THE PAST, PRESENT, AND FUTURE OF OPIATES

Leonard Rappa, PharmD, BCPP
Board Certified Psychiatric Pharmacy Specialist
Professor, Florida A&M University
College of Pharmacy and Pharmaceutical Sciences
Broward Health Imperial Point, Ft. Lauderdale, Florida

email: leonard.rappa@famu.edu
Recognize signs and symptoms of a drug use disorder

Understand the severity of opiate addiction and abuse in America

Assess the risks of co-prescribing certain medications with opiates

Evaluate prescribing patterns and overdoses specific to Florida

Comprehend the significance of opium and its derivatives to mankind

Be able to identify situations in which an opiate blocker should be recommended or used

Identify medications used for detoxification and post-detox Medication Assisted Therapy
EFFECTS ON SOCIETY

♦ #1 national health problem

♦ $80 billion a year in “economic burden” from opioid epidemic in the past

♦ US lifespan is decreasing
  ★ More deaths, illness, accidents, disabilities than any other health problem
  ★ Death from prescription drug overdoses has replaced car accidents as the leading cause in adults under 50

  ★ DAWN (Drug Abuse Warning Network)
    ☑ http://www.samhsa.gov/data

♦ Opiate addiction & abuse directly correlates with higher doses and longer duration of use

*National Center for Health Statistics and National Safety Council*
WHAT DO WE KNOW ABOUT THE OPIOID CRISIS?

♦ From the National Institutes of Health (NIH.gov), Centers for Disease Control (CDC.gov), the Substance Abuse and Mental Health Services Administration (SAMHSA.gov), and the National Institutes of Drug Abuse (DrugAbuse.gov)

♦ $115 billion economic burden to the US in 2017

♦ Cost of treatment reduces overall societal costs

♦ Opiate Use Disorder is a medical disease that is not easily fixed!!!
DSM 5 Diagnostic Criteria

Pattern of opioid use leading to significant impairment or distress within a 12-month period:

- Taking in larger amounts or over a longer period than was intended
- Desire or unsuccessful efforts to cut down or control use
- Spending a lot of time to get, use, or recover from use
- Craving, or a strong desire or urge to use opioids
- Failure to fulfill major role obligations at work, school, or home
- Continuing to use despite persistent or recurrent social or interpersonal problems
- Important social, occupational, or recreational activities are given up or reduced
- Use in situations that are physically hazardous
- Continued use regardless of worsened physical or psychological problems
- Increased tolerance, so need to use more opiate for same effect
- Opioids are used to relieve or avoid withdrawal symptoms
Genetic traits found – can predispose or protect
- Thousands of genes with some key pathways identified
- [http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.0040002](http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.0040002)

Gene variabilities in drug metabolism

Gene expression and opiate receptor availability

Other common elements:
- Environmental trauma and stressors contribute
- High mental health comorbidity
- Higher rates of Antisocial Personality Disorder
THREE BRAIN REGIONS

- **Nucleus Accumbens (NA)**
  - Anterior in the mesolimbic system
  - Mediates the positive reward behaviors

- **Amygdala (striatum)**
  - Mediates the negative or fear-motivated behaviors

- **Prefrontal cortex (PFC)**
  - Involved in decision making by assigning stimuli to direct behavioral response

ABOUT OPIATES
**WHAT IS AN OPIATE?**

- **OPIATE** or **OPIOID**
  - Resins extracted from seed pod of *poppy* plants
    - Drugs derived from the opium poppy
  - Natural endorphins
  - Any of several synthetic compounds having effects similar to natural opium alkaloids and their derivatives
    - Having agonist effects at the opioid receptors in the body
## OPIATE RECEPTOR EFFECTS

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Mu}_1 (\mu_1)$</td>
<td>Analgesia, euphoria</td>
</tr>
<tr>
<td>$\text{Mu}_2 (\mu_2)$</td>
<td>Constipation, respiratory depression</td>
</tr>
<tr>
<td>Kappa ($\kappa$)</td>
<td>Supraspinal &amp; spinal analgesia, dysphoria, hallucinations</td>
</tr>
<tr>
<td>Delta ($\Delta, \delta$)</td>
<td>Psychotomimetic effects, slowed GI transit Analgesia through the endorphin, enkephalin, and dynorphin system</td>
</tr>
</tbody>
</table>
PRESCRIPTION OPIATE CLASSES

♦ Schedule I (illegal) II, III, IV, and V

♦ Natural
  ★ Codeine (various) (CIII and CV)
  ★ Morphine (MSContin, Kadian, others) (CII)

♦ Synthetic
  ★ Butorphanol (Stadol®) (CIV)
  ★ Fentanyl (Actiq®/Duragesic®) (CII)
  ★ Meperidine (Demerol®) (CII)
  ★ Methadone (Dolophine®) (CII)
  ★ Pentazocine (Talwin®) (CIV)
  ★ Tapentadol (Nucynta/ER) (CII)
  ★ Tramadol (Ultram/ER) (CIV)

Italics indicate the drug is a mixed agonist/antagonist
PRESCRIPTION OPIATE CLASSES

♦ Schedule I (illegal) II, III, IV, and V

♦ Semi-synthetic
  ★ Buprenorphine (Suboxone, Subutex®, Butrans®) (CII)
  ★ Diacetylmorphine (Heroin) (CI - illegal)
  ★ Hydromorphone (Dilaudid®) (CII)
  ★ Hydrocodone (Hycodan® / various) (CII)
  ★ Nalbuphine (Nubain®) (not controlled)
  ★ Oxycodone (Percodan®, Percocet, Oxycontin) (CII)
  ★ Oxymorphone (Opana, Numorphan) (CII)

Italics indicate the drug is a mixed agonist/antagonist
DEFINITIONS

◆ Abuse
  ★ Misuse or excessive use of anything
  ★ 0.6-8% who receive Rx opiates abuse them
  ★ 35 million have used opioids non-medically

◆ Addiction
  ★ A chronic brain disease
  ★ Habitual psychological and physiological dependence on a substance or practice
  ★ Not using as planned / out of voluntary control

◆ Pseudoaddiction
  ★ Increased pain forces patient to seek increased doses
Psychological dependence
- Drug craving and drug-seeking behaviors
- 5.7-37.1% show drug-seeking behaviors

Physical dependence
- A biological adaptation at the cellular level
- Result is tolerance – need more drug to get same result
- 3.1-25% become physically dependent

Withdrawal
- A syndrome caused by the abrupt cessation of the use of a drug in an habituated individual
- Withdrawal effects seen if stopped
- Patient appears “drug-seeking” but is not doing it for pleasure
## 2017 NATIONAL SURVEY ON DRUG USE AND HEALTH (NSDUH)

<table>
<thead>
<tr>
<th>% OF US POPULATION</th>
<th>DRUG BEING MISUSED</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.6*</td>
<td>Any illicit drug</td>
<td>Use is significantly increasing</td>
</tr>
<tr>
<td>8.9*</td>
<td>Marijuana</td>
<td>Use is significantly increasing</td>
</tr>
<tr>
<td>1.4</td>
<td>Prescription opiates</td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td>Sedatives / tranquilizers</td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>Cocaine</td>
<td>Use is increasing in Florida</td>
</tr>
<tr>
<td>0.6</td>
<td>Stimulants</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>Hallucinogens</td>
<td></td>
</tr>
<tr>
<td>0.2*</td>
<td>Methamphetamine</td>
<td>Use is significantly decreasing</td>
</tr>
<tr>
<td>0.2</td>
<td>Inhalants</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>Heroin</td>
<td>Use is increasing</td>
</tr>
</tbody>
</table>

(Past year use in ≥ 12 y.o) from www.samhsa.gov

* Indicates a statistically significant change from last year
Mechanism of addiction can be physical, psychological, or both.

Abuse liability of a drug may be related to its potency & half-life:
- Greater potency = more concentrated effects
- Drugs with shorter half-lives wear off quicker and trigger a desire for re-dosing with the drug

Routes of abuse:
- Oral, intravenous, rectal, vaginal, nasal, ophthalmic, and topical
USA consumes 30-80% of the world’s opiates
- Americans consumed 99% of the world’s hydrocodone in 2014
  - #1 dispensed drug in 2014
  - 4.4% of the world’s population
- 80% of opiate Rx’s are from 20% of prescribers
- 65% of prescriptions are for acute treatment
- 3-4% are for chronic therapy
- DEA has lowered annual production quotas for opiates by 35-46%

International Narcotics Control Board
PAIN AND ADDICTION

♦ Pain and addiction are interrelated
♦ Over 2 million Americans live with addiction to opioids
♦ 11-15% of Americans live with daily chronic pain
♦ 43% of Americans have frequent minor pains


♦ NIH website: https://www.nih.gov

♦ Incident Opioid Use Disorder – 0.7%-16.3%

♦ 75% of the world has little to no access to opiates

RX PILLS

♦ ≈ 650,000 prescriptions for opiates dispensed daily

♦ 70% of abused Rx’s come from a relative or friend’s Rx
  ★ Rx abuse accounts for 25%-30% of all drug abuse
  ★ May be leftover from unused Rx, sold, or stolen

♦ Opiate quantities peaked in 2010 at 782 MME* per capita

*MME = “morphine milligram equivalents”
Rx Pills

- Opiate prescriptions peaked in 2012 with 255 mil. Rx’s
  - 83 per every 100 people

- 21-29% prescribed opioids for chronic pain misuse them
  - 8-12% develop an opioid use disorder

- 4-6% of prescription opiate abusers transition to heroin

- 75-80% of today’s heroin abusers began with prescription opiate abuse (NIDA)
Opioid overdoses are 5 x higher than in 1999

2016 - 42,000 Americans died of opioid overdose

Overdoses increased 30% from July 2016 to Sept. 2017
- In 52 areas in 45 states
  - Midwestern saw opioid overdoses increase 70%
  - Opioid overdoses in large cities increase by 54% in 16 states
Overdose Deaths Involving Opioids, by Type of Opioid, United States, 2000-2016

- Any Opioid
- Other Synthetic Opioids (e.g., fentanyl, tramadol)
- Heroin
- Natural & Semi-Synthetic Opioids (e.g., oxycodone, hydrocodone)
- Methadone

½ of opioid-related deaths involve benzos

- US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics
- Risk is 5x greater in first 90 days of a new prescription

17-29% of patients co-prescribed a benzodiazepine

- 80% ↑ from 2001-2013
- Black Box Warning issued against combination

1 in 5 opioid users also may abuse gabapentin

- Gabapentin use ↑ risk of overdose death by 50%
- Gabapentin was 10th most prescribed drug in 2016


BMJ 2017;356:j760 http://dx.doi.org/10.1136/bmj.j760

Floridians are 6.4% of US population

At least 16 overdose deaths a day

Opiate-related deaths have ↑ 35% from 2015 to 2016*
  ★ Majority in Manatee County
  ★ Broward & Palm Beach counties have highest # of overdose deaths from any drug

*According to the FDLE
FLORIDA PRESCRIBING

ioneer 2013 – 13.6 million Rxs in FL for opiates

- **70 Rxs** for every 100 people
- US average was **79 Rxs** for every 100 people

- From 2013 to 2015 – Rxs ↓ by 7.3%
  - 2015: **63 Rxs** for every 100 people

- Neonatal Abstinence Syndrome (NAS)
  - **6.3 per 1000 in FL vs. 6 per 1000 nationally**
FLORIDA OPIATE STATISTICS

- **2015** - 670.9 morphine mg equivalents (MME) prescribed per capita
  - National average is 642.1 MME

- **2018** – 549 facilities for substance abuse services
  - National total is 12,284

- In FL, 5.3% of drug treatment paid by Medicaid
  - 24.2% nationally
2014 – up to 98% of those in FL needing Addiction Treatment are not receiving it

Syringe Exchange Programs

- Only 2 in Florida (Miami-Dade county)
  - Not legally permitted in this state
- 310 nationally

*According to the FDLE*
In 2016 - Opioids were present and/or cause of death in 5,725 cases

★ 22.9 deaths per 100,000
- National average is 9.7 deaths per 100,000

★ 2,798 pure opiate overdose deaths
- 14.4 / 100,000
- National average is 13.3 / 100,000

Drug-related deaths in FL

Facilities that provide MAT

amfAR Opioid & Health Indicators database  http://opioid.amfar.org/FL
HIV IN FLORIDA

- 11% of Americans with HIV live in FL

- Florida has highest rate of newly diagnosed HIV
  - 28 per 100,000 vs. 14.7 nationally (2016) – 90% higher

- 2015 – 8% of newly diagnosed HIV in FL was from IDU (intravenous drug use)
  - 9.1% nationally

- 2014 – 18.1% of ALL American HIV cases from IDU
  - Florida was approx. 13%

NIDA (www.drugabuse.gov)
HISTORY OF OPIATE ADDICTION
Used around the world for over 5000 years
- The most important medicine to some societies
- *Ancient Sumerians* called it the “joy plant”
- Rituals, pain, and pleasure

*Ancient Minoans* (2600-1100 BC) detailed a method for extracting the latex out of the poppy

*Ancient Greeks* called this latex “*opium*”
15th Century
★ Brought to China by The British East India Co.
Laudanum – Early 1500s
★ Paracelsus – Swiss-German Alchemist
★ Derived from the Latin verb laudare, to praise
★ 10% Tincture of opium (≈ 1% morphine) + EtOH
  ○ Different recipes mixed it with crushed pearls, musk, amber, saffron, castor, ambergris, mercury, hashish, cayenne pepper, ether, chloroform, belladonna, whiskey, wine, brandy and nutmeg
16th Century
★ Brought to America with the pilgrims

17th Century
★ Thomas Jefferson used it to treat chronic diarrhea
   ○ Grew poppies on his estate
   ○ He remarked that his use was “habitual”

Addiction later recognized when mixed with tobacco
1805 – *Morphine* isolated from the poppy by Friedrich Sertürner
- Named after Greek god of dreams, *Morpheus*
- Opium latex ≈ 12% morphine
- Wife later overdosed
- Merck began marketing it commercially in 1827

1856 - *Hypodermic needle* invented
- Gave quick high
  - Easy to get from catalogs and magazines
- High rates of addiction after the Civil War (1861-1865)
  - Exact statistics are unknown
19th CENTURY (cont.)

- **1874** – diacetyl-morphine processed from morphine by English chemist Charles R.A. Wright

- **1876** – Opium Dens outlawed in China Town (San Francisco)
  - Fear that Chinese men lured white women into debauchery

- **1888** – 15% of Rx’s in Boston were opiates

https://www.forbes.com/sites/carmendrah/2017/06/12/five-things-heroins-curious-chemistry-history/#4e978528157c
1890s - Opium imports peaked

- Used in most households for coughing, diarrhea, and pain
  - *Mrs. Winslow’s Soothing Syrup*
  - For “fussy” children
- In many other “patent” medications
- Regulations and laws restricting use were non-existent
  - No quality control
By 1895, 1 in 200 Americans addicted to opiates
★ Mostly by upper to middle class white women

1898 – Bayer’s “less addictive” cough suppressant
★ For “consumption” and pneumonia
★ Heroin name means “strong” in German and also refers to an ancient heroic Greek demigod
★ Bayer aggressively marketed it
  ◦ Producing approximately one ton of heroin annually
★ Exported heroin to 23 countries within one year
★ “Tolerance” discovered by physicians in 1899

Sears & Roebuck Catalog
★ $1.50 -- 2 vials of heroin + 2 syringes

Aspirin developed by Bayer one year later
By 1905 ≈ 25% males in China were addicted

1913 – more heroin addicts than morphine

1914 – *Harrison Narcotic Tax Act*
- Heroin outlawed
- Passed because of xenophobia
  - Apocalyptic warnings about various ethnic groups committing unspeakable acts of murder and mayhem
    - Especially “seducing” honest white women
EARLY 20th CENTURY

- “Addiction is a moral failing”
- Government tax stamps needed to dispense it
  - 10,000 doctors arrested in 1st five years
- Stamps were never created or used
- **1924** – heroin production banned/outlawed
- **1925** - League of Nations banned nonmedical use of opiates
1960s – recreational use by the counterculture and Vietnam Vets
★ Surveys found that 20% of soldiers in Vietnam self-identified as an addict
★ Janis Joplin overdosed on heroin in 1970 at age 27
1970s – More xenophobia
★ Heroin increased crime in inner cities
★ Nixon increased drug laws
1973 – Drug Enforcement Administration (DEA) created
1980 – Article in *Journal of Medicine* reported that addiction is rare in treatment of chronic pain
1995 – Oxycontin® heavily marketed
★ Purdue later sued by gov’t in 2007
“Stepped on”, “scrambled”, or “cut”

★ Diluent is added to a drug to increase volume
  ○ Decreases potency to increase profit

★ Most commonly is lactulose
  ○ Can be powdered sugar, corn starch, flour, powdered milk, strychnine, veterinarian drugs, melamine, anthrax, ground drywall, vitamin C, caffeine, talc, baby formula, nicotinamide (Vit. B3), lidocaine, mannitol, sodium bicarbonate

★ Xylazine to cut heroin
  □ A veterinarian-used analog of clonidine (horse tranquilizer)
  □ Abused by itself in Puerto Rico

★ Spiked with other drugs (to mimic or add to the effect)
  ○ Especially fentanyl
“Nod”
★ Nodding off after injecting heroin

“Chasing the dragon”
★ Trying to achieve the first high ever felt
★ When a person melts a drug on tinfoil and then inhales the moving smoke

“Junkie”
★ In New York in the 1920s
★ Morphine & heroin addicts made their livings from salvaging scrap metals from local junk heaps
Diacetyl-morphine is processed from morphine

- 2-4 x more potent than morphine

Most abused and the rapidly acting of the illicit opiates

Black Tar Heroin ("Brown"/"Muck")

- Incomplete acetylation of morphine
- Low purity (~30%) brownish heroin

75% of world’s heroin supply originates in Afghanistan
/heroin

- **Mexican** drug cartels smuggle it to U.S.
- **Dramatic rise in use in last 5+ years**
  - Since 9/1/11 with PDMP in FL
  - Many former hydrocodone & oxycodone users
- **HIGH RISK of overdose or death**
  - First time use or long-term users
  - Drug dealers may spike their drugs with fentanyl or other narcotics to increase demand and $$
    - An overdose (O.D.) increases demand because it’s considered more potent
SYTHETIC OPIATES

Made in labs in China & Mexico

Fentanyl, Sufentanyl, Acetylfentanyl, Carfentanil, U-47700, W-18

- Schedule I substances
- 5 to 10,000 x more potent than morphine
  - Fentanyl is 80-100 x more potent than morphine
  - Danger: transdermal contact can be fatal!
- Used IV or snorted, and can be disguised as, or laced with, heroin
  - Sold as “fake Xanax” pills
- High risk of respiratory depression
  - Overdoses can be treated with large & repeated doses of naloxone (Narcan®/Evzio®)
EARLY 21st CENTURY

- 2010 - Opiate prescriptions peaked
  - 782 Morphine Mg Equivalents (MME) dispensed per capita
- 2012 - 5% of population > 12 y.o. misused an opiate
- Operation “Pilluted” – 280 people arrested (5/20/2015)
  - Closed most of Broward County’s pill mills
- 2016 - 5 billion oxycodone tablets dispensed
- 116 out of 186 (66%) total fatal overdoses involve opioids
  - MANY from illicit fentanyl
  - Increase of 97% from 2015
NALOXONE (NARCAN®/EVZIO®)

- Available **without** an Rx in Florida and most states
- **Not orally active** (IV/IM/SQ/intranasal only)
- Binds *competitively* to opioid receptors
  - Does not produce analgesia
    - Used to reverse toxic effects of agonist and agonist–antagonist opioids
- Injection Dose: 0.4 to 2mg - can repeat every 2-3 min
  - May need to *repeat* doses later (20-60 minutes)
  - Short $t_{1/2}$ ($\approx 1.5$ hrs)
NALOXONE (NARCAN®/EVZIO™)

♦ Narcan® nasal spray 4mg in 0.1ml
  ★ $150 for 2 in a box

♦ Auto-injection (Evzio™)
  ★ 0.4mg/0.4 mL & 2mg/0.4ml
  ★ $3800 to $5800 for 2
  ★ Covered by most insurances
  ★ Has voice guidance
  ★ Comes with training sampler
MODERN RECREATIONAL OPIATE TRENDS
**KRATOM**

- **7-hydroxymitragynine**
  - Tropical evergreen tree in the coffee family
  - *Mitragyna speciosa* - Native to SE Asia & Thailand
  - It is psychoactive, and leaves are chewed to uplift mood and to treat native’s health problems

- At low doses, it produces **stimulant effects**
  - Also **entheogenic** due to indole alkaloids

- At high doses, it agonizes of alpha, and mu/delta opiate receptors and causes **euphoria**
  - Sold as a natural painkiller at Kava “juice bars”
    - e.g., Kavasutra (www.kavasutra.com)
KRATOM

- Not currently banned, but a “drug of concern”
  - FDA can seize “dietary supplements” if suspect
- Can be addictive
  - Has a recognizable withdrawal syndrome
- Effects can last 2-5 hours
  - Overdoses can be treated with naloxone
- Side effects vary from mild to psychosis, respiratory depression, convulsions, hallucinations, and confusion
- Krypton: mitragynine & O-desmethyltramadol
Also called “Purple drank” and “Lean”

Promethazine and codeine cough syrup
- Mixed in to soda with Jolly Ranchers candy
- Usually combined with alcohol or other drugs

Referenced in popular music since the late 90’s
- DJ Screw died of an OD in 2000
- Lil Wayne hospitalized in 2013

May cause respiratory depression, seizures, death
OPIATE WITHDRAWAL
AVOIDING WITHDRAWAL

Some people continue to use to avoid any distressing withdrawal symptoms
- May or may not still get “high” from the drug use

- Opiate withdrawal is rarely fatal!!!
  - Can be extremely uncomfortable
OPIATE WITHDRAWAL

♦ ↑ BP & ↑ pulse

♦ “Flu-like” symptoms:
  ★ Runny nose
  ★ Nausea
  ★ Vomiting
  ★ Diarrhea
  ★ Yawning
  ★ Sneezing
  ★ Wide pupils
  ★ Tear secretion

♦ Typical effects
  ★ Sedation
  ★ Irritability
  ★ Anxiety
  ★ Lack of interest
  ★ Slurred speech
  ★ Horripilation
    ￮ Goose bumps
    ￮ “Cold Turkey”
  ★ Leg jerks
    ￮ “Kicking” the habit
DETOXIFICATION

- **Primary objective**
  - To relieve withdrawal symptoms while the patient adjusts to a drug-free state

- **Done with or without an opiate substitute**

- **Use C.O.W.S.**
  - Clinical Opiate Withdrawal Scale

**DETOXIFICATION**

- **Short-term** – less than 5 days
  1. Abrupt cessation & manage symptoms with **clonidine**
  2. Convert dose to **buprenorphine** & taper
     - Buprenex, Suboxone, Subutex

- **Long-term** – 28, 90, and 180 days
  - Tapering with a long-acting opiate (methadone) or **buprenorphine**

- **Naloxone** can be used for a “quick detox”
  - Causes **instant** withdrawal
  - Done under general anesthesia
    - Rapid or Ultra-rapid Opioid Detoxification
TAPERING OFF OPIATES

♦ Rapid taper

♦ Due to non-compliance
  ★ Convert multiple agents (if present) to 1
  ★ Taper by 25% every 3-7 days
  ★ Shorter interval for shorter half-life medication

♦ Slow taper

♦ Due to lack of benefit or side effects / complications
  ★ Taper by 10% per week until 20% of original dose remains
  ★ Taper remaining by 5% until off

Augment with non-pharmacologic therapies
Centrally-acting alpha-2 ($\alpha_2$) agonist

Attenuates the sympathetic response to withdrawal
  ★ i.e., patient’s body doesn’t over-react with physical symptoms

Causes a rapid and significant decrease in withdrawal signs and symptoms

Usual oral dose is 0.1-0.2mg PO Q6h
  ★ Watch BP!
Available after August 2018

Centrally-acting alpha-2 (\(\alpha_2\)) agonist (like clonididine)
  - Attenuates the sympathetic response to withdrawal

Available in 0.18 mg tablets
  - Recommended dose is 3 tablets Q6h for up to 14 days

Causes a rapid and significant decrease in withdrawal signs and symptoms

Watch BP!
Percutaneous nerve field stimulator
- PNFS placed behind patient’s ear
- Reduces the symptoms of opioid withdrawal
  - Can use up to 5 days during acute phase
- Affects the Occipital Nerves and Cranial Nerves V, VII, IX and X

- Avg COWS of 20 ↓ to 7.5 in 20 min.
- ↓ to 3.1 after 60 minutes
- ↓ to 0.6 after 5 days

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585271.htm
POST-DETOXIFICATION THERAPIES
TREATMENTS FOR OPIATE USE DISORDER

- Narcotics Addiction Treatment Act of 1974
- Drug Abuse Treatment Act (DATA) of 2000

Abstinence
- Opiates are tapered
- An opiate blocker can be used
  - (Revia®/ Vivitrol®/ naltrexone)
- Naltrexone was approved in 1984 for opiate addiction

“Harm-reduction” model
- “Medication Assisted Therapy”
  - MAT
- Methadone
  - Specialty clinic-based treatment
  - Evidence-based since the 1950’s
- Buprenorphine
  - With or without naloxone
  - Prescribed by credentialed physicians only
GUIDELINES FOR TREATMENT

- ALL treatments should include psychotherapy and counseling
  - Drugs treat symptoms & should be used as adjunctive treatment
- Choice of treatment should be based on level of severity
- MAT is not substituting one drug for another
- Begin with low doses and continue with the lowest effective doses
- Inform patients of sedation, dependence, and potentiation with other CNS agents
- Patients must avoid alcohol and other drugs!
Any prescriber of controlled substances risks creating an addicted individual
★ As little as one use of an opiate can spawn an addiction
★ Refill of an opiate Rx doubles the risk of addiction

Only specially licensed professionals can detox and/or treat the addiction
★ Only 1 in 20 doctors prescribe MAT
★ Only 1/3 of addiction treatment centers offer MAT
★ Naltrexone does not have special licensing requirements

“Harm reduction” model of treatment reduces HIV infections, crime, and risk of death
★ Includes providing sterile syringes and/or MAT
MAT IN A SPECIALTY TREATMENT PROGRAM*

*Does not include office-based prescribing

2015: 17,670 patients in Florida receiving methadone treatment
   ★ Increased from 13,711 (29%↑) in 2011

2015: 2,922 patients in Florida receiving buprenorphine therapy
   ★ Increased from 1,248 (234%↑) individuals in 2011

Higher doses of MAT lead to better success and ↓ overdoses

2017 Meta-analysis
   ★ Methadone treatment reduces all cause mortality by 320%
      ○ Overdose mortality decreased by 480%
   ★ Buprenorphine reduces all cause mortality by 220%
      ○ Overdose mortality decreased by 330%

BMJ 2017;357:j1550  http://dx.doi.org/10.1136/bmj.j1550  *

*According to the FDLE
Competitive antagonist at opioid receptor sites

Naltrexone Depot (VIVITROL™)**
- Long-lasting opiate antagonist for monthly use (380mg)
  - Approved in April 2006
- Studies with long-acting depot form Vivitrol™ in Russia demonstrated extraordinary outcomes regarding drug abstinence, tx. retention, and decreased cravings
- Vivitrol = buprenorphine + naloxone in efficacy*
  - n=570 / p=0.44 → no difference

*Lancet Online. 11/14/2017 http://dx.doi.org/10.1016/S0140-6736(17)32812-X
**Drugs 2002;5(8):835-8
NALTREXONE (REVIA® / VIVITROL®)

- **Not to be used during active withdrawal**
  - Must wait 7-14 days post-detox or opioid withdrawal will occur

- **Oral dose - 50mg po QD or IM dose - 380mg Q4W**

- **Monitor for hepatic toxicity, nausea, HA, dizziness, anxiety and sedation**

- **Studies show a reduction in (re-)incarcerations when used with behavior therapy**

- **Compliance and motivation are major factors**
  - **32-58%** successful in compliant patients
    - Abstinence rates diminish over time

Cochrane Database of Systematic Reviews 2003;(2):CD001333.
Used as a prescribed opiate substitute
Medication is taken orally QD
Suppresses withdrawal for 24 to 36 hours and relieves cravings
  - Half-life is 15-60 hours
  - Full μ agonist
  - Can cause dysphoria and euphoria
Detox: 15-40 mg/day not to exceed 21 days
  - Withdrawal can be severe & protracted
Maintenance: 20-120 mg/day
Facility must be licensed to dispense it!!!
Cost savings of $3-4 for every dollar spent
  - Includes costs of crime and lost productivity

BUPRENORPHINE + NALOXONE

- Mixed partial *mu* opiate agonist & *kappa* antagonist (blocks dysphoria)
  - Prescriber MUST be licensed to prescribe it
    - DEA # changes to begin with “X”
  - Lower risk of abuse vs. methadone
  - Ceiling effect if dosed too high
    - Safer for respiratory depression
    - Combined with other opiates may cause withdrawal
- Usual dose is 4-24mg sublingually daily
Safe and effective for office-based detox
- 16 mg buprenorphine daily
- Up to 21% avoided outside opiates vs. 5.8% on placebo (p<0.001)

Retention rates in programs < methadone

High dose buprenorphine may suppress heroin use > methadone

Doses ≥ 8mg/d have best success
- QOD dosing also successful

Short-acting opiate receptor blocker

Not used for abstinence but to deter abuse

★ Not orally active (only useful if combination tablets are liquefied & injected)

Counteracts the effects of opioids and can be used to treat overdoses

Dose: 0.4 to 2 mg/dose IV/IM/subcutaneously

★ Continuous infusion: 0.005 mg/kg loading dose followed by 0.0025 mg/kg/hr
Subutex® (buprenorphine) SL tabs

Buprenorphine + Naloxone
- Bunavail® buccal film
- Zubsolv® SL tablets
- Suboxone® is a 4:1 ratio of buprenorphine to naloxone

Butrans® and Subsys® are NOT approved
LONG-ACTING BUPRENORPHINE PRODUCTS

♦ Probuphine® (Buprenorphine implant)
  ★ 320mg in 4 implantable subdermal rods in upper arm
  ★ Must be surgically replaced every 6 months
  ★ Discontinue after each arm used

♦ Sublocade® monthly SQ depot injection
  ★ Start with 300mg x 2 months in abdomen
  ★ Maintenance is 100mg (up to 300mg) a month
  ★ Available in pre-filled syringes
    ⊙ 100mg/0.5ml or 300mg/1.5ml
Risk Evaluation and Mitigation Strategies

- Methods to reduce severe side effects and bad outcomes
- Must register a patient before being able to dispense opiate to them

REMS now applies to ALL opiates

- Key messages need to be communicated to patients:
  - Warn patients not to self-administer non-prescribed benzodiazepines or alcohol
  - Keep out of the sight and reach of children
  - Keep their medication safe to protect them from theft
  - Never give to anyone else
  - Advise patients that selling or giving away medication is against the law
Medications infused through a spinal pump

★ Ziconotide (Prialt®) solution
- An N-type calcium channel antagonist
- 25 mcg/mL & 100 mcg/mL concentration
- Delivered by a spinal infusion pump
- Can cause cognitive impairment, hallucinations, and changes in mood or consciousness

★ Baclofen (Gablofen®)
- Injectable version of Liorisal®
- A GABA (gamma-aminobutyric acid) agonist
- Used for severe spasticity of cerebral or spinal origin
- 90–800 mcg/day dosing

★ Morphine Sulfate (Infumorph) – preservative-free
- Only 4% reaches the CNS
- Micro-infused at 0.2–10 mg/day

All incur risks of infection to the CNS
ADDRESSING THE CRISIS
CURRENTLY, WHAT ARE WE DOING?

- Legislation to close pill mills
- Prescription Drug Monitoring Programs (PDMP)
  - Needs full interstate implementation
- Increasing access to naloxone for overdoses
- Legislation to limit prescription quantities
NEW FLORIDA LEGISLATION – JULY 2018

- HB13 FS 456.44(3) - Controlled substance prescribing
- Limits C-II Rx’s for acute pain to a **3-day supply**
- Patient can get a 7-day supply if medically necessary by writing “ACUTE PAIN EXCEPTION” on Rx
- Rx’s for chronic pain must specify “NONACUTE PAIN”
  - Patient must be seen by prescriber LESS THAN every 3 months
- Prescribers must complete a 2-hour CE on responsibly prescribing opioids
- Florida’s PDMP will be upgraded for EMR integration
  - Inter-state collaboration is ultimate goal
  - Prescribers MUST check PDMP before prescribing
- Immediately refer patients with signs or symptoms of substance abuse to a board-certified pain management physician, an addiction medicine specialist, or a mental health addiction facility

http://www.leg.state.fl.us/STATUTES/index.cfm?App_mode=Display Statute&Search_String=&URL=0400-0499/0456/Sections/0456.44.html
FY 2017 - SAMHSA awarded $485 mil state targeted response grants

2017 - Trump Administration’s Involvement

- 10/26/2017 - declared the opioid crisis a Nationwide Public Health Emergency
- National “Take Back Day” collected 456 tons of expired / unneeded meds
- INTERDICT Act - Signed on 1/10/2018 against illegally imported fentanyl
- Feb 2018 - the Prescription Interdiction & Litigation task force (PIL)
  - Attorney General Jeff Sessions
  - To keep manufacturers and distributors of opioids accountable
- Joint Criminal Opioid Darknet Enforcement (J-CODE) Team
  - For law enforcement to disrupt online sales of illicit opioids

https://www.whitehouse.gov/briefings-statements/president-donald-j-trump-combatting-opioid-crisis/
HEAL INITIATIVE

April 2018 - NIH launched HEAL Initiative

- Helping to End Addiction Long-term
- “Aggressive, trans-agency effort to speed scientific solutions to stem the national opioid public health crisis”

Goals:

- Improve Treatments for Opioid Misuse and Addiction
  - Expand therapeutic options for opioid addiction, overdose prevention and reversal
  - Enhance treatments for infants born with Neonatal Abstinence Syndrome (NAS)/ Neonatal opioid withdrawal syndrome (NOWs)
  - Optimize effective treatment strategies for opioid addiction

- Enhance Pain Management Therapies
  - Understand the biological underpinnings of chronic pain
  - Accelerate the discovery and pre-clinical development of non-addictive pain treatments
  - Advance new non-addictive pain treatments through the clinical pipeline

https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/heal-initiative-research-plan
THE FUTURE OF THE OPIOID CRISIS
More prescriber education
  ★ Utilizing *Risk Reduction Strategies* and *Pain Treatment Algorithms*
  ★ [www.sempguidelines.org](http://www.sempguidelines.org)

Increase access and insurance coverage (+ Medicare/Medicaid) for detoxification, addiction treatment programs and **MAT**

Medicaid and insurance companies instituting Pharmacy “**Lock-In**” Programs
  ★ One pharmacy / one doctor

Comprehend the genetic component to addiction

Developing new non-addictive treatments of pain
APADAZ™

- Benzhydrocodone and acetaminophen tablets
- A pro-drug that needs to be metabolized to work

Kappa receptor agonists/antagonists

- CERC-501, Samidorphan, Difelikefalin, others

Blue-181 by Blue Therapeutics

- Acts on receptors in the spinal cord
- Soon to start human trials

BU08028 – an orvinol analog

- Nociceptin/orphanin FQ peptide (NOP) receptor agonist

NKTR-181 by Nektar Therapeutics

- Long-acting, selective mu-opioid agonist with low CNS penetration
**FUTURE OF PAIN MANAGEMENT**

- **SPRINT endura™ and SPRINT extensa™**
  - SPR Therapeutics
  - Peripheral nerve stimulation system
  - Leads are implanted percutaneously
    - Single or dual leads
  - Use for up to 60 days
  - Controller is Bluetooth enabled
- **Medical marijuana**
  - Early studies showing lower doses of opiates needed

[https://www.sprtherapeutics.com](https://www.sprtherapeutics.com)

Currently Still:

- Enough opiates for every American adult to have 52 pills
- Drug overdose is the leading cause of death in those < 50 years old
- 6 in 10 deaths from overdose caused by opiates
- >2 million people have an Opioid Use Disorder
- Only 20% in treatment & only 1/3 getting MAT
QUESTIONS???
REFERENCES

REFERENCES


♦ Foundation for AIDS Research. (2017, Jan. 5). Opioid and Health Indicators Database. Retrieved Feb. 6, 2018, from opioid.amfar.org/indicator/AMAT_fac


REFERENCES


REFERENCES


♦ The National Safety Council can provide medical experts for medical meetings and conferences. Learn more and submit a speaker request at nsc.org/SpeakersBureau.


♦ SAMHSA (2017, Sept.). Results from the 2016 National Survey on Drug Use and Health: Detailed Tables. Retrieved Feb. 6, 2018 from samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.htm#tab4-4B

REFERENCES


References


https://www.forbes.com/sites/carmendrahl/2017/06/12/five-things-heroins-curious-chemistry-history/#4e978528157c

https://en.wikipedia.org/wiki/Papaver_somniferum

https://en.wikipedia.org/wiki/Heroin


REFERENCES

QUESTIONS
(??????)

Email: leonard.rappa@famu.edu