

Naltrexone for Prevention of Relapse in Opioid Addiction

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Disclosure

I have no disclosures concerning financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation

Objectives

Pharmacists

1. Describe the pathophysiology of opioid addiction, and summarize the challenges that patients face in preventing relapse
2. Evaluate the effectiveness of the currently available Naltrexone formulations in patients most likely to benefit from an approved opioid dependence treatment plan
3. Identify appropriate Naltrexone dosing regimens for patients that are initiated on one of the currently approved formulations to prevent relapse in opioid addiction

Pharmacy Technicians

1. Summarize the issue of opioid misuse in this country and challenges patients face in preventing relapse
2. Differentiate between the correct indications and dosage forms of Naltrexone

Presentation Question #1

How many people died from overdoses involves opioid medications in the United States 2015?

- A. 5,000 – 10,000
- B. 10,000 – 20,000
- C. 20,000 – 30,000
- D. 30,000 – 40,000

Statistics on the United States Opioid Crisis

- According to the Centers for Disease Control, in 2015 approximately 28,000 people died from overdoses involving opioid medications
 - ~13,000 people died from overdoses involving heroin
 - ~15,000 people died from overdoses involving prescription opioids
- On average, 91 people died from an opioid related overdose per day in 2015

2015 Opioid Overdoses per 100,000 Individuals



1. Hedegaard H, Warner M, Miniño AM. Drug overdose deaths in the United States, 1999–2016. NCHS Data Brief, no 294. Hyattsville, MD: National Center for Health Statistics; 2017. CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016.
2. Centers for Disease Control and Prevention. Vital Signs: Today's Heroin Epidemic – More People at Risk, Multiple Drug-Abused. MMWR 2015.

Methadone

Mechanism of Action
Opioid receptor agonist

Suboxone

Mechanism of Action
Opioid receptor partial agonist/Opioid receptor antagonist

Medications for the Prevention of Relapse

Naltrexone

Mechanism of Action
Opioid receptor antagonist

Medications for the Prevention of Relapse

Methadone
Full agonist:
generates effect

Buprenorphine
Partial agonist:
generates limited effect

Naltrexone
Antagonist:
blocks effect

3. "Medication-Assisted Treatment Improves Outcomes for Patients With Opioid Use Disorder." *The Pew Charitable Trusts*, 22 Nov. 2016.
www.pewtrusts.org/en/research-and-analysis/fact-sheets/2016/11/medication-assisted-treatment-improves-outcomes-for-patients-with-opioid-use-disorder.

Naltrexone Pharmacokinetics

Parameter	Intramuscular Formulation	Tablet Formulation
Volume of Distribution	1350L	
Metabolism	Hepatic (Active Metabolite: 6-Beta-Naltrexol)	
Excretion	Renal (53-79%)	
Elimination Half Life	5-10 Days (Dependent on Polymer Erosion) 6-Beta-Naltrexol: 5-10 Days	4 Hours 6-Beta-Naltrexol : 13 Hours

4. "Vivitrol Package Insert." *United States Food and Drug Administration*, Allermes Pharmaceuticals, www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897r0151bl.pdf.
5. "Revia Package Insert." *United States Food and Drug Administration*, Teva Pharmaceuticals, www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897r0151bl.pdf.

Study Title: Comparative Effectiveness of Extended-Release Naltrexone Versus Buprenorphine-Naloxone for Opioid Relapse Prevention (X:BOT)

- Published Date: 14 November 2017
- Background: Multicenter, Open-Label, Randomized, Controlled Trial
- Study Design: Patients randomly assigned to receive either monthly injections of IM Naltrexone or daily self-administered Buprenorphine-Naloxone sublingual film for 24 weeks
- Primary Outcome: Opioid relapse-free survival during 24 weeks of outpatient treatment
 - Relapse: 4 consecutive weeks of any non-study opioid use by urine toxicology or self-report, or 7 consecutive days of self-reported use

6. Lee, Joshua, et al. "Comparative Effectiveness of Extended-Release Naltrexone Versus Buprenorphine-Naloxone for Opioid Relapse Prevention (X:BOT)." *The Lancet*, 14 Nov. 2017.

Results from X:BOT Trial

Total Participants: 570 Naltrexone Cohort n = 283, Buprenorphine/Naloxone Cohort n = 287	
Successful Initiation on Treatment Protocol	Naltrexone: 204/283 (72%) Buprenorphine/Naloxone: 270/287 (94%) p < 0.0001
Opioid Week Relapse Intent-to-Treat Population	Naltrexone: 185/283 (65%) Buprenorphine/Naloxone: 163/287 (57%) P < 0.036
Relapse-Free Survival (Weeks) Intent-to-Treatment Population	Naltrexone: 8.4 Weeks Buprenorphine/Naloxone: 14.4 Weeks p < 0.0040

6. Lee, Joshua, et al. "Comparative Effectiveness of Extended-Release Naltrexone Versus Buprenorphine-Naloxone for Opioid Relapse Prevention (X:BOT)." The Lancet, 14 Nov. 2017.

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24 Week Relapse Per-Protocol Population (n = 474)	Naltrexone: 106/204 (52%) Buprenorphine/Naloxone: 150/270 (56%) p = 0.44
Relapse-Free Survival (Weeks) Per-Protocol Population (n = 474)	Naltrexone: 20.4 Weeks Buprenorphine/Naloxone: 15.2 Weeks p = 0.49
There was additionally found to be no difference between the two treatment groups in terms of average opioid craving by the end of the study.	

6. Lee, Joshua, et al. "Comparative Effectiveness of Extended-Release Naltrexone Versus Buprenorphine-Naloxone for Opioid Relapse Prevention (X:BOT)." The Lancet, 14 Nov. 2017.

Naltrexone Adverse Effects and Counseling Points

Common Adverse Effects (>20%)

- Nausea (IM Version)
- Injection Site induration (IM Version)
- Injection Site Reaction (IM Version)

Counseling Points

- FDA approved for alcohol withdrawal and opioid withdrawal
- IM Dose: 380mg IM Gluteal Injection Every 4 Weeks
- Oral Dose: Start with 25mg daily. May increase to 50mg daily if no withdrawal symptoms occur. Continue to titrate up as needed.
- Patient must be opioid free for 7-10 days prior to initiation of therapy (Both Formulations)

4. "Vivitrol Package Insert." United States Food and Drug Administration, Alkermes Pharmaceuticals, www.accessdata.fda.gov/drugatfd/label/2010/021897d15bl.pdf.
5. "Revia Package Insert." United States Food and Drug Administration, Teva Pharmaceuticals, www.accessdata.fda.gov/drugatfd/label/2010/021897d15bl.pdf.

Cost of Therapy for Opioid Relapse Prevention Medications

Approximate Cost of 1 Month of Therapy for Medications to Prevent Relapse to Opioid Addiction	
IM Naltrexone	~\$1300.00
PO Naltrexone	~\$150.00
PO/SL Suboxone	~\$280.00
PO Methadone	~\$10.00

Precautions with Intramuscular Naltrexone

www.vivitrolrems.com

- Dear Healthcare Provider Letter
- Vivitrol Patient Counseling Tool
- Visual Aid Reinforcing Proper Vivitrol Injection Technique

WARNING: HEPATOTOXICITY
 Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses and is contraindicated in acute hepatitis or liver failure. Use of VIVITROL should be discontinued in the event of symptoms or signs of acute hepatitis


4. "Vivitrol Package Insert." United States Food and Drug Administration, Allermes Pharmaceuticals, www.accessdata.fda.gov/drugatfda_docs/label/2010/021897s0151b1.pdf

Presentation Question #2

Criminal justice offenders who were addicted to opioids can be placed in a mandatory relapse prevention program

A. True
 B. False


Judicially Mandated Naltrexone Use



**Michael's Story of Kicking the 'H' Out of Heroin:
Collaborating to Maintain His Sobriety**

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Study Title: Extended Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders

- Published Date: 31 March 2016
- Background: Multicenter, Open-Label, Randomized, Controlled Trial
- Study Design: Participants were randomly assigned, in a 1:1 ratio, to extended-release naltrexone in six monthly injections or usual treatment for opioid-relapse prevention
- Primary Outcome: Time to opioid relapse event
 - Primary outcome defined as 10 or more days of opioid use in a 28-day period as assessed by self-report or by testing of urine samples obtained every 2 weeks. A positive or missing sample represented 5 days of opioid use.

7. Lee, Joshua D., et al. "Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders." *New England Journal of Medicine*, vol. 374, no. 13, 2016, pp. 1232-1242. doi:10.1056/nejmoa1505409.

Trial Results: Injectable Extended Release Naltrexone for Opioid Dependence

Total Participants: 308 Naltrexone Cohort n = 153, Usual Treatment Cohort n = 155	
Patients with Confirmed Abstinence	Naltrexone: 10.5 Weeks Placebo: 5.0 Weeks p < 0.001
Relapse Rate	Naltrexone: 66/153 (43.1%) Placebo: 99/155 (63.9%) P < 0.001
Opioid Negative Urine Samples	Naltrexone: 71.1% Placebo: 55.7% p < 0.001

7. Lee, Joshua D., et al. "Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders." *New England Journal of Medicine*, vol. 374, no. 13, 2016, pp. 1232-1242. doi:10.1056/nejmoa1505409.

Conclusions

Advantages and Disadvantages of Naltrexone

Advantages	Disadvantages
2 Different Formulations	Cost of IM Injection
Easier Adherence	IM Injection in Clinic
Not Controlled	
No Abuse Potential	

Questions?

References

1. Hedegaard H, Warner M, Miniño AM. Drug overdose deaths in the United States, 1999–2016. NCHS Data Brief, no 294. Hyattsville, MD: National Center for Health Statistics. 2017/ CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016.
2. Centers for Disease Control and Prevention. Vital Signs: Today's Heroin Epidemic – More People at Risk, Multiple Drugs Abused. MMWR 2015.
3. "Medication-Assisted Treatment Improves Outcomes for Patients With Opioid Use Disorder." The Pew Charitable Trusts, 22 Nov. 2016. www.pewtrusts.org/en/research-and-analysis/fact-sheets/2016/11/medication-assisted-treatment-improves-outcomes-for-patients-with-opioid-use-disorder.
4. "Vivitrol Package Insert." United States Food and Drug Administration, Alkermes Pharmaceuticals, www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s015lbl.pdf.
5. "Revia Package Insert." United States Food and Drug Administration, Teva Pharmaceuticals, www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s015lbl.pdf.
6. Lee, Joshua, et al. "Comparative Effectiveness of Extended-Release Naltrexone Versus Buprenorphine-Naloxone for Opioid Relapse Prevention (K801)." *The Lancet*. 14 Nov. 2017.
7. Lee, Joshua D., et al. "Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders." *New England Journal of Medicine*, vol. 374, no. 13, 2016, pp. 1232–1242, doi:10.1056/nejmoa1505409.

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Pharmacist CE Questions

1. According to data from the Centers for Disease Control and Prevention, approximately how many people died from overdoses involving prescription opioids in 2015
A. 5,000 B. 10,000 C. 15,000 D. 20,000
2. In patients who have been previously dependent on opioids, how long is it recommended that they remain opioid free before initiating therapy with either oral or intramuscular Naltrexone
A. 1-2 Days B. 3-5 Days C. 5-6 Days D. 7-10 Days
3. What is the correct dosage for the monthly Naltrexone intramuscular injection that patients receive to prevent relapse in opioid dependence?
A. 140mg B. 260mg C. 380mg D. 500mg

Pharmacy Technician CE Questions

1. According to the Centers for Disease Control and Prevention, approximately how many people die each day from an opioid overdose in the United States
A. 30 to 40
B. 60 to 70
C. 90 to 100
D. 120 to 130
2. Which of the following is a correct indication for using Naltrexone
A. Prevention of relapse for opioid dependence
B. Prevention of relapse for alcohol dependence
C. Constipation
D. A and B
