New Drugs of Abuse

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Objectives

Become Familiar With:

- **Federal Analog Act**
- **Presentation and management of patients intoxicated by synthetic cannabinoids**
- **Incidence and symptoms of exposures to cannabis-containing products in children**
- **Recognition and treatment of cannabinoid hyperemesis**

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Federal Analog Act (1986)

- Section of US Controlled Substances Act
- Drugs "substantially similar" to Schedule I or II treated as such

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Three Parts to US Federal Analog Act

1. "Chemically substantially similar"

[AND EITHER]

2. Effects similar to substance in Schedule I or II

OR

3. Represented as having the effects of a controlled substance

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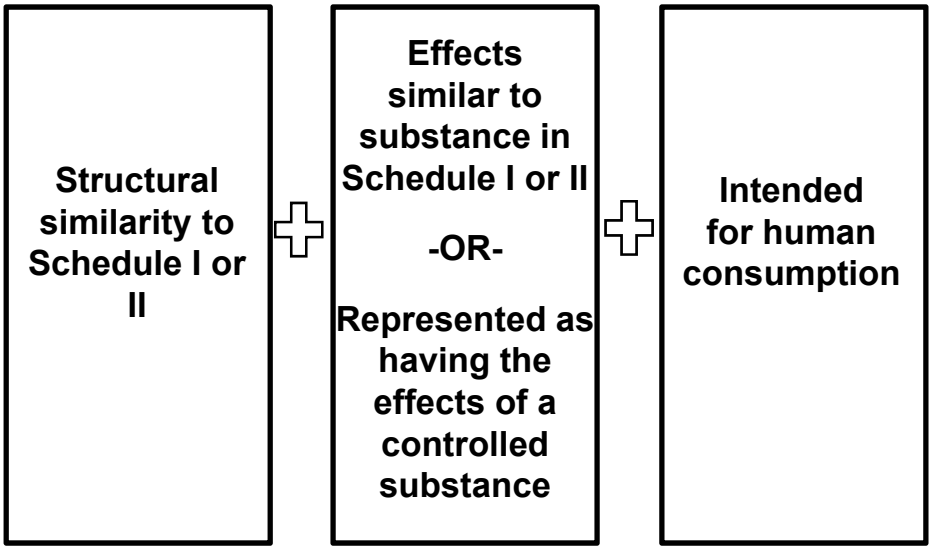
Three Parts to US Federal Analog Act



What is an analogue?

- **Layperson: major chemical structures in common with another chemical**
- **Scientist: two chemical molecules which differ only by the transposition of *one atom* (Br^- for I^-) or *simple functional group* (H for CH_3)**

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What is an analogue?

- **Layperson: major chemical structures in common with another chemical**
- **So[illegible] two chemical m[illegible]s which di[illegible]nsposition of [illegible] (Br for I) [illegible] *functional group* (H for CH_3)**

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DEA Defines:

A controlled substance *analogue* is

structurally or pharmacologically substantially similar to
and is
intended for human consumption

or represented as being similar to a Schedule I or II substance
and is not an approved medication in the United States

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Summary:

The Federal Analog Act has been helpful, but there are problems:

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1. Analog definition vague

Summary:

The Federal Analog Act has been helpful, but there are problems:

1. Analog definition vague
2. To qualify, product must be "intended for human consumption"

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Synthetic Cannabinoids

- Appeared on the Internet in 2006
  - Peaked 2011 – 2013, died off
  - Re-emerging in 2015
- Agonize endogenous cannabinoid receptors
  - JWH-018, JWH-073, CP-47,497, many others
  - More potent than Δ^9-tetrahydrocannabinol

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Agonists at CB_1 &CB_2 receptors

- CB1 receptor
  - Euphoric or psychoactive effects of the drug
- CB2 receptor
  - Found mainly in the immune system
  - Plays a minor role in pain control
  - Possible role in mood & behavior regulation

Synthetic Cannabinoids

- Reemerged in 2015
  - 2015: PC calls four times that in 2014
- Severe effects include
  - Seizures, status epilepticus
  - Renal failure
  - Death

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TOXICOLOGY OBSERVATION

K2—Not the Spice of Life; Synthetic Cannabinoids and ST Elevation Myocardial Infarction: A Case Report

Rita G. McKeever · David Vearrier · Dorian Jacobs · Gregory LaSala · Jolene Okaneku · Michael I. Greenberg

The Appeal

- Novelty
- "Legal" high
- Generally not detected on drug screen

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Synthetic Cannabinoids

- Many different products
  - "Spice", "K2", "Keisha Kole", "Summit", "AK-47"
- $25 - $40 per packet
  - More expensive than marijuana

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Synthetic Cannabinoids

- Ingredients listed as plant or herbal material
  - Accuracy unknown
  - Product dipped in or sprayed with synthetic cannabinoids
- Labeled, "not for human consumption"
- Chemical structures change frequently

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J. Med. Toxicol. (2015) 11:426–429
DOI 10.1007/s13181-015-0482-z

TOXICOLOGY OBSERVATION

Cluster of Acute Toxicity from Ingestion of Synthetic Cannabinoid-Laced Brownies

Adebisi I. Obafemi[1] · Kurt Kleinschmidt[1] · Collin Goto[1] · Drew Fout[2]

Published online: 13 May 2015

Abstract
Introduction Synthetic cannabinoid receptor agonists (SCRAs) are emerging designer drugs of abuse. Most reports on the health effects of these drugs are case reports. Unlike SCRAs, marijuana has classically been used via many routes be AM-2201. All the patients were discharged from the ED in stable condition within 10 h of the exposure.
Conclusion Oral exposure of 11 patients to brownies laced with analytically confirmed SCRA resulted in neuropsychiatric and cardiovascular symptoms. This series reflects that like

Clinical Effects

- **Peak within 30 min**
- **Symptoms last 2-3 hours**

- **2 Toxidromes:**
  - **Severe agitation, HTN, tachycardia, seizures, renal failure, rhabdomyolysis**
  - **Drowsiness, coma, bradycardia and hypotension**

Clinical Effects

- Hypokalemia
- Vomiting
- Xerostomia
- Intense psychosis, paranoia, hallucinations

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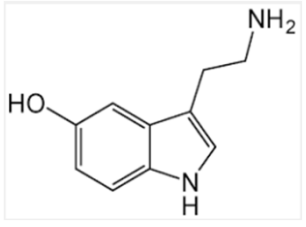
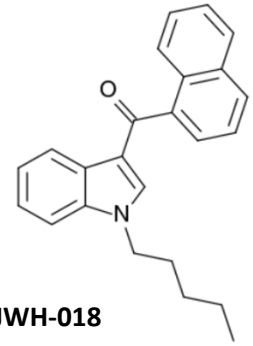
Serotonin Syndrome

- JWH-018 and similar synthetics are structurally similar to serotonin



Serotonin



JWH-018

Images from Wikipedia

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Serotonin Syndrome

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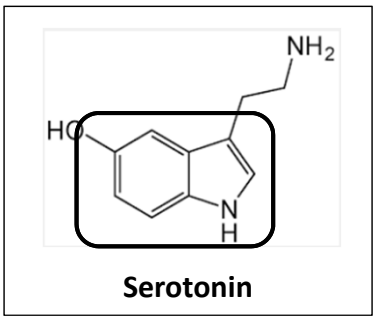

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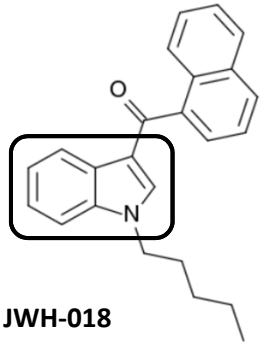

JWH-018

Images from Wikipedia

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Diagnosis of Serotonin Syndrome

Hunter Criteria

1. **IF (spontaneous clonus = yes) THEN serotonin toxicity = YES**
2. **ELSE IF (inducible clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES**
3. **ELSE IF (ocular clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES**
4. **ELSE IF (tremor = yes) AND (diaphoresis = yes) THEN serotonin toxicity = YES**
5. **ELSE IF (hypertonic = yes) AND (temperature > 38C) AND [(ocular clonus = yes) OR (inducible clonus = yes)] THEN serotonin toxicity = YES**
6. **ELSE serotonin toxicity = NO**

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Laboratory Evaluation

- Most products not detected on routine urine drugs of abuse screen
- Some labs can detect some metabolites in saliva, blood and urine (LC-MS/MS)
- Testing as dictated by clinical scenario

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Treatment

- Supportive
- Benzodiazepines
  - Agitation
  - Tachycardia
  - Hypertension

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Status

- DEA's emergency scheduling authority used to temporarily classify 5 synthetic cannabinoids as Schedule I in 2010
- Became law in 2012
- Others not scheduled

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Summary:

Synthetic cannabinoids are back again

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Summary:

Synthetic cannabinoids are back again

1. More potent than THC
2. Severe consequences include hypokalemia, psychosis, excited delirium, seizures
3. Treatment is supportive

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Marijuana: Current Status

- ~50% of US states have legalized medical marijuana
- 4 states have legalized recreational marijuana use
  - Washington
  - Colorado
  - Alaska
  - Oregon
- A few countries have legalized its use
- Many states countries have decriminalized its use

Exploratory Ingestions on the Rise

- Increased availability → increased exploratory ingestions
- States with legalized marijuana have significantly higher exposure rates in children (2.82 times higher)

Marijuana Exposure Among Children Younger Than Six Years in the United States

Clinical Pediatrics
1–9

DOI: 10.1177/0009922815589912
cpj.sagepub.com
SAGE

Bridget Onders, BS[1,2], Marcel J. Casavant, MD[3,4], Henry A. Spiller, MS, D.ABAT[3,4], Thiphalak Chounthirath, MS[1], and Gary A. Smith, MD, DrPH[1,4,5]

Outcomes

- Ingestion accounts for most exposures
- Marijuana food products attractive to young children
  - Often have especially high THC content

Outcomes

- Most common effects
  - Drowsiness or lethargy
  - Ataxia
  - Agitation or irritability
- Most exposures result in symptoms for < 24h
- Cases of seizures, coma and respiratory failure have been reported

Summary

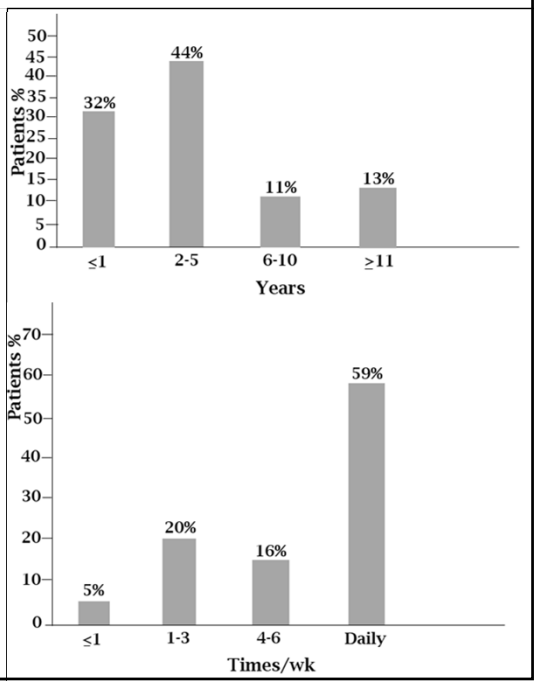
- Increased availability of marijuana products has lead to increased exploratory ingestions
- Commonest symptoms are neurological: drowsiness, ataxia, lethargy
- Serious symptoms have been reported: seizures, coma, respiratory failure, death
- Education and child-resistant packaging are strategies that may decrease child exposures

Cannabinoid Hyperemesis

- Marijuana is well-known for antiemetic properties
- Long-term, frequent use is associated with *CH*
- Pathophysiology not well-understood
  - Central effects of long-term use on the HPA axis might play a major role

Use Characteristics

- Duration
  - Varies widely: 4mo – 27y
    prior to sx onset
  - Most start within 1-5 years from onset of use
  - ~ 1/3 using < 1 year
- Frequency
  - Most (59%) daily
  - ~ ¼ using ≤ 3x/week



Mayo Clin Proc. 2012;87(2):114-119

Characteristics of CH Patients

Characteristic	Value
Age (y), mean ± SD	32.3 ± 9.89
Male gender	67%
Ethnicity	80% Caucasian; Hispanics and African Americans comprise < 5% each
Nicotine use	49% yes; 51% no
Alcohol use	78% are non-users
Employment-status	63% are employed

Mayo Clin Proc. 2012;87(2):114-119

Clinical Manifestations

- **Cyclic nausea vomiting: relieved with hot showers (91%)**
- **Abdominal pain**
  - **Most often epigastric**
  - **Pain characteristics vary**
- **Autonomic symptoms in some patients**
  - **Flushing**
  - **Chills**
- **Bowel habits often unchanged**

Proposed Clinical Criteria for CH
Essential for diagnosis *Long-term cannabis use*
Major features *Severe cyclic nausea and vomiting* *Resolution with cannabis cessation* *Relief of symptoms with hot showers or baths* *Abdominal pain, epigastric or periumbilical* *Weekly use*
Supportive features *Age < 50 years* *Weight loss of > 5 kg* *Morning predominance of symptoms* *Normal bowel habits* *Negative laboratory, radiographic and endoscopic test results*

Mayo Clin Proc. 2012;87(2):114-119

Treatment

- **Supportive care**
  - **Not very effective, but important**
  - **Hot showers**
- **Discontinue marijuana use**
  - **Hyperemetic phase typically lasts 24-48h**
  - **Symptom duration for one month or greater after marijuana abstinence has been reported**

Treatment

- Risk of relapse is high with return to use
  - Drug rehab referral & patient education

Summary

- A cyclical vomiting syndrome associated with frequent marijuana use does exist
  - Pathophysiology poorly understood
  - Relief with hot showers is uniquely characteristic of CH
- Treatment must include cessation of use

Cannabinoid hyperemesis syndrome and synthetic cannabinoids

Effects of state-specific marijuana legalization

Drugs of Abuse Update 2016

Glenn Burns, MD, FACEP
Medical Toxicology Fellow
Assistant Professor
Department of Emergency Medicine
The Ohio State University Wexner Medical Center

Topics

- **Buprenorphine**
- **Fentanyl**
- **Novel synthetic opioids**

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Objectives - *Buprenorphine*

1. Understand the mechanism of action of buprenorphine
2. Describe types and complications of abuse
3. Be aware of unique complications seen in pediatric exposures

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Background on buprenorphine

- Approved in USA in 2000 as alternative to methadone
- Requires special certification to prescribe in USA
- Often combined with naloxone under various brand names (*Suboxone, Zubsolv*)

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Buprenorphine – Mechanism of action

- Partial μ-receptor agonist at commonly prescribed doses (8-16mg)
- Effective at suppressing opioid withdrawal and cravings with less potential re-enforcing effects
- Better safety than methadone with less respiratory depression or risk of QT prolongation

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Buprenorphine – Mechanism of action

- At therapeutic doses, buprenorphine produces nearly complete occupancy of the μ-receptor with a very high affinity and slow dissociation.
- High affinity can displace other opioids and make treatment in overdose more challenging.

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Buprenorphine – Mechanism of action

- As a partial agonist-antagonist medication, buprenorphine is generally considered to have a “ceiling effect”, that is a maximal effect of the drug to cause CNS and respiratory depression.

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Buprenorphine – abuse complications

- Naloxone added to some formulations to prevent diversion.
- IV abuse leads to public health complications seen in other IV drug abuse patients

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Buprenorphine – pediatric exposures

- Important as children have different physiological response
- Small doses have large impact
- Most common exploratory opioid ingestion in kids less than 6 years old

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Buprenorphine – pediatric exposures

- The unique effect on pediatric exposures is often left out of the training to obtain a license to prescribe buprenorphine
- Parents of think of buprenorphine as a “safer drug” and studies have shown low rate of parental education

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Buprenorphine – pediatric exposures

- Most drugs of abuse urine tests will be negative in buprenorphine exposure
- Some providers assume the naloxone in combination drugs is protective

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Objectives - *Fentanyl*

1. Understand changes in fentanyl abuse over the last few years
2. Describe mechanism of action of unique complications for fentanyl abuse
3. Be aware of public health implications and some initiatives to combat fentanyl.

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Background on fentanyl

- Short acting, synthetic opioid agonist 50-100x more potent than morphine
- Transmucosal and transdermal patch for out-of-hospital use
- Substituted for heroin or added to heroin since 1970's

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Background on fentanyl

- Fentanyl analogs more power than fentanyl exist
- Some are used medically, other have no clinical typical clinical application

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Fentanyl – Changes in abuse

- Recent spike in abuse related deaths due to increased access to easily injectable forms
- Many reasons for this change
  - Economics
  - Logistics
  - Penalty for smuggling

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Fentanyl – Unique complications of IV abuse

- Death traditionally attributed to the idea that potency as direct cause.
- The mechanism of action of death from fentanyl was presumed to be the same as that of other opioids

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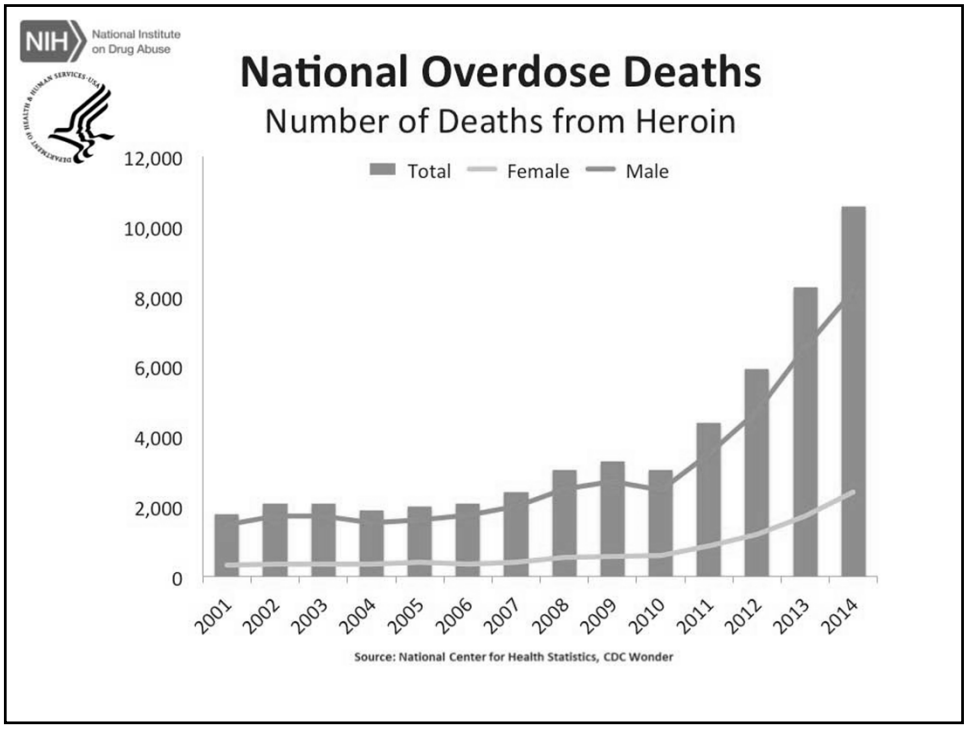

Fentanyl – Unique complications of IV abuse

- **Recently, a new mechanism of action has been proposed thanks to new information from autopsies of opioid overdoses**
- **Not well understood yet**

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Fentanyl – Unique complications of IV abuse

- Not a complication recognized by the drug using community and is unique to fentanyl among opioids
- Drug Abuse community often mistakenly seeks out fentanyl now as “the good stuff”

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Fentanyl – Public Health Implications

- Rapidity of death not well understood, but makes rescue methods less effective.
- Need to educate all first responders on the use of naloxone in this time critical diagnosis.
- Public Health is looking for a new message to make drug users aware

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Objectives – *Emerging opioids*

1. Be aware of emergence of new class of synthetic opioids
2. State where drugs are appearing and some of the complication associated
3. Know limitations of testing for these drugs

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Emerging Opioids – emerging class

- New class of fully synthetic opioids, the "W" class (W-18) and the "U" class (U-47700)
- Not new to science, but new to the drug abuse world.

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Emerging Opioids – emerging class

- **Available on the street and internet, often sold as another product.**
- **Not regulated well and do not fall under the national drug control programs of many countries yet.**

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Emerging Opioids – emerging class

- **Much more potent than morphine**
  - ***U-47700*** **10x more powerful than morphine**
  - ***W-18*** **is a staggering 10,000 more potent than morphine**

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Emerging opioids – where found

- Europe has identified these drugs, some countries making illegal
- Being seen in USA – recently Dallas, TX
- Mostly has been coming out of Asia

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Emerging Opioids – limitations of testing

- Won't show up on any standard testing available
- Currently U-4770 has investigational test at NMS labs in PA.

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Emerging Opioids – limitations of testing

- Clinical presentation atypical for opioids. Severe pulmonary edema with a refractory narrow complex tachycardia.
- DEA has reports from across USA of opioid overdoses presenting with hypertension, tachycardia and pulmonary edema

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Review - Buprenorphine

1. Mechanism of action of buprenorphine
2. Types and complications of abuse
3. Unique complications seen in pediatric exposures

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Review - Fentanyl

1. Changes in fentanyl abuse over the last few years
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3. Public health implications and some initiatives to combat fentanyl

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Review – Novel Opioids

1. The new class of synthetic opioids
2. Where the drugs are and some of the complication associated with them
3. Limitations of testing for these drugs

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