Pharmacology of Opiate Dependence Medication

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Anthony Sones, CRS, Tadiso Inc.
Please share your tools and resources!

Email Kaynaat.Syed@haponline.org
Today’s Recovery Story…

Anthony Sones, CRS

- Certified Recovery Specialist, Tadiso Inc.
- Runs 3 Recovery homes, In the Solution Foundation
- Opioid prevention education w/ Pittsburgh EMS
Pharmacology of Medications for Opioid Use Disorder

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Outline

Why medications for Opioid Use Disorder?
How do you choose between options?
What new medications are available and how do they work?
What’s new in the treatment of special populations?
Why do we need medications?

- Detoxification followed by counseling alone results in relapse in an overwhelming number of cases
  - VA trial 112 entered detox 6 were in treatment and opiate free at 90 days (Journal of Addictive Diseases, 2006; 25(4):27-35)
  - 516 patients tapered with buprenorphine over 7 or 28 days. Only 18% were opiate free at 1 month follow up and 13% opiate free at 3 months (Addiction 2009; 104(2): 256-65)
Why do we need medications?

- Detoxification followed by counseling alone increases the risk for overdose and death
  - 276 opiate addicted patients entered rehab, 24 overdosed and died over an 8 year follow up, 6 in the first 4 weeks (Drug Alcohol Depend 2010; 108: 65-69)
  - 137 detoxified opiate addicted patients were followed, 5 died within a year of discharge from rehab, 3 within the first 4 months (BMJ 2003; 326:959-60)
Opioid overdose death rates continue to rise

Figure 3. National Drug Overdose Deaths Involving Any Opioid, Number Among All Ages, by Gender, 1999-2017

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018
Figure 3. National Drug Overdose Deaths Involving Any Opioid, Number Among All Ages, by Gender, 1999-2017

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Medications for opioid use disorder (OUD)

What are the approved medications?

- Methadone
- Naltrexone
- Buprenorphine
Considerations in Choosing medications

- Contraindications & warnings
- Patient characteristics
- Patient preference
Methadone contraindications

- Allergic to methadone
- Respiratory depression
- Paralytic ileus
- Respiratory depression acute asthma
Methadone warnings

- Elderly or debilitated patients
- Head injury
- Prolonged QT interval
- Label warning for sedation
Methadone patient characteristics

- Does not want detoxification
- Prefers a full agonist
- Does not want naltrexone or buprenorphine
Buprenorphine contraindications

- Allergic to buprenorphine or naloxone
Buprenorphine warnings

- Severe hepatic impairment
- Head injury
- Comorbid sedative use
- Possibility of precipitated withdrawal
- Label warning for sedation
Buprenorphine patient characteristics

- Patients not dependent on sedatives or alcohol
- Patients who can manage medications
- Patients with a stable place to live
- Psychiatrically stable
Naltrexone contraindications

• Full agonist opioid therapy
• Physical dependence on opioids
• Very high BMI
• Allergic to naltrexone
• Sensitivity to polylactide-co-glycolide, carboxymethylcellulose, or any components of the diluent.
Naltrexone warnings

- Severe liver disease
- Pregnancy
- Loss of tolerance
• Alcohol use to intoxication in the 30 days before randomization was a significant moderator: during the treatment phase, those who reported being recently intoxicated before randomization to XR-NTX relapsed to opioids at a rate (56%) similar to TAU (58%), while those without alcohol intoxication in the prior 30 days had a lower rate of opioid relapse (41% vs. 65%, respectively, P<0.04).
Methadone vs. sublingual buprenorphine

Retention in MMT often Superior to Buprenorphine

Addiction. 2014 109(1);79–87
XR-NTX vs. sublingual buprenorphine

Relapse-free Survival Over 24 Weeks

A

B

Advances in the treatment of Opioid Use Disorder

- Focus on new buprenorphine products
  - Probuphine
  - Cam 2038 (Brixadi)
  - Sublocade
Adequate Adherence in Less Than 50% of Patients

• In a trial involving subjects with opioid use disorder participating in office based buprenorphine treatment, it was found that only 48% of the subjects were adherent to the medication as defined as having 80% or more of their visits associated with a positive UDS for buprenorphine. (Am. J. Addict., 2016, 25, 110–117)

• In an examination of medical and pharmacy claims data over a year, only 32% of patients participating in office based buprenorphine treatment took buprenorphine on 80% or more days. (J. Subst. Abuse Treat., 2014, 46, 456–462)
Buprenorphine is diverted

Percent of Applicants Who Knew of Drugs Being Sold on the Street

![Graph showing percent of applicants who knew of drugs being sold on the street from 2005 to 2009. The graph compares different drugs and shows an increasing trend for Buprenorphine and Naloxone, Methadone, Oxycodone, and Amitriptyline.]

Drug Alcohol Depend. 2012; 120:190-195
What injectables / implantables are available?

- Probuphine: approved in the US
- Sublocade (RPB 6000): approved in the US
- Brixadi (CAM 2038): pending approval in the US (Dec 2020)
Probuphine: old technology applied to a new problem

EVA polymer + Buprenorphine = Probuphine®

26 mm long, 2.5 mm diameter
Probuphine trial #3

In patients stabilized on 8 mg or less:
- 6 months on buprenorphine
- On 8 mg or less for 90 days prior to trial
- Abstinent for 90 days prior to the trial

Probuphine was not inferior in the primary outcome “responder”

Probuphine was superior to sublingual buprenorphine in promoting complete abstinence

Probuphine was superior to sublingual buprenorphine in delaying time to first opiate use during the trial

JAMA, 2016; 316(3): 282-290
CAM 2038 - Brixadi

In vivo formation of nanostructured buprenorphine gel depot

- FluidCrystal® injection depot technology
- Multiple small volume fixed dosages in prefilled syringes
- Room temperature storage

Injection of liquid  Gel formation triggered by water uptake  Slow release of drug  Complete resolution of depot matrix
CAM2038 promoted abstinence from opioids

Percent of no illicit opioid use versus time CAM2038 versus SL BPN/NX (FDA)

Negative urines and self-reports for illicit opioid use by week. Missing imputed positive.  
Negative urines and self-reports for illicit opioid use by week. Missing not imputed.


Source: Data on file

Missing urine samples imputed as positive. * P<0.05

Missing urine samples treated as missing. * P <0.05

○ denotes random urine samples collected during the month
CAM2038 reduced opioid withdrawal and craving

Effective long-acting suppression of withdrawal and cravings

Mean withdrawal (COWS score: 0-48)

Mean craving score (Need to use VAS)

Sublocade (RBP 6000) for opioid use disorder

- Developed by Indivior (Reckitt Benckiser spin off)
- Once a month injectable buprenorphine
- Atrigel system – liquid polymer solidifies in tissue
- Prefilled syringe
- Tested a little differently than CAM 2038
  - Straight up active (2 doses) vs. Placebo
Sublocade for OUD

Sublocade Promotes Abstinence from Opioids

**RBP-6000: PRIMARY & SECONDARY ENDPOINTS**

**Primary:** CDF of % urine samples negative for opioids + negative self-reports of illicit opioid use (Weeks 5 to 24)

**Key secondary:** ≥80% of urine samples negative for opioids + negative self-reports of illicit opioid use (Weeks 5 to 24)

![Graph showing percentage of subjects with abstinence](image)

Sublocade suppressed opioid withdrawal and craving

**Clinical Opiate Withdrawal Scale (COWS) + Craving VAS**

Mean COWS (LOCF)

Mean Opiate Craving VAS (LOCF)

- **RBP-6000 300/100 mg + IDC (n=194)**
- **RBP-6000 300/300 mg + IDC (n=196)**
- **Placebo + IDC (n=99)**

Special populations

- Update on the treatment of OUD in Pregnancy
- Update perioperative treatment with buprenorphine
How do you treat OUD in pregnant women?

- Treatment with methadone or buprenorphine is recommended over detoxification and drug free treatment.
  - Less relapse
  - Less fetal exposure to maternal drug use
  - Less fetal exposure to other maternal risk behaviors
  - Enhanced compliance with obstetric care
  - Enhanced neonatal outcomes
The MOTHER study offered new options

- 175 pregnant opiate dependent women
- Flexible dose
- Double blind double dummy
- Primary outcomes
  - Number of neonates requiring treatment for NAS,
  - Peak NAS score,
  - Total amount of morphine needed to treat NAS,
  - Length of the hospital stay for neonates,
  - Neonatal head circumference.
Buprenorphine was superior to Methadone in Several NAS Outcomes

Buprenorphine for pregnant women

18% dropout methadone

33% dropout buprenorphine

Perioperative management of buprenorphine

Figure 1. Algorithm for perioperative management of buprenorphine. BUP = buprenorphine.
Questions and Discussion

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