Review of Opioid Pharmacology and Emerging Treatment Options for Opioid Dependence

KRISTEN MCLAIN, PHARMD
PGY2 CRITICAL CARE PHARMACY RESIDENT
UNIVERSITY OF ILLINOIS AT CHICAGO
42ND ANNUAL ASPSN CONVENTION
SEPTEMBER 25, 2016
Objectives

- Describe the pharmacology of commonly prescribed opioid medications.
- Discuss emerging treatment options for patients with opioid dependence.
Disclosure

No actual or potential conflicts of interest to disclose.
NOW, THEREFORE, I, BARACK OBAMA, President of the United States of America, by virtue of the authority vested in me by the Constitution and the laws of the United States, do hereby proclaim September 18 through September 24, 2016, as Prescription Opioid and Heroin Epidemic Awareness Week. I call upon all Americans to observe this week with appropriate programs, ceremonies, and activities that raise awareness about the prescription opioid and heroin epidemic.

IN WITNESS WHEREOF, I have hereunto set my hand this sixteenth day of September, in the year of our Lord two thousand sixteen, and of the Independence of the United States of America the two hundred and forty-first.

BARACK OBAMA
History of Opioids

- Opium poppy originally cultivated in Mesopotamia ~3400 BC

- Natural opioids derived from the resin of the opium poppy, *Papaver somniferum*

- Derived from *opos*, the Greek word for “juice”
Review of Opioid Pharmacology
Terminology

- **Opium**: a mixture of alkaloids from the poppy seed
- **Opiates**: alkaloids that occur naturally (morphine or codeine)
- **Opioids**: all compounds that work at the opioid receptors
- **Narcotic**: from the Greek word for “stupor”, was originally used to describe medications for sleep. Legal term for drugs with abuse or addictive potential
Opioid Receptors

- Central nervous system (CNS), pituitary gland, gastrointestinal (GI) tract, grey matter of the brain, and dorsal horn of the spinal cord

- Stimulated by endogenous peptides produced in response to noxious stimuli
  - Endorphins: Bind to the mu (\( \mu \)) receptor
  - Enkephalins: Relatively selective delta (\( \delta \)) ligands
  - Dynorphins: highly selective at the mu (\( \mu \)) receptor
<table>
<thead>
<tr>
<th>Mu (μ) Receptors</th>
<th>Brainstem and Medial Thalamus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
<td></td>
</tr>
<tr>
<td>Physical dependence</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
</tr>
</tbody>
</table>
Kappa (κ) Receptors | Limbic Areas, Brain Stem, and Spinal Cord

<table>
<thead>
<tr>
<th>Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Psychomimetic effects</td>
</tr>
<tr>
<td>• Anxiety</td>
</tr>
<tr>
<td>• Strange thoughts</td>
</tr>
<tr>
<td>• Nightmares</td>
</tr>
<tr>
<td>• Hallucinations</td>
</tr>
</tbody>
</table>
Delta (δ) Receptors | Brain

Analgesia

• Without many adverse effects

Not well understood
Opioid Classification

- **Pure Mu (μ) agonists (morphine)**
  - Opioid analgesics

- **Agonists-antagonists (butorphanol)**
  - Agonist at Kappa (κ) receptor to produce weak analgesia
  - Weak antagonist at the Mu (μ) receptor
  - Results in more dysphoria and psychomimetic effects
  - Lower risk of respiratory depression

- **Pure antagonists (naloxone)**
  - Reverse CNS and respiratory depression in overdose situations
  - Block the Mu (μ) and Kappa (κ) receptors
  - Do not produce analgesia
Opioid Adverse Effects
Central Nervous System

- Sedation
- Euphoria
- Dysphoria
- Changes in mood
- Mental clouding
- Myoclonus
Neuroendocrine

Decreased release of gonadotropin-releasing hormone and corticotropin-releasing factor from the hypothalamus

Decreased levels of luteinizing hormone, follicle-stimulating hormone, adrenocorticotrophic hormone, and β-endorphins

May alter levels of testosterone and cortisol
Respiratory

Mu (μ) receptor primarily involved in respiratory depression, although activation of the kappa (κ) receptor also contributes

Brain-stem less responsive to carbon dioxide

Increased respiratory depression

Depress cough reflex in the medulla
Cardiovascular

Peripheral vasodilation
  • Release of histamine

Decreased peripheral resistance

Inhibition of baroreceptor reflexes

Methadone associated with torsades de pointes
  • EKG for monitoring
Gastrointestinal

Nausea and vomiting
- Chemoreceptor trigger zone in the medulla
- Sensitize vestibular system
- Slowing of GI motility

Constipation
- Delayed gastric emptying
- Decreased gut motility
- Decreased peristalsis

May lead to
- Ileus
- Fecal impaction
- Obstruction

Tolerance does not develop to constipation
Genitourinary

- Increased smooth muscle tone
  - Bladder spasms and urgency

- Increased urethral sphincter tone
  - Difficult urination and urinary retention
Biliary

- Increased smooth muscle tone
- Sphincter of Oddi
- Decreased pancreatic and biliary secretions
- Biliary spasm
### Skin and Eye

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing of face and neck</td>
<td>• Dilated blood vessels</td>
</tr>
<tr>
<td>Histamine release</td>
<td>• Itching</td>
</tr>
<tr>
<td>Miosis</td>
<td>• High doses of pure mu (µ) agonists</td>
</tr>
</tbody>
</table>
Overdose

- Respiratory depression
- Somnolence
- Stupor
- Coma
- Cold, clammy skin
- Miosis
- Pulmonary edema
- Bradycardia
- Hypotension
- Death
Opioid Dependence
# Opioid Tolerance and Dependence

<table>
<thead>
<tr>
<th>Tolerance</th>
<th>Physical dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Larger dose required to produce same response</td>
<td>• Occurrence of a withdrawal syndrome after stopping or quickly decreasing dose of opioid without titration</td>
</tr>
<tr>
<td>• Does not occur for constipation or neuroendocrine effects</td>
<td>• Should avoid abrupt discontinuation</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Addiction</td>
<td></td>
</tr>
<tr>
<td>• Behavior pattern involving the continued use of a substance for nonmedical reasons despite harm</td>
<td></td>
</tr>
<tr>
<td>• Compulsive use, craving</td>
<td></td>
</tr>
</tbody>
</table>
Opioid-Use Disorders

2013 Diagnostic and Statistical Manual of Mental Disorders
Opioid-Use Disorder Criteria

- Use of an opioid in **increased amounts or longer than intended**
- Persistent wish or unintended effort to cut down or control opioid use
- Excessive time spent to obtain, use, or recover from opioid use
- Strong desire or urge to use an opioid
- **Interference of opioid use with important obligations**
  - Continued opioid use despite resulting interpersonal problems, social problems, or both
  - Elimination or reduction of important activities because of opioid use
- Use of an opioid in **physically hazardous situations**
  - Continued opioid use despite resulting physical problems, psychological problems, or both
- **Need for increased doses** of an opioid for effects, **diminished effect per dose**, or both
- Withdrawal when dose of an opioid is decreased, use of a drug to relieve withdrawal, or both
Opioids in the United States

~3 million people in the United States have a current or past opioid-use disorder

~400,000 have used heroin in the past month

~4 million have reported nonmedical use of prescription pain killers

## Treatment of Opioid Withdrawal

- Can improve patient’s health and facilitate participation in a rehabilitation process
  - Think more clearly once acute withdrawal phase has passed

- Medically supervised withdrawal is usually not sufficient to produce long-term recovery
  - May increase risk of overdose among patients who have lost their tolerance to opioids

- Repeated misuse of opioids produces tolerance and long-lasting craving
  - Requires additional treatment in order to avoid relapse
Acute Withdrawal Syndromes

- Diarrhea
- Dilated pupils
- Generalized pain
- Restlessness
- Anxiety
- Diaphoresis
Symptoms of Abstinence After Discontinuation

Begin **within hours** after receiving prior dose of **shorter-acting opioids** such as heroin and decrease greatly by day 4.

Withdrawal begins after **several days** with **long-acting opioids** and decreases at approximately day 10.

Opioid **antagonist-precipitated withdrawal** begins immediately and lasts ~1 hour after administration.
## Withdrawal Treatment

| Most effective approach is to prescribe a long-acting oral opioid | • Relieves symptoms  
• Can be gradually tapered |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Only licensed addiction-treatment programs and physicians can administer opioids to treat opioid-use disorders</td>
<td>• Medically supervised withdrawal can involve use of nonopioid medications to control symptoms</td>
</tr>
</tbody>
</table>
| Less effective, but more available and does not require specialty clinic | • α₂-adrenergic agonists  
• Benzodiazepines |
Generally Available Treatment Options

**Autonomic overactivity**
- $\alpha_2$-adrenergic agonists: clonidine (Catapres), tizanidine (Zanaflex)
- Increased HR, BP, anxiety, chills, piloerection

**Anxiety, insomnia**
- Benzodiazepines: temazepam (Restoril), diazepam (Valium)
- Other sedating drugs

**Gastrointestinal**
- Diarrhea: loperamide (Imodium)
- Antiemetic: prochlorperazine (Compazine), ondansetron (Zofran)

**Pain**
- Nonsteroidal anti-inflammatory drugs: naproxen (Aleve)

**Efficacy**
- Not as effective in relieving symptoms as methadone or buprenorphine taper

Cochrane Database Syst Rev 2014;3:CD002024
Opioids for Withdrawal Treatment

- Methadone and Buprenorphine
- Only available in specialty programs or physicians with special training
- Long-acting mu-opioid receptor agonists
- Diminish symptoms and then wean off drug
- Oral medications for ease of administration
Methadone Taper

Oral mu-opioid agonist

Half-life: 15 to 40 hours

First dose to minimize withdrawal but not oversedate patients

Doses decreased 10-20% every 1 to 2 days over several weeks

Can be tapered quicker (1 week) in inpatients who are inpatient for withdrawal from short-acting drugs (Ex: heroin)
Buprenorphine Taper (Buprenex, Suboxone, Subutex)

Mu-opioid receptor partial agonist, delta-receptor agonist, and kappa-receptor antagonist

Sublingual monotherapy or combination with naloxone as a sublingual film strip

Half-life: 3 hours (Does not dissociate easily from mu-opioid receptors)

Less sedation and respiratory depression compared to methadone

May precipitate more intense withdrawal: Initiate 12 to 18 hours after last opioid administration for patients abusing short-acting opioids

Initial dosing to stabilize patient for 3 to 5 days

Dose decreased over 2 or more weeks
Naltrexone (ReVia, Vivitrol)

Mu-opioid receptor antagonist

Abstinence-Oriented Opioid Rehabilitation

Blocks opioid effects to help maintain abstinence in highly motivated patients who have completed detoxification and are at risk for relapse

Oral tablets daily (ReVia) or extended-release monthly IM injection (Vivitrol)

Patients must be free of psychological opioid dependence
Opioid Maintenance Approach

- Opioid-dependent patients who are hesitant or unable to discontinue opioids
- Avoid past reinforcement associated with needles
- Inexpensive and long-acting to avoid daily withdrawal symptoms and enhance adherence
# Opioid Maintenance Approach

## Goals

- Improve health
- Avoid contaminated needles and risk of HIV/hepatitis C infection
- Improve interpersonal relationships
- Ability to work
- Decreased cravings and reward effects of illicit opioids
- Decreased crimes to pay for illicit drugs
# Methadone Maintenance

- Offered only through approved clinics

- Require daily patient participation in order to receive the drug initially

- Patients must have opioid-use disorders with physiologic features or have high risks associated with relapse (Ex: pregnancy)

- Overdose is possible if titrated too quickly during initial stages

- QT prolongation can contribute to cardiac arrhythmias with doses > 100 mg/day
Methadone Maintenance

Induction and early stabilization (Weeks 1 and 2)
• Begin 15-30 mg and increase by 10-15 mg every 3-5 days up to 50-80 mg/day for most patients

Late stabilization (Weeks 3 – 6)
• Adjust dose based on side effects, craving, and adherence (Typical dose 80-100 mg/day)

Maintenance (Week 6 – 1 year)
• Consider weaning from methadone after > 1 year
Buprenorphine Maintenance

Physicians must be approved to prescribe buprenorphine for maintenance
- Originally limited to 30 patients, increased to 275 patients in July 2016

Reduces opioid withdrawal symptoms
- Partially blocks intoxication from other opioids

Risk for overdose during induction
- Mortality lower with buprenorphine than methadone for induction

Maintenance therapy involves combination of buprenorphine with naloxone in 4:1 ratio
- Does not precipitate withdrawal unless it is injected intravenously
Buprenorphine Maintenance

Induction and early stabilization (~7 days)
- Begin with 4-8 mg and increase to 16 mg/day on the second day with further daily increases by day 7

Stabilization (~ Week 8)
- Increase doses to as high as 32 mg/day depending on craving and side effects

Maintenance (Week 9 – 1 year)
- Consider weaning after ~1 year

N Engl J Med 2016;375:357-68
Methadone vs Buprenorphine

Direct comparisons show improved outcomes with both medications

Methadone may be associated with higher rates of patient retention

Buprenorphine is more expensive, but safer than methadone during induction

J Subst Abuse Treat 2010;39:340-52
Cochrane Database Syst Rev 2008;2:CD002207
J Stud Alcohol Drugs 2013;74:605-13
Probuphine: buprenorphine implant

Approved by the FDA in May 2016 for the maintenance treatment of opioid dependence

Each implant contains buprenorphine 80mg to deliver a continuous low dose over 6 months

For patients who are stable on low-moderate doses of other forms of buprenorphine
2016 CDC Guidelines for Prescribing Opioids for Chronic Pain

| Provides recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care |
| Improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain |
| Improve safety and efficacy of pain treatment |
| Reduce the risks associated with long-term opioid therapy |
| • Opioid use disorder |
| • Overdose |
| • Death |

Patient Case

JD 39 year old male with a skull defect following aneurysm clipping with simultaneous decompressive craniectomy for a subarachnoid hemorrhage. About 25 months later he now presents for cranioplasty.

PMH: HTN, opioid dependence

Patient has been on Suboxone maintenance for 18 months. He was initially started on Suboxone 24mg/6mg sublingual film daily. He has since been tapered down to Suboxone 8 mg/2mg sublingual film daily.
Patient Case

Would you expect JD’s pain to require lower or higher amounts of pain medication to control post-operatively?

Would you continue JD’s home maintenance dose of Suboxone 8mg/2mg sublingual film daily while he is admitted as an inpatient?
Patient Case

JD expresses concern about receiving Suboxone in addition to the fentanyl and morphine he received during and after his procedure.

The physician who prescribed his Suboxone warned him about injecting pain medications while taking Suboxone. He is worried that he will go into withdrawal because he has received IV pain medications during his admission.
Patient Case

Naloxone has no clinically significant effect when administered by the sublingual route, although blood levels of the drug are detectable.

Withdrawal effects due to naloxone administration are only of concern when the sublingual film is dissolved and administered intravenously.
Patient Case

JD refuses his Suboxone 8mg/2mg sublingual film. He states that at home he splits the film into two pieces and takes half in the morning and the remaining half in the evening.

He insists that taking the entire dose at once will make him very sick and asks if he can take the rest of his dose later.
Patient Case

Suboxone prescribing information only recommends divided doses on Day 1 of induction.

Patients will receive Suboxone 2mg/0.5mg or 4mg/1mg and may titrate up in increments of 2mg or 4mg approximately every 2 hours, **under supervision**, up to 8mg/2mg based on control of acute withdrawal symptoms.

On Day 2 and thereafter, patients should take prescribed dose once daily.
Key Points

- Opioids exert their effects by binding at the mu, delta, or kappa receptors.
- Opioids have a wide variety of effects on the body, depending on receptor type and location.
- Opioid dependence remains a problem in the United States, with many patients at an increased risk for withdrawal.
- Methadone and buprenorphine may be used for opioid maintenance therapy.
- Important for healthcare providers to be aware of opioid use disorders and the various treatment regimens available.
Review of Opioid Pharmacology and Emerging Treatment Options for Opioid Dependence

KRISTEN MCLAIN, PHARMD
PGY2 CRITICAL CARE PHARMACY RESIDENT
UNIVERSITY OF ILLINOIS AT CHICAGO
KMMCLAIN@UIC.EDU