VIVITROL®

(naltrexone for extended-release injectable suspension)

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- VIVITROL 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 with VIVITROL
  - Patients should not be actively drinking at the time of initial VIVITROL administration

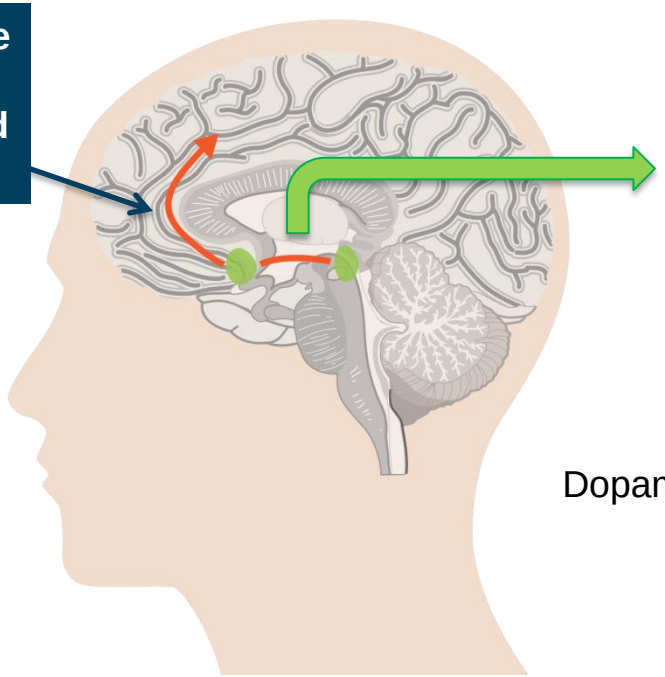
- VIVITROL is indicated for the prevention of relapse to opioid dependence, following opioid detoxification
  - Opioid-dependent patients and opioid-using patients, including those being treated for alcohol dependence, should be opioid-free for a minimum of 7–10 days before starting VIVITROL

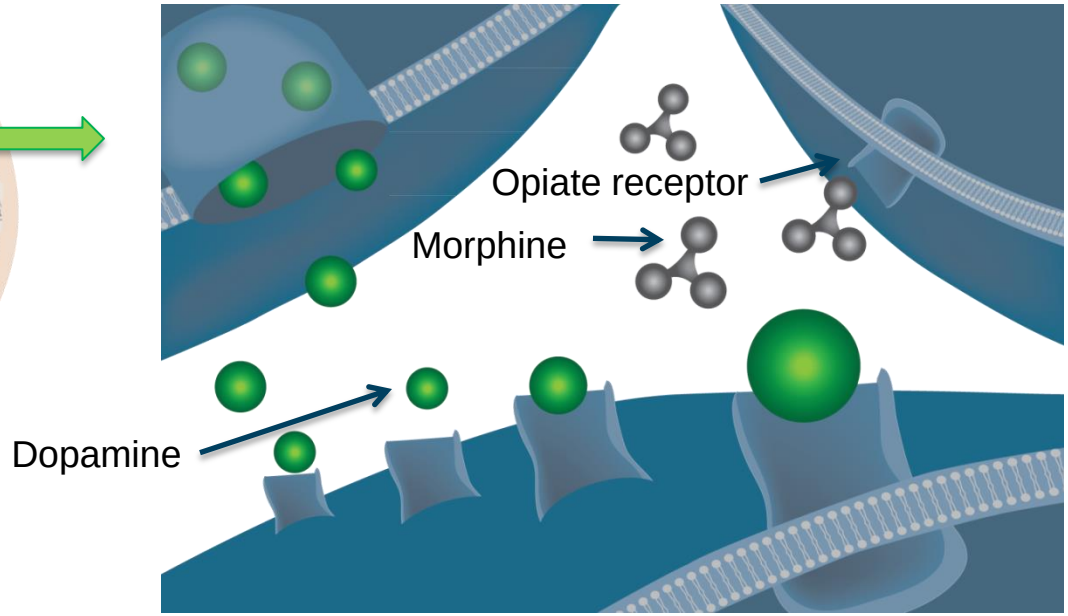
- Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

Drugs of Abuse Increase Dopamine in the Reward Pathway

Morphine binding in reward pathway

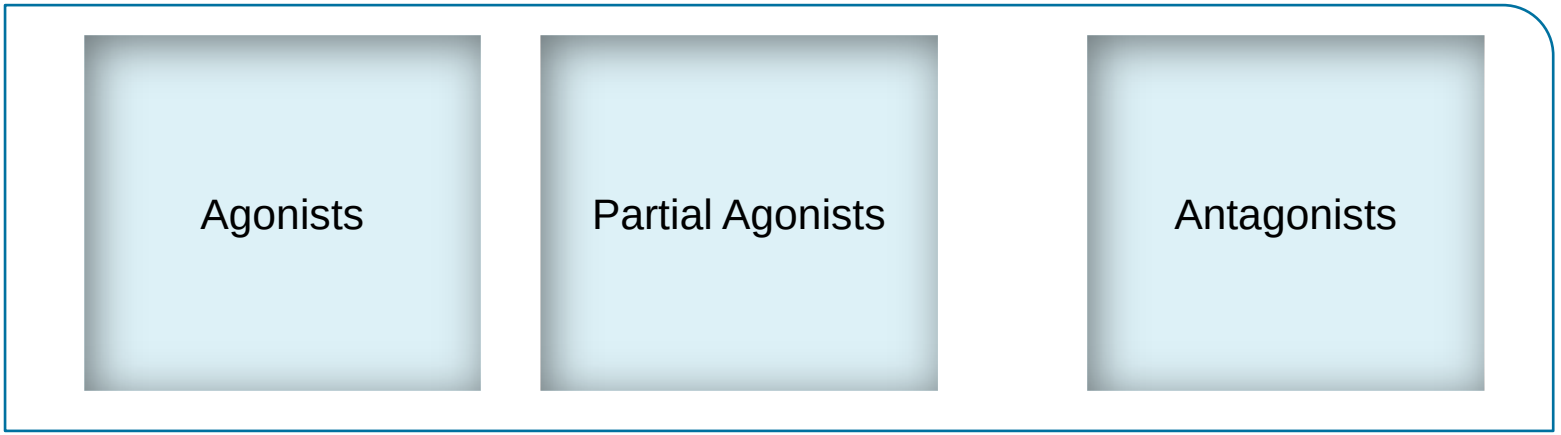




- Morphine binding in the reward pathway and the effect of opioids on the nucleus accumbens[1,2]
  - Opiates bind to opiate receptors on the terminal of a neuron[3]
  - Opiate receptor activation inhibits release of GABA and glutamate[3]
  - The inhibition of GABA (a dopamine inhibitor), releases the “brakes” from the neighboring dopaminergic neurons allowing it to fire more rapidly, which increases dopamine levels[4]
  - Signals that arrive at a dopamine terminal lead to excess release of dopamine[2]

1. National Institute on Drug Abuse. The Neurobiology of Drug Addiction, 3: Morphine binding within the reward pathway. 2007.
2. National Institute on Drug Abuse. The Neurobiology of Drug Addiction, 4: Opiates binding to opiate receptors in the nucleus accumbens. 2007.
3. Ruiz P, Strain EC. *Lowinson and Ruiz’s Substance Abuse, 5th ed*. 2011.
4. Kreek MJ. *J Clin Invest*. 2012.

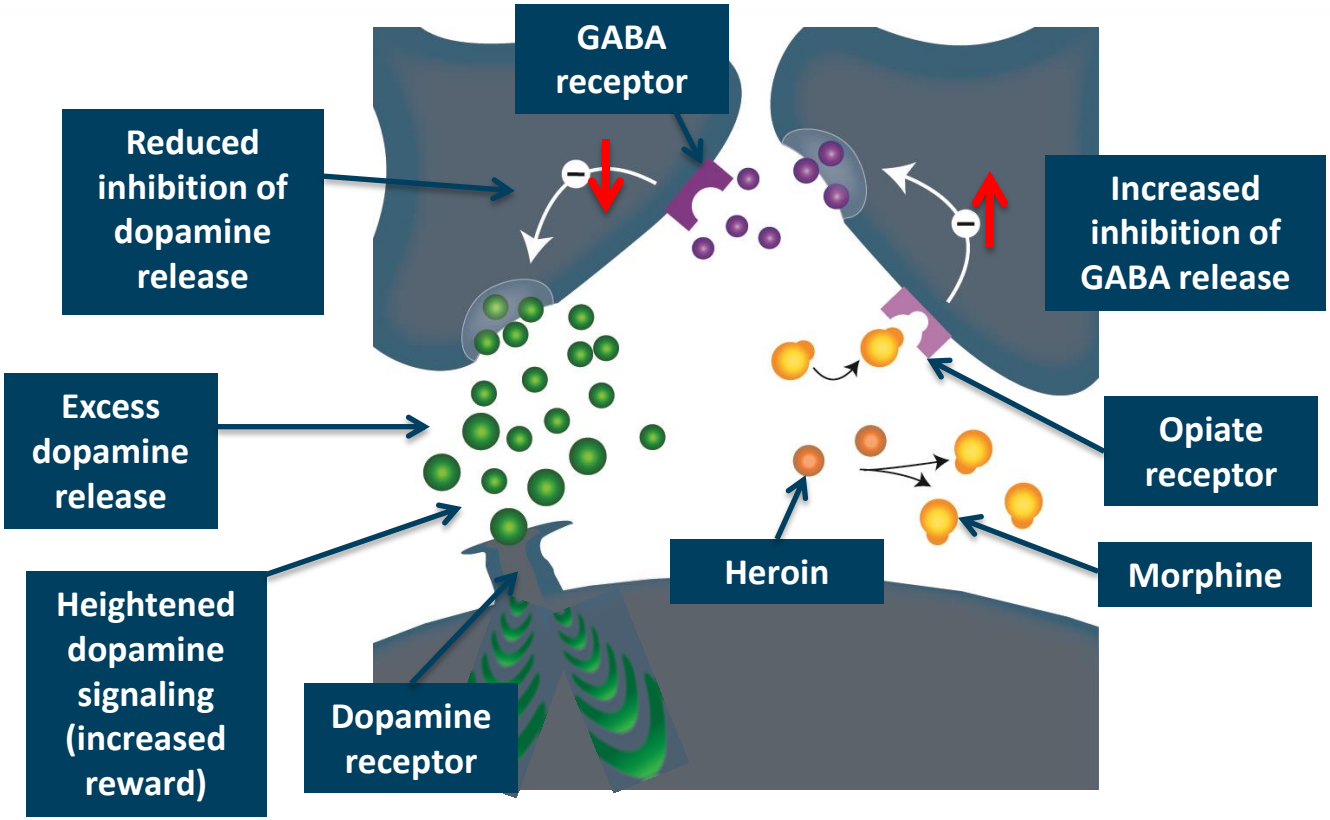
Opioid Dependence: Major Pharmacotherapy Categories



- Full or partial agonist therapy does not require opioid detoxification prior to initiation but can contribute to prolonged physical opioid dependence and lead to withdrawal if discontinued[1,2,3,4,5]
- Antagonists are not addictive and do not lead to withdrawal if discontinued; however, opioid detoxification is required prior to initiating therapy in order to avoid precipitation of withdrawal[6]

1. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain Physician.* 2008;Opioid Special Issue 11:S133-S153.
2. McDonald J, Lambert DG. Opioid receptors. *Cont Educ Anaesth Crit Care Pain.* 2005;5(1):22-25.
3. Tortora GJ, Derrickson B. *Principles of Anatomy and Physiology, 13th ed*. Hoboken, NJ: John Wiley & Sons; 2012:480.
4.Ruiz P, Strain EC. *Lowinson and Ruiz's Substance Abuse, 5th ed*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
5. Suboxone sublingual film [full prescribing information]. Richmond, VA: Reckitt Benckiser Pharmaceuticals Inc; 2011.
6. Substance Abuse and Mental Health Services Administration booklet. *The facts about naltrexone for treatment of opioid addiction.* Printed 2009. Revised 2012. HHS Publication No. (SMA) 12-4444. store.samhsa.gov/shin/content//SMA12-4444/SMA12-4444.pdf.

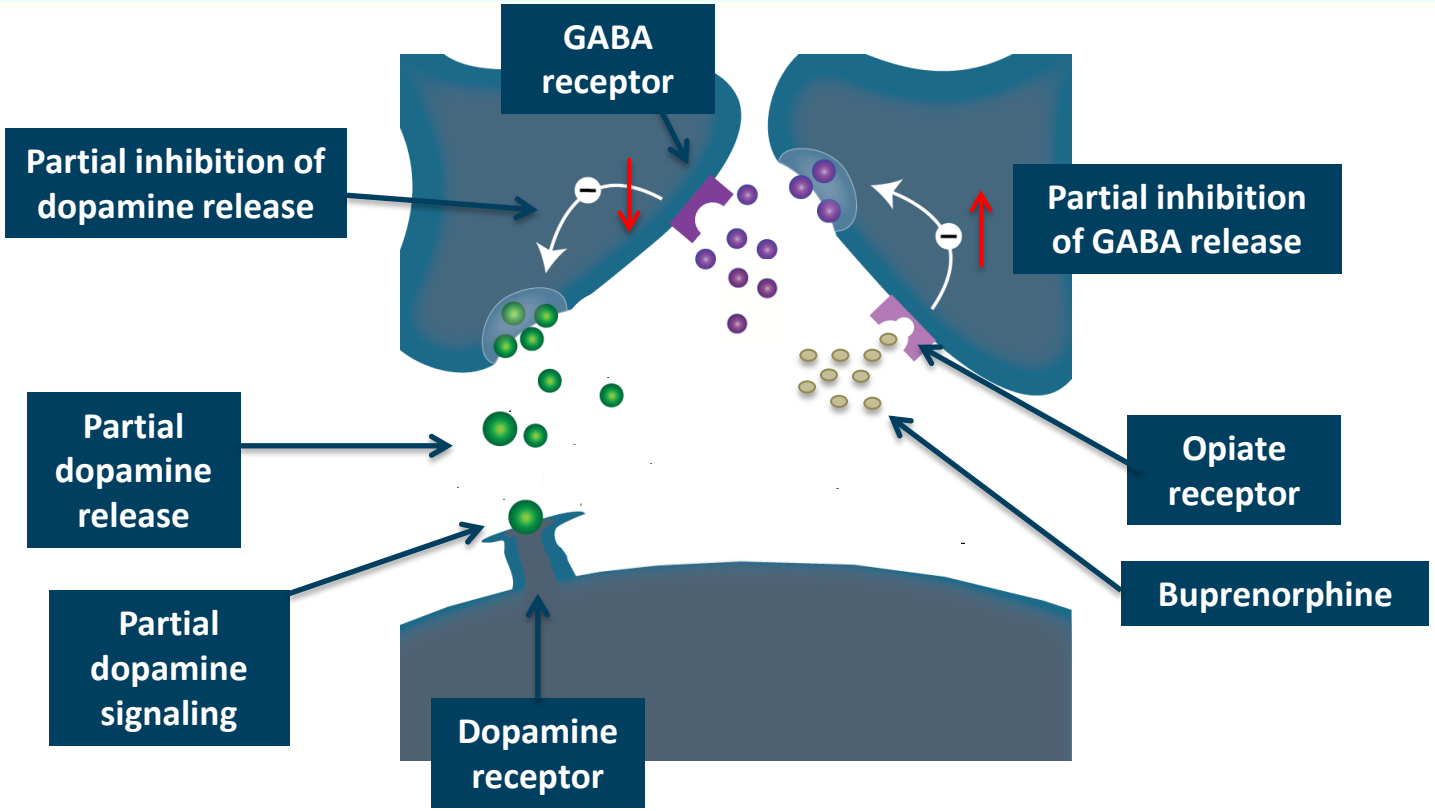
Opioid Agonists



- Agonists, such as opioid analgesics, illicit opioids (eg, heroin) and methadone, activate opioid receptors, which causes excess dopamine release
- A full agonist binds to the receptor and activates it by changing its shape, inducing a full receptor response

DOLOPHINE®, Full Prescribing Information. 2014.

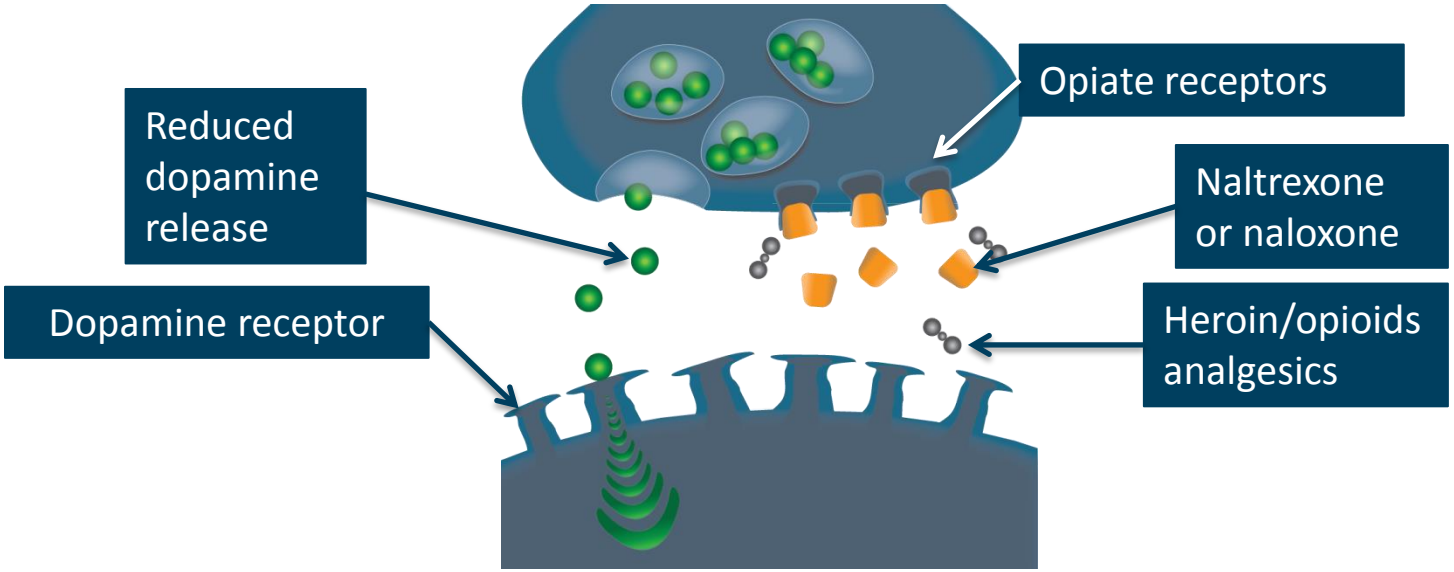
Partial Agonists



- Partial agonists, such as buprenorphine, have the same effect as agonists but have a ceiling effect
- A partial agonist binds to the receptor and activates it with a smaller shape change in the receptor that induces a partial receptor response

SUBOXONE®, Full Prescribing Information. 2014.

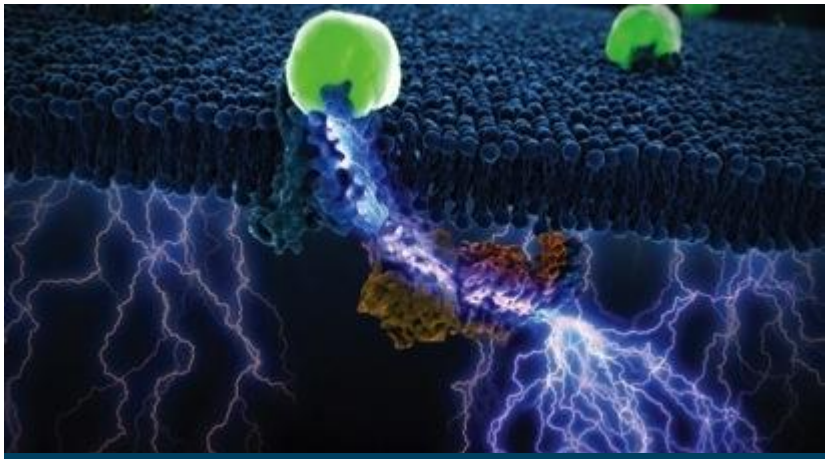
Opioid Antagonist



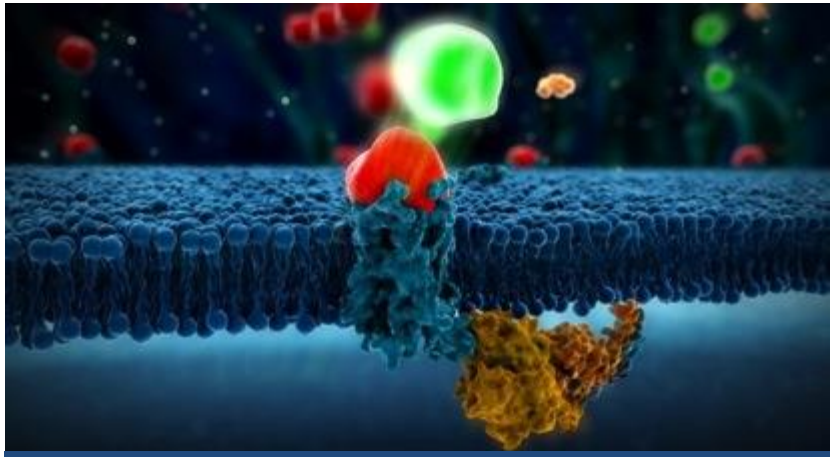
- Bind to and block opioid receptors, preventing the receptors from being activated by agonist compounds[1]
- XR-NTX blocks the reinforcing, subjective, and pleasurable effects associated with illicit opioid use by preventing opioid receptors from being activated by illicit opioids [2]
- Naloxone is another antagonist that can be added to partial agonist therapy, buprenorphine, to reduce the potential for diversion and illicit use[3]
  - Naloxone also binds to opioid receptors without producing a euphoric effect, which inhibits the psychoactive effects of opioid agonists[3]

1. Center for Substance Abuse Treatment .*TIP 40*. 2004.
2. VIVITROL Prescribing Information. Alkermes, Inc.; 2013.
3. Mauger S, et al. *Neuropsychiatr Dis Treat*. 2014;10:587-598.

Extended-release Naltrexone Mechanism of Action



- The brain's ultimate neurotransmitter of reward is dopamine[1]
- The μ-opioid receptor is a key mechanism for promoting excessive dopamine release[1]

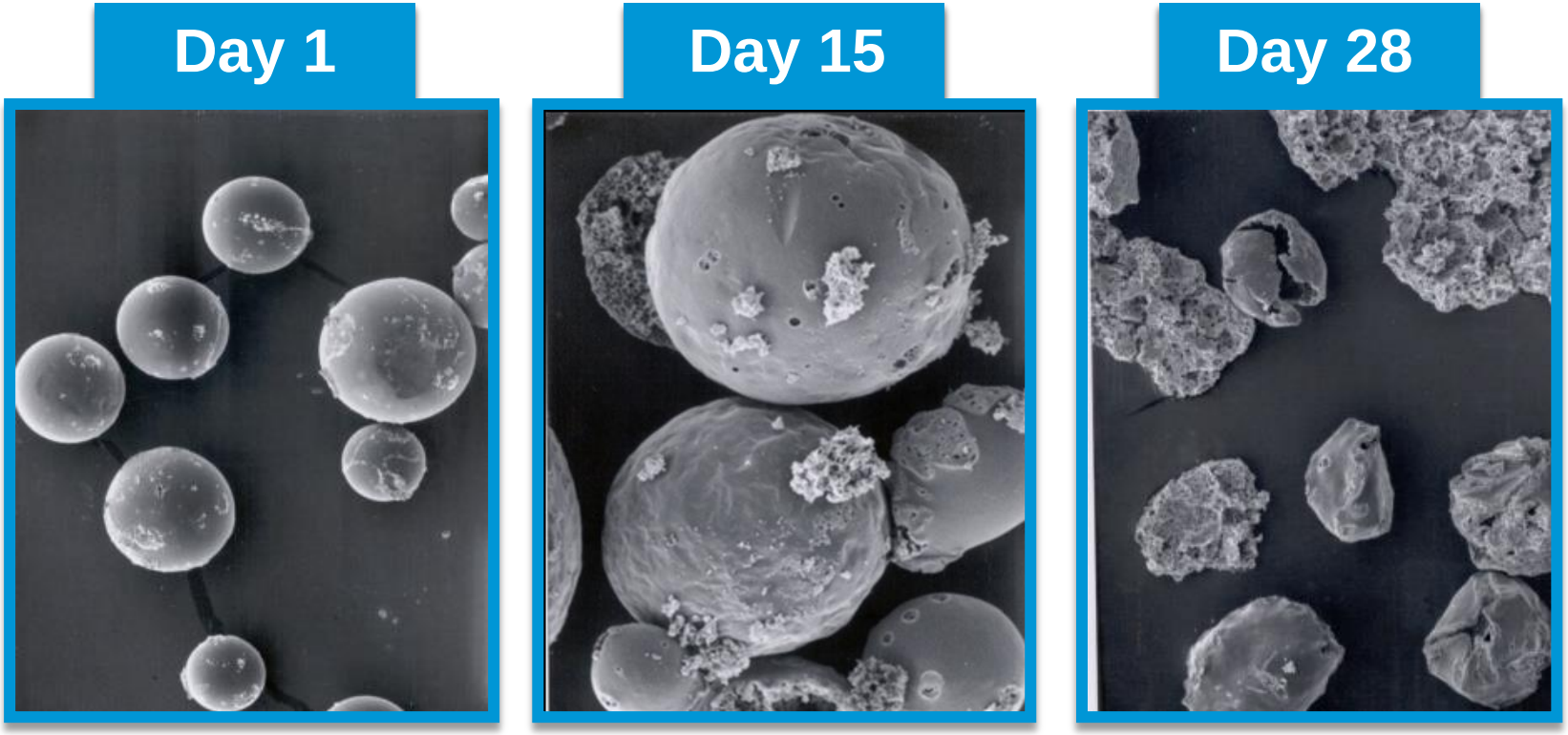


- XR-NTX blocks the μ-opioid receptors through competitive binding[1]
- This reversible blockade prevents opioid drugs from reaching the receptors and producing a "high"[1]
- Although XR-NTX's mechanism of action in alcohol dependence is not completely understood, this blockade is thought to prevent the increased dopamine release responsible for the pleasurable, reinforcing effects of alcohol[2]

1. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect.* 2002;1(1):13-20. 2. VIVITROL [prescribing information]. Waltham, MA: Alkermes, Inc; rev July 2013.

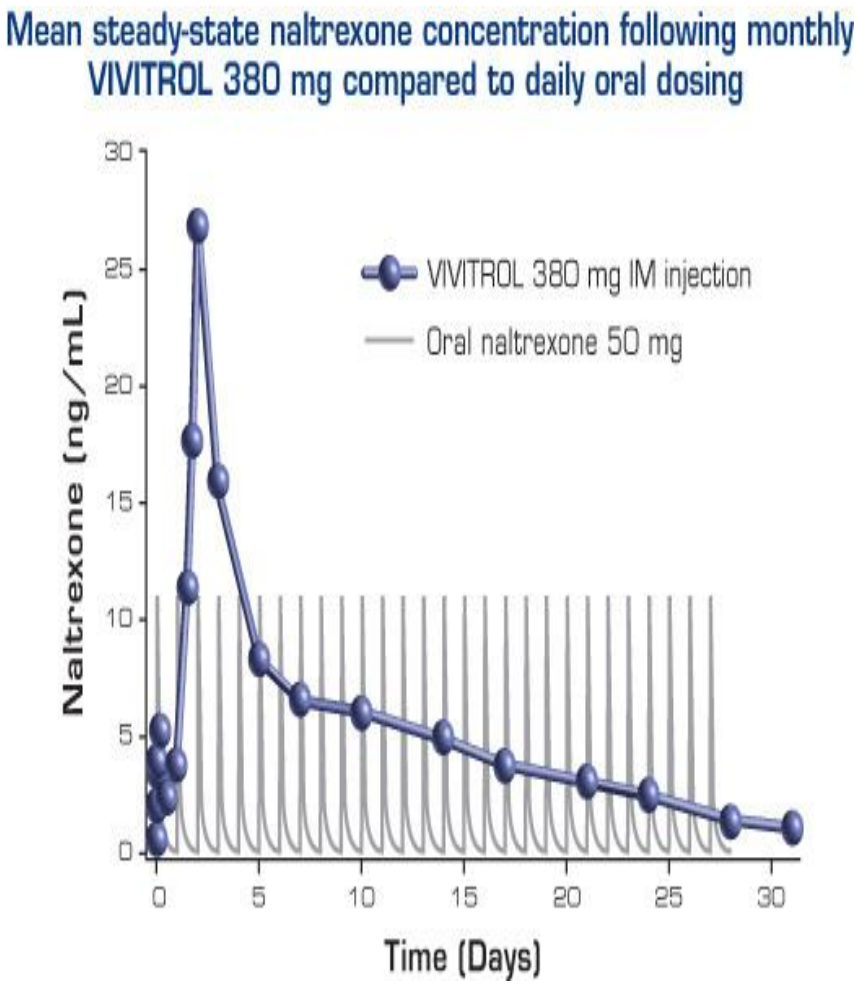
Polylactide-co-glycolide (PLG) polymer

- Polylactide-co-glycolide (PLG) polymer allows extended release of the active ingredient, naltrexone
- Polymer eventually metabolized and eliminated as CO_2 and H_2O



Dean RL. *Front Biosci.* 2005;10:643-655.

Extended-release Naltrexone Pharmacokinetics



- Reduced first-pass hepatic metabolism vs oral naltrexone[1]
- Systemic naltrexone exposure ~4x greater than oral with less than 1/3 the monthly dose[1]
  - 380mg/30d of XR-NTX vs 1500mg/30d of oral naltrexone
- Initial peak at ~2 hours post injection, 2nd peak ~2-3 days later[2]
- Elimination of naltrexone and its metabolites occurs via urine; minimal excretion of unchanged naltrexone
  - Caution is recommended in patients with moderate to severe renal impairment
    - Mild renal insufficiency (CrCl=50-80ml/min), no dosage adjustment necessary
- Elimination Half-life: 5-10 days (dependent on erosion of polymer)

1. Dunbar JL, et al. *Alcohol Clin Exp Res*. 2006; 30:480-490
2. VIVITROL Prescribing Information. Waltham, MA: Alkermes, Inc; rev July 2013

Contraindications

- Patients receiving opioid analgesics
- Patients with current physiologic opioid dependence
- Patients in acute opioid withdrawal
- Any individual who has failed the naloxone challenge test or has a positive urine screen for opioids
- Patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of diluent

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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