# DRUGS USED IN MANAGEMENT OF PAIN

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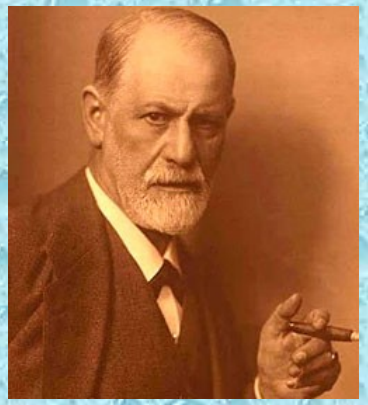
MEDICAL PHARMACOLOGY

# 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

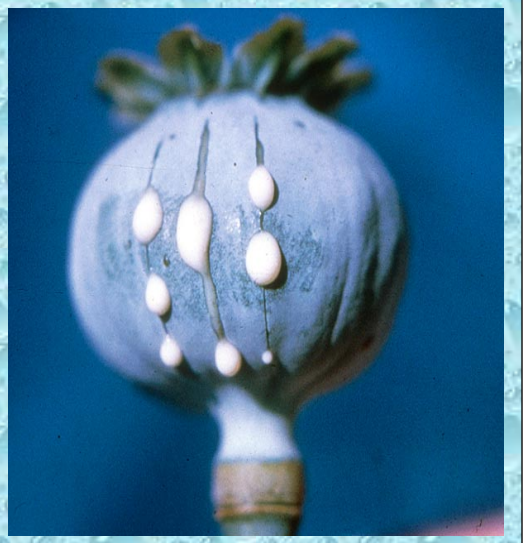
# DRUGS USED IN MANAGEMENT OF PAIN

## 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

## WHAT IS PAIN?

- **"The fifth vital sign"** – American Pain Society 2003
- Identifying pain as the fifth vital sign suggests that the assessment of pain should be as automatic as taking a client's BP and pulse

# DRUGS USED IN MANAGEMENT OF PAIN

## WHY SHOULD WE TREAT PAIN?

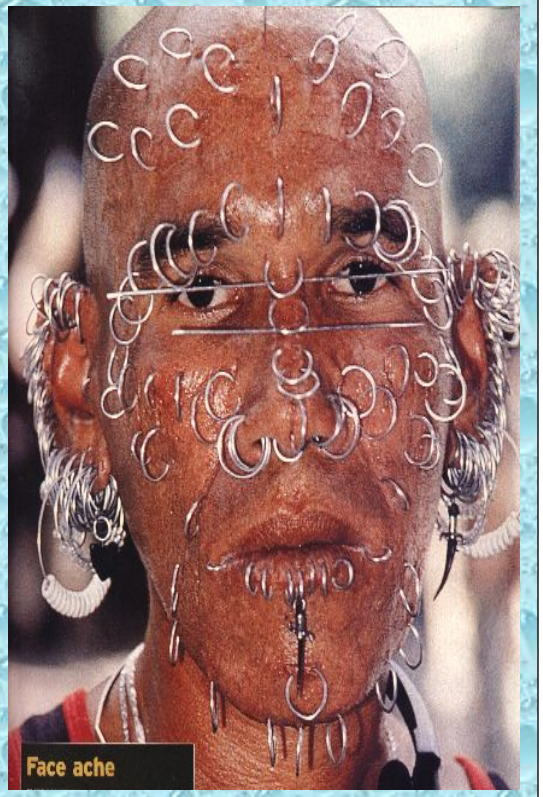
Pain is a miserable experience

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

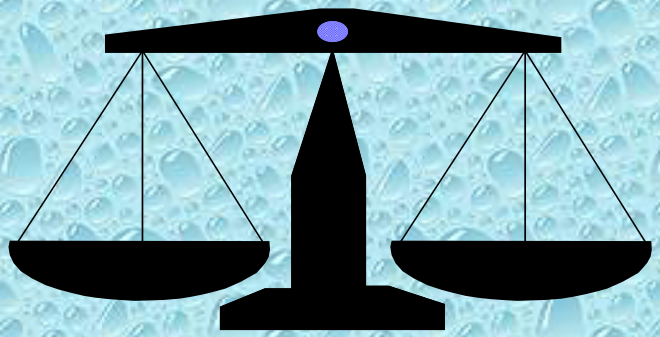


# CLASSES OF DRUGS USED IN MANAGEMENT OF PAIN

- NSAIDs
- Opioids
- Adjuvant drugs

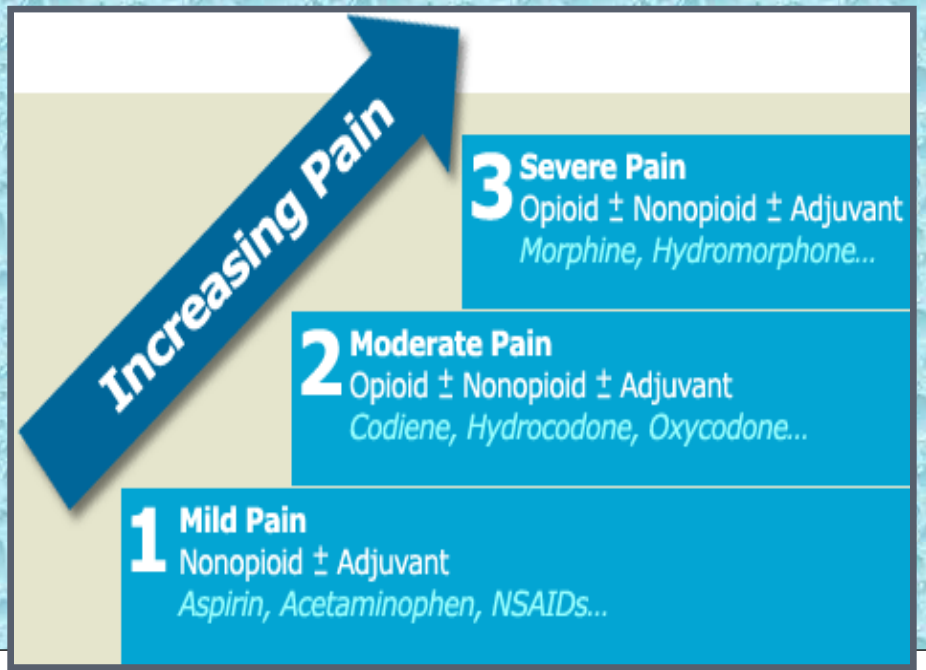
# CLASSES OF DRUGS USED IN MANAGEMENT OF PAIN

Analgesia



Side-effects

## 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

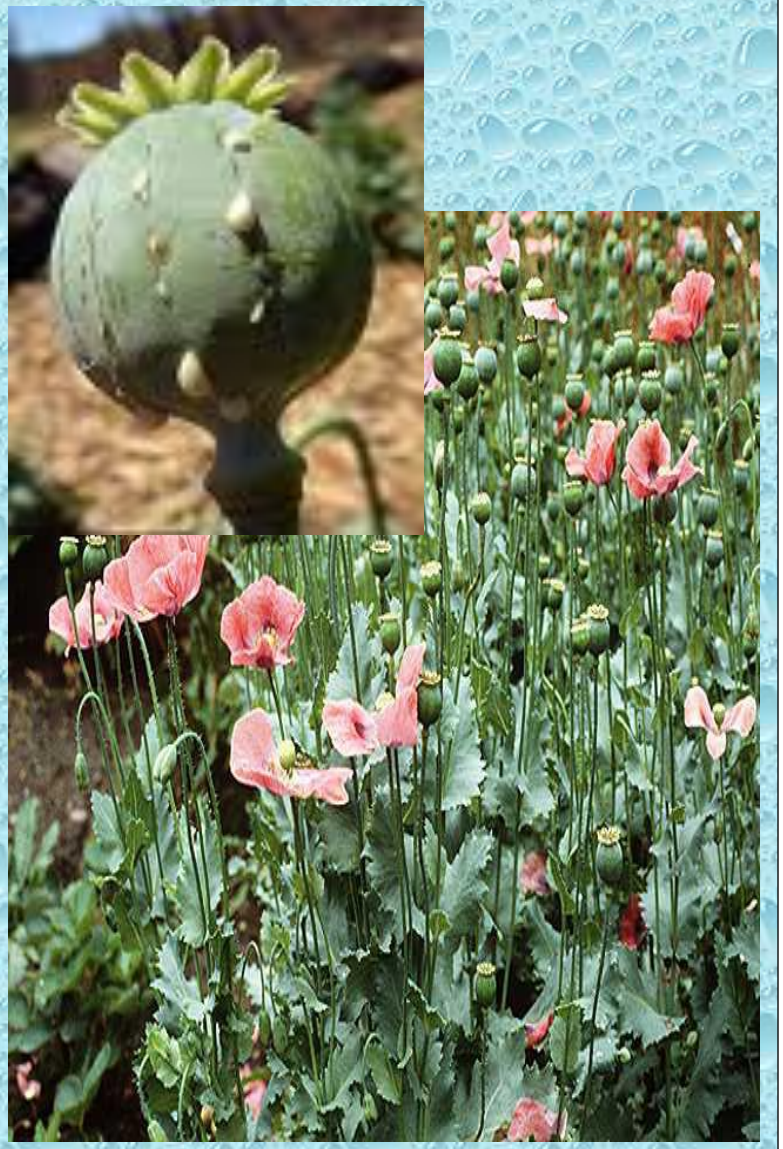
# OPIOIDS

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

**E**ndogenous 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 |
| $Mu_2$ | 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**

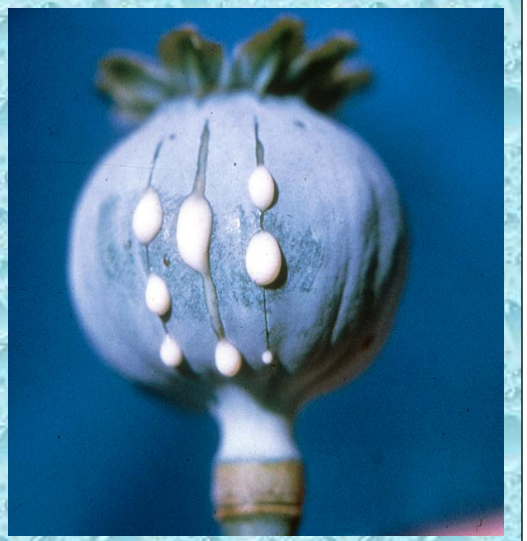
**Nociceptin ligand**

***All of them are typical G-protein coupled receptors***

# CLASSIFICATION OF OPOIDS

**According to their source**

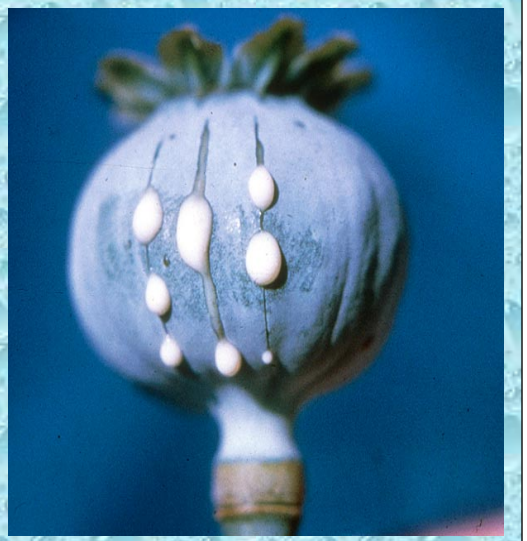
| | |
|---|---|
| Natural | Morphine, Codeine |
| Semisynthetic | Heroin |
| Synthetic | Pethidine, Methadone |



# CLASSIFICATION OF OPOIDS

**According to their source**

**According to agonistic/antagonistic actions**



**Agonists**; Morphine, Codeine, Pethidine, Methadone

**Mixed agonist /antagonist**; Pentazocine

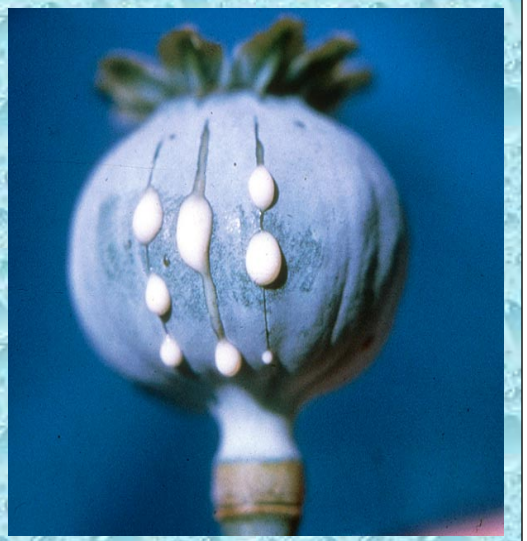
**Pure antagonist**; Nalaxone, Naltraxone

# CLASSIFICATION OF OPOIDS

According to their source

According to agonistic/antagonistic actions

According to their specificity of action on receptors

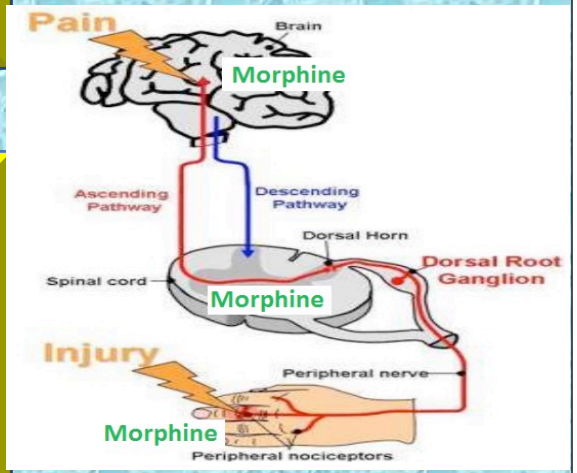


Morphine, codeine, heroin → μ-receptor agonists

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

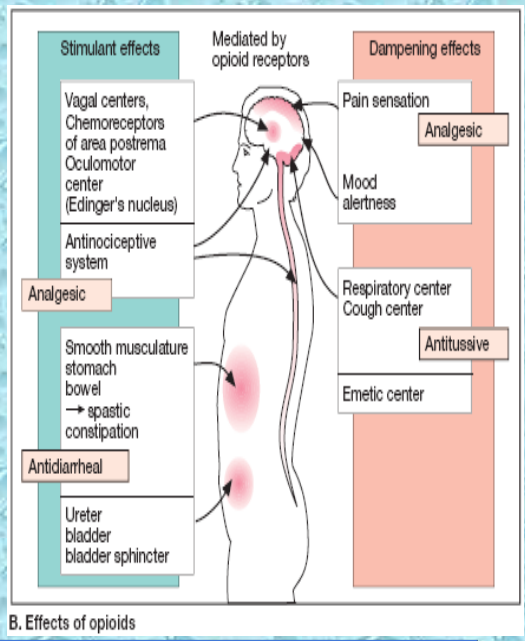
Respiratory depression

Depression of cough reflexes

Nausea & vomiting → ↑CRTZ

Pin point pupil (miosis)

Releases histamine from mast cells

B. Effects of opioids

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

# MORPHINE

## TOLERANCE & DEPENDENCE

## TOLERANCE


## 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

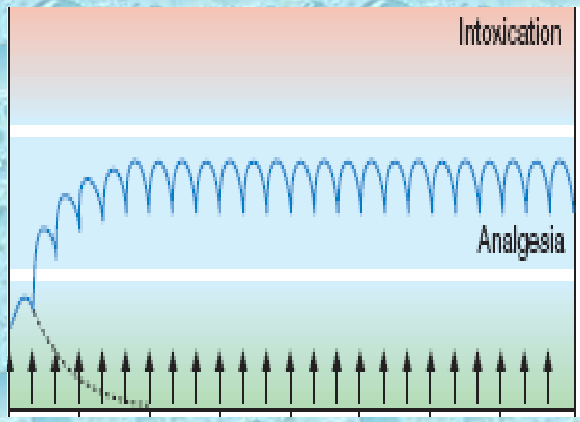
## PHARMACOKINETICS

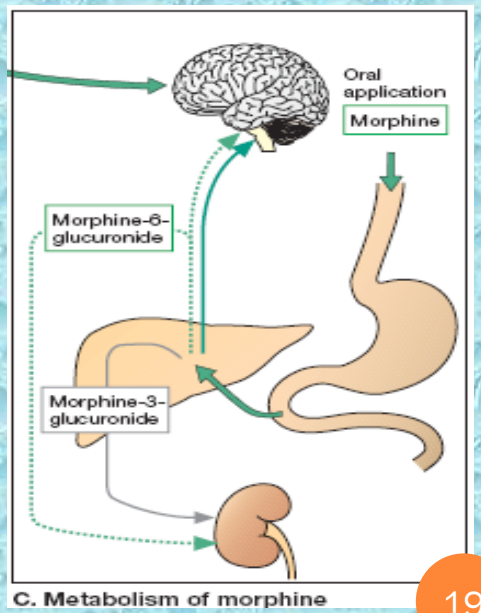
t ½ is 2-3h

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

## 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.

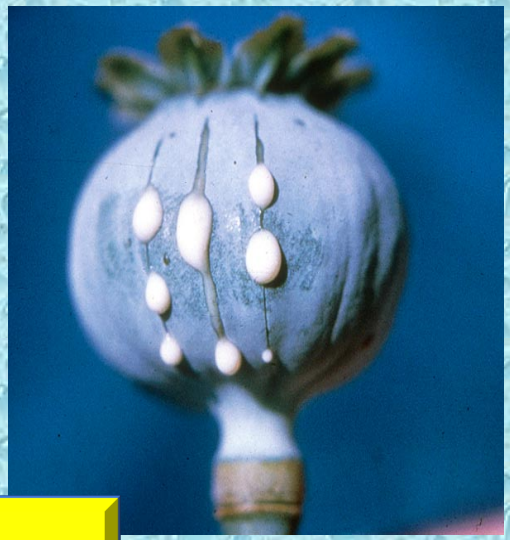
# MORPHINE

## 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

# TRAMADOL

## 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)

Synthetic, more effective κ agonist

## 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).

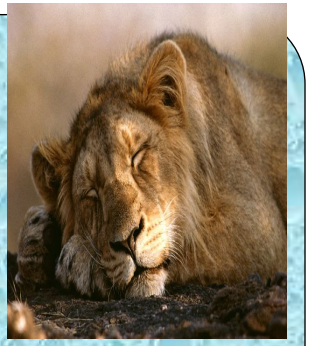
## ADRS

Tremors, Convulsions, Hyperthermia, Hypotension

Blurred vision, Dry mouth, Urine retention

Tolerance & Addiction

# FENTANYL



Synthetic, μ agonist, more potent than pethidine & morphine

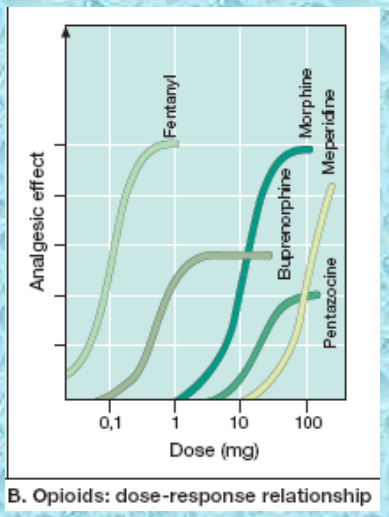
## CLINICAL USES

Analgesic supplement during anesthesia, (IV or intrathecal)

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

In combination with droperidol as NEUROLEPTANALGESIA

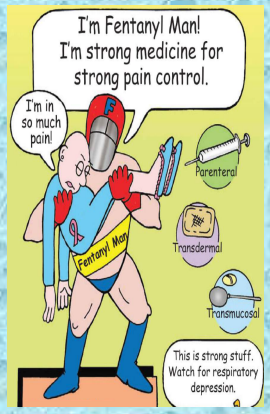
In cancer pain & severe postoperative pain; (transdermal patch changed every 72 hrs).



B. Opioids: dose-response relationship

## ADRS

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



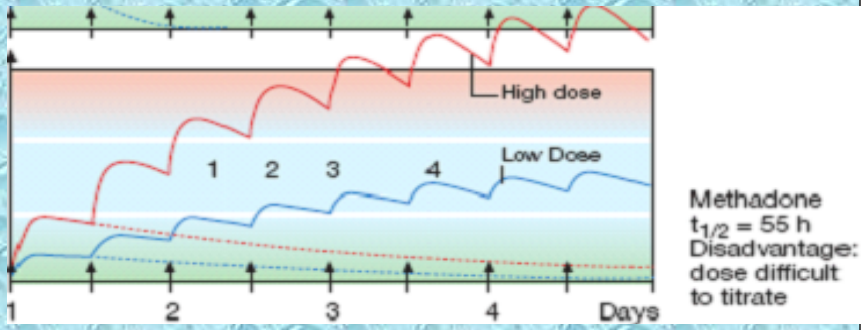
# METHADONE

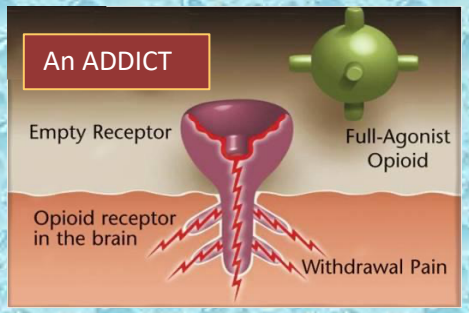
Weaker synthetic μ- agonist

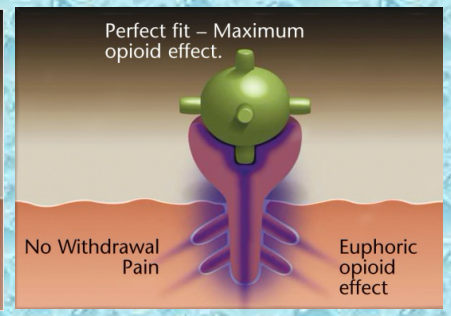
In non addicts, it causes tolerance & dependence but not as severe as that of morphine

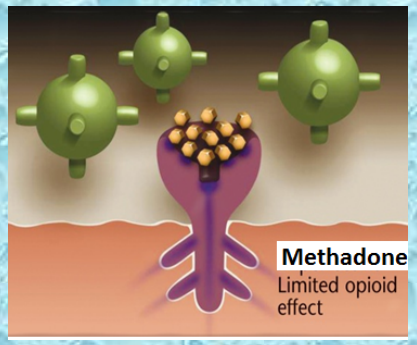
t½ 55 h

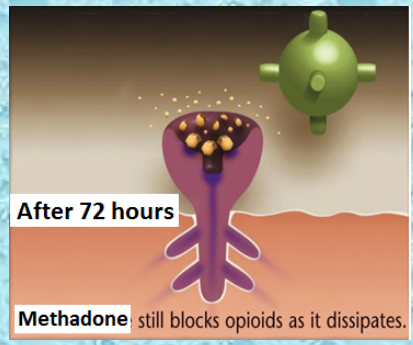
Used to treat opioid withdrawal



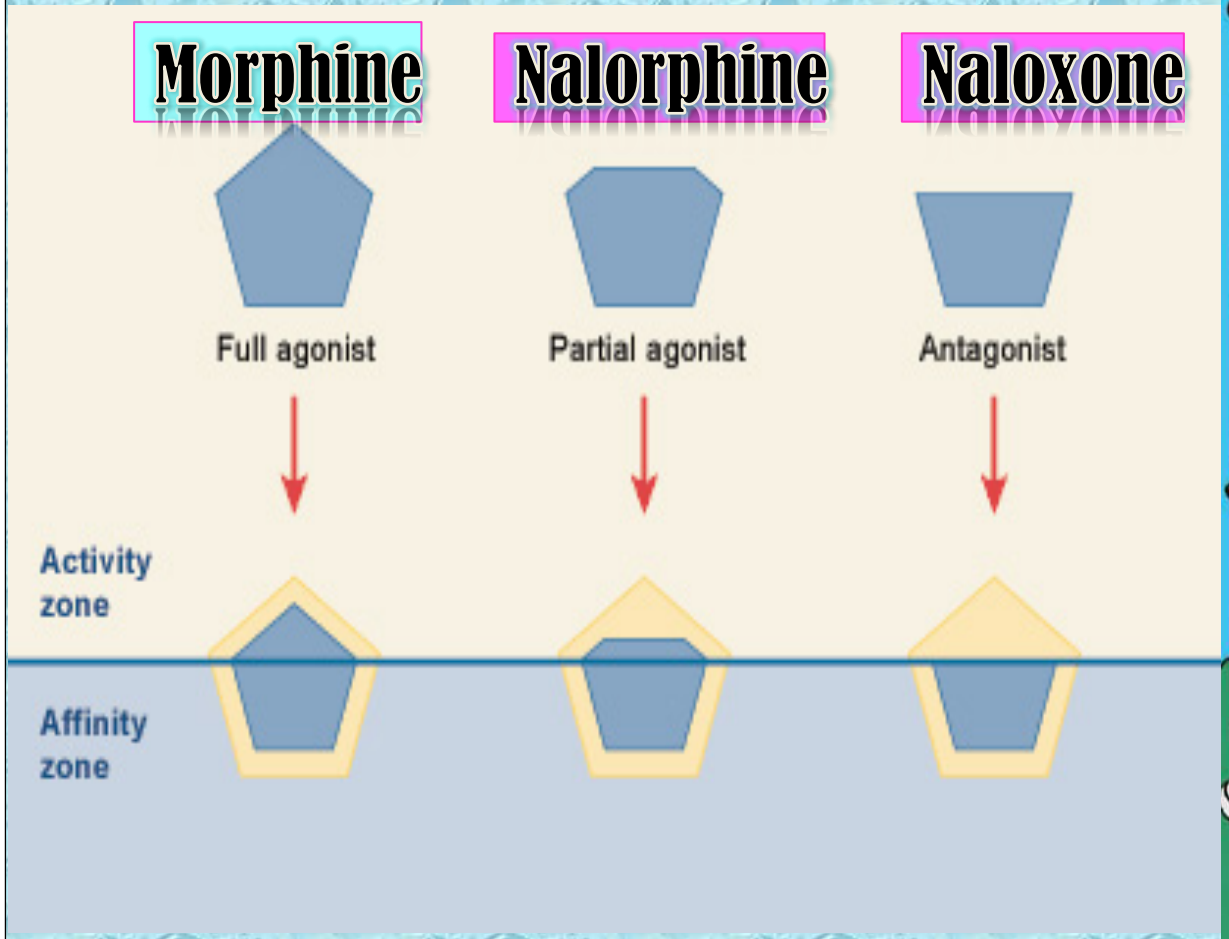



# OPIOID ANTAGONISTS




# 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**].