Objectives

1. Participants will understand the full impact of the current opioid epidemic upon the treatment field as well as directly upon the individuals treated.

2. Participants will become familiar with the most common drugs of abuse, their pharmacology as well as their interaction with each other.

3. Participants will become familiar with the various types of drug testing available including understanding their benefits and pitfalls.

4. Participants will develop a knowledge base that will enhance their ability to utilize drug testing as part of their therapeutic approach to the treatment of individuals with substance use disorders.
Opioids (Opiates?)

Opioids

Compounds with agonist effects at the mu opioid receptor:

- Opiates: natural substances derived from opium: morphine, codeine and thebaine (paramorphine, similar to both morphine and codeine used as a base compound for many semi-synthetic opioids).
- Semi-synthetic opioids: modifications of a naturally occurring opiate: heroin from morphine; buprenorphine and oxycodone from thebaine.
- Synthetic opioids: fully synthetic compounds: methadone and fentanyl
Historical Perspective

- Civil War: Introduction of the hypodermic needle and morphine analgesia
- Harrison Act (1914): Prohibition on prescription of narcotics (opioids) to individuals with addictions:
  - Many physicians prosecuted/fears of opioid prescribing
  - Increased drug trafficking and crime associated with opiate (heroin) and cocaine abuse
- 1974: First methadone maintenance program for opioid addiction.

Prequel to Abuse of Prescription Opioids

- In 1971 President Richard Nixon officially declared “a war on drugs” and in 1973 he created the Drug Enforcement Administration (DEA) to coordinate the efforts of all other agencies.
- In 1984 Nancy Reagan launched her “Just Say No” campaign
- 1989 President George H. W. Bush presented a national drug control strategy that included the largest budget increase in U.S. history. Unfortunately, even though there were large seizures of drugs and many individuals were imprisoned, we have continued to see an increase in drug use.
Abuse of Prescription Opioids

In 1995, Purdue Pharma developed OxyContin. After an aggressive marketing campaign, this drug became a significant option for chronic pain management. Physicians began prescribing this drug in excess quantities.

In its original form, OxyContin was crushable which allowed individuals to snort or inject very large quantities of oxycodone at one time. OxyContin became the most widely abused prescription drug in history. This was the beginning of what we now know as a familiar term: prescription drug abuse.

Abuse of Prescription Opioids

- Eventually, Purdue Pharma reformulated OxyContin into a non-crushable form, but it was too late.

- Pill mills were going full throttle. By evaluating the fifth vital sign, hospitals and emergency departments were attempting to achieve an expected smiley face from the individuals they served.
Abuse of Prescription Opioids

• Then, we saw the rise of oxycodone! When attention was brought to that drug as a problem:
  
  • Methadone use for pain management began to be prescribed!
  
  • Eventually, oxycodone re-emerged as the leader.

**Wow! What were we chasing?**
Abuse of Prescription Opioids

People were dying:

• In 1999 there were 4,030 opioid-related deaths and in 2010 there were 16,665 but the U.S. population only increased by less than 10%. Centers for Disease Control, 2011

• During this time, an acetaminophen-free hydrocodone was being developed.

• The FDA approved Zohydro made by Pernix Therapeutics anyway! And, lo and behold, Purdue Pharma came back with its own version: Hysingla.

Abuse of Prescription Opioids

Due to the prescription drug abuse, states had been clamping down on pain clinics. Many states developed their own rules for pain and also developed prescription drug monitoring programs. Unfortunately, Florida was very late in that endeavor.

While neighboring states were clamping down, bus loads of people were coming to Florida pain clinics for those excessive quantities of opioids and benzodiazepines. This busing of individuals from out of state to Florida was called the “Oxycontin Express.”
Abuse of Prescription Opioids

- The Federal Centers for Disease Control labeled Florida the epicenter of prescription drug diversion because it had weak regulatory oversight of pain management practices, limited regulation of physician dispensing habits and, most importantly, no prescription drug monitoring program.
- Florida became known as the “Pill Mill” capital of the country.

Abuse of Prescription Opioids

- According to the Drug Enforcement Administration (DEA):
  - Florida had over 900 unregulated pain management clinics in 2010.
  - These clinics employed 90 of the top 100 oxycodone dispensing physicians in the country.
  - Of the top 50 oxycodone dispensing clinics in the U.S., 49 were located in Florida and were selling more than 1 million oxycodone pills a month.

Sources: Florida’s Prescription Diversion and Abuse Roadmap, 2012-2015
The Florida PDMP Foundation, Inc.
Before new regulations were enacted by the Florida legislature, it was projected from state medical examiners reports that about **seven persons** each day **died** of prescription drug overdose, primarily due to oxycodone abuse.

Source: Florida’s Prescription Drug Diversion and Abuse Roadmap 2012–2015

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**Abuse of Prescription Opioids**

Florida’s prescription drug monitoring program, E-FORCSE (the Electronic-Florida Online Reporting of Controlled Substances Evaluation), eventually began operation in 2011.

*As of June 2016 only 23.7% of all licensed healthcare practitioners were registered to use it!*

https://www.flsenate.gov/Session/Bill/2017/557/Analyses/h0557e.HHS.PDF
Prescription Opioid Abuse Takes a Back Seat

• Unfortunately, the black market business machine made its next move; heroin became much cheaper than prescription opioids.

• Our local methadone clinics began seeing increasing numbers of individuals using heroin and not the all-too-familiar and popular prescription opioids.

• The next concern became Krokodil (Desomorphine). It also was called, “From Russia with Love.” It was known as the “poor man’s heroin” in Russia or “the world’s deadliest drug”. Highly addictive, it was made by combining codeine with ethanol, gasoline, red phosphorus, iodine, hydrochloric acid, and paint. Unfortunately, those individuals who used it died after witnessing their flesh’s being eaten away..

Prescription Opioid Abuse Takes a Back Seat

Thankfully, what was thought to be a minor miracle occurred as we only saw its introduction to this country in 2013 and it spread no further.

One might speculate that the reason why it did not spread any further is that another drug came along which is the cause of our present epidemic:

Fentanyl
The manufacturing and distribution of fentanyl and its analogs is more than an epidemic... it's chemical warfare.

The United States is in the midst of an opioid epidemic with fentanyl fueling the crisis. Drug overdose deaths in 2016 most likely exceeded 65,000, according to the Provisional Counts of Drug Overdose Deaths—published by the CDC in August, 2017. The death count is the latest consequence of an escalating public health crisis; opioid addiction now is becoming even more deadly due to an influx of illicitly manufactured fentanyl and fentanyl analogs.
A Bit of Data

THE IMPACT OF ADDICTION ON AMERICA
NEARLY **250 MILLION**

prescriptions for opioids are written each year.

This is more than enough to give every adult in our country their own bottle.

--

MORE

American adults used prescription painkillers than used cigarettes, smokeless tobacco or cigars combined in 2015.

--

Substance Abuse and Mental Health Services Administration, 2016
Nationwide

• In 1999 there were 4,030 opioid-related deaths and in 2010 there were 16,665 but the U.S. population only increased by less than 10%.

Centers for Disease Control, 2011

Nationwide

• During 2013 – 2014 the number of drug products that law enforcement obtained that tested positive for fentanyl increased by 426%. Synthetic opioid-involved overdose deaths (excluding methadone) increased by 79%.

Centers for Disease Control, 2016
NDEWS National Drug Early Warning System, 2016
Nationwide

• In March and October 2015, the DEA and the Centers for Disease Control (CDC) respectively issued nationwide alerts identifying illicitly manufactured fentanyl (IMF) as a threat to public health and safety. IMFs are being mixed in unknown concentrations with heroin.

Centers for Disease Control, 2016
NDEWS National Drug Early Warning System, 2016

Nationwide

• In the fourth quarter of 2016, the DEA laboratory system noted a decrease in fentanyl seized from approximately 65% to 50% due to a 300% increase in furanyl fentanyl

Centers for Disease Control, 2016
NDEWS National Drug Early Warning System, 2016
Nationwide

• There have been nine other intravenous morphine infusion (IMF) drugs identified aside from fentanyl (which is 50 to 100 times more potent than morphine) and carfentanil (that is more than 10,000 times more potent than morphine).

• Is this the current generation’s AIDS crisis? In 2015 52,000 people died of drug overdoses; the peak year for AIDS related deaths was 51,000 in 1995.

• According to STAT, there are now greater than **140 deaths a day from opioids**. Every 3 weeks there are **more deaths than due to the terrorism that happened 9/11**.

New York, March 16, 2017
The New York Times, June 5, 2017

---

Provisional Counts of Drug Overdose Deaths
Jan 2016-2017

<table>
<thead>
<tr>
<th>Drug overdose deaths</th>
<th>Data quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of deaths for 12 month-ending</td>
</tr>
<tr>
<td></td>
<td>Jan 2016</td>
</tr>
<tr>
<td>US Total</td>
<td>52,858</td>
</tr>
<tr>
<td>32 Reporting Jurisdictions</td>
<td>256,841</td>
</tr>
<tr>
<td>Alaska</td>
<td>126</td>
</tr>
<tr>
<td>Arkansas</td>
<td>378</td>
</tr>
<tr>
<td>Colorado</td>
<td>913</td>
</tr>
<tr>
<td>Delaware</td>
<td>181</td>
</tr>
<tr>
<td>Florida</td>
<td>3,224</td>
</tr>
<tr>
<td>Georgia</td>
<td>1,259</td>
</tr>
<tr>
<td>Illinois</td>
<td>1,893</td>
</tr>
<tr>
<td>Indiana</td>
<td>1,228</td>
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<tr>
<td>Iowa</td>
<td>303</td>
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<tr>
<td>Kentucky</td>
<td>1,523</td>
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<tr>
<td>Louisiana</td>
<td>899</td>
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<tr>
<td>Maine</td>
<td>270</td>
</tr>
<tr>
<td>Maryland</td>
<td>1,819</td>
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<td>Minnesota</td>
<td>857</td>
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<td>Missouri</td>
<td>1,096</td>
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<td>Nebraska</td>
<td>122</td>
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<tr>
<td>New York City</td>
<td>987</td>
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<td>North Dakota</td>
<td>426</td>
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<td>Ohio</td>
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<td>Washington</td>
<td>1,154</td>
</tr>
<tr>
<td>Wyoming</td>
<td>94</td>
</tr>
</tbody>
</table>

Centers for Disease Control
Fentanyl is Now Florida’s Deadliest Drug

• Fentanyl is now killing more Floridians than any other single drug. Palm Beach County leads the state in deaths caused by that powerful opioid.

• In the first six months of 2016, a mix of street drugs, including heroin and fentanyl, killed 225 people in Palm Beach County.

• The deadly cocktail of heroin mixed with fentanyl or Carfentanil figured in 220 deaths in Miami-Dade County in 2015.

• 90% of fatal drug overdoses in Broward County involved heroin, fentanyl or other opioids.

Palm Beach Post May 5, 2017

Local

• In 2015, Florida heroin deaths escalated to 779, a 74% increase from 2014; and a 2400% increase from 2010. Fentanyl deaths increased over 69% (538 to 911) from 2014-15.

• In 2015, North Florida heroin deaths rose to 45, a 181% increase from 2014; and a 10,000% increase from 2010. Fentanyl deaths increased nearly 70% (33 to 56) from 2014-15.

• Overdose victims – 2015 – Jacksonville Fire and Rescue Department (JFRD) responded to 2,114; 2016 – JFRD responded to 3,114.

• 911 calls have tripled.

• In 2015 – cost of transporting overdose (OD) victims was $1,895,388.00; 2016 cost $3,143,376.00 with current trend projections reaching $4,451,124.00 in 2017. JFRD is transporting one OD victim every 2 hours.

• Naloxone use by paramedics has increased fivefold with one-tenth of medical supply budget spent on naloxone.

Drugs Identified in Deceased Persons by Florida Medical Examiners 2015 Annual Report
Jacksonville Fire & Rescue Department: Response to Overdoses

Source: Jacksonville Fire & Rescue Department

<table>
<thead>
<tr>
<th>Month</th>
<th>9-1-1 Call Received as OD</th>
<th>Narcan Doses Given</th>
<th>Treated as OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan-17</td>
<td>173</td>
<td>75</td>
<td>132</td>
</tr>
<tr>
<td>Feb-17</td>
<td>167</td>
<td>90</td>
<td>140</td>
</tr>
<tr>
<td>Mar-17</td>
<td>196</td>
<td>71</td>
<td>161</td>
</tr>
<tr>
<td>Apr-17</td>
<td>203</td>
<td>82</td>
<td>185</td>
</tr>
<tr>
<td>May-17</td>
<td>177</td>
<td>88</td>
<td>174</td>
</tr>
<tr>
<td>Jun-17</td>
<td>173</td>
<td>104</td>
<td>170</td>
</tr>
<tr>
<td>Jul-17</td>
<td>222</td>
<td>92</td>
<td>185</td>
</tr>
<tr>
<td>Aug-17</td>
<td>214</td>
<td>107</td>
<td>190</td>
</tr>
<tr>
<td>Sep-17</td>
<td>196</td>
<td>100</td>
<td>192</td>
</tr>
<tr>
<td>Oct-17</td>
<td>201</td>
<td>100</td>
<td>147</td>
</tr>
<tr>
<td>Nov-17</td>
<td>151</td>
<td>79</td>
<td>133</td>
</tr>
<tr>
<td>Dec-17</td>
<td>127</td>
<td>83</td>
<td>154</td>
</tr>
<tr>
<td>Jan-18</td>
<td>145</td>
<td>79</td>
<td>133</td>
</tr>
<tr>
<td>Feb-18</td>
<td>148</td>
<td>96</td>
<td>132</td>
</tr>
<tr>
<td>Mar-18</td>
<td>156</td>
<td>74</td>
<td>145</td>
</tr>
<tr>
<td>Apr-18</td>
<td>150</td>
<td>90</td>
<td>145</td>
</tr>
<tr>
<td>May-18</td>
<td>204</td>
<td>72</td>
<td>166</td>
</tr>
<tr>
<td>Jun-18</td>
<td>195</td>
<td>97</td>
<td>147</td>
</tr>
<tr>
<td>Jul-18</td>
<td>165</td>
<td>91</td>
<td>144</td>
</tr>
<tr>
<td>Aug-18</td>
<td>127</td>
<td>106</td>
<td>125</td>
</tr>
<tr>
<td>Sep-18</td>
<td>198</td>
<td>114</td>
<td>150</td>
</tr>
<tr>
<td>Oct-18</td>
<td>212</td>
<td>131</td>
<td>179</td>
</tr>
<tr>
<td>Nov-18</td>
<td>186</td>
<td>78</td>
<td>174</td>
</tr>
<tr>
<td>Dec-18</td>
<td>221</td>
<td>102</td>
<td>202</td>
</tr>
<tr>
<td>Jan-19</td>
<td>171</td>
<td>100</td>
<td>146</td>
</tr>
</tbody>
</table>

JFRD Overdose Data Report

Source: Jacksonville Fire and Rescue Department
Local

- In 2016, Duval County had 106 murders and 464 overdose deaths (up from 201 in 2015).
- Age distribution of drug-related deaths in Duval County - 20-60 years old with 86.9% being Caucasian.
- The morgue is continually over capacity! There has been a 1900% increase in OD deaths due to heroin since 2011.
- Duval has the second highest in the state for Neonatal Abstinence Syndrome (NAS) cases in 2016.
- A sampling of urines from a lab servicing the nation analyzing positive heroin samples in Florida from 2013 to 2016 found a 56.41% increase in associated fentanyl positivity (not testing for the other IMF’s). Gateway detox: 100% of all heroin + urines are + for Fentanyl.
- **Almost 2 deaths per day in Duval County.**

How Common is Opioid Dependence?

Approximately 2.5 million Americans were dependent on prescription opioid pain killers or heroin in 2012. We don’t know the real numbers now!

*The Florida Times-Union March 17, 2017*
Pharmacology

Opioid Pharmacology

- Types of opioid receptors:
  - Mu
  - Kappa
  - Delta
- Addictive effects occur through activation of mu
- Role of kappa and delta receptors in the addictive process are not well defined
Mu Receptor Drugs

- Morphine
- Methadone
- Hydromorphone
- Codeine
- Fentanyl
- Heroin
- Buprenorphine
- Oxycodone
- Hydrocodone

Function of a Full Mu Agonist

- Activates the mu receptor
- Highly reinforcing
- Most abused
- Includes heroin, methadone, oxycodone, others
Function of a Partial Mu Agonist

• Activates the receptor at lower levels
• Is relatively less reinforcing
• Is less abused
• Buprenorphine

Function of a Mu Antagonist

• Occupies without activating
• Is not reinforcing
• Blocks and will displace agonist opioid types
• Includes naloxone and naltrexone (Vivitrol)
The Action of Heroin (Morphine)
### Equianalgesic Opioid Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equianalgesic Doses (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parenteral</td>
</tr>
<tr>
<td>Morphin</td>
<td>10</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.3</td>
</tr>
<tr>
<td>Codeine</td>
<td>100</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
</tr>
<tr>
<td>Meperidine</td>
<td>100</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10*</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100*</td>
</tr>
</tbody>
</table>

*Not available in the US


NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.
<table>
<thead>
<tr>
<th>Kinetic Parameters (Chart)</th>
<th>oral bio-availability (avg)</th>
<th>onset of effect</th>
<th>average half life (hr.)</th>
<th>plasma protein binding</th>
<th>typical duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>codeine</td>
<td>70-90%</td>
<td>45-60m</td>
<td>produg</td>
<td>7.25%</td>
<td>4-6h</td>
</tr>
<tr>
<td>pethidine</td>
<td>40-60%</td>
<td>20-40m</td>
<td>3.5h</td>
<td>60-80%</td>
<td>2-4h</td>
</tr>
<tr>
<td>morphine</td>
<td>30-40%</td>
<td>30-45m</td>
<td>2.4h</td>
<td>35%</td>
<td>3-4h</td>
</tr>
<tr>
<td>oxycodone</td>
<td>60-80%</td>
<td>45-60m</td>
<td>3.5h</td>
<td>45%</td>
<td>4-6h</td>
</tr>
<tr>
<td>hydrocodone</td>
<td>60-80%</td>
<td>45-60m</td>
<td>3.5h</td>
<td>unknown</td>
<td>4-6h</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>24%</td>
<td>30m</td>
<td>2.6h</td>
<td>8-10%</td>
<td>2-3h</td>
</tr>
<tr>
<td>oxymorphone</td>
<td>10%</td>
<td>20-40m</td>
<td>1.3h</td>
<td>10-12%</td>
<td>3-4h</td>
</tr>
<tr>
<td>levorphanol</td>
<td>-50%</td>
<td>20-40m</td>
<td>11.16h</td>
<td>40%</td>
<td>4-6h</td>
</tr>
<tr>
<td>methadone</td>
<td>80%</td>
<td>60-90m</td>
<td>22h</td>
<td>80-90%</td>
<td>6-12h</td>
</tr>
<tr>
<td>fentanyl</td>
<td>-10-15%</td>
<td>10-20m</td>
<td>3.5h</td>
<td>80%</td>
<td>1-2h</td>
</tr>
<tr>
<td>buprenorphine</td>
<td>-10-15%</td>
<td>60m</td>
<td>36h</td>
<td>90%</td>
<td>4-12h</td>
</tr>
<tr>
<td>tramadol</td>
<td>70%</td>
<td>60-90m</td>
<td>6.7h</td>
<td>20%</td>
<td>4-6h</td>
</tr>
<tr>
<td>tapentadol</td>
<td>30-40%</td>
<td>30-45m</td>
<td>4.5h</td>
<td>20%</td>
<td>2-4h</td>
</tr>
</tbody>
</table>
Benzodiazepines

Medical Indications for Use

- Anxiolytic
- Sedative/hypnotic
- Anticonvulsant
- Muscle relaxant
- Alcohol and benzo withdrawal

Except for inpatient detox, beware of use in this population!
Benzodiazepines/Barbiturates Neurophysiology

GABAa Receptor

- Benzodiazepine site
- Non-benzodiazepines
- Agonists
- Antagonists
- Inverse agonists

- Barbiturates
- Etomidate
- Etasolate

- General anaesthetics
- Propofol
- Remifentanil
- Halothane
- Ethanol

Subsynaptic membrane
Non-benzo-benzos ("Z" Drugs)

Sedative Hypnotics: Half Life
- Eszopiclone (Lunesta): 6h
- Zaleplon (Sonata): 1h
- Zolpidem (Ambien): 3h
Benzodiazepines + Opioids

DEATH
Alcohol

Alcohol: Good, Bad or Just Ugly?
15.1 million adults in the U.S. suffer from alcohol abuse or dependence.

## Concentration-Effect Relationship

<table>
<thead>
<tr>
<th>Blood Alcohol Content (BAC) [%]</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02-0.03</td>
<td>Mood elevation. Slight muscle relaxation.</td>
</tr>
<tr>
<td>0.05-0.06</td>
<td>Relaxation and warmth. Increased reaction time. Decreased fine muscle coordination.</td>
</tr>
<tr>
<td>0.08-0.09</td>
<td>Impaired balance, speech, vision, hearing, muscle coordination. Euphoria.</td>
</tr>
<tr>
<td>0.14-0.15</td>
<td>Gross impairment of physical and mental control.</td>
</tr>
<tr>
<td>0.20-0.30</td>
<td>Severely intoxicated. Very little control of mind or body.</td>
</tr>
<tr>
<td>0.40-0.50</td>
<td>Unconscious. Deep coma. Death from respiratory depression</td>
</tr>
</tbody>
</table>
Alcohol Facts

- Metabolism decreases BAC by .015 per hour
- Average male reaches .08 after 3-4 standard (2-3 for women) drinks in one hour
- A typical "night out" sees a BAC of .1 to .2 (1-2 standard drinks)
- Return to BAC of 0 will take more than 10 hours after last drink.
- Impairment will last 20 – 30 hours
- See next slide for a “typical day”

Impairment

Hung over state

- Dehydration
- Metabolic acidosis
- Hypoglycemia
- Disequilibrium
- Sleep debt
- Cognitive impairment
Alcohol + Opioids

DEATH

Tolerance
Pharmacological Phenomena

Tolerance

- Tolerance can be defined as the reduction in response to the drug after repeated administrations.
  - Drug (dose) increases $\uparrow$ --- drug effect $\uparrow$
  - Repeated drug administration $\rightarrow$ tolerance
  - Thus a higher dose is required to produce the same effect that was once obtained at a lower dose.

Example:
Diazepam produces sedation at doses of 5 to 10 mg in a first-time user $\rightarrow$ repeated user may require several hundreds of milligrams to produce desired effect (due to development of tolerance)

Tolerance

- Graph showing the difference in response between a naive user and a chronic user with respect to dose (log scale).
Final Note on Tolerance

Once tolerance to a drug effect has developed, it is not irreversible. A period of abstinence from a drug increases users’ sensitivity to drug effects they may have become highly tolerant to in the past. If the user does not take into account the loss of tolerance, it could result in death by overdose if they try to use the same amount.

Acute tolerance reverses in a short time. However, protracted tolerance requires more extended abstinence to reverse. For example, when taking the same amount of cocaine a few days after using, a cocaine user may again experience its pleasurable effects. However, an alcoholic with protracted tolerance may have to abstain for years before his/her tolerance begins to reverse.

What Happens When You Mix Heroin + Fentanyl?
Addiction Hijacks The Brain. **Fentanyl** Hijacks The Mind, Body and Soul!

Fentanyl And Fentanyl Analogs

**Fentanyl** (and Norfentanyl a metabolite of fentanyl), 50 to 100 times more potent than morphine, and 30 to 50 times more potent than heroin. Fentanyl is also used as a recreational drug, leading to thousands of overdose deaths from 2000 to 2017.

**Carfentanil Oxalate** is a potent synthetic opioid that has similar properties as heroin and has been used as an elephant tranquilizer. Recently, though, Carfentanil has made headlines due to its deadly consequences. It is 100 times more potent than fentanyl, which is a drug that is 50 times more potent than heroin. Carfentanil is 10,000 times more potent than morphine. An amount smaller than a few grains of salt can be lethal.
Sufentanil is a synthetic opioid between 5-10 times more potent than its parent drug fentanyl. It is used to treat pain primarily along with anesthesia during surgery or childbirth.

Remifentanil is a synthetic opioid used to induce or supplement general anesthesia. Remifentanil is approximately twice as potent as fentanyl, and 100-200 times as potent as morphine.

(+)-Cis-3-methylfentanyl is a designer drug and fentanyl analogue with an estimated potency 400 to 6000 times greater than morphine.

Acetyl Norfentanyl is a major metabolite of acetyl fentanyl, a designer drug and fentanyl analog with a potency 40 times greater than heroin and 80 times greater than morphine.
Fentanyl And Fentanyl Analogs

**Butyryl Fentanyl** is a designer drug that has been associated with numerous overdose deaths around the world. In 2016, the U.S. Drug Enforcement Administration (DEA) classified butyryl fentanyl as a schedule I controlled substance.

**Acetyl Fentanyl** is a designer drug with a potency 40 times greater than heroin and 80 times greater than morphine. In 2013, the CDC issued a health alert for acetyl fentanyl, reporting 14 overdose deaths in Rhode Island.

Fentanyl And Fentanyl Analogs

**Alfentanil** is a potent but short-acting synthetic opioid analgesic drug used for anaesthesia in surgery. The drug is 1/4 to 1/10 the potency of fentanyl and around 1/3 of the duration of action, but with an onset of effects 4x faster than fentanyl.

**Furanyl Fentanyl HCl** is an opioid analgesic that is an analogue of fentanyl and has been sold as a designer drug. The drug is so potent that it can cause a fatal overdose just through skin absorption. Furanyl fentanyl is a new compound and medical experts believe it could be as much as 30 to 50 times more potent than any other similar drugs.
CHINGLABS.COM
This lab in China is where people in the U.S. used to be able to obtain directly fentanyl and its analogs.

Clinical Use of Drug Testing as Recommended by American Society of Addiction Medicine (ASAM)

Appropriate Use of Drug Testing in Clinical Medicine, Journal of Addiction Medicine: May/June 2017
Clinical Use of Drug Testing as Recommended by American Society of Addiction Medicine (ASAM)

- Drug testing’s use as a therapeutic tool
- Drug testing’s use in assessment
- Process of drug testing in addictions treatment
- Identifying substances of interest

Clinical Use of Drug Testing as Recommended by American Society of Addiction Medicine (ASAM) Continued

- Responding to test results
- Responding to unclear test results
- Test scheduling frequency
Screening and Confirmation Technology

Types of Screening Tests

Instrument/Reagent (Laboratory)
EMIT

Point-of-Care Tests (Non-Instrumented)
Instant products: Integrated cups, dips, oral fluid tests
Screening Tests

Screening Tests (Urine or Saliva)
- Initial point of care (POC) or laboratory (EMIT) tests
- Both use immunoassay technology

What Do Screening Tests Tell Us?
- Qualitative positive or negative result
- Whether a drug class is present (i.e. opiates)

What Do Screening Tests Not Tell Us?
- Screens do not tell us specific drug or combination present (i.e. is the opiate positive a result of heroin? Hydrocodone? Codeine?)
- Screens do not provide a reliable or usable quantitative result
- Screens cannot tell us if there has been any cross reactivity caused by prescriptions and/or diet that may result in a “false positive”

Benzodiazepine Metabolism
Urine Drug Screening for Benzodiazepines

- Immunoassay most easily tests for diazepam breakdown products
- Clonazepam can be detected at high doses
- Lorazepam is very difficult to detect
- Alprazolam depends on reagent and threshold
  - Need to ask for gas chromatography (GC/MS) or liquid chromatography-mass spectrometry (LC/MS/MS)!

Urine

- ASAM considers urine “the most well-established and well-supported biological matrix for presumptive detection of substance use in a clinical setting.”
- Urine Sample Integrity
- Signs of urine sample tampering
- What to do with questionable samples

*Appropriate use of Drug Testing in Clinical Addiction Medicine, Journal of Addiction Medicine May/June 2017.*
Screening For Opioids
Possible Limitations

(+)
Some medications/drugs (Tylenol with/codeine, Vicodin, Lortab, Dilaudid, morphine, Percocet, OxyContin, heroin, etc. can result in a positive opiate (OPI) screen.

(×)
A positive screening result can be interpreted many ways. Without knowing exactly what opiate/opioid it is, you cannot draw accurate conclusions.

Separate Metabolic Pathways
The following illustrates the different metabolic pathways of both OPI and OXY. Opiates (represented in blue) have a completely separate metabolic pathway to OXY (represented in orange). This is a helpful reference to illustrate how the laboratory utilizes mass spectrometry results to identify specific analytes in a specimen.
Simplified Schematic of Metabolic Pathways for Opioids

poppy seeds* → morphine → 6-monoacetyl morphine (6-AM)

* Not specifically detected by the assay

References:

- (I)
- (II)
- (III)
- (IV)
- (V)

Additional notes:

- Oxycodeone → Oxymorphone
- Codeine → Morphine
- Hydrocodone → Hydromorphone
Fentanyl and New Synthetics Require Labs to Keep Up!

- Many new “synthetic” forms of fentanyl including acetyl fentanyl, furanyl fentanyl, butyryl fentanyl, carfentanil are becoming a major problem.

- Chemists/drug designers are modifying fentanyl to change the chemical composition.

- Screens are non-specific vs. absolute specificity in LC/MS/MS – Screens could be detecting more than the known compound.

- Designers create these drugs to prevent detection from mass spectometry.

Design Opioid Panel for Fentanyl and Fentanyl Analogs

Laboratory confirmation tests now are available that detect not only fentanyl usage but also detect synthesized fentanyl analogs that may not be picked up by traditional testing methods, including:

<table>
<thead>
<tr>
<th>Expanded Fentanyl Method</th>
<th>(±)-Cis-3-methylfentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>(+)-Cis-3-methylfentanyl</td>
</tr>
<tr>
<td>Norfentanyl</td>
<td>Acetyl Fentanyl</td>
</tr>
<tr>
<td>Carfentanil Oxalate</td>
<td>Acetyl Norfentanyl</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>Butyryl Fentanyl</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Alfentanil</td>
</tr>
<tr>
<td>Remifentanil Acid</td>
<td>Furanyl Fentanyl HCl</td>
</tr>
</tbody>
</table>
Screening Technology: Non-Specific

- Rapid test strips use antibodies that recognize the shared segment of the drug.
  The blue part represents the portion of the different compounds that are similar.
- This means one screening test can detect many drugs within a family.

Confirmation Technology: Highly Specified

- Verifies by weight of the drug making it very specific.
- Each new version needs to specifically be set up for the confirmation to work.
What Is EtG?

Ethyl Glucuronide (glu-ˈkyūr-ə-nīd) - EtG is a direct biological marker that is formed in the body after the consumption of ethanol, typically from drinking alcoholic beverages. When someone consumes even relatively small amounts of alcohol, EtG is formed and can be detected. EtG may be detectable as soon as 2 hours after use and may be detected for up to 50+ hours past consumption. A biomarker is any substance, structure, or process that can be measured in the body.

- Unique biological markers of alcohol use (only alcohol consumed can create EtG)
- Direct marker indicating recent use
- It is not detected in the urine of abstinent individuals (didn’t use any alcohol, body won’t create EtG)
- Non volatile, water soluble
- Longer detection window than traditional alcohol tests
- Stable in stored specimens
- Highly specific and sensitive

ETHYL GLUCURONIDE
Testing Limitations/Complexities

Degradation

Did you know?
Ethyl Glucuronide (EtG) may degrade in a urine specimen when left at room temperature for too long, and bacteria can cause the level to decrease. For example, this means that potentially, if you collected a sample on Thursday, but it didn’t get to your lab until Monday, the level of EtG in the urine could have dropped below the laboratory cut off. What to do?

1. Refrigerate any sample that is expected to be shipped to a lab for further testing.

2. Especially if a sample is collected at the end of the week (Friday) and does not make FedEx pick up, ensure it is refrigerated over the weekend.

3. Make sure that the laboratory can also detect EtS (Ethyl Sulfate). EtS does not degrade in a specimen.
EtG Testing Limitations/Complexities

Utilizing EtG/ethyl sulfate (EtS) testing is the best possible solution for alcohol abstinence monitoring that otherwise would go undetected with traditional alcohol testing.

EtG/EtS levels are not thought to be a direct determinant of the amount of alcohol consumed. One of the reasons is variability due to concentration. Other variables that are not easy to correct for include the individual's productive capacity for EtG and EtS, which can vary based on genetics, medications, and other factors (liver disease, chronicity of exposure, etc.).

The detection of EtG and EtS offers greater sensitivity and accuracy for the determination of recent ethanol ingestion than by detection of either biomarker alone.

Comparing Variations Between GC-MS & LC-MS/MS

- The tandem mass spectrometer in liquid chromatography-tandem mass spectrometry (LC-MS/MS) is more specific than the Gas chromatography-mass spectrometry (GC-MS) as it provides additional structural information not captured by the GC-MS.

- Liquid chromatography does not require any derivatization steps and therefore is more reliable. It has been shown that derivatization can lead to false-positives (e.g. methamphetamine).

- LC-MS/MS utilizes a "soft" ionization preserving the parent molecule for analysis. GC-MS uses electron impact, a harder ionization process, which can degrade the parent molecule. From a laboratory workflow standpoint, LC-MS/MS requires less sample preparation. That causes a faster turn-around time for providers.
Drug Testing Confirmation

- GC/MS; LC/MS/MS
- Absolute specificity; no false +
  - Absolute specificity to determine exact drug in the sample (i.e. Heroin, Fentanyl, Xanax, etc.)
- QUANTITATIVE RESULT
- Definitive for court

Lab Based Oral Fluid Testing
Testing Made Easy

- Easily administered single step procedure that takes only minutes
- Fast collection with saturation indicator to identify sufficient volume
- Shy bladder concerns eliminated - prevent long waits for individuals to provide urine specimen

Proven Reliability And Accuracy

- Delivers proven laboratory reliability
- The ability to detect drug use within minutes, whereas urine you must wait for drugs to metabolize

Test Anytime/Anywhere

- Gender neutral collection (No private restroom requirement)
- Enables direct observation during collection
- Eliminates the risk of adulteration by substitution, dilution, or additives

Effective Testing In The Field
Case Managers/Investigators do not always have access to controlled collection sites. Testing may be administered in client’s homes, workplace, or a public restroom in which observation is not always possible.

Avoid Adulteration
While donors are getting more and more sophisticated in terms of beating a urine test (substitution, dilution, adding oxidants/bleach to specimen to kill presence of drug, etc.) oral fluid testing is 100% observed and therefore, resistant to adulteration.

Gender Neutral Collection
Oftentimes, case managers are of the opposite gender of the donor, which again makes observed collections unrealistic. Oral Fluid testing provides an ideal solution and eliminates the need for same sex collectors.
Hair Testing

• Is able to find drugs used up to 3 months prior
• Costly
• Collection is invasive
• Many labs do not provide
• Results do not hold up in court

Case Vignette # 1

25-year-old female in detox with altered mental status and sent to local emergency department:
• WHY?
• Implications if treated as usual
• Potential solutions
Medication-Assisted Treatment Options

Methadone

- Is for opioid dependence only
- It is a highly regulated Schedule II opioid
- DCF, DEA and Board of Pharmacy perform regular and stringent audits of methadone clinics
- Is the gold standard for pregnant women due to potential fetal demise from withdrawal
- Stops withdrawal symptoms and craving
- Most researched medication used in the treatment of addiction
- Individuals don’t get high once stabilized
- Tolerance is not as much of a factor with this medication
- Do not confuse its abuse with the methadone prescribed from pain clinics
Methadone works very well for heroin and prescription opioid dependence.

Methadone is not working as well for treatment of the abuse of fentanyl or its analogs!

Case Vignette # 2

26-year-old female stable on 120 mg methadone presents with withdrawal symptoms.
• WHY?
• Implications if treated as usual
• Potential solutions
Suboxone/Subutex

- Given sublingual. Takes approx. 10 minutes to dissolve. Buccal and implants available.
- A partial mu agonist with reduced abuse potential. Long duration of action. Holds tight to the mu receptor.
- Individuals rarely need more than 16mg, though max dose is 32 mg.
- Must be in withdrawal before the induction process is started.

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Equivalent to Methadone 1 mg</th>
<th>Time for Effects to Wear off</th>
<th>Onset of Withdrawal</th>
<th>Peak of Withdrawal</th>
<th>End of Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>0.01 mg</td>
<td>1 h</td>
<td>3-5 h</td>
<td>8-12 h</td>
<td>4-5 days</td>
</tr>
<tr>
<td>Meperidine</td>
<td>20 mg</td>
<td>2-3 h</td>
<td>4-6 h</td>
<td>8-12 h</td>
<td>4-5 days</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5 mg</td>
<td>3-6 h</td>
<td>8-12 h</td>
<td>36-72 h</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.5 mg</td>
<td>4-5 h</td>
<td>4-5 h</td>
<td>36-72 h</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Heroin</td>
<td>1-2 mg</td>
<td>4 h</td>
<td>8-12 h</td>
<td>36-72 h</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Morphine</td>
<td>3-4 mg</td>
<td>4-5 h</td>
<td>8-12 h</td>
<td>36-72 h</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Codeine</td>
<td>30 mg</td>
<td>4 h</td>
<td>8-12 h</td>
<td>36-72 h</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>0.5 mg</td>
<td>4-8 h</td>
<td>8-12 h</td>
<td>36-72 h</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Methadone</td>
<td>NA</td>
<td>8-12 h</td>
<td>36-72 h</td>
<td>96-144 h</td>
<td>14-21 days</td>
</tr>
</tbody>
</table>

Na: not applicable.
Source: Reference 6.
Case Vignette # 3
45-year-old male on buprenorphine tests positive for naloxone
• WHY?
• Implications
• Potential solutions

Vivitrol

• For opioid and alcohol dependence.
• Injectable form of Naltrexone; a full mu receptor antagonist. It fully covers the receptor and does not allow opioids to attach.
• This is not an opioid. Not mood-altering and not addictive.
• A monthly injection. The pill form can be taken every day, but compliance is a problem and side effects are a greater possibility.
• Blocks action of opioids and reduces cravings for opioids.
• Reduces craving for alcohol and reduces effect.
Case Vignette # 4

54-year-old male using Vivitrol found unresponsive. His family called 911:
- WHY?
- Implications
- Potential solutions

This is an *epidemic* that is growing faster than we ever imagined. The cost in lives and money is pushing the envelope of everything the system has to offer. We need a *solution now***!
Questions And Answers

Thank You

References

Dr. Raymond M. Pomm

Raymond M. Pomm, M.D. is Vice President of Medical Services at River Region Human Services and Medical Director for Gateway Services at River Region Human Services and Medical Director for Gateway Community Services. Board certified in psychiatry, addiction psychiatry, and addiction medicine, he has been a leader in the addiction field as it relates to the evaluation and treatment of co-occurring disorders and management of impaired professionals. He is a certified Medical Review Officer, served on the Governor’s Commission on Mental Health and Substance Abuse, and has been an expert consultant to the Florida Board of Bar Examiners. Dr. Pomm has written multiple publications on issues surrounding addiction and urine testing. He has received multiple awards including, “The Marie Award,” from the American Association for the Treatment of Opioid Dependence and the 2007 Annual Medical Leadership Award from the Florida Society of Addiction Medicine. A graduate of Meharry Medical College, he received his undergraduate degree in psychology from University of Tennessee.

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