

Cutting Edge Issues in Naloxone Pre-Hospital Usage

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Objectives

Objectives for Pharmacists

- Describe the impact of novel synthetic opioids on naloxone dosage requirements
- Describe the potential role of pharmacists in community heroin injection sites

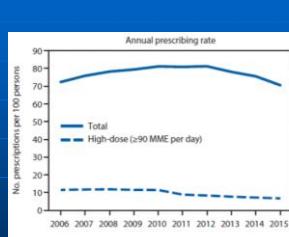
Objectives for Technicians

- Describe current trends regarding novel synthetic opioid usage
- Describe pros and cons of community heroin injection sites

"Some mistakes are too much fun to only make once." - Paisley

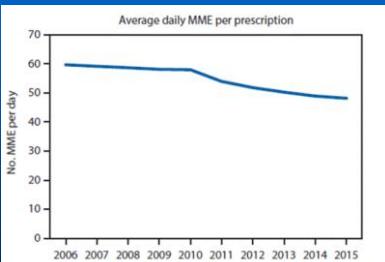
- 1979: 13 deaths related to "China White", heroin containing α -Methylfentanyl
- 1981: placed on Schedule I
- 10 new analogs created
- 2002: Moscow theater 170 died after gassed with cafentanil
- 2013: acetyl fentanyl found in heroin in Rhode Island/PA – 50 deaths

Total Prescriptions per year



Guy GP Jr, Zhang K, Bohm MK, et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017;66:697–704. DOI:

Opioid Prescribing is declining



Guy GP Jr, Zhang K, Bohm MK, et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017;66:697–704. DOI:

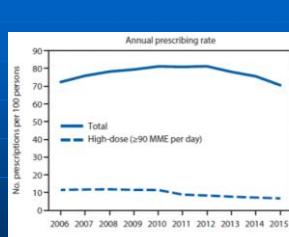
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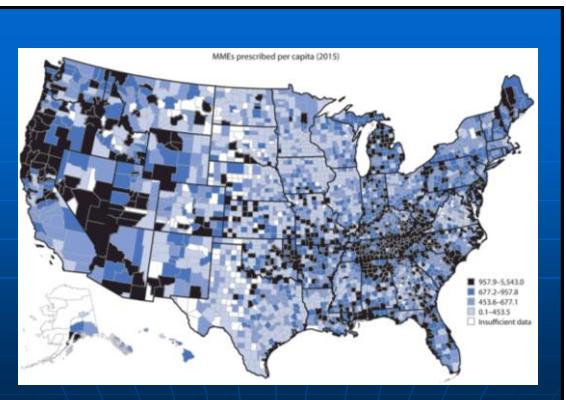
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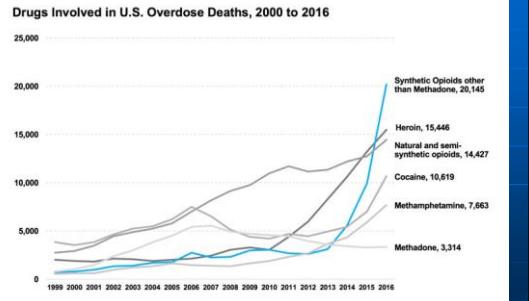
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Today-Deaths are Rising



<https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates> accessed 6/6

Carfentanil

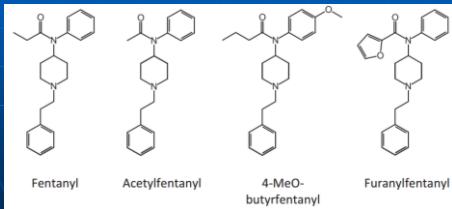
7.6% of opioid deaths in last half of 2016

Most common cause of mortality among all fentanyl analog deaths (43%)

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Fentanyl Derivatives

- At least a dozen have emerged
- Clandestine production



Helander A, Backberg M, Beck O. Intoxications involving the fentanyl analogs acetyl/fentanyl, 4-methoxybutyrylfentanyl and furanylfentanyl: results from the Swedish STRIDA project. Clin Tox. Published on line Feb 5, 2016.

What about NM?

Fentanyl and analogs are involved in about 10% of opioid overdose deaths

Most are polydrug

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First Responder Safety Advisory



(U) Synthetic Opioid Threats in El Paso County and Regionally

(U) "Fentanyl can kill you. Fentanyl is being sold as heroin in virtually every corner of our country. It's produced clandestinely in Mexico, and (also) comes directly from China. It is 40 to 50 times stronger than street-level heroin. A very small amount ingested, or absorbed through your skin, can kill you." Drug Enforcement Administration Acting Deputy Administrator Jack Riley (10 June 2016 DEA Warning to Police and Public)

(U//FOUO) Clandestine synthetic opioids are causing overdose deaths in El Paso County and regionally. The drugs pose a high risk of toxic exposure to unsuspecting Medical and Law Enforcement First Responders.

(U//FOUO) Clandestine Synthetic Opioid Overdoses in El Paso County and Regionally
(U//FOUO) Demand for opioids has increased in El Paso.² A growing local population of

Fentanyl Overdose Deaths
2014 - AUG 2016
EL PASO COUNTY, TX

West Texas HIDTA. Published October 2016

Counterfeit Pills



Joint Regional Intelligence Center. Risk to First Responders from Increased Seizures of New Forms of Fentanyl Published July 28, 2016

Counterfeit Pills

(U//FOUO) Counterfeit 30 Milligram Oxycodone Pills Containing Fentanyl
(Source: DEA) 2*

(U//FOUO) Counterfeit Oxycodone Pills Containing U-47700
(Source: DEA) 4*

West Texas HIDTA. Published October 2016

Rolling Stone

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TRENDING Think 2016 Was Bad? Check Out These 10 Movies Similarly Be Worse

Watch Prince Starr, Kneys Of Love, Bob Seger Pay Tribute... 10 Worst Movies of 2016 Inside Dan Auerbach's Old School New Solo LP

U-47700: Everything You Need to Know About Deadly New Drug

Like predecessors spice and bath salts, deadly chemical U4 has made its way from foreign labs to American drug users

- Developed in 1970s by Upjohn
- No human data until 2016
- Has mu and kappa activity
- About 7 times the potency of morphine

O'Hera ME. U-47700: everything you need to know about deadly new drug. Rolling Stone. October 4, 2016.

Carfentanil

NDEWS National Drug Early Warning System
Funded at the Center for Substance Abuse Research by the National Institute on Drug Abuse

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Elephant Sedative Carfentanil Becomes Deadly Street Drug

Elephant Sedative Carfentanil Becomes Deadly Street Drug

On September 10th, CBC News released an article discussing carfentanil and recent overdoses. Carfentanil was originally manufactured for veterinary use, designed to immobilize large hooded animals, such as moose or elephants. It is now being used and seized by law enforcement. For more information regarding carfentanil and its effects, please refer to the NDEWS Drug Information Page for Carfentanil.

<https://ndews.umd.edu/node/1656>. Accessed 10/24/2016

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Buy Carfentanil Drug

Buy Carfentanil

4-(1-(acetyloxy)phenyl)enanth-1-(2-(phenylethyl)-4-piperidinocarbonyl acid methyl ester

Reference: Carfentanil
Quantity: 1
214743615 items in stock

\$361.00
\$280.00 -25%
\$211.00 per kg

Share on Facebook! Post Add to cart

<http://www.researchchemc.com/en/486-buy-carfentanil-drug.html> Accessed 10/24/2016

Elephant Care International

Drug Index Formulary Contents Introduction Compounding Pharmacies Medication Techniques Drugs Sorted by Therapeutic Class Ophthalmic Products Appendices Disclaimer Sitemap ECI Home

Carfentanil

a) African elephants: 0.0021 mg/kg; supplement with 0.0005 mg/kg if needed; agitated or aggressive animals may require higher doses; reverse with 0.08 mg/kg naltrexone or naloxone (Kreger et al. 2002)

b) For wild African elephants the following doses of carfentanil are recommended:
Calves with shoulder heights of 60-115 cm: 1 mg
Calves with shoulder heights of 116-144 cm: 3 mg
Calves with shoulder heights of 145-165 cm: 5 mg
Calves with shoulder heights of 166-200 cm: 7 mg
Adult females: 10 mg
Adult males: 13 mg
These doses can be reduced by 25% for elephants in captivity (Raath, 1999).

■ 50 grams is enough for 4348 wild African elephants or 5800 captive

<http://www.elephantcare.org/Drugs/carfentanil.htm> Accessed 11/7/2016

Treatment

- Minimal human studies
- Minimal information on naloxone
- Naltrexone 100 mg per 1 mg of carfentanil in animals.
 - 380 mg IM every 4 weeks in humans

George AV, Lu JJ, Pisano MV, Metz J, Erickson TB. **Carfentanil--an ultra potent analgesic with a narrow therapeutic index**. Am J Emerg Med. 2010 May;28(4):530-2.

Headlines

6/28/17 Newsweek

Fentanyl Found in Georgia Resists Life-Saving Naloxone Antidote (acrylfentanyl and tetrahydrofuran fentanyl)

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13 mcg/kg naloxone will bump off an opioid and occupy 50% of receptors

- 1 mg in an 80 kg man reverses half your receptors
- The most common IV dose progression is
 - 0.04 mg
 - 0.4 mg
 - 2 mg
 - 4 mg
 - 10 mg

Melichar JK et al > Eur J Pharmacol 2003;459:217-9
Connors NJ et al. J Med Toxicol 2016;12:276-81

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Is carfentanil 10,000 times as potent as morphine?

- For pain control: maybe
- For respiratory depression: likely not
- For response to naloxone: likely not
- Fentanyl and analogs DO NOT BIND MORE TIGHTLY THAN NALOXONE TO THE OPIOID RECEPTOR

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Potency is related to how much drug gets to the receptor

- Octanol-water coefficient
- Morphine: 6
- Fentanyl: 9950
- Carfentanil 13,500
- Naloxone: in between morphine and fentanyl; actively transported

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Elk can be reversed with 2:1 naloxone: carfentanil

Human volunteers given labeled carfentanil 0.1-0.6 mcg
naloxone 2 mg blocked 80.6% of receptors at 5 minutes
naloxone 2 mcg/kg blocked 42.6%

Kim S et al. J Nucl Med 1997;38:1726-31.

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Human occupational case



43 yo M DMV splashed in face, eyes, mouth when dislodging Elk dart from a tree
Drowsy in 2 minutes
Gave naltrexone 100 mg from antidote kit

Successful!

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High dose fentanyl reversed with naloxone 2 mg

18 patients ingested hydrocodone tablets contaminated with fentanyl 0.6-6.9 mg per tablet

17 required bolus naloxone, one needed 8 mg
4 needed infusion 26-39 hours

Sutter ME et al. Acad Emerg Med 2016;24:106-13.

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And cases where “it did not work”

26 yo M chewed a few patches
Did not respond to 2 mg intranasal naloxone
Work up with 1 mg IV naloxone

Was this really resistant fentanyl or just unpredictable nasal absorption?

Zuckerman M et al. Prehosp Emerg Care 2014;18:550-4.

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High doses need in Chicago

55 cases of fentanyl overdose
Success with 0.4 to 12 mg naloxone

12 mg is still less than the classic titration (16.4 mg total)

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One case widely quoted

34 yo M found down, RR 9
Just shorted a white powder, turned blue, stopped breathing

EMS gave 2 mg naloxone IV with no improvement

In ED pH 6.92, **pCO₂ 138!!!!!!**

ED gave 2 mg naloxone IV with no improvement
He was intubated and woke up 32 hours after exposure

Blood, urine positive for carfentanil + other analogs

Uddayasankar et al. Pharmacotherapy 2018; April

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| Location | Drug | Highest Reversal Dose | Outcome | Caveat |
|-----------------------|-------------------------------------|-----------------------|---------------|-----------------------------------------------------------------------------|
| Chicago 2005-6 | Fentanyl | 12 mg | Good response | |
| Chicago 2010 | Carfentanil/ xylyazine | 100 mg naltrexone | Good response | 100 mg naltrexone is more potent than naloxone |
| Boston 2014 | Fentanyl patch (chewed) | 1 mg | Good response | No response to 2 mg IN |
| B.C., Canada 2016 | Furan/fentanyl | 3 mg | Good response | |
| California 2016 | Fentanyl tablet (as much as 6.9 mg) | 8 mg | Good response | Many patients needed repeat naloxone doses later than typically recommended |
| Manitoba, Canada 2018 | Carfentanil | 4 mg | No Response | pCO ₂ 138 mm Hg |

So do you need more naloxone?

New drugs cause respiratory depression in small doses

Naloxone normal escalating strategy will mostly work

You may need to re-dose naloxone more frequently

Make sure patient is warm, use bag valve mask, ventilate

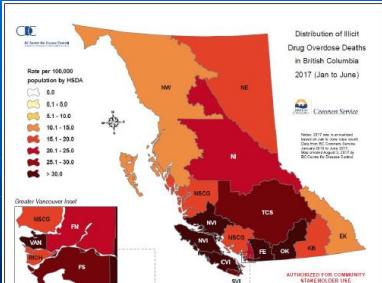
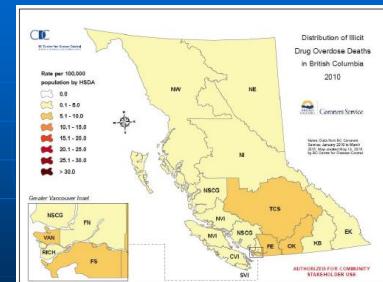
Thanks to Andrew Stolbach
The Tox & The Hound episode “Is this anything?”

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Are Safe Injections Sites a Good Idea?

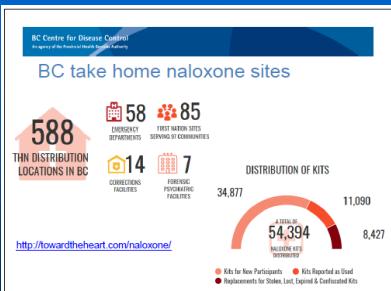
The Vancouver Experience

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What BC is doing about it

- Improve monitoring and Surveillance
 - Overdose Cohort: to identify who is at risk, where to target, and assess interventions
 - Preventing overdose before it happens
 - Immediate response to overdose
 - Recognize and respond to OD
 - Improve access to naloxone
 - Drug use in supervised observed settings



What do you do there?

Check in

Use your own drug with syringes provided at nurse station

Hang out for a while

Interact with trained staff

Get checked for HIV, hepatitis

Get wound care

Get treatment referral

Leave safely

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Advantages

Reduce overdose deaths
public injection has twice the fatal rate
Prevents reuse of needles
Prevent HIV and Hepatitis transmission
Save annual medical costs
Reduce street-based drug use
Link people to services and treatment

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Disadvantages/Concerns

Do they implicitly condone drug use?
Do they lead to increased drug use?
Is there really a safe way to inject illicit drugs?
What about federal and state laws? DEA is against it
Stereotype about junkies in the neighborhood
Will it increase crime?

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Where are they in the US?

San Francisco to start July 2018
expect to save \$3.5 million/year in medical costs
Chosen from a list of non profits that operate needle exchanges

Philadelphia offering private organizations to set them up
expect to prevent 76 deaths per year
expect to save \$12.5-75 million/year

Seattle is taking initial steps
city council has allocated money for a site

Ithaca, Denver, New York City considering the idea

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What is the role of the pharmacist?

Currently provide clean needles
Currently provide opioid substitution
Have an interest in increasing their role

Could provide dosing advice for "drug resistant" cases
Some have suggested locating them in hospital pharmacies

Barriers
Legal
Time
Compensation
Training
fear

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