Un “Comfortably Numb”: The Evolving Opioid Epidemic

Rachel Beck, PhD, F-ABFT
UAB Dept. of Pathology
Laboratory Medicine
Learning Objectives

• Understand the transmission of pain and current opioid therapies.

• Describe new designer opioid abuse trends.

• Recognize the abuse potential of designer opioids analogues.
Transmission of Pain

• What is pain?

• How does the body respond to pain?

• How do analgesics effect pain?
What is Pain?

• A response to a painful stimuli.
• The body’s way of telling us something is wrong.
• Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.¹

¹ International Association for the Study of Pain 1991
Pain Perception

• Nociception
  – Includes nociceptors (nerve endings), spinal cord, and brain

• Contact with stimuli
  – Mechanical, thermal, or chemical damage

https://www.ucl.ac.uk/anaesthesia/StudentsandTrainees/PainPathwaysIntroduction

Nociception (Cont’d)

• Reception – nerve ending senses stimuli
  – Specialized sensory receptors create electronic signal

• Transmission of signal
  – Action potential transmitted down axon

• Pain center reception

https://www.ucl.ac.uk/anaesthesia/StudentsandTrainees/PainPathwaysIntroduction

Body’s Response to Pain

• After contact with stimuli

• Body’s response occurs in 3 separate locations
  – Site of stimuli
  – In the spinal cord
  – Brain
Body’s Response to Pain (Cont’d)

• Damaged cells around source release
  – Bradykinin, prostaglandins, and histamines
    • Stimulate nociceptors (nerve endings)

• Pain signal transmitted to cell body (dorsal horn in spinal cord)
  – Release of K^+
    • Reflexive muscular contraction (avoid stimuli)

• Midbrain releases natural pain agonist

https://www.ucl.ac.uk/anaesthesia/StudentsandTrainees/PainPathwaysIntroduction
Body’s Response to Pain

http://humanphysiology.academy/Neurosciences%202015/Chapter%202/P.2.2%20Spinal%20Reflexes.html
Natural Pain Agonist

- Endorphins,
- Enkephalins, and
- Dynorphins

- Activate descending pathway
- Bind to receptors at second order neuron level

Opioid Receptors

• G-protein coupled receptors - plasma membrane
• Controls nerve activity, smooth muscle, metabolism, rate and force of cardiac contraction, and secretion of most glands
• Binding of opioid agonist results in conformational change
• Located in brain, spinal cord, vascular, cardiac, airway/lung, gut, and in circulating immune/inflammatory cells
Agonist Activity on GPCR

MECHANISM OF ACTION:

Opioid receptors.

Acts on G-Protein coupled receptors.

Inhibits Adenyl cyclase.

Promotes opening of K⁺ channels & inhibits opening of Ca⁺² channels.

Reduces neuronal excitability & increases K⁺ conductance.

Causes hyperpolarization & shows inhibitory pathway & relieves pain.

http://www.slideshare.net/banuman35/sirishasemnar
Opioid Agonist Action

- Binds to receptor
- Prevents cell repolarization
- Disrupts action potential of signal transmission

Does not alleviate pain; prevents the body’s transmission of the pain signal to the brain
# Opioid Receptor Types

- **Mu (µ) – MOR**
- **Delta (δ) – DOR**
- **Kappa (κ) – KOR**
- **Nociceptive – NOR**
- **Sigma (σ)**

## Table 10.1: Location, Function, and Endogenous Ligand for Opioid Receptor Subtypes

<table>
<thead>
<tr>
<th>Receptor subtype</th>
<th>Endogenous ligand (prohormone source)</th>
<th>Location (most dense)</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ</td>
<td>Endomorphins (unknown), endorphins (POMC)</td>
<td>Thalamus, periaqueductal gray, raphe nuclei, spinal cord, striatum, brain stem, nucleus accumbens, amygdala, hippocampus</td>
<td>Analgesia, reinforcement, cardiovascular and respiratory depression, antitussive, vomiting, sensorimotor integration</td>
</tr>
<tr>
<td>δ</td>
<td>Enkephalin (proenkephalin), endorphins (POMC)</td>
<td>Neocortex, striatum, olfactory areas, substantia nigra, nucleus accumbens, spinal cord</td>
<td>Analgesia, reinforcement, cognitive function, olfaction, motor integration</td>
</tr>
<tr>
<td>κ</td>
<td>Dynorphins (prodynorphin)</td>
<td>Pituitary, hypothalamus, amygdala, striatum, nucleus accumbens</td>
<td>Neuroendocrine function, water balance, feeding, temperature control, dysphoria, analgesia</td>
</tr>
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μ Opioid Receptor

• Receptors are found in CNS (brain and spinal cord), peripheral, and immune cells
  – Presynaptic and inhibit neurotransmitter release
  – Inhibit release of GABA
  – Increase dopamine

• Controls analgesia and respiratory depression

• Involved in miosis, euphoria, reduced GI motility

• Mu (μ1) – supraspinal analgesia

• Mu (μ2) – spinal analgesia, respiratory depression
**δ & Κ Opioid Receptor**

- **Delta (δ)**
  - Located in brain, periphery, and spinal cord
  - Binding sites for enkephalins peptides
  - Analgesia, dysphoria, delusions, hallucinations

- **Kappa (κ)**
  - Located in Dorsal Horn of spinal cord and brain stem
  - Analgesia, miosis, sedation
NOR & σ Receptors

• Nociceptive (NOR)
  – Shares sequence homology with other opioid receptors
  – Little to no binding affinity with classical opioids
  – Located in brain

• Sigma (σ)
  – Binding is not limited to opioids
  – Central excitation
    • Tachycardia, hypertension, hallucinations
  – Not antagonized by naloxone
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<th>Receptor</th>
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<tr>
<td>Analgesia - Supraspinal</td>
<td>μ, δ</td>
</tr>
<tr>
<td>Analgesia – Spinal</td>
<td>κ</td>
</tr>
<tr>
<td>Respiratory Depression</td>
<td>μ, κ</td>
</tr>
<tr>
<td>Miosis</td>
<td>μ, κ</td>
</tr>
<tr>
<td>Euphoria</td>
<td>μ</td>
</tr>
<tr>
<td>Decreased GI Activity</td>
<td>μ</td>
</tr>
<tr>
<td>Drowsiness, sedation</td>
<td>μ, κ</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>μ</td>
</tr>
<tr>
<td>Changes in Body Temperature</td>
<td>μ</td>
</tr>
<tr>
<td>Mental Clouding</td>
<td>μ</td>
</tr>
<tr>
<td>Tolerance</td>
<td>μ</td>
</tr>
<tr>
<td>Increased Addiction Potential</td>
<td>μ</td>
</tr>
<tr>
<td>Reduced Addiction Potential</td>
<td>κ</td>
</tr>
<tr>
<td>Diuresis</td>
<td>κ</td>
</tr>
<tr>
<td>Delusions, hallucinations</td>
<td>δ, σ</td>
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Current Therapies
Opioid History

- 3,000 B.C. – Opium growth and use recorded (Dysentery)
- 1800’s – Morphine isolated and used for treatment
- 1874 – Heroin discovered (cough & sedative)
- 1939 – Semisynthetic opioids available
- 1980’s and 1990’s - Pain as the 5th Vital Sign (P5VS) initiative (Joint Commission on Accreditation of Healthcare Organizations-JCAHO)
- 1996 – Oxycotin® becomes available

https://www.deamuseum.org/ccp/opium/history.html
http://www.alternet.org/drugs/10-startling-facts-about-history-heroin
http://www.narconon.org/drug-information/heroin-history.html
Opium

- Opiate derived from Greek word *opos* meaning “juice”
- Papaver Somniferum plant (poppy) has two major alkaloids
  - Morphine and codeine
  - Precursors to the diverse opioid drug classification
- Routes of administration: nasal insufflation, IV/subcutaneous, sublingual, oral ingestion, etc.
- Crosses the blood brain barrier

Baselt (2014) Disposition of Toxic Drugs and Chemicals in Man 10th Ed.
Terminology

• Opiate
  – Natural alkaloids of poppy plant
  – Morphine, codeine, papervine, thebaine

• Opioid
  – Semi-synthetic and synthetic compounds
  – Methadone, hydrocodone, heroin

All opiates are opioids, but not all opioids are opiates
Terminology

OPIATES

OPIOIDS
Opioid Structures

Morphine
Codeine
Levorphanol
Loperamide
Di-Acetyl-Morphine
(Tapentadol
Methadone
(Heroin)
# Opioid Effects

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<th>Location</th>
<th>Organ System</th>
<th>Effects</th>
</tr>
</thead>
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<td>CNS</td>
<td>Brain and Spinal Cord</td>
<td>Analgesia, Euphoria, Sedation, Decreased Respirations, Decreased Cough Reflex, Miosis, Truncal Rigidity, Nausea and Vomiting</td>
</tr>
<tr>
<td>Peripheral</td>
<td>GI System</td>
<td>Constipation, Decreased Gastric Motility, Esophageal Reflux</td>
</tr>
<tr>
<td></td>
<td>Other Smooth Muscles</td>
<td>Depression of Renal Function, Decreased Uterine tone, Urinary Retention</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>Itching and Sweating, Flushing of the face, neck, thorax</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular System</td>
<td>Decreased blood pressure and heart rate</td>
</tr>
<tr>
<td></td>
<td>Immune System</td>
<td>Decreased formation of rosettes by human lymphocytes, Decreased Cytotoxic activity of natural killer cells</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Behavioral Restlessness</td>
</tr>
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Abuse Effects

- Euphoria/Rush,
- Tension Relief,
- Depressed cognitive function,
- Feelings of distance,
- Reduced sensation of pain,
- Heavy sensation of extremities,
- Dry mouth

Baselt (2014) Disposition of Toxic Drugs and Chemicals in Man 10th Ed.
## Opioids

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<th>Analgesic Potency</th>
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<td>Strong µ agonist, weak κ and δ agonist</td>
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<td>Weak µ agonist, weak δ agonist</td>
<td>0.1</td>
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</tr>
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<td>Strong µ agonist</td>
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<td>Levorphanol</td>
<td>Strong µ and κ agonist</td>
<td>4 – 5</td>
<td>Schedule II</td>
</tr>
<tr>
<td>Loperamide</td>
<td>Strong µ agonist, weak δ agonist</td>
<td>0.64</td>
<td>Schedule V</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>µ agonist, norepinephrine reuptake inhibition</td>
<td>0.05</td>
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<td>Methadone</td>
<td>Strong µ agonist</td>
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</tr>
<tr>
<td>Fentanyl</td>
<td>Strong µ agonist</td>
<td>50 – 100</td>
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Therapeutic Uses

- Diarrhea – loperamide, diphenoxylate
- Cough Suppression – codeine and hydrocodone
- Analgesia
  - Both acute and chronic pain
  - Mild to moderate pain: codeine, hydrocodone, tramadol
  - Severe pain: morphine, meperidine, fentanyl, hydromorphone, oxycodone
- General anesthesia – fentanyl, alfentanil, and sufentanil
Tolerance

- Definition: requirement for more of drug (larger dose) to receive same or lesser effect
- Developed after repeated use
  - Observed in 2 to 3 weeks
- Does not apply to all effects elicited by a substance

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<th>High</th>
<th>Moderate</th>
<th>Minimal to None</th>
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<td>Analgesia</td>
<td>Cardiovascular Effects</td>
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<td>Euphoria, Dysphoria</td>
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<td></td>
<td>Convulsions</td>
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<td>Respiratory Depression</td>
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<td>Effects of the Antagonists</td>
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<td></td>
<td></td>
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<td>Cough Suppression</td>
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Did You Know?

• Opioid epidemic attributed to both illicit and prescription opioid use/abuse

• In 2014, 1.9 million Americans had a substance use disorder involving prescription pain relievers
  – 586,000 had a substance use disorder involving heroin.

• 4.3 million Americans engaged in non-medical use of prescription painkillers in the last month

• 1.4 million people used prescription painkillers non-medically for the first time in the past year

http://www.samhsa.gov/atod/opioids
Opioid Epidemic

- 1874 – Heroin Discovered
- 1996 – Oxycotin available
- 2006 – Reports of laced heroin
- 2010 – Drug deterrent formulation oxycotin released
- 2015 - Heroin now laced with Furanyl Fentanyl, Carfentanil, and W-18
Opioid Structures

Morphine

Codeine

Levorphanol

Loperamide

Di-Acetyl-Morphine (Heroin)

Tapentadol

Methadone
Fentanyl Analogs

- Fentanyl
- Furanyl Fentanyl
- Acetyl Fentanyl
- Lofentanil
- Carfentanil
- Sufentanil

Morphine
Designer Opioids

3-OH-PCP

U-47700

MT-45

AH-7921

W-15

U-50488

W-18

Morphine
# Designer Opioids

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<td>Furanyl Fentanyl</td>
<td>Activity not confirmed; suspected strong μ agonist</td>
<td>??</td>
<td>Schedule I</td>
</tr>
<tr>
<td>Lofentanil</td>
<td>Strong μ, δ, κ and NOR agonist**</td>
<td>6000 – 8000</td>
<td>Legal</td>
</tr>
<tr>
<td>Carfentanil</td>
<td>Strong μ, δ, and κ agonist**</td>
<td>1000 – 3000</td>
<td>Schedule II</td>
</tr>
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<td>250 – 1000</td>
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<td>Weak μ agonist, strong κ agonist</td>
<td>0.2 - 0.5</td>
<td>Legal</td>
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<td>AH-7921</td>
<td>Strong μ agonist; κ agonist</td>
<td>1.0</td>
<td>Schedule I</td>
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<tr>
<td>3-OH-PCP</td>
<td>Strong μ agonist, weak κ and δ agonist, σ agonist</td>
<td>430</td>
<td>Schedule I*</td>
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<tr>
<td>MT-45</td>
<td>Strong κ and σ agonist, weak μ and δ agonist**</td>
<td>0.8</td>
<td>Proposed Schedule I</td>
</tr>
<tr>
<td>W-15</td>
<td>Activity not confirmed**</td>
<td>5.4??</td>
<td>Legal</td>
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<td>W-18</td>
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<td>10,000??</td>
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* Controlled by individual states
** Naloxone (Narcan®) resistant
Designer Opioid Dangers

• Tolerance – larger doses required to illicit same effects

• Potency – amount required to produce an effect of given intensity

Designer Opioids In the News

Pink: Stronger Than Heroin, But Legal In Most States

By: Andrew Blankstein
October 15th, 2016

U-47700

Large animal tranquilizer linked to 19 deaths in Wayne County
Heroin is laced with carfentanil, a drug 10,000 times stronger than morphine

Carfentanil

October 10th, 2016
Designer Opioids In the News

Furanyl Fentanyl

Mother shares story of losing son to mail-order drug

By: David Sentendrey
October 20th, 2016

MT-45

PDEA warns public on 7 new dangerous substances

Friday, August 12, 2016
Opioid Addiction Treatment

• Rehabilitation facilities
  – Methadone Maintenance Therapy – weak mu receptor agonist
  – Naltrexone – receptor antagonist

• Probuphine – upper arm implant (6 month dose)
  – Same active ingredient as Suboxone (buprenorphine)
  – Partial receptor agonist

• Ibogaine – not commercially available in US
  – Schedule I drug
  – Three phases (hallucinations, analytical, & stimulant)
  – Adverse reactions include death
Opioid Overdose Treatment

• Respiratory support
  – Tracheal Intubation (endo or oro depending on state)

• Oxygenation

• Administer naloxone by IV or IM (bolus)

• Activated charcoal in GI

http://emedicine.medscape.com/article/815784-treatment#showall
http://www.fingerlakesdailynews.com/shared/inc/client/16/articles/images/1071680153-narcan.jpg
Narcan

• Naloxone – mu receptor antagonist
• Available in nasal spray to family and friends of addicts (0.4 mg dose)
• Effective
  – Nasal/IM administration 5 – 10 mins
  – IV administration 1 – 2 mins.
• Clinical $T_{1/2}$ is 20 – 60 mins.
• Duration of effects 2 – 3 hours
• Dose 0.05 to 2 mg/bolus not to exceed 10 mg
• Practice “start low and go slow”

How to Give Nasal Spray Naloxone

1. Pull or pry off yellow caps

2. Pry off red cap

3. Grip clear plastic wings.

4. Gently screw capsule of naloxone into barrel of syringe.

5. Insert white cone into nostril; give a short, vigorous push on end of capsule to spray naloxone into nose: one half of the capsule into each nostril.

6. Push to spray.

If no reaction in 2-5 minutes, give the second dose.

Effects

Narcan has a stronger affinity to the opioid receptors than the heroin, so it knocks the heroin off the receptors for a short time and lets the person breathe again.
Summary

• Designer opioid abuse is a growing problem

• Evidence of opioid use/abuse should not be ignored just because of a negative drug test

• Further testing for novel opioid-like compounds may be necessary
FENTANYL AND FENTANYL ANALOGS

- Fentanyl is a Schedule II short-acting synthetic opioid that is often used to treat chronic pain. It is 25 to 40 times more potent than heroin and 50 to 100 times more potent than morphine by weight (DEA, 2015b, 2015c; NIDA, 2012).

- Fentanyl and fentanyl analogs are abused for their "intense, albeit short-term high and temporary feelings of euphoria" (DEA, 2015c).

- Pharmaceutical fentanyl can be illegally diverted for abuse. It comes in a variety of forms, including patches, lozenges, tablets, and films (CDC, 2015; DEA, 2015c).

- Illicitly-produced, non-pharmaceutical fentanyl and fentanyl analogs, such as acetyl fentanyl, are emerging in the illicit drug market. They can be snorted or injected in powder form or swallowed as a pill (DEA, 2015a, 2015b, 2015c).
Resources

• National Institute on Drug Abuse (NIDA) – National Drug Early Warning System (NDEWS)
  https://www.drugabuse.gov/drugs-abuse/emerging-trends-alerts

• Substance Abuse and Mental Health Services Administrations (SAMHSA) –
  http://www.samhsa.gov/atod/opioids

• Center for Disease Prevention (CDC) –
17. Huang et al. (2016) pp: 34, doi: http://dx.doi.org/10.1101/065623


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