How Do Adulterants Like Quinine, Metamizole, Carfentanil, Nitazenes, Xylazine, and Medetomidine Impact the Opioid Epidemic?

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Objectives

- At the conclusion of the program, the successful learner will be able to:
  - Discuss myriad adulterants present in illicit heroin products and their risks.
  - Discuss the implications of carfentanil or nitazene adulteration of products and their risks.
  - Discuss the two main alpha-2 agonist adulterants now appearing in illicit fentanyl (or analogue) products, or that are being used a stand-alone illicit substances of abuse.
  - Compare and contrast the mechanism of action of xylazine and medetomidine with traditional opioids
  - Describe the controversy surrounding the role of naloxone in patients experiencing respiratory depression on carfentanil, nitazene, xylazine or medetomidine and how it could impact the naloxone protocol for bystanders and first responders
  - Describe unique risks that can occur with xylazine and medetomidine products and potential treatment options

Who am I?

Media pieces with a reach >3.5 billion including NBC News, USA Today, New York Times, LA Times, Boston Globe, WNPR, DoctorRadio, Prevention, Newsweek, WebMD, CNBC, and over 100 other sites.

ASHP Award for Sustained Contributions to the Literature, ASHP Drug Therapy Research Award, ACCP Young Investigator of the Year, AACP Lyman Award, AACP Weaver Award.

UConn Distinguished Professor, CETL Teaching Fellow, Provost's Award for Public Engagement

Pharmacist and clinical pharmacologist at UConn with >400 publications and 19,970 citations

Listed on Elsevier's list of "Top 2% of Scientists Worldwide"

Investigated drug (prescription, OTC, and illicit), dietary supplement, and device or surgical procedure induced diseases for 30 years

Provided simulation training on naloxone utilization, distributed naloxone and fentanyl test strips at community events, and served as a substance use speaker and panelist

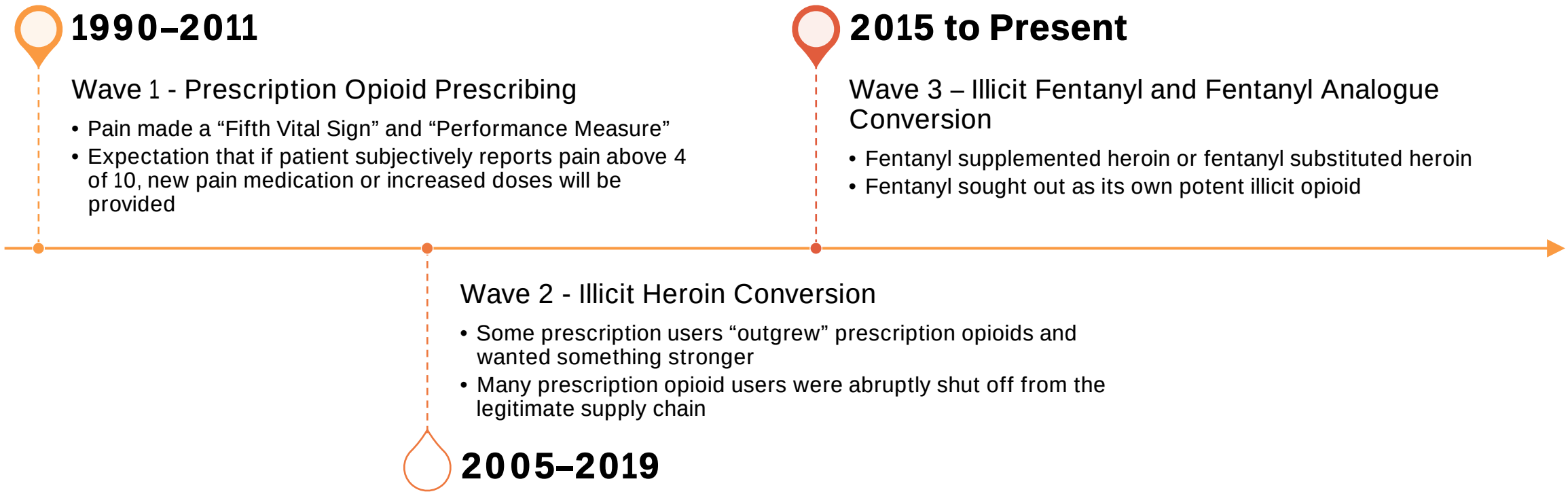
Inaugural chair of the Kratom Consumer Advisory Council, a council supported by the Global kratom Coalition that devises best practices for the safe use of kratom products in the US*

Director of one of only 14 Evidence-based Practice Centers designated by the federal Agency for Healthcare Research and Quality 2007-2020

https://pharmacy.uconn.edu/person/c-michael-white/

*The GKC reimburses me for the time spent leading the KCAC and educating/advocating for its position statements.

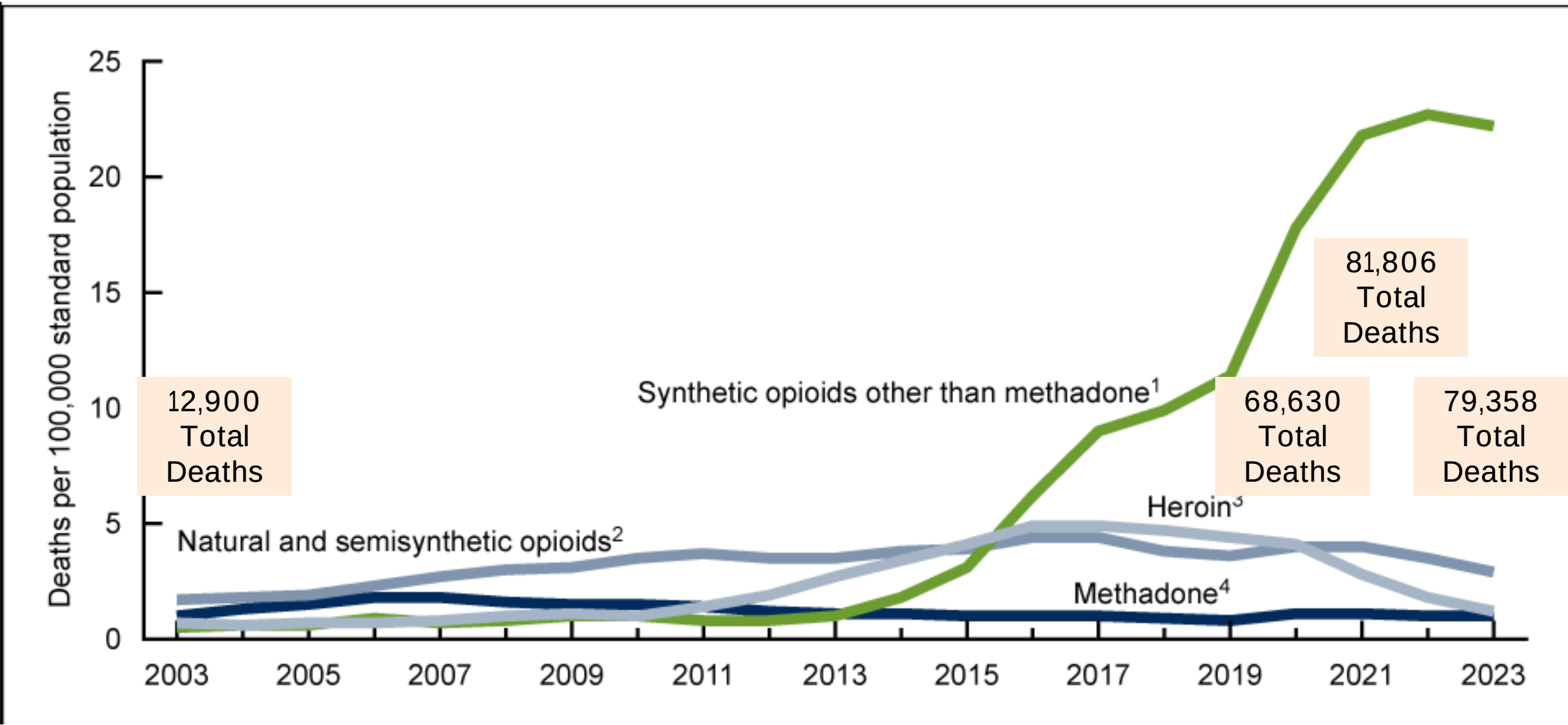
First Three Waves of the Opioid Epidemic



https://pmc.ncbi.nlm.nih.gov/articles/PMC6675668/

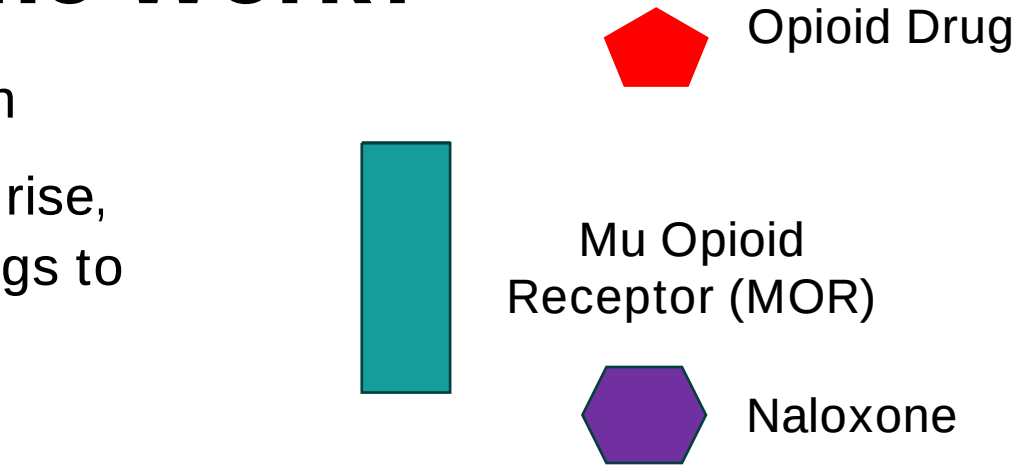
Death Due to First Three Waves of Opioid Epidemic

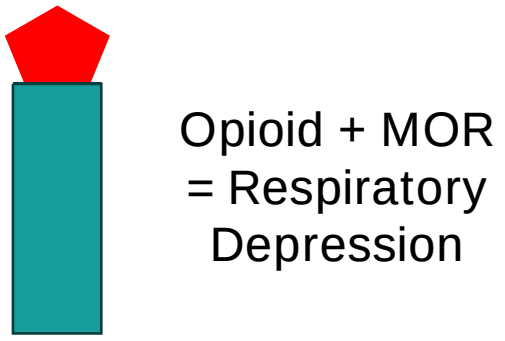
https://www.cdc.gov/nchs/products/databriefs/db522.htm



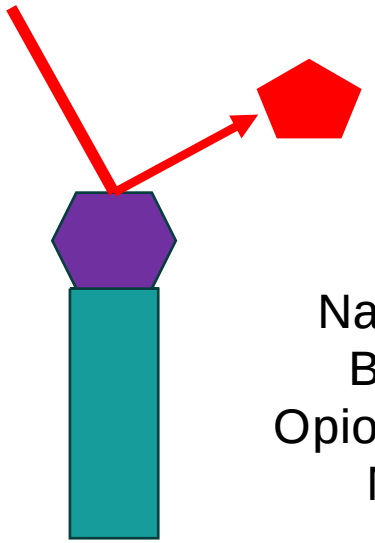
How Do Opioids Cause Respiratory Depression and How Does Naloxone Work?

- Breathing is an involuntary brain function
- When carbon dioxide levels in the blood rise, the brainstem detects it and tells the lungs to breath more rapidly and more deeply
  - Pain is a stimulator to breath more rapidly
- Stimulating mu opioid receptors (MOR) in the brainstem desensitizes detection of rising carbon dioxide and the stimulus to breath diminishes
- Naloxone blocks MOR receptors, re-establishes respiratory drive





Opioid + MOR = Respiratory Depression



Naloxone Blocks Opioids From MOR

https://pmc.ncbi.nlm.nih.gov/articles/PMC6938398/
https://www.ncbi.nlm.nih.gov/books/NBK546642/

Public Access to Naloxone Has Been Effective

- Two doses of naloxone over 95% effective at restoring breathing in opioid only overdoses
- Naloxone made an over-the-counter product nationwide
- Pharmacists allowed to prescribe naloxone in several states
- CDC, State and Local Heath Departments begin training & distributing naloxone free of charge to the community
- North Carolina Program (2013-2016):
  - Counties distributing 100+ kits/100,000 people saw reduced opioid overdose death rates
  - 352 lives saved with $2,742 saved per dollar spent

Drug Alcohol Depend. 2019;204:107536. doi: 10.1016/j.drugalcdep.2019.06.038.

How to Use Naloxone (traditional guidance)

1. **Check for suspected overdose signs:**
    1. Sleepiness or trouble breathing.
    2. Call "wake up" and gently shake the person.
2. **Administer naloxone (nasal spray):**
    1. Tilt head back, insert spray tip into nostril, press plunger.
3. **Call 911:** Monitor the person and administer additional doses (alternating nostrils), if necessary and available, every 2–3 minutes until EMS arrives.
4. **Post-revival:** Stay with the individual until emergency services take over.

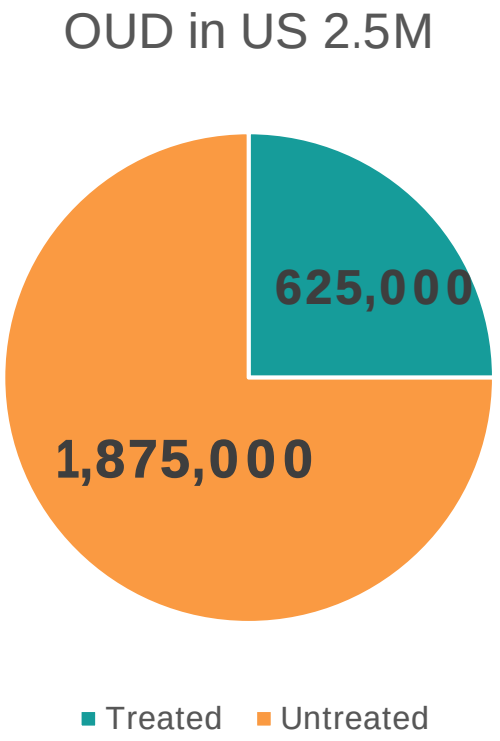
Opioid Induced Respiratory Depression Not the Only Risk of Opioids

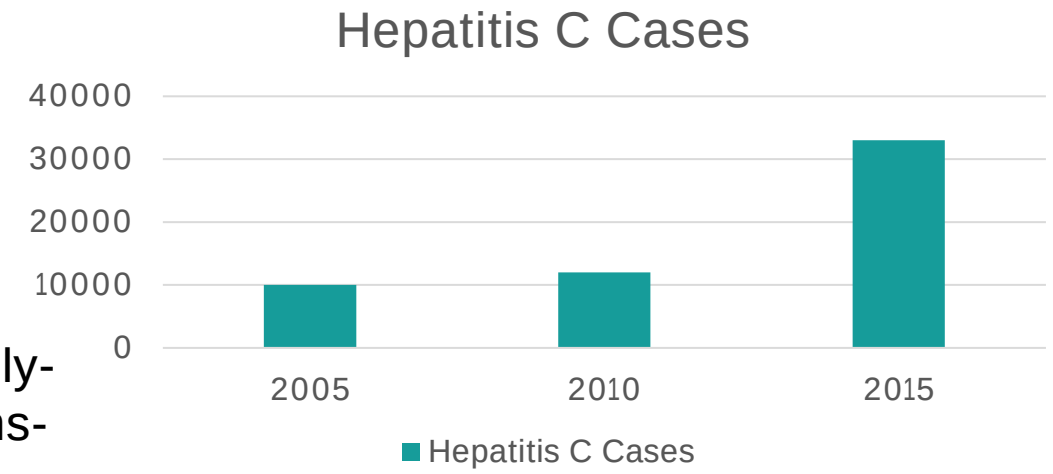
- Aspiration (liquid or food sucked into lungs)
- Severe constipation
- Needle use/sharing = bleeding, sepsis, HepB, HepC, HIV, UTI
- Arrhythmias (K+ channel induced, not MOR) – Methadone, Loperamide, Mitragynine
- Hypotension
- Inability to hold a job
- Inability to care for self or others

Naloxone does not impact these

Impact of OUD on US

- OUD costs the US $1 trillion annually
  - Healthcare, jail, social services, lost productivity
- OUD 12X higher among homeless vs. non-homeless US veterans
- ~50% of the decline in U.S. labor force participation among working-age men attributed to OUD
- 2.8% of oral chronic opioid users switch to intravenous opioids yearly
- 9% of new HIV infections annually are from injectable substances of abuse
- HepC infections linked closely with injectable opioid use





https://pmc.ncbi.nlm.nih.gov/articles/PMC4767561/

https://pmc.ncbi.nlm.nih.gov/articles/PMC7559328/

https://nida.nih.gov/news-events/news-releases/2023/08/only-1-in-5-us-adults-with-opioid-use-disorder-received-medications-to-treat-it-in-2021

Types of Heroin

- The heroin ingredient itself comes in three forms:
  - Black tar heroin – only 25% purity
  - Brown heroin – purity between that of white and black tar
  - White heroin – heroin with fewer contaminants/impurities
- Heroin product increasingly contain hidden recipe, not a single ingredient

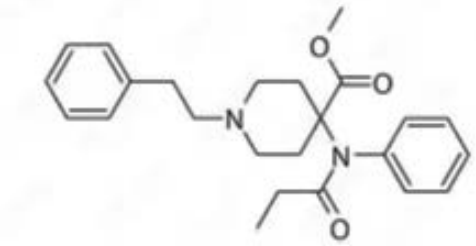
https://www.honeylake.clinic/blog/what-are-5-types-of-heroin/

Adulterants in Heroin Products

- Quinine added to contribute to the initial hypotensive “rush” that heroin provides
  - Quinine can prolong the QTc interval and increase the risk of arrhythmias
- Metamizole – muscle relaxant, analgesia and euphoria booster
  - Pulled from US market in 1977 for causing agranulocytosis and aplastic anemia, liver damage, and hypersensitivity reactions
- In 2024, medetomidine started replacing metamizole in some heroin products
- Illicit heroin product impurities induce fever, chills, and rigors when injected
  - Acetaminophen is commonly added to reduce the fever effects and boost the analgesic effects
    - Too much acetaminophen can cause liver damage (esp mixed with alcohol or other acetaminophen use)
  - Antihistamines like diphenhydramine are commonly added to prevent chills and rigors from impurities in heroin and can block its metabolism through CYP2D6 prolonging effects

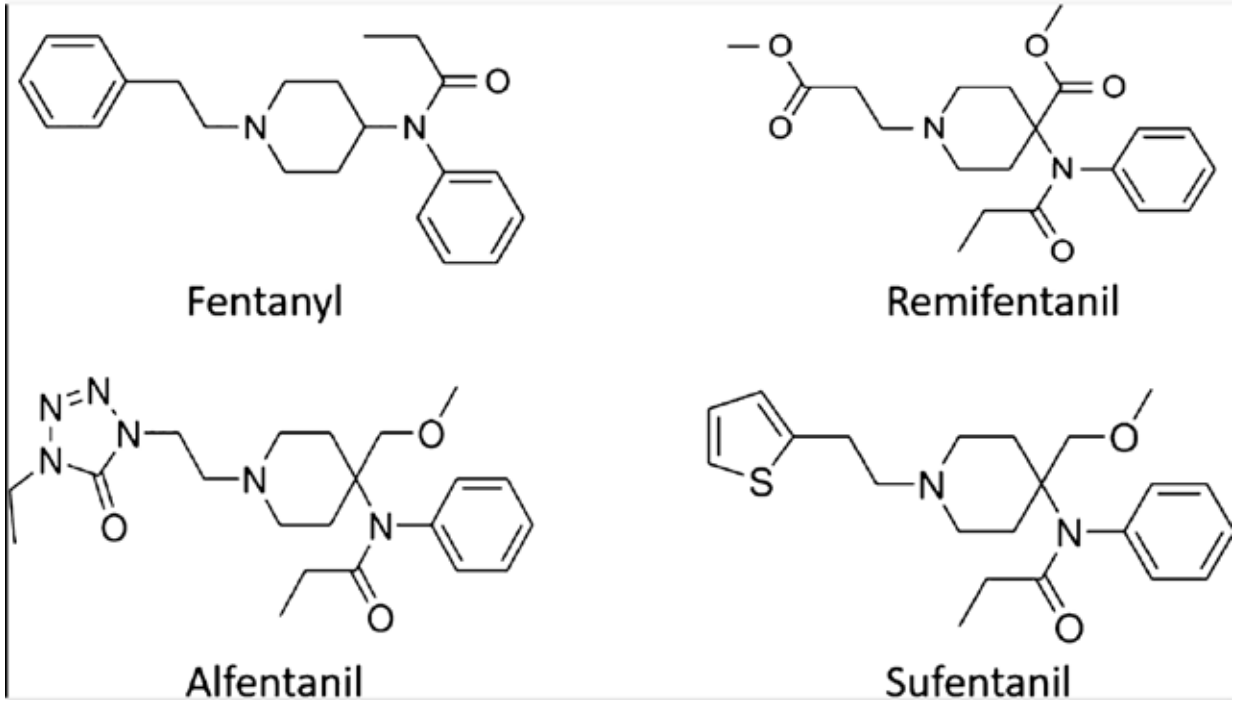
https://accp1.onlinelibrary.wiley.com/doi/pdf/10.1002/jcph.1860

Fentanyl and Analogues



Carfentanil

- Fentanyl and analogues are dosed in mcg instead of mg (1 mg = 1000 mcg)
  - Easier to smuggle into US, much more potent effects than heroin
- Cheaper to produce, sometimes mixed with heroin, cocaine, benzos
- Greater purity than heroin, but fentanyl and analogue products increasingly being cut with alpha-2 agonists
- Carfentanil is ~100X fentanyl potency, more resistant to naloxone, and has a longer half life



Fentanyl

Remifentanil

Alfentanil

Sufentanil

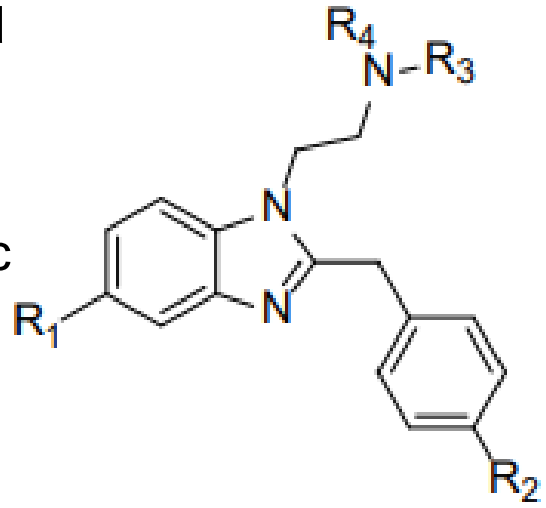
https://pmc.ncbi.nlm.nih.gov/articles/PMC5967713/

https://journals.sagepub.com/doi/10.1177/87551225251326811

https://fherehab.com/learning/nitazines-carfentanyl-dangerous-opioids

Nitazenes: NKOTB

- Developed as experimental opioids in the 1950s, DCed because they were too dangerous
- Extremely potent synthetic opioid subclass
- Adulterant in illicit heroin, fentanyl, oxycodone, benzos, or cocaine products
- ~20X more potent than fentanyl



	R_1	R_2	R_3	R_4
metonitazene	NO_2	OCH_3	CH_2CH_3	CH_2CH_3
metodesnitazene	H	OCH_3	CH_2CH_3	CH_2CH_3
etonitazene	NO_2	OCH_2CH_3	CH_2CH_3	CH_2CH_3
etodesnitazene	H	OCH_2CH_3	CH_2CH_3	CH_2CH_3
protonitazene	NO_2	$OCH_2CH_2CH_3$	CH_2CH_3	CH_2CH_3
butonitazene	NO_2	$OCH_2CH_2CH_2CH_3$	CH_2CH_3	CH_2CH_3
isotonitazene	NO_2	$OCH(CH_3)_2$	CH_2CH_3	CH_2CH_3
clonitazene	NO_2	Cl	CH_2CH_3	CH_2CH_3
flunitazene	NO_2	F	CH_2CH_3	CH_2CH_3
etonitazepyne	NO_2	OCH_2CH_3	$-CH_2CH_2CH_2CH_2-$	
etonitazepipne	NO_2	OCH_2CH_3	$-CH_2CH_2CH_2CH_2CH_2-$	

https://www.deadiversion.usdoj.gov/drug_chem_info/benzimidazole-opioids.pdf

https://fherehab.com/learning/nitazines-carfentanyl-dangerous-opioids

Implications of Fentanyl and/or Nitazene Analogue Adulteration

- With China crackdown on illicit fentanyl manufacturers, increasing trend to supplement with what is on hand, carfentanil or nitazenes
- Extreme potency means microgram dosing (1,000 mcg = 1 mg)
  - Small errors in weighing out ingredient during product creation can lead to unpredicted effects, overdose, and death
  - Insufficient blending time of powders in products can leave lethal amounts in some units and subpotent amounts in other units
- There is a potential that first dose naloxone could be less effective, with the second dose becoming more important to establish effects

https://pmc.ncbi.nlm.nih.gov/articles/PMC10878679/

https://www.acsh.org/news/2024/12/29/will-carfentanil-laced-fentanyl-render-naloxone-useless-49202

Alpha-2 Agonists (Xylazine and Medetomidine)

- Xylazine investigated as a human antihypertensive agent in 1962
  - Serious hypotension and bradycardia, xylazine not FDA approved for human use
  - Approved as an animal tranquilizer and muscle relaxant
- Medetomidine approved as an animal sedative and analgesic
- Being added to illicit opioid products (usually fentanyl) to boost the euphoria
  - No blood dyscrasias like with metamizole
  - Less tolerance builds to the alpha-2 receptor effects than opioid ones over time
    - Tolerance to opioid effects means needing to use higher doses over time for same effect

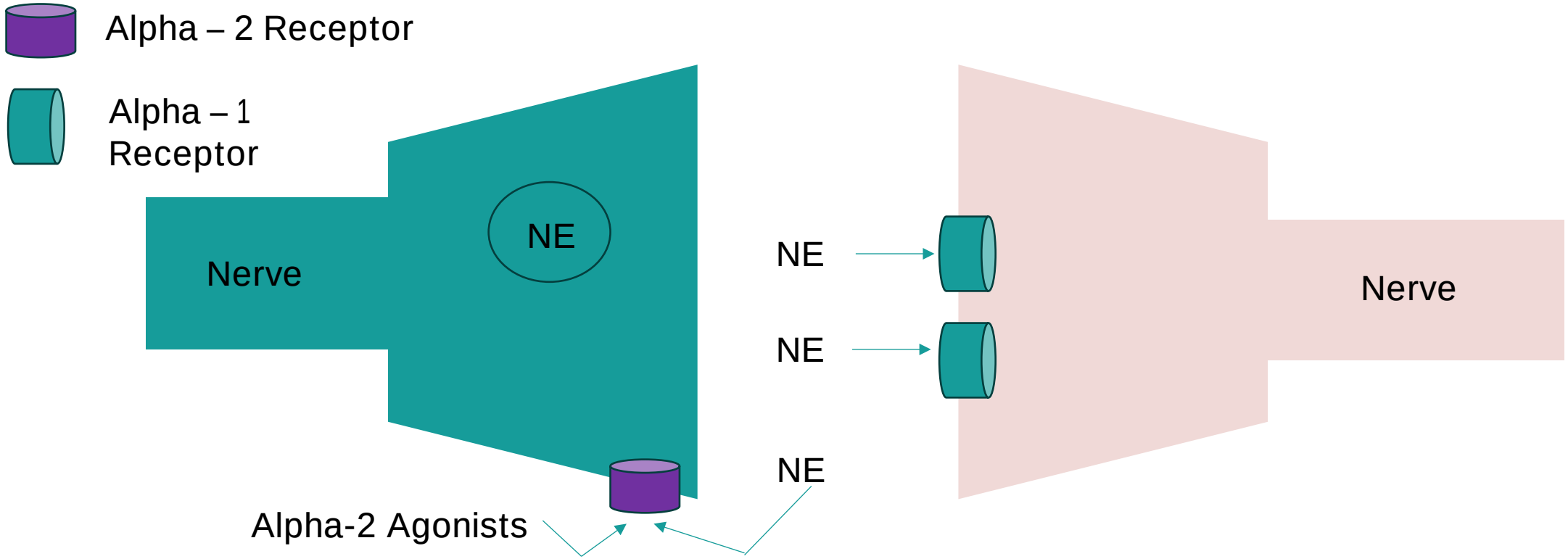
https://theconversation.com/animal-tranquilizers-found-in-illegal-opioids-may-suppress-the-lifesaving-medication-naloxone-and-cause-more-overdose-deaths-253037

https://journals.sagepub.com/doi/10.1177/87551225251326811

Xylazine and Medetomidine Pharmacology

NE Norepinephrine

https://journals.sagepub.com/doi/10.1177/87551225251326811



- NE is made and stored at pre-synaptic nerve terminal. Released when nerve is stimulated
- Stimulates post-synaptic alpha-1 receptor to activate postsynaptic nerve
- If NE (or xylazine or medetomidine) hits the alpha-2 receptor, it makes less NE and can hyperpolarize the nerve rendering it ineffective

Xylazine and Medetomidine Pharmacology

- Central nervous system alpha-2 receptor stimulators
- Can reduce norepinephrine production and hyperpolarize the pre-synaptic nerves stopping normal nerve communication
- Co-localized on similar nerves as opioids
  - Sedation, hypnotic, anesthesia
  - Cyanosis - poor tissue oxygenation (organ damage, skin sores and ulcers)
  - Euphoria
  - Hypotension
  - Respiratory depression

https://journals.sagepub.com/doi/10.1177/87551225251326811

Xylazine and Medetomidine

- A combination fentanyl + alpha-2 receptor stimulator product might be less likely to cause respiratory depression than fentanyl only (lower fentanyl dose needed for same euphoria)
  - BUT, if respiratory depression occurs, standard naloxone doses might not work on the alpha-2 agonist component
- Xylazine being used as an alpha-2 agonist only substance of abuse (i.e. Tranq)
  - Respiratory depression unlikely to be treated by standard doses of naloxone

https://theconversation.com/animal-tranquilizers-found-in-illegal-opioids-may-suppress-the-lifesaving-medication-naloxone-and-cause-more-overdose-deaths-253037

https://journals.sagepub.com/doi/10.1177/8755122525132681 1

Clinical Effects

- Systematic review of 76 patients with sole xylazine use (many were veterinarians or vet staff)
  - Naloxone was used in 16 patients, reported ineffective in 6 of the cases (effectiveness not reported in the other 10 cases)
  - The review included subset assessment of 11 case reports in which the xylazine dosage and clinical findings were reported
    - All 11 patients were sedated, 55% were comatose, 73% received mechanical ventilation, 64% had bradycardia, 45% had hyperglycemia, and 64% had miosis (small pupils)
- Clonidine is an alpha-2 agonist that is used in humans to lessen withdrawal symptoms in substance use disorders. In clonidine overdoses, naloxone doses of 10 mg have been required to successfully treat the resulting respiratory depression in adults.

https://journals.sagepub.com/doi/10.1177/87551225251326811

Where Did the Products Come From, Where Are the Now?

- Fentanyl or analogue + xylazine was first identified in Puerto Rico in 2001, with US mainland identification in 2006
- Initially found in Connecticut, Pennsylvania, and Maryland but now national problem
  - Over 1/3 fentanyl or analogue products contain xylazine
  - Office of National Drug Control Policy named xylazine an emerging threat on April 12, 2023.
- Medetomidine first detected in Toronto, Canada in 2023
  - By February 2024, medetomidine was noted in 11% of fentanyl products
- Medetomidine-adulterated fentanyl and heroin products moved to the United States through Chicago in May of 2024
- These adulterated products moved to Pittsburgh and then Philadelphia in June 2024, where over 160 hospitalizations were seen over 3 days in Philadelphia alone
- Medetomidine adulterated products most recently appeared in New England starting in August of 2024 with overdoses noted by clinicians at UMass Medical Center

https://journals.sagepub.com/doi/10.1177/87551225251326811

How Does Xylazine and Medetomidine Change Naloxone Treatment Recommendations

- Importance of calling 911 sooner
  - If naloxone ineffective, having EMS arrive sooner is valuable
- Importance of bystander rescue breathing
  - If naloxone ineffective, rescue breathing provides the only oxygenation until EMS arrives
  - Rescue breath training and face shields with naloxone valuable
- Importance of having more than two boxes of naloxone on hand valuable
  - One naloxone box has two 3 mg or 4 mg nasal syringes (total of 6 or 8 mg per box)
  - Some data on clonidine (another alpha-2 agonist) suggests $\geq$10 mg of naloxone is needed to reverse respiratory depression effects form alpha-2 agonists (mechanism not clear)

https://journals.sagepub.com/doi/10.1177/87551225251326811

Initial Naloxone Dosing 4 mg vs. 8 mg

- 3 mg or 4 mg IN doses commonly used
  - 8 mg IN doses approved in 2021, not commonly used
- Assessment of 49 patient encounters 2014-2020 vs. 2021-2022
  - Mean total naloxone dose was 3.1 mg (2014–20) vs. 4.4 (2021–22); $p = 0.2$)
  - Trend towards needing two doses of 3mg in 2021-2022 but only one dose of 4mg
- NY State tested 8 mg vs. 4 mg single doses from March 2022 to August 2023
  - 8 mg not more effective than 4 mg doses (99% of people survived in both groups)
  - Opioid withdrawal symptoms, including vomiting, 37.6% vs. 19.4% ($p<0.05$)
  - Disorientation (66.3% vs. 58.5%) and lethargy (52.5% vs. 43.5%) were similar
- Meta-analysis finds 4mg IN doses effective
  - 8mg doses similarly effective but can cause more tachycardia and withdrawal

https://pmc.ncbi.nlm.nih.gov/articles/PMC10878679/

https://www.jem-journal.com/article/S0736-4679(25)00139-8/abstract

https://www.health.ny.gov/press/releases/2024/2024-02-08_naloxone_study.htm

Possible Modified Regimen

1. **Check for suspected overdose signs**
2. **Call 911 WHILE prepping first naloxone dose**
    - Activate EMS system earlier
3. **Administer naloxone (nasal spray)**
    - Tilt head back, insert spray tip into nostril, press plunger
4. **If unsuccessful, provide rescue breathing during two-minute wait**
5. **Administer naloxone (dose 2) into other nostril if two-minutes passed and unsuccessful**
6. **Provide rescue breathing until EMS arrives**

If more naloxone is available, it can continue to be given every two-minutes and if unsuccessful, give rescue breathing in between the additional doses.

Xylazine Skin Sores and Infections

- Injection of fentanyl or analogue products enhances xylazine's Cmax and euphoric effect
  - Intradermal or intravenous
- Xylazine adulterated products or xylazine only products can induce cyanosis through reductions in cardiac output, which can reflexively cause skin vasoconstriction
  - Drops in blood flow to the skin can compromise immune response, protection from microbes, delay wound healing, or cause ischemic necrosis
- Respiratory depression + direct skin vasoconstriction enhances risks of tissue damage from xylazine
- Patients with injection site skin infections or ulcers need prompt treatment with antimicrobials
  - Ulcerated tissue could require debridement and hyperbaric treatment to facilitate wound healing

https://dermnetnz.org/topics/xylazine-induced-skin-ulcers

Conclusions

- Metamizole and acetaminophen adulterate many heroin products and can increase the risk of liver damage
  - Metamizole can also cause blood dyscrasias
- Xylazine and medetomidine are alpha-2 agonists that enhance opioid euphoric effects and can induce coma and cyanosis with or without respiratory depression
  - Standard dose naloxone may not reverse animal tranquilizers, at least with standard dosing
  - An alteration in the naloxone dosing protocol might be in order
- Xylazine can induce skin vasoconstriction resulting in serious necrotic ulcers requiring aggressive treatment

Self Assessment Question

- What is the name of the muscle relaxant added to cut heroin products to enhance the euphoric effects but that can cause agranulocytosis and aplastic anemia?

A. Quinine

B. Diphenhydramine

C. Metamizole

Self Assessment Question

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Self Assessment Question

- Why are acetaminophen and antihistamines commonly added to black tar heroin but less commonly in white powder heroin?

A. Black tar heroin comes from Mexico where they have access to acetaminophen and antihistamines, where white powder heroin comes from Columbia and the ingredients are not available

B. Black tar heroin has lower purity and causes injection reactions that the acetaminophen and antihistamines counteract

C. Acetaminophen and antihistamines directly cause euphoria

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A. To reduce opioid side effects

B. To kill off customers faster

C. To enhance euphoria and slow down the rate of tolerance that fentanyl users experience

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Self Assessment Question

- How could the inclusion of carfentanil, nitazenes, xylazine or medetomidine change the procedure to administer naloxone when coming across a patient with severe respiratory depression? [CHOOSE THREE RIGHT ANSWERS]
  A. Naloxone should no longer be used
  B. Call 911 right away so EMS can arrive on scene faster
  C. Use more than 1 box of naloxone if available and the previously administered doses were ineffective
  D. Provide rescue breathing for the two minutes after each naloxone administration if the patient did not revive from the dose

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- Why does xylazine use increase the skin related risks of injecting substances of abuse? [CHOOSE EACH RIGHT ANSWER]

A. Xylazine causes skin vasoconstriction which compromises innate infection control

B. Xylazine causes skin vasoconstriction which can worsen the extent of ulceration

C. Xylazine causes skin vasoconstriction which compromises innate infection control and worsens the extent of ulceration

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