Faculty
of Science

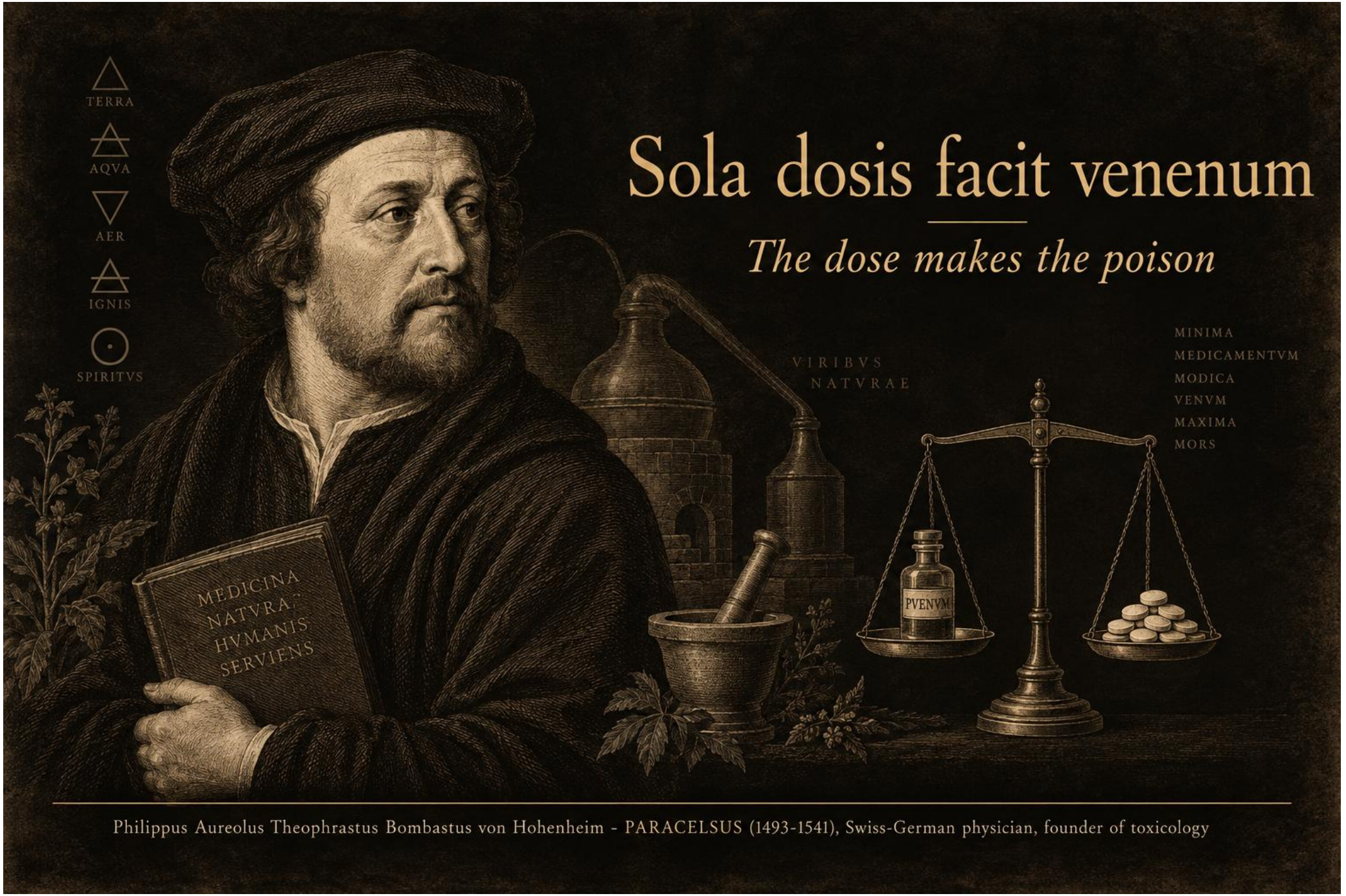
Palacký University
Olomouc

Department of Cell
Biology and Genetics

TOXICOLOGY

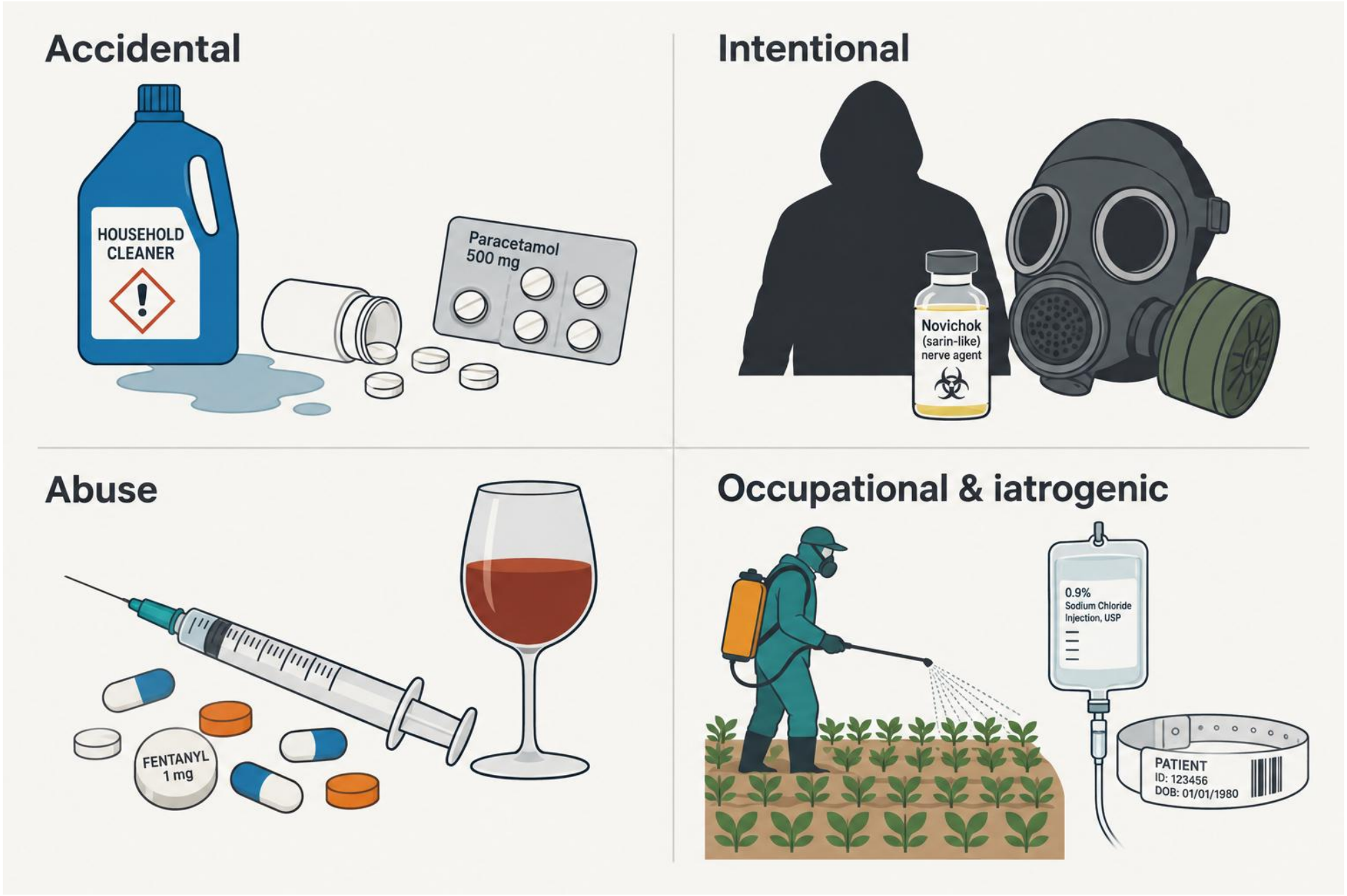
Intoxications: Symptoms & Therapy

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Department of Cell Biology & Genetics | Faculty of Science, Palacký University Olomouc
Follow-up MSc programme in Molecular and Cellular Biology



Philippus Aureolus Theophrastus Bombastus von Hohenheim - PARACELSUS (1493-1541), Swiss-German physician, founder of toxicology

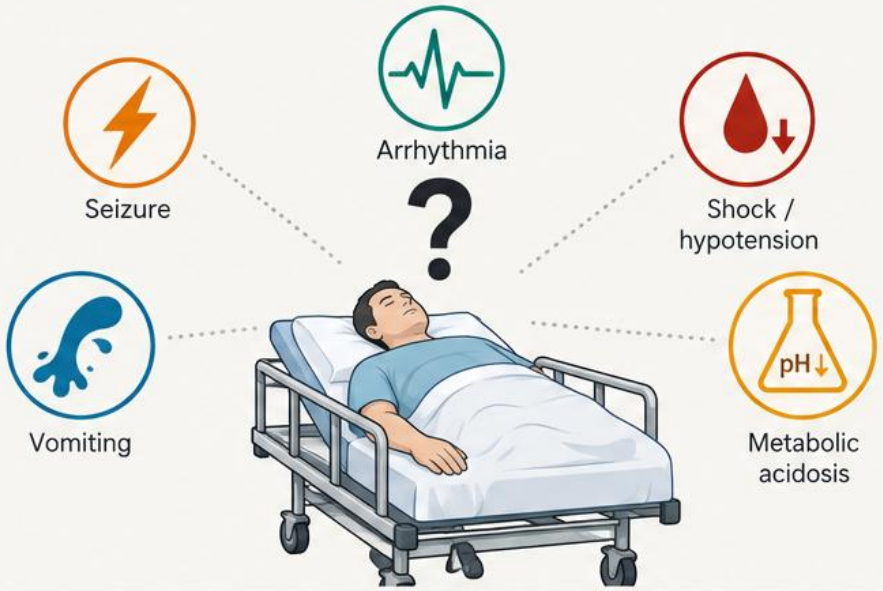
Classification of intoxications



Diagnosis

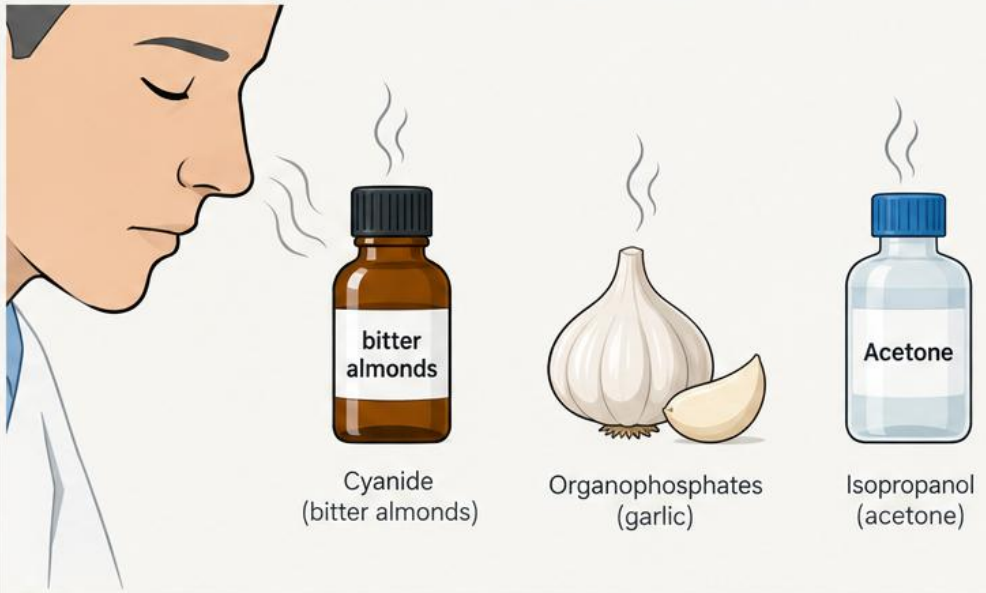
Non-specific presentation

Acute poisoning can mimic many conditions



Odours

Characteristic odours can suggest specific toxins



Cyanide (bitter almonds)

Organophosphates (garlic)

Isopropanol (acetone)

Skin signs

Skin appearance can provide important clues



Cyanosis
(e.g. methaemoglobinaemia)

Cherry-red skin
(carbon monoxide)

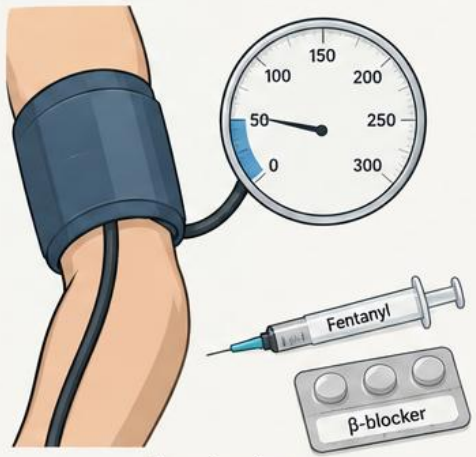
Drug-related rashes may also occur

Blood pressure

Toxins can cause hypertension or hypotension



Hypertension
(e.g. adrenaline, amphetamines)



Hypotension
(e.g. fentanyl, beta-blockers)

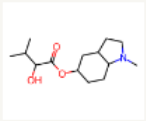
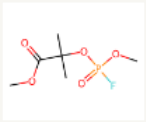
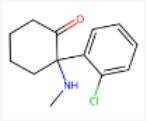
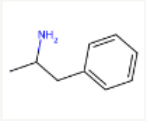
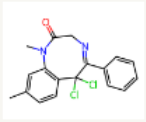
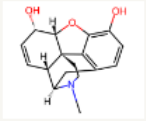
Symptoms I - heart rate, arrhythmia, mucosa, respiration

- **Bradycardia:** digitalis, beta-blockers, Ca-channel blockers, organophosphates
- **Tachycardia:** sympathomimetics, amphetamine, TCAs, cocaine, alcohol, anticholinergics
- **Arrhythmia:** TCAs (QRS widening - sodium-channel block), digitalis (Na/K-ATPase), cocaine
- **Mucosa:** dry = anticholinergics; hypersalivation = organophosphates, carbamates; lesions = acids, alkaline hydroxides
- **Respiration - depression:** alcohol, opioids, barbiturates, sedatives
- **Tachypnoea:** salicylates (hyperventilation), CO; Kussmaul breathing = salicylates, methanol, ethylene glycol (metabolic acidosis)
- **Pulmonary oedema:** organophosphates (bronchorrhoea); non-cardiogenic = salicylates, opioids; pneumonitis = hydrocarbons, kerosene

Symptoms II - CNS and gastrointestinal tract

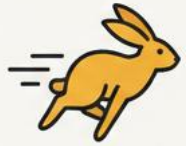
- **Seizures:** TCAs, cocaine, amphetamines, salicylates, organophosphates, isoniazid, alcohol withdrawal
- **Miosis:** opioids, phenothiazines, barbiturates, organophosphates, clonidine
- **Mydriasis:** anticholinergics, sympathomimetics, cocaine, TCAs, LSD, methanol
- **Nystagmus:** barbiturates, carbamazepine, alcohol, phenytoin (hydantoins)
- **Delirium/psychosis:** anticholinergics, sympathomimetics, alcohol, LSD, cocaine, heavy metals
- **Coma:** alcohols, anticholinergics, opioids, sedatives, hypnotics, CO, salicylates
- **Faintness/paralysis:** organophosphates, carbamates, heavy metals, botulism
- **GIT - diarrhoea, vomiting:** iron, phosphorus, heavy metals, lithium, mushrooms, organophosphates

Toxidromes - toxic + syndrome (empiric diagnosis at the bedside)

Toxidrome	BP	HR	RR	Temp	Pupils	Bowel sounds	Sweating	Examples
Anticholinergic	~	↑	~	↑	↑ mydriasis	↓	↓	 atropine, antihistamines, TCAs
Cholinergic (OP)	~	~	~	~	↓ miosis	↑	↑	 organophosphates, carbamates
Hallucinogenic	↑	↑	↑	~	↑	↑	~	 LSD, ketamine
Sympathomimetic	↑	↑	↑	↑	↑	↑	↑	 cocaine, amphetamine, MDMA
Sedative-hypnotic	↓	↓	↓	↓	~	↓	↓	 benzodiazepines
Opioid	↓	↓	↓↓	↓	↓ pinpoint	↓	~	 morphine, fentanyl

Arrows: ↑ increased, ↓ decreased, ~ unchanged. Structures: atropine, sarin (OP), ketamine, amphetamine, diazepam, morphine.

ANTICHOLINERGIC
all DRY & FAST



hot as a hare: hyperthermia



dry as a bone: dry skin and mucosa



red as a beet: flushing



mad as a hatter: delirium



blind as a bat: mydriasis



full as a flask: urinary retention



fast as a fiddle: tachycardia

CHOLINERGIC
all WET & SLOW

S 

Salivation

L 

Lacrimation

U 

Urination

D 

Defecation

G 

GI upset

E 

Emesis

Identification of noxae

1

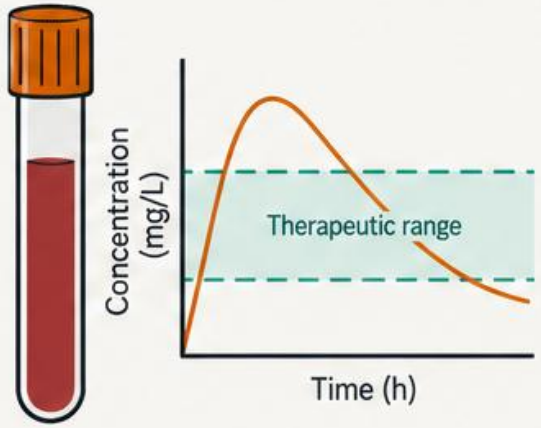
History & scene



- what, when, how much
- witnesses, empty packages
- suicide note, occupation

2

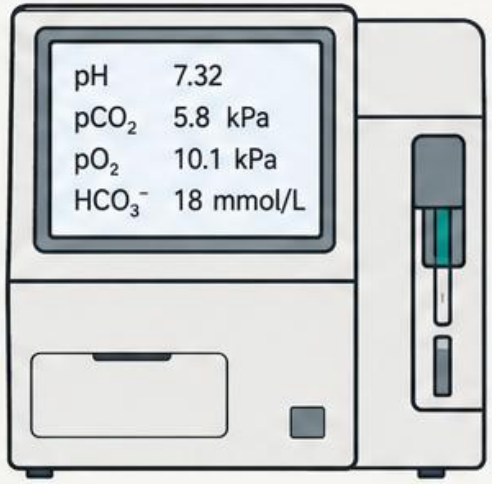
Quantification (TDM)



- selected drugs only
- routine TDM labs
- e.g. lithium, digoxin, AEDs

3

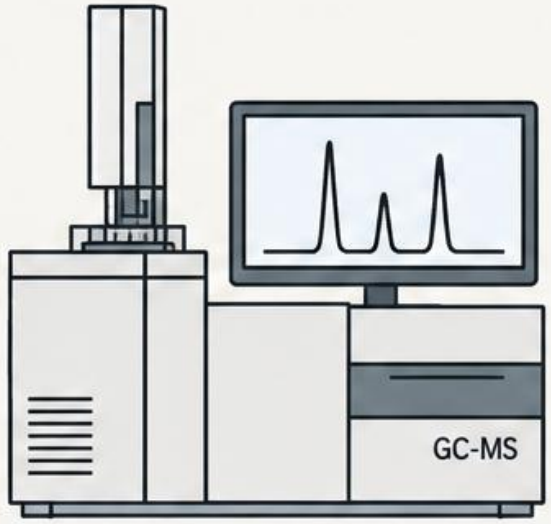
Clinical biochemistry



- blood gases, acidosis
- anion & osmolar gap
- standard panel: glucose, Na, K, urea

4

Analytical chemistry



- general screening (GC-MS)
- targeted quantification
- LC-MS/MS

Management

1 Vital functions (ABCDE)



- airway, breathing, circulation
- supportive care alone saves most lives
- ventilation = single most life-saving intervention

2 Decontamination



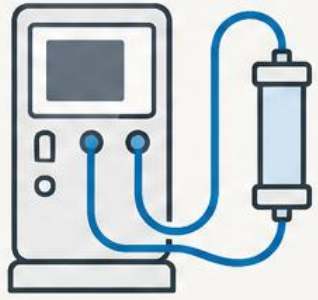
- only if indicated and early
- charcoal, skin washing
- whole bowel irrigation

3 Specific antidotes



- exist for only ~15-20 poisons
- but for those they are time-critical

4 Enhanced elimination



- multi-dose charcoal
- urinary alkalinisation
- extracorporeal methods

5 Consultation & follow-up



- poison centre 24/7
- psychiatric evaluation after intentional poisoning

Principle: treat the patient, not the poison — time is the most important 'antidote'

Decontamination - what is actually recommended today

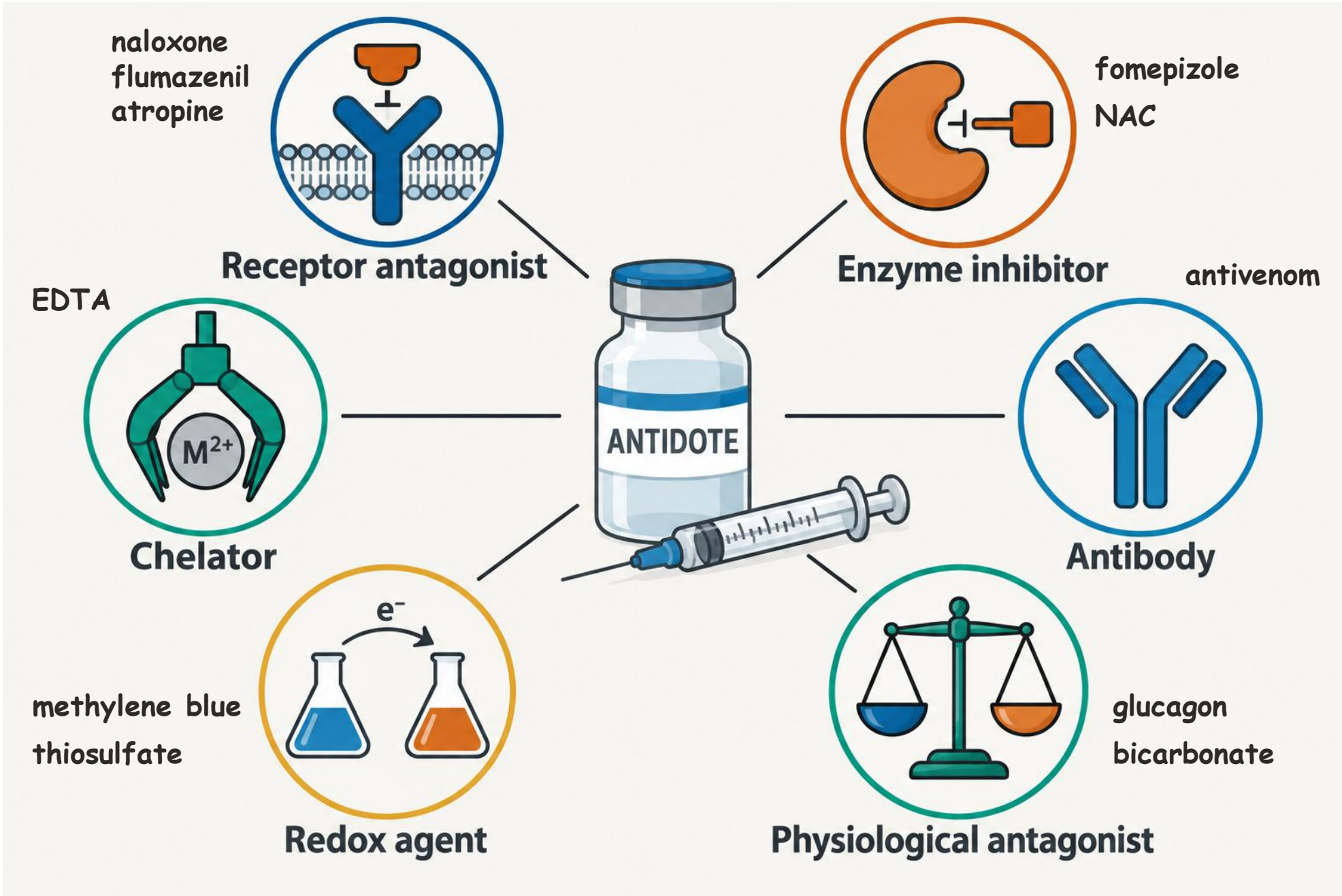
- **Activated charcoal:** most effective within 1 h; multi-dose charcoal for carbamazepine, theophylline, quinine, dapsone (enterohepatic recirculation)
- **Charcoal is NOT for:** corrosives (acids, alkali), hydrocarbons (aspiration risk), alcohols, iron, lithium, cyanide
- **Gastric lavage:** largely abandoned - only exceptional, <1 h, life-threatening amount, no better alternative
- **Whole bowel irrigation (PEG):** lithium, iron, sustained-release formulations, body packers
- **Skin & eye:** remove clothes, copious washing (organophosphates - protect the staff first)

Elimination of noxae - what is current practice

- **Multi-dose activated charcoal:** carbamazepine, theophylline, quinine, dapsone - interrupts enterohepatic recirculation ('gastrointestinal dialysis')
- **Urinary alkalinisation:** salicylates - the only standard 'forced diuresis' left; forced ACID diuresis is obsolete (risks outweigh benefit)
- **Haemodialysis (EXTRIP criteria):** toxic alcohols, lithium, salicylates, metformin (lactate), valproate, theophylline; barbiturates if needed
- **Haemoperfusion:** largely historical - replaced by modern dialysis/CRRT for most indications
- **Lipid emulsion:** local anaesthetic systemic toxicity (LAST) and lipophilic cardiotoxins - 'lipid sink'

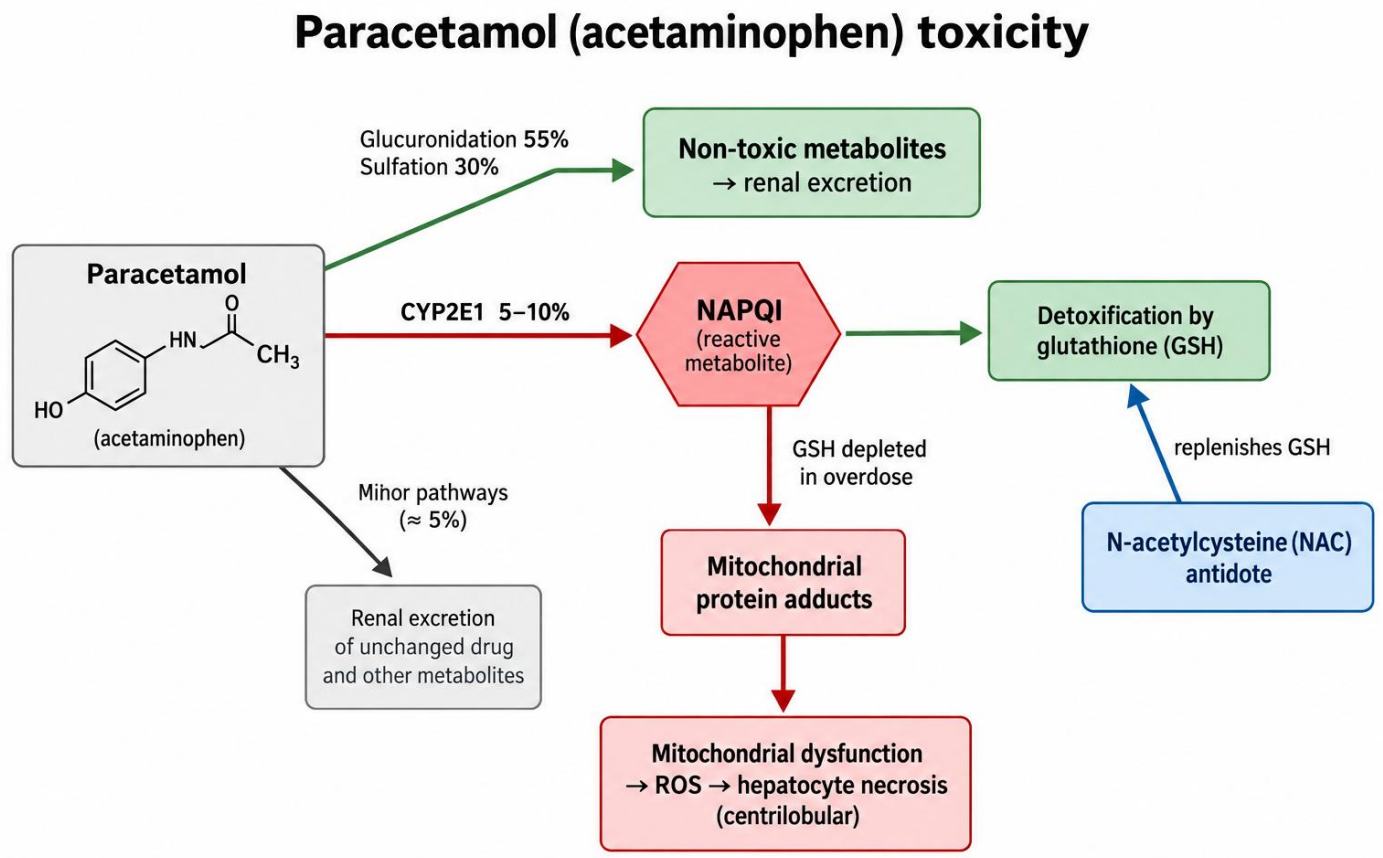
Antidotes

➢ **Only a small number of poisons** have a specific antidote (~15-20 of thousands of noxae)



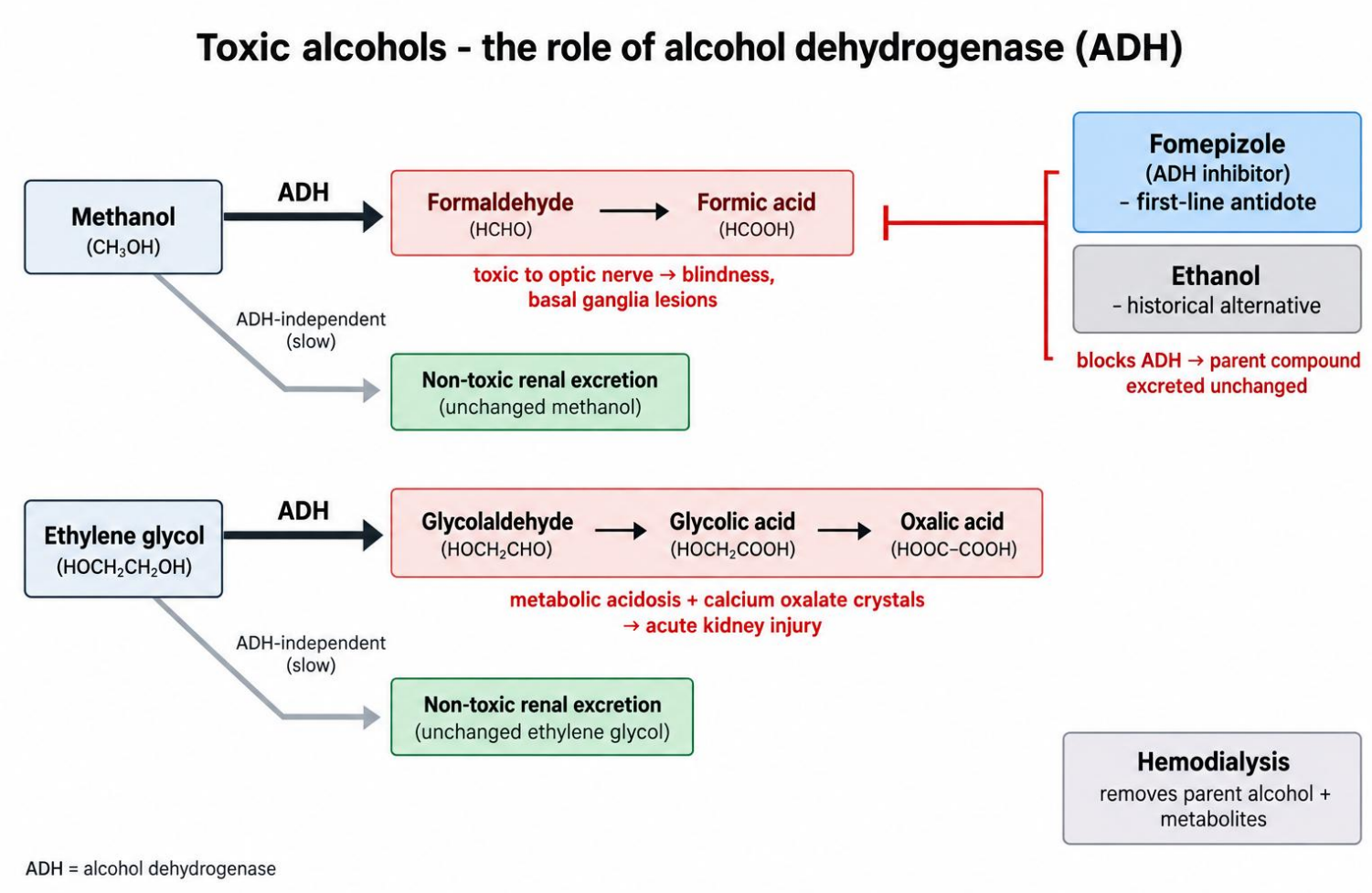
Paracetamol:
the molecular story of the most common fatal poisoning

- **~90% of the dose:** glucuronidation + sulfation -> non-toxic metabolites
- **5-10% via CYP2E1 -> NAPQI:** detoxified by glutathione (GSH)
- **Overdose:** GSH depleted -> NAPQI binds mitochondrial proteins -> ROS -> centrilobular hepatocyte necrosis
- **Risk factors:** CYP2E1 induction (chronic ethanol, isoniazid), low GSH (malnutrition, HIV)
- **Course:** 0.5-24 h nausea -> 24-72 h latent with rising ALT -> 72-96 h liver failure -> recovery
- **Antidote NAC:** replenishes GSH - most effective <8-10 h



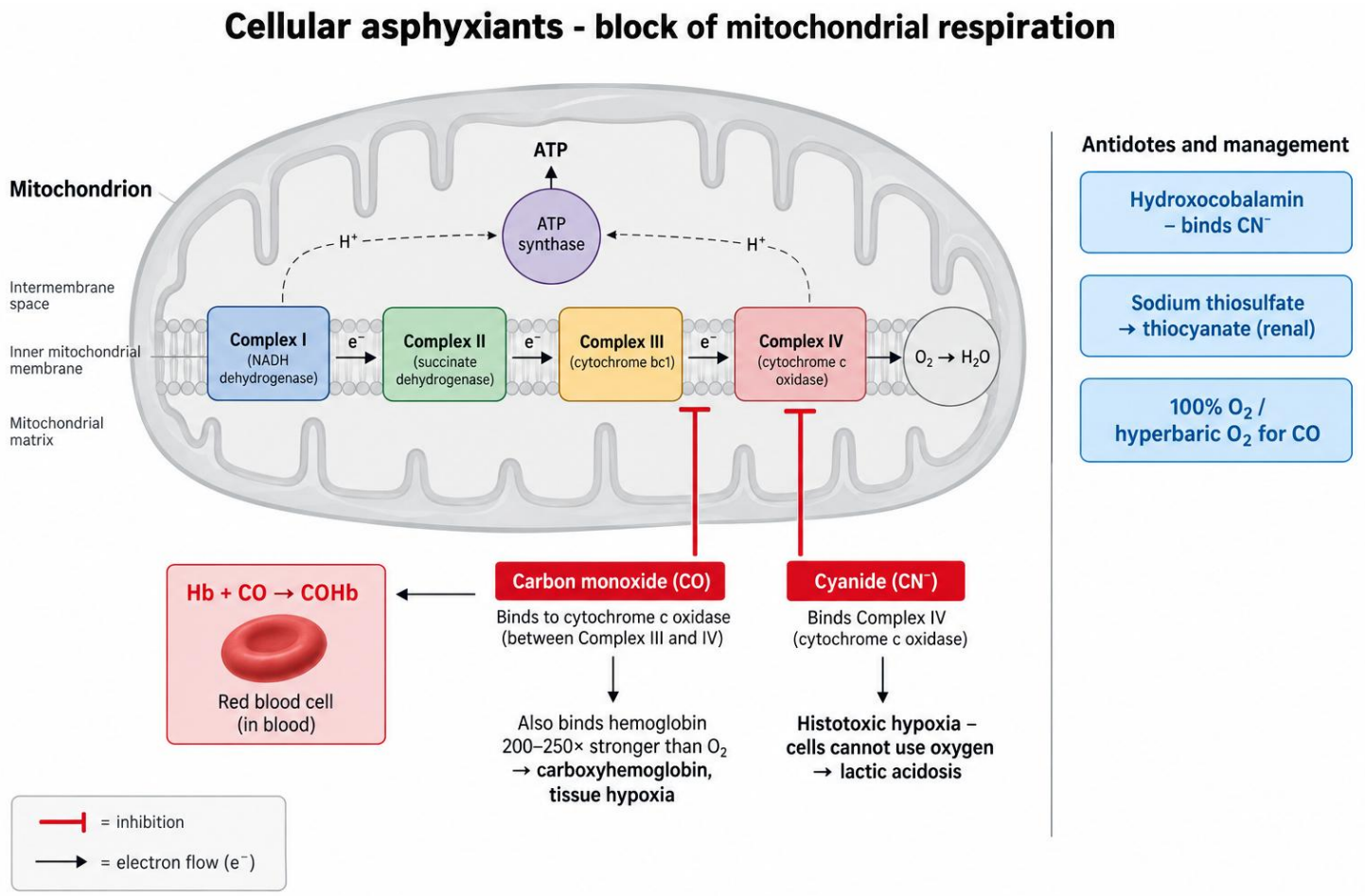
Toxic alcohols: the parent is innocent, the metabolite kills

- **Methanol:** ADH -> formaldehyde -> formic acid -> optic nerve injury (blindness), basal ganglia lesions
- **Ethylene glycol:** ADH -> glycolic acid (acidosis) -> oxalic acid -> Ca-oxalate crystals -> AKI, hypocalcaemia
- **Laboratory:** high anion gap + high osmolar gap
- **Fomepizole:** ADH inhibitor, first-line - blocks formation of toxic metabolites; ethanol = historical alternative
- **Haemodialysis:** removes the parent alcohol and the metabolites in severe cases
- **Sources:** moonshine, windscreen fluids, antifreeze - also epidemics in alcoholics



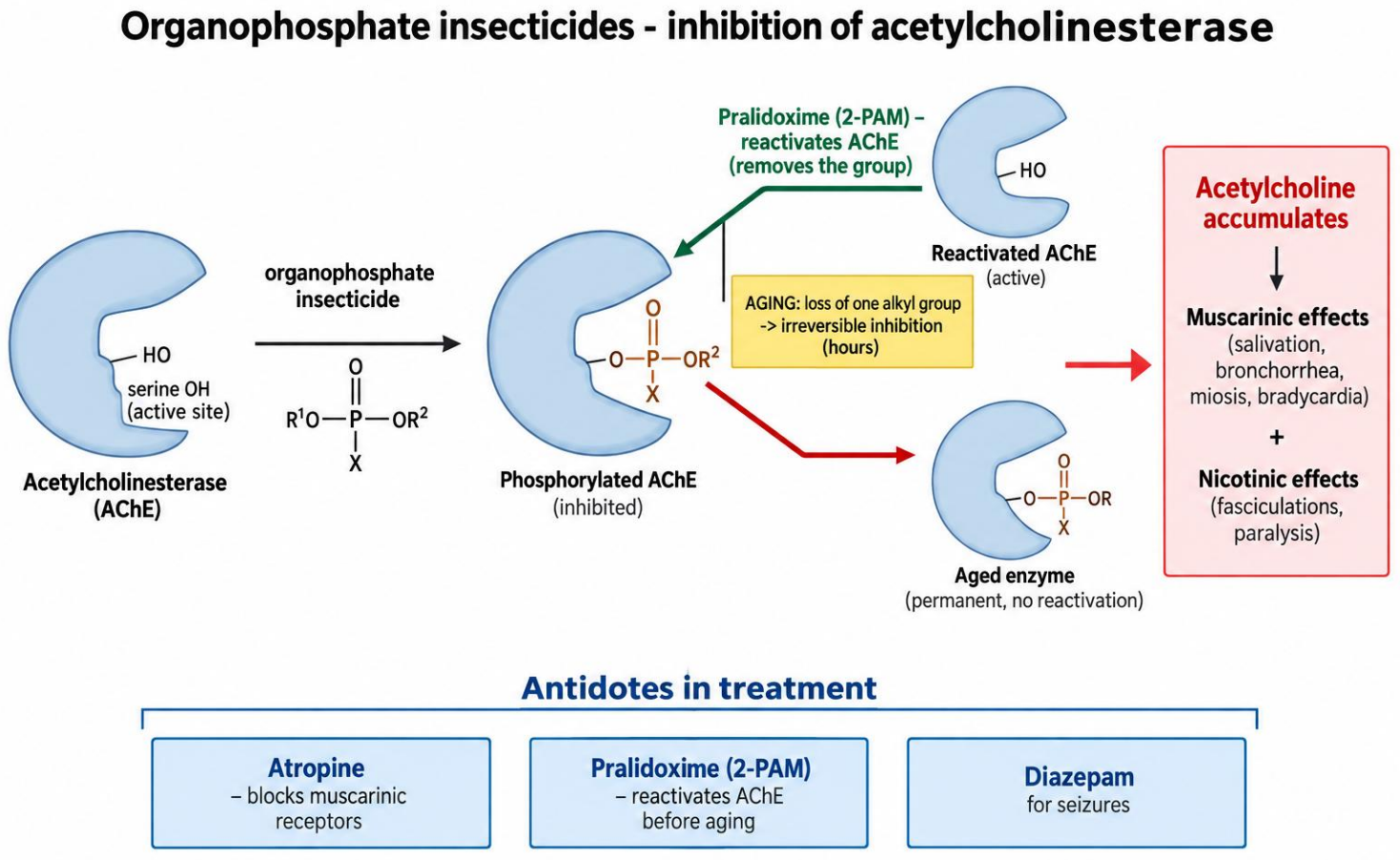
Cellular asphyxiants: cyanide & carbon monoxide

- **Cyanide:** binds complex IV (cytochrome c oxidase) -> histotoxic hypoxia -> lactic acidosis; sources: fires (HCN), industry, amygdalin plants
- **Carbon monoxide:** Hb affinity 200-250x that of O_2 -> carboxyhaemoglobin -> tissue hypoxia; also blocks complex IV; delayed neuropsychiatric syndrome
- **CO burden:** the most common lethal poisoning worldwide (~31,000 deaths/yr)
- **CN antidotes:** hydroxocobalamin (binds CN-) + sodium thiosulfate (rhodanese -> thiocyanate); nitrites only as third line
- **CO treatment:** 100% O_2 (displaces CO), hyperbaric O_2 in selected cases; measure COHb by co-oximetry



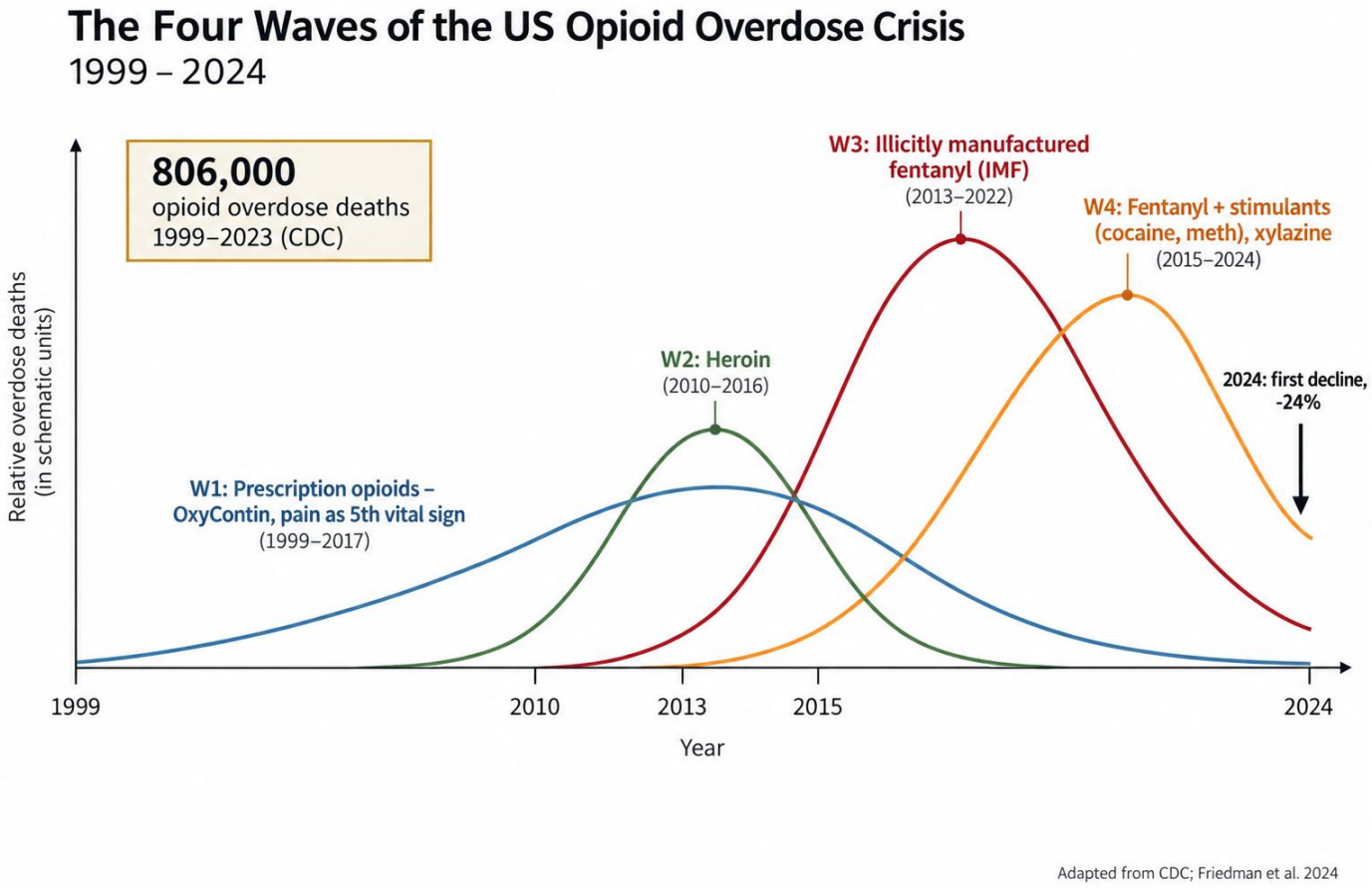
Organophosphates: ageing of the enzyme decides the therapy

- **Mechanism:** phosphorylation of the serine OH of acetylcholinesterase -> acetylcholine accumulates
- **Ageing:** loss of one alkyl group -> irreversible inhibition; pralidoxime works only BEFORE ageing
- **Symptoms:** muscarinic (SLUDGE, bronchorrhoea, miosis, bradycardia) + nicotinic (fasciculations, paralysis) + CNS seizures
- **Therapy:** atropine (muscarinic) + pralidoxime (reactivation) + diazepam (seizures); decontaminate the patient AND the staff
- **Weaponized:** sarin, VX, Novichok (Salisbury 2018) - identical biochemistry, military potency

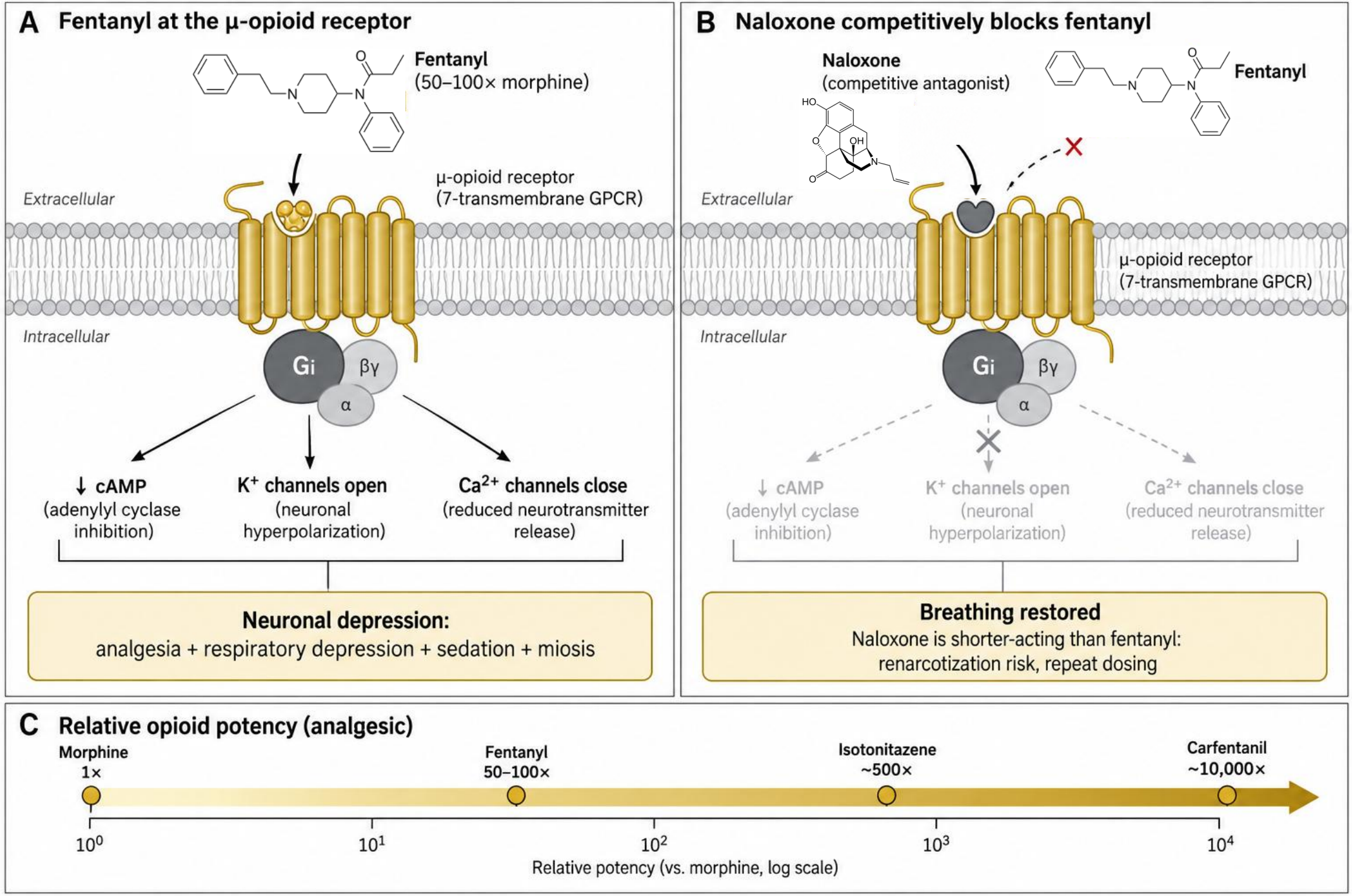


The opioid crisis - four waves of a shifting epidemic

- **Wave 1 (1999-2017):** prescription opioids - OxyContin (1996), pain as the 'fifth vital sign', aggressive marketing
- **Wave 2 (2010-2016):** heroin - prescription restrictions pushed users to the illicit market
- **Wave 3 (2013-2022):** illicitly manufactured fentanyl - saturated the drug supply, pressed into counterfeit pills
- **Wave 4 (2015-):** fentanyl + stimulants (cocaine, methamphetamine) - polysubstance deaths; xylazine & medetomidine adulterants
- **Burden:** ~806,000 opioid overdose deaths 1999-2023; 2024 brought the first decline (-24%)
- **Europe:** nitazenes now more widespread than fentanyl analogues (29 vs 18 countries reporting in 2024, UNODC)

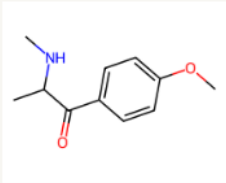


Four waves of the US overdose crisis (CDC; Friedman et al. 2024).


A Fentanyl at the μ-opioid receptor
Fentanyl
(50–100× morphine)
μ-opioid receptor
(7-transmembrane GPCR)
Extracellular
Intracellular
Gi
βγ
α
↓ cAMP
(adenylyl cyclase inhibition)
K+ channels open
(neuronal hyperpolarization)
Ca2+ channels close
(reduced neurotransmitter release)
Neuronal depression:
analgesia + respiratory depression + sedation + miosis
B Naloxone competitively blocks fentanyl
Naloxone
(competitive antagonist)
Fentanyl
Extracellular
Intracellular
μ-opioid receptor
(7-transmembrane GPCR)
Gi
βγ
α
↓ cAMP
(adenylyl cyclase inhibition)
K+ channels open
(neuronal hyperpolarization)
Ca2+ channels close
(reduced neurotransmitter release)
Breathing restored
Naloxone is shorter-acting than fentanyl:
renarcotization risk, repeat dosing
C Relative opioid potency (analgesic)
Morphine
1×
Fentanyl
50–100×
Isotonitazene
~500×
Carfentanil
~10,000×
10^0
10^1
10^2
10^3
10^4
Relative potency (vs. morphine, log scale)

NPS designer drugs: ~1,400 substances reported to UNODC (153 countries)

1. Stimulants – synthetic cathinones

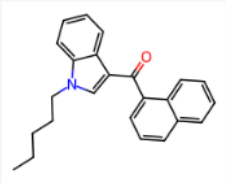


methedrone, MDPV, alpha-PVP

slang: “tšaka”, “bath salts”



2. Synthetic cannabinoids (SCRAs)

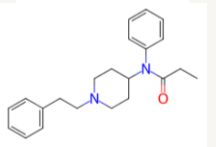


JWH-018

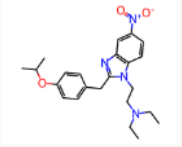
slang: “Spice”, “K2”, “bylinný mix”



3. Opioid agonists



fentanyl



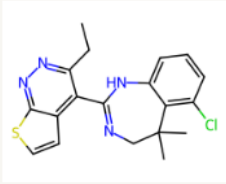
isotonitazene (nitazene)

fentanyl & analogues (500× morphine); nitazenes

slang: “china white”, “M30”, “iso”



4. Benzodiazepine-type

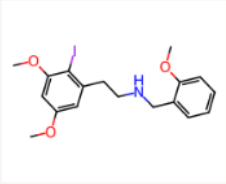


bromazepam, etizolam

slang: “etizo”, fake “Xanax”



5. Classic hallucinogens

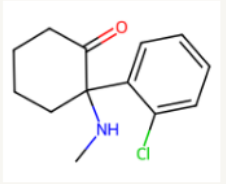


25I-NBOMe, 2C series, tryptamines

slang: “N-bomb”, “lisky”



6. Dissociatives



ketamine and PCP analogs

slang: “K”, “special K”, “angel dust”



NPS = new psychoactive substances; UNODC = United Nations Office on Drugs and Crime.