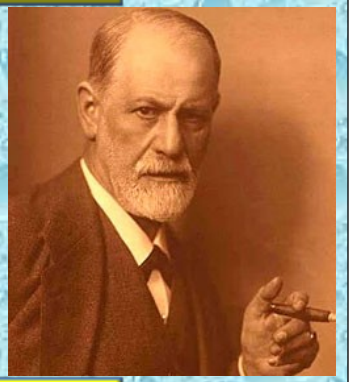
DRUGS USED IN MANAGEMENT OF PAIN

A CASE OF OVERDOSE



Sigmund Freud, the father of psychoanalysis

His cancer of the jaw was causing him increasingly severe **PAIN** and 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 and pharmacodynamic effects of morphine and its synthetic derivatives

Hints on the properties and clinical uses of morphine antagonists

DRUGS USED IN MANAGEMENT OF PAIN

WHY SHOULD WE TREAT PAIN?

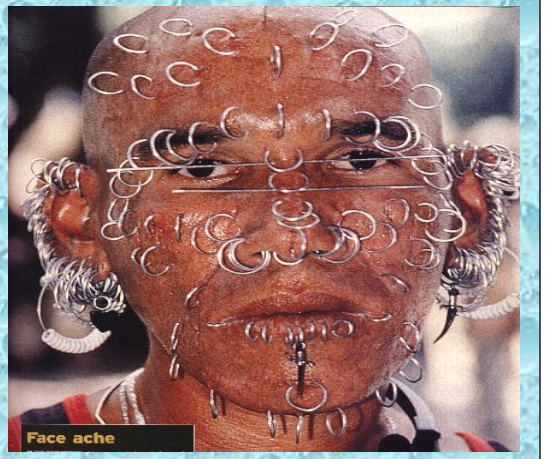
Pain is a miserable experience

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

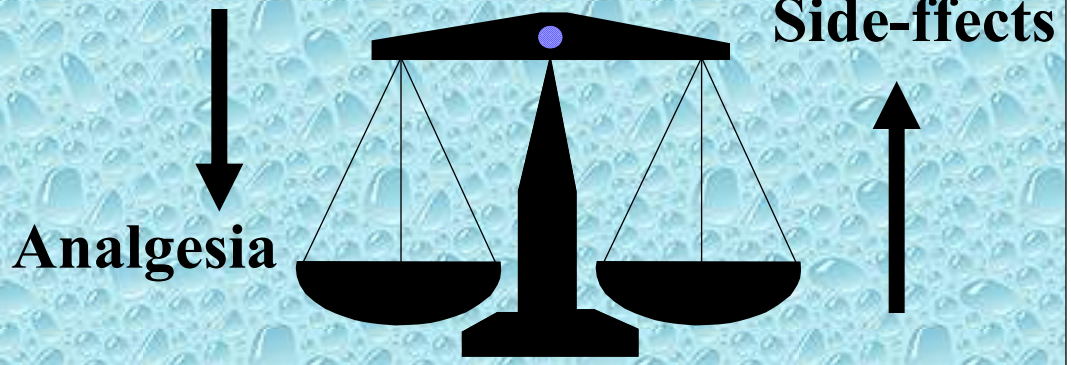


DRUGS USED IN MANAGEMENT OF PAIN

CLASSES OF DRUGS USED IN MANAGEMENT OF PAIN

- NSAIDs
- Opioids
- Adjuvant drugs

- WHO Pain Ladder



NSAIDS

Generally the first 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 ceilling effect to analgesia

ADJUVANT DRUGS

e.g. Anxiolytics,
Neuroleptics,
Antidepressants
Antiepileptics

Primarily indicated for clinical conditions other than pain

May modify the perception of pain

Remove the concomitants of pain such as anxiety, fear, depression

OIOIDS

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

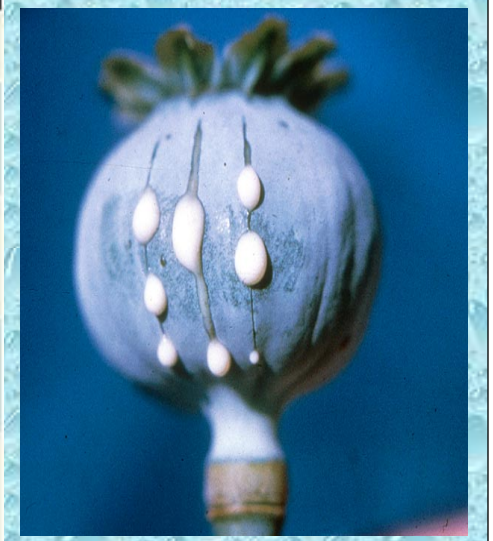
The natural products include *morphine, codeine, papaverine* and *thebaine*

Opiates are drugs derived from opium and semisynthetic and synthetic derivatives

Opioids refer to opiates and endogenous opioid peptides, e.g. **β–** endorphin

OPIOID RECEPTORS

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



μ_1

μ_2

δ

k

ORL-1

Nociceptin receptor

Antagonizes dopamine transport

All of them are typical G-protein coupled receptors

CLASSIFICATION OF OPOIDS

According to their source

Natural	Morphine
Semisynthetic	Heroin
Synthetic	Pethidine, Methadone

CLASSIFICATION OF OPOIDS

According to agonistic/ Antagonistic actions

Agonists; Morphine, Codeine, Pethidine, Methadone

Mixed agonists /antagonists; Pentazocine,

Pure antagonist; Nalaxone, Naltraxone,

CLASSIFICATION OF OPOIDS

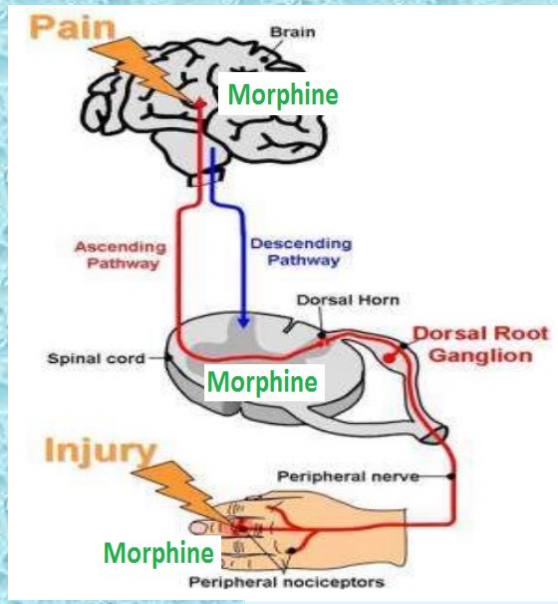
According to their specificity of action on receptors

Morphine,codeine, heroin→μ -receptor agonists

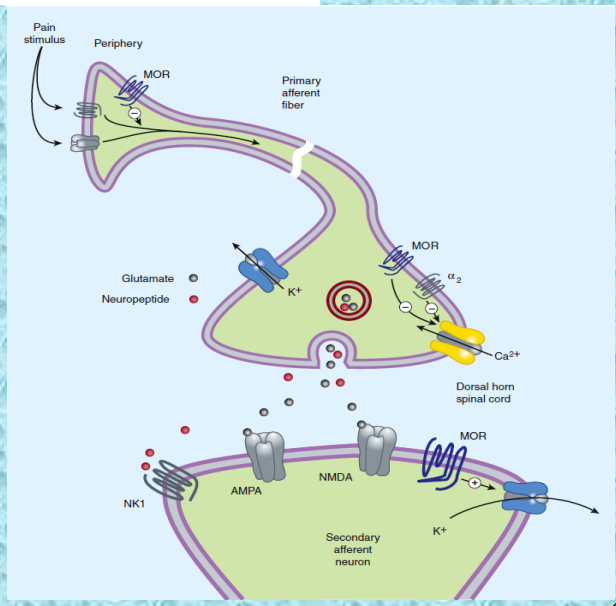
Pentazocine agonist at k –receptors & antagonist at μ-receptors

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



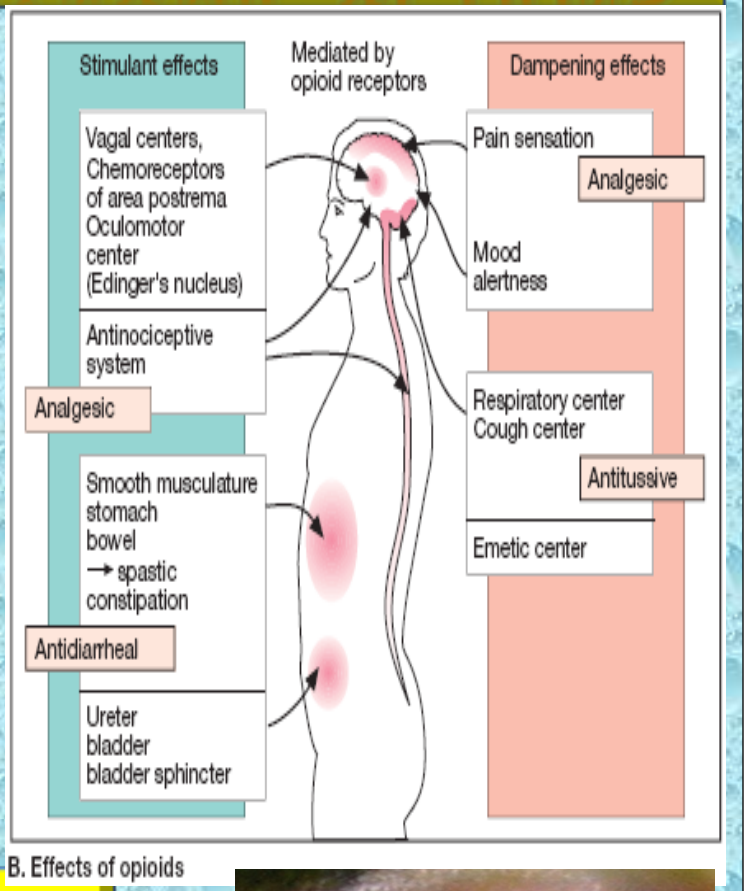
MORPHINE

PHARMACODYNAMIC ACTIONS

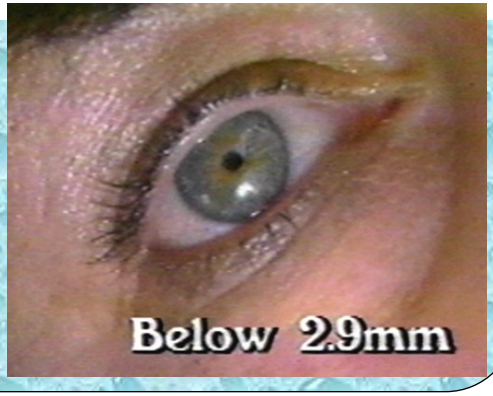
- Analgesia [in acute & chronic pain]
- Euphoria
- Respiratory depression
- Depression of cough reflexes
- Nausea & vomiting → ↑CRTZ
- Pin point pupil
- Releases histamine from mast cells

-Effects on GIT:-↑in tone ↓motility →severe constipation

-Contraction of gall bladder +constriction of biliary sphincter →↑pressure in the biliary tract



B. Effects of opioids



MORPHINE

TOLERANCE & DEPENDENCE

TOLERANCE

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

Tolerance develops to respiratory depression, analgesia, euphoria and sedation

MORPHINE

TOLERANCE & DEPENDENCE

DEPENDENCE

Physical dependence:-
Withdrawal manifestations
develops upon stoppage.

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

Psychological dependence lasting for months / years → craving

MORPHINE

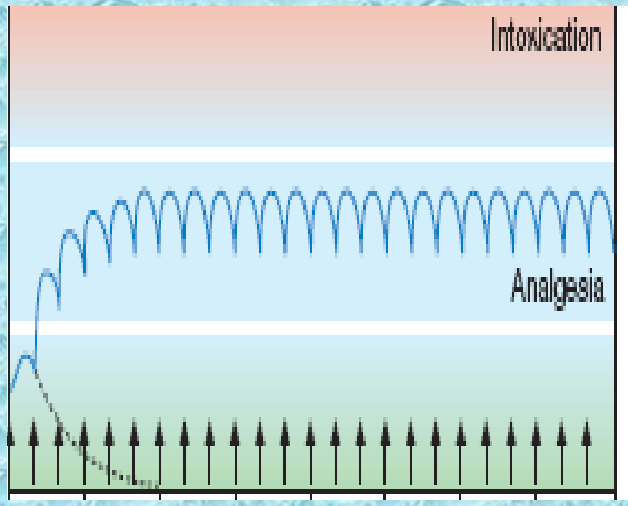
PHARMACOKINETICS

t ½ is 2-3h

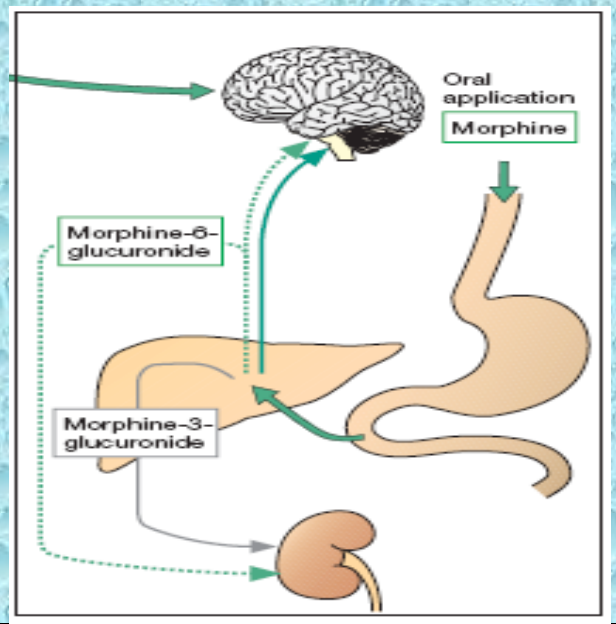
It is slowly & erratically absorbed orally (bioavailability 20-40%).
-Medically given by SC, IM or IV injection.

Metabolized by conjugation with glucuronic acid

Undergoes enterohepatic recycling,
-crosses BBB
-crosses placenta.



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



C. Metabolism of morphine

MORPHINE

CLINICAL INDICATIONS

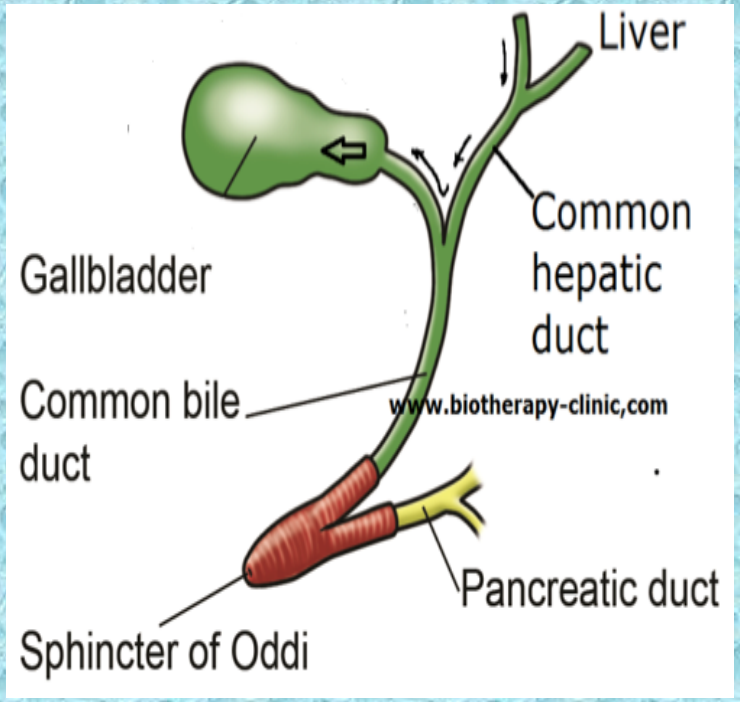
CONTROL PAIN; cancer pain, severe burns, trauma
Severe visceral pain (not renal/biliary colics, acute pancreatitis)

Acute pulmonary edema

Myocardial ischemia

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

Preanesthetic medication



MORPHINE

ADRS

- CONSTIPATION
- RESPIRATORY DEPRESSION
- ITCHING
- NAUSIA,VOMITING
- CONSTRICTED PUPIL
- SEDATION

Clinics

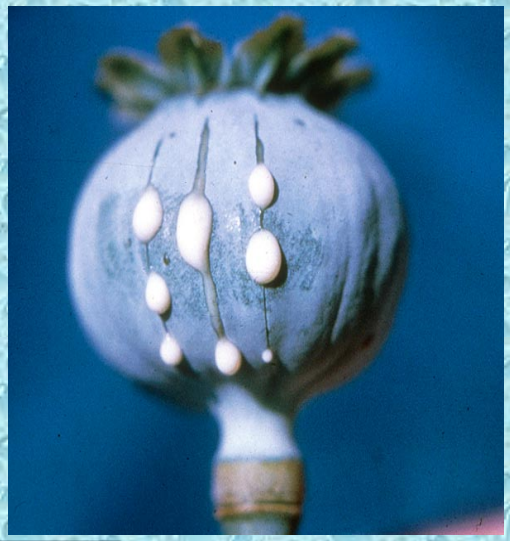
MORPHINE

CONTRINDICATIONS

HEAD INJURY

BRONCHIAL ASTHMA or impaired pulmonary function

Biliary colic



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

With MAOIs

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

CODEINE

- μ Agonist
- Dependence < morphine
- Used in mild & moderate pain, cough, diarrhea

TRAMADOL

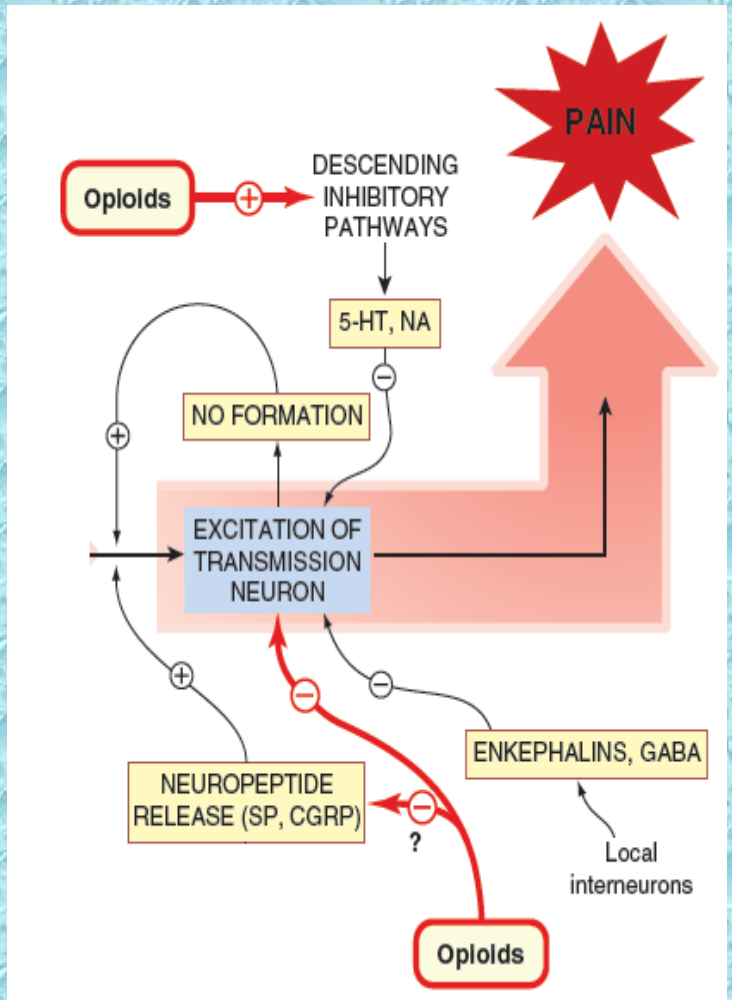
Synthetic, μ agonist , less potent than morphine

Inhibits also NE & 5HT reuptake

Can be given orally; more oral bioavailability

Indications

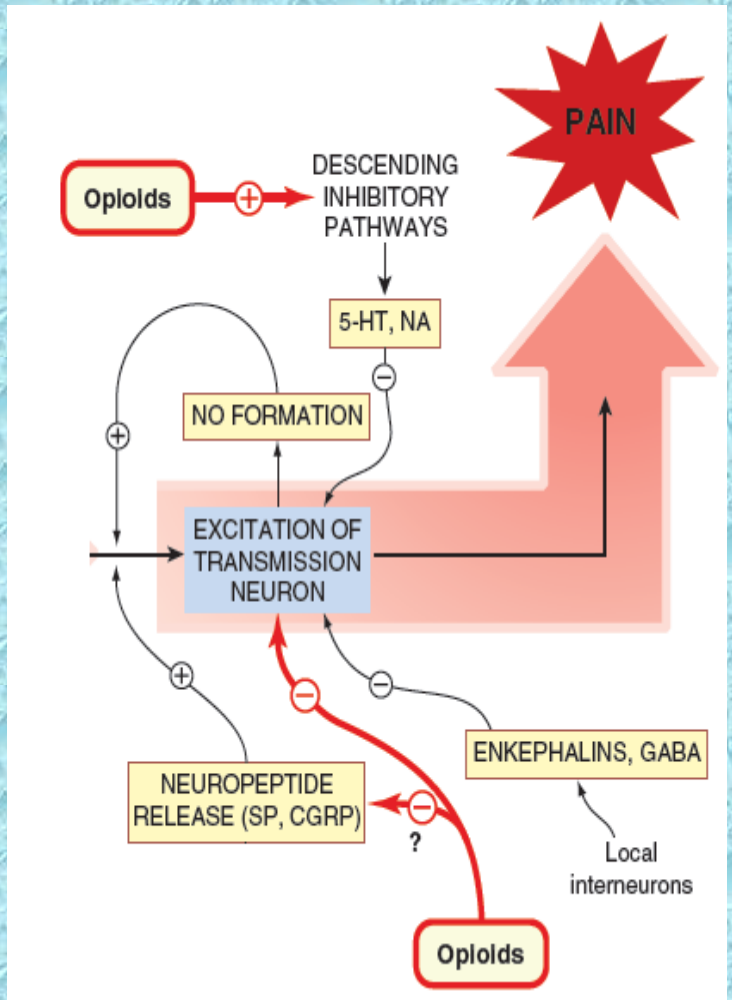
-Mild - moderate acute & chronic visceral pain
-During labor



TRAMADOL

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)

INDICATIONS

As in morphine but not in cough & diarrhea

Preanaesthetic medication

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

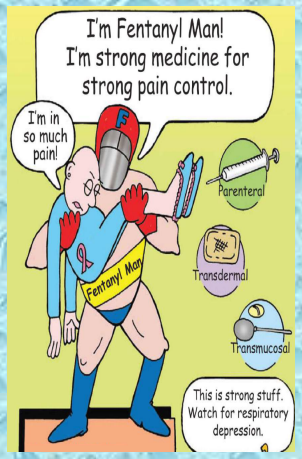
CLINICAL USES

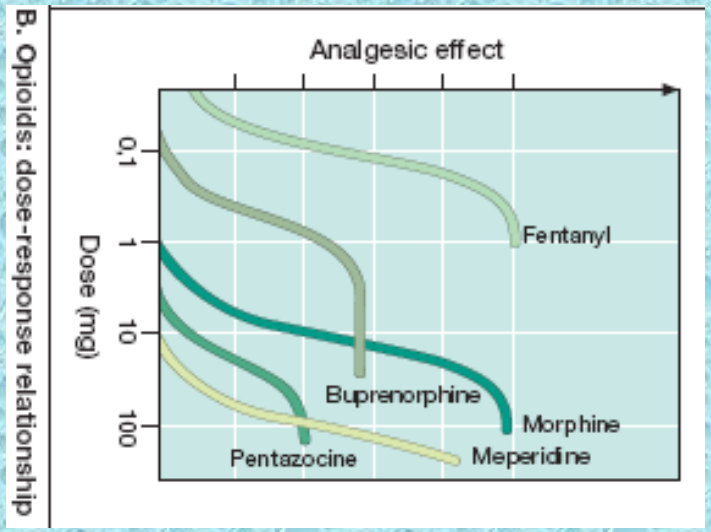
Analgesic supplement during anesthesia, (IV or intrathecal)

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).

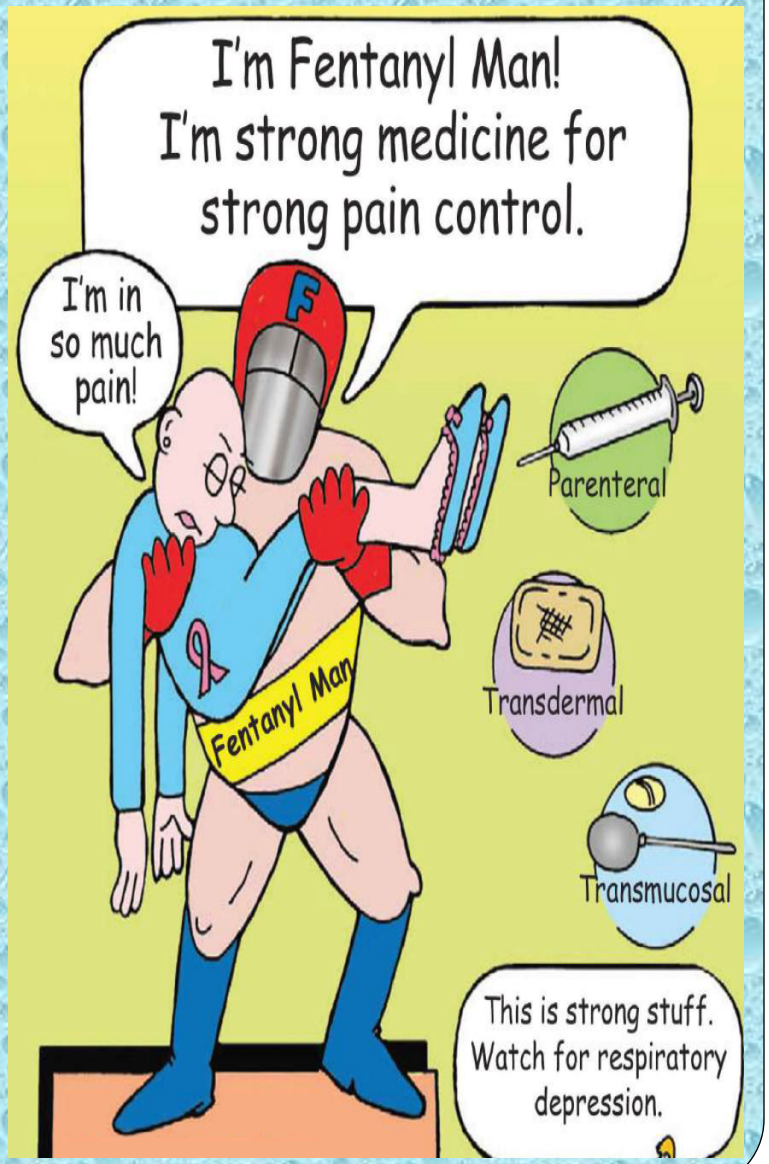




FENTANYL

ADRS

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

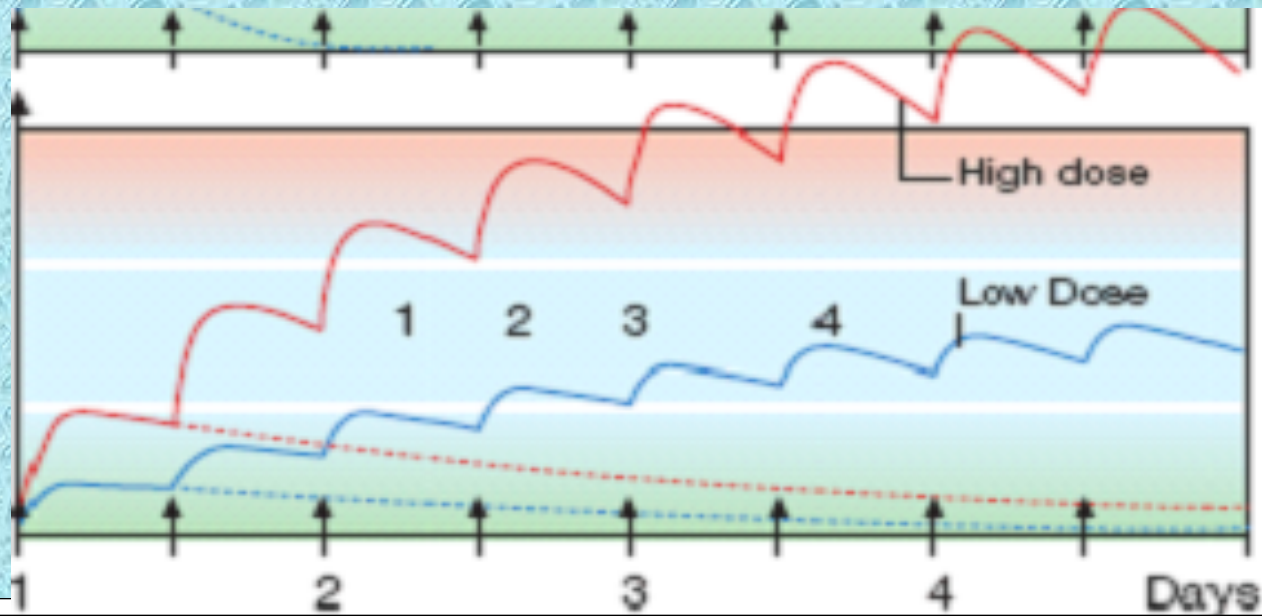


METHADONE

Weaker synthetic μ- agonist

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

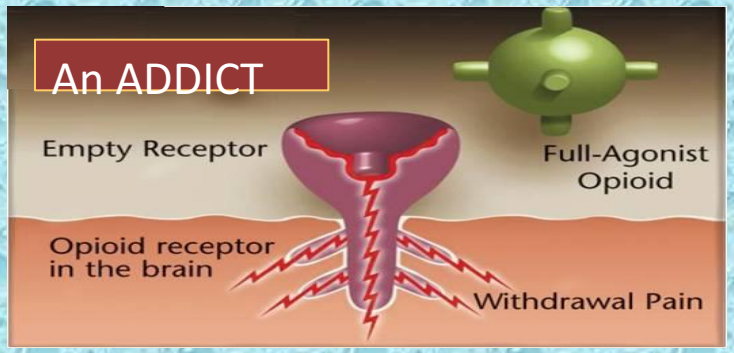
t½ 55 h

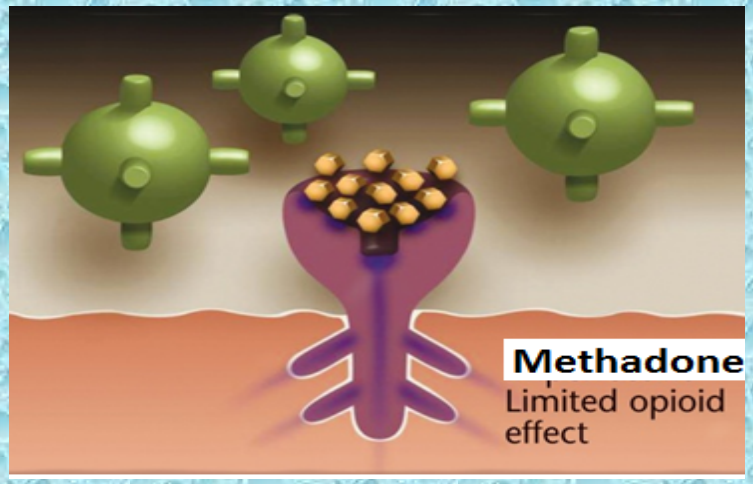


Methadone
$t_{1/2}$ = 55 h
Disadvantage:
dose difficult
to titrate

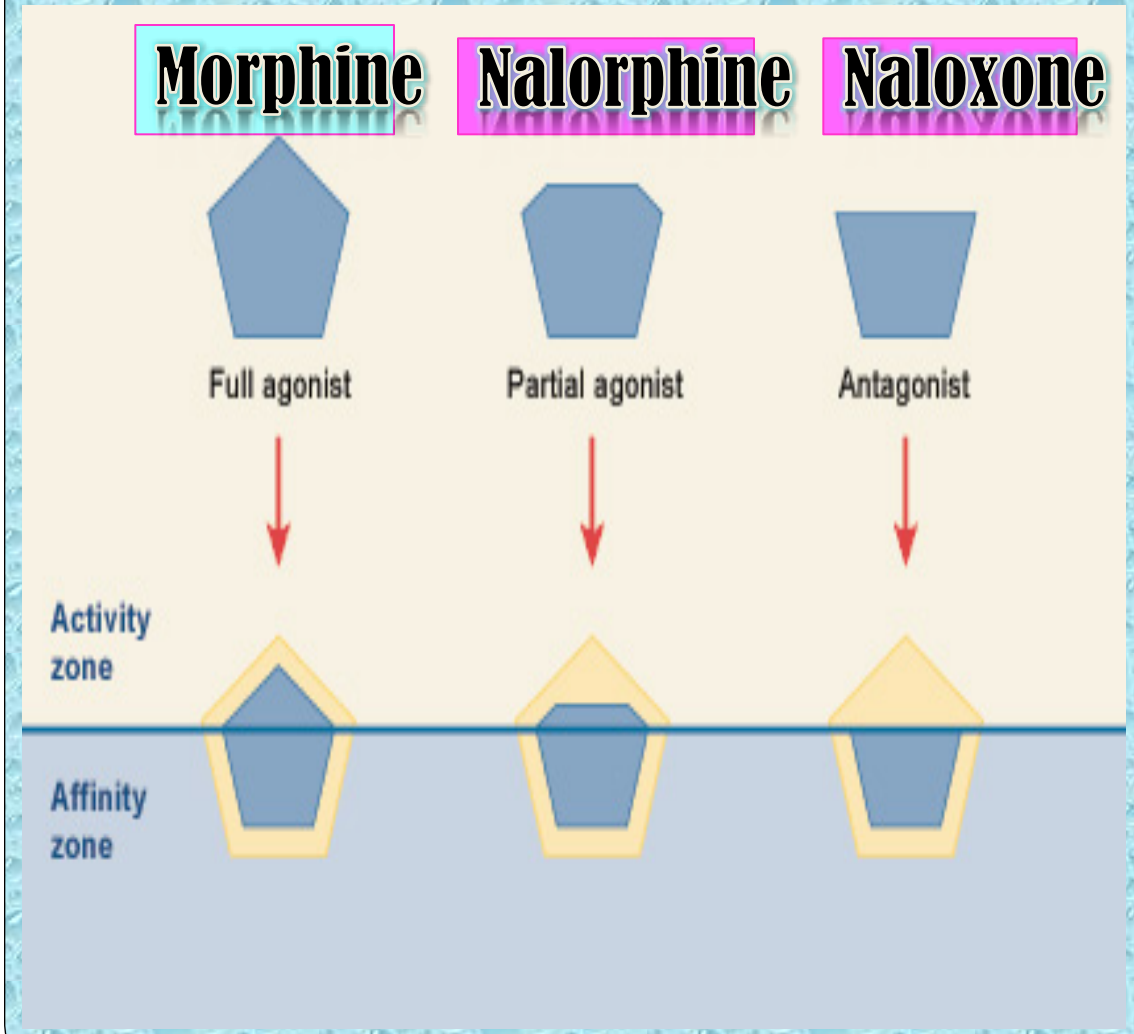
METHADONE

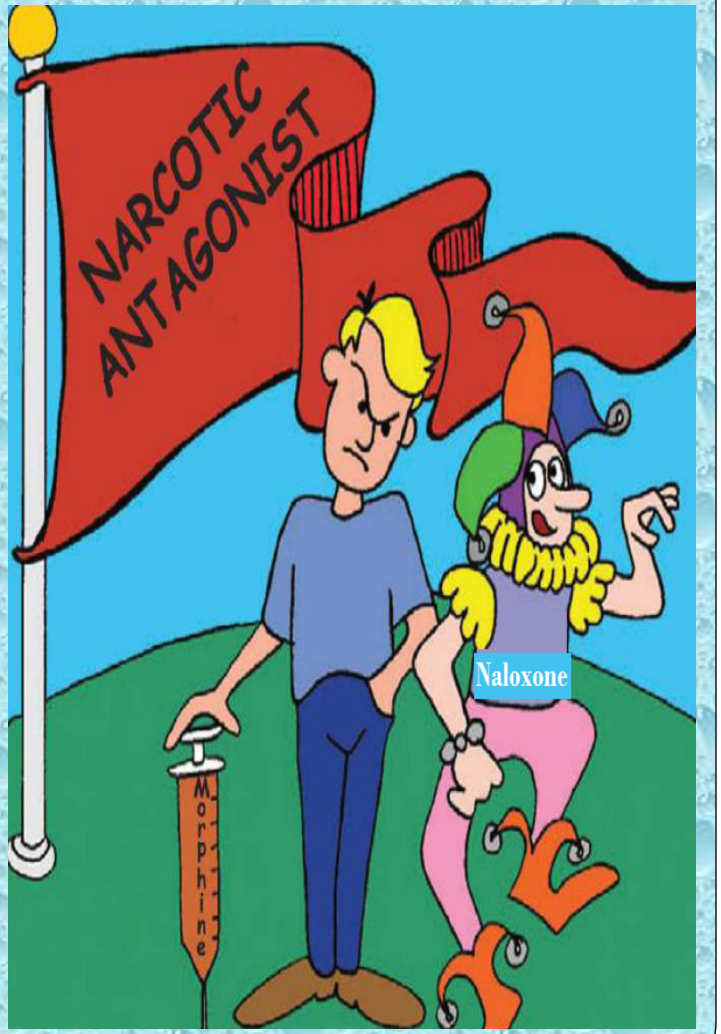
Used to treat opioid withdrawal





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**]

AT-121

Experimental analgesic, 100 times more potent than morphine

A bifunctional analgesic , acting as an agonist at both the μ-opioid receptor and the nociceptin receptor

The interaction with the nociceptin receptor blocks the abuse and dependence-related side effects