UCL School of Pharmacy

Heroin and related opiates

2025

What are opiates?

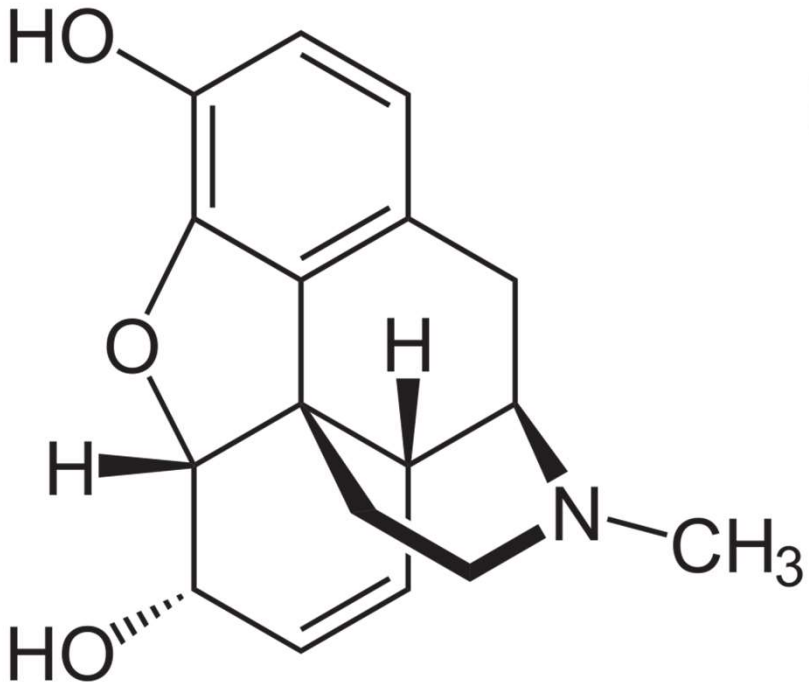
- **Opiates:** are a group of drugs extracted from the gummy latex ('milk') harvested from the seed-pod of the Asian poppy, ***Papaver somniferum.***

- **Opium** is produced from the sun-dried latex, and the alkaloids **morphine** and **codeine** are derived from opium.

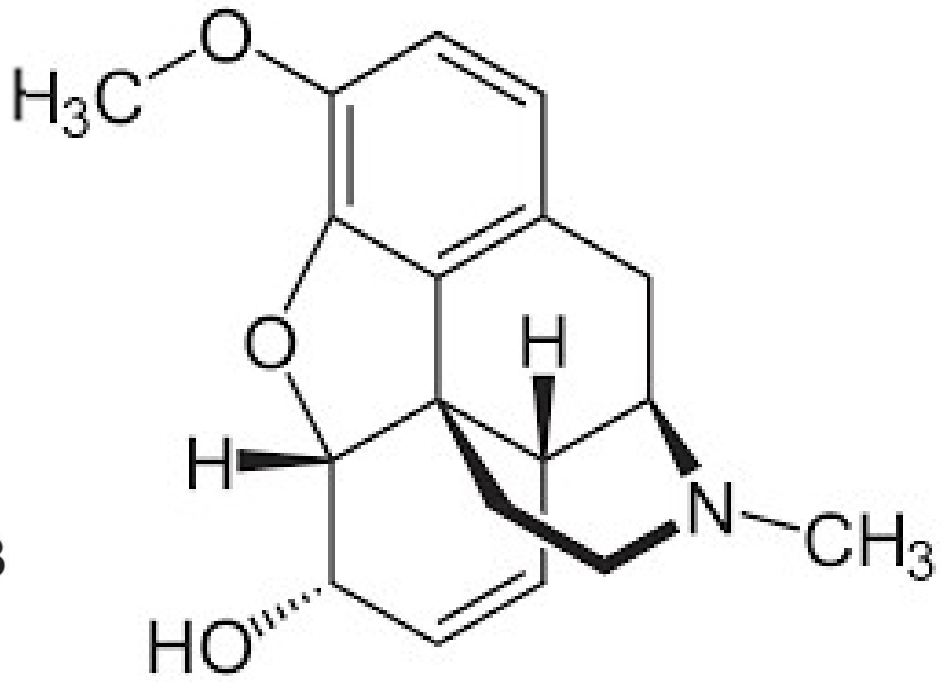
What are opiates?

Afghanistan produces more than 90% of illicit heroin globally, and more than 95% of the European supply (2021). This is despite the $8.4 billion apparently spent by the US in counter-narcotics programs.

What are opiates?



Morphine



Codeine

What are opiates?

- **Morphine:** (named after Roman God of dreams, ***Morpheus***) is the classical opiate receptor agonist against which other opiate agonists are compared for analgesic potency.

- It can be given orally, i/v, epidural, intrathecal or via rectal routes.

What are opiates?

- **Codeine:** is a natural derivative of morphine with much weaker (~0.1% as potent), shorter-acting analgesic activity. In the body, it is metabolized to morphine in order to exert its analgesic properties. [P450 2D6 liver enzyme].

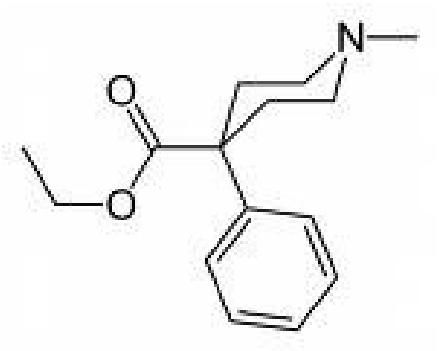
- It can be given orally, i/v, or i/m.
- It is commonly used as an antitussive.

What are opiates?

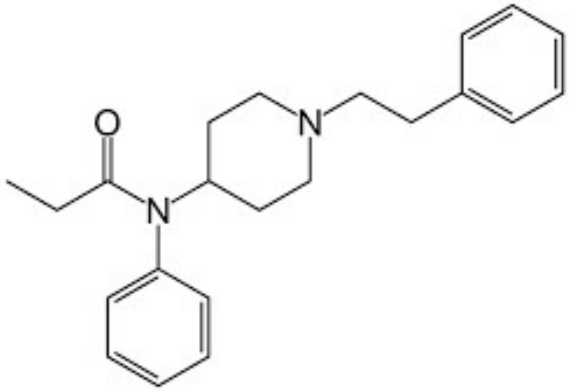
- **Other opiate-related synthetic drugs:**

Heroin, methadone, buprenorphine, dihydrocodeine, pethidine, fentanyl, remifentanil, dipipanone, oxycodone, hydrocodone, hydromorphone, meptazinol, tramadol, dextromethorphan, pentazocine, tapentadol.

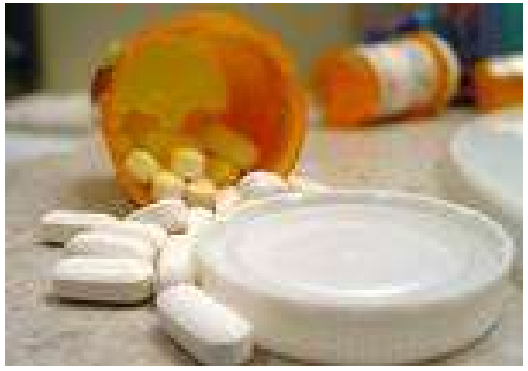
- **Opiates:** are used medically to relieve severe pain without causing loss of consciousness, but also have a high potential for abuse.

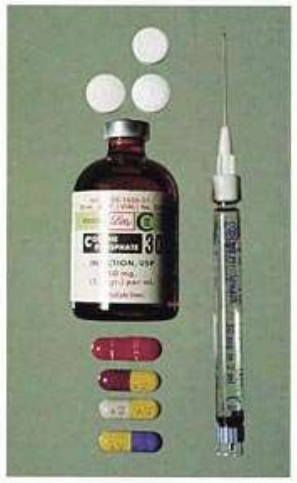


Pethidine



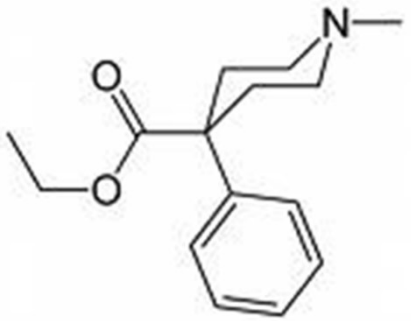
Fentanyl





What are opiates?

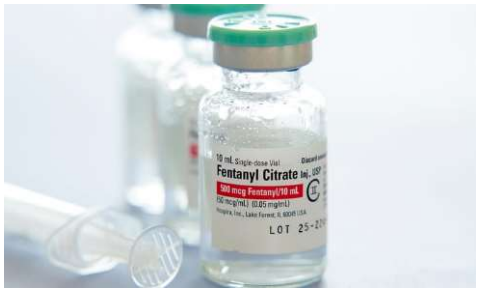
- **Pethidine (hydrochloride):** is a synthetic opiate with powerful analgesic properties, used for the treatment of moderate to severe pain particularly during labour and delivery. It is less effective than morphine but has a faster onset of action and shorter clinical effect (2-3 hrs).
- It can be given orally, s/c, i/v, or i/m.

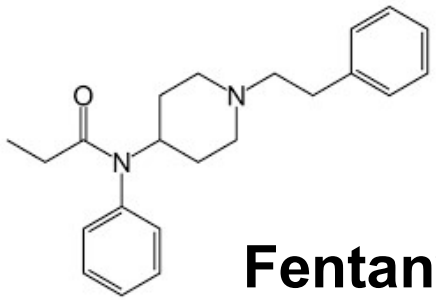


Pethidine

What are opiates?

- **Fentanyl** is another synthetic opiate with very powerful analgesic effects, used to prevent pain after surgery and other medical procedures. It is ~100 times more potent than morphine, has a more rapid onset of action and an effect of 1-2 hrs.
- It can be given i/v (during anaesthesia), orally (sublingual tablets/lozenges), intra-nasally, or as transdermal patches for chronic pain.





Fentanyl

What are opiates?

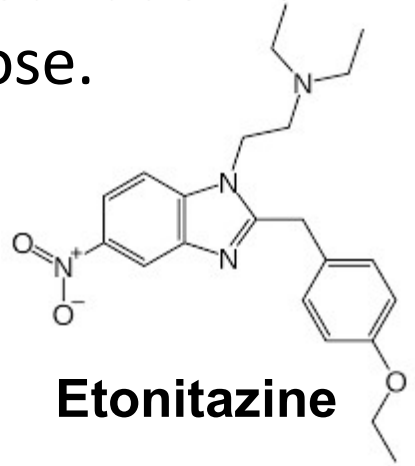
- **Fentanyl is more deadlier than heroin!** The photo below compares a lethal dose of heroin (~30 mg) with a lethal dose of fentanyl (~3 mg) and derivative **carfentanil** (~20 μg). It is so dangerous that even an accidental touch or breath of the powder can be fatal (police, forensic labs). It is believed that the singer *Prince* died from an accidental overdose of Fentanyl.

What are opiates?

- **Fentanyl abuse** is now at crisis level in the USA and is rapidly becoming a problem also for drug abusers in the UK, since it is being mixed with street heroin to make it more potent. It is estimated that drug overdoses killed ~64,000 people in the USA in 2016, many of these deaths being blamed on fentanyl overdoses. In the UK, 60 deaths were linked to fentanyl abuse in 2017.

Nitazines

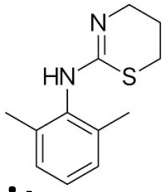
- **Nitazenes:** are synthetic opioid drugs which have recently appeared on the US, UK and EU drugs scenes: *e.g*. **Butonitazine**, **Flunitazine**, **Metonitazine** or **Etonitazine** (500 times more potent than heroin), sold alone (white powder/crystals/tablets-often mis-sold as oxycodone) or mixed with other drugs – heroin, cocaine, cannabis or benzodiazepines. Being highly potent, some fatal nitazine drug overdoses have been recorded in the UK. It is believed that the main source of illicit nitazines nowadays is China. Originally synthesized in the 1950's as alternatives to morphine, they were never released due to their high potency and high potential for overdose.



Etonitazine

Tranq

- A new and particularly worrying development in the USA is the deadly “flesh-eating” drug mixture known as **Tranq** or **Tranq-dope (the “Zombie drug”).** This consists of a mixture of heroin/fentanyl and the animal tranquillizer **xylazine** and causes the same “high” as opioids do. The drug is also beginning to penetrate the UK and European drug scenes.



Xylazine

- After i/v injection, it can cause painful necrotic skin sores, slow to heal, which can eventually lead to limb amputation as well as fatal overdoses. It can also be smoked or snorted. Since xylazine is a non-opioid (α_2-adrenergic receptor agonist), it does not respond to naloxone as an antidote on overdosing. On repeated use it causes excessive sleepiness and respiratory depression hence the “Zombie” reference. ~2,500 people died in NY from Tranq overdoses in 2021.

History

- **Opiates,** have been used both medically and non-medically for centuries. 6,000 yr old Summerian texts refer to the opium poppy as the ‘joy plant’.

- **Turkish and Arab traders took opium to China** in 6th or 7th century A.D. where it was used as a medicine until about the 17th century where it was realised it could be smoked. It was outlawed in China in 1796!

History

- **In later years,** the British supplied China with most of its opium (grown in India) making Britain (the *British East India Company*) the **world's largest drug dealer.**

- **During Victorian times,** taking opium in the form an alcoholic tincture - **laudanum** and in pill form became generally popular as a remedy for “nerves” or to stop coughing and diarrhoea.

- **By 19th century,** morphine was purified in soluble form and with the introduction of the hypodermic needle, injection of morphine solution became the common method of administration.

Heroin

- **Heroin (diacetylmorphine) –** first synthesized from morphine in 1874 - introduced in medicine in 1898 **as a safe, non-addictive remedy for morphine addiction !!** Later, was sold as a specific treatment for coughs.

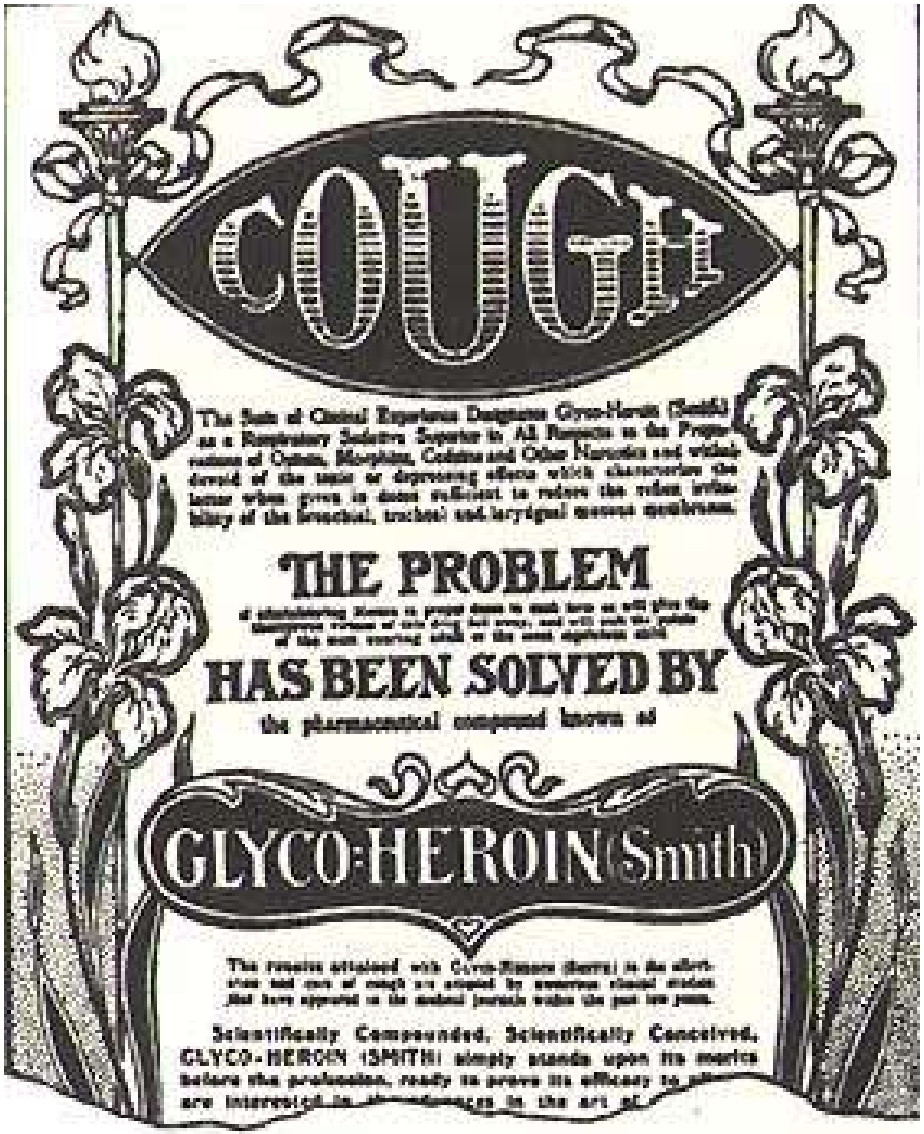
- **Heroin** produced **dependency** very rapidly in some individuals.

- **Heroin and other opiates -** made **illegal** in UK in 1920 with arrival of Dangerous Drugs Act.

Heroin: a powerful remedy for coughs!

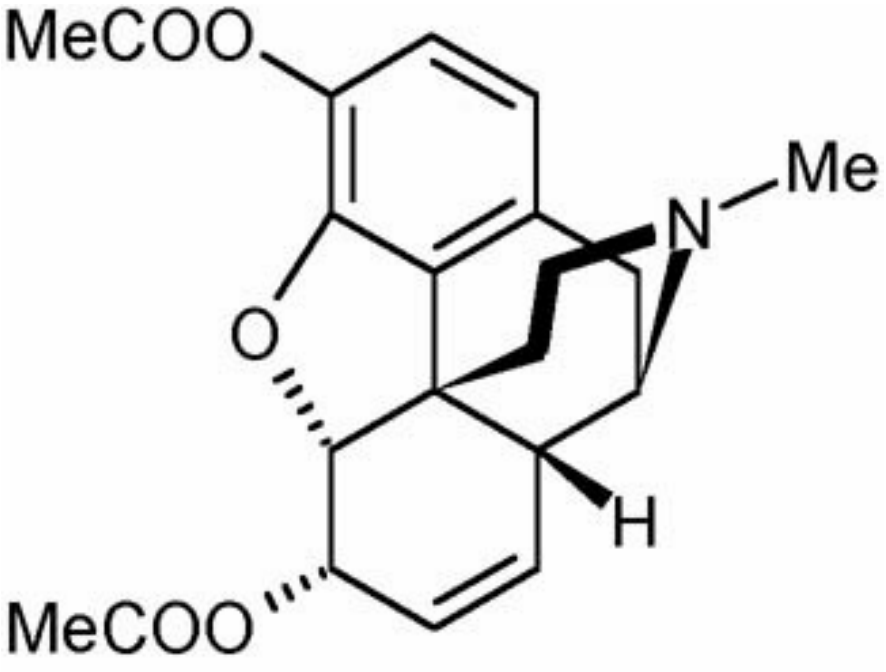
Advertisement from 1901 Medical Journal

Heroin: a powerful remedy for coughs!



Advertisement from 1903 Medical Journal

Heroin



Heroin
(*Diacetylmorphine*)

Heroin

- **Pure heroin** is a white odourless, crystalline powder with a bitter taste – rarely available on the street. Most illicit heroin varies in colour from **white to dark brown powder** (due to impurities or additives), which is dissolved in water and injected.

- **Most street-bought preparations of heroin** are diluted ('cut') with **glucose, starch, powdered milk,** or other substances such as **caffeine, quinine, flour, chalk and talcum powder.** The amount of actual heroin in a cut batch can then range from ~3-99%. There is no way to know the purity of a batch.

Heroin

- **Other heroin impurities** derived from the original poppy plant source can also be present, depending on how effective the illicit manufacturing process has been: these can include: **morphine, codeine, thebaine and noscapine.**

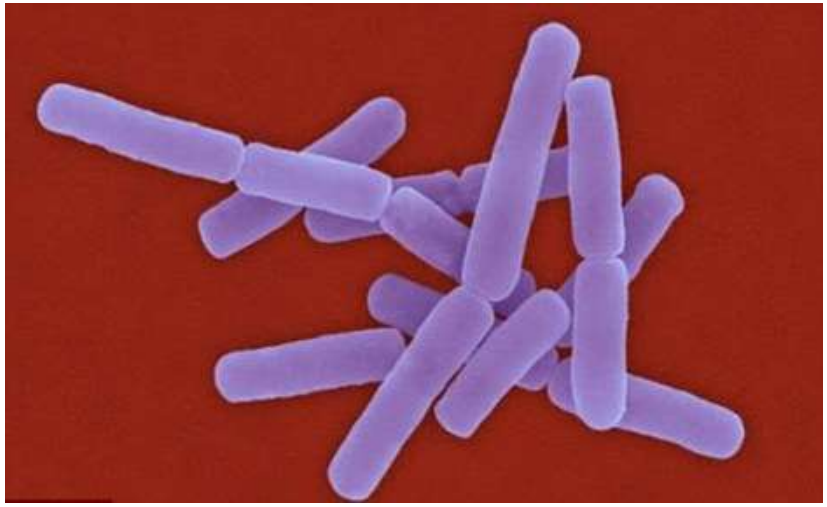
- **Black tar heroin** is a very impure, cheaper form of heroin derived from the incomplete acetylation of morphine and other opium derivatives – mainly produced in Mexico. It comes as a black/brown powder or sticky black tar, usually cut with lactose.

Mexican 'black tar' heroin

Heroin

- **Heroin: how much does it cost?** Nowadays, street heroin may cost as little as **£10** for a 100 mg bag (~€40/g), and its purity can be very high.

- Some street heroin is so pure, it can kill users instantly! Some batches have in the past been contaminated with **Anthrax**, leading to the death of many intravenous users!



Bacillus anthracis

Heroin

- **Common street (slang) names for heroin include:**

Dope, Smack, H, Horse, Junk, China white, Chiva, Black tar, Brown sugar, Skag, White stuff, Mexican horse, Mud, Dragon…..

- **Sometimes heroin is sold combined with other drugs to obtain a certain high:**

- Heroin and Marijuana: *(Atom bomb)*
- Heroin and Ecstasy: *(H bomb)*
- Heroin and LSD*:* *(Beast)*
- Heroin and Cocaine: *(Speedball, Dynamite)*

Heroin

Cheap *nyaope* drug destroying South African townships: 18 March 2015

*A cheap, highly addictive drug called **nyaope** (whoonga) is destroying impoverished townships in South Africa. Those caught taking the mixture of low grade heroin, marijuana, cleaning detergents, rat poison and chlorine face a 15-year jail term.*

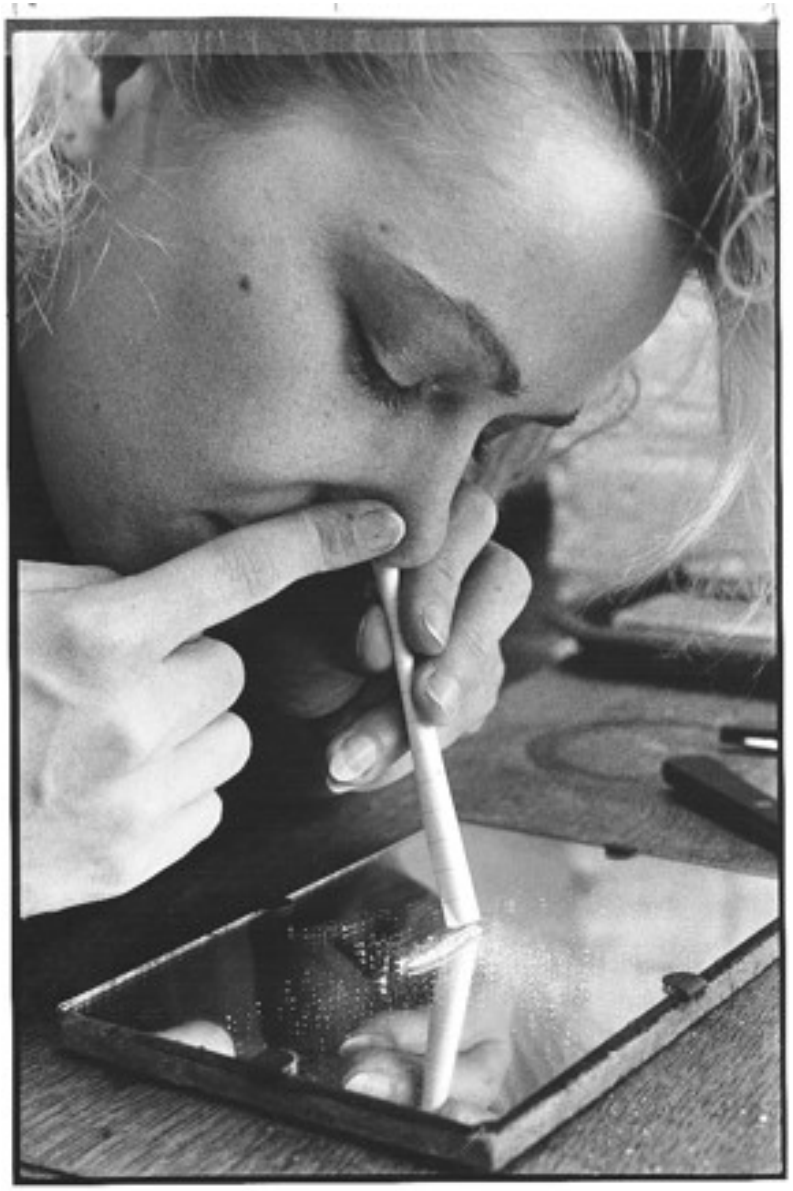
How is heroin administered?

- **Street users** usually inject heroin solutions under the skin **("skin popping")** or directly into a vein or muscle.

- The drug may also be **"snorted"** into the nose, **smoked** (where high purity heroin is available), or taken **orally or rectally.**

- **Injection** - most practical way to administer low-purity heroin -snorting may be preferred by new users as it eliminates risk of acquiring syringe-borne diseases:- **HIV/AIDS, hepatitis,** and stigma of i/v heroin use.

How is heroin administered?



Snorting heroin

Over £15 million worth of British banknotes are destroyed annually as a precaution, due to heavy contamination with heroin, cocaine, ecstasy or other illicit drugs. ~80% of all circulating notes are believed to be contaminated.

How is heroin administered?

Typically, an intravenous heroin abuser may inject up to four times a day.

A "low end" analgesic dose of heroin would be about **1 mg.** Most users start with doses much higher than this. Snorted doses of heroin probably start at between **5 and 20 mg** of pure heroin and i/v doses probably start between **5 and 10 mg**. A medicinal i/v dose for acute or chronic pain is **2.5-5.0 mg**.

Is opium still smoked?

Opium smoker (chasing the dragon)

In the 19th century, *opium dens* were opium was openly sold and smoked were quite prevalent around the world, particularly in China, but also in the US, Canada, France, and notably, Victorian London! Nowadays, obviously less popular but in the late 90's, new opium dens appeared in rural Laos (Vang Vieng), SE Asia, where it still continues to be a problem.

Is opium still smoked?

Opium smoker (chasing the dragon)

Opium smoking is also common in rural Afghanistan and Iran; sometimes whole families (men, women and children) can be addicted. In Afghanistan, it is estimated that more than a million people are addicted to opiate drugs.

What are the effects of heroin?

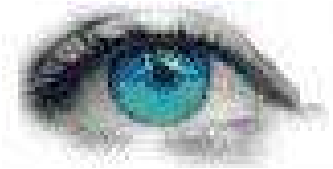
- **Short-term effects** of injected heroin appear in ~7-8 seconds -disappear in a few hours or days. Heroin rapidly enters brain -converted to morphine- binds to opioid receptors (***μ,δ,κ***). Heroin makes user feel intense pleasure ("high").

- **When smoked or sniffed (snorted),** peak effects are less intense- usually felt in ~10-15 minutes.

- **After initial CNS stim;** higher brain centres are depressed: ↓coughing and breathing reflexes; ↓ heart rate; extremities feel heavy; mouth is dry.

What are the effects of heroin?

- **Side-effects:** restlessness, nausea, vomiting, shallow breathing, constipation, itching, cold skin, sleepiness. **Pupils constricted**.



- **After very large doses,** user cannot be awakened; **pinpoint pupils**, skin cold, moist, bluish; profound **respiratory depression**→ coma and death.

- **Overdose and death** are common, particularly on the street, where the amount of drug contained in a "hit" cannot be accurately gauged.

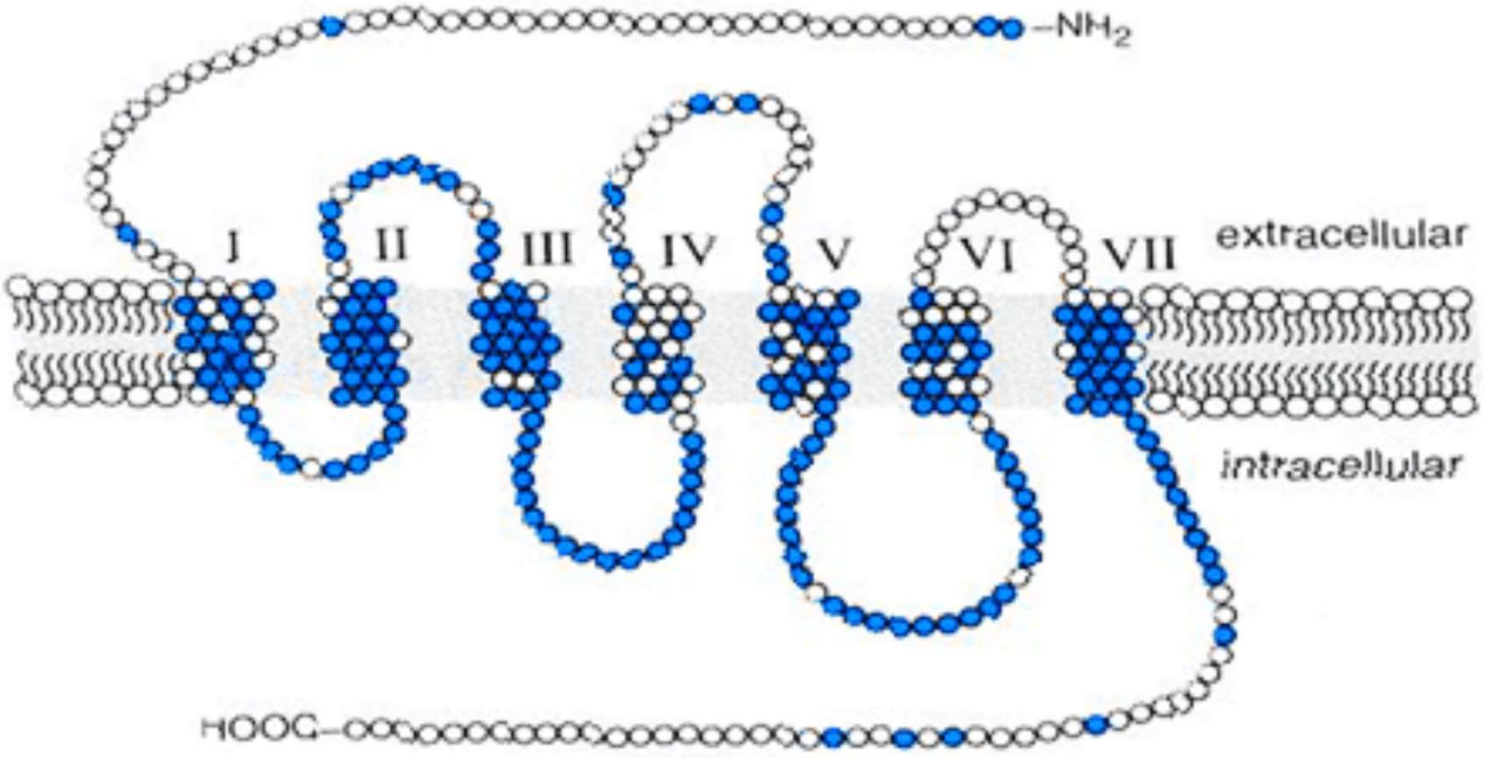
Opiate receptor function

Table 1. Opioid Receptor Activity

Receptor	Activity
Mu (μ)	Supraspinal and spinal analgesia, euphoria, miosis, sedation, constipation, respiratory depression, addiction, hormonal changes
Kappa (κ)	Supraspinal and spinal analgesia, diuresis, sedation, miosis, dysphoria, psychomimetic effects, respiratory depression, constipation
Delta (δ)	Supraspinal and spinal analgesia

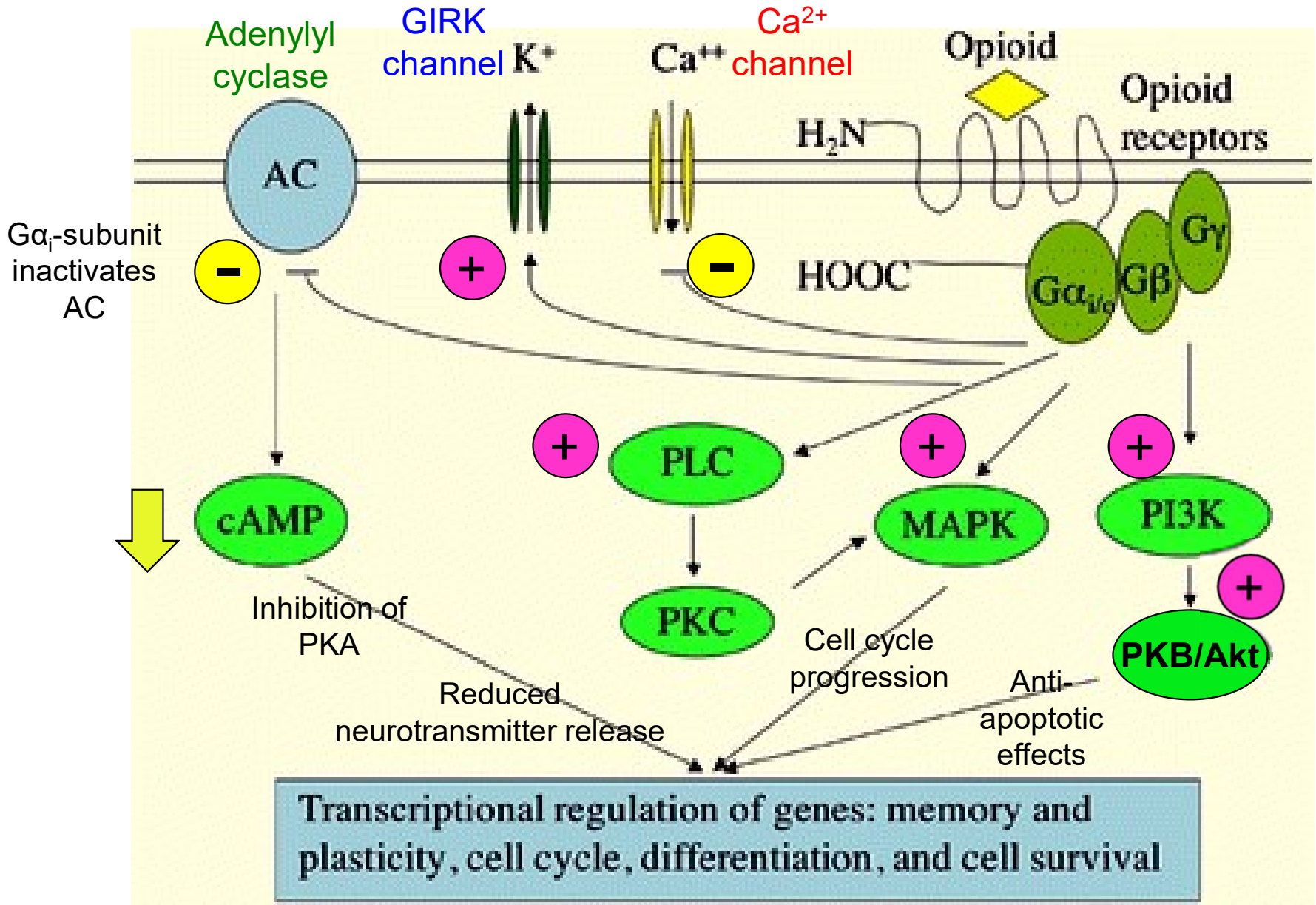

Take a
Break!

Opiate receptor structure



Schematic of a μ-opiate receptor

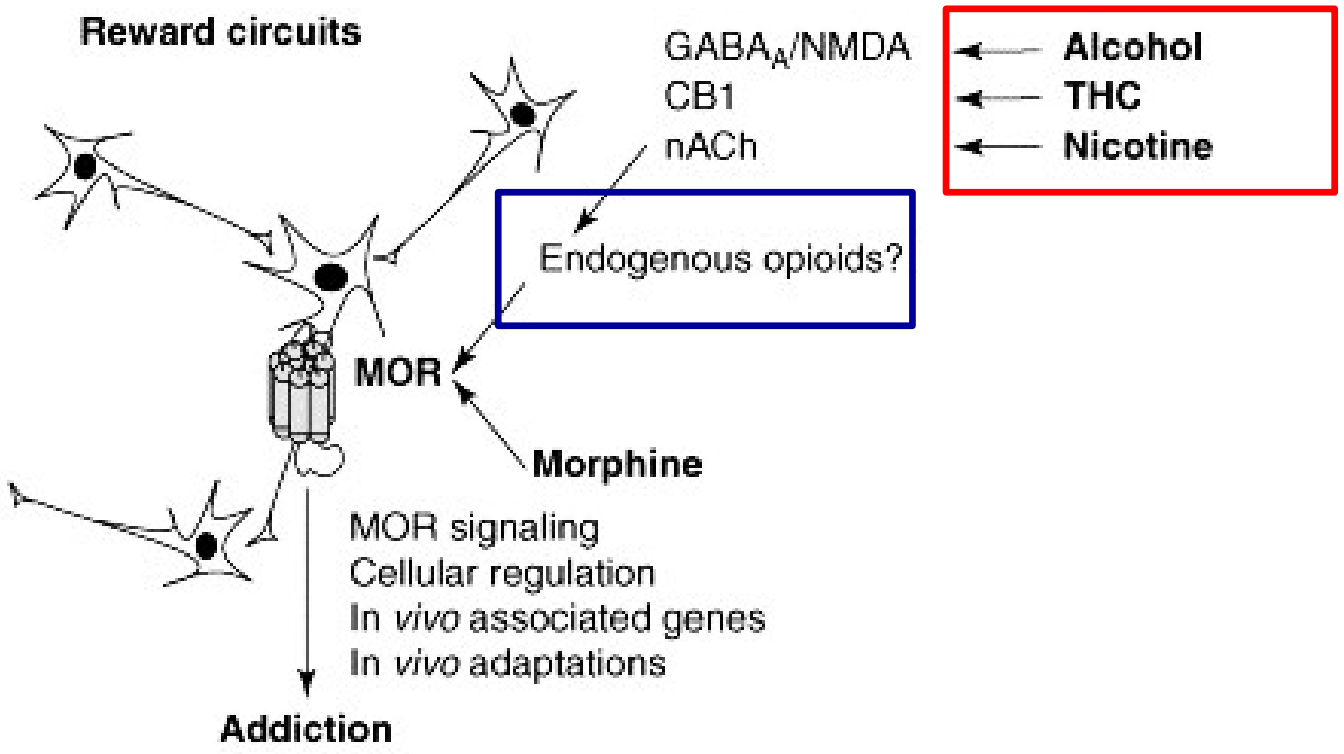
Opiate receptor coupling



MAPK: mitogen-activated protein kinase

PI3K: Phosphatidylinositol 3-kinase

μ-opiate receptors and addiction



Mu opioid receptors (MOR) are distributed along reward circuits where they are believed to mediate the reinforcing activities of opiates and perhaps also other addictive drugs like alcohol, THC and nicotine, through the release of endogenous opioid peptides that activate μ-receptors.

Effects of long-term heroin use

Long-term complications appear after repeated opiate use over a long period.

- **Injecting heroin regularly** can lead to scarred and/or collapsed veins. Chronic opiate users may develop ***endocarditis,*** due to unsterile injection techniques.

- **Smoking heroin regularly** can lead to ***pneumonia*** and other lung complications. Loss of appetite can result in **malnutrition.** Chronic **constipation** is also common. Women can have irregular periods and men can become impotent.

Effects of long-term heroin use

- **Serious personal problems** can develop. Using drugs can become more important than family and friends.

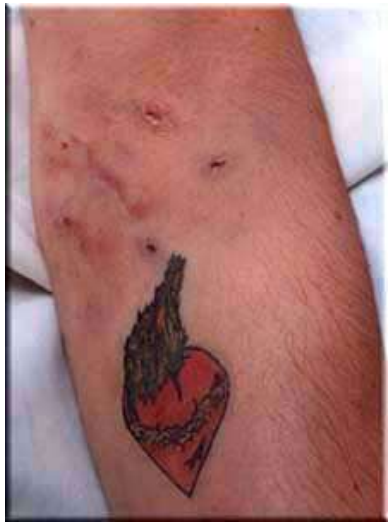
- **Babies born to heroin-addicted mothers** are often premature and underweight, and go through withdrawal at birth (Neonatal Abstinence syndrome; :NAS) They can be infected with HIV, hepatitis or blood poisoning.

- **Drug users who share needles** are at a high risk of acquiring **HIV** infection and developing **AIDS.**

Effects of long-term heroin use

- **Unsterile injection techniques** can also cause skin abscesses, cellulitis, hepatitis B and C), and even brain damage. Tetanus is also common.

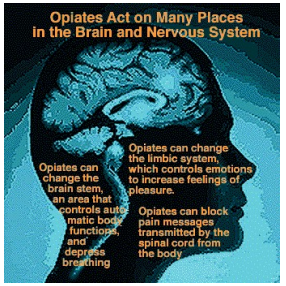
- **Repeated sniffing of heroin** damages the nose.



Tolerance and dependence

➢ **Tolerance: with regular long-term use** (or even occasional use over a long period of time) - needing more and more of drug to get the same intensity of effect, develops tolerance to many of the desired effects of the opioids.

➢ **Chronic users** may also become **psychologically** and **physically dependent** on opioids, due to neurochemical and molecular changes in the brain.



Tolerance and dependence

➢ **Psychological dependence:** exists when a drug is so central to a person's thoughts, emotions, and activities that the need to continue its use becomes a **craving** or **compulsion.**

➢ **With physical dependence:** body has adapted to presence of drug, and withdrawal symptoms of discomfort **(similar to flu)** occur if use of drug is reduced or stopped abruptly; positive pleasure is replaced by relief at simply taking the drug to maintain 'normality‘.

Withdrawal symptoms

- **Withdrawal from heroin** may occur as early as a few hours after the last administration.

- **Symptoms include:**

restlessness, yawning, runny nose, sneezing, tears, aches, sweating or chills with goose bumps **("cold turkey"),** diarrhoea, tremor, abdominal cramps, low blood pressure and involuntary leg movements. These symptoms are accompanied by a strong **craving** for the drug.

Withdrawal symptoms

- **Major withdrawal symptoms** peak between 48 and 72 hours after the last dose then gradually subside after a week. After-depression, stress, weakness, sleeplessness and **drug craving** can however, last for several weeks or months.

- ***Heroin withdrawal is never fatal*** to otherwise healthy adults, but sudden withdrawal by heavily dependent users who are in poor health can be fatal.

Treatment of heroin addiction

The basic approaches to heroin addiction treatment are:

- **Detoxification** (supervised withdrawal from drug dependence, either with or without medication) over a few days in a hospital or as an outpatient;

- **In therapeutic communities,** patients live for at least 3 to 6 months in a highly structured drug-free environment and are encouraged to help themselves.

Treatment of heroin addiction

- **Traditional detox programs** utilize the “cold turkey” approach, or mild sedation while patient goes through withdrawal.

Success is questionable in most cases because patients often cannot withstand debilitating withdrawal symptoms - fever, vomiting, diarrhoea, severe cramping, and nausea, lasting from one to two weeks.

Treatment of heroin addiction

- **Traditional detox programs:** After several unsuccessful attempts to overcome addiction or dependency, the prospect of experiencing withdrawal symptoms and the inability to remain clean over time causes many patients to give up hope and continue using drugs rather than face additional suffering and failure, consequently destroying the patient's self-esteem.

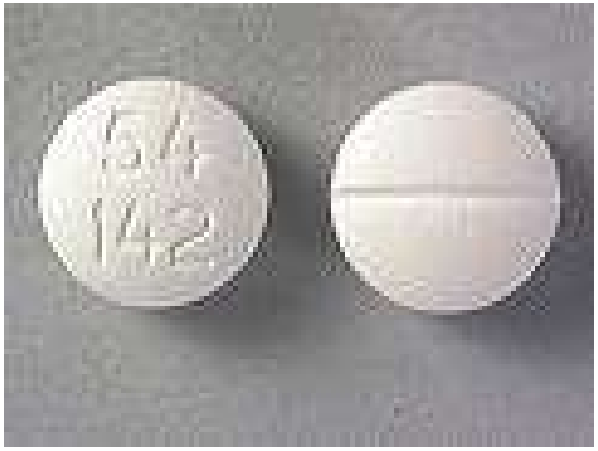
Treatment of heroin addiction

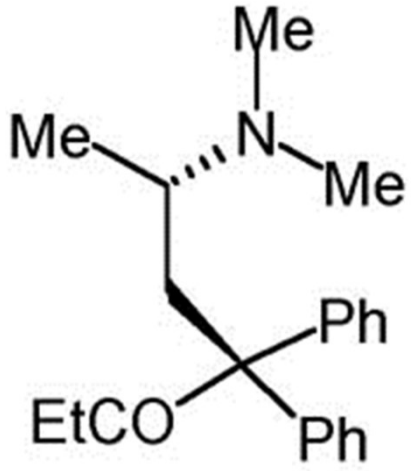
- **Methadone-based programmes** – (methadone maintenance) - substitutes one addiction for another, enslaving patients to return day after day for their medication.

Methadone has long-lasting effects and is one of the most difficult drugs to detox. from. Some methadone maintenance patients remain in these types of programs for 20-years.

Treatment of heroin addiction

- **Methadone maintenance (+ counselling):** uses methadone 15-40 mg as a heroin substitute on a daily basis, coupled with a gradual reduction of the methadone dose over several weeks/ months, until complete abstinence is achieved.





Methadone

Treatment of heroin addiction

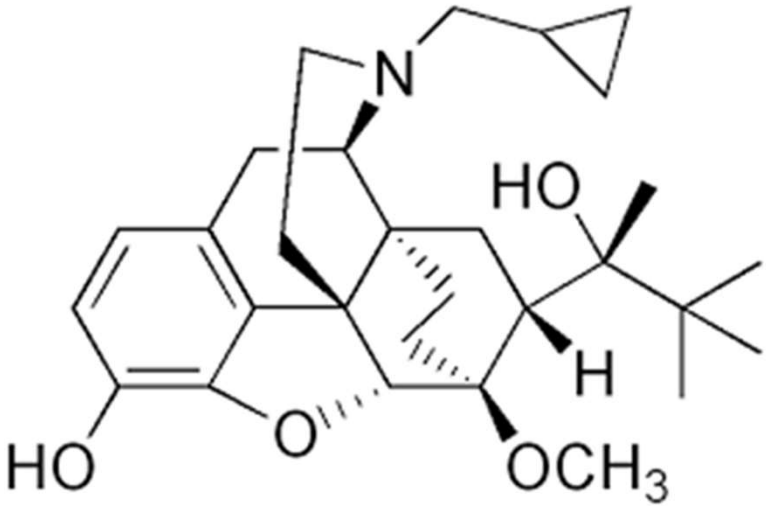
Other pharmaceutical approaches include:-

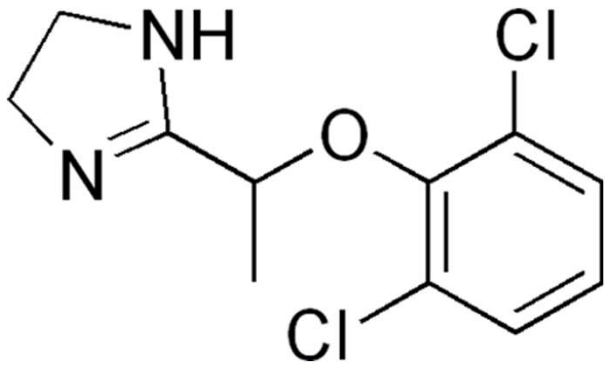
*● **Buprenorphine (*Subutex*),** a **μ-opioid partial agonist** - thrice weekly dosing – as a methadone alternative.

● **Lofexidine (*BritLofex*),** a **central α_2-adrenergic agonist** (similar to clonidine) can be used to control some unpleasant withdrawal symptoms (due to sympathetic over-activity).

*A 32 mg prolonged-release solution of buprenorphine for injection (Buvidal) is also available, administered as a weekly or monthly subcutaneous injection.

Treatment of heroin addiction





*Buprenorphine

Lofexidine

*The USA Food and Drug Administration recently approved a new drug ***Zubsolv,*** to treat opioid addiction that combines **buprenorphine** and **naloxone** in a 4:1 ratio (July 2013). Now also licenced in Europe (Nov 2017).

Neonatal Abstinence Syndrome

- The general rise in the use of methadone (or other) replacement therapy (MMT) and or prescription/illegal opiate abuse/abuse in pregnant women has resulted in an increased incidence of Neonatal Abstinence Syndrome (NAS) in new-born infants.

- **NAS is essentially an infant withdrawal syndrome typically characterised by symptoms such as:**

  - Excessive high-pitched crying/irritability
  - Reduced sleep
  - Tremors/increased muscle tone/convulsions
  - Sweating/increased respiration/hyperthermia
  - Repetitive yawning/sneezing
  - Excessive sucking/feeding/vomiting/diarrhoea

Neonatal Abstinence Syndrome

- Symptoms can show within 24-72 hours of birth and last up to 5 days. Midwives use a scoring chart to assess for NAS symptom severity.

- Pharmacological intervention is usually with methadone/morphine replacement, extended over 3-4 weeks.

- **Oral morphine** 60 µg/kg every 4 hours, increased to 80 µg if necessary.

- Add **oral phenobarbitone solution** if not controlled; 15 mg/kg o.d. decreasing to 8 mg/kg o.d.

Neonatal Abstinence Syndrome

- After symptoms are controlled, decrease morphine dose gradually by 10 µg/kg/dose until symptoms dissipate. It has been suggested that adding clonidine to standard opioid therapy reduced overall duration of therapy for neonatal abstinence.

- **Naloxone** is not used at delivery as it can precipitate abrupt withdrawal symptoms and seizures. The severity of NAS is apparently reduced by breast feeding. Long-term effects of pre/postnatal opiate exposure on infant development are not known.

Ref: ***Logan BA, Brown MS., Hayes MJ. (2013). Neonatal Abstinence Syndrome: Treatment and Pediatric Outcomes. Clin Obstet Gynecol. 56(1): 186–192***

Accelerated detox programs

The Waismann Method (USA) -example of an accelerated opiate addiction treatment program.

- Treatment begins in hospital - patient undergoes complete physical examination - pre-med given, followed by general anaesthetic (to suppress withdrawal symptoms) under intensive care.

A Premier Rapid Detox Center Waismann Method Beverly Hills, California

Accelerated detox programs

- **Under sedation,** patient undergoes accelerated procedure to block brain opiate receptors - additional medications given to modify and accelerate physical reactions to rapid withdrawal while patient is carefully monitored.

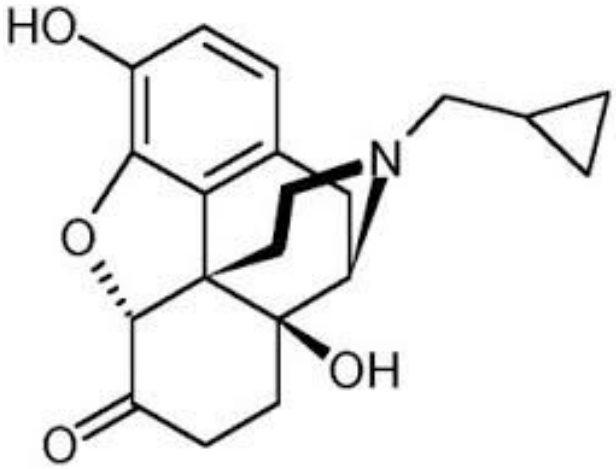
- **After ~ 4-6 hrs, process is completed** - patient recovers in ICU through following day. On awakening, patient is no longer physically dependent on opiates- no awareness of experiencing withdrawal - patients usually discharged after 1-3 days in hospital.

Accelerated detox programs

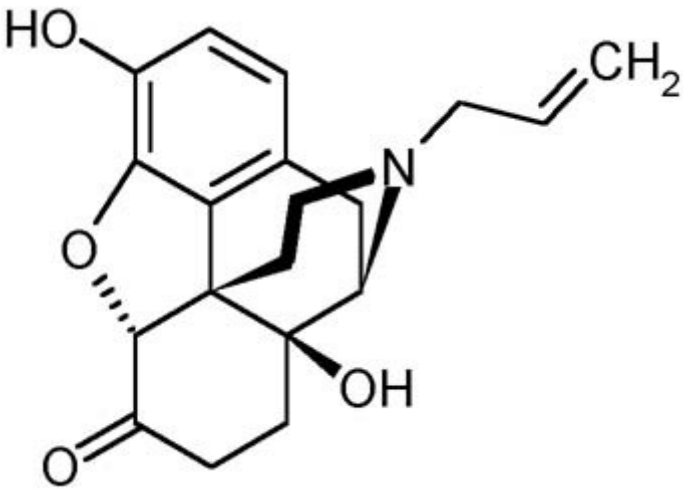
- **The cost of the standard Waismann rapid detox treatment procedure** is currently **$21,800 to $28,800**, for a 5-10 day inpatient program (March; 2025). The cost includes inpatient 24 hour hospital treatment, a private room, medical services, and a few days of recovery care. More severe opiate addictions requiring longer treatment may cost considerably more!

Accelerated detox programs

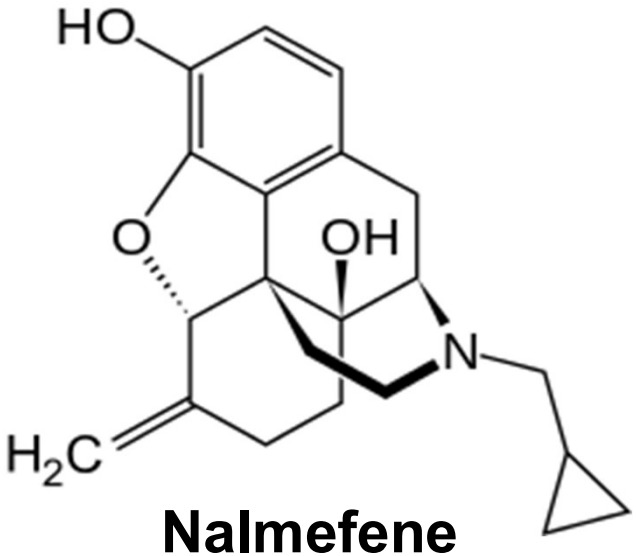
- **Naltrexone** or **Naloxone** given orally (or via implant) daily for up to 1 yr as part of rehabilitation - eliminates physical cravings, and blocks any euphoric narcotic effects if patient takes opiates again.



Naltrexone



Naloxone



Nalmefene

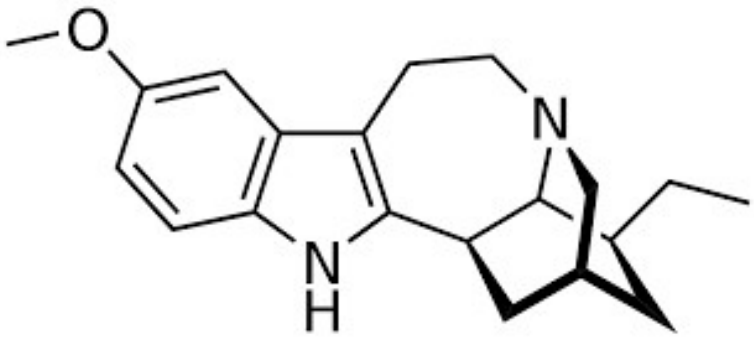
Nalmefene is another opioid receptor antagonist developed in the 1970's that has recently been introduced to reduce craving in the treatment of **alcohol addiction**.

Accelerated detox programs

- **At the OAD Clinic (Belgravia, London)** a Naltrexone Implant and Rapid Opiate Detoxification program uses oral or i.m. sedatives in place of general anaesthesia to combat acute withdrawal symptoms. The average cost of a stay at a rehabilitation centre is between £2,000 and £8,000 per week, for most private clinics.

Ibogaine therapy for heroin addiction

- **Ibogaine** is an indole alkaloid extracted from the root of the iboga plant (*Tabernanthe iboga*), which has hallucinogenic and stimulant properties. Iboga has been used traditionally in West Central Africa in religious rituals, to produce dreamy visions, stupor and unconsciousness, and also for relief of fatigue, thirst and hunger, to enhance hunting skills, and to provoke experiences of "contact with the ancestors".

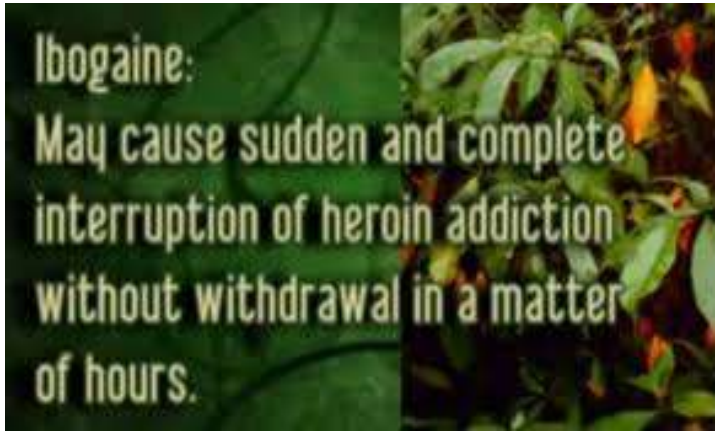


Ibogaine

Ibogaine therapy for heroin addiction

- **Informal treatment of heroin addiction** with ibogaine and other psychedelic agents: LSD and psilocybin was trialled in the USA in the 60's, leading to some notable and persistent reduction in drug cravings and withdrawal symptoms associated with heroin use.

- This led to use in self-help groups of heroin addicts, who employed the iboga root and ibogaine extracts in treatment for opiate addiction, and also to terminate withdrawal from amphetamines and cocaine.



Ibogaine therapy for heroin addiction

Mechanisms of therapeutic effects

Like other psychedelics, Ibogaine (and its active metabolite noribogaine) acts as an agonist at central **$5HT_{2A}$, $5HT_{2c}$** and **$5HT_3$** receptors, causes the **presynaptic release of 5HT**, inhibits serotonin reuptake, but also acts as a non-competitive NMDAR antagonist, a muscarinic agonist, a non-competitive nicotinic antagonist and a low affinity kappa-opioid receptor agonist.

Ibogaine therapy for heroin addiction

- **Banned in the US in 1967**, it remains available in the UK and other countries for unlicensed use, but US trials in 1990's were terminated due to safety concerns. The most serious problem is the risk of sudden death, particularly in patients with pre-existing cardiac conditions **[hERG K^+ channel inhibition]**.