The Low Down on the High Life: Management of Acute Toxicities from Drug Abuse

A HealthTrust Member Webinar
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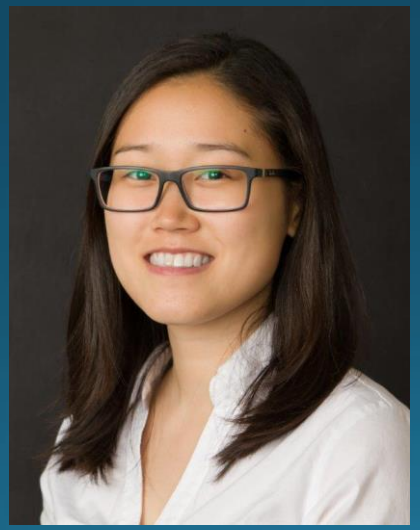

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Disclosures

- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.

- The presenters have no financial relationships with any commercial interests pertinent to this presentation.

Learning Objectives for Pharmacists & Nurses

- List the signs and symptoms seen from the overdose of the medications discussed
- Identify patients with suspicion of overdose due to medication abuse or misuse
- Describe the mechanism of toxicities
- Identify treatment options available to manage or reverse the overdose

Learning Objectives for Pharmacy Techs

- Identify the signs and symptoms related to overdose of the medications discussed
- Recall how to prepare a naloxone drip
- Describe how to prepare an isoproterenol drip

The Lowdown

- In 2014, over 10 million Americans reported use of illicit and prescription opioids for non-medical purposes
- In 2016, an estimated 60,000 deaths in the U.S. were due to drug overdoses
- As abusers develop tolerance or prefer different "highs," users seek out other alternatives such as cheaper over-the-counter, prescription or designer drugs

Source: Suzuki J, et al. *Drug and Alcohol Dependence* 2017;171:107-16.
O'Donnell JK, et al. *MMWR* 2017;66(43):1197-1202.

Loperamide

Loperamide

- Class: over-the-counter, synthetic opioid
- Mechanism: inhibits peristaltic activity by μ receptor agonism of the mesenteric plexus of the large intestine
- Dose: 4 mg PO once followed by 2 mg PO for each subsequent loose stool (max 16 mg/day)
- Adverse effects: nausea, constipation, drowsiness and headache

Sources: Vakkalanka JP, et al. *Annals of Emergency Medicine* 2017;69(1):73-8.
Eggleston W, et al. *Annals of Emergency Medicine* 2017;69(1):83-6.

Loperamide

- Pharmacokinetics/Pharmacodynamics (PK/PD) in healthy patients
  - Peak plasma times of 4-5 hours
  - Half-life between 7-19 hours
  - Poor oral bioavailability
  - P-glycoprotein (P-gp) efflux transporter substrate
  - Metabolized by CYP3A4 and CYP2C8
  - Eliminated primarily unchanged in feces
- Toxicokinetics
  - Half-life between 9 to 35 hours
  - Decreased GI motility may result in delayed absorption
    - Symptoms may occur 22 hours post ingestion

Sources: Sklerov J, et al. *Journals of Analytical Toxicology* 2005;29:750-4.
Eggleston W, et al. *Clinical Toxicology* 2015;53:495-6.
OConnell CW, et al. *Heart Rhythm Case Reports* 2016;2:232-6.

Concomitant Use with P-gp and CYP450 Modulators

- Loperamide is a P-gp efflux transporter substrate and is metabolized by CYP450 enzymes
- Cases of concomitant use with quinine, quinidine, black pepper and cimetidine have been reported
- Animal studies have shown increased loperamide levels in the brain with concomitant use with P-gp inhibitors

Sources: Nieto Montesinos R, et al. *Drug metabolism and Disposition.* 2014;42:700-6.
Borron SW, et al. *The Journal of Emergency Medicine* 2017;53(1):73-84.

Misuse and Abuse

- Most common reasons of misuse and abuse
  - Self-treatment for opioid withdrawal
  - Achieve opioid-like high
- Other common names
  - "Poor man's methadone"
  - "Poor man's heroin"
  - "Lope"
- Accessibility
  - Inexpensive, over-the-counter alternative to methadone and opiates

Sources: Vakkalanka JP, et al. *Annals of Emergency Medicine* 2017;69(1):73-8.
Borron SW, et al. *The Journal of Emergency Medicine* 2017;53(1):73-84.

Misuse and Abuse

- Sources of abuse information
  - Online drug forums
  - Online blogs
- FDA Warning (June 6, 2016)
  - Warning for serious cardiac adverse events

Sources: Marraffa JM, et al. *Clinical Toxicology* 2014;52:952-7.
Vakkalanka JP, et al. *Annals of Emergency Medicine* 2017;69(1):73-8.
Borron SW, et al. *The Journal of Emergency Medicine* 2017;53(1):73-84.

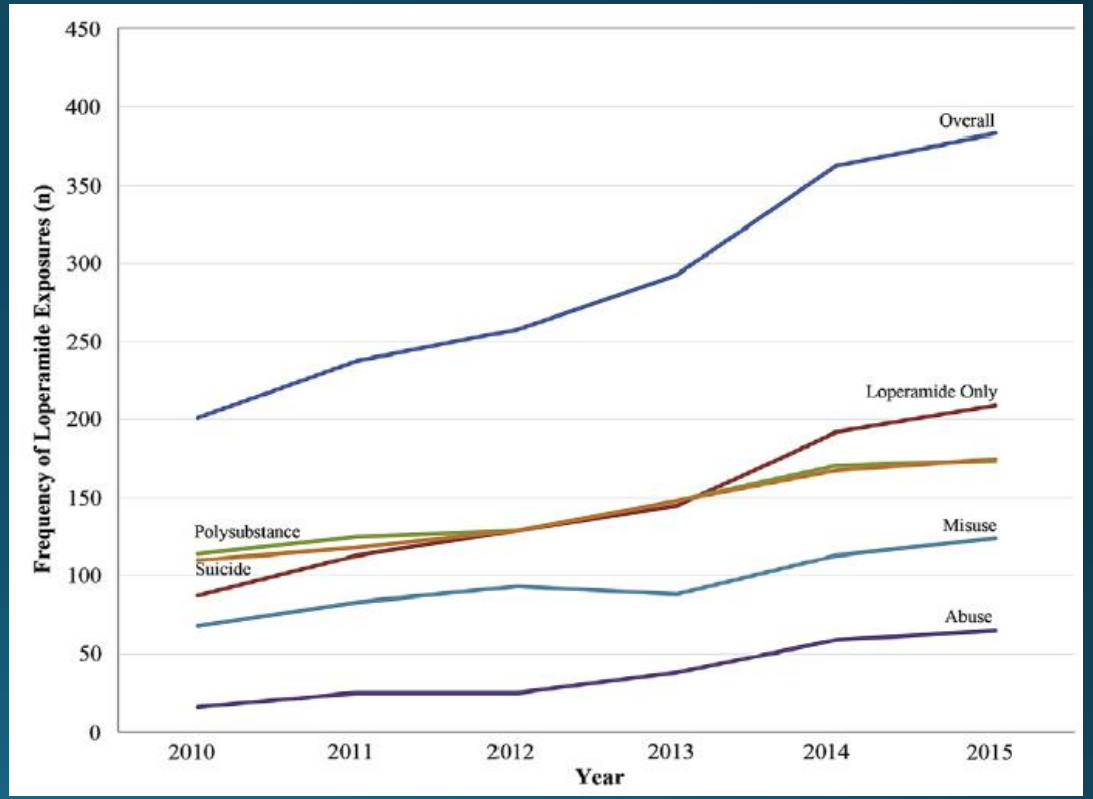
Intoxication Epidemiology

- Median age: 41 years old
- From 2010–2015, 1,736 cases of intentional exposure to loperamide have been reported
  - 50.4% were single agent exposures
  - Males were more likely to intentionally abuse
  - Females were more likely to use for suicidal attempts
- After 2011, patients began to use loperamide for self-treatment of opioid withdrawal

Sources: Lasoff DR, et al. *Pharmacotherapy* 2017;37(2):249-53.
Vakkalanka JP, et al. *Annals of Emergency Medicine* 2017;69(1):73-8.

Intoxication Epidemiology

- 91% increase in reported incidences in 6-year period
- ~40 more cases each year have been reported
- Reported doses range from 32 mg to 792 mg per day
- Opioid abusers and those with opioid dependence are the highest risk patient population



Sources: Vakkalanka JP, et al. *Annals of Emergency Medicine* 2017;69(1):73-8.
Borron SW, et al. *The Journal of Emergency Medicine* 2017;53(1):73-84.

Mechanism of Cardiotoxicity

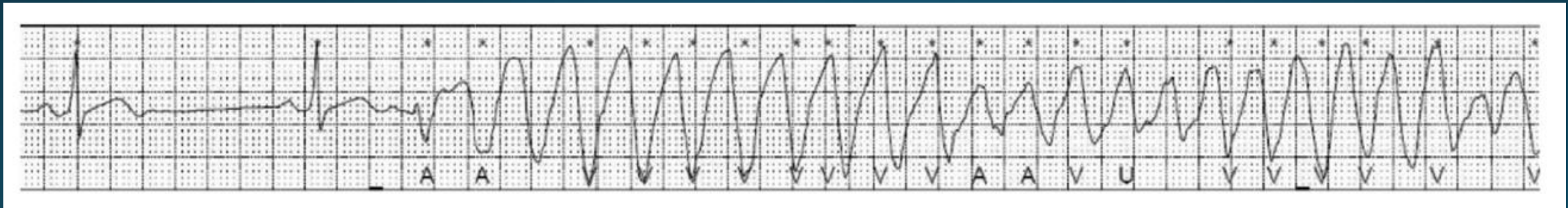
- Potassium channel blockade
  - Inhibits human *ether-a-go-go*-related gene (HERG) potassium channel
  - Blocks potassium channels at loperamide levels of 15.7 – 20.5 ng/mL
- Sodium channel blockade
  - Inhibits human cardiac sodium channels
  - Blocks sodium channels at loperamide levels of 114 – 141 ng/mL
- Calcium channel blockade
  - Inhibits L-type Ca^{2+} channels

Sources: Eggleston W, et al. *Annals of Emergency Medicine* 2017;69(1):83-6.
Enakpene EO, et al. *The American Journal of Medicine* 2015;128(10):1083-6.
OConnell CW, et al. *Heart Rhythm Case Reports* 2016;2:232-6.
Wu PE, et al. *Annals of Emergency Medicine* 2017;70(2):245-52.

Signs and Symptoms of Intoxication

- Syncope
- Respiratory depression
- Myoclonic jerking
- Palpitations

- Cardiotoxicity
  - QTc prolongation
  - QRS widening
  - Dysrhythmias (monomorphic or polymorphic wide complex ventricular rhythms, Torsades de pointes, ventricular fibrillation, bradycardia)
  - Cardiomegaly
  - Cardiac arrest



Sources: Eggleston W, et al. *Clinical Toxicology* 2015;53:495-6.
OConnell CW, et al. *Heart Rhythm Case Reports* 2016;2:232-6.
Borron SW, et al. *The Journal of Emergency Medicine* 2017;53(1):73-84.

Diagnostic Testing

- Urine drug screens
  - Negative for opioids
- Electrolytes
  - Sodium, magnesium and phosphorous levels within normal limits
- Loperamide serum levels
  - Normal: 0.24 – 1.2 ng/mL
  - Reported: 32 – 140 ng/mL

Sources: OConnell CW, et al. *Heart Rhythm Case Reports* 2016;2:232-6.
Eggleston W, et al. *Annals of Emergency Medicine* 2017;69(1):83-6.
Marraffa JM, et al. *Clinical Toxicology* 2014;52:952-7.

Treatment Options

- Consider activated charcoal in patients with normal mental status if given within 2–4 hours post ingestion
- Consider naloxone for respiratory depression
- Ventricular dysrhythmias
  - Intravenous magnesium sulfate
    - 2 grams over 15 min
  - Intravenous sodium bicarbonate drip
    - Loading dose of 1–2 mEq/kg then infuse 150 mEq in 1 L D5W at 100–200 mL/hr
- Treat cardiopulmonary arrest with CPR and ACLS
- Consider intravenous lipid emulsion for severely unstable patients

Sources: Eggleston W, et al. *Annals of Emergency Medicine* 2017;69(1):83-6.
Marraffa JM, et al. *Clinical Toxicology* 2014;52:952-7.
Litovitz T, et al. *J Toxicol Clin Toxicol* 1997;35(1):11-9.
Wu PE, et al. *Annals of Emergency Medicine* 2017;70(2):245-52.

Case Reports

Patient	Case 1
History and Presentation	28-year-old male with history of depression and substance use disorder presents with shortness of breath, generalized fatigue, and near-syncope
Home Medications	Previously on buprenorphine/naloxone and currently on loperamide 200–400 mg/day
Diagnostic Testing/ Laboratory Values	Urine screen (+) cannabinoids, benzodiazepines, and amphetamines EKG: QRS 168 ms and QTc 693 ms
Treatment	• In ED, given 4 ampules of sodium bicarbonate and magnesium sulfate 2 grams • In ICU, started on sodium bicarbonate and magnesium infusions • On day 3, developed refractory Torsades de pointes and treated with defibrillation, intravenous lidocaine, and isoproterenol drip • Afterwards, managed with pacemaker

Source: Katz KD, et al. *The Journal of Emergency Medicine* 2017;53(3):339-44.

Case Reports

Patient	Case 2
History and Presentation	28-year-old male with history of Crohn's disease and substance use disorder presents with syncope and recurrent wide complex tachycardia
Home Medications	Amitriptyline (unknown dose) and loperamide 792 mg/day
Diagnostic Testing/ Laboratory Values	Urine screen (-) EKG: QRS 162 ms and QTc 647 ms
Treatment	• Experienced both sustained and non-sustained pulseless ventricular tachycardia refractory to magnesium sulfate, potassium chloride, sodium bicarbonate, lidocaine, and fatty acid emulsion • Finally controlled on transvenous pacemaker then transitioned to isoproterenol drip

Source: Marraffa JM, et al. *Clinical Toxicology* 2014;52:952-7.

Treatment Options

- Refractory QTc prolongation
  - Intravenous isoproterenol in D_5W or NS
    - Mechanism of action in QTc prolongation: increases heart by β_1/β_2 adrenoceptor agonism which shortens QT interval and effective refractory period
    - 2-10 mcg/min titrated to heart rate of 90 – 110 bpm
    - Tachyphylaxis has been reported
  - Overdrive pacing with a transvenous electrical pacemaker
    - Hemodynamically unstable patients

Abbreviations: D_5W dextrose 5% in water; NS normal saline

Sources: Thomas SHL, et al. *Br J Clin Pharmacol* 2016;81(3):420-7.
Eggleston W, et al. *Annals of Emergency Medicine* 2017;69(1):83-6.
Katz KD, et al. *The Journal of Emergency Medicine* 2017;53(3):339-44.

Tramadol

Tramadol

- Class: centrally acting, synthetic analogue of codeine
- Mechanism: inhibits the reuptake of norepinephrine and serotonin and also acts as a weak μ receptor agonist
- Dose
  - Immediate release: 50 to 100 mg PO every 4 to 6 hours (max. 400 mg/day)
  - Extended release: 100 mg PO daily titrated to max. 300 mg/day
- Adverse effects: flushing, dizziness, headache, drowsiness, constipation, nausea and vomiting

Sources: Mehrpour O, et al (July 8th 2015). Tramadol Poisoning, Toxicology Studies, Ana Cristina Andreazza, IntechOpen, DOI: 10.5772/60439.
Pothiawala S, et al. *Proceedings of Singapore Healthcare* 2011;20(3):219-23.
Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: http://online.lexi.com. Accessed April 25, 2018.

Tramadol

- PK/PD in healthy patients
  - Peak effect between 2–3 hours
  - Peak plasma times of 2 hours (immediate release) or 4 to 12 hours (extended release)
  - Half-life 6 hours (immediate release) or 8 to 10 hours (extended release)
  - Bioavailability of 75% to 95%
  - Metabolized by demethylation (by CYP3A4 and CYP2D6), glucuronidation, and sulfation
  - Active metabolite O-desmethyltramadol
  - Eliminated through urine

Sources: Pothiawala S, et al. *Proceedings of Singapore Healthcare* 2011;20(3):219-23.
Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH.
Available at: http://online.lexi.com. Accessed April 25, 2018.

Misuse and Abuse

- Most common reasons for misuse and abuse
  - Intentional/suicide attempts
  - Recreational
  - Accidental
  - Medically overdosed
- Accessibility
  - Available as a prescription medication
  - Currently classified as a C-IV scheduled medication

Sources: Mehrpour O, et al (July 8th 2015). Tramadol Poisoning, Toxicology Studies Ana Cristina Andreazza, IntechOpen, DOI: 10.5772/60439.

Intoxication Epidemiology

- Occurs more commonly in young, single males in the third decade of life with previous history of drug addiction and psychological problems and suicide
- High-risk patients also include those with genetic CYP450 polymorphisms
- Primarily through oral ingestion
- Mortality of tramadol intoxication is low

Sources: Mehrpour O, et al (July 8th 2015). Tramadol Poisoning, Toxicology Studies Ana Cristina Andreazza, IntechOpen, DOI: 10.5772/60439.
Shadnia S, et al. *Human & Experimental Toxicology* 2008;27:201-5.

Signs and Symptoms of Intoxication

- Seizures
- Anxiety
- Unconsciousness
- Central nervous system depression
- Nausea/vomiting
- Tachycardia
- Coma
- Respiratory depression
- Cardiovascular collapse
- Serotonin syndrome

Source: Shadnia S, et al. *Human & Experimental Toxicology* 2008;27:201-5.
Pothiawala S, et al. *Proceedings of Singapore Healthcare* 2011;20(3):219-23.

Seizures

- Tramadol metabolite (O-desmethyltramadol) affects CNS status and can cause seizures
- Generally, resolves within 24 hours post-ingestion
- Risk factors for tramadol-induced seizures:
  - History of a seizure disorder
  - Concomitant use of medications that can also cause seizures
  - Ethanol withdrawal
  - Use of CNS depressants
  - Head injury

Source: Mehrpour O, et al (July 8th 2015). Tramadol Poisoning, Toxicology Studies Ana Cristina Andreazza, IntechOpen, DOI: 10.5772/60439.

Seizures

- Least reported tramadol dose that led to a seizure is 100 mg
- Single seizure reported to occur at mean dose of 1100 mg
- Multiple seizures reported to occur at mean dose of 2000 mg
  - Incidence of recurrent seizures 7%
- Complications from tramadol-induced seizures:
  - Trauma
  - Intra-articular dislocation
  - Tongue laceration

Sources: Mehrpour O, et al (July 8th 2015). Tramadol Poisoning, Toxicology Studies Ana Cristina Andreazza, IntechOpen, DOI: 10.5772/60439.
Shadnia S, et al. *Basic & Clinical Pharmacology and Toxicology* 2-12;111:133-6.

Serotonin Syndrome

- Due to increased synthesis, decreased metabolism, increased release or inhibited reuptake of serotonin at the receptor
- Clinical manifestation
  - Neuromuscular hyperactivity, autonomic hyperactivity and altered mental status
- Occurs after tramadol overdose or after tramadol use with other medications

Sources: Mehrpour O, et al (July 8th 2015). Tramadol Poisoning, Toxicology Studies
Ana Cristina Andreazza, IntechOpen, DOI: 10.5772/60439.
Pothiawala S, et al. *Proceedings of Singapore Healthcare* 2011;20(3):219-23.

Serotonin Syndrome

- Drug-drug Interactions
  - Antidepressants: selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, triptans and lithium
- Resolves within 24 hours post-ingestion

Source: Pothiawala S, et al. *Proceedings of Singapore Healthcare* 2011;20(3):219-23.

Diagnostic Testing

- Urine drug screens
  - Not detected on opiate screens
- Tramadol serum levels
  - Normal: 0.1 – 0.8 mg/L
  - Toxic levels: 1 – 2 mg/L
  - Lethal levels: >2 mg/L

Sources: Suzuki J, et al. *Drug and Alcohol Dependence* 2017;171:107-16.
Pothiawala S, et al. *Proceedings of Singapore Healthcare* 2011;20(3):219-23.

Treatment Options

- Mainly supportive care
- Activated charcoal may be considered if patient presented within 1–2 hours of ingestion and can tolerate it
- Seizures: benzodiazepines
  - Prophylactic antiepileptic not suggested
- Serotonin Syndrome
  - Discontinue offending agents
  - Reduction in hyperthermia
  - Cyproheptadine

Sources: Pothiawala S, et al. *Proceedings of Singapore Healthcare* 2011;20(3):219-23.
Shadnia S, et al. *Basic & Clinical Pharmacology and Toxicology* 2-12;111:133-6.
Mehrpour O, et al (July 8th 2015). Tramadol Poisoning, Toxicology Studies
Ana Cristina Andreazza, IntechOpen, DOI: 10.5772/60439.

Fentanyl & Carfentanil

Fentanyl

- Class: synthetic opioid
- Mechanism: μ-opioid receptor agonist
- Potency: 50–100 times more potent than morphine
- Available as injection, buccal film or tablet, lozenge, sublingual spray or tablet, and transdermal patch
- Adverse effects: confusion, drowsiness, headache, sedation, constipation, dyspnea

Sources: Kuhlman JJ, et al. *Journal of Analytical Toxicology* 2003;27:499-504.
Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH.
Available at: http://online.lexi.com. Accessed April 25, 2018.

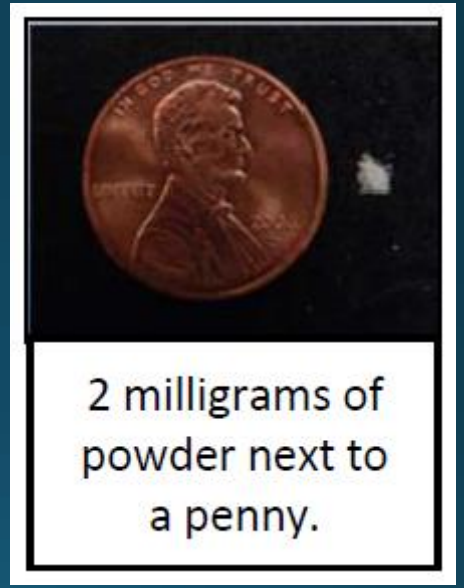
Fentanyl

- PK/PD in healthy patients
  - Onset of action of 2–3 min. (injection) up to 6 hours (transdermal patch)
  - Duration of action of 30–60 min. (injection) up to 96 hours (transdermal patch)
  - Highly lipophilic
  - Half-life of 2–4 hours (IV infusion)
  - Mechanism through hepatic enzymes
  - Excreted through urine and feces

Sources: Kuhlman JJ, et al. *Journal of Analytical Toxicology* 2003;27:499-504.
Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH.
Available at: http://online.lexi.com. Accessed April 25, 2018.

Carfentanil

- Class: synthetic opioid and analogue of fentanyl
- Mechanism: μ-opioid receptor agonist
- Indication: tranquilizer for large animals
  - (elephants, gazelles, polar bears, rhinoceroses, etc.)
- Potency: 100 times more potent than fentanyl or 10,000 times more potent than morphine
- Dosage forms: powder, blotted paper, tablets, patch or spray



Sources: Misailidi N, et al. *Forensic Toxicol* 2018;36:12-32.
Drug Enforcement Administration. *Carfentanil: A Dangerous New Factor in the U.S. Opioid Crisis*. N.p.: United States. Drug Enforcement Administration, 2016. PDF.

Carfentanil

- PK/PD
  - Large volume of distribution
  - High lipophilicity
  - Highly protein bound
  - Has long half-life
  - Metabolized by CYP enzymes

Source: Misailidi N, et al. *Forensic Toxicol* 2018;36:12-32.

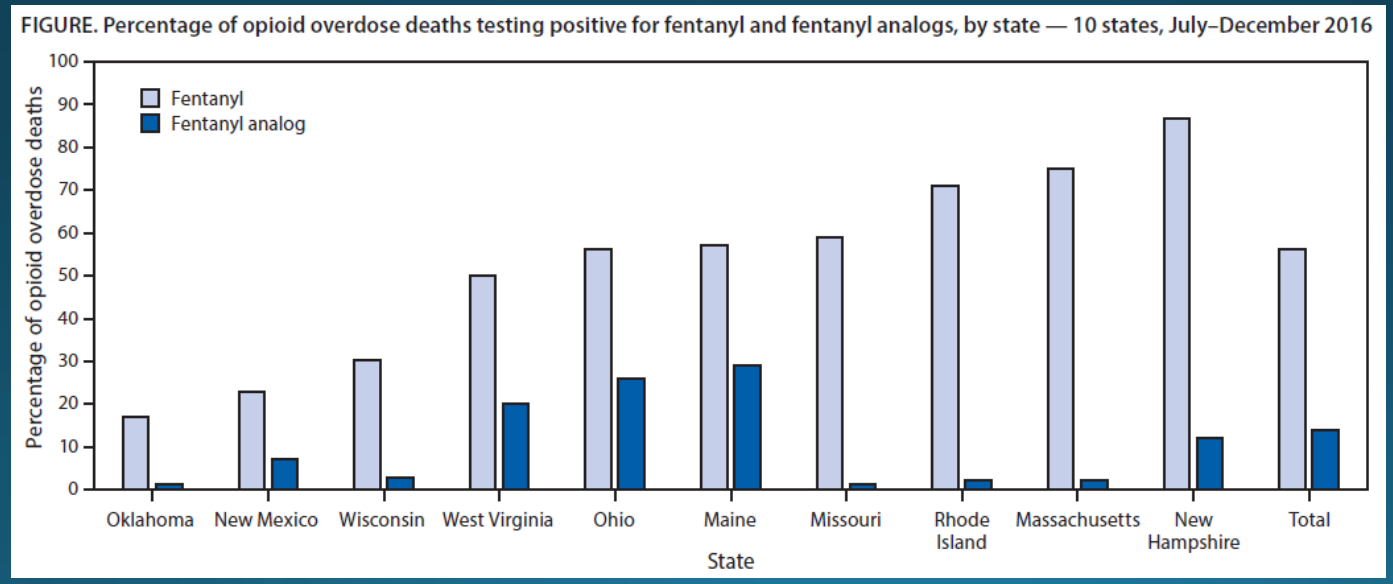
Misuse and Abuse

- Most common reasons of misuse and abuse
  - Achieve opioid high
  - Accidental
- Other common names
  - "Gray death" – carfentanil
- Accessibility
  - Removal of fentanyl transdermal patches from prescription users
  - Occupational exposure
  - Online sources
  - Carfentanil often labeled and sold as heroin, oxycodone or alprazolam
  - Currently, classified as C-II scheduled medications

Sources: Suzuki J, et al. *Drug and Alcohol Dependence* 2017;171:107-16.
Kuhlman JJ, et al. *Journal of Analytical Toxicology* 2003;27:499-504.
Misailidi N, et al. *Forensic Toxicol* 2018;36:12-32.

Intoxication Epidemiology

- From 2013 to 2016, there has been a five-fold increase in overdose deaths due to synthetic opioids
- In the CDC's Enhanced State Opioid Overdose Surveillance, 56.3% and 7.6% of opioid overdose deaths were due to fentanyl and carfentanil, respectively



Source: O'Donnell JK, et al. *MMWR* 2017;66(43):1197-1202.

Intoxication Epidemiology

- Most commonly used by non-Hispanic white males, aged 25 – 44 years
- Routes of administration: snorting, ingestion, smoking, injection and rarely transdermal
- Mixed with each other, heroin or cocaine

Source: O'Donnell JK, et al. *MMWR* 2017;66(43):1197-1202.

Signs and Symptoms of Intoxication

- Cold and clammy skin
- Nausea/vomiting
- Pinpoint pupils
- Disorientation
- Lethargy
- Sedation
- Sudden drowsiness
- Respiratory depression
- Heart failure
- Weak pulse

Source: Misailidi N, et al. *Forensic Toxicol* 2018;36:12-32.

Diagnostic Testing

- Urine drug screens
  - Not detected on opiate screens
- Fentanyl serum levels
  - Normal: 0.3 – 5 ng/mL
  - Hypoventilation seen: >1.5 ng/mL
  - Reported: 25 – 35 ng/mL

Sources: Suzuki J, et al. *Drug and Alcohol Dependence* 2017;171:107-16.
Kuhlman JJ, et al. *Journal of Analytical Toxicology* 2003;27:499-504.

Patient Handling Precautions

- Carfentanil
  - Can be absorbed accidentally through skin or inhalation
  - Handling precautions
    - Wear gloves at all times; drug paraphernalia, patches and other objects may still contain traces of fentanyl or its analogues
    - Wear mask or Hazmat team should be contacted for exposure to loose powders
  - Be aware of signs of exposure
    - Respiratory depression or arrest, drowsiness, disorientation, sedation, pinpoint pupils and clammy skin
    - May occur within minutes
  - Seek medical attention if exposed

Sources: Suzuki J, et al. *Drug and Alcohol Dependence* 2017;171:107-116.
Drug Enforcement Administration. *Carfentanil: A Dangerous New Factor in the U.S. Opioid Crisis*. N.p.: United States. Drug Enforcement Administration, 2016. PDF.

Treatment Options

- Maintain airway, breathing and circulation
- Supportive therapy
- Remove any transdermal fentanyl patches found
- Antidote: naloxone
  - Bolus: 0.4 to 2 mg IV/IM/subcutaneous; may repeat every 2 to 3 min.
    - May require 6 or more boluses for carfentanil overdose
  - Intravenous infusion in D_5W or NS
    - Typically made as a concentration of 4 mcg/mL

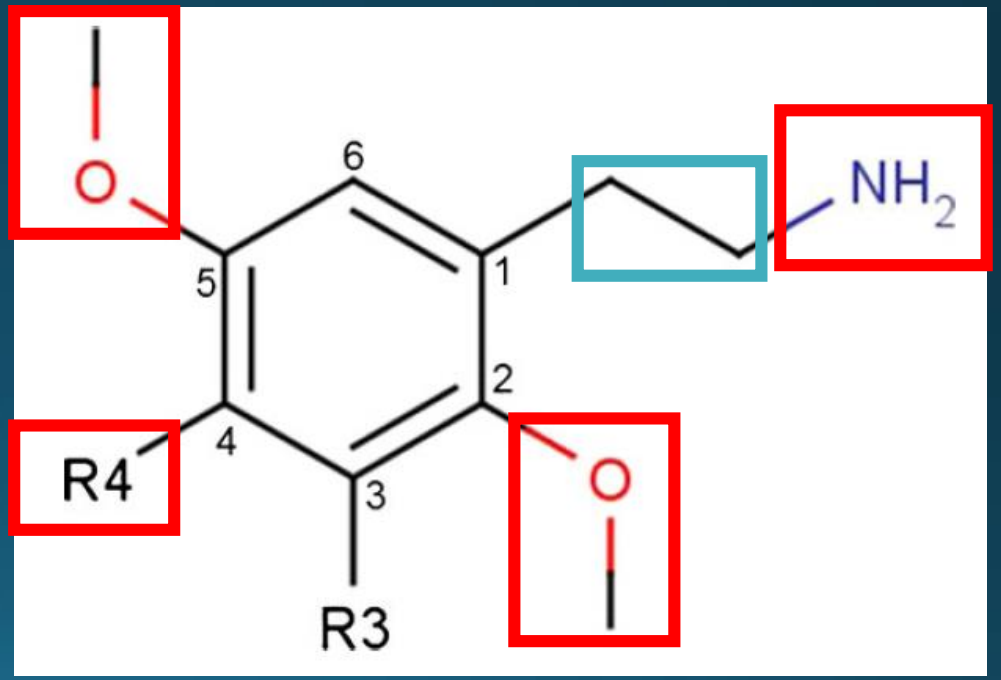
Abbreviations: D_5W dextrose 5% in water; NS normal saline

Sources: Suzuki J, et al. *Drug and Alcohol Dependence* 2017;171:107-116.
Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: http://online.lexi.com.
Accessed April 25, 2018. Misailidi N, et al. *Forensic Toxicol* 2018;36:12-32.

2C Drugs

2C Drugs

- Class: phenethylamine-based structure
- Mechanism: acts as either an agonist or antagonist to 5-HT_2 and α-adrenergic receptors
- Hallucinogenic activity from structure of 2Cs
- Dosage forms: tablet, capsule, powder or liquid
  - Products may not contain dosages as labeled
- Route of administration: oral or insufflation (nasally)



Source: Dean BV, et al. *J Med Toxicol* 2013;9:172-8.

2C Drugs

2C	Chemical name	Dosage	Duration (h)
2C-B	4-Bromo-2,5-dimethoxyphenethylamine	12–24 mg	4–8
2C-C	4-Chloro-2,5-dimethoxyphenethylamine	20–40 mg	4–8
2C-D	4-Methyl-2,5-dimethoxyphenethylamine	20–60 g	4–6
2C-E	4-Ethyl-2,5-dimethoxyphenethylamine	10–25 mg	8–12
2C-G	3,4-Dimethyl-2,5-dimethoxyphenethylamine	20–35 mg	18–30
2C-G-3	3,4-Trimethylene-2,5-dimethoxyphenethylamine	16–25 mg	12–24
2C-G-5	3,4-Norbornyl-2,5-dimethoxyphenethylamine	10–16 mg	32–48
2C-I	4-Iodo-2,5-dimethoxyphenethylamine	14–22 mg	6–10
2C-N	4-Nitro-2,5-dimethoxyphenethylamine	100–150 mg	4–6
2C-P	4-Propyl-2,5-dimethoxyphenethylamine	6–10 mg	10–16
2C-SE	4-Methylseleno-2,5-dimethoxyphenethylamine	~100 mg	6–8
2C-T	4-Methylthio-2,5-dimethoxyphenethylamine	60–100 mg	3–5
2C-T-2	4-Ethylthio-2,5-dimethoxyphenethylamine	12–25 mg	6–8
2C-T-4	4-Isopropylthio-2,5-dimethoxyphenethylamine	8–20 mg	12–18
2C-T-7	4-Propylthio-2,5-dimethoxyphenethylamine	10–30 mg	8–15
2C-T-8	4-Cyclopropylmethylthio-2,5-dimethoxyphenethylamine	30–50 mg	10–15
2C-T-9	4-(t)-Butylthio-2,5-dimethoxyphenethylamine	60–100 mg	12–18
2C-T-13	4-(2-Methoxyethylthio)-2,5-dimethoxyphenethylamine	25–40 mg	6–8
2C-T-15	4-Cyclopropylthio-2,5-dimethoxyphenethylamine	>30 mg	Several hours
2C-T-17	4-(s)-Butylthio-2,5-dimethoxyphenethylamine	60–100 mg	10–15
2C-T-21	4-(2-Fluoroehtylthio)-2,5-dimethoxyphenethylamine	8–12 mg	7–10

Source: Dean BV, et al. *J Med Toxicol* 2013;9:172-8.

2C Drugs

- PK/PD
  - Time of onset: 1 – 2.5 hours (oral), 5 – 15 min (insufflation)
  - Duration of action: 6 – 10 hours
  - Metabolized by O-demthylation, deamination by monoamine oxidase-A (MAO-A) and MAO-B enzymes, and oxidation

- Drug-Drug Interactions
  - MAO inhibitors
  - Reuptake of monoamines (norepinephrine, dopamine, serotonin) may be reduced

Sources: Maxwell, J. C. *Substance Abuse Trends in Texas:June 2014*. N.p.: Preceedings of the Community Epidemiology Work Group, June 2014. PDF.
Dean BV, et al. *J Med Toxicol* 2013;9:172-8.

Misuse and Abuse

- Most common reasons of misuse and abuse
  - Hallucinogenic effects
- Other common names
  - "Nexus," "Erox," "Performax," "Toonics," "Bromo Mescaline," "Spectrum," and "Venus"
  - Marketed as MDMA's replacement
- Accessibility
  - Internet, social media sites, raves, night clubs and sold in head shops
- Sources of abuse information
  - Online drug forums

Source: Dean BV, et al. *J Med Toxicol* 2013;9:172-8.

Intoxication Epidemiology

- Predominantly adolescent males
- From 2005–2013, 59 cases reported to Texas Poison Control Center
- 7 deaths have been reported in literature

Sources: Maxwell, J. C. *Substance Abuse Trends in Texas:June 2014*. N.p.: Preceedings of the Community Epidemiology Work Group, June 2014. PDF.
Dean BV, et al. *J Med Toxicol* 2013;9:172-8.

Signs and Symptoms of Intoxication

- Tachycardia
- Agitation
- Hallucination
- Drowsiness
- Mydriasis
- Confusion
- Hypertension
- Euphoria
- Empathy
- Nausea/vomiting
- Respiratory depression
- Seizures

Sources: Maxwell, J. C. *Substance Abuse Trends in Texas:June 2014*. N.p.: Preceedings of the Community Epidemiology Work Group, June 2014. PDF.
Dean BV, et al. *J Med Toxicol* 2013;9:172-8.

Signs and Symptoms

- Low doses
  - Increased visual, auditory and tactile sensations
- Moderate doses
  - Hallucinations
- Higher doses
  - Unpleasant hallucinations and sympathomimetic effects
- Symptoms last for approximately 20 minutes
- At peak "high," extreme hallucinations and suicidal thoughts may last for 30 minutes

Source: Dean BV, et al. *J Med Toxicol* 2013;9:172-8.

Excited Delirium

- In periods of high dopamine surge, the brain is unable to express enough dopamine transporters to pump it out of the brain
- Characterized by delirium, agitation, violence, hyperactivity, and hyperthermia
- Clinical manifestation of toxicity that may lead to sudden death or cardiopulmonary arrest

Treatment Options

- No antidotes available for 2C drugs
- Mainly symptom-based supportive care
- Maintain airway, breathing and circulation
- Dysphoria: place in calm environment until symptoms resolve
- Excited delirium: treat with rapid sedation, fluid resuscitation and reduction in hyperthermia
- Agitation: may consider benzodiazepines and neuroleptics
- Hyperthermia: sedation and rapid cooling

Source: Dean BV, et al. *J Med Toxicol* 2013;9:172-8.

Summary

- Clinical manifestations of the discussed intoxications may vary from opioid-like symptoms, cardiotoxicity, seizures and more
- Consider intoxication in differential for patients with opioid-like symptoms, a negative opiate urine drug screen and a history of drug abuse
- Treatment includes symptom-based supportive care and use of available reversal agents

Assessment Question 1 – Pharmacists and Nurses

1. Which population of patients are highest at risk for loperamide abuse?
    a. History of opioid dependence
    b. History of dextromethorphan abuse
    c. History of benzodiazepines dependence
    d. History of amphetamine abuse

Response 1 – Pharmacists and Nurses

1. Which population of patients are highest at risk for loperamide abuse?
   a. **History of opioid dependence**
   b. History of dextromethorphan abuse
   c. History of benzodiazepines dependence
   d. History of amphetamine abuse

Assessment Question 2 – Pharmacists and Nurses

2. What are signs and symptoms of tramadol toxicity??
    a. Seizures
    b. Serotonin syndrome
    c. Unconsciousness
    d. All the above

Response 2 – Pharmacists and Nurses

2. What are signs and symptoms of tramadol toxicity??
    a. Seizures
    b. Serotonin syndrome
    c. Unconsciousness
    d. All the above

Assessment Question 3 – Pharmacists and Nurses

3. All of the following are appropriate treatment options for 2C drug overdose except:
    a. Symptom management
    b. Naloxone
    c. Benzodiazepines
    d. Fluid resuscitation

Response 3 – Pharmacists and Nurses

3. All of the following are appropriate treatment options for 2C drug overdose except:
   a. Symptom management
   b. Naloxone
   c. Benzodiazepines
   d. Fluid resuscitation

Assessment Question 4 – Pharmacists and Nurses

4. What is the mechanism of QT prolongation in loperamide overdose??
    a. Potassium channel blockade
    b. Sodium channel blockade
    c. Calcium channel blockade
    d. None of the above

Response 4 – Pharmacists and Nurses

4. What is the mechanism of QT prolongation in loperamide overdose??
   a. **Potassium channel blockade**
   b. Sodium channel blockade
   c. Calcium channel blockade
   d. None of the above

Assessment Question 1 – Pharmacy Techs

1. The typical concentration of naloxone IV continuous infusion is 4 mg/mL.
    a. True
    b. False

Response 1 – Pharmacy Techs

1. The typical concentration of naloxone IV continuous infusion is 4 mg/mL.
   a. True
   b. False

Assessment Question 2 – Pharmacy Techs

2. Isoproterenol can be diluted in either D5W or NS.
    a. True
    b. False

Response 2 – Pharmacy Techs

2. Isoproterenol can be diluted in either D5W or NS.
   a. **True**
   b. False

Assessment Question 3 – Pharmacy Techs

3. What are the signs and symptoms of a fentanyl overdose?
    a. Respiratory depression
    b. Loss of consciousness
    c. Pinpoint eyes
    d. All of the above

Response 3 – Pharmacy Techs

3. What are the signs and symptoms of a fentanyl overdose?
    a. Respiratory depression
    b. Loss of consciousness
    c. Pinpoint eyes
    d. All of the above