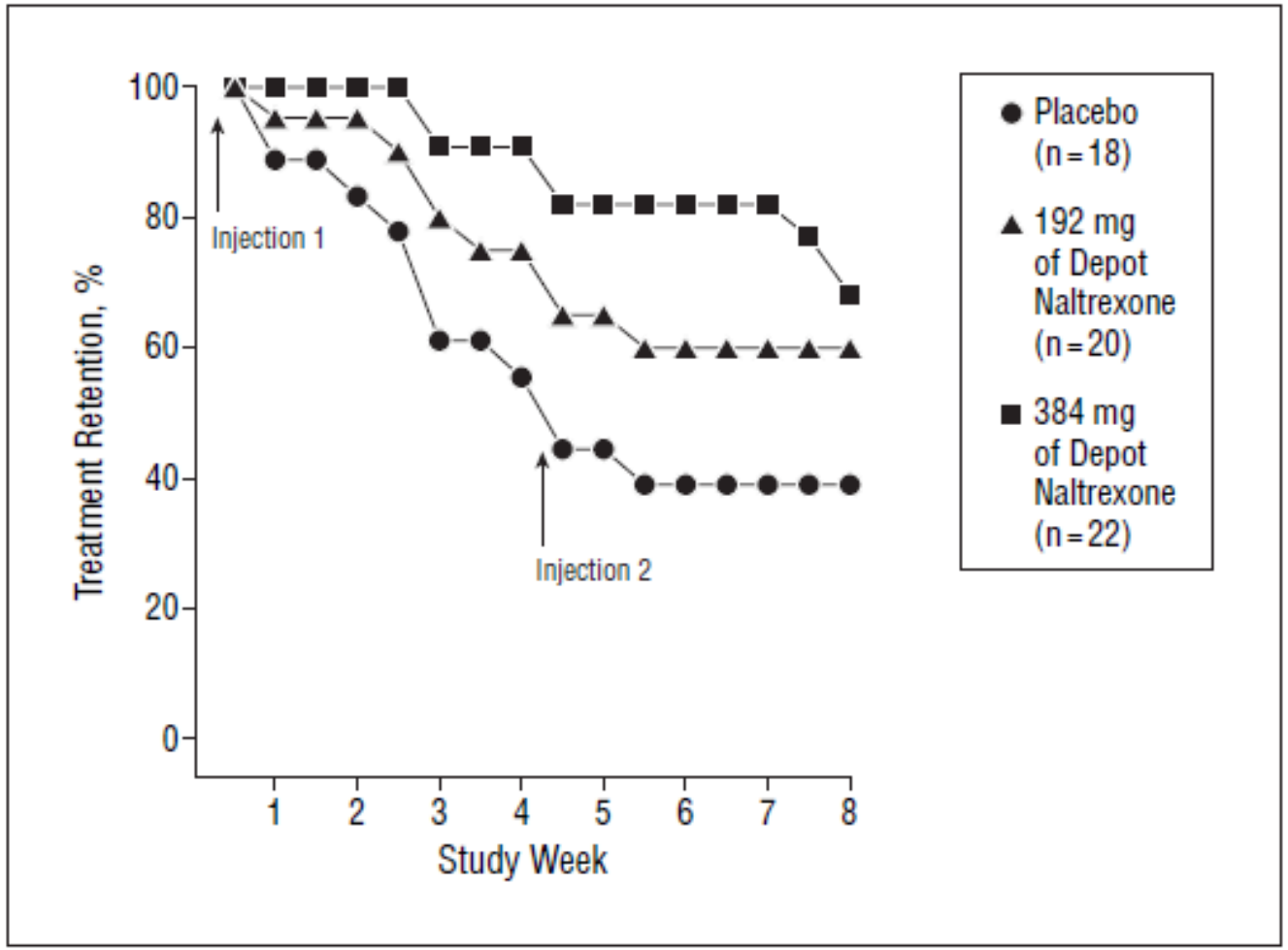


Figure 2. Retention in treatment by study week and treatment group.

Comer SD 2006

Evidence for injectable naltrexone

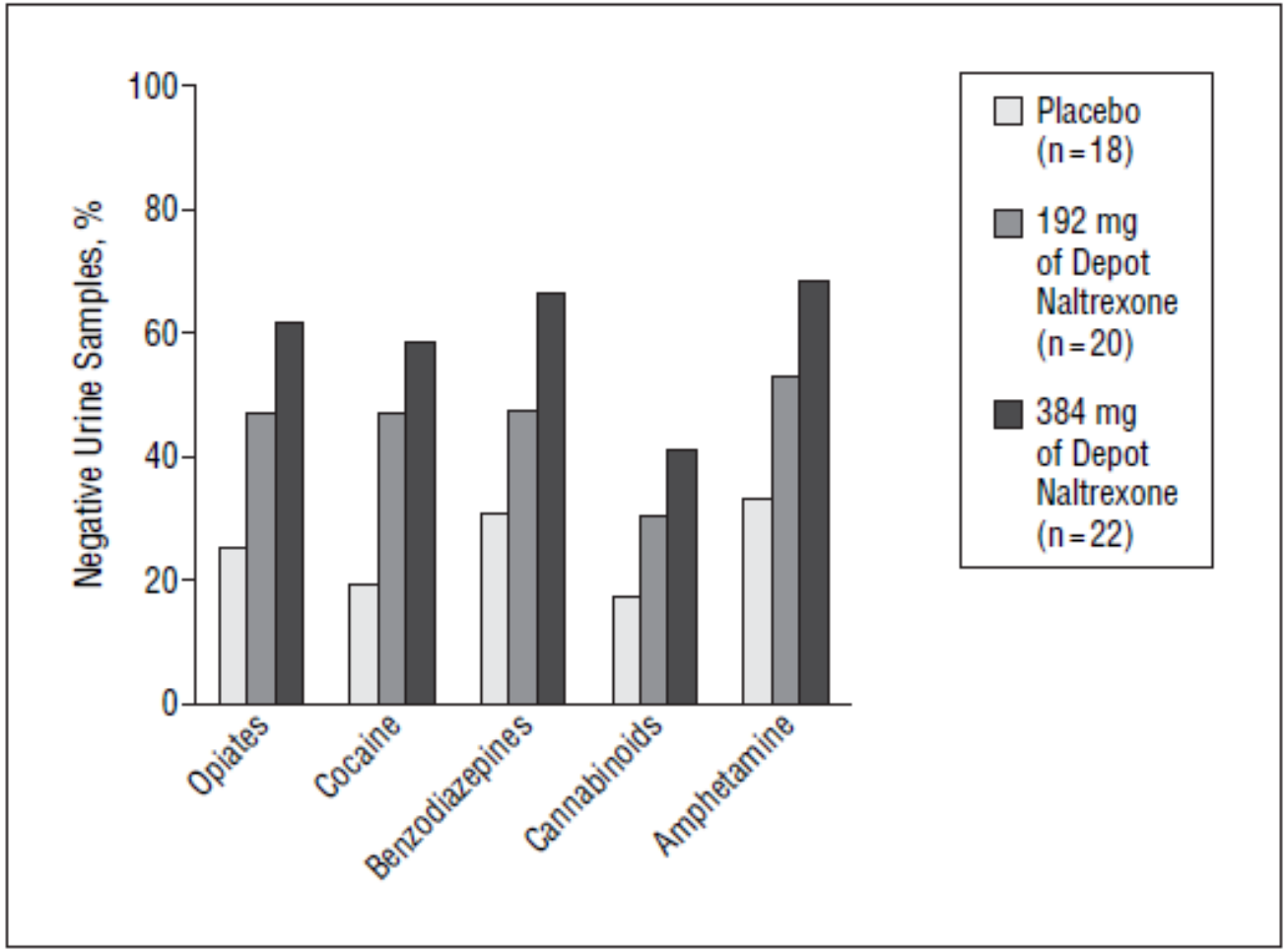


Figure 3. Percentage of urine samples negative for various drugs of interest. Missing urine samples were considered positive.

Comer SD 2006

Evidence for injectable naltrexone

Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial

Evgeny Krupitsky, Edward V Nunes, Walter Ling, Ari Illeperuma, David R Gastfriend, Bernard L Silverman

- Double blind, placebo controlled, RCT, 24 weeks
  - 380 mg IM naltrexone vs. placebo
  - 12 bi-weekly counselling sessions
  - 250 patients at 13 sites
- Outcomes: confirmed abstinence (UDS/self report), opioid free days, craving, retention, relapse

Krupitsky E, 2011

Evidence for injectable naltrexone

- Confirmed Abstinence:
  - 90.0% naltrexone(69.9-92.4)
  - 30.0% in placebo (11.4-63.8)
- Opioid Free days (median)
  - 99.2% naltrexone(89.1-99.4)
  - 60.4% in placebo (4632-94.0)
- Craving (-10.1 vs. 0.7)
- Retention (168 days vs. 96 days)
- Well tolerated

Krupitsky E, 2011

Evidence for injectable naltrexone

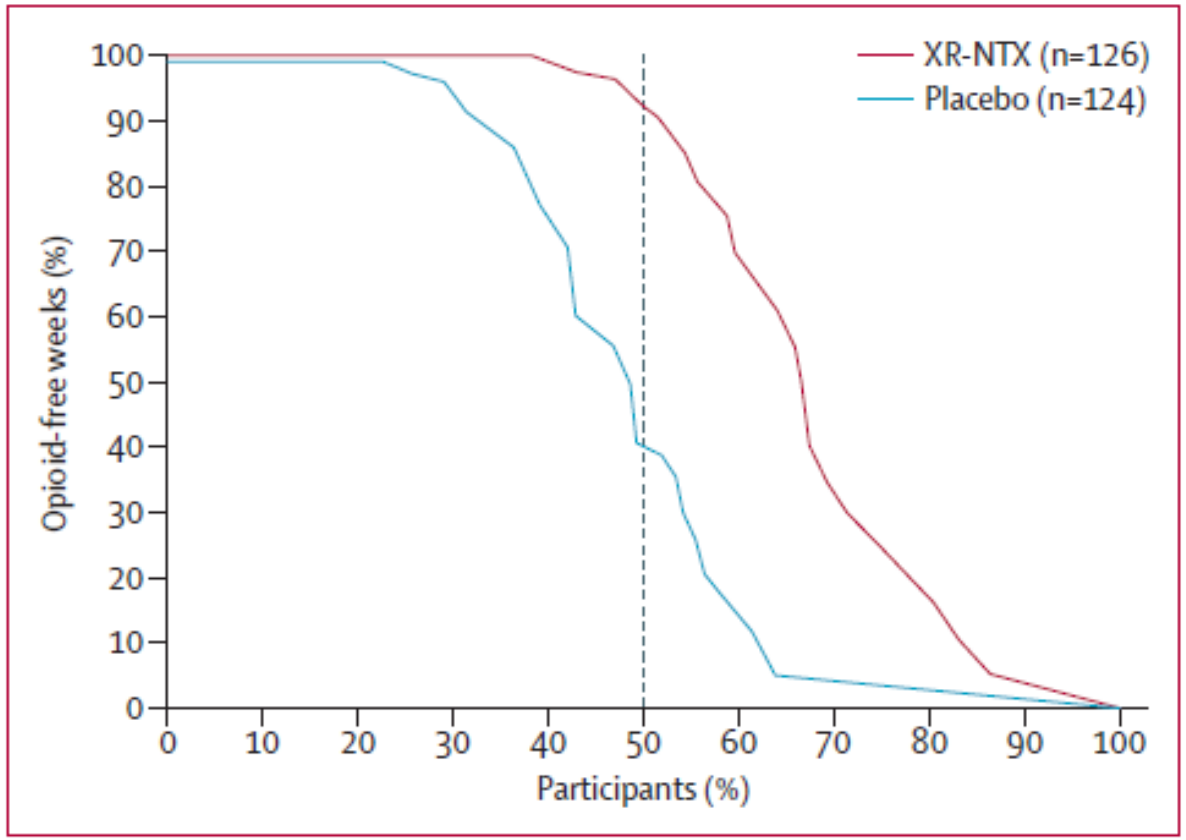
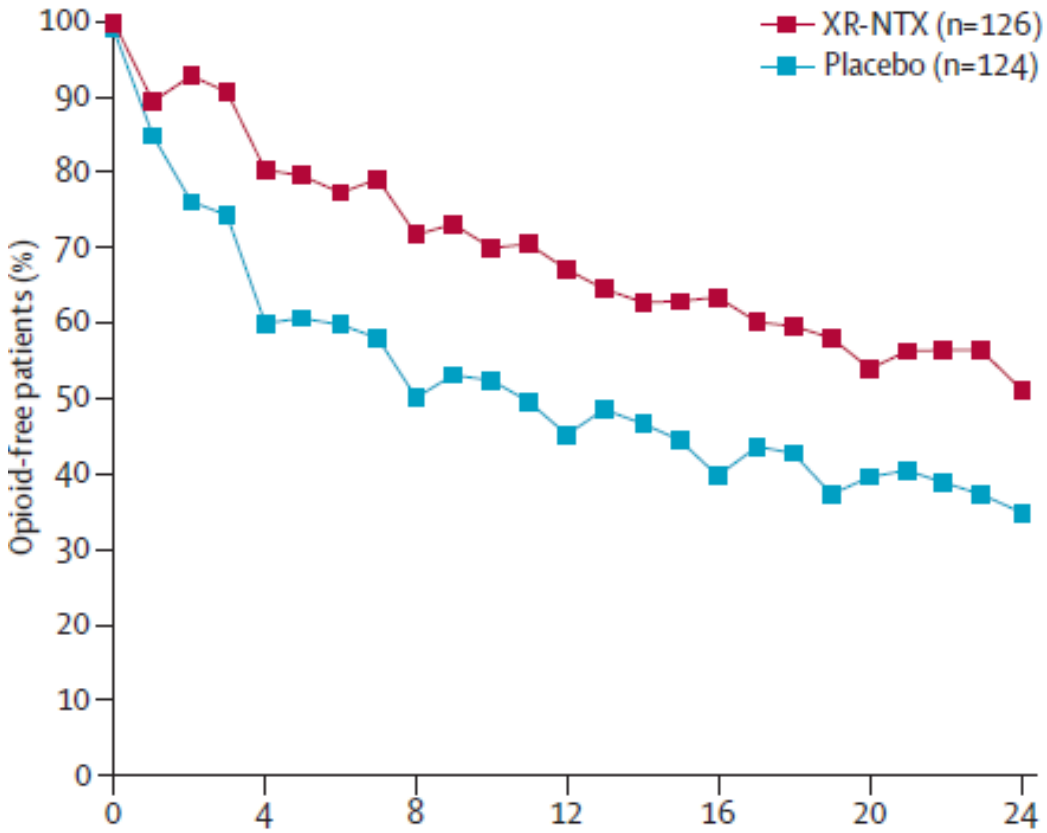
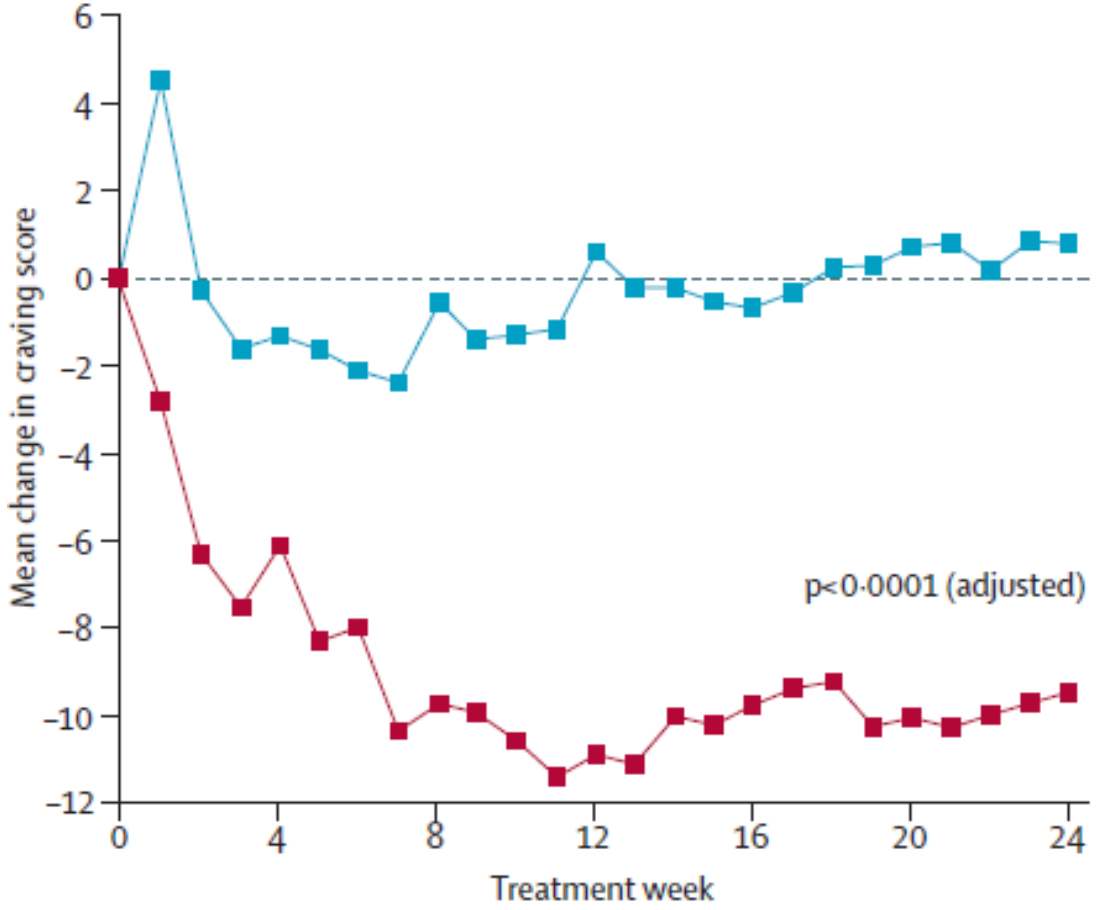


Figure 2: **Percent of confirmed opioid-free weeks (cumulative) among participants treated with XR-NTX compared with placebo**
XR-NTX=extended-release naltrexone.

Krupitsky E, 2011

Evidence for injectable naltrexone





Krupitsky E, 2011

Risks Associated with IM Naltrexone for OUD treatment

- *Risk of accidental opioid overdose*
  - Used opioids at or near the end of the 1 month dosing interval
  - Used opioids after missing a dose of extended-release injectable naltrexone
  - Attempted to overcome the opioid blockade
  - Patients on naltrexone may have reduced tolerance to opioids
    - May then have increased sensitivity to injected opioids
- Counter:
  - education, relapse prevention plan, consider opioid agonists
  - Dose more frequently than every 4 weeks

Bisaga A 2011; Gibson AE 2007

Risks Associated with IM Naltrexone for OUD treatment

- *Risk of precipitated withdrawal*
  - Complete detoxification may not have occurred
    - Generally 7-10 days from any opioid use
- *Adverse events*
  - *Injection site reactions*
    - *Intramuscular gluteal muscle*
    - *Alternate buttocks*
    - *Both 1.5 and 2 inch needles can be used*
  - *Liver adverse effects*
    - *If received more than 5 fold normal dose*

	XR-NTX (n=126)	Placebo (n=124)	p value
Nasopharyngitis	9 (7%)	3 (2%)	0·14
Insomnia	8 (6%)	1 (1%)	0·036
Hypertension	6 (5%)	4 (3%)	0·75
Influenza	6 (5%)	5 (4%)	>0·99
Injection site pain	6 (5%)	1 (1%)	0·12
Toothache	5 (4%)	2 (2%)	0·45
Headache	4 (3%)	3 (2%)	>0·99
≥1 adverse event	63 (50%)	40 (32%)	0·005
≥1 drug-related adverse event	33 (26%)	12 (10%)	0·001
≥1 serious adverse event*	3 (2%)	4 (3%)	0·72
Discontinued owing to adverse events	2 (2%)	2 (2%)	..

Data are number (%). XR-NTX=extended-release naltrexone. *Three patients in the XR-NTX group reported four serious adverse events (infectious processes, eg, AIDS or HIV) and four patients in the placebo group reported five serious adverse events (two infectious, one drug dependence, one psychotic disorder, and one peptic ulcer).

Table 3: **Clinical adverse events**

Krupitsky E, 2011

Who are good patients for IM naltrexone?

1. People who have not had treatment success with opioid agonists
2. People who have a high level of motivation for abstinence
3. People on agonists who wish to change their medication
4. Adolescents or young adults with opioid use disorder
5. People with short or less severe history of physical opioid dependence
6. Preferred:
   - Professional boards
   - Supervisors
   - Drug court judges
   - Military

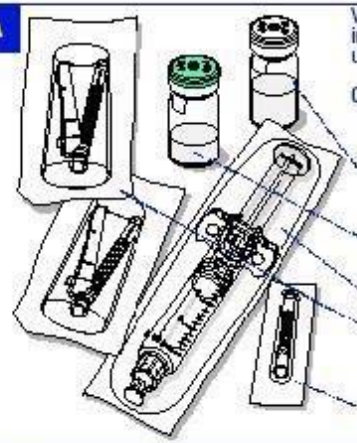
Other Considerations - Injectable Naltrexone

- Wear medical alert card and/or notification
- The efficacy of extended release naltrexone has been shown only in conjunction with behavioral support
  - It has not been studied as a SOLE treatment
- Behavioral Therapies
  - Individual counseling
  - Group counseling
  - Brief Interventions

Directions for Use:
To ensure proper dosing, it is important that you follow the preparation and administration instructions outlined in this document.

Product to be prepared and administered by a healthcare professional.
Do not substitute carton components.
Keep out of reach of children.
Prepare and administer the VIVITROL suspension using aseptic technique.

A



VIVITROL (naltrexone for extended-release injectable suspension) is supplied in single use cartons.

Carton Contents:

- 1 - Package Insert / Directions for Use
- 1 - Patient Package Insert
- 1 - Diluent for the Suspension of VIVITROL Microspheres
- 1 - Vial Containing VIVITROL Microspheres
- 1 - Prepackaged Syringe
- 2 - 1½ inch 20G Administration Needles with Safety Device [one spare]
- 1 - ½ inch 20G Preparation Needle [Not For Administration]

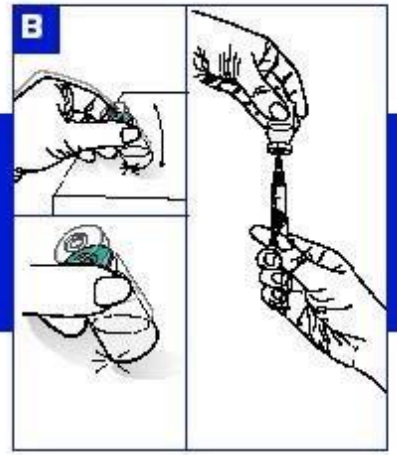
THE CARTON SHOULD NOT BE EXPOSED TO TEMPERATURES EXCEEDING 25 °C (77 °F).

VIVITROL must be suspended only in the diluent supplied in the carton, and must be administered with the needle supplied in the carton. Do not make any substitutions for components of the carton.

The entire carton should be stored in the refrigerator (2-8 °C, 36-46 °F). Unrefrigerated, VIVITROL Microspheres can be stored at temperatures not exceeding 25 °C (77 °F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25 °C (77 °F). VIVITROL should not be frozen.

Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

B



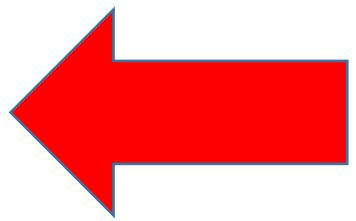
1. Remove the carton from refrigeration. Prior to preparation, allow drug to reach room temperature (approximately 45 minutes).

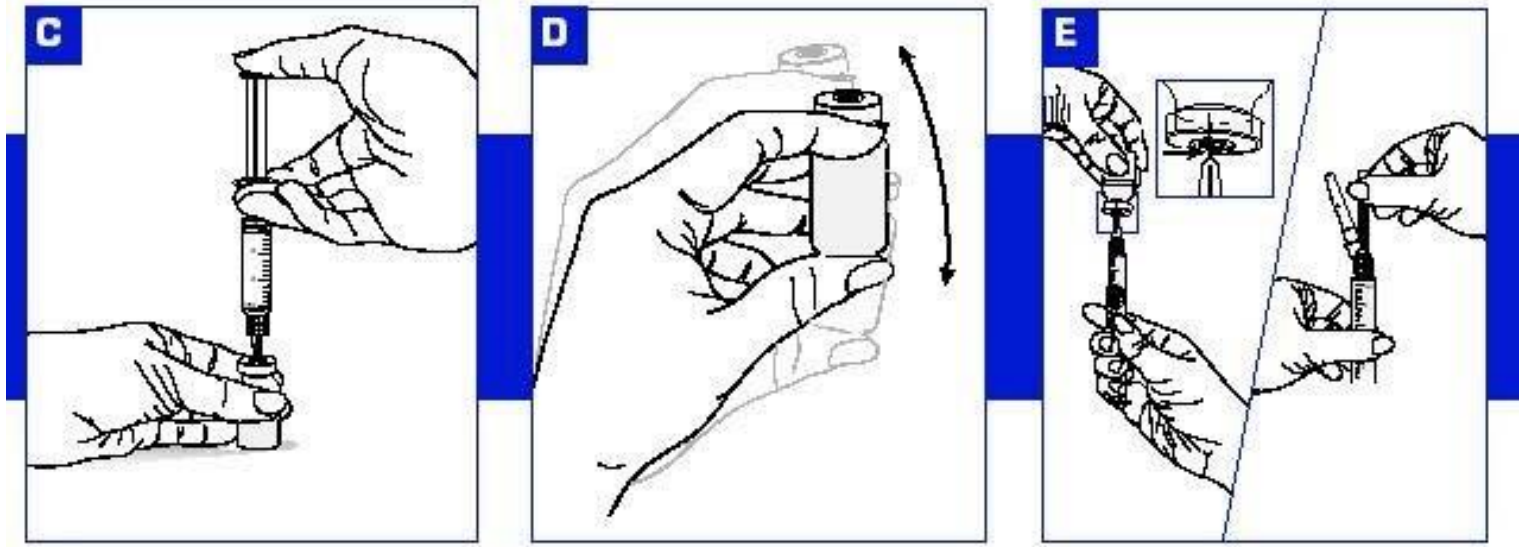
2. To ease mixing, firmly tap the vial on a hard surface, ensuring the powder moves freely. (see Figure B)

3. Remove flip-off caps from both vials. DO NOT USE IF FLIP-OFF CAPS ARE BROKEN OR MISSING.

4. Wipe the vial tops with an alcohol swab.

5. Place the ½ inch preparation needle on the syringe and withdraw 3.4 mL of the diluent from the diluent vial. Some diluent will remain in the diluent vial.
(see Figure B)





Inject the 3.4 mL of diluent into the VIVITROL Microsphere vial. (see Figure C)

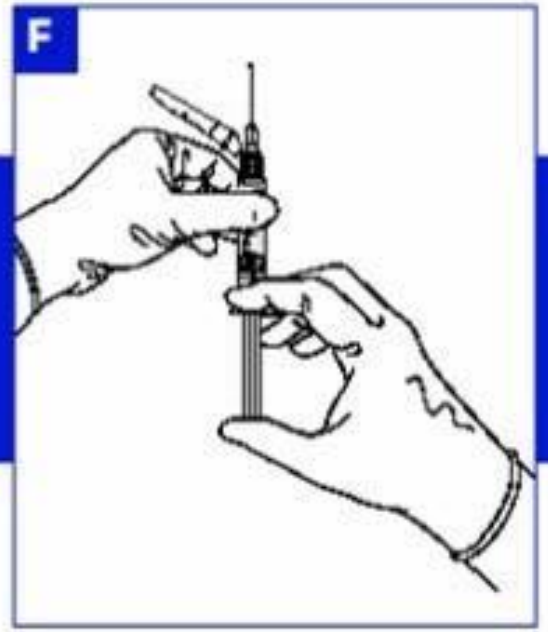
Mix the powder and diluent by **vigorously** shaking the vial for approximately 1 minute. (see Figure D) Ensure that the dose is thoroughly suspended prior to proceeding to Step E.

A PROPERLY MIXED SUSPENSION WILL BE MILKY WHITE, WILL NOT CONTAIN CLUMPS, AND WILL MOVE FREELY DOWN THE WALLS OF THE VIAL

1. Immediately after suspension, withdraw 4.2 mL of the suspension into the syringe using the same preparation needle.

2. Remove the preparation needle and replace with a 1½ inch administration needle for immediate use. (see Figure E)

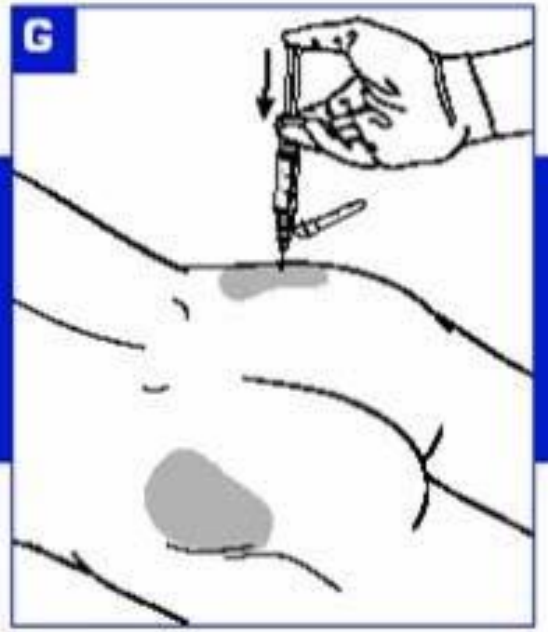
F



Prior to injecting, tap the syringe to release any air bubbles, then push gently on the plunger until **4 mL** of the suspension remains in the syringe. (see Figure F)

THE SUSPENSION IS NOW READY FOR IMMEDIATE ADMINISTRATION.

G



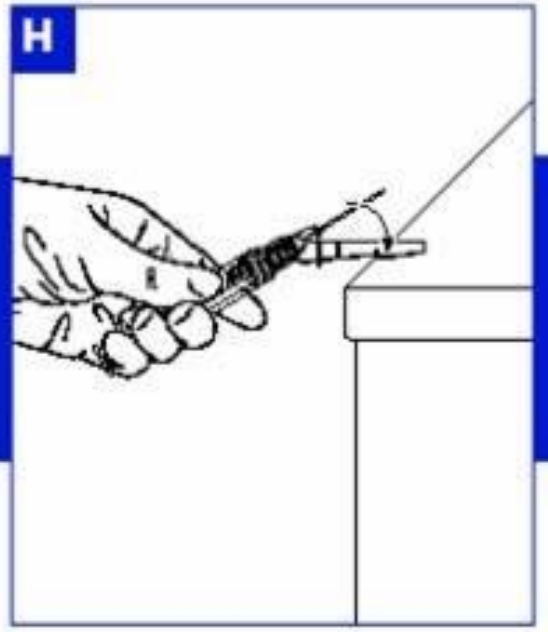
1. Administer the suspension by deep intramuscular (IM) injection into a gluteal muscle, alternating buttocks per injection. Remember to aspirate for blood before injection. (see Figure G)

2. Inject the suspension in a smooth and continuous motion.

3. If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the carton and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection.

VIVITROL must NOT be given intravenously.

H



After the injection is administered, cover the needle by pressing the safety sheath against a hard surface using a one-handed motion away from self and others. (see Figure H)

Activation of the safety sheath may cause minimum splatter of fluid that may remain on the needle after injection.

DISPOSE OF USED AND UNUSED ITEMS IN PROPER WASTE CONTAINERS

The naloxone challenge test?

The naloxone challenge test

- There is no completely reliable method for determining whether a patient has had an adequate opioid-free period
- A NALOXONE challenge test may be helpful

Intravenous

- Inject 0.2 mg naloxone
- Observe for 30 seconds for signs or symptoms of withdrawal
- If no evidence of withdrawal, inject 0.6 mg of naloxone
- Observe for an additional 20 minutes

Subcutaneous

- Administer 0.8 mg naloxone
- Observe for 20 minutes for signs or symptoms of withdrawal

- Individual patients may respond to lower doses of naloxone (0.1 mg)

My take…

- Most providers do not have ready access to naloxone
- Confirm no opioids either by laboratory tests and/or patient report
  - Rapport with patient is important!
- Most trials had a ***run-in period*** of oral naltrexone before injectable naltrexone
  - Provide 50 mg of oral for 1 week
  - If no problems, start injection
- If patient has precipitated opioid withdrawal…
  - Treat symptomatically

CASE: Brutus Discussions

- Is Brutus appropriate for XR-Naltrexone?

- How do you actually start Brutus on this medication?

DISCUSSION

Next VIP CHAT!

Wednesday, Oct 31, 2018 Noon-12:30 PM (New! 5th Wednesday of the month)

The case of Spooky Sam – Addressing Medical Marijuana for Patients in Addiction Treatment