Naltrexone for Opioid Use Disorder

A Project RAMP Resource

Adam J. Gordon, MD MPH FACP DFASAM CMRO

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LEARNING OBJECTIVES

• Be able to inform patients regarding the use and latest literature of the use of naltrexone for the treatment of opioid use disorder
• 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
CONFLICT OF INTEREST AND DISCLOSURE

• Dr. Gordon has no fiduciary conflicts of interest
• Some of the material presented herein has been previously published from work at the University of Pittsburgh, University of Utah, and the Veterans Health Administration
• The views expressed in this presentation are Dr. Gordon’s and do not necessarily reflect the position or policy of any institution, agency, or government
• Buprenorphine (BUP) = buprenorphine + naloxone unless otherwise stated
INTRODUCTIONS
DSM 5 DEFINITION: Substance Use Disorder

- Failure to fulfill role obligations at work, school, or home
- Recurrent use in hazardous situations
- Continued use despite substance-related social or interpersonal problems
- Tolerance
- Withdrawal/physical dependence
- Loss of control over amount of substance consumed
- Preoccupation with controlling substance use
- Preoccupation with substance use activities
- Impairment of social, occupational, or recreational activities
- Use is continued despite persistent problems related to substance use
- Craving or a strong desire to use a substance
- Legal problems related to a substance

Criteria:
2-3 (mild)
4-5 (moderate)
6 or more (severe)
OPIOIDS: Balloons, Bags, and Pills
DSM 5 DEFINITION:
Opioid Use Disorder (2 or greater)

- Failure to fulfill role obligations at work, school, or home
- Recurrent use in hazardous situations
- Continued use despite opioid-related social or interpersonal problems
- Tolerance
- Withdrawal/physical dependence
- Loss of control over amount of opioids consumed
- Preoccupation with controlling opioid use
- Preoccupation with opioid use activities
- Impairment of social, occupational, or recreational activities
- Use is continued despite persistent problems related to opioid use
- Craving or a strong desire to use opioids

Criteria:
2-3 (mild)
4-5 (moderate)
6 or more (severe)
Opioid Use Disorders are increasing

• The abuse of and addiction to opioids is a serious global problem that affects the health, social, and economic welfare of all societies.
  • 26.4 million-36 million people

• In US
  • Pain relievers: 2,100,000
  • Heroin: 467,000
  • Since 1999, the number of unintentional overdose deaths from prescription pain relievers has >4X
  • There is also growing evidence to suggest a relationship between increased non-medical use of opioid analgesics and heroin abuse in the United States

Volkow ND, presentation to the Senate Caucus on International Narcotics Control, 2014
ONDCP, World Drug Report 2012
SAMHSA, Results from 2012 NSDUH, 13-4795, 2013
Pradip, SAMHSA, 2013
Opioid Use: Medical Complications

- Medical costs are often associated with opioid injection
  - Mental illness
    - An environmental and disease stressor
    - Co-morbid interactions
  - Trauma and infections
  - Hepatitis and HIV

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Abcesses/cellitis, pulmonary infections, endocarditis, rhinosinusitis</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma, pulmonary edema, respiratory depression</td>
</tr>
<tr>
<td>Nervous</td>
<td>Seizures, cerebral dysfunction</td>
</tr>
<tr>
<td>Ocular</td>
<td>Strabismus, fungal infections</td>
</tr>
<tr>
<td>Urological</td>
<td>Renal disease</td>
</tr>
<tr>
<td>Gyne/OB</td>
<td>Fetal growth restriction, placental changes, neonatal abstinence syndrome, congenital disease</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>CAD, endocarditis, arrhythmias</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Calcium inhibition, hypercholesterolemia, hypo-/hyper-thermia, hyperkalemia</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Pituitary enlargement, hormonal alterations</td>
</tr>
</tbody>
</table>

Gordon, Physical Illness and Drugs of Abuse, 2010
Volkow ND, presentation to the Senate Caucus on International Narcotics Control, 2014
Opioid Use: Withdrawal

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

• Increased number of ER visits involving nonmedical use of opioid analgesics
• Increased admissions for primary abuse of opiates other than heroin
• Increased overdose deaths due to prescription opioids
• Opioids account for the greatest proportion of the prescription drug abuse problem
• Nonmedical use of opioid pain relievers costs insurance companies up to $72.5 billion annually in health-care costs

SAMHSA, DAWN 2007
SAMHSA, TEDS Highlights- 2007
Mack KA, CDC, MMWR Surveil Summ. 2013
Paulozzi. Drug Saf., 2006
Coalition Against Insurance Fraud., 2007
Volkow ND, presentation to the Senate Caucus on International Narcotics Control, 2014
Is the epidemic due to PCPs?

- Opioids are “environmentally available”
  - drastic increases in the number of prescriptions written and dispensed
    - From 76 million to 207 million (1991 to 2013)
    - US: 100% of hydrocodone and 81% of oxycodone worldwide
  - greater social acceptability for using medications for different purposes
  - aggressive marketing by pharmaceutical industry
Is the Primary Care Office Appropriate for Treatment?

• Willingness and knowledge of primary care physician
• Stage of change and willingness of patient
• Severity and chronicity of alcohol use disorder
• Psychosocial support available within family and community
• Prior treatment response
• Availability of psychosocial and behavioral treatments
• Adherence to treatment plan
Primary Care Conundrums

• PCPs are confronted with patient challenges:
  • Prescription opioid misuse, opioid use disorders, and opioid related morbidity and death are increasing
  • Increased attention to pain and addressing pain
  • Increased mental health co-morbidity

• PCPs are confronted with assessment and treatment challenges:
  • Lack of education on opioid (and pain) assessment, treatment, referral
  • No uniform screening procedures (no evidence either)
  • Relative lack of access to pain/addiction referral resources
  • Patient preferences
  • Role out of collaborative care models
ADDICTIVE DISORDERS?

THEY ARE TREATABLE!
(by “normal” health care providers)
Addiction Disorders are Treatable LIKE ANY OTHER CHRONIC ILLNESS

• Type 1 Diabetes
  • 30% to 50% relapse each year requiring additional medical care
  • Significant societal consequences

• Hypertension and Asthma
  • 50% to 70% relapse each year requiring additional medical care
  • Significant societal consequences

• Alcohol and Other Drug Diseases
  • 40% to 60% relapse each year
  • Significant societal consequences
  • Few patients receive treatment!

• Why the difficulty in engagement and treatment of addiction?
• Why is it so vexing for health care providers to treat addiction?
Treatment: Overview

- Psychosocial treatments help many persons with alcohol use disorder reduce their drinking or achieve abstinence
  - 40% to 70% relapse within a year
- Neuroscientific advances suggest the possibility of developing medications to enhance the effectiveness of psychosocial treatments
- These medications target neurotransmitter systems that mediate alcohol reward associated with its abuse liability and/or ameliorate neurochemical dysfunction in those with a biological predisposition to the disease
CASE SET 1: MARY
CASE SET 1: MARY

• Mary is a 38 year old married, female
  • G2P2 without significant past medical history
  • She works at a diner
  • Non-smoker, non-drinker
  • Recently hurt her back moving boxes. Received physical therapy for 2 months.
  • On NSAIDS and vicodin 1 tab every 6 hours, dispensed 2x a month

• Regarding Vicodin
  • “Doc, my back is hurting and I need help to function. The percocet helps me. It reduces my pain. It provides me a pick me up and energizes me. I need it. It seems like I need more of it to control the pain lately.”
CASE SET 1: MARY- QUESTIONS

• With this limited information, does Mary have a problem and if so, what type?

• What additional questions should you inquire to Mary regarding her opioid use consumption?

• What treatment, if any would you consider?
Does Mary have Opioid Use Disorder (2 or greater)???

- Failure to fulfill role obligations at work, school, or home
- Recurrent use in hazardous situations
- Legal problems related to opioid use
- Continued use despite opioid-related social or interpersonal problems
- Tolerance
- Withdrawal/physical dependence
- Loss of control over amount of opioids consumed
- Preoccupation with controlling opioid use
- Preoccupation with opioid use activities
- Impairment of social, occupational, or recreational activities
- Use is continued despite persistent problems related to opioid use
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Criteria:
2-3 (mild)
4-5 (moderate)
6 or more (severe)
Naltrexone for opioid use disorder

• Oral naltrexone was approved in 1984 for treatment of opioid use disorder

• Injectable naltrexone approved in October 2010 to treat people with opioid use disorder
  • Allows steady state of medication for 4 weeks
  • Reduces ability of patients to stop and start oral naltrexone
Oral and Injectable Naltrexone
Oral Naltrexone
Oral Naltrexone

• Naltrexone hydrochloride tablets is 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
• May 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 of management that includes some measure to ensure the patient takes the medication
Oral Naltrexone – Reported Side Effects

• Blurred vision or eye problems
• Fast heartbeat
• Mood changes, hallucinations (seeing or hearing things), confusion, thoughts of hurting yourself
• Nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice
Oral Naltrexone

• Major contraindication:

  current or recent use (in the last 7 to 14 days) of any type of opioid drug
## Oral Naltrexone Summary

<table>
<thead>
<tr>
<th><strong>Contraindications</strong></th>
<th>Currently using opioids or in acute opioid withdrawal; anticipated need for opioid analgesics; acute hepatitis or liver failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Examples of drug interactions</strong></td>
<td>Opioid analgesics (block action); yohimbine (use with naltrexone increases negative drug effects)</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Other hepatic disease; renal impairment; history of suicide attempts. If opioid analgesia is required, larger doses may be required, and respiratory depression may be deeper and more prolonged</td>
</tr>
<tr>
<td><strong>Serious adverse reactions</strong></td>
<td>Will precipitate severe withdrawal if patient is dependent on opioids; hepatotoxicity (uncommon at usual doses). Pregnancy Category C</td>
</tr>
<tr>
<td><strong>Common side effects</strong></td>
<td>Nausea; abdominal pain; constipation; dizziness; headache; anxiety; fatigue</td>
</tr>
</tbody>
</table>
| **Usual adult dose** | **Oral dose**: 50 mg daily  
**Before prescribing**: Evaluate for possible current opioid use; consider a urine toxicology screen for opioids, including synthetic opioids; obtain liver function tests  
**Follow-up**: Monitor liver function tests periodically |
Injectable Naltrexone
Evidence for injectable naltrexone

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; Jani L. Rothenberg, PhD; Herbert D. Kleber, MD; Kyle Kampman, MD; Charles Dachts, 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
Evidence for injectable naltrexone

Table 1: Demographic Characteristics of the 66 Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n = 10)</th>
<th>112 mg of Naltrexone Group (n = 20)</th>
<th>224 mg of Naltrexone Group (n = 22)</th>
<th>Total (n = 42)</th>
<th>( P ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (61)</td>
<td>16 (80)</td>
<td>19 (86)</td>
<td>46 (55)</td>
<td>.25</td>
</tr>
<tr>
<td>Female</td>
<td>8 (39)</td>
<td>4 (20)</td>
<td>3 (14)</td>
<td>14 (33)</td>
<td></td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>White</td>
<td>10 (50)</td>
<td>8 (40)</td>
<td>6 (27)</td>
<td>24 (57)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>3 (14)</td>
<td>6 (14)</td>
<td>.51</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (5)</td>
<td>4 (20)</td>
<td>1 (5)</td>
<td>6 (14)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>3 (15)</td>
<td>0</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (5)</td>
<td>2 (5)</td>
<td>.25</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15-30 No. (%)</td>
<td>3 (15)</td>
<td>4 (20)</td>
<td>4 (18)</td>
<td>11 (26)</td>
<td>.05</td>
</tr>
<tr>
<td>&gt;30-50 No. (%)</td>
<td>7 (35)</td>
<td>16 (80)</td>
<td>18 (82)</td>
<td>41 (98)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>40 (11)</td>
<td>42 (10)</td>
<td>41 (11)</td>
<td>41 (11)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>35-99</td>
<td>36-99</td>
<td>16-96</td>
<td>18-19</td>
<td></td>
</tr>
<tr>
<td>Heroin use, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime, y</td>
<td>15.1 (11.9)</td>
<td>17.7 (12.1)</td>
<td>19.7 (8.0)</td>
<td>17.7 (11.4)</td>
<td>.29</td>
</tr>
<tr>
<td>Past month, d</td>
<td>29.2 (23.5)</td>
<td>28.7 (4.2)</td>
<td>28.4 (2.4)</td>
<td>27.2 (2.2)</td>
<td>.56</td>
</tr>
<tr>
<td>Methadone use, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime, y</td>
<td>1.5 (3.3)</td>
<td>1.1 (1.7)</td>
<td>3.0 (2.7)</td>
<td>3.9 (3.5)</td>
<td>.06</td>
</tr>
<tr>
<td>Past month, d</td>
<td>9.9 (13.9)</td>
<td>9.0 (8.4)</td>
<td>9.7 (3.5)</td>
<td>9.5 (8.4)</td>
<td>.47</td>
</tr>
<tr>
<td>Other opioid use, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime, y</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Past month, d</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Cocaine use, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime, y</td>
<td>4.4 (3.5)</td>
<td>4.0 (4.8)</td>
<td>4.7 (3.2)</td>
<td>4.8 (3.6)</td>
<td>.34</td>
</tr>
<tr>
<td>Past month, d</td>
<td>3.1 (4.0)</td>
<td>7.1 (4.8)</td>
<td>7.1 (4.8)</td>
<td>5.7 (4.7)</td>
<td>.10</td>
</tr>
<tr>
<td>Alcohol use, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime, y</td>
<td>6.0 (4.1)</td>
<td>3.0 (0.0)</td>
<td>2.3 (0.0)</td>
<td>3.6 (4.1)</td>
<td>.11</td>
</tr>
<tr>
<td>Past month, d</td>
<td>12.0 (13.2)</td>
<td>9.0 (11.3)</td>
<td>9.0 (11.3)</td>
<td>9.0 (11.3)</td>
<td>.51</td>
</tr>
<tr>
<td>Cannabis use, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime, y</td>
<td>0.6 (0.3)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>.11</td>
</tr>
<tr>
<td>Past month, d</td>
<td>12.0 (13.2)</td>
<td>9.0 (11.3)</td>
<td>9.0 (11.3)</td>
<td>9.0 (11.3)</td>
<td>.51</td>
</tr>
</tbody>
</table>

*P values for comparisons of the distributions of sex and age among treatment groups are based on the Cochran-Mantel-Haenszel (general association) test stratified by medical center. P-values for comparisons of the distributions of age and drug use among treatment groups are based on a 2-way analysis of variance model containing the effect of treatment and medical center.

Comer SD 2006
Evidence for injectable naltrexone

Figure 1. Plasma levels of naltrexone (A) and 6-β-naltrexol (B) by study week and treatment group. Error bars represent standard deviation.
Evidence for injectable naltrexone

Figure 2. Retention in treatment by study week and treatment group.
Evidence for injectable naltrexone

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

[Diagram showing trial profile with details on eligibility screening, randomisation, and completion]

Krupitsky E, 2011
Evidence for injectable naltrexone

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX (n=126)</th>
<th>Placebo (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.4 (4.8)</td>
<td>29.7 (3.6)</td>
</tr>
<tr>
<td>Men</td>
<td>113 (90%)</td>
<td>107 (86%)</td>
</tr>
<tr>
<td>White</td>
<td>124 (98%)</td>
<td>124 (100%)</td>
</tr>
<tr>
<td>Duration of opioid dependence (years)</td>
<td>9.1 (4.5)</td>
<td>10.0 (3.9)</td>
</tr>
<tr>
<td>Days of pre-study inpatient detoxification</td>
<td>18 (9)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Opioid craving scale</td>
<td>18 (23)</td>
<td>22 (24)</td>
</tr>
<tr>
<td>HIV serology positive</td>
<td>51 (40%)</td>
<td>52 (42%)</td>
</tr>
<tr>
<td>Hepatitis C positive</td>
<td>111 (88%)</td>
<td>117 (94%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%). XR-NTX=extended-release naltrexone.

Table 1: Demographics and baseline clinical characteristics
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.
Evidence for injectable naltrexone

Krupitsky E, 2011
Evidence for injectable naltrexone

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX (n=126)</th>
<th>Placebo (n=124)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>9 (7%)</td>
<td>3 (2%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8 (6%)</td>
<td>1 (1%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (5%)</td>
<td>4 (3%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Influenza</td>
<td>6 (5%)</td>
<td>5 (4%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>6 (5%)</td>
<td>1 (1%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Toothache</td>
<td>5 (4%)</td>
<td>2 (2%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (3%)</td>
<td>3 (2%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>≥1 adverse event</td>
<td>63 (50%)</td>
<td>40 (32%)</td>
<td>0.005</td>
</tr>
<tr>
<td>≥1 drug-related adverse event</td>
<td>33 (26%)</td>
<td>12 (10%)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥1 serious adverse event*</td>
<td>3 (2%)</td>
<td>4 (3%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Discontinued owing to adverse events</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>--</td>
</tr>
</tbody>
</table>

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
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 if still using
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
Who are good patients for IM naltrexone?

- For those who undergo detoxification
- For those with increased stress/relapse risk
- Short or less severe history of physical dependence
- Due to agonist/addiction issues
  - Professional boards
  - Supervisors
  - Drug court judges
  - Military
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. People not interested in agonist therapy
5. Adolescents or young adults with opioid use disorder
Who are good patients for IM naltrexone?

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PAIN and Injectable Naltrexone

• Treat pain aggressively

• Non-pharmacologic therapies:
  • Physical Therapy
  • Massage
  • Acupuncture
  • Mindfulness

• Pharmacologic
  • NSAIDS, Regional blocks, Neuropathic agents
  • Opioids...
Opioids and Injectable Naltrexone

• Few clinical trials about reversing the opioid receptor blockade

• In emergencies:
  • Higher than usual dose of rapid acting opioid medication is needed
  • Monitored by professionals

• Where medical alert card and/or notification
Additional Treatment

• 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
CASE SET 2: Angel

Well isn't that special
CASE SET 2: Angel

• Angel is a 23 year old honorably discharged Veteran of the Marines and is now working as a health tech as a local marine base clinic
• She sustained a spinal fracture and amputation of her left leg in the service
• She has no significant past medical history
• She is on no medications
• She recently began to use heroin sporadically, once or twice a week
• She is worried about disclosure of her opioid use disorder and has not sought treatment
CASE SET 2: Angel - QUESTIONS

• Is Angel a good candidate for pharmacotherapy for her opioid use disorder?

• What are medications and treatments that should be offered Angel?
  • Are there any considerations regarding the type of pharmacotherapy?
Special:

The naloxone challenge test *controversy* in administration
The naloxone challenge test *controversy*

• 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
  • If signs of opioid withdrawal are still observed following naloxone challenge
  • If signs occur, the naloxone challenge can be repeated in 24 hours.
The naloxone challenge test *controversy*

**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, especially those with opioid dependence, may respond to lower doses of naloxone. In some cases, 0.1 mg IV naloxone has produced a diagnostic response.
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
Treat opioid withdrawal syndrome (OWS)

- Clonidine 0.1 mg po q2 hours prn for tremors
- Anti-emetic for vomiting
- Anti-diarrheal for diarrhea
- NSAIDS for cramps
- Etc...

- Most precipitated withdrawal can be treated over 1-2 days
DISCUSSION

Further questions, please contact me!

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