Analgesic Drugs

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Pain management

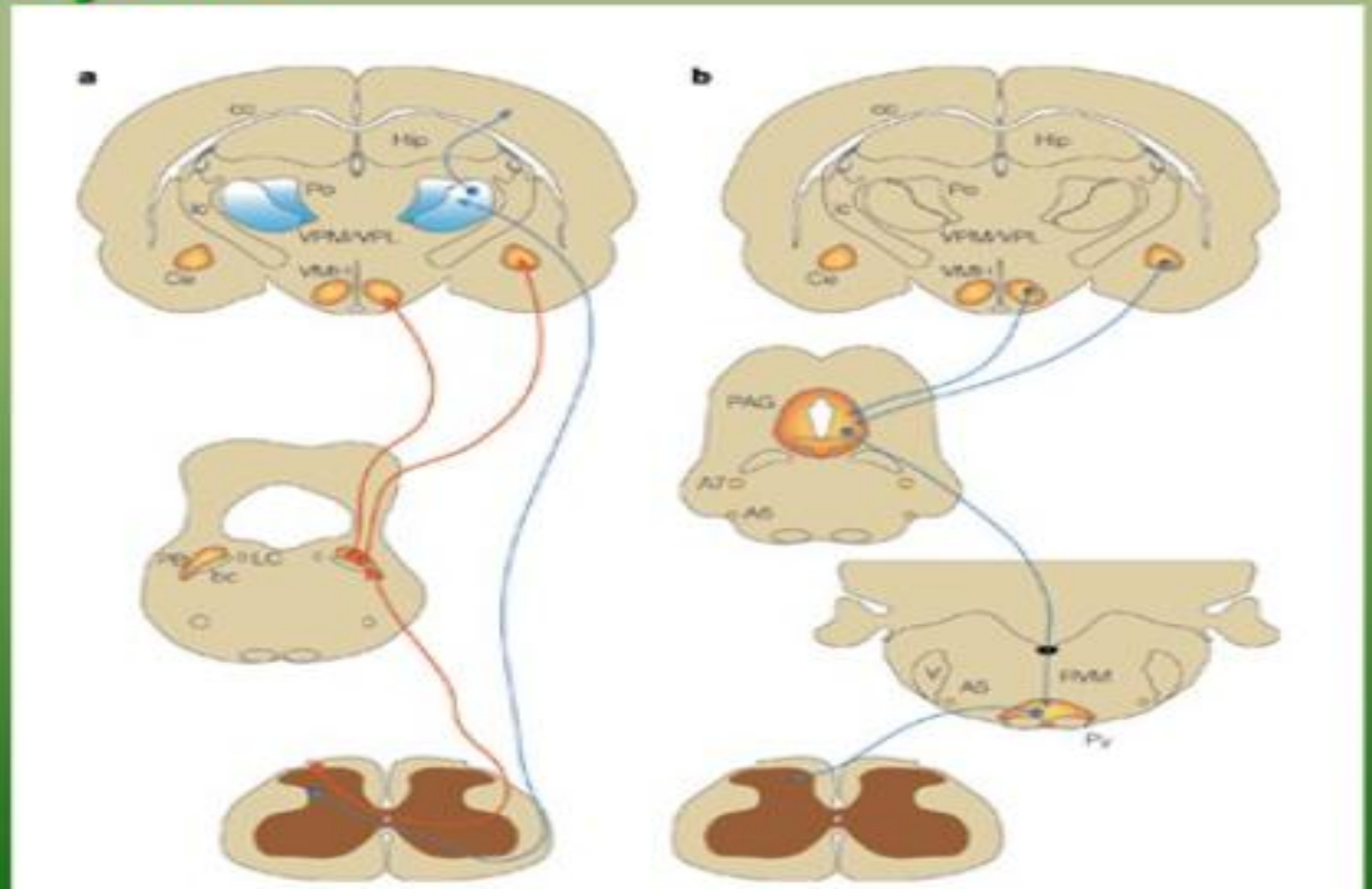
What is pain?

- A protective mechanism to warn of damage or the presence of disease.

- Part of the normal healing process
- A protective mechanism to warn of damage or the presence of disease

The structures that take part in perception of pain: thalamus, hypothalamus, reticular formation, limbic system, occipital and frontal areas of cortex

System which conducts and perceives pain - nociceptive



Major Sources of Pain

Source	Area Involved	Characteristics	Treatment
Somatic	body framework	throbbing, stabbing	narcotics, NSAIDS
Visceral	kidneys, intestines, liver	aching, throbbing, sharp, crampy	narcotics, NSAIDS
Neuropathic	Nerves	burning, numbing, tingling	narcotics, NSAIDS, antidepressants, anticonvulsants

Classification of Pain By Onset and Duration

- Acute pain
  - Sudden in onset
  - Usually subsides once treated
- Chronic pain :
  - Persistent or recurring
  - Often difficult to treat

Analgesic drugs

Analgesic: The drugs which are used to relieve or decrease pain (without the loss of consciousness) are called analgesics.

- These are also called as pain killers or pain relievers.
- Antipyretic: A drug given to reduce or stop fever.
- Inflammation: A basic way in which the body reacts to infection, irritation or other injury, the key feature being redness, warmth, swelling and pain.

- What is an Analgesic
- Analgesics reduce the effect of pain without causing any mental confusion, paralysis or any other disturbances in the nervous system so that you actually get rid of the pain without any imbalance in the nervous system. The analgesic drugs can act in many ways on the peripheral or central nervous system, but they do not eliminate the sensation of pain as in the case of anaesthetics.

Analgesics classification (depending on types)

1. Narcotics:

(Opioids (morphine & morphine like drugs)

These types of analgesic drugs are taken for medical use in prescribed doses, where they act by relieving the pain and producing sleep. If the dose of this analgesic drug increases then it can lead to coma, convulsion and finally result in death.

Morphine is the most common type of narcotic analgesic used nowadays, they are also referred to as opiates since they are obtained from the opium poppy.

Narcotic analgesics or painkillers are mostly used for relieving postoperative pain, cardiac pain and the pain of terminal cancer.

- Natural (as codeine)
- Semi synthetic e.g. di-hydromorphine &diacetylmorphine (heroin)
- Synthetic e.g. pethidine
- Endogenous opiates asendorphins & encephalins

2. Non-narcotic- NSAID

Non-narcotic (non-addictive) analgesics

This type of drug is generally used for relieving the skeleton pain which can happen due to arthritis. Aspirin and paracetamol are the most common drugs in this case. When you take aspirin, it acts by inhibiting the synthesis of the chemical known as prostaglandins by chemical reactions which causes inflammation in the tissues and as a result the sensation of pain is felt.

These drugs also help in reducing fever and preventing platelet coagulation. The anti-blood-clotting action is the reason why aspirin is used for the prevention of heart attacks.

- Aspirin , Paracetamol , Diclofenac , Piroxicam , Ibuprofin , Ketoprofin

Analgesics are divided into

Narcortic analgesics
(opioid analgesics)

e.g. Morphine

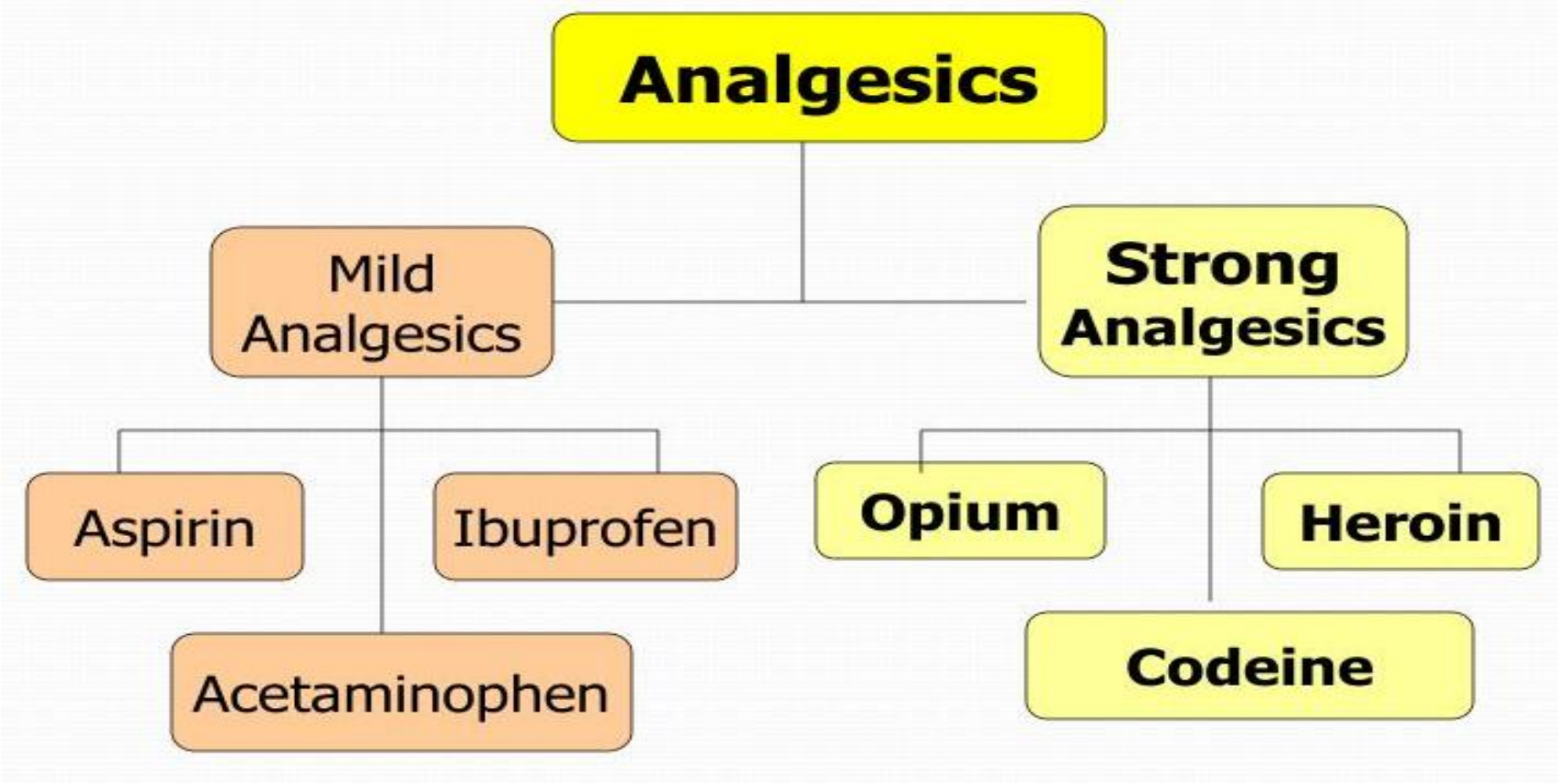
Non- narcotic analgesics
(non- opioid analgesics)
(non- steroidal
anti-inflammatory drugs)
NSAIDs

e.g. Aspirin

Narcotic analgesics:

- There are two types of narcotic analgesics.
- The opiates and the opioids (derivatives of opiates).
- Opiates are the alkaloids found in opium (a white liquid extract of unripe seeds of the poppy plant).
- Opioids are any medication which binds to opioid receptors in the central nervous system or gastrointestinal tract.
- Opioids are used in medicine as strong analgesics, for relief of severe or chronic pain. Interestingly, there is no upper limit for the dosage of opioids used to achieve pain relief, but the dose must be increased gradually to allow for the development of tolerance to adverse effects (for example, respiratory depression).

Analgesics classification (depending on strangth)



Strong Analgesics

- Only Available by prescription
- Used to relieve severe pain associated with injuries, heart attacks, or chronic diseases such as cancer
- Most strong analgesics are derived from the opium poppy or synthetically produced
- Basically three types: Natural, semi-synthetic, and synthetic.

Opioid analgesics

- Opioid include natural (Morphine), semisynthetic (Heroin) and synthetic (Fentanyl).
- They reduce moderate to severe pain without loss of consciousness.
- They act by binding to specific receptors located primarily in the brain and spinal cord.

CLASSIFICATION OF OPIOIDS

- Strong agonists
- Moderate / low agonists
- Mixed agonists antagonists
- Antagonists
- Others

- **Strong agonists**

Morphine
Mepridine (Pethdine)
Methadone
Heroin (acetyl morphine)
Fentanyl
Alfentanyl

B) **Moderate Agonists**

- Codeine , oxycodone
- Propoxyphene

C) Mixed: Agonist/Antagonist

- Pentazosine
- Buprenorphine (partial agonist at μ receptors)

D) Pure Antagonist:

- Nalaxone
- Naltraxone
- Nalmefene

Mechanism of strong analgesics

- The human body contains “natural opiates” in the brain called endorphins
- These are produced in the body during extreme conditions such as “running high” and extreme injuries.
- When these are absorbed by receptors in the brain the body feels analgesia and the pain is reduced.
- Opiates derived from the poppy act in the same way as endorphins but are not natural to the human body.
- The “high” is produced because of the absorption of opiates is quicker than endorphins.
- Drugs such as naloxone act to fill the receptors in the brain but are not analgesics and thus are used to prevent overdoses on analgesics. (Naloxone, sold under the brand name Narcan among others, is a medication used to reverse the effects of opioids. It is commonly used to counter decreased breathing in opioid overdose).
- Endorphins are not used as analgesics because the cannot be stored and are unstable.
- Presynaptically: Opioid receptor activation can close voltage – gated calcium ion channels to inhibit neurotransmitter release. (serotonin, glutamate and substance P).
- Postsynaptically: Activation of these receptors can open potassium ion channels to cause membrane hyperpolarization(inhibitory post synaptic potential). - Direct inhibition of neurons in ascending pathways.

History of Opioids / Opium

- Opium is extracted from poppy seeds (Papaver somniforum)

- Used for thousands of years to produce:
  - Euphoria
  - Analgesia
  - Sedation
  - Relief from diarrhea
  - Cough suppression
- Opium (poppy tears, lachryma papaveris) is the dried latex obtained from opium poppies (Papaver somniferum). Opium contains up to 12% morphine, an opiate alkaloid, like codeine, papaverine noscarpine (benzoisochinolon derivatives)



Opioid receptors

- Narcotic analgesics produce pharmacological effects by interacting with specific opiate receptors. At least five major types of opiate receptors have been recognised. These include mu (morphine) and kappa (ethylketazocine) receptor types.
- Opioid receptors are group of G-protein coupled receptors with opioids as ligands.
- The endogenous opioids are dynorphins, enkephalins, endorphins, endomorphins and nociceptin.

- Subtypes of opiod receptors:

mu, delta, kappa, epsilon, sigma

Opiod Receptor Activation

Response	Mu-1	Mu-2	Kappa	Delta	Sigma
Analgesia	★	★	★	★	
Respiratory depression		★			
Euphoria		★		★	
Dysphoria			★		
Decrease GI motility		★			
Physical Dependence		★			
Mania, hallucination					★

Morphine CNS

Depressant effects

- Analgesia
- Indifference to surroundings
- Mood and subjective effects
- Depression of respiration
- Cough centre
- Temperature regulating centre
- Vasomotor centre

Stimulate effects

- CTZ (nausea, vimiting)
- Edinger Wesphal nucleus

(III nerve –producing miosis)

- Vagal centre (bradycardia)
- Certain cortical areas and hippocampal

Morphine can be used as an analgesic to relieve:

- Pain in myocardial infarction
- Pain associated with surgical conditions, pre- and postoperatively (pre-anesthetic medication, balanced anesthesia, surgical analgesia)
- Pain associated with trauma, burns
- severe chronic pain, e.g., cancer
- Pain from kidney stones, renal colic, ureterolithiasis, etc (pain may be valuable for diagnosis: should not be relived by analgesic unless proper assessment of the patient has been done)
- Traumas of thorax accompanied by cough (morphine depresses central links of coughing reflexes)

Morphine

- **Morphine** : is the major analgesic drug contained in crude opium and is the prototype strong agonist. Morphine may be given by injection (intravenous or intramuscular) or by mouth, often as slow-release tablets.
- It is metabolized to morphine-6-glucuronide, which is more potent as an analgesic.
- **Actions of Morphine:**

➢ Analgesia

➢ Euphoria and sedation

➢ Respiratory depression and suppression of cough

➢ Nausea and vomiting

➢ Reduced gastrointestinal motility, causing constipation

➢Histamine release, causing bronchoconstriction.

Applications in Dentistry

- Narcotic (opioid) analgesics are extremely effective in reducing acute dental and postoperative pain.
- The narcotic analgesics have established a niche for the treatment of pain in those situations where the NSAIDs are less effective.
- Hydrocodone, oxycodone, codeine, and occasionally meperidine are the narcotics used to treat dental pain.

MORPHINE HYDROCHLORIDE

routes of administration

- subcutaneously and intramuscularly
  (analgesic action after 10-15 min)
- oral administration – presystemic elimination
  (20-60 % enters general blood circulation)
- sublingually – quick absorption
- i.v. is indicated even in emergency
- Epidural or intrathecal (into the spinal canal) injection produces segmental analgesia lasting 12 hours without affecting other sensory, motor or autonomic modalities

Duration of analgesic action – 4-6 hours

Maximum single dose of morphine is 0,02 g,
maximum daily dose – 0,05 g

Side effects of morphine

- Respiratory depression
- Vomiting (excitation of starting zone of vomiting center)
- bradycardia (increasing of tone of n. vagus nuclei)
- spasm of sphincters of gastro-intestinal tract accompanied by constipations
- increasing of tone of smooth musculature of urinary and bile-excreting tracts (retentions of urination, bile stasis)
- Decreasing of BP

CONTRAINDICATIONS FOR ADMINISTRATION OF MORPHINE

- acute respiratory depression
- renal failure (due to accumulation of the metabolites morphine-3-glucuronide and morphine-6-glucuronide)
- chemical toxicity (potentially lethal in low tolerance subjects)
- raised intracranial pressure, including head injury (risk of worsening respiratory depression)
- Biliary colic

❑Precauntation

- pain that accompanies chronic inflammatory pain
- children before the age of 2 years

Tolerance

- Tolerance is a diminished responsiveness to the drug's action that is seen with many compounds
- Tolerance can be demonstrated by a decreased effect from a constant dose of drug or by an increase in the minimum drug dose required to produce a given level of effect
- Physiological tolerance involves changes in the binding of a drug to receptors or changes in receptor transductional processes related to the drug of action
- This type of tolerance occurs in opioids

Addiction

- Physical Dependence
- Physiological dependence
- Withdrawal reactions

Psychological effects and addiction: Tolerance & dependency

Tolerance is one of the brain compensating mechanisms that gradually reduce the effects of drugs.

Psychological dependency:

influenced by the reward system of the brain

Physical dependency:

drug deprivation leading to physical symptoms (e.g. pain, severe tremors, convulsions)

Drug dependency:

drug intake in order to prevent or diminish the physical or psychological disturbances of withdrawal (abstinence phenomenon)

Withdrawl Reactions

Acute Action

- Analgesia
- Respiratory Depression
- Euphoria
- Relaxation and sleep
- Tranquilization
- Decreased blood pressure
- Constipation
- Pupillary constriction
- Hypothermia
- Drying of secretions
- Reduced sex drive
- Flushed and warm skin

Withdrawl Sign

- Pain and irritability
- Hyperventilation
- Dysphoria and depression
- Restlessness and insomnia
- Fearfulness and hostility
- Increased blood pressure
- Diarrhea
- Pupillary dilation
- Hyperthermia
- Lacrimation, runny nose
- Spontaneous ejaculation
- Chilliness and "gooseflesh"

Codeine

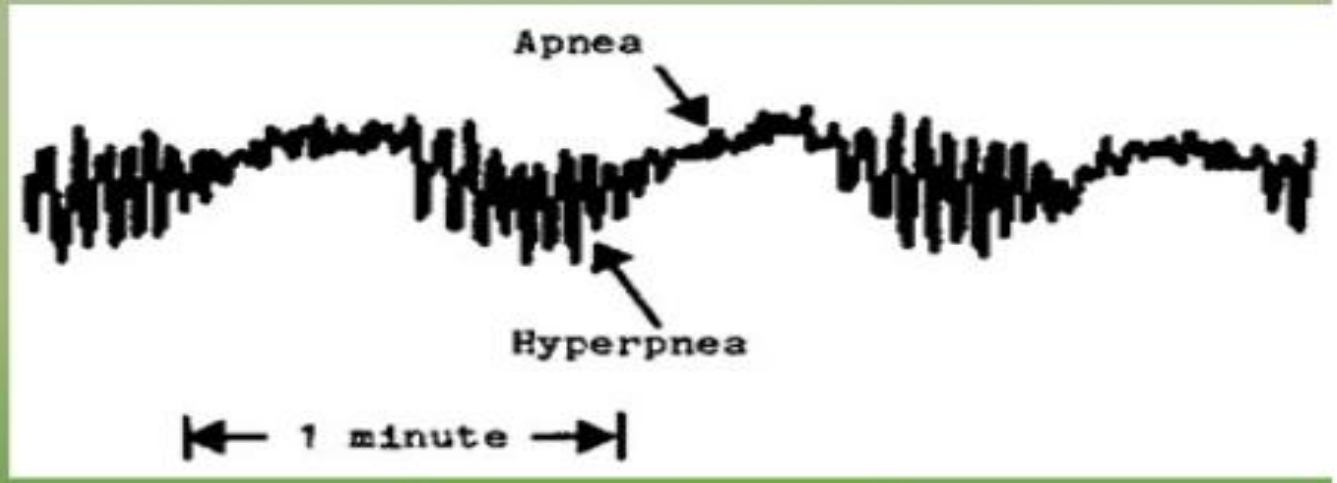
- Codeine opium alkaloid
- analgesic action is not strong, but anticough effect is considerable
- administered as an anticough drug of central action
- combination with non opiod analgesics
- (eg. Paracetamol) is supra-additive

Acute poisoning with opioid analgesics

- Respiratory Depression
- Euphoria
- Relaxation and sleep
- Tranquilization
- Decreased blood pressure
- Constipation
- Pupillary constriction
- Hypothermia
- Drying of secretions
- Flushed and warm skin

Triad in case poisoning with morphine

Acute miosis (Pinpoint pupils)



Cheyne Stokes respiration

deep *tendon reflexes increased*

Treatment of acute poisoning

- **Naloxon** (antagonist of opioid receptors)

  intravenously - 0,4-1,2 mg

  general dose of naloxon should not overcome 10 mg

- stomach lavage (for morphine enterohepatic circulation is typical) with 0,05-0,1% solution of potassium permanganate and 0,5 % tannin solution
- suspension of 20-30 g of activated charcoal
- salt laxative agents (sodium sulfate)
- forced diuresis
- atropine sulfate
- inhalation of carbogen (5-7 % CO_2 and 93-95 % O_2)

Tramadol

Generic name: tramadol

Brand names: ConZip, Qdolo, Ultram, Ultram ER

Drug class: Narcotic analgesics.

❑What is tramadol?

Tramadol is a pain medicine similar to an opioid and is classified as a synthetic opioid. It acts in the central nervous system (CNS) to relieve pain.

Tramadol is used to treat moderate to severe pain in adults.

❑Dosing information

Usual Adult Dose for Pain:

- Adults (17 years or older): 50 to 100 mg orally every 4 to 6 hours as needed for pain
- For patients not requiring rapid onset of analgesic effect: Initial dose: 25 mg orally once a day; titrate in 25 mg increments every 3 days to reach a dose of 25 mg four times a day; thereafter increase by 50 mg as tolerated every 3 days
- Maximum dose: 400 mg per day.
- Unlike aspirin, acetaminophen and codeine, which have an analgesic duration of approximately four hours, tramadol provides analgesia for five to six hours after dental surgery.
- Also, tramadol successfully managed pain for patients with chronic periodontitis, chronic pulpitis and alveolitis.

Heroin

- **Heroin:**
- Heroin is synthesized from morphine by a relatively simple esterification reaction of two alcohol (phenol) groups with acetic anhydride (equivalent to acetic acid).
- Heroin is much more potent than morphine but without the respiratory depression effect.
- A possible reason may be that heroin passes the blood-brain barrier much more rapidly than morphine.
- Once in the brain, the heroin is hydrolyzed to morphine which is responsible for its activity.

Heroin

- What are the effects of heroin?
- Heroin enters the brain rapidly and binds to opioid receptors on cells located in many areas, especially those involved in feelings of pain and pleasure and in controlling heart rate, sleeping, and breathing.
- **Short-Term Effects**
- People who use heroin report feeling a "rush" (a surge of pleasure, or euphoria). However, there are other common effects, including:
- dry mouth
- warm flushing of the skin
- heavy feeling in the arms and legs
- nausea and vomiting
- severe itching
- clouded mental functioning
- going "on the nod," a back-and-forth state of being conscious and semiconscious

Long-Term Effects

- People who use heroin over the long term may develop:
- insomnia
- collapsed veins for people who inject the drug
- damaged tissue inside the nose for people who sniff or snort it
- infection of the heart lining and valves
- abscesses (swollen tissue filled with pus.
- constipation and stomach cramping
- liver and kidney disease
- lung complications, including pneumonia
- mental disorders such as depression and antisocial personality disorder
- sexual dysfunction for men
- irregular menstrual cycles for women.

Fentanyl synthetic opioid analgesic of short action

- Analgesic activity is 300 times higher than of morphine analgesic effect after intravenous introduction – after 1-3 min, lasts for minused with neuroleptic droperidol (complex drug – “talamonal”) for neuroleptic analgesia form of analgesia achieved by the concurrent administration of a neuroleptic such as droperidol and an analgesic such as fentanyl.
- Anxiety, motor activity, and sensitivity to painful stimuli are reduced; the person is quiet and indifferent to surroundings

Fentanyl transdermal system

Should be used for long-term (chronic) pain requiring continuous narcotic pain is designed to release the drug into the skin at a constant rate ranging from 25 to 100 micrograms/h,

Drugs	Uses	Adverse Effects
Morphine	Widely used for acute and chronic pain	Sedation Respiratory depression Tolerance and dependence Euphoria
Methadone	Chronic pain Maintenance of addicts	As morphine but little euphoric effect Accumulation may occur because of long half-life
Pethidine	Acute pain	As morphine, anticholinergic effects Risk of excitement and convulsions
Pentazocine	Mainly acute pain	Irritation at injection site. May precipitate morphine withdrawal syndrome

Fentanyl	Acute pain Anesthesia	As morphine
Codeine	Mild pain	Mainly constipation No dependence liability
Dextropropoxyphene	Mild pain	Respiratory depression May cause convulsions No longer recommended
Tramadol	Acute (mainly postoperative) and chronic pain	Dizziness May cause convulsions