Opiate Overdose

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- Opium refers to the dried extract of the poppy plant (Papaver somniferum)

- Opiates are a subset of opioids that are either derived from poppy or synthesized from any drug that is found in poppy or synthesized from one. It does not matter if the drug is synthetic or naturally occurring

- The term **opioid** is a broader term that includes opiates and refers to any substance, natural or synthetic, that **binds to the brain's opioid receptors**

- Pure opium is a mixture of alkaloids grouped in to two

- Phenanthrene group: morphine, codeine, and thebaine
- Benzylisoquinoline group: papaverine and noscapine (narcotine).

- The poppy plant is a herb growing upto 1 metre in height.
- Each plant bears 5 to 8 capsules which are incised in their unripe state to extract a milky fluid that on drying yields opium.

Unripe poppy capsule with incisions

Crude opium

- Opiates, such as codeine, or morphine, are natural derivatives of these alkaloids

- Opium cultivation is banned in India except on license from the central government, for growing the plant strictly for the pharmaceutical industry
- India produces 70 to 80% of opium that is used worldwide by pharmaceutical companies to manufacture drugs (morphine, codeine, and pethidine).
- Unfortunately, Significant quantity of opium is funnelled into a global smuggling racket

Pharmacologic uses of opioids

Derivative	*Nature*	*Classification*	*Use*
Buprenorphine	Semisynthetic	Partial agonist	Analgesic, pre-anaesthetic medication
Butorphanol	Semisynthetic	Agonist-antagonist	Analgesic
Codeine	Natural	Agonist	Antitussive
Dextromethorphan	Semisynthetic	—	Antitussive
Diphenoxylate	Synthetic	Agonist	Antidiarrhoeal
Fentanyl	Synthetic	Agonist	Adjunct to anaesthesia
Heroin	Semisynthetic	Agonist	—
Hydrocodone	Semisynthetic	Agonist	—
Hydromorphone	Semisynthetic	Agonist	—
Levorphanol	Semisynthetic	Agonist	Analgesic
Loperamide	Synthetic	Agonist	Antidiarrhoeal
Methadone	Synthetic	Agonist	Analgesic, treatment of heroin abuse and opiate abstinence syndrome

Morphine	Natural	Agonist	Analgesic
Nalbuphine	Semisynthetic	Agonist-antagonist	Analgesic
Nalmefene	Semisynthetic	Antagonist	Treatment of opiate poisoning
Naloxone	Semisynthetic	Antagonist	Treatment of opiate poisoning
Naltrexone	Semisynthetic	Antagonist	Treatment of opiate poisoning and alcoholism
Oxycodone	Semisynthetic	Agonist	Analgesic
Oxymorphone	Semisynthetic	Agonist	—
Paregoric (tincture of opium)	Natural	Agonist	Analgesic
Pentazocine	Semisynthetic	Agonist-antagonist	Analgesic
Pethidine (meperidine)	Synthetic	Agonist	Analgesic
Propoxyphene	Synthetic	Agonist	Analgesic
Tramadol	Synthetic	Agonist	Analgesic

Classification

- **A . Natural Opium**

Opium, Morphine, Codeine

- **B. Synthetic Derivatives**

Meperidine, Fentanyl, Methadone

- **C. Semi-synthetic Derivatives**

Buprenorphine, Hydromorphone, Oxymorphone, Hydrocodone, Oxycodone, Heroin

Fatal dose

Opiate	*Usual Fatal Dose*	*Usual Therapeutic Dose*
Morphine	200 mg	10 to 15 mg
Codeine	800 mg (7 to 14 mg/kg)	10 to 60 mg
Etorphine	0.03 to 0.12 mg	—
Heroin	50 mg	—
Hydrocodone	100 mg	—
Crude Opium	500 mg	—
Pethidine	1 gm	50 to 150 mg
Methadone	100 mg	5 to 10 mg
Pentazocine	300 mg	30 to 60 mg
Propoxyphene	1 gm	100 to 150 mg
Diphenoxylate	200 mg	10 to 20 mg

Mechanism of action

- Opioids share the ability to stimulate a number of specific opiate receptors in the CNS, causing sedation and respiratory depression
- Activation of opioid receptors results in inhibition of synaptic neurotransmission in the central nervous system (CNS) and peripheral nervous system (PNS).
- Opioids bind to and enhance neurotransmission at 3 major classes of opioid receptors

Mechanism of action

Receptor	Location	Actions	Drugs	Comments
Mu	Cerebral Cortex (Lamina IV), Thalamus, periaqueductal gray (the cerebral aqueduct within the tegmentum of the midbrain.)	Mu-1 Analgesia, Mu-2 Respiratory depression, Physical dependence	Morphine Fentanyl Codeine Naloxone	Classic effects of opioids act at this receptor, Mu 1 Present in low conc at birth.
Delta	Frontal Cortex, limbic system, olfactory tubercle	Analgesia, respiratory depression, euphoria, dependence	Enkephalin, endogenous, opioid peptides	Functional significance unclear

Receptor	Location	Actions	Drugs	Comments
Kappa	Spinal Cord	Spinal Analgesia, sedation, low Physical dependence	Dynorphin. Mixed antagonist	Ceiling effects, may cause withdrawal
Sigma	cerebellum, brainstem, motor nuclei, and substantia nigra. *Sigma receptors are also* found in high density in many tissues outside of the nervous system.	Psychomimetic, hallucinations, dysphoria, Tachycardia, hypertension, respiratory and vasomotor stimulation	Phencyclidine Katamine Pentazocine	

Toxicokinetics

Absorption

- GI tract, subcutaneous, intramuscular or intravenous injection
- The bioavailability of oral form is less due to due to significant first-pass metabolism in the liver

Distribution

- Extent of protein-binding is variable depending on the exact nature of the opiate
- 7% for codeine, 96% for buprenorphine, 34% for Morphine.

- Metabolism of morphine is conjugation with glucuronic acid to produce active morphine-6-glucuronide
- Excretion occurs in the urine as morphine-3-glucuronide

TABLE II–39. COMMON OPIATES AND OPOIDS[a]

Drug	Type of Activity	Usual Adult Dose[a] (mg)	Elimination Half-Life (h)	Duration of Analgesia (h)
Butorphanol	Mixed	2	3–4	3–4
Codeine	Agonist	60	2–4	4–6
Fentanyl	Agonist	0.2	1–5	0.5–2
Heroin[b]	Agonist	4	(b)	3–4
Hydrocodone	Agonist	5	3–4	4–8
Hydromorphone	Agonist	1.5	1–4	4–5
Meperidine	Agonist	100	2–5	2–4
Methadone	Agonist	10	20–30	4–8[c]
Morphine	Agonist	10	2–4	3–6
Nalbuphine	Mixed	10	5	3–6
Oxycodone	Agonist	4.5	2–5	4–6
Pentazocine	Mixed	50	2–3	2–3
Propoxyphene	Agonist	100	6–12	4–6

[a]Usual dose: Dose equivalent to 10 mg of morphine.
[b]Rapidly hydrolyzed to morphine.
[c]Sedation and coma may last 2–3 days

Medical Syndromes in opiate abusers

Syndrome onset and Duration	Characteristics
Opiate Intoxication	Conscious, sedated, mood normal to euphoric, pinpoint pupils, history of recent opiate use
Acute overdose	Fear of withdrawal, anxiety, drug craving, drug seeking behavior, lacrimation, dilated pupils restlessness, yawning, nausea nasal stuffiness, rhinorrhea

Drug Interaction

- Depressant effect of opiates is enhanced by Alcohol, Phenothiazines, Cyclic antidepressant and MAOIs.
- Concomitant administration of Cimetidine can result in mental confusion.

Clinical Manifestations

Acute poisoning :

- Coma
- Pinpoint pupils
- Bradypnea, (tachycardia and ECG readings of sinus tachycardia and nonspecific ST-T segment changes have been reported)
- Cynasosis
- Non-cardiogenic pulmonary oedema "heroin-lung"
- Hypotension
- Hypothermia
- Convulsions

Chronic poisoning :

- American Psychiatric Association diagnostic criteria for opiate dependence and for categorizing the severity of dependence

Severity	Symptoms
Mild	Few Symptoms, mild impairment of social and occupational activities
Moderate	Intermediate between mild and severe
Severe	Many symptoms: marked impairment of occupational and social activities
Partial remission	During past 6 months there has been some opiate use and some dependence symptoms
Full remission	During past 6 months there has been no opiate use and no dependence symptoms

- Urinary retention
- Pupils may be dilated in the presence of severe acidosis, hypoxia, or respiratory depression. Pethidine often causes mydriasis
- Seizures
- Cramping and constipation
- Hyperkalaemia with overdose
- opiates cross the human placenta
- Foetuses demonstrate distress and acidosis and whose mothers received opiates 1 to 3 hours prior to delivery, or multiple doses, may be at increased risk for respiratory depression (absent foetal breathing movements)

Opiate dependence : at least three of the following must be present

- Taken in large amounts, or over long period than the person intended
- Intense desire for the drug or has made unsuccessful attempts to cut down intake.
- Patient is frequently under the influence of the drug, or undergoing withdrawal when expected to be studying or working
- Demonstrates tolerance to the drug
- Demonstrates characteristic withdrawal syndrome
- Opiates are taken to relieve or avoid withdrawal reaction
- Social, occupational or recreational activities are given up or reduced.

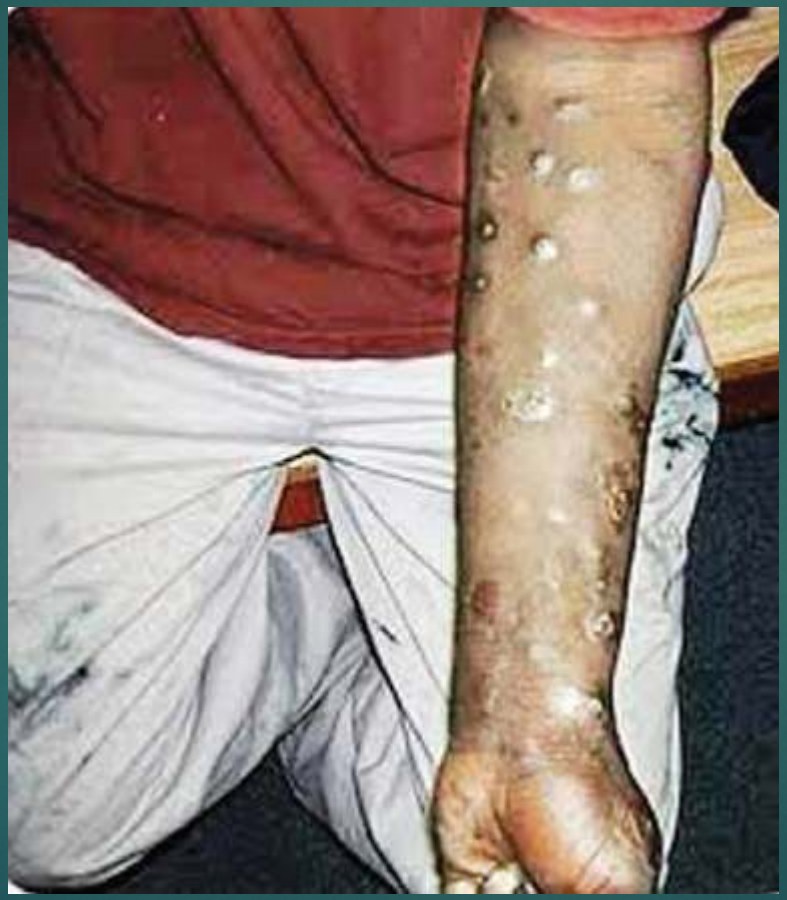
Signs of opiate addiction

- Unusual changes in behavior, mood swings, Depression, anger irritability alternating periods of Euphoria.
- Loneliness and isolation
- Denial of primary symptom of addiction
- Domestic strife, fights arguments
- Need to be near their drug source
- Overspending, legal problems
- Sexual drive decrease

- Pills, syringes, alcohol bottles found around.
- Bloody swabs or tissues found at home.
- Habit of locking themselves
- Pinpoint pupils
- Evidence of withdrawal, Diaphoreses and tremors.
- Weight loss and pale skin
- Undetected addicts found in comatose.
- Untreated addicts are found dead

- Abrupt cessation of opiate intake can cause a withdrawal reaction (cold turkey).
- Amnesia, confusion, and occasional hallucinations can also occur
- Compartment syndrome may occur following abuse of narcotic injections, such as heroin

Skin lesions – Heroin addict



- Neonatal withdrawal may be seen in the infants of addicted mothers 12 to 72 hours after birth.

- Infants may be dehydrated, irritable, and experience tremors and cry continually and may have diarrhoea.

Opiate withdrawal

Anticipatory 3 to 4 hrs	Early 8 to 10hrs	Fully developed 1 to 3 days	Protracted Abstinence Up to 6months
Anxiety, craving, drug seeking behavior	Restlessness, yawning, nausea, sweating, rhinorrhoea, lacrimation, mydriasis, stomach cramps, drug seeking behavior	Tremor, piloerection, vomiting, diarrhea, muscle spasm, hypertension, tachycardia, fever, chills, impulse driven drug seeking behavior	Hypotension, bradycardia, insomnia, anorexia, stimulus driven opiate craving

Diagnosis

- Needle marks, dermal scars – suggestive of addiction
- Evidence of hypoglycemia, hypoxia, and hypothermia
- Most opiates detected in urine and blood by GC, GC-MC, HPLC
- Hair Analysis
- Semi quantitative and qualitative homogeneous enzyme assay detect morphine, methadone, codeine, and hydromorphone and higher concentration of Nalorphine and Pethidine.
- Monitor the arterial blood gases and pulse oximetry, PFT and CXR in patient with significant exposure
- In overdose heroin may be detected for as long as 36 hrs.
- Save the syringe or other equipment from an overdose for analysis of toxic substance.

Treatment

Acute Poisoning :

- Treatment is based on the clinical presentation then on specific lab data.

Emergency and Supportive measures

Airway Maintenance

- Endotracheal Intubation, assisted ventilation
- Ventilation with small tidal volume 6 ml/kg is preferred if ARDS develops.
- Pulmonary artery wedge pressure –relatively low while still maintaining adequate cardiac output, BP and urine output.

GUT Decontamination

- **Ipecac induced emesis-** not recommended – Potential CNS Depression and seizures.

- Administration of the activated charcoal within a hour is very effective

Antidote

- **Naloxone –** Antagonizes opioid effects by competing for the μ, κ and σ opiate receptor sites in the CNS, with the greatest affinity for the μ receptor.
- The usual initial dose is 1.2 mg for an adult and 0.4 mg for a child
- Repeat doses of 2 mg may be given to achieve a clinical effect
- Best route of administration is IV, but if venous access is difficult
- Drug can be injected sublingually or intramuscularly, or even

Antidote

- Single bolus dose of naloxone is usually short-lived, repeated doses are required
- The onset of effect following IV naloxone administration is 1-3 minutes; maximal effect is observed within 5-10 minutes.
- A repeat dose is indicated for partial response and can be repeated as often as needed
- Some investigators state that a naloxone infusion is better than repeated injections

Antidote

- **Naltrexone :** An opioid antagonist with a longer duration of action
- it must not be given to an opiate-dependant patient who has not been detoxified.
- Dose: 50 mg/day orally, which may have to be continued for several weeks or months

Antidote

- **Nalmefene**
- Nalmefene is a naltrexone derivative with pure opiate antagonistic effects, and has a longer duration of effect than naloxone in acute opiate poisoning
- It is usually given intravenously beginning with 0.1 mg, and if withdrawal reaction does not occur, 0.5 mg is administered, followed by 1 mg in 2 to 5 minutes (if necessary). Nalmefene can also be given intramuscularly or subcutaneously

- **Physostigmine salicylate :** 0.04mg/kg IV – reversing the respiratory depression if the regular opiate antidotes are not available.

CHARASTERISTIC OF ANTIDOTE

	Naloxone	Nalmefene
Elimination half-life	60–90 min	10–13 h
Duration of action	1 h	1–4 h*
Metabolism	Liver (glucuronidation)	Liver (glucuronidation)
Cost (equivalent doses)	$0.91/0.4 mg	$4.38/0.25 mg
Advantages	Lower cost; shorter action; more human experience	Longer duration lowers risk of recurrent respiratory depression for most (but not all) opioids
Disadvantages	More frequent dosing or constant infusion	Cost; may cause prolonged opioid withdrawal

*High doses (eg, > 6 mg) may increase the duration of action but are not recommended at this time. (Clinical studies suggest that a single 50-mg oral dose of nalmefene may block opioid effects for 48 h.)

- Convulsions – Benzodiazepines 5 to 10 mg initially repeat every 5 to 10 min as needed.

- It is not necessary if Naloxone is available.

- Monitor- Respiratory depression, hypotension, arrythmias. hypoxia, electrolyte disturbance and
- Treat hypoglycemia with IV dextrose 50 ml

- Hypotension : 10 to 20 ml/kg of isotonic fluid. If hypotension persist –
- Dopamine 5mcg /kg/min or Noradrenaline 0.5 to 1 mcg/min and titrate to maintain adequate BP.
- Prevention of Rhabdomyolysis: Early aggressive fluid replacement – help renal insufficiency.

- Mannitol, Furosemide - To maintain the urine output.
- Haemodialysis : Norpethidine neurotoxicity

Chronic Poisoning treatment

- Gradual withdrawal of opiate
- Substitution therapy- methadone 30 to 40 mg/d and gradual taper
- Beta Adrenergic blocker Propranolol 80 mg- Relieve anxiety craving. No effect on physical symptom.
- Gabapentin with Clonidine and Naltrexone : 0.1mg Clonidine TID for 7 days Naltrexone 50 mg BID – 14 days and Gabapentin 600 mg BID on all for 21 days.)

- Antispasmodics for abdominal cramps with Vomiting and Diarrhea.
- Tranquillizers or bed time sedation if required
- Psychiatric counseling.