The Opioid Epidemic and Naloxone Use

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Objectives

• Discover new drug compounds and other factors contributing to The Opioid Epidemic
• Navigate the impact and applicability of the 2016 CDC Guidelines for Prescribing Opioids for Chronic Pain
• Review recommendations relevant to deciding length of therapy, use of non-opioid therapies, and evaluating for harm and misuse
• Explore pharmacologic and therapeutic considerations related to the prescribing and administration of naloxone
• Discuss the need and public health impact for expanded naloxone access
• Review available practitioner tools and trainings, including, but not limited to, Prescription Drug Monitoring Programs
New and Non-Controlled Drugs

• Non-Controls
  • Less concerning to family/friends, easy to obtain
  • Self-treat withdrawal
  • Pharmacokinetic modification of other drugs
    • HIV medications, enzyme inhibitor

• Available and Concealable
  • Sold online, gas stations, tobacco shops
  • Vaporizers, e-cigs
  • Drug Screening negative

• Legality—United States Controlled Substance Act
  • §813. Treatment of controlled substance analogues
    • A controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law as a controlled substance in schedule I.

Psychoactive Synthetics

• Modification of existing drugs or chemicals
  • Abuser desires: cannabinoid-like high
  • Unknown toxicities

Synthetic Marijuanas

• Agonists of Cannabinoid Receptors
  • “Herbal incense” or “Potpurri”
    • “Not for human consumption”
  • May be in some sports drinks
  • More potent than THC
Synthetic Marijuana—Effects

- Paranoia, hallucinations, agitation, confusion, combative and aggressive behavior
- Tachycardia, hypertension hyperthermia
- Nausea, vomiting, hyperemesis
- Stroke, MI
- Acute Kidney Injury

- Stroke, MI

Cathinone

- Khat plant
  - Leaves chewed or steeped
- Stimulant & euphoric effects
- Release or reuptake inhibition of serotonin, dopamine, norepinephrine
Synthetic Cathinone
“Bath Salts”

Act like cocaine
• Increase extracellular dopamine and epinephrine
  • Methyleneoxyprovalrene (MDPV)
  • Alpha-PVP (Gravel, flakka)

Act like MDMA—Ecstasy
• Increase serotonin release or inhibit reuptake
  • Mephedrone
  • Methylone

Up to 10x more potent than cocaine
*Most “Molly” tabs (+ cathinones)

Toxic Impact—Bath Salts

Onset
5-20 min

Duration
2-4 hours

Damaging clinical effects may last **days-weeks**

• Extreme agitation
  • Paranoia, hallucinations, violence, teeth grinding

<table>
<thead>
<tr>
<th>Tachycardia</th>
<th>Dilated pupils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Hyperthermia</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Sweating</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Tremors</td>
</tr>
<tr>
<td>Seizures</td>
<td>Serotonin syndrome</td>
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</tbody>
</table>
Gabapentin

- Analog of GABA
- Increased prescribing
- Abuser desired effects:
  - Euphoria, marijuana-like high, sociability, calm or relaxing sensation
  - Enhances effects of opioids
  - Withdrawal self-treatment
- Toxicity:
  - CNS depression, nystagmus, hypotension, hyperkinesia

Quetiapine

- Atypical antipsychotic
  - Dopamine and serotonin antagonist
- Abuser desired effects:
  - Calming, hallucinogenic
- Withdrawal results in:
  - Nausea, vomiting, diaphoresis, orthostasis, tachycardia, nervousness
- Toxicity:
  - Lethargy, coma
  - Tachycardia, QTc prolongation, hypotension

2016 Systematic Review of Gabapentin Misuse
Addiction

15-22% opioid users were misusing gabapentin

2013-2015 Review of Prescription Claims
Clinical Drug Investigation

Top 1% gabapentin users:
11,274 mg/day
Max daily dose?

Also known as:
- Jailhouse heroin
- Suzie Qs
- Baby heroin
- Q-Ball
  Cocaine + quetiapine
### Venlafaxine & Bupropion

<table>
<thead>
<tr>
<th>Venlafaxine</th>
<th>Bupropion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin, norepinephrine, dopamine reuptake inhibitor</td>
<td>Dopamine, norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>“Baby ecstasy”</td>
<td>“Poor man’s cocaine”</td>
</tr>
<tr>
<td>Snorted, ingested</td>
<td>Snorted, ingested, Injected, smoked</td>
</tr>
</tbody>
</table>

- **Abuser desires:** Euphoria, amphetamine-like highs
- **Toxicity:** Agitation, tachycardia, QRS prolongation, hypotension, seizures serotonin syndrome (venlafaxine only)

### Clonidine

- **Alpha-2 adrenergic agonist**
- **Abuser desires:**
  - Opioid-boosting effect
  - Self-treat withdrawal symptoms
- **Toxicity:**
  - Hypotension, bradycardia, CNS & respiratory depression, hyporeflexia, constricted pupils

Prescribing for opiate withdrawal symptoms

Anxiety, sweating, runny nose, cramping, tachycardia

Role of Naloxone?
“Krokodil”

Desomorphine
• 3-10 x more potent than heroin
• Characterized by:
  • Green scaly skin
  • Tissue and bone necrosis
  • Gangrene
  • Ulcers if used IV

No confirmed cases in US
Common in Russia

Heroin

• Diacetylmorphine
• Smoked, IV, snorted, ingested
• Cut or blended with:
  • Fentanyl
    • About 50x more potent than heroin
  • Benzodiazepines
  • Diphenhydramine
  • Acetyl fentanyl
  • Clenbuterol (b2 agonist- veterinary drug)
  • Desmethyltramadol (metabolite of tramadol)
  • Caffeine

Also Known As: Dope, Junk, Horse, Tar, Smack, China White

*May also be cut with baking soda, sugar, laundry detergent, crushed OTC drugs, talcum powder, rat poison & more
Surge in Heroin Use

2010 Crackdown on “Pill Mills”

<table>
<thead>
<tr>
<th>Year</th>
<th>Opioid Deaths Per 100,000 Americans</th>
<th>Heroin Deaths Per 100,000 Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>5.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Decreased to</td>
<td></td>
<td>Increased to</td>
</tr>
<tr>
<td>2013</td>
<td>5.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Street values for opioids now $25-$80 per pill

A single hit of Heroin = $10

National Overdoses 2015-2016

Over 18 months (Q1 2015-Q3 2016)

20% increase in deaths from drug overdose nationwide

Source: National Center for Health Statistics
Ethanol & Benzodiazepines

New Benzodiazepines
• Etizolam, flubromazepam, others
• Not commercially available in US-online sales
  • “Research chemicals”

Abuse & Misuse include:
• Concommitant use with opioids or heroin to magnify effects
• Date rape

Drugs in Decedents—Jan to June 2016

Frequency of Occurrence of Drugs in Decedents:
- 17.7% Benzos
- 35.7% Opioids

Others include:
- Codeine
- Methadone
- Hydromorphone
- Hydrocodone
- Methamphetamine
- Cocaine
- Cannabis
- MDMA
- Fentanyl Analogs
- Heroin
- Opioids
### Opioid Overdose

#### Opiate Toxidrome

<table>
<thead>
<tr>
<th>Pharmacology</th>
<th>Binding to Mu, Kappa, Delta receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Status</td>
<td>Sedation, lethargy, coma, unresponsive</td>
</tr>
<tr>
<td>Pupils</td>
<td>Miosis</td>
</tr>
<tr>
<td>Vitals</td>
<td>Shallow respirations, Respiratory depression, Hypotension, Bradycardia, Hypothermia</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>Decreased bowel sounds, Hyporeflexia, Blue lips, fingertips</td>
</tr>
</tbody>
</table>

#### Potency Compared to Morphine

<table>
<thead>
<tr>
<th>General Potency Guide</th>
<th>Rough Estimate Equivalent Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfentanil 10,000x</td>
<td>0.0001 mg</td>
</tr>
<tr>
<td>Fentanyl 80-100x</td>
<td>0.01 mg</td>
</tr>
<tr>
<td>Hydromorphone 4-7x</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Oxycodone 1.5x</td>
<td>0.6 mg</td>
</tr>
<tr>
<td>Morphone</td>
<td>1 mg</td>
</tr>
<tr>
<td>Hydrocodone 0.5x</td>
<td>2mg</td>
</tr>
<tr>
<td>Codeine 0.3x</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

4/5 heroin users began their addiction by misusing prescription pain medications.
Carfentanil

- Synthetic opioid: 10,000 times more potent than morphine
- No acceptable medical use in humans
  - Tranquilizing agent for elephants, large mammals
- Comes as:
  - Powder, spray
  - Tablets, blotter paper
- Overdose may occur after:
  - Dermal exposure
  - Accidental powder inhalation

Lethal Doses of Each Drug
Risk Factors for Overdose

- Mixing opioids (especially with benzos or EtOH)
- Method of administration
  - Injection into vein or muscle, smoking
- Minimal or no recent use
  - Short period of abstinence will lower tolerance
- Jail, rehab or detox
- Morphine Milligram Equivalents ≥ 50 MME/day
- Medical History
  - Prior overdoses or substance abuse
  - Sex, current illness, chronic conditions

Morphine Milligram Equivalent Doses

**MME** is calculated with drug-specific equivalency factors

Calculates a *morphine dose equivalent to the ordered opioid*

Why do we care?

In a national sample of Veterans Health Administration (VHA) patients with chronic pain receiving opioids from 2004–2009:

<table>
<thead>
<tr>
<th>Patients Overdosed</th>
<th>Average 98 MME/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All other patients</td>
<td>Average 48 MME/day</td>
</tr>
</tbody>
</table>
How to Calculate

1. Determine the total daily amount of each opioid the patient takes (short-acting & long-acting)

2. Convert each to MMEs—multiple dose for each opioid by the conversion factor (see table)

3. ADD the MMEs together

Do NOT use MMEs to determine dose for converting one opioid to another

OVERDOSE may occur

Morphine Milligram Equivalent Doses

<table>
<thead>
<tr>
<th>Opioid (mg/day except where noted)</th>
<th>Conversion Factor*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Fentanyl trans (mcg/hr)</td>
<td>2.4</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>4</td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>1-20 mg/day</td>
<td>4</td>
</tr>
<tr>
<td>21-40 mg/day</td>
<td>8</td>
</tr>
<tr>
<td>41-60 mg/day</td>
<td>10</td>
</tr>
<tr>
<td>≥ 61-80 mg/day</td>
<td>12</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>3</td>
</tr>
</tbody>
</table>

Ideal: 50 MME/day
- 50mg hydrocodone
- (10 tabs Vicodin 5/300)
- 33mg oxycodone
- (2 tabs oxycodone 15mg)
- 12 mg methadone
- (~3 tabs methadone 5mg)

90 MME/day
- 90 mg hydrocodone
- (9 tabs Lortab 10/325)
- 60 mg oxycodone
- (2 tabs oxycodone 30mg)
- ~20mg methadone
- (4 tabs methadone 5mg)

*These dose conversions are estimated and do not account for individual pharmacokinetic variation
2016 CDC Guideline for Prescribing Opioids for Chronic Pain
A Clinical Review of 12 Recommendations

Risks vs. Benefits

• In chronic pain: **no evidence** showing long-term benefits of opioid use vs. no opioids
  • Outcomes (1 yr later) include both pain and function

• Extensive evidence suggesting benefits of nonpharmacologic and nonopioid therapy, with less harms
CDC Guidelines for Prescribing Opioids for Chronic Pain

- **Nonpharmacologic and nonopioid therapy are preferred for chronic pain.** If opioids must be used, they should be combined with:
  - Nonpharmacologic therapy
    - Cognitive behavioral therapy
    - Exercise therapy
    - Intervenotional treatments
  - Nonopioid therapy
    - NSAIDS or acetaminophen
    - Antidepressants
    - Anticonvulsants

**Vigilance:** red flags for nonopioid abuse?

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Before Starting Opioid Therapy

- **Risks and realistic benefits should be discussed**
  - Emphasize functional improvement as primary goal
  - Use validated instruments

**PEG Assessment Scale**
- Pain average
- Interference with Enjoyment of life
- Interference with General activity

Clinically meaningful improvement=30%

- Side effects: constipation, dry mouth, N/V, confusion, etc
- Dependence, addiction, respiratory depression, death
Before Starting Opioid Therapy

• Clinician responsibility for managing therapy should be discussed
  • Periodic reassessment
  • Adherence to nonopioid therapies
  • Planned use of precautions to reduce risk to the patient
    • Prescription Drug Monitoring Program (PDMP) → E-FORSCE
    • Drug testing
    • Naloxone use

Reassess at least every 3 months

Initial Prescribing & Follow Up

• When starting opioids for chronic pain, prescribe immediate-release (IR) opioids
  • Use the lowest effective dose
  • Greater than 3-7 days rarely needed
  • Weigh risk vs. benefits of doses ≥50 morphine milligram equivalents (MME)/day
  • Avoid increasing dosage to ≥90 MME/day

• Avoid prescribing opioids and benzodiazepines concurrently

• Physicians should offer & arrange evidence-based treatment for patients with opioid abuse disorder
Be Vigilant—Warning Signs

- **Pay attention to the following behaviors:**
  - Arriving after regular hours or wants appointment at end of office hours
  - “Just visiting” friends or relatives, or forgot to pack their medicine
  - Claiming to have damaged, lost, or stolen prescriptions
    - “Hydrophilic Medicine” excuse
  - Unusual knowledge about opioid medications
  - Stating that specific nonopioids do not work, or allergic to them
  - Pressuring the doctor by eliciting sympathy or guilt or by direct threats
    - Identify manipulative behavior and seek help from peers

- **For examination:**
  - Appearing sedated, intoxicated, or to be experiencing withdrawal
  - Textbook description of symptoms but vague medical history
  - Providing old clinical report and/or x-ray (often from interstate)
  - Declining exam, diagnostic tests, or permission to obtain past records
  - Inability to provide the name of PCP, or doctor is unavailable

Be Vigilant—Warning Signs

- **Protect Yourself:**
  - Use triplicate copies of prescriptions
  - Protect prescription pads or computer prescription paper
  - Keep samples locked
  - Do not put NPI # on prescription pads
  - Do NOT dispose of/destroy patient medications

- **Vigilance for Doctor Shopping:**
  - Communicate with other doctors when suspecting
  - Close relationship with pharmacies
  - Utilize PDMP
Naloxone

• Indications: suspected or known opioid overdose; complete or partial reversal of opioid depression

• Pharmacology: Pure opioid antagonist that competes and displaces opioids at opioid receptor sites

• Routes of administration: IV, IM, IN, subQ
  • Dose 0.04mg-2mg
  • Almost all are now 2mg

If no response is observed after 10 mg total, consider other causes of respiratory depression

Benefit is temporary! Will wear off in 30-90 minutes. May need repeat dosing.
Evzio® vs Narcan®

- Alternate nostrils with each dose
- Intranasal onset of action is slightly delayed compared to IM or IV routes

After Naloxone Administration

- Naloxone is **not** a substitute for medical care
- Acute opioid withdrawal: pain, tachycardia, hypertension, fever, sweating, abdominal cramps, diarrhea, nausea, vomiting, agitation, and irritability

Nasal spray less likely to precipitate severe opioid withdrawal
Nasal spray may not provide an adequate and timely reversal
Post-Administration: Monitoring is Necessary

• “Use with caution” in:
  • Cardiovascular history/cardiovascular meds
  • Seizure history

• Abrupt reversal may result in:
  • Hypotension or hypertension
  • Pulmonary edema
  • Cardiovascular instability, ventricular fibrillation

Narcan Administration Manatee County, FL

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2016</th>
<th>% Change</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>325 admin</td>
<td>2504 admin</td>
<td>670% increase</td>
</tr>
<tr>
<td></td>
<td>administrations</td>
<td>administrations</td>
<td></td>
</tr>
</tbody>
</table>

Cost Per Naloxone Dose: $43.79

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2016</th>
<th>Total 2013-2016</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>$14,232</td>
<td>$109,650</td>
<td>$213,739</td>
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Increased Need for Naloxone Access

From the office of
GOVERNOR RICK SCOTT
COMMUNICATIONS OFFICE
PRESS RELEASE
FOR IMMEDIATE RELEASE
May 3, 2017

GOV. SCOTT DIRECTS STATEWIDE PUBLIC HEALTH EMERGENCY FOR OPIOID EPIDEMIC

TAMPA, Fla. – Today, following the Centers for Disease Control and Prevention (CDC) declaring a national opioid epidemic, Governor Rick Scott signed Executive Order 17-11 directing a Public Health Emergency across the state. By signing the Emergency Order, it will allow the state to immediately draw down more than $27 million in federal grant funding from the United States Department of Health and Human Services (HHS) Opioid State Targeted Response Grant which was awarded to Florida on April 21 to provide prevention, treatment and recovery support services. Without the order, it would have taken months for the state to distribute these funds to local communities. In addition to declaring a Public Health Emergency, Surgeon General Dr. Celeste Philip will issue a standing order for Naloxone, an emergency treatment for opioid overdose. This will ensure first responders have immediate access to this lifesaving drug to respond to opioid overdoses.

Governor Scott said, “Today, I issued an executive order which allows the state to immediately draw down more than $27 million in federal grant funding which will immediately be distributed to communities across the state to deal with the opioid epidemic. HHS Secretary Dr. Tom Price awarded the Opioid State Targeted Response Grant to Florida and I want to thank the Trump Administration for their focus on this national epidemic. I have also directed State Surgeon General Dr. Celeste Philip to declare a Public Health Emergency and issue a standing order for Naloxone in response to the opioid epidemic in Florida.

“Public Health Emergency”

“Provide prevention, treatment, and recovery support”

“Standing order for Naloxone in response to the opioid epidemic”

Useful Tools

Substance Abuse and Mental Health Services Administration (SAMHSA)

• National Treatment Referral Helpline
  • 1-800-662-HELP (4357)

• National Substance Abuse Treatment Facility Locator
  • Search by state, city, county, and zip code
  • http://www.findtreatment.samhsa.gov/TreatmentLocator

• Buprenorphine Physician & Treatment Program Locator
  • http://www.buprenorphine.samhsa.gov/bwns_locator
E-FORSCE: Florida’s Prescription Drug Monitoring Program (PDMP)

• E-FORSCE: Electronic-Florida Online Reporting of Controlled Substance Evaluation

• 23.7% of all licensed healthcare providers are registered

• Through the use of PDMP, we have seen:
  • Reduction in average morphine milligram equivalents (MME) per patient
  • Reduction in multiple provider episodes (MPE) per patient

*Part of a clinician's responsibility for managing therapy

E-FORSCE Legislative News!

• As of February 2017, a designee of a prescriber or practitioner may have direct access to the E-FORSCE secure web portal
  • The practitioner accepts responsibility that their team is trained & for their designee’s actions within the portal

• E-FORSCE Homepage
  • http://www.floridahealth.gov/statistics-and-data/e-forcse/

• E-FORSCE Training Guide
Additional Resources

• DEA Website:  [www.dea.gov](http://www.dea.gov)
  • Drug Fact Sheets, Office of Diversion Control

• National Institute on Drug Abuse
  • [www.drugabuse.gov](http://www.drugabuse.gov)

• CDC Guidance for Prescribing Opioids
  • [https://www.cdc.gov/drugoverdose/prescribing/guideline.html](https://www.cdc.gov/drugoverdose/prescribing/guideline.html)

• American College of Preventative Medicine
  • Guidelines, Tools & Resources, Controlled Substance Agreements
  • [http://www.acpm.org/?UseMisuse_Launch](http://www.acpm.org/?UseMisuse_Launch)

• Psychoactive substances: Erowid: [www.erowid.org](http://www.erowid.org)

Treatment of Complex Cases

• **Poison Control**
  • Data collection

All AAPCC member poison centers upload data to NPDS every 8 minutes providing a near real-time snapshot of poison call conditions nationwide.
References