DRUGS USED IN MANAGEMENT OF PAIN

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MEDICAL PHARMACOLOGY
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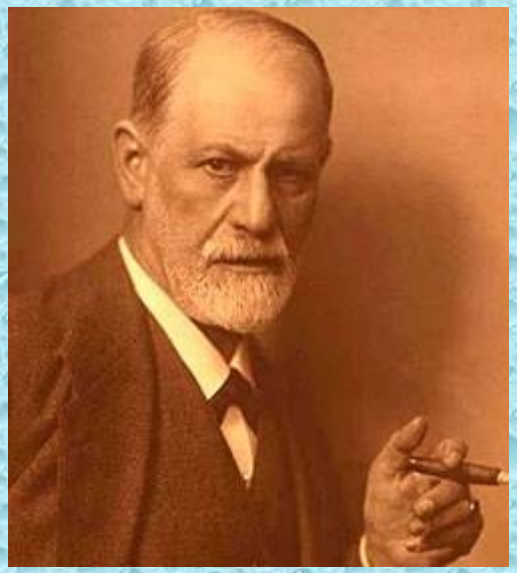
DRUGS USED IN MANAGEMENT OF PAIN

A CASE OF OVERDOSE

Sigmund Freud, the father of psychoanalysis



His cancer of the jaw was causing him increasingly severe **PAIN** & agony

He begged his friend and doctor, Max Schur to relieve him.

His doctor administered increasing doses of **MORPHINE** that resulted in Freud's death on 23 September 1939

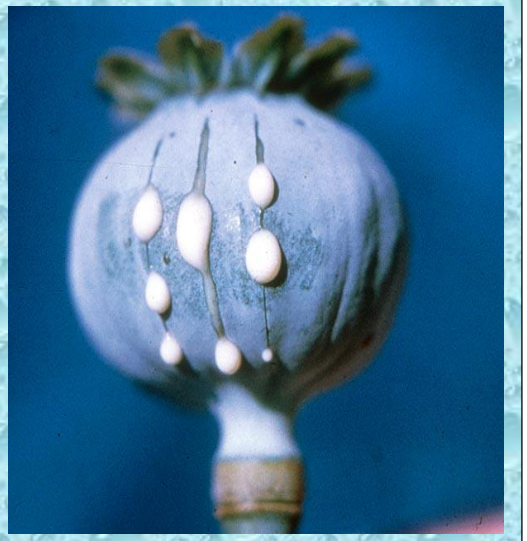
WHAT EFFECT OF MORPHINE CAUSED THE DEATH OF **SIGMUND FREUD?**

EUTHENASIA

DRUGS USED IN MANAGEMENT OF PAIN

ILOS

Categorize the different classes of drugs used to relieve pain



Detail on the mechanism of action, pharmacokinetics & pharmacodynamic effects of morphine & its synthetic derivatives

Hints on the properties & clinical uses of morphine antagonists.

DRUGS USED IN MANAGEMENT OF PAIN

WHY SHOULD WE TREAT PAIN?

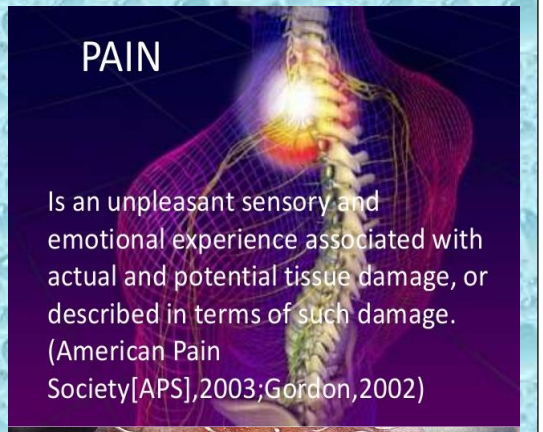
Pain is a miserable experience

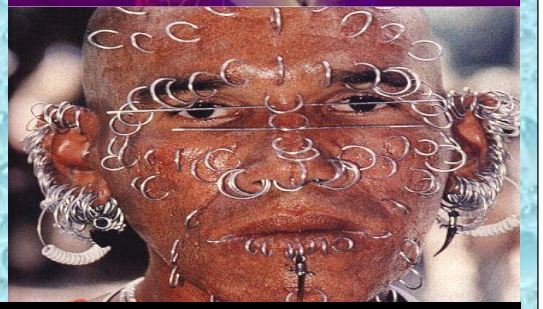
Pain is the most common reason patient seek medical advice

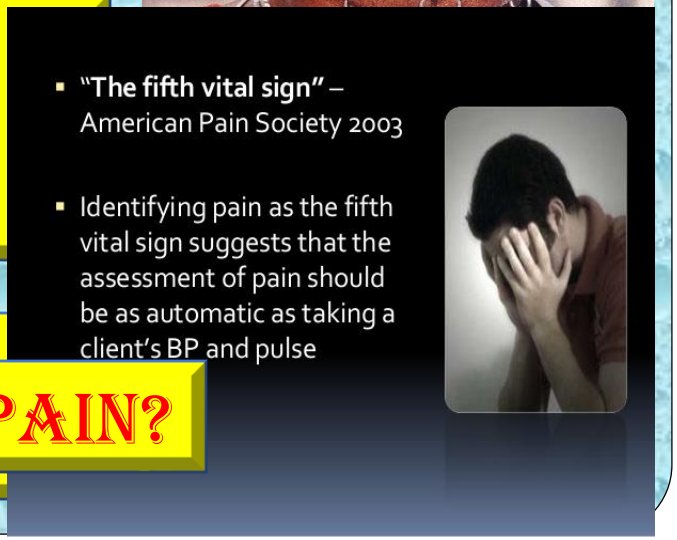
Impairs the patient functional ability & psychological well being

Pain increases sympathetic output
-Increases myocardial oxygen demand
-Increases BP, HR

Pain limits mobility
-Increases risk for DVT/PE



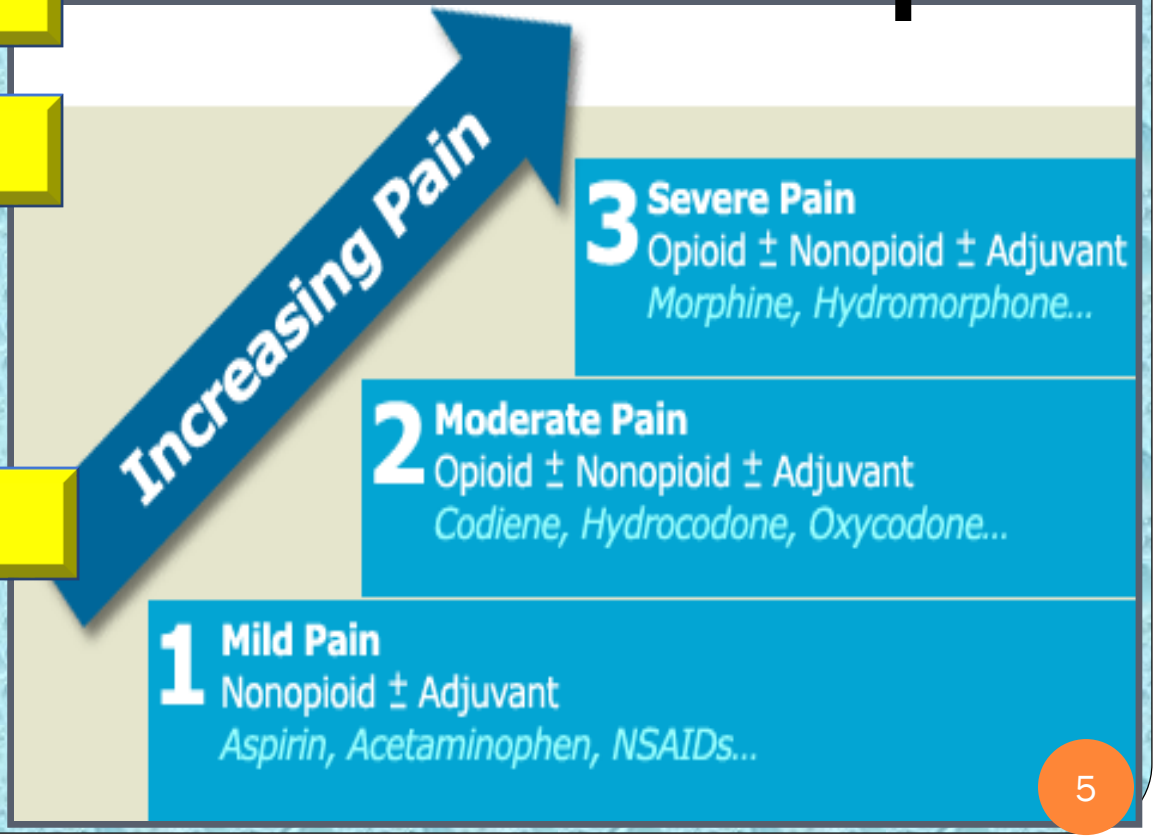




WHAT IS PAIN?

CLASSES OF DRUGS USED IN MANAGEMENT OF PAIN

- NSAIDs
- Opioids
- Adjuvant drugs
- WHO Pain Ladder



NSAIDS

Generally the 1st class of drugs used for controlling pain

Work at site of tissue injury to prevent the formation of the nociceptive mediators

Can decrease opioid use by ~30% therefore decreasing opioid-related side effects

They neither cause tolerance or dependence

Has a ceiling effect to analgesia.

ADJUVANT DRUGS

e.g. Anxiolytics,
Neuroleptics,
Antidepressants
Antiepileptics

May modify the perception of pain & remove the concomitants of pain such as anxiety, fear, depression

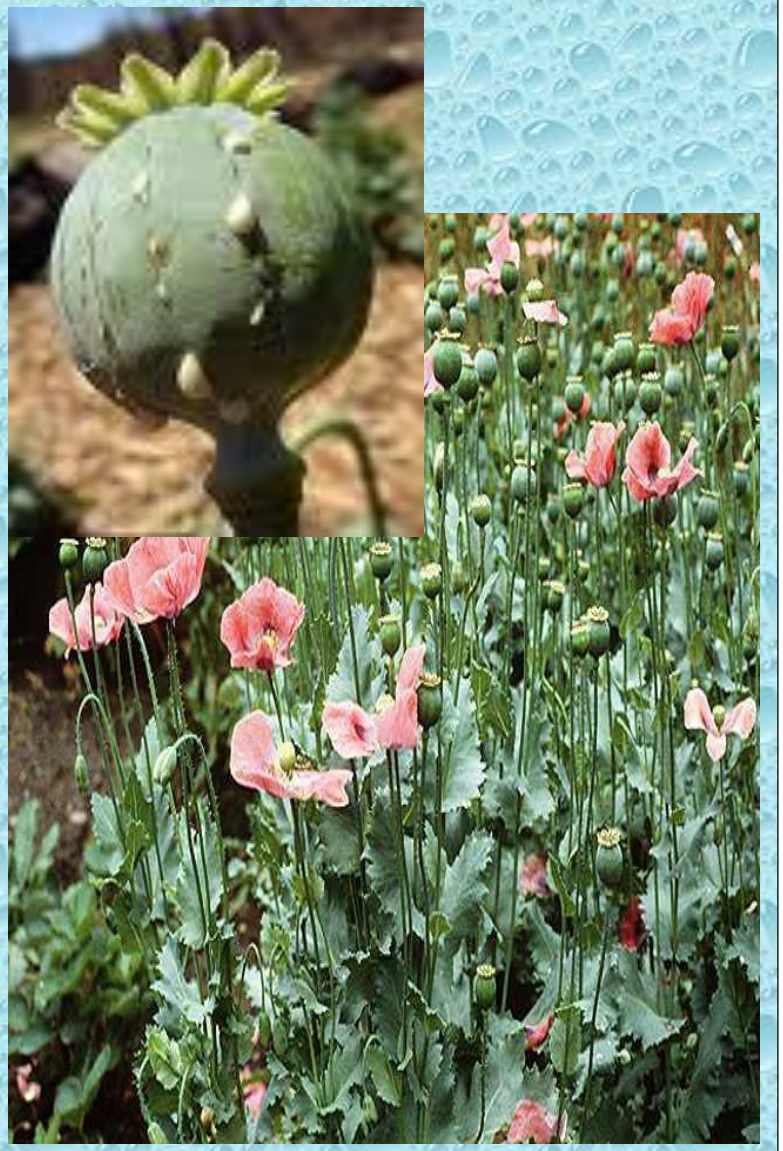
OPIOIDS

Opium is derived from the juice of the opium poppy, *Papaver somniferum*

The **natural** products include *morphine, codeine, papaverine* & *thebaine*

Opiates are drugs derived from opium & semisynthetic & synthetic derivatives

Endogenous opioid peptides, e.g. Endorphins, enkephalins & dynorphins.



OPIOID RECEPTORS

Anatomical distribution in brain, spinal cord, & the periphery

OPIOID RECEPTORS		
Opioid Receptor Class		Effects
Mu_1	μ	Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential
Mu_2	μ	Respiratory depression, cardiovascular and gastrointestinal effects, miosis, urinary retention
Delta	δ	Spinal analgesia, cardiovascular depression, decreased brain and myocardial oxygen demand
Kappa	k	Spinal analgesia, dysphoria, psychomimetic effects, feedback inhibition of endorphin system

ORL-1 **receptor**

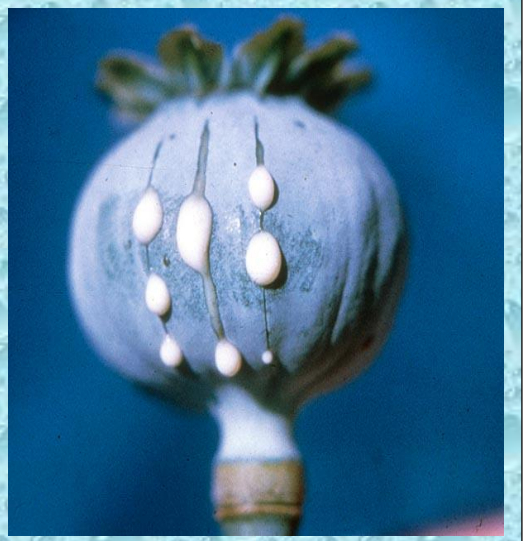
Nociceptin ligand

All of them are typical G-protein coupled receptors

CLASSIFICATION OF OPOIDS

According to their source

Natural	Morphine, Codeine
Semisynthetic	Heroin
Synthetic	Pethidine, Methadone



According to agonistic/antagonistic actions

Agonists; Morphine, Codeine, Pethidine, Methadone

Mixed agonist /antagonist; Pentazocine

Pure antagonist; Nalaxone, Naltraxone

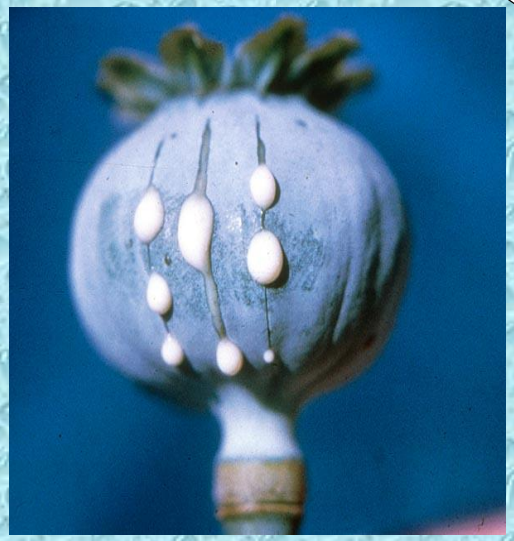
CLASSIFICATION OF OPOIDS

According to their specificity of action on receptors

Morphine, codeine, heroin → μ-receptor agonists

Pentazocine agonist at k –receptors & antagonist at μ-receptors.

MECHANISM OF ACTION

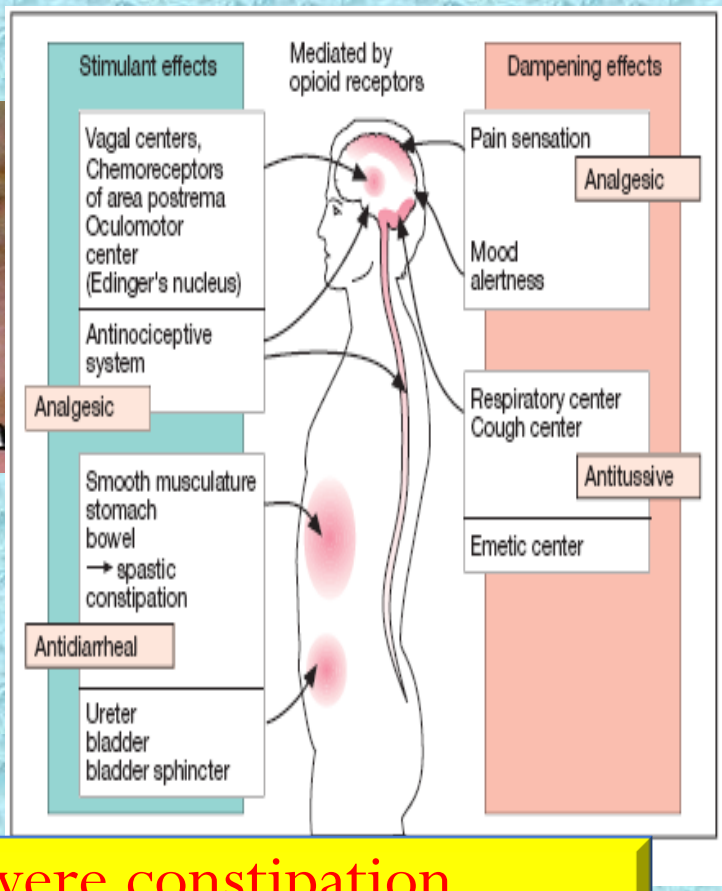


Binding to presynaptic opioid receptors coupled to Gi → ↓ AC & cAMP → ↓ voltage-gated Ca^{2+} channels → ↓ excitatory transmitter.

Binding to postsynaptic receptors → ↑ opening of K channels → ↓ neuronal excitability.

PHARMACODYNAMIC ACTIONS OF MORPHINE

- Analgesia [in acute & chronic pain]
- Euphoria & sedation
- Respiratory depression
- Depression of cough reflexes
- Nausea & vomiting → ↑CRTZ
- Pin point pupil (miosis)
- Releases histamine from mast cells



Effects on GIT:- ↑in tone ↓ motility → severe constipation.
Constriction of biliary sphincter → ↑pressure in the biliary tract & biliary colic.
Depress renal function & contract gall bladder .

MORPHINE

TOLERANCE & DEPENDENCE

TOLERANCE

Tolerance occurs rapidly with opioids (with morphine 12–24 hours)

Tolerance develops to respiratory depression, analgesia, euphoria & sedation

DEPENDENCE

Physical dependence (abstinence)
Withdrawal manifestations develops upon stoppage.

Lasting for a few days (8-10 days) in form of ↑ body ache, insomnia, diarrhea, gooseflesh, lacrimation

Psychological dependence lasting for months / years → craving

MORPHINE

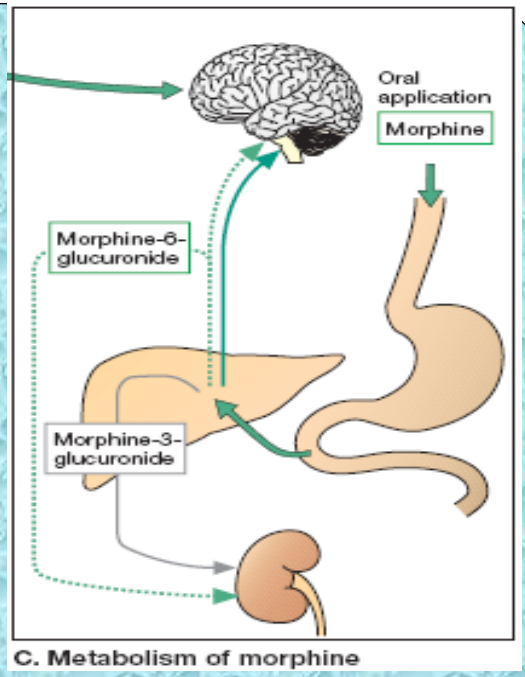
PHARMACOKINETICS

t ½ is 2-3h

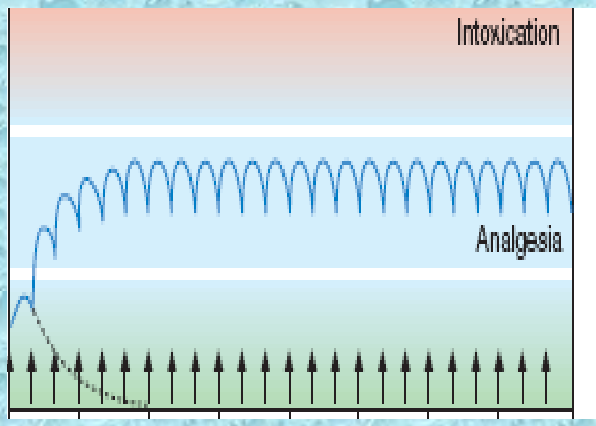
It is slowly & erratically absorbed orally (bioavailability 20-40%).
-Medically given by SC, IM or IV injection.

Metabolized by conjugation with glucuronic acid

Undergoes enterohepatic recycling,
-crosses BBB
-crosses placenta.



C. Metabolism of morphine



Morphine
$t_{1/2}$ = 2 h
at low dose
every 4 h
Disadvantage:
frequent dosing
for sustained
analgesia

MORPHINE

CLINICAL INDICATIONS

CONTROL PAIN; cancer pain, severe burns, trauma, Severe visceral pain (not renal/biliary colics, acute pancreatitis)

Acute pulmonary edema

Myocardial ischemia

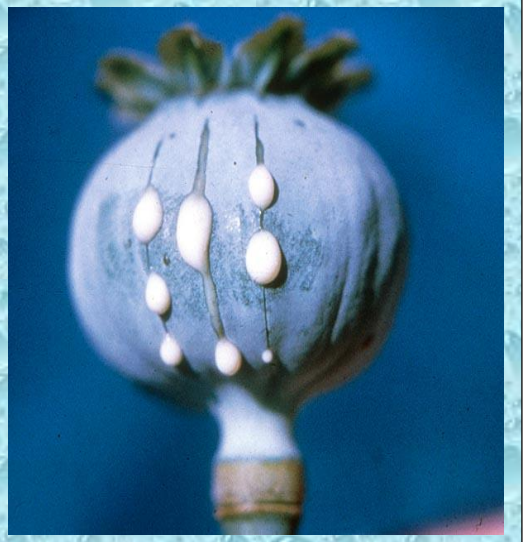
Non painful conditions e.g. heart failure (to relieve distress)

Pre-anesthetic medication.

MORPHINE

ADRS

- CONSTIPATION
- RESPIRATORY DEPRESSION
- CVS: HYPOTENSION (DECREASE SYSTOLE & DIASTOLE BP) ON LONG TERM USE
- ITCHING
- NAUSEIA, VOMITING
- CONSTRICTED PUPIL
- SEDATION.



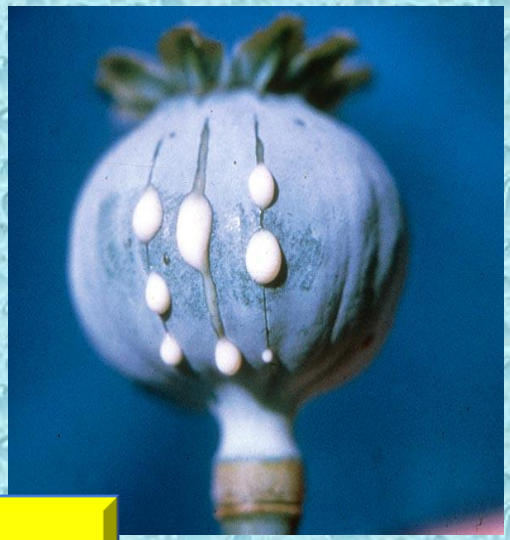
MORPHINE

CONTRAINDICATIONS

HEAD INJURY

BRONCHIAL ASTHMA or impaired pulmonary function

Biliary colic & pancreatic pain



Elderly are more sensitive; ↓metabolism, lean body mass & renal function

With MAOIs

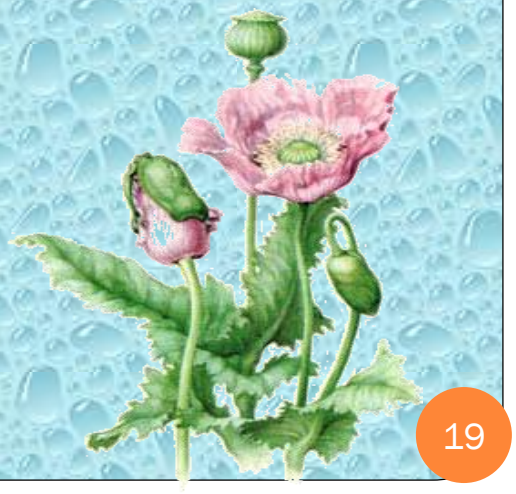
Not given infants, neonates or during child birth → ↓conjugating capacity → accumulate → ↓ respiratory

CODEINE

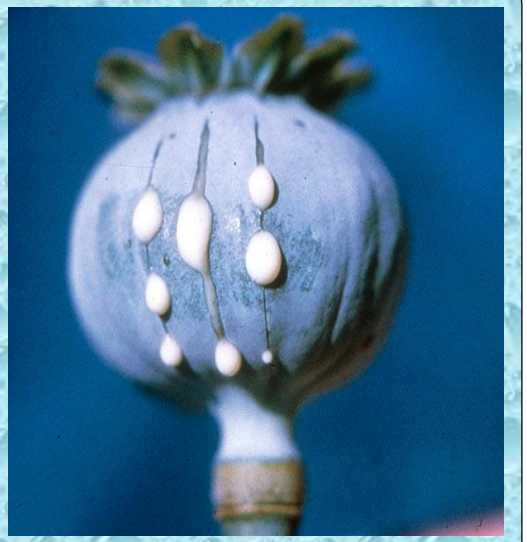
Natural opioid, **μ agonist**

Dependence < morphine

Used in mild & moderate pain, cough, diarrhea.



TRAMADOL



Synthetic, μ agonist , less potent than morphine

Inhibits also NE & 5HT reuptake

Can be given orally; more oral bioavailability

Indications

-Mild - moderate acute & chronic visceral pain
-During labor

ADRS

-Seizures (not in epileptics), Nausea, Dry mouth, Dizziness, Sedation
-Less adverse effects on respiratory & C.V.S.

PETHIDINE (MEPRIDINE)

Synthetic, more effective κ agonist

ACTIONS

LESS analgesic, constipating, depressant on faetal respiration than morphine

No cough suppressant effect

Has atropine –like action (Smooth muscle relaxant)

PETHIDINE (MEPRIDINE)

ADRS

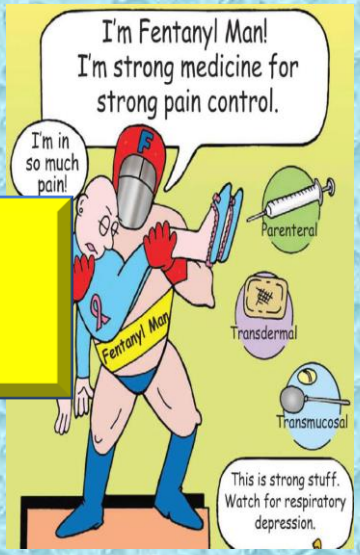
- Tremors, Convulsions, Hyperthermia, Hypotension
- Blurred vision, Dry mouth, Urine retention
- Tolerance & Addiction

INDICATIONS

- As in morphine but not in cough & diarrhea
- Preanaesthetic medication (better)
- Used in obstetric analgesia (No ↓ resp.)
- Used in severe visceral pain; renal & biliary colics (sm. relaxant)

FENTANYL

Synthetic, μ agonist, more potent than pethidine & morphine



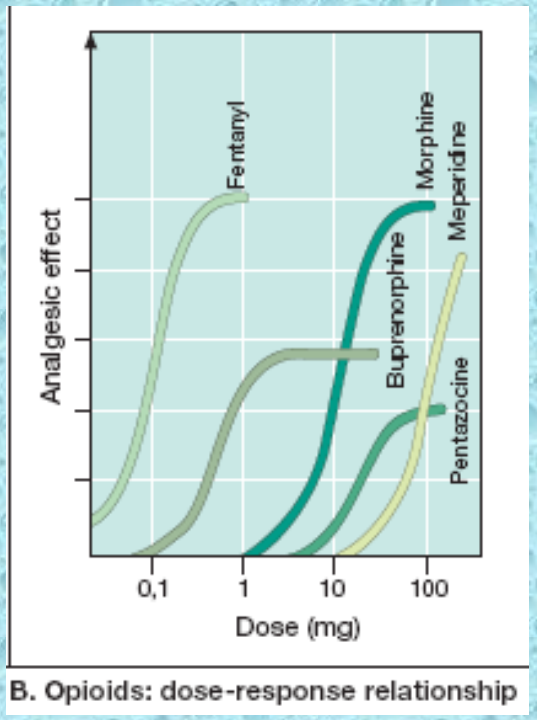
CLINICAL USES

Analgesic supplement during anesthesia, (IV or intrathecal)

To induce & maintain anesthesia in poor-risk patients [stabilizing heart]

In combination with droperidol as NEUROLEPTANALGESIA

In cancer pain & severe postoperative pain; (transdermal patch changed every 72 hrs).



B. Opioids: dose-response relationship

FENTANYL

ADRS

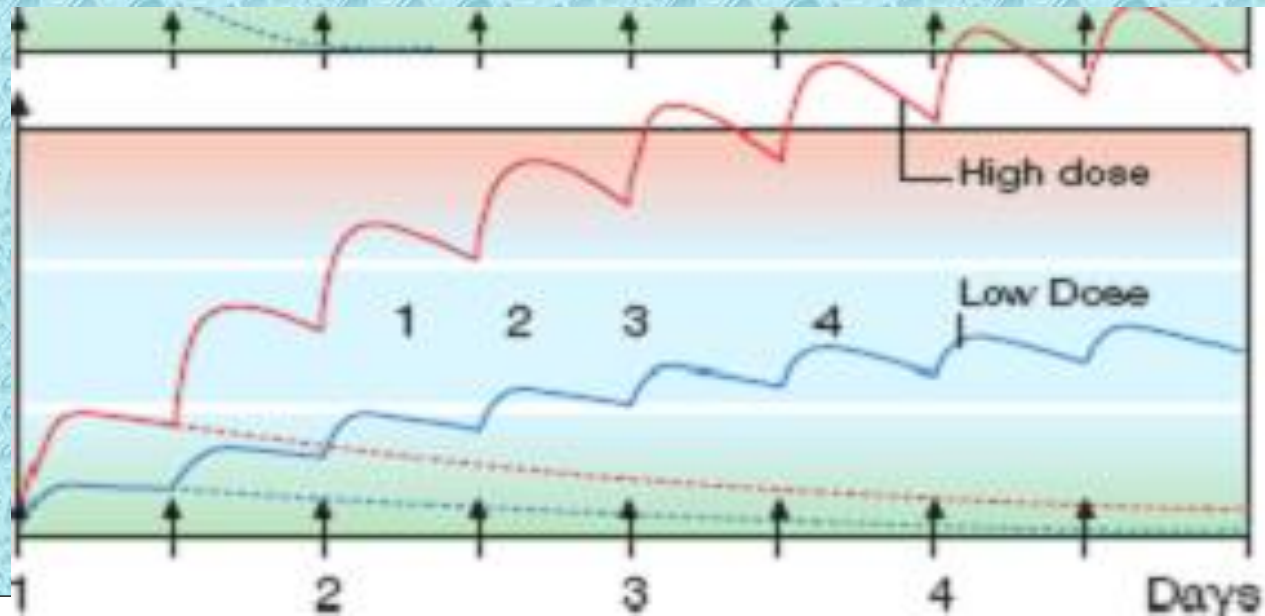
Respiratory depression (most serious)
CV effects are less
Bradycardia may still occur.

METHADONE

Weaker synthetic μ- agonist

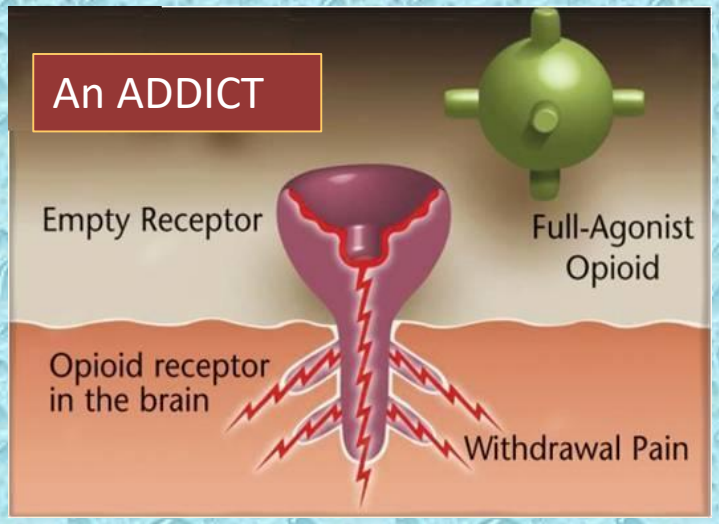
In non addicts, it causes tolerance & dependence but not as severe as that of morphine

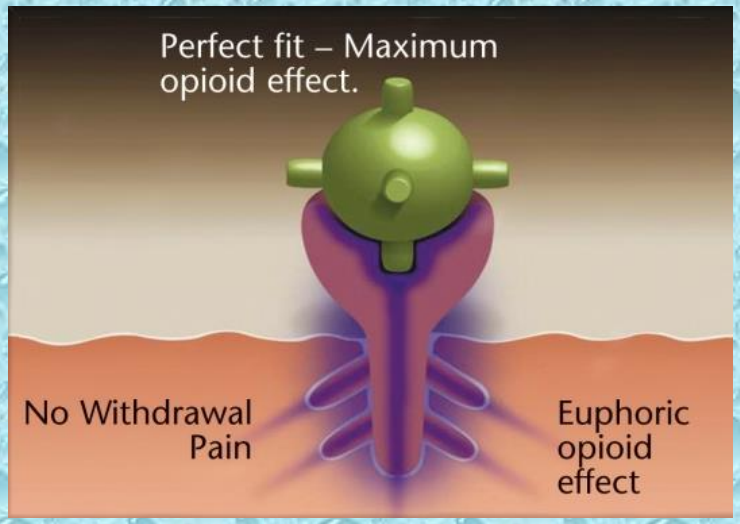
t½ 55 h

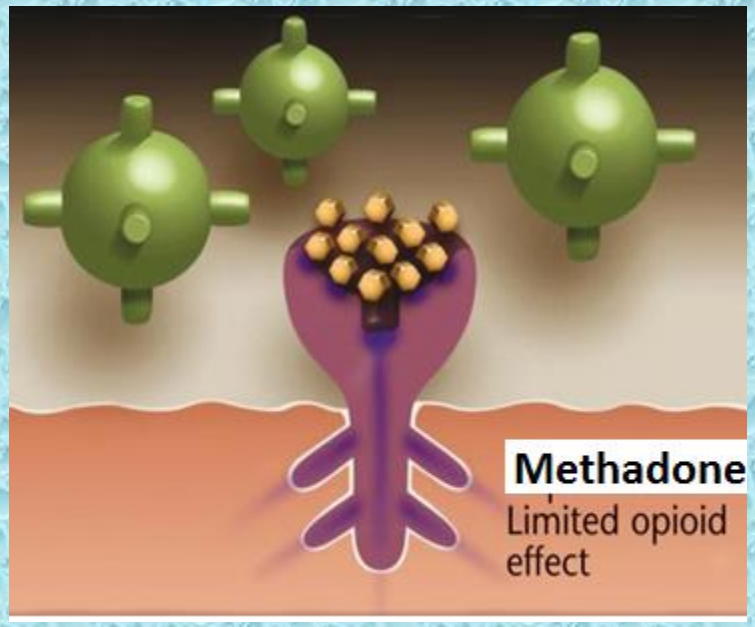


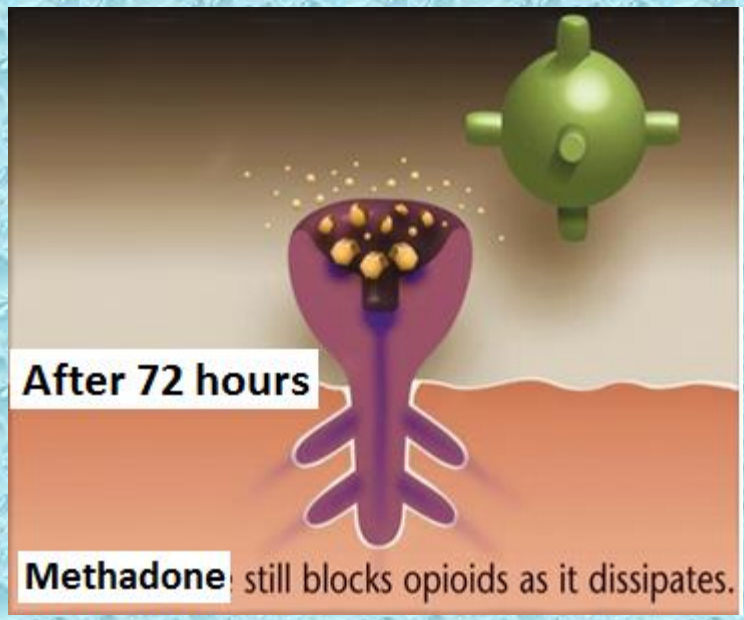
Methadone
$t_{1/2}$ = 55 h
Disadvantage:
dose difficult
to titrate

Used to treat opioid withdrawal

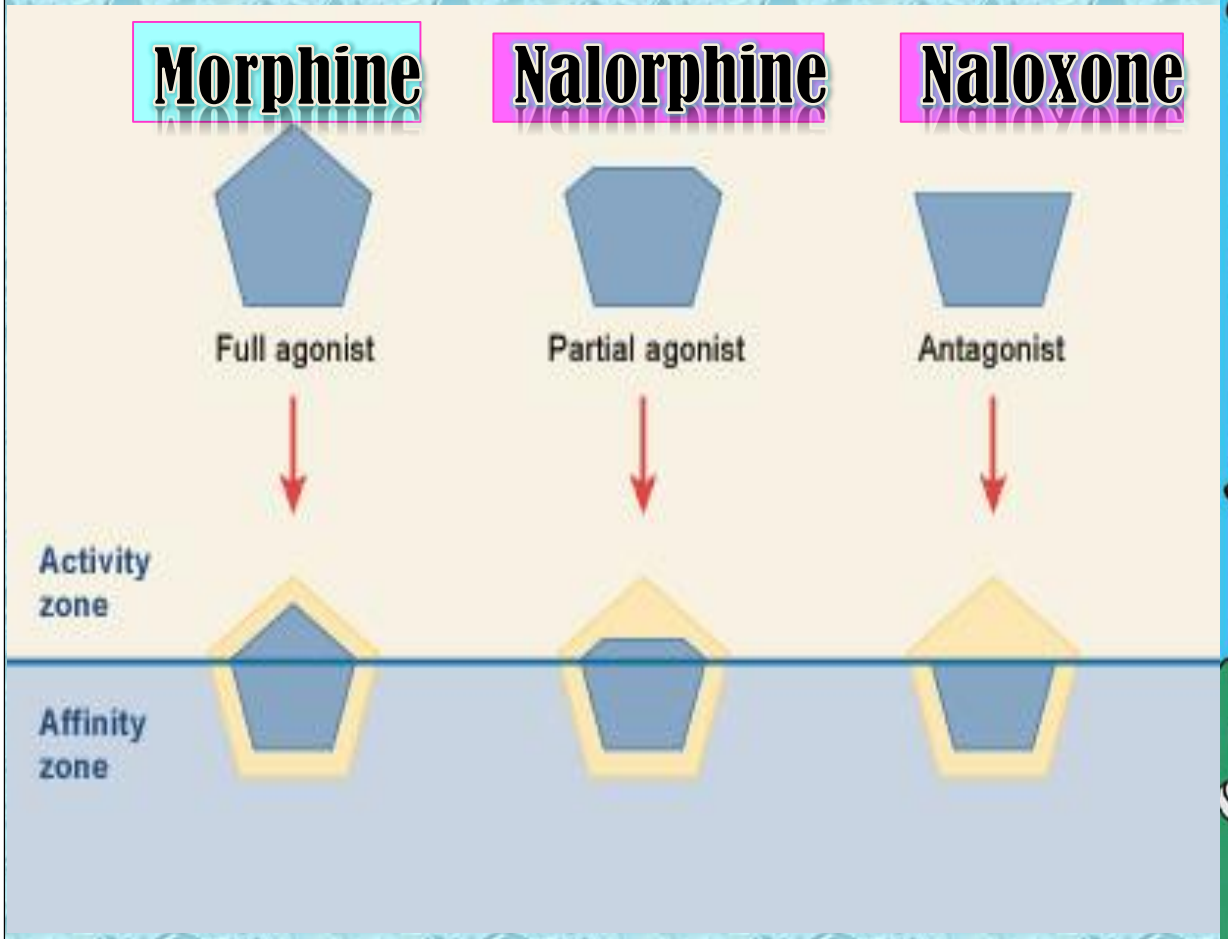


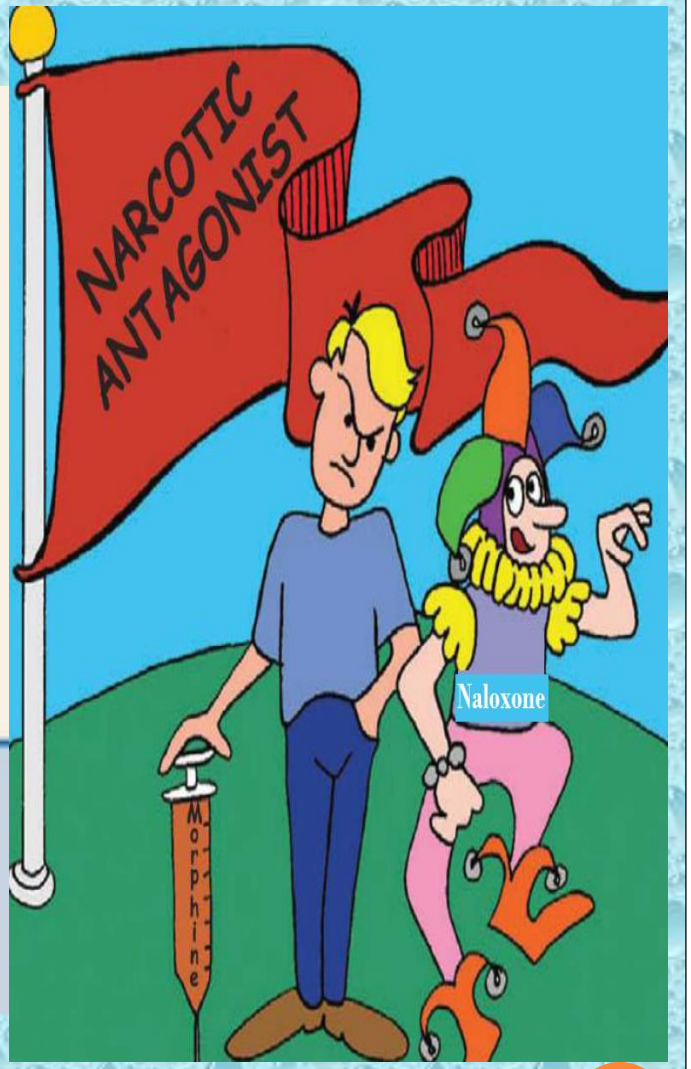






OPIOID ANTAGONISTS





NALOXONE

Pure opioid antagonist

Used to treat respiratory depression caused by opioid overdose

To reverse the effect of analgesia on the respiration of the new born baby

Effect lasts only for 2-4 hours

Precipitates withdrawal syndrome in addicts

NALTREXONE

Very similar to naloxone but with longer duration of action [$t_{1/2}$=**10h**].