Fentanyl:
An Old Drug Creating New Problems.

Understanding the Pharmacology, Debunking the Myths, and Considering the Treatment Options.

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March 30, 2023

How We Are Organized

PHC is a County Organized Health Systems (COHS) Plan

Non-Profit Public Plan

Low administrative Rate (less than 4 percent) allows for PHC to have a higher provider reimbursement rate and support community initiatives

Local Control and Autonomy

A local governance that is sensitive and responsive to the area's healthcare needs

Community Involvement

Advisory boards that participate in collective decision making regarding the direction of the plan

About Us

Mission:

To help our members, and the communities we serve, be healthy.

Vision:

To be the most highly regarded managed care plan in California.

Disclosures

I have no relevant financial disclosures related to this talk

The opinions expressed herein are mine alone, and do not represent the opinions of my employing institutions

Outline

History

Epidemiology

How it gets to market

Pharmacology

Unique attributes

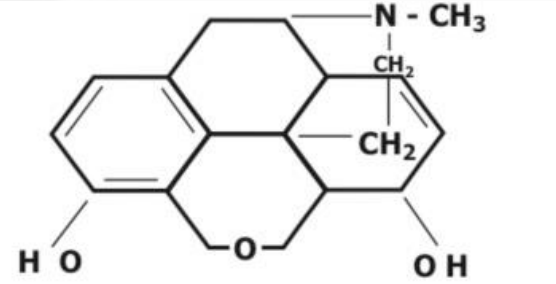
- Respiratory depression
- Respiratory muscle rigidity
- Lack of cross tolerance with other opioids
- Reduced sensitivity to naloxone/antagonists

Treatments implications: overdose reversals and maintenance treatment

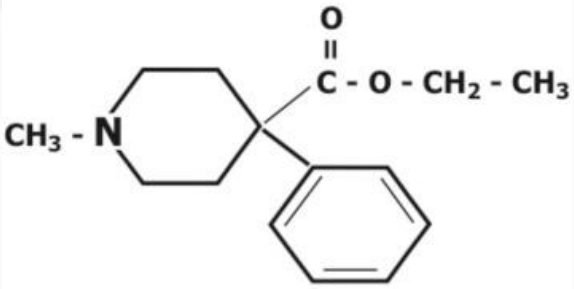
History

Dr. Paul Janssen (Janssen Pharmaceutica, founded 1953)

- Seeking effective, potent, rapid-acting analgesics
  - Only morphine and meperidine available at that time (slow onset, not potent, trouble penetrating BBB)
- Hypothesized piperidine ring was key to analgesic effects
- Started work on manipulating meperidine (less complex than morphine), adding side chains to increase fat solubility
- 1960 → first synthesized **fentanyl**
  - 100-200x more potent than morphine



Morphine



Meperidine

Piperidine

Stanley 2014

History

Used extensively in Europe 1960s, but opposition to its FDA approval in US

- Dr Robert Dripps → concerns re: rigidity and potency (abuse potential)
- Compromise:
  - Approved in 1968 as anesthetic but only in combination with droperidol
    - Droperidol → "bad high" if misused
    - 50:1 (droperidol:fentanyl) → "Innovar"

Stanley 2014

History

1972: fentanyl approved as mono-product

1970s: first overdose deaths reported (some patients, mostly providers)

1980-90s: Janssen synthesizes other fentanyl analogues:

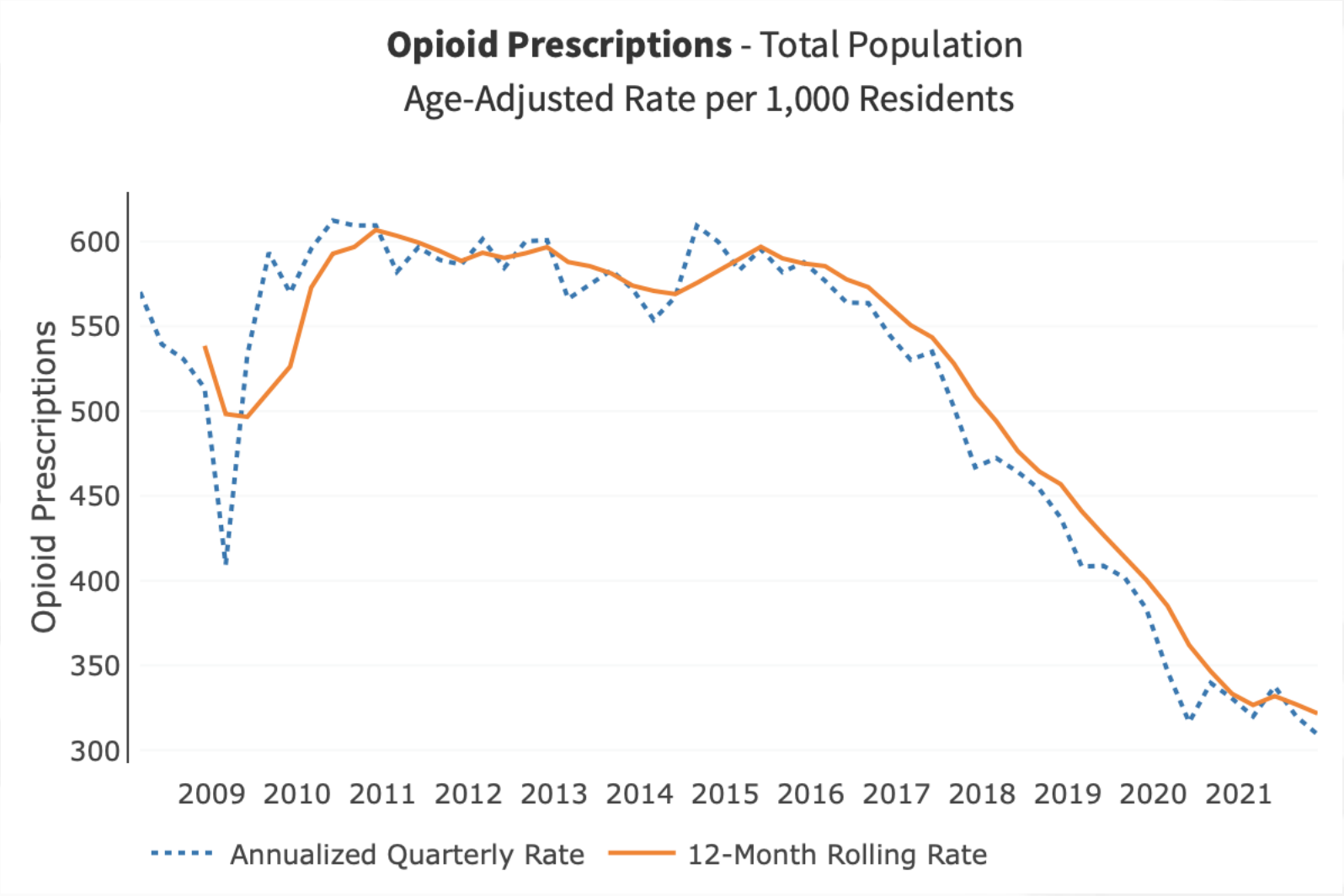
- Remifentanil, sufentanil, alfentanil, carfentanil

Late 80s: Duragesic patch (opioid tolerant folks, cancer pain, steady blood levels x 2-3days)

1990s: Oralet pre-anesthetic/surgery “lollipops” (adults and children) → 1998 Actiq (less candy-like, cancer breakthrough pain)

Intrathecal, epidural and local uses, too.

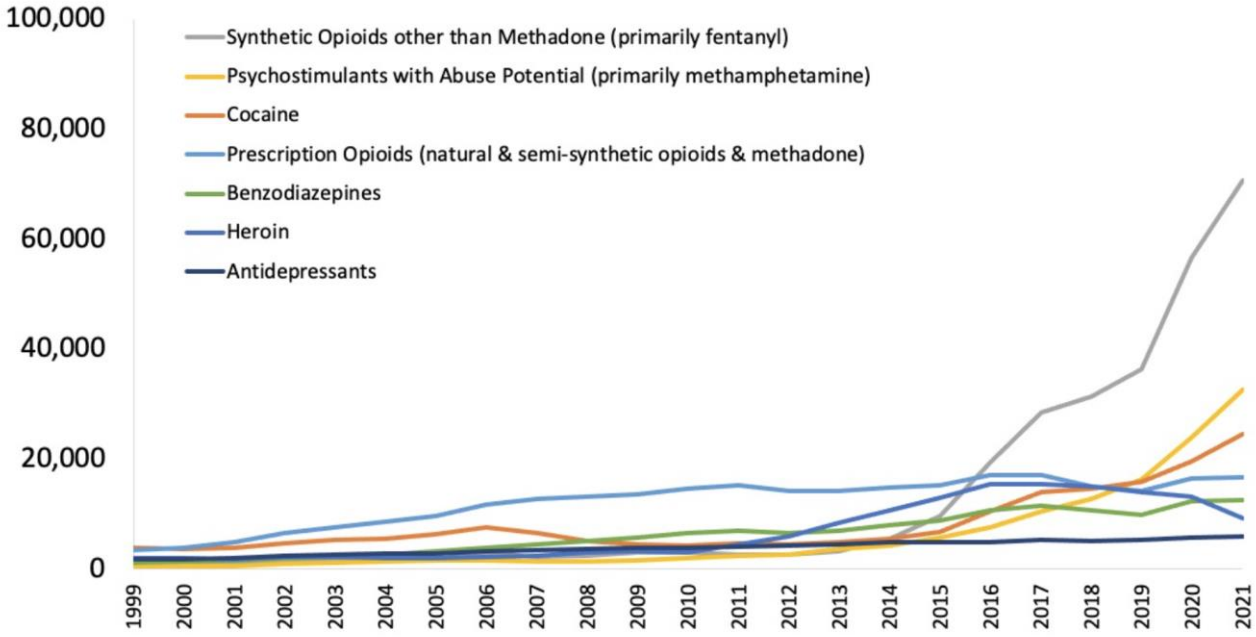
Epidemiology



NIDA 2023; CDPH 2023

Epidemiology

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2021

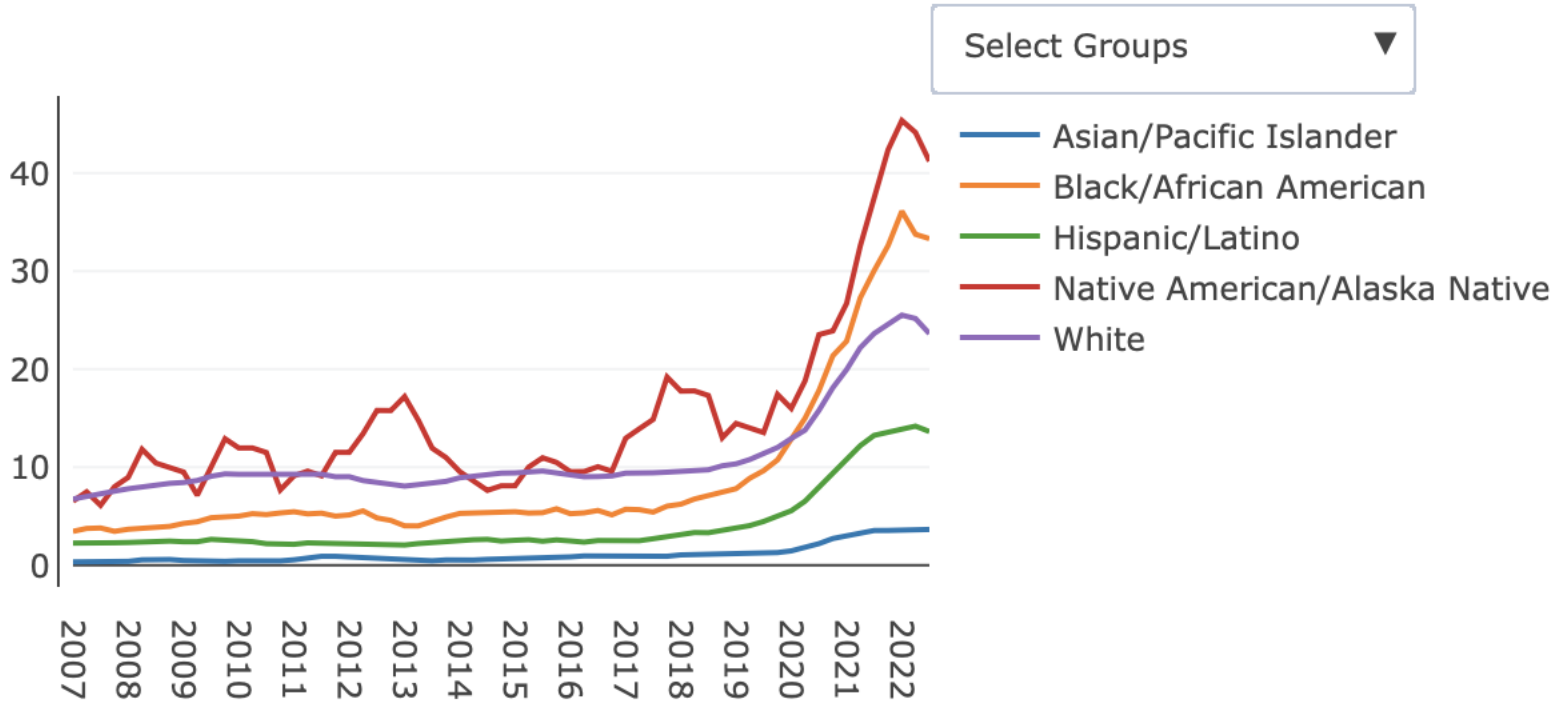


*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

Epidemiology

Demographic Breakdown

Any Opioid-Related Overdose Deaths by Race/Ethnicity, Crude Rate per 100,000 Residents



NIDA 2023; CDPH 2023

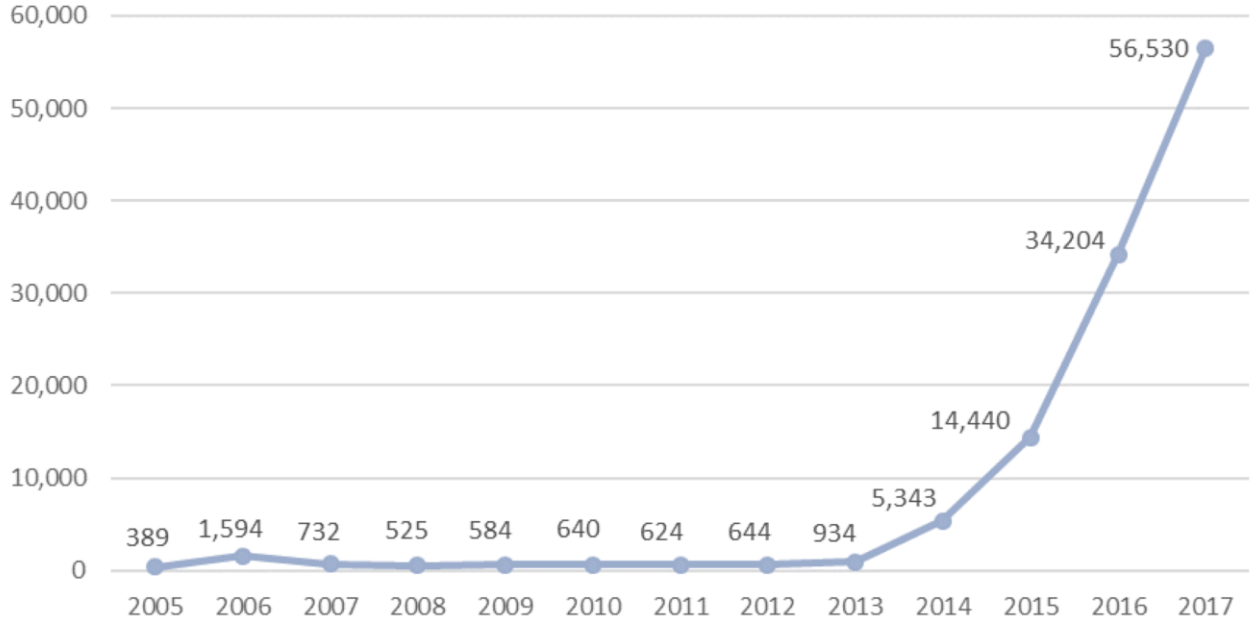
Epidemiology

More than 4.5 million fentanyl pills, 3,000 pounds of methamphetamine seized in Arizona investigation, DEA says

By Raja Razek, CNN

Published 7:00 PM EST, Sun February 26, 2023

Figure 2. Forensic Laboratory Reports of Fentanyl, 2005 – 2017



Source: DEA

DEA 2019; CNN 2023

Epidemiology

ELSEVIER

Drug and Alcohol Dependence

Volume 227, 1 October 2021, 109003

Transition from injecting opioids to smoking fentanyl in San Francisco, California

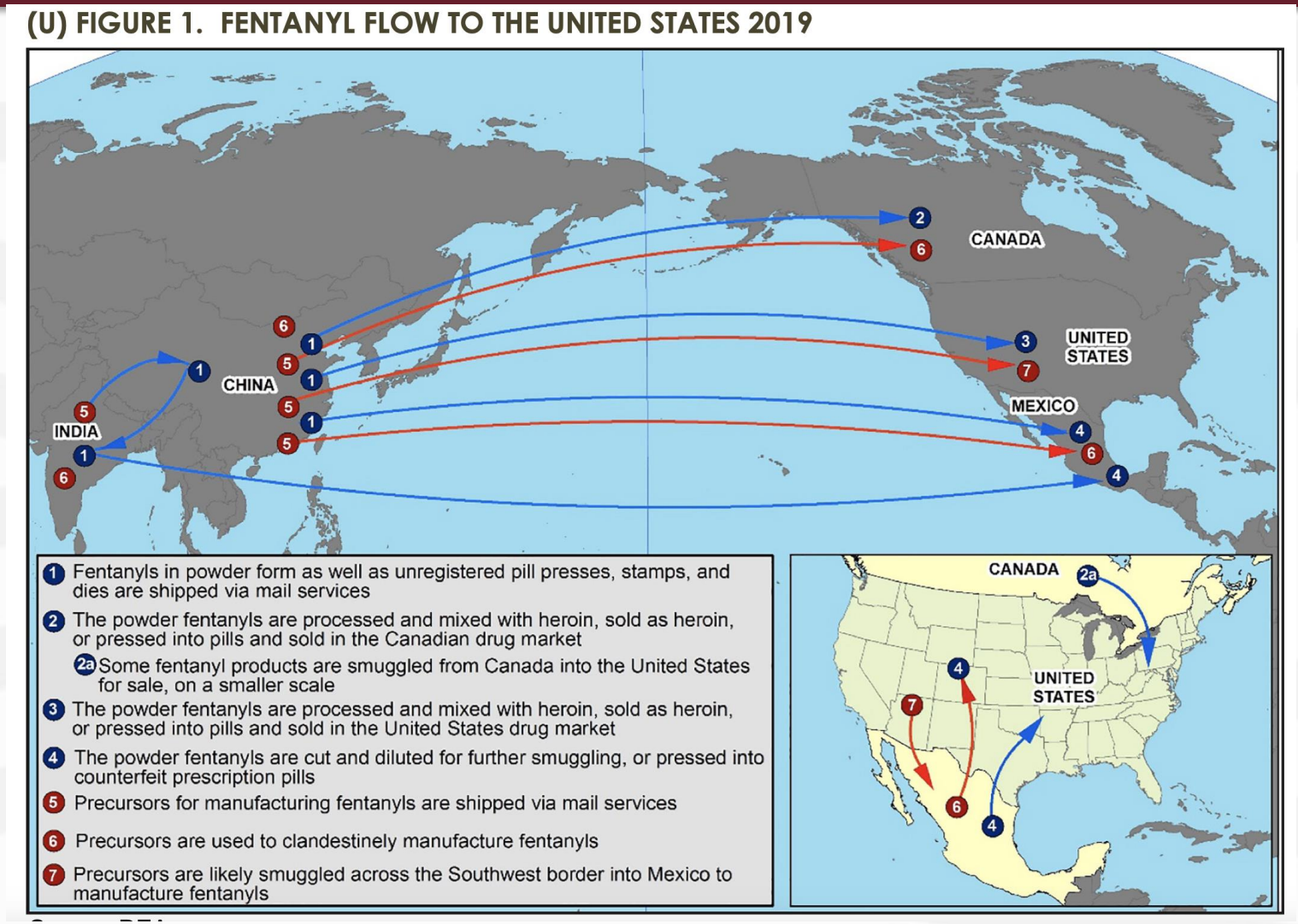
Alex H. Kral [a], Barrot H. Lambdin [a b c], Erica N. Browne [a], Lynn D. Wenger [a], Ricky N. Bluthenthal [d], Jon E. Zibbell [a], Peter J. Davidson [e]

Show more

- # of individuals injecting drugs decreased 2018-2020
- Among people who inject drugs that used fentanyl, # days smoke fentanyl went up
- Motivation for switch: difficulty finding veins
- After switching, better reported feeling of drug, improved health, reduced stigma

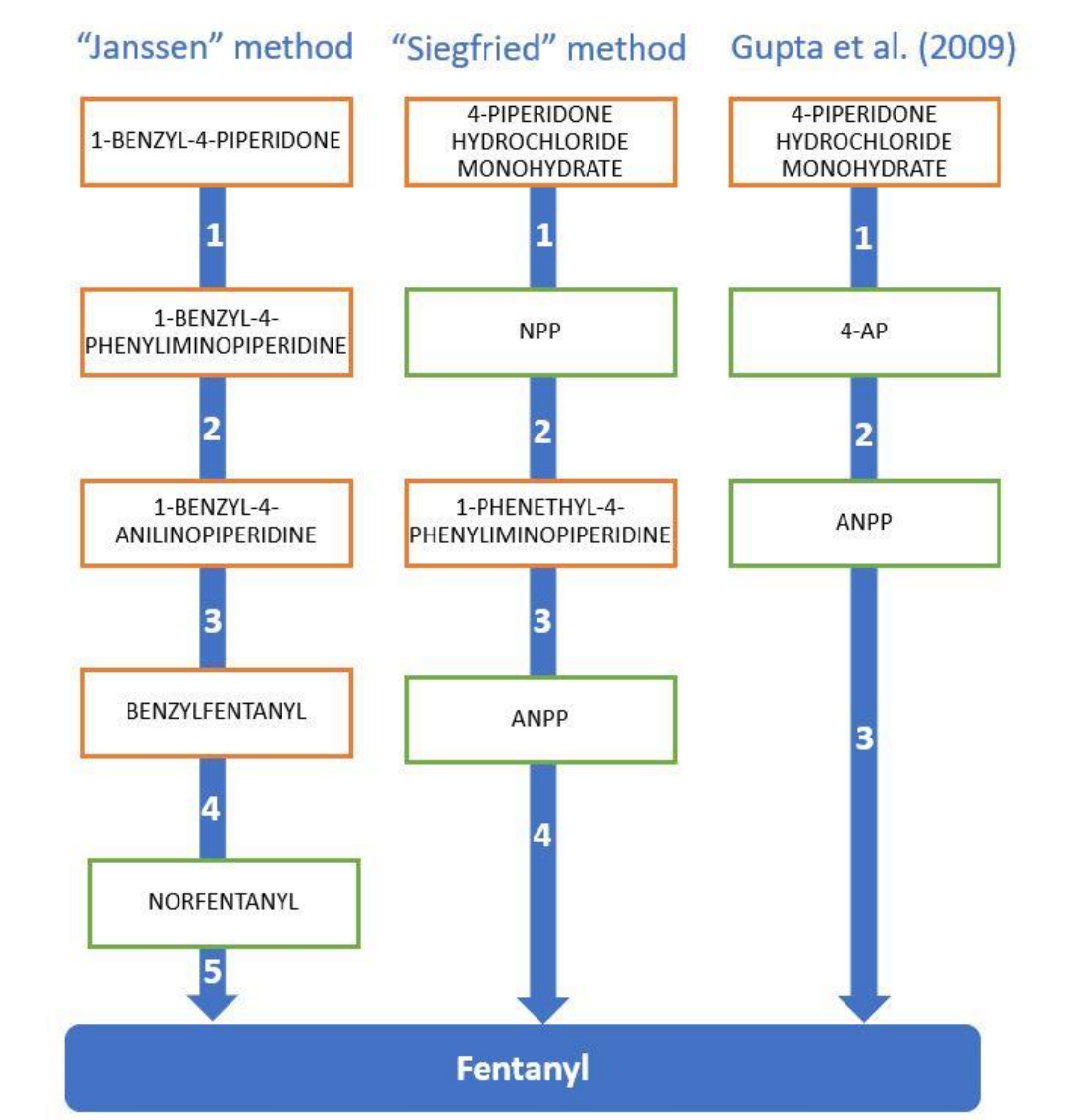
Kral 2021

Where does fentanyl come from?



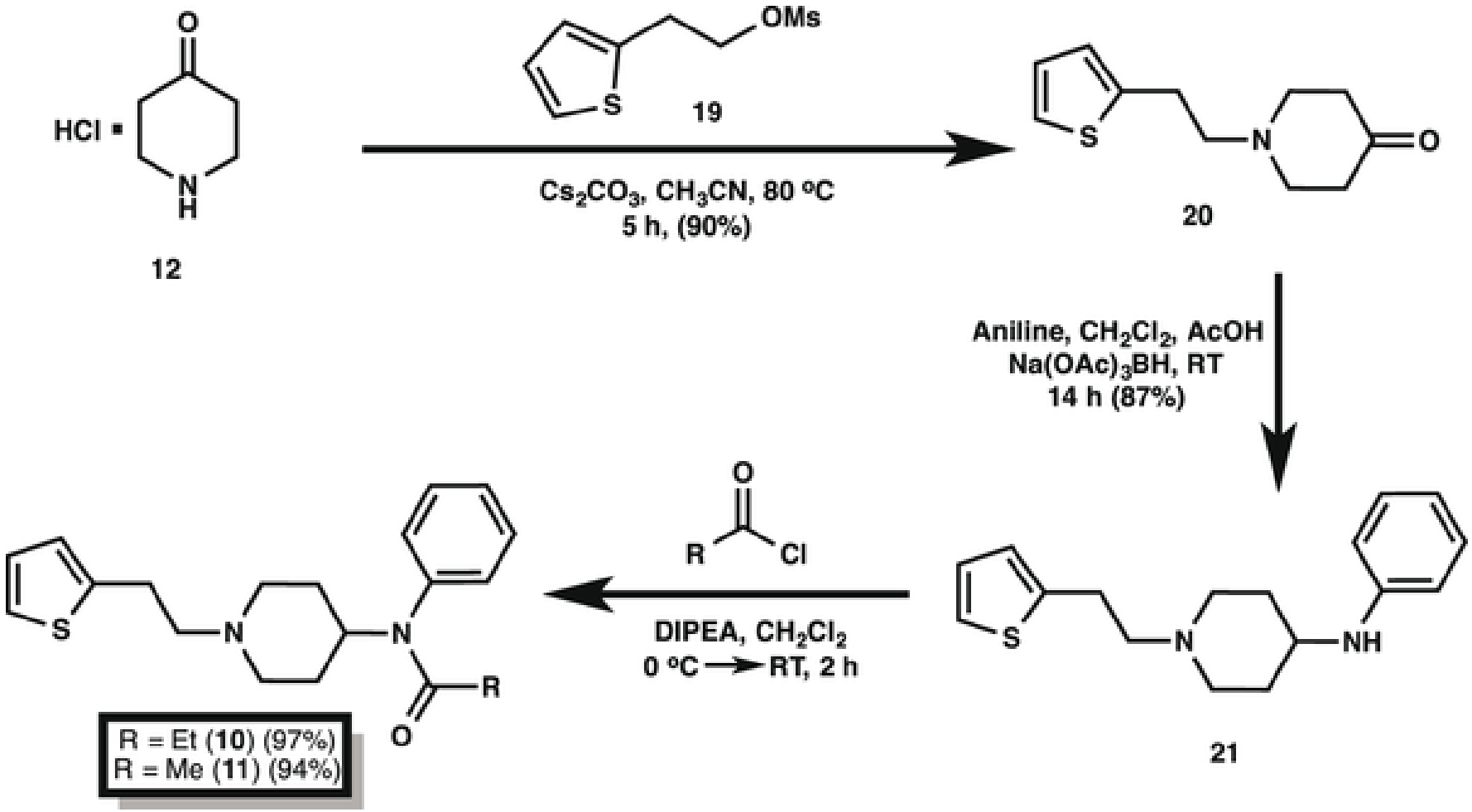
DEA 2020

How is fentanyl made?



UNODC 2022

Synthesis of Fentanyl.



Valdez 2014

Pharmacology

Bioavailability

- Oral → not so good (30-40% bioavailability—first pass metabolism CYP 3A)
- Transmucosal (50-76%), Intravenous (near 100%), Intranasal (60-90%), transdermal (92%), smoked/inhaled (unknown→?12-100%)

Times of onset

- Transmucosal (sublingual (5-10min), buccal (10-15min)), intravenous (1-2min), intranasal (5-10min), transdermal (8-16hrs)

Duration of action

- 2-4hrs (transmucosal, intravenous)
- 17hrs (transdermal, AFTER patch removal)—continues to elute from subcutaneous fat

Cyp3a4 (ritanovir, diltiazem, phenobarbital (inducer)) to norfentanyl (inactive)

Stanley 2014;
Lötsch 2013

Effects of Fentanyl/Advantages Over Other Opioids

Fatigue, sedation, nausea, vomiting, dizziness, respiratory depression (leading to apnea in higher doses), bradycardia (secondary to a central vagal stimulating action), and unconsciousness/anesthesia in higher doses irrespective of the mode of administration

High intrinsic efficacy (ability to produce a response once bound to the receptor) and so need to occupy only a small proportion of the available receptors to produce that response;

- This suggests that they are less likely to be affected by the loss of receptor function that underlies heroin tolerance and are able to 'break through' heroin-induced tolerance and produce respiratory depression even in heroin-tolerant individuals.

Advantages over morphine: rapid onset, less constipation, less histamine release and less venodilation, short duration of action

What is Different About Fentanyl?

Ability to orient uniquely at the receptor site/access alternative receptor binding sites

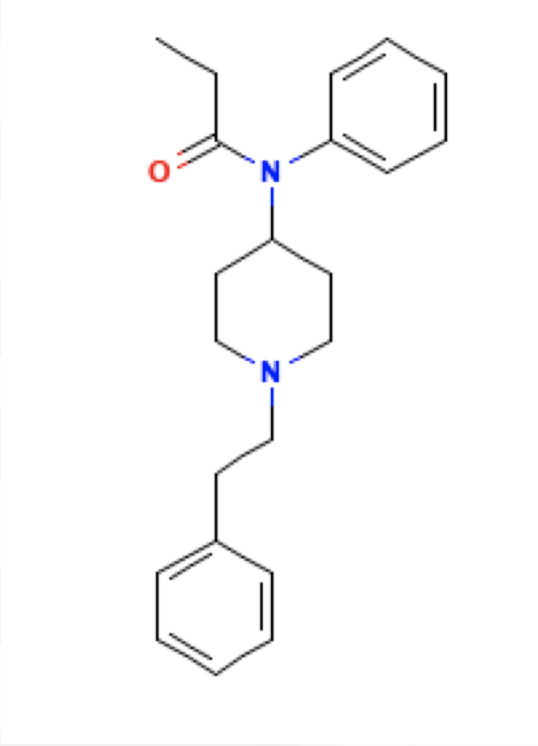
Respiratory depression

Respiratory muscle rigidity

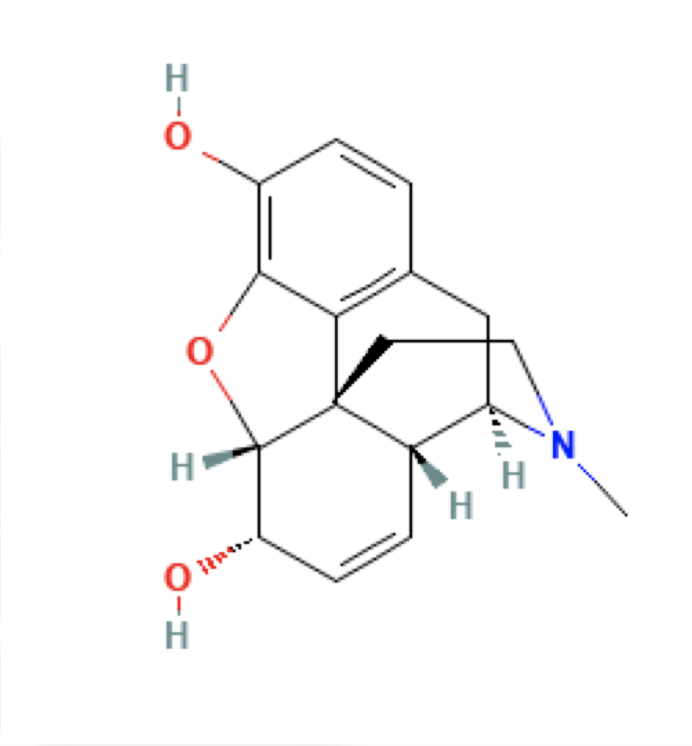
Lack of cross tolerance with other opioids

Reduced sensitivity to naloxone/antagonists

The Key → **Lipophilicity**

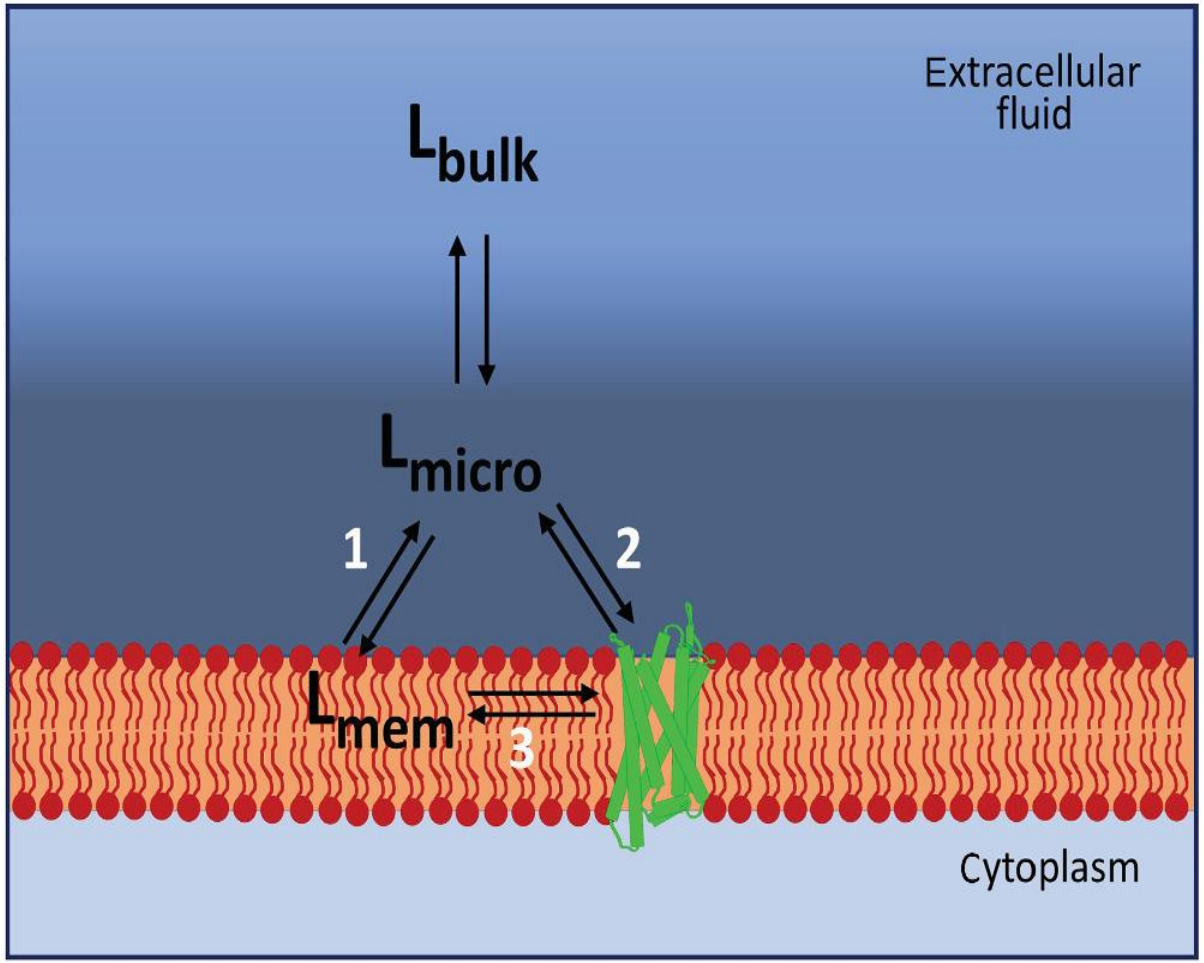


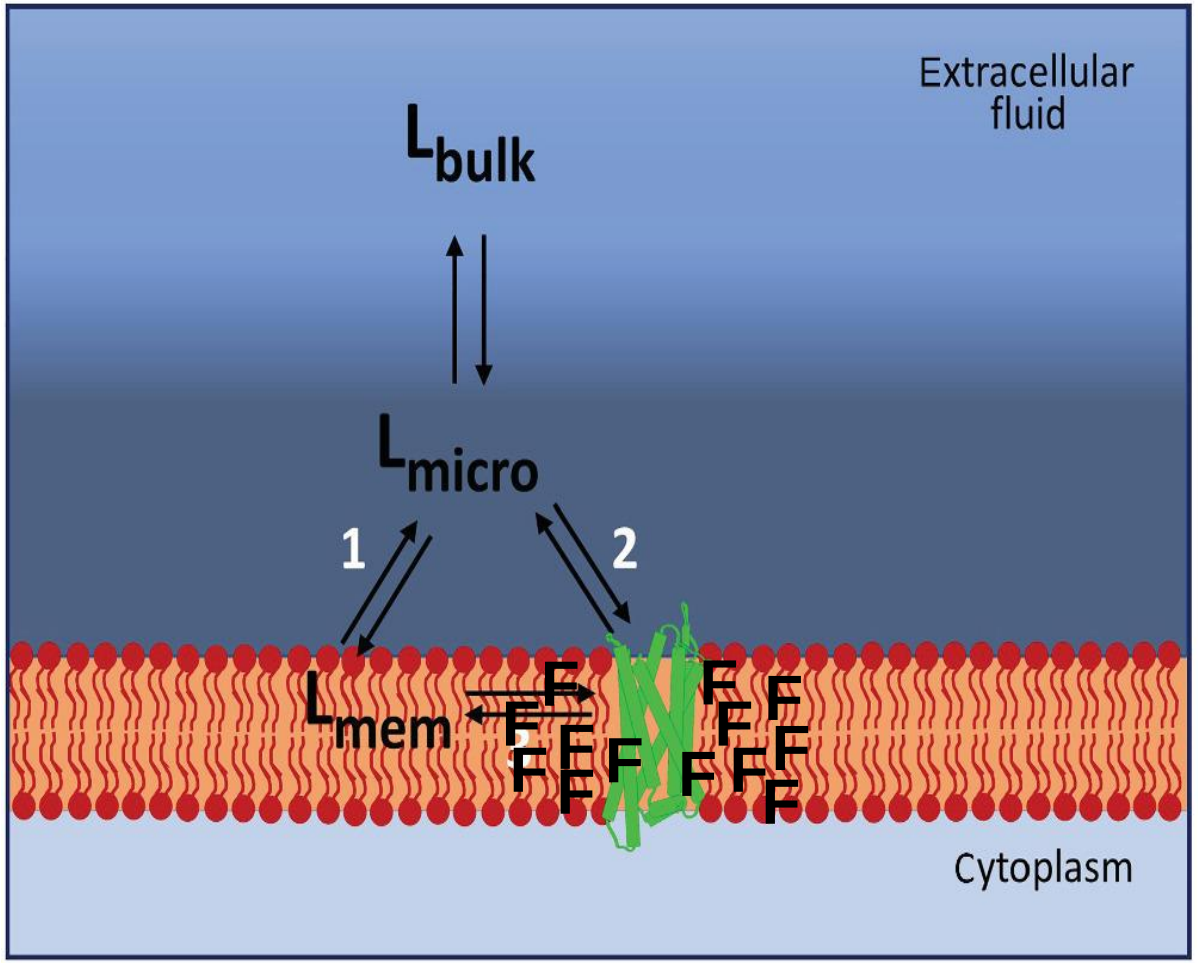
Fentanyl



Morphine

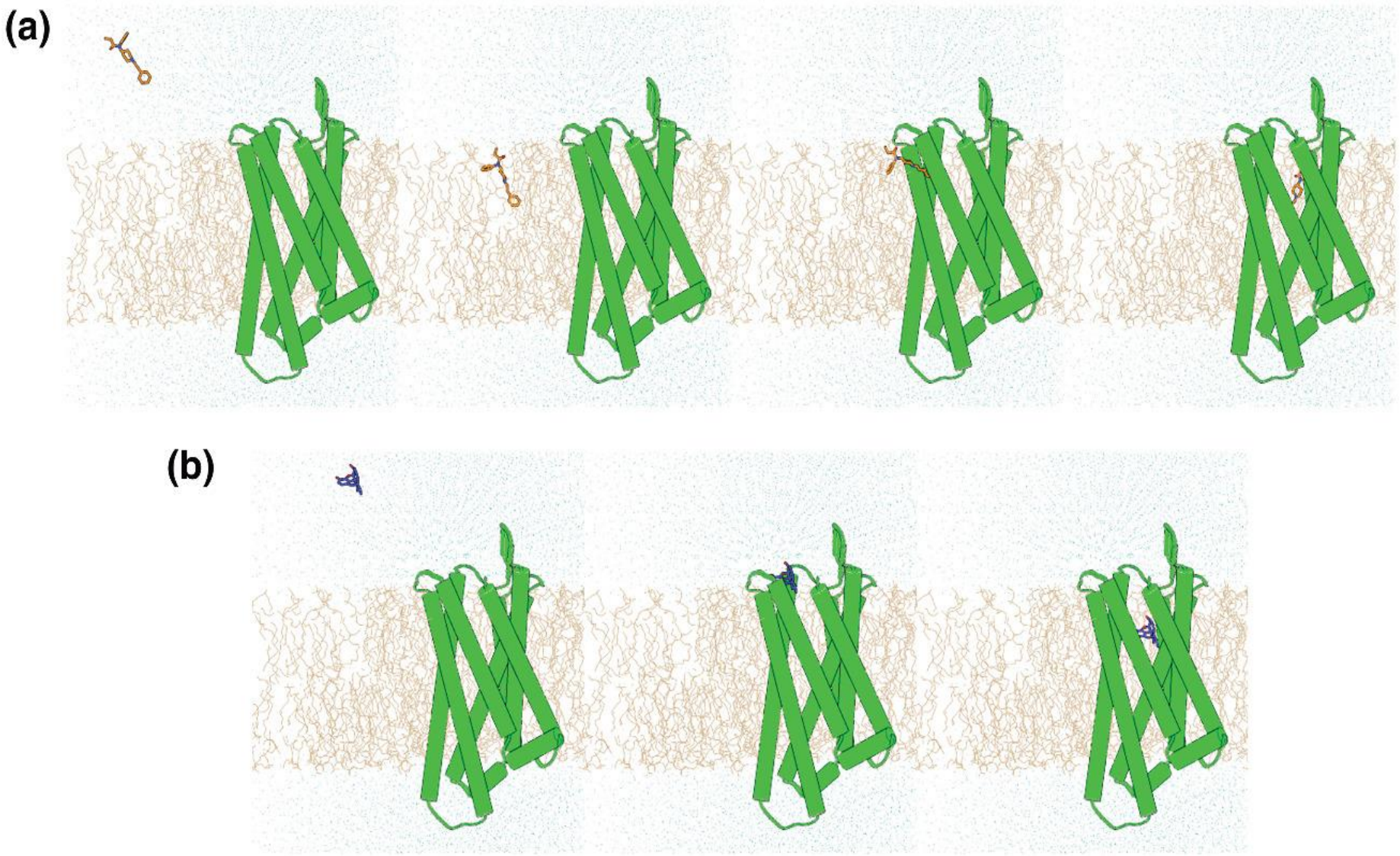
The anomalous pharmacology of fentanyl





British J Pharmacology, First published: 24 May 2021,
DOI: (10.1111/bph.15573)

The anomalous pharmacology of fentanyl



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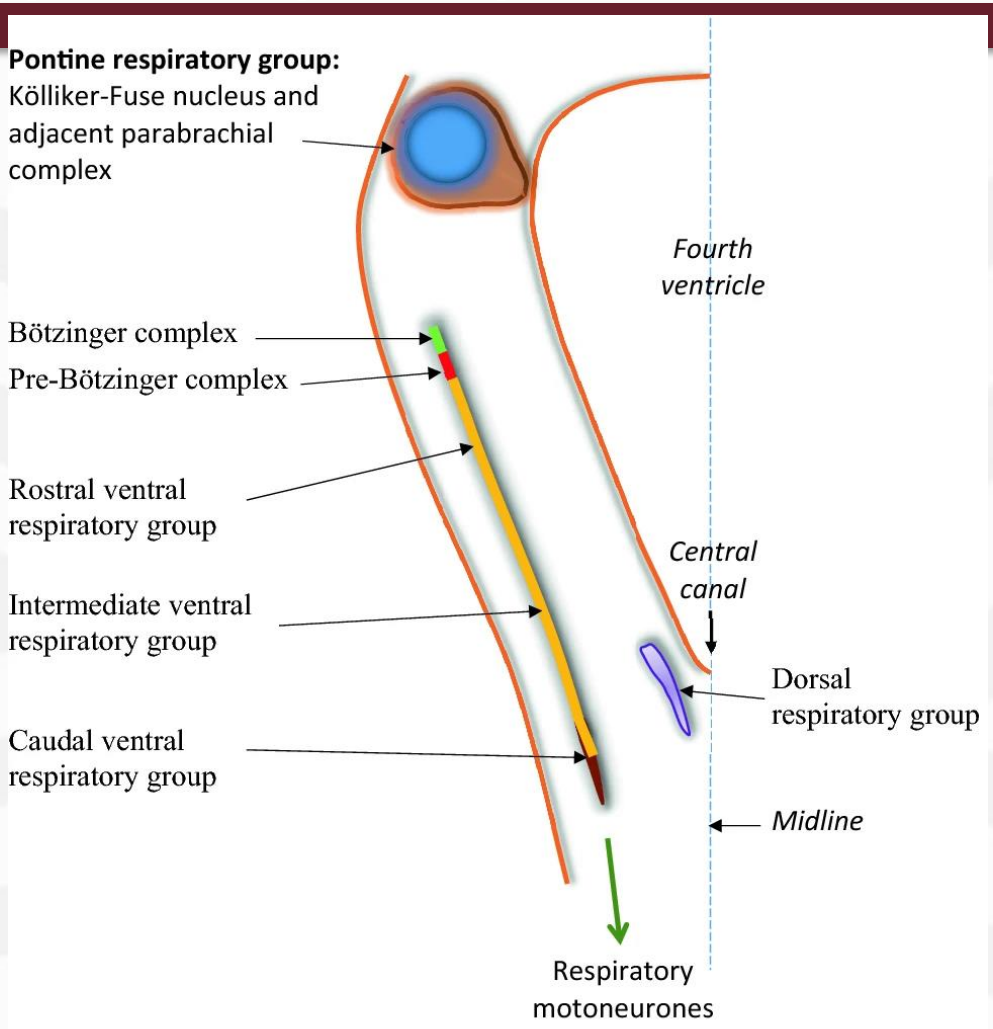
Respiratory Depression



Brainstem respiratory centres

Baldo 2022

Respiratory Depression

Heroin and other opioids depress respiration by acting on μ opioid receptors to reduce the response to raised partial pressure of carbon dioxide (pCO_2) and lowered partial pressure of oxygen (pO_2), and thus reduce the drive to breathe.

Deaths in heroin overdose → 30+ minutes to occur after injection

Fentanyl overdose deaths → <5 minutes, potentially before remedial action can be taken

- In a study of 48 overdoses in Ohio, norfentanyl, fentanyl's metabolite, was not detected at all in 42% of the cases. This potentially suggests that the individuals died too rapidly before any fentanyl could be metabolized to any appreciable degree

Differential development of respiratory depression tolerance vs. tolerance to euphoria

Gill 2019; Burns 2016; Hill 2016

Respiratory muscle rigidity/Vocal Cord Acute Closure

"Wooden Chest Syndrome" phenomenon→may contribute also to decreased response to naloxone

- 1-2min after IV infusion, 8-15min duration
- Dose administered, and speed of infusion are key

Can happen at serum levels lower than respiratory depression (in anesthesia, managed with paralytics—succinylcholine)

Why/How?

- Mu-opioid receptor agonism in the locus cerelues→noradrenergic surge from LC to spinal cord
- Mu-receptor mediated medullary cholinergic receptors (motor center that controls respiratory mechanics)

Opioid antagonists DO NOT address adrenergic and cholinergic systems involved in VCC/WCS

Torralva 2019; Burns 2016

Lack of Cross-Tolerance to Other Opioids

Question: Does prolonged heroin or other opioid use result in tolerance to respiratory depression caused by Fentanyl?

Answer: Not really

- Tolerance results from a reduction in number of functional mu-receptors, but since fentanyl has higher efficacy (needs to occupy fewer receptors) it offsets any decreases in number of mu-receptors

Reduced Sensitivity to Naloxone

- Two studies (2017; 2018) showed that EMS responders used more doses of naloxone per patient in 2015 relative to 2012 and 2016 relative to 2013, respectively
  - Advocates point to this as a need for higher doses of naloxone
  - BUT, does this represent actually availability bias? Higher prevalence of other co-consumed sedating drugs? (Xylazine etc.)
- Three other studies showed that the median dose of naloxone administered in successful reversals did not differ based on the presence or absence of naloxone
- Other studies have shown that regular doses of naloxone successfully reverse fentanyl overdoses

Hill 2022

Reduced Sensitivity to Naloxone

Not just a matter of affinity at the receptor—that is governed by equilibrium

- This suggests that there is a **non-equilibrium-mediated i**nteraction between naloxone and fentanyl at the mu-receptor
  - Wooden Chest Syndrome and Vocal Cord Closure??

Higher doses of Narcan?—risk of pulmonary edema and catecholamine surge, and concerns about fear of worse withdrawal

Britch 2022
Hill 2022

Naloxone implications

What is key is the **time** to administration, not so much the dose itself

- With fentanyl, need to be able to administer naloxone within a few minutes

Other strategies

- Longer acting antagonists? (nalmefene→8-11hrs)
- Buprenorphine?
- Respiratory stimulants? (NMDA receptor antagonists→esketamine?)
- Wearable devices? (Purdue Univ→subcutaneous device detects respiratory depression via ECG, then magnetically releases naloxone)

Britch 2022

Just Use Test Strips?

https://www.otisspunkmeyer.com/fundraising/chocolate-chip-cookie

Buprenorphine implications

Two areas of concern:

- 1) Precipitated Withdrawal when starting someone on buprenorphine
- 2) Will buprenorphine “Hold” an individual (reduce cravings)

1) Due to high lipophilicity, an individual may be continuing to elute fentanyl from fat stores after the anticipated half life has passed, increasing the chance of precipitating withdrawal

- Precipitated withdrawal can be mitigated by:
  - A) waiting for longer times and providing adjunctive medications
  - B) administering more buprenorphine if withdrawal occurs

Buprenorphine implications

2) Possible that fentanyl will have desensitized mu-receptors to an extent greater than anticipated, due to its high efficacy

- To better match opioid balance, perhaps either:
  - A) Need to wait longer for steady state levels to achieve reduction in cravings
  - B) Higher doses of buprenorphine may be needed

Inadvertent Exposure OD?

Lots of concerns about inadvertent exposure to fentanyl leading to unintentional overdose situations

- DEA published a video on this
- San Diego Sheriff's Department posted a video as well
- Most of these have been debunked

Inadvertent Exposure OD?

Airborne?

- At the highest airborne concentration encountered by workers, an unprotected individual would require nearly **200 min of exposure** to reach a dose of 100 mcg of fentanyl.

Transdermal?

- Recall: up to 18 hours for transdermal patch (with a formulation of fentanyl designed to enhance TD absorption)
  - Like putting tobacco leaf on your arm vs. a nicotine patch
- If bilateral palmar surfaces were covered with fentanyl patches, it would take approximately 14 min to receive 100 mcg of fentanyl

American College of Medical Toxicology (ACMT) and American Academy of Clinical Toxicology (AACT) Position Statement:

- Nitrile gloves sufficient; coveralls if very heavy contamination
- Splash guard if working with liquids
- N95 if heavy contamination (“exceptional situations)
- Wash with water, not with hand sanitizer
- Know signs of OD, use naloxone if needed

Moss 2017

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Pharmacology

- Chest wall rigidity (usually only after IV)—Stanley
- Tolerance issues: tolerance develops more slowly for respiratory depression
- Test strips
- Time window to respiratory depression is key: 2-5min after IV administration, 2-3hrs thereafter (Suzuki)
- Rapidly taken into cells and tissues, so plasma levels drop fast
- Cyp3a4 (ritanovir, diltiazem, phenobarbital (inducer)) to norfentanyl (inactive)

Stanley 2014