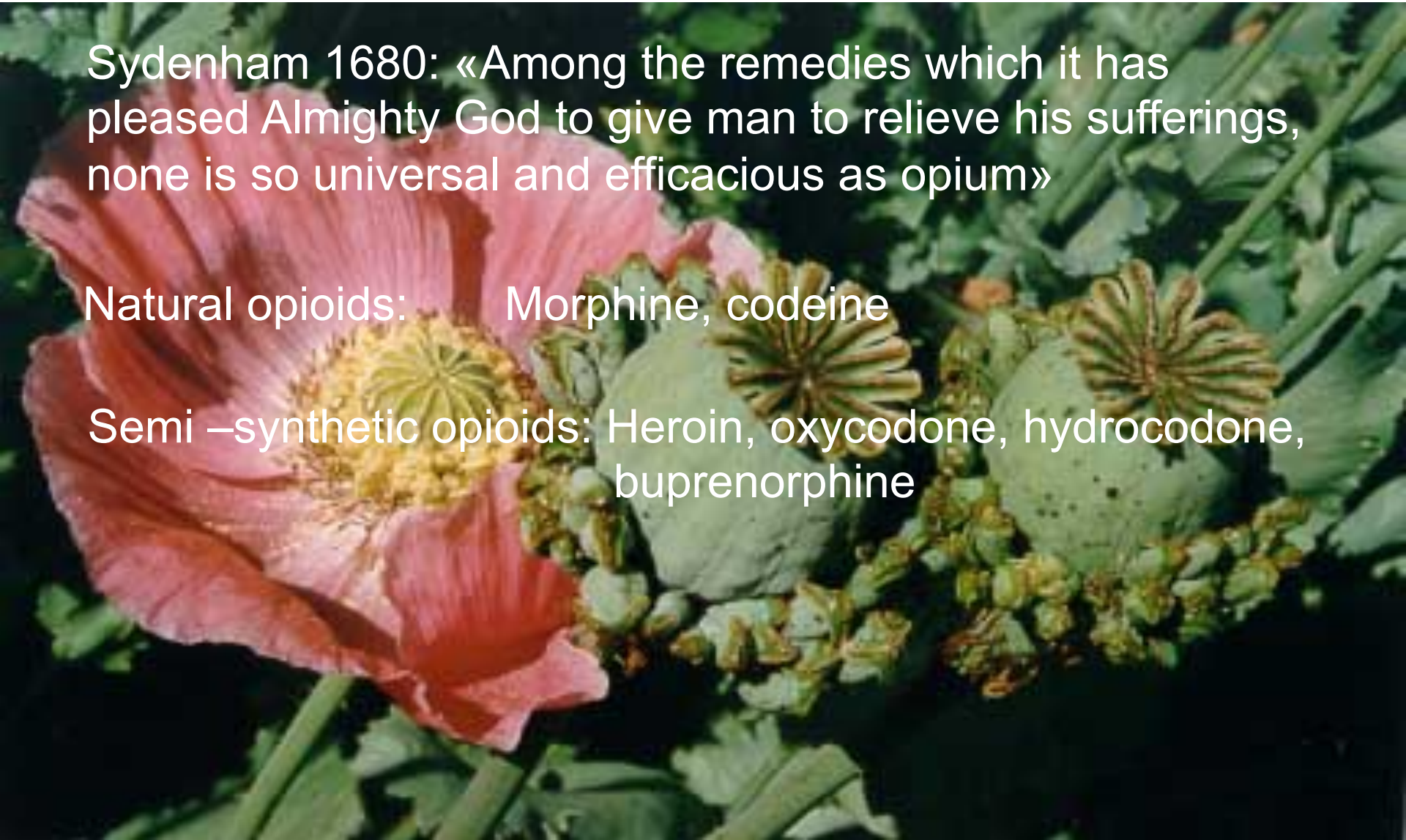
Clinical pharmacological aspects of heroin and fentanyl overdoses

Ola Dale
Professor
Norwegian University of Technology of Science
St. Olav's University Hospital, Trondheim, Norway

Opioids



Sydenham 1680: «Among the remedies which it has pleased Almighty God to give man to relieve his sufferings, none is so universal and efficacious as opium»

Natural opioids: Morphine, codeine

Semi –synthetic opioids: Heroin, oxycodone, hydrocodone, buprenorphine

The synthetic opioids :

- morphinan derivatives (levorphanol, butorphanol),
- diphenylheptane derivatives (**methadone**, propoxyphene),
- benzomorphan derivatives (pentazocine, phenazocine)

- **phenylpiperidine derivatives** (pethidine, alfentanil, **fentanyl,** sufentanil and remifentanil)

Opioids

Natural and synthetic compounds with the same pharmacological characteristics as morphine:

analgesia

respiratory depression

potential for abuse - euphoria

Opioids: mechanism of action

They act through the μ-opioid receptor

Over-all opioids are inhibitory

They calm things down

Overdose symptoms

Respiratory depression/failure

Sedation/unconsciousness

Pupillary constriction- pin-point pupils

Heroin

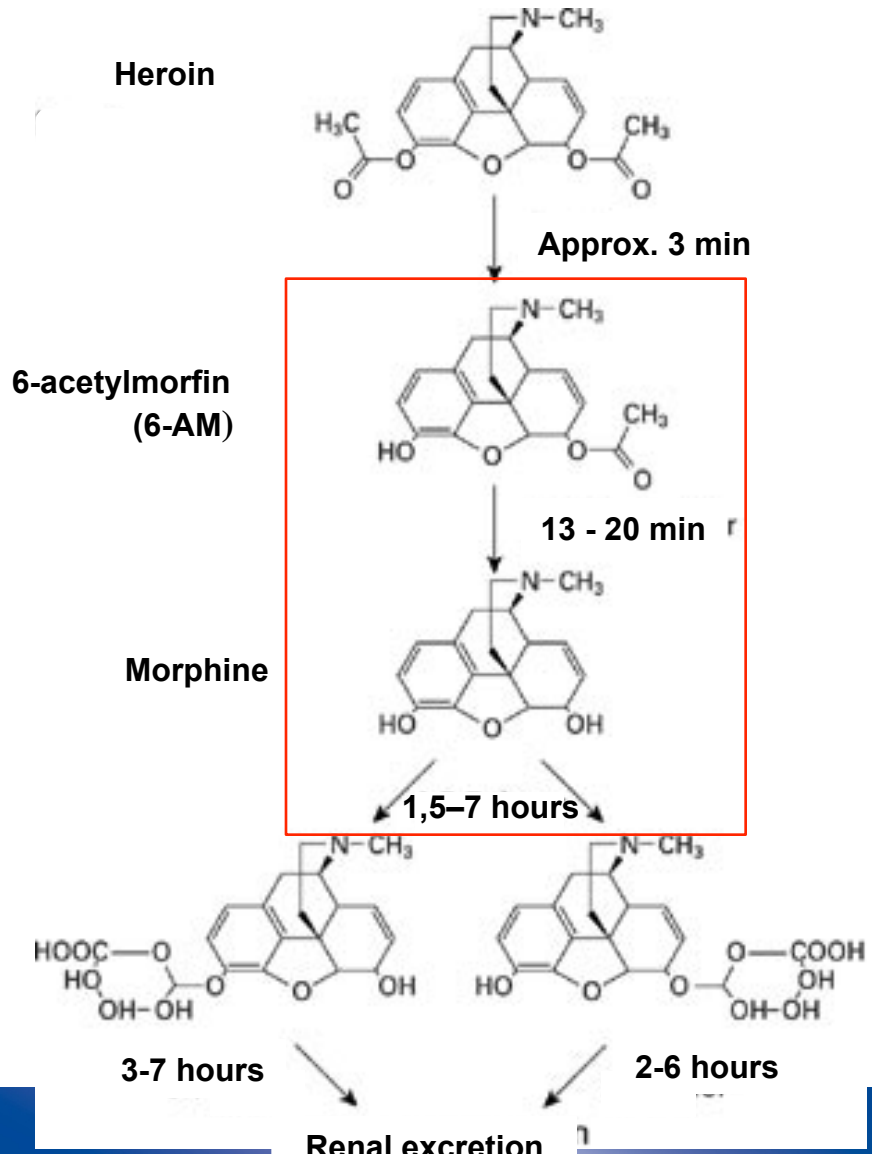
1874: Synthesized for the first time from morphine

1895: Bayer marketed heroin as a ***non-addictive*** morphine substitute and cough suppressant

Today:

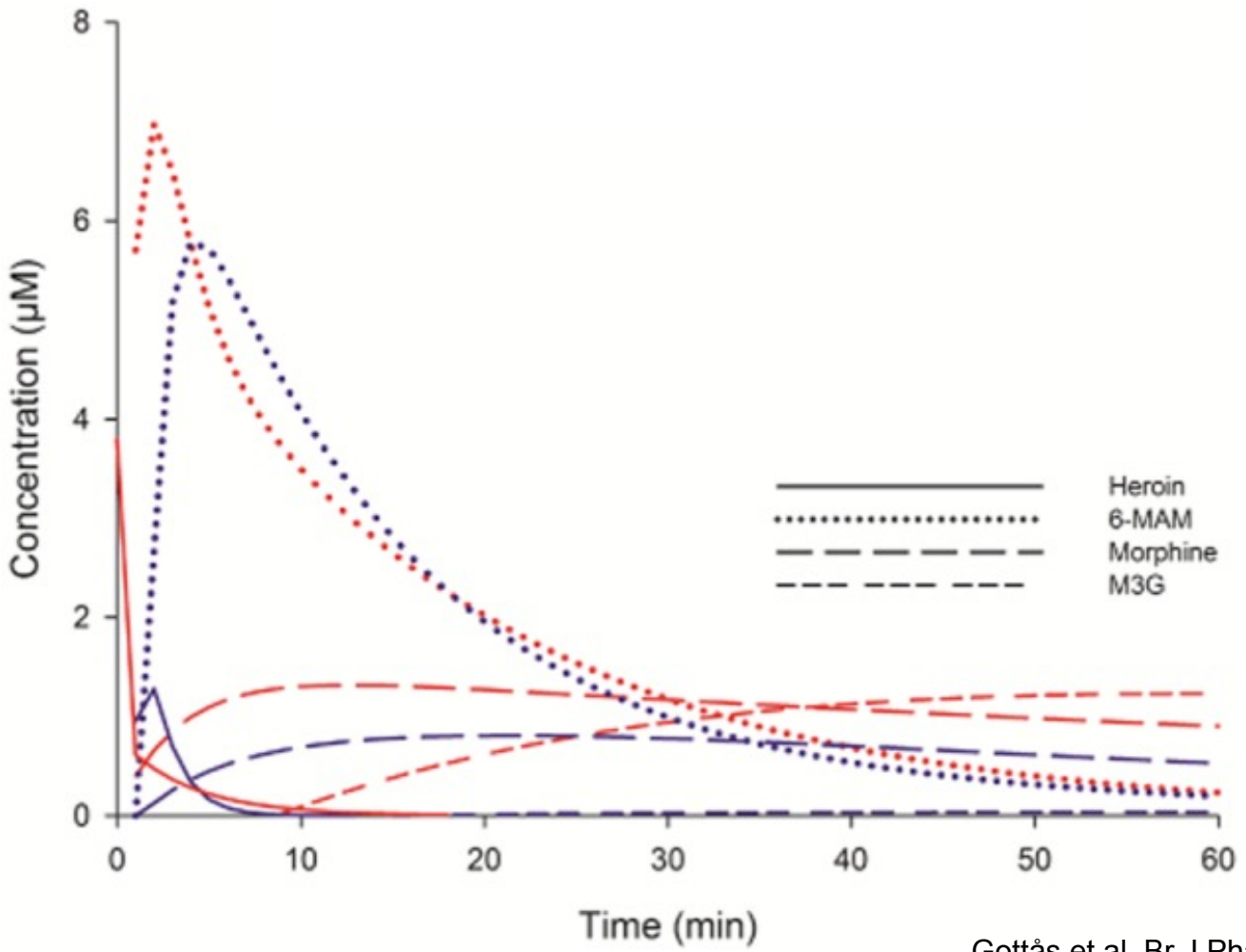
- Illicit recreational drug
- Used as an analgesic and in treatment of opioid addiction (diamorphine) in some countries

Heroin is a prodrug

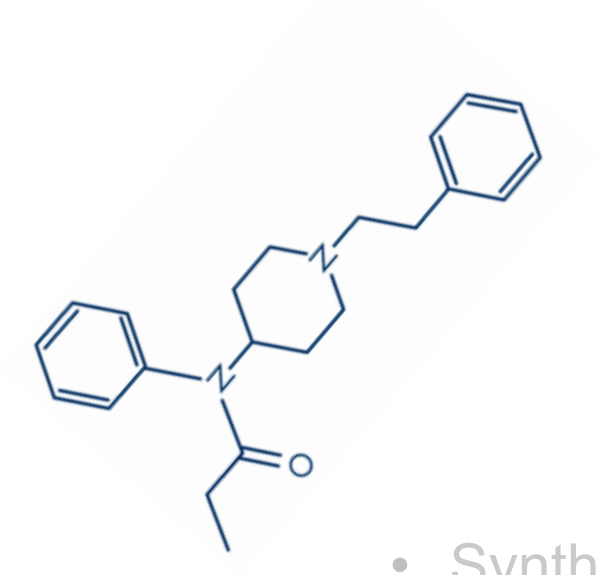


Rook et al. Basic &Clinical Pharmacol & Toxicol 2006;98:86-96

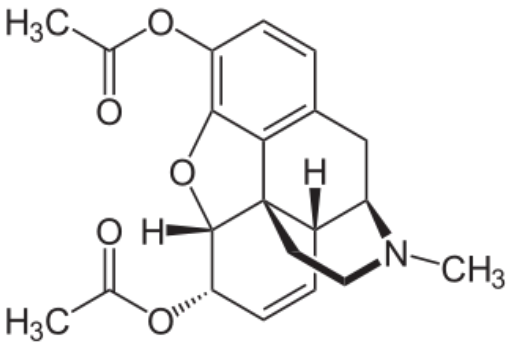
Brain uptake of heroin and metabolites in rat



Gottås et al. Br J Pharmacol 2013; 170: 546-56



Fentanyl



- Synthesized by Janssen in 1959
- Under international control in 1964
- Extensively used in anesthesia and for pain control
- Potency:
  - 50-100 times x morphine
  - 25-50 times x heroin
- Passes mucosal membranes easily
- Short duration of action of single doses
- Duration of action increases with multiple/large doses
- Patch

Fentanyl congeners/derivates/analogues Human and animal use

Human use

Alfentanil

Sufentanil

Remifentanil

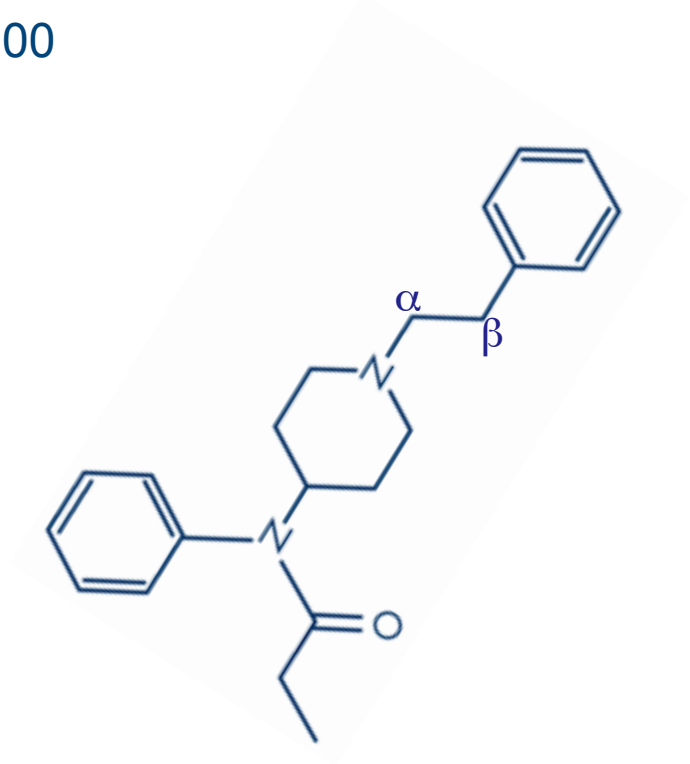
Animal use

Carfentanil

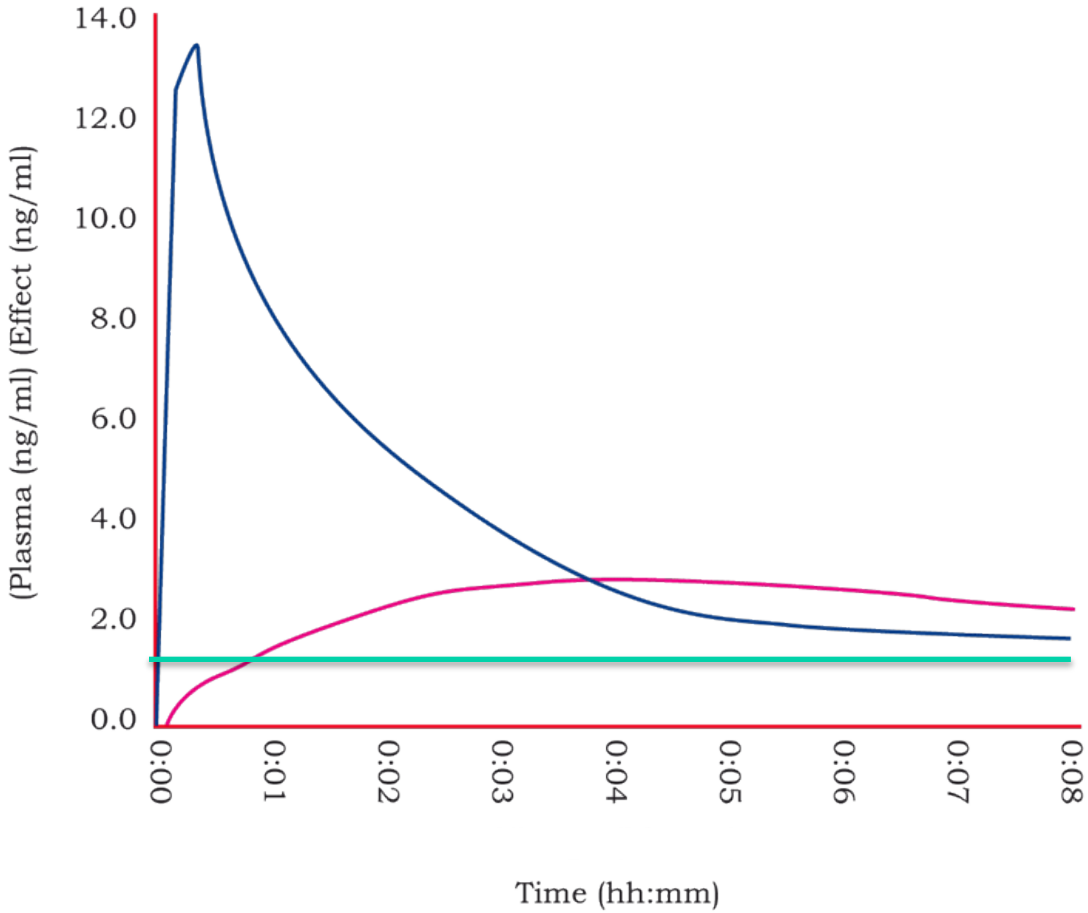
Fentanyl analogues non-pharmaceutical fentanyls (NPF)

Acetyl-alphamethyl-fentanyl, Alpha-methylfentanyl, Alpha-methylthiofentanyl, Beta-hydroxyfentanyl, Beta-hydroxy-3 methylfentanyl, 3-methylfentanyl, 3-methylthio-fentanyl, Para-fluoro-fentanyl, Thiofentanyl….

+++++ >200



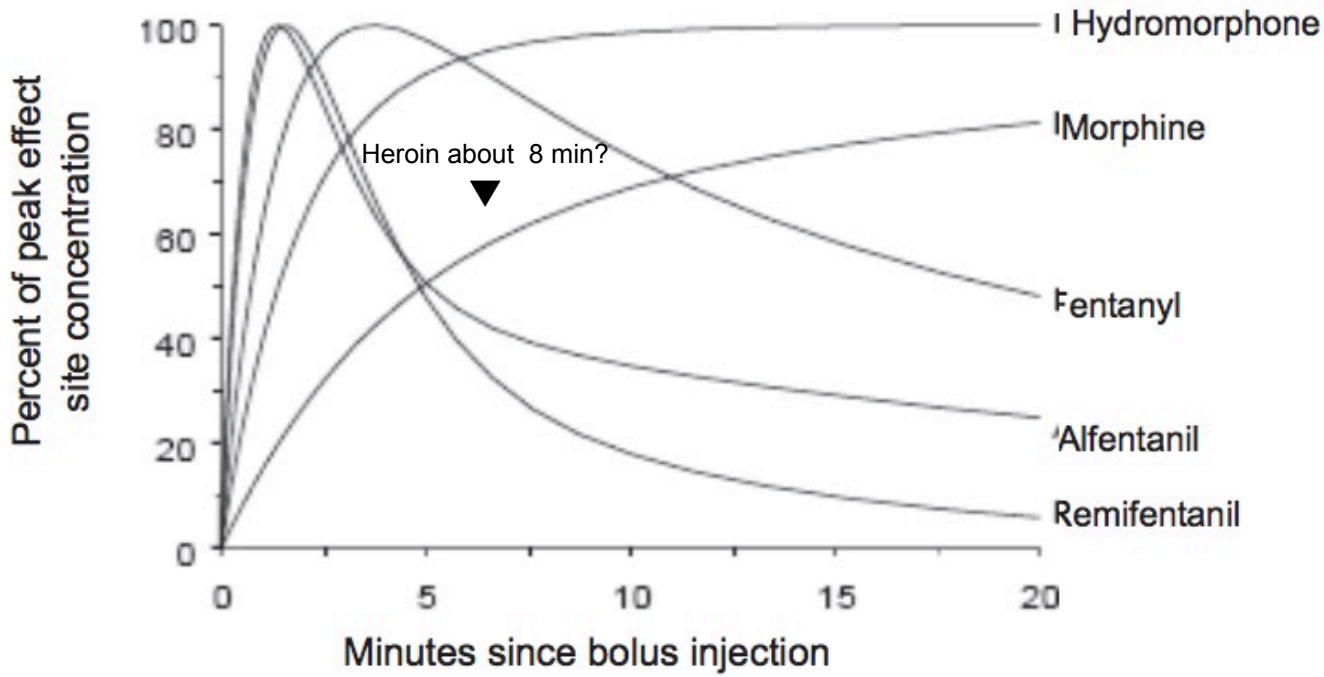
Fentanyl IV injection



Tafur LA et al. Rev Col Anesth 2010; 38: 68-83

Comparison of Peak Effect Times

Onset and duration of action of each opioid depend on their lipid solubility and ionization



https://gas.careteamapp.com/OpioidQuestions

Characteristics of some opioids

	Relative potency (estimates)	Time to max effect (min)	Elimination half-life (h)
Heroin- 6-AM	5	8 ?	0.3
Morphine	1	19	3.2
Fentanyl	100	4.2	7.9
Sufentanil	>500	4.2	9.4
Alfentanil	25	1.8	1.9
Remifentanil	200	1.8	0.06
Carfentanil	>10.000	?	7.5?

Column 1: Various sources
Column 2, 3 (- carfentanil): Evers, Maze and Kharasch. Anesthetic Pharmacology ed 2, Cambridge University Press 2011

Fentalog overdoses
Chest wall rigidity- stiff or wooden chest

Chest wall rigidity:

- Depends on dose and speed of injection
- Can occur or recur up to several hours after intake (fda.gov)
- Makes rescue-assisted ventilation very difficult
- Needs to be recognized early
- Reversed by naloxone
- Significant factor in rapid death from fentanyl abuse?

Modified from Guro Søe Eriksen

Fentalogs and serotonin syndrome

Potentially life-threatening

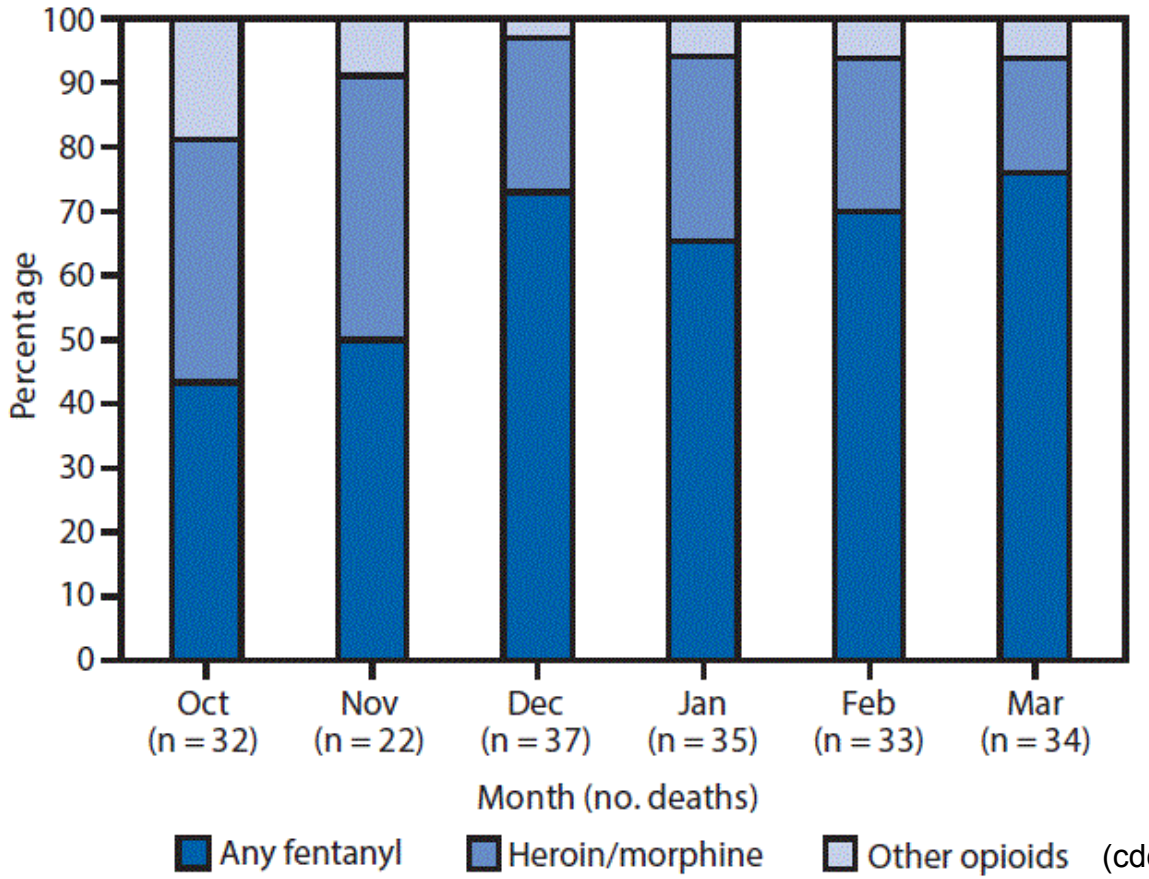
Reported after concomitant intake of fentanyl and serotonergic drugs, e.g. antidepressants

Symptom clusters:

- Altered mental status (e.g. agitation, hallucinations, coma)
- Autonomic hyperactivity (e.g. tachycardia, hyperthermia)
- Neuromuscular abnormalities (e.g. rigidity)

Onset of symptoms usually occurs hours to a few days after intake

Bar chart showing the percentage of opioid overdose deaths involving fentanyl, heroin/morphine (without fentanyl), and other opioids (without fentanyl, heroin/morphine) in three counties, Massachusetts, October 2014–March 2015



(cdc.gov, Weekly/April 14, 2017)

Fentalog overdoses
Atypical signs

Atypical signs: (cdc.gov, Weekly/April 14, 2017)

- Immediate discoloration of lips
- Gurgling sounds
- Stiffening of the body or seizure-like activity
- Foaming at the mouth
- Confusion or strange affect

Modified from Guro Søe Eriksen

Heroin, fentanyl and carfentanil

Source: U.S. Drug Enforcement Administration

Accidental Exposure?

The Viral Story About the Cop Who Overdosed by Touching Fentanyl Is Nonsense

The terrifying tale has been reported as fact, but toxicologists doubt that it is medically possible.

8.9k 40

By Jeremy Samuel Faust

Fentanyl cannot cause clinically significant effects, let alone near-death experiences, from mere skin exposure.

Barry Logan, Fentalogs: Pharmacology, Toxicology & Analytics - Archiva NMS lab Webinars

Summary of main points

- Heroin and fentalogs act trough mu-opioid receptor- reversal by naloxone
- Heroin effects mediated by 6-AM and morphine
- Fentalogs are in general more, some extremely more, potent than heroin
- Fentalogs in general displays a shorter time to maximum effect than heroin
- Unknown whether fentalogs intrinsically cause more rapid and profound respiratory depression than heroin.
- Heroin and fentalog overdoses are often indistinguishable
- Fentalogs can cause chest wall rigidity that can be reversed by naloxone.
- Fentalogs may induce serotonin syndrome
- Quick administration/ re-administrations often necessary after fentalog intake.

Modified from Guro Søe Eriksen, with permission

Thank you for your attention