Analgesic opioids

HISTORY:

Theophrastus (botanist) III a.c.

Arabia: use against dysentery

Morphine 1806 (Serturner) Codeine 1832 (Robiquet)
Papaverine 1848 (Merck)

Opioid receptors (1972-73)

Different receptor types (1976)

Opioid peptides (1975)

OPIOIDS – Modern History

In 1973, Martin and Snyder begin binding studies that will lead to the cloning of three main types of opioid receptors in the central nervous system: μ, δ and κ

In 1975 Hughes and Kosterliz isolated, purified and sequenced the first two endogenous peptides with morphine-like activity called enkephalin (from brain)

Soon after, two other classes of endogenous opioid peptides, the dynorphins and the endorphins, were isolated

In 1994 the nociceptin / orphanin FQ receptor was cloned

In 2000, the commission of the International Union of Pharmacology adopted the terms MOP, DOP, and KOP to indicate the receptors of the opioid peptides μ, δ and κ, respectively. The commission also recommended the NOP terms for the N / OFQ receptor

ENDOGENOUS OPIOID SYSTEM

Control and modulatory functions:

- **sensory role:** prominent in the inhibition of pain stimuli (posterior spinal cord horns, periaqueductal gray, thalamus)
- **modulatory role:** in gastrointestinal, endocrine and autonomic functions (ventral part of the brainstem, hypothalamus)
- **emotional role:** evident in the powerful reward and addictive properties of opioids (hippocampus, amygdala, limbic structures)

  cognitive role: in modulation of learning and memory

Tabella 25.1. Peptidi Oppioidi Naturali.

Oppiodi endogeni	Struttura Aminoacidica	Attività recettoriale			
		MOP	DOP	KOP	NOP
Endomorfina 1	Tyr-Pro-Trp-Phe	+++			
Endomorfina 2	Tyr-Pro-Phe-Phe	+++			
[Leu^5]encefalina	Tyr-Gly-Gly-Phe-Leu	++	+++		
[Met^5]encefalina	Tyr-Gly-Gly-Phe-Met	++	+++		
Dinorfina A	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln	++		+++	
Dinorfina B	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Tyr	+	+	+++	
b-endorfina	Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu	+++	+++		
a-Neoendorfina	Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys	+	+	+++	
b-Neoendorfina	Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro	++	+	++	
Nocicettina/ Orfanina FQ	Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Glu				+++

Opioids actions

Central nervous system

Analgesia. Sedation, euphoria or dysphoria. Nausea and vomiting. Myosis. Respiratory depression. Cough reflex depression

Hormonal actions

Increased prolactin secretion and inhibition of GHRH, CRF, ACTH, FSH, LH. Decreased release of β-endorphin

Depressive actions on the immune system

Respiratory System

Slight bronchoconstriction. Respiratory depression

Cardiovascular System

Cutaneous vasodilation and itching (histamine release). Vasodilation of the capacitance and resistance vessels: orthostatic hypotension

Gastrointestinal System

Decreased gastrointestinal secretion, decreased gastric motility. Constipation and antidiarrheal effect. Hypertonus of the sphincter of Oddi

Toxicogenic action

Tolerance. Psychic physical addiction with withdrawal syndrome

Therapeutic uses of opioids

Analgesia (eg surgery, cancer)

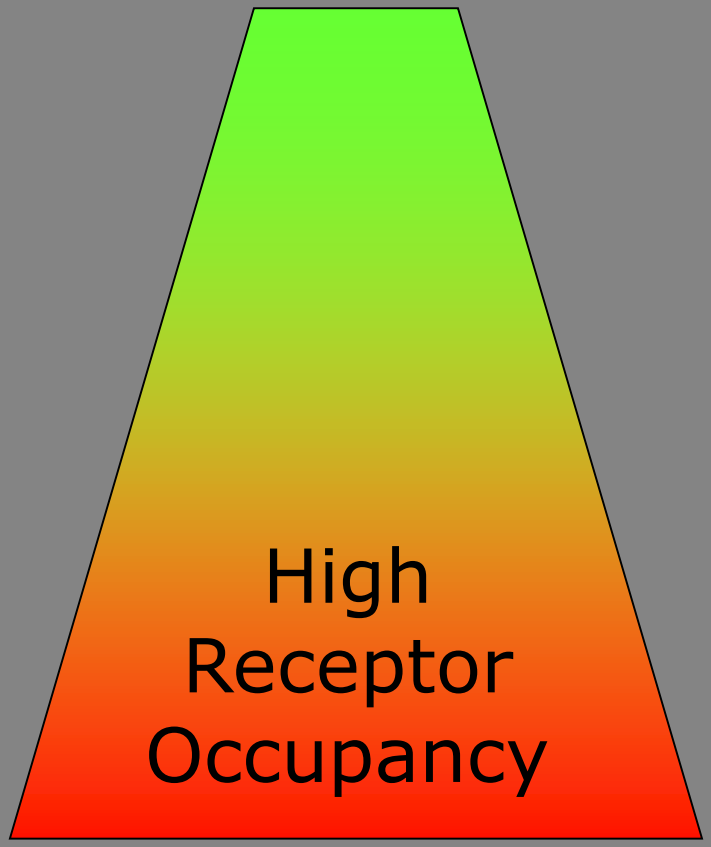
Treatment of diarrhea

Treatment of cough (reflex)

Treatment of acute pulmonary edema

EXOGENOUS OPPIOIDS
relative potency

HYDROPHILIC

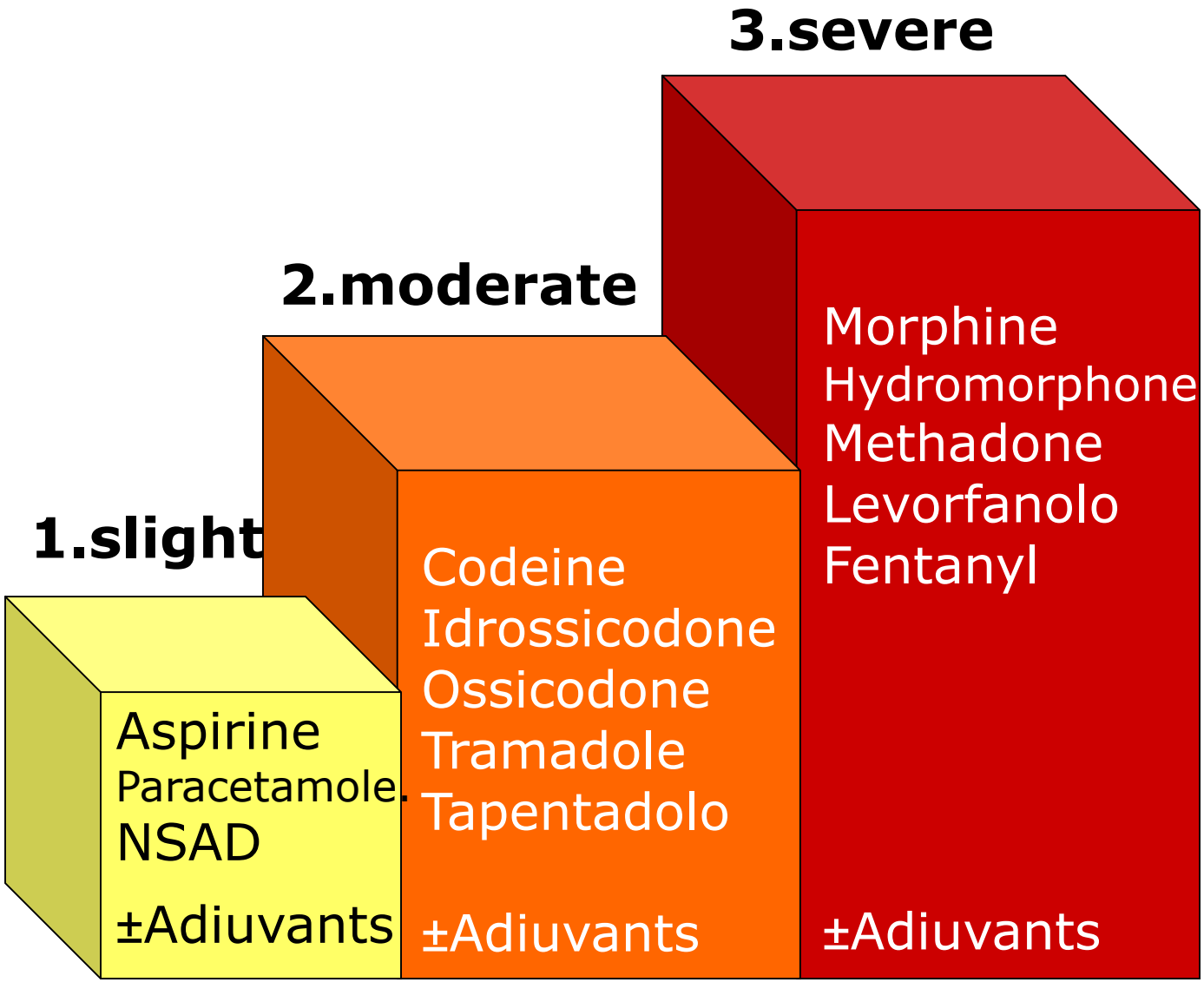


LIPOPHILIC

Propoxifene, Morphine
Codeine, Ossicodone
Hydrocodone, Methadone

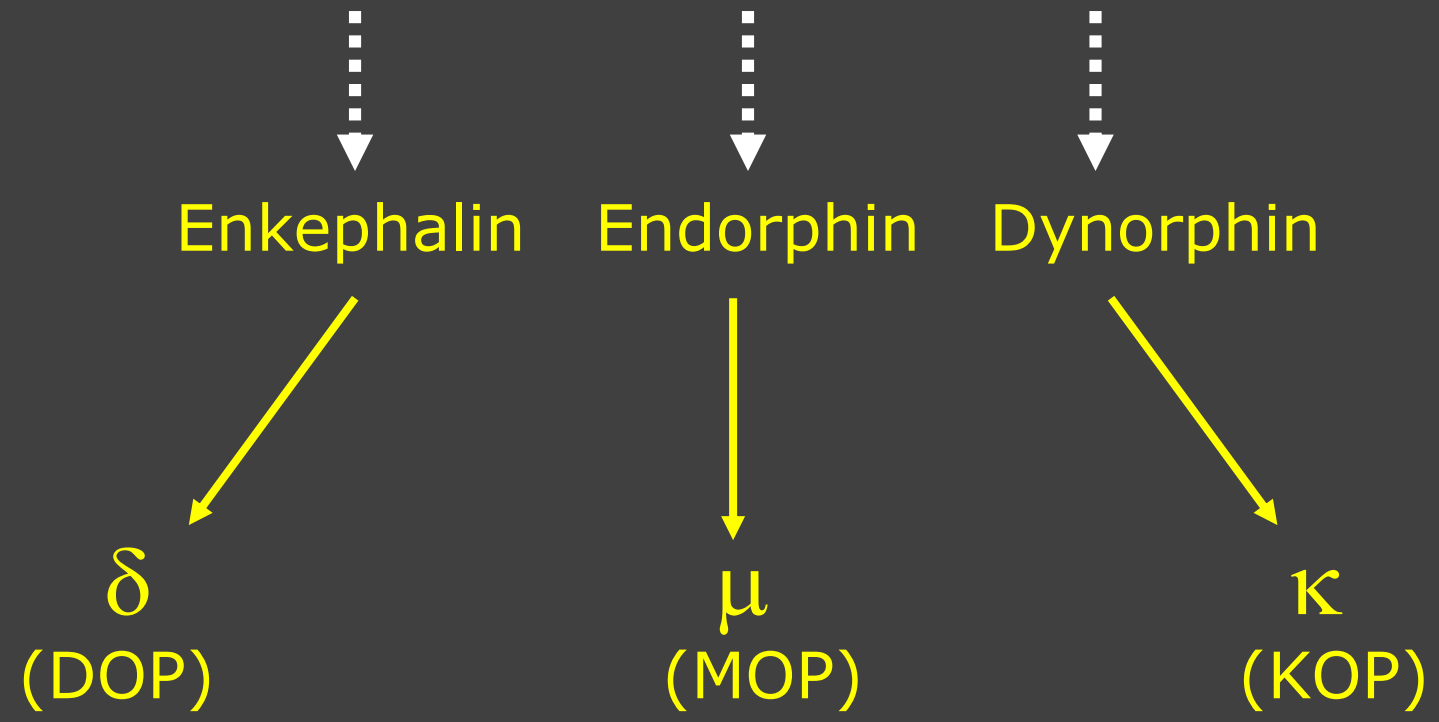
Fentanyl, Alfentanil Sufentanil,
Remifentanil
Carfentanil, Lofentanil

Treatment of pain based on severity of pain



Opioid Receptors

ENDOGENOUS OPIOID SYSTEM



LOCAL OPIOID RECEPTORS IN THE CNS AND IN INTESTINAL AND BLADDER PLEXUS

RECEPTOR MECHANISMS

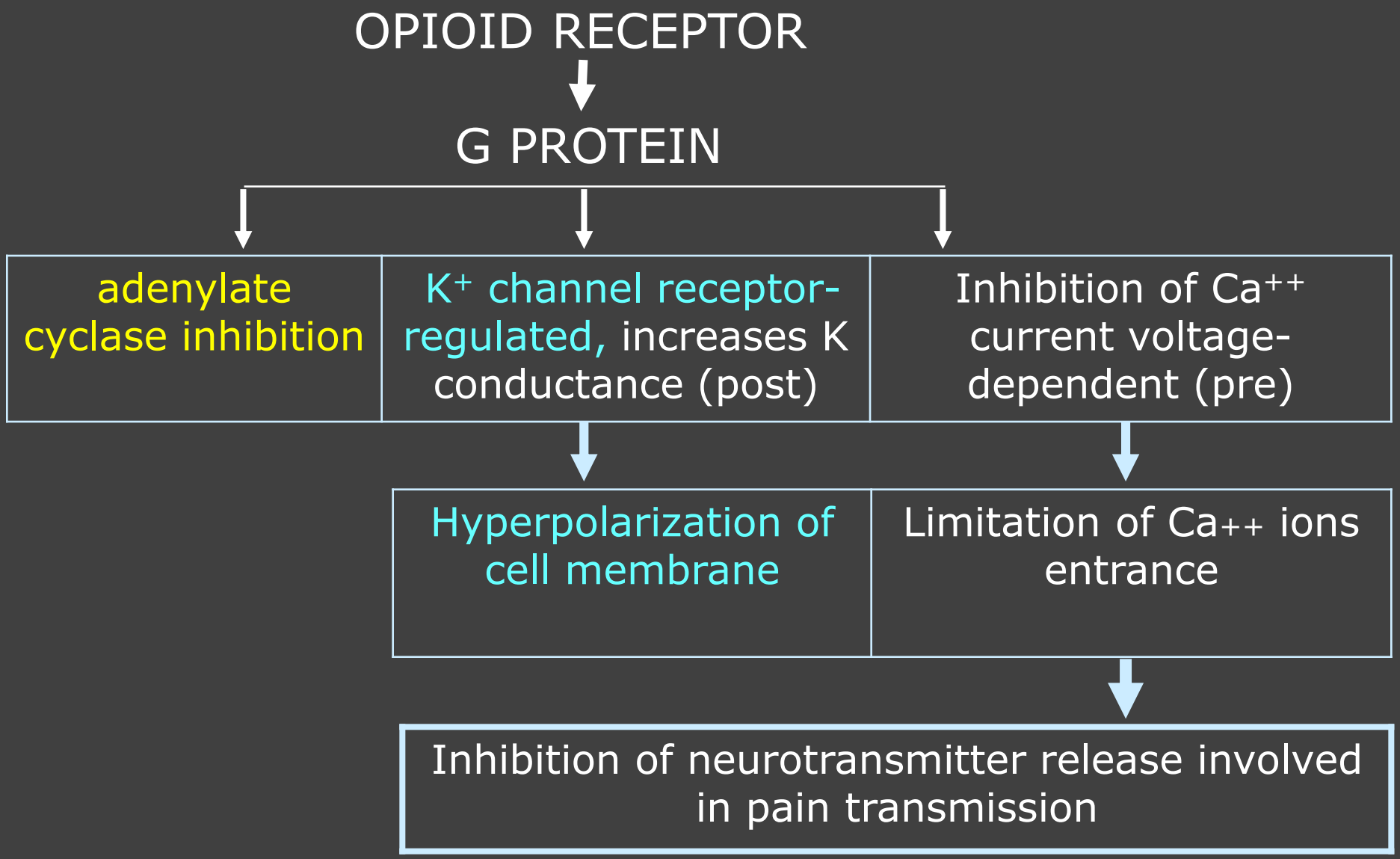


Table 41.1 Functional effects associated with the main types of opioid receptor

	μ	δ	κ
Analgesia			
Supraspinal	+++	–	–
Spinal	++	++	+
Peripheral	++	–	++
Respiratory depression	+++	++	–
Pupil constriction	++	–	+
Reduced gastrointestinal motility	++	++	+
Euphoria	+++	–	–
Dysphoria	–	–	+++
Sedation	++	–	++
Physical dependence	+++	–	+

Table 41.2 Selectivity of opioid drugs and peptides for receptor subtypes

	μ	δ	κ
Endogenous peptides			
β-Endorphin	+++	+++	+++
Leu-enkephalin	+	+++	–
Met-enkephalin	++	+++	–
Dynorphin	++	+	+++
Opiate drugs			
Pure agonists			
Morphine, codeine, oxymorphone, dextropropoxyphene	+++	+	+
Methadone	+++	–	–
Meperidine	++	+	+
Etorphine, bremazocine	+++	+++	+++
Fentanyl, sufentanil	+++	+	–
Partial/mixed agonists			
Pentazocine, ketocyclazocine	+	+	++
Nalbuphine	+	+	(++)
Nalorphine	++	–	(++)
Buprenorphine	(+++)	–	++
Antagonists			
Naloxone	+++	+	++
Naltrexone	+++	+	+++

Localization and mechanisms of opioid receptor transduction

Trunk and brain bulb: breathing (CO_2 center), nausea, vomiting, blood pressure, pupil diameter, stomach secretion
Medial thalamus: affective component
Hypothalamus: neuroendocrine secretion (↓GHRH, CRH, LH, FSH , ACTH, ↑prolactin)
Limbic system (Hippo. Amyg. Ctx. N. accumbens): emotional component, gratification (↑dopamine)

Spinal cord, trigeminal nerve, PAG: pain sensorial stimuli

Periphery: sensory nerve endings

Immune cells: ↓indeterminate role

Opioids-mediated Analgesia

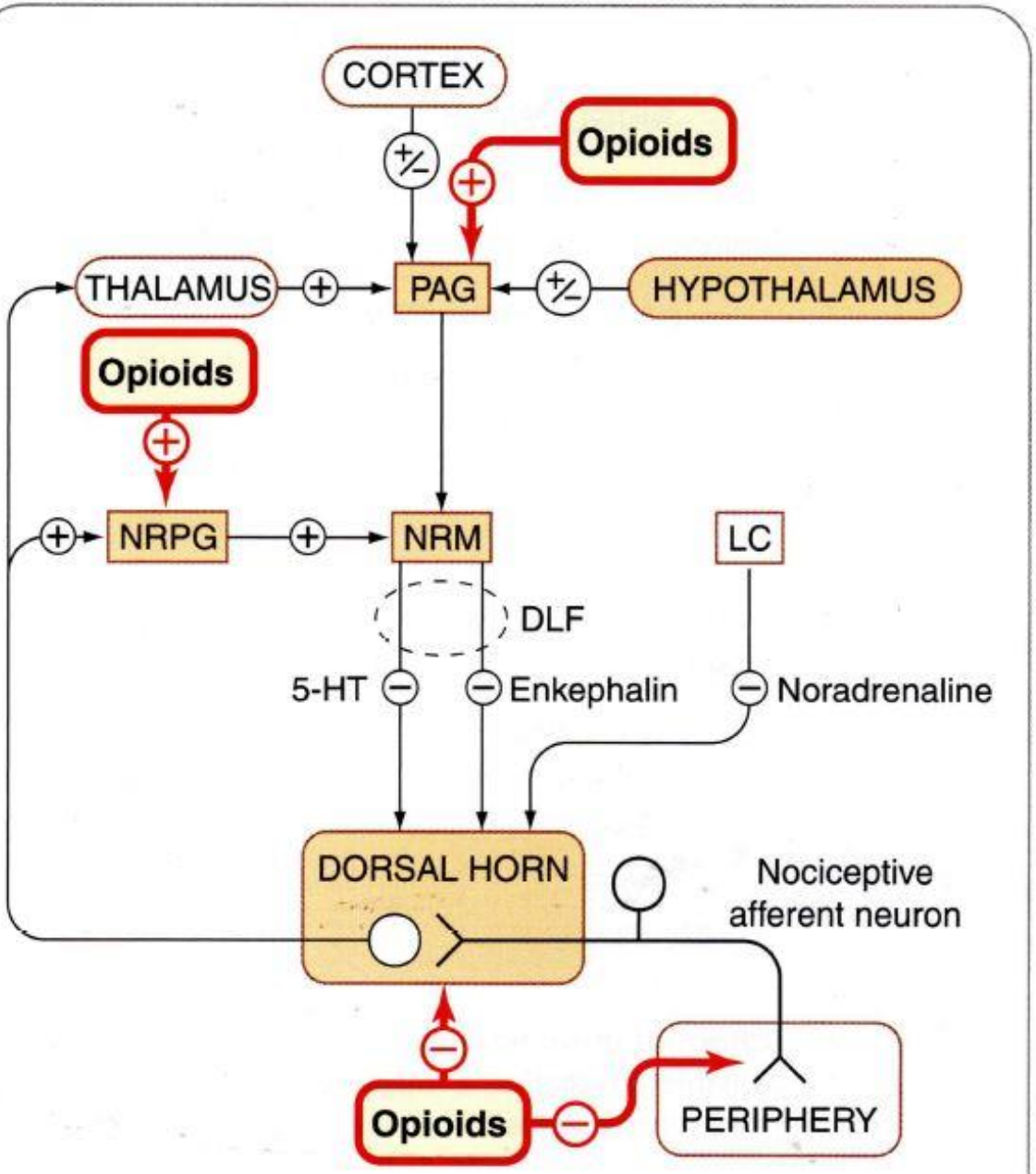


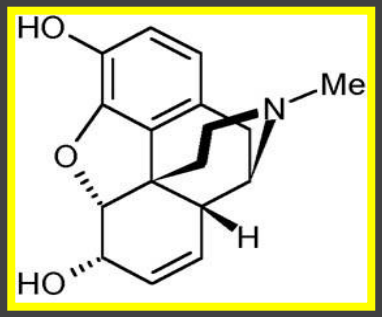
Fig. 41.5 The descending control system, showing the main sites of action of opioids on pain transmission. Opioids excite neurons in the periaqueductal grey matter (PAG) and in the *nucleus reticularis paragigantocellularis* (*NRPG*), which in turn project to the rostroventral medulla, which includes the *nucleus raphe magnus* (*NRM*). From the NRM, 5-hydroxytryptamine (5-HT)- and enkephalin-containing neurons run to the *substantia gelatinosa* of the dorsal horn, and exert an inhibitory influence on transmission. Opioids also act directly on the dorsal horn, as well as on the peripheral terminals of nociceptive afferent neurons. The *locus coeruleus* (*LC*) sends noradrenergic neurons to the dorsal horn, which also inhibit transmission. The pathways shown in this diagram represent a considerable oversimplification but depict the general organisation of the supraspinal control mechanisms. Shaded boxes represent areas rich in opioid peptides. (For more detailed information, see Fields & Basbaum, 1994.) DLF, dorsolateral funiculus.

Opioid Drugs

Tabella 27.3. Caratteristiche farmacocinetiche e terapeutiche di farmaci oppioidi

Farmaco	Potenza	Via di somministrazione	Uso terapeutico	Emivita	Metabolismo	Tipo recettoriale	Effetti Collaterali
Morfina	++	i.t., i.v., s.c., p.o.?	Dolore Acuto e Cronico	$T_{1/2}$ 3-4 h	M-6 glucuronide	MOP, DOP	Sedazione, depr. respiratoria, nausea, vomito, stipsi, euforia, tolleranza, dipendenza, prurito
Idromorfone	+++	p.o., i.m.,i.v.	Dolore Acuto e Cronico	$T_{1/2}$ 2-4 h	Metaboliti inattivi	MOP	Come Morfina
Codeina	+	p.o.,i.m.	Dolore moderato, Tosse	$T_{1/2}$ 2-4 h	M-6 glucuronide Morfina	MOP, DOP	Poco sensibile a naloxone, non provoca dipendenza
Petidina Meperidina	+	p.o.,i.m.	Dolore acuto	$T_{1/2}$ 2-4 h Norpetidina $T_{1/2}$ 10-15 h	Norpetidina (stimolante)	MOP, DOP, KOP	Analgesico con effetti anticolinergici; può causare eccitazione, convulsioni dovute a Norpetidina
Fentanile	+++	i.v., i.t., cerotto	Dolore Acuto, Anestesia	$T_{1/2}$ 1-1.5 h	Rapido	MOP	Come Morfina, non libera istamina
Remifentanile	++++	i.v.	Anestesia di breve durata	$T_{1/2}$ 10 min	Molto rapido	MOP	Come Fentanile
Metadone	++	p.o., i.m.,s.c.	Dolore Cronico, Disintossicazione	$T_{1/2}$ 24 h	Metabolismo lento, entrata in azione lenta	MOP	Come Morfina, blando euforizzante, di pendenza diversa
Dextro propossifene	+	p.o.	Dolori Acuti e Cronici moderati	$T_{1/2}$ 4 h	Norpropossifene $T_{1/2}$ 24 h	MOP, ??	Depr. respiratoria, convulsioni dovute Norpropossifene
Tramadolo	+	p.o., i.v.	Dolore Acuto postoperatorio e Cronico	$T_{1/2}$ 4-6 h		MOP, ??	Convulsioni, perdita di equilibrio; non causa a) depressione respiratoria; b) dipendenza; c) tolleranza
Loperamide	+++	p.o.	Diarrea			MOP	
Pentazocina	+	i.m.	Dolore Acuto	$T_{1/2}$ 2-4 h		MOP, KOP ant/ago	Ipertensione, tachicardia
Buprenorfina	++++	i.m., sublinguale, i.t. i.v.,i.m.	Dolore Acuto e Cronico, Disintossicazione	$T_{1/2}$ 12 h	Metabolizzato velocemente nel fegato	MOP, KOP ago/antag	Depr. respiratoria insensibile a Naloxone
Naloxone	+++		Iperdosaggio, effetti collaterali di oppioidi	$T_{1/2}$ 2-3 h	Rapida inattivazione epatica, breve durata d'azione	MOP, DOP, KOP	Rimbalzo da Morfina ed
Naltrexone	++	p.o., s.c., i.v.,i.m.	Iperdosaggio, effetti collaterali di oppioidi	$T_{1/2}$ 10-12 h	Inattivazione epatica, durata d'azione media	MOP, DOP, KOP	Eroina Non permette il rimbalzo

MORPHINE



PHARMACOKINETICS

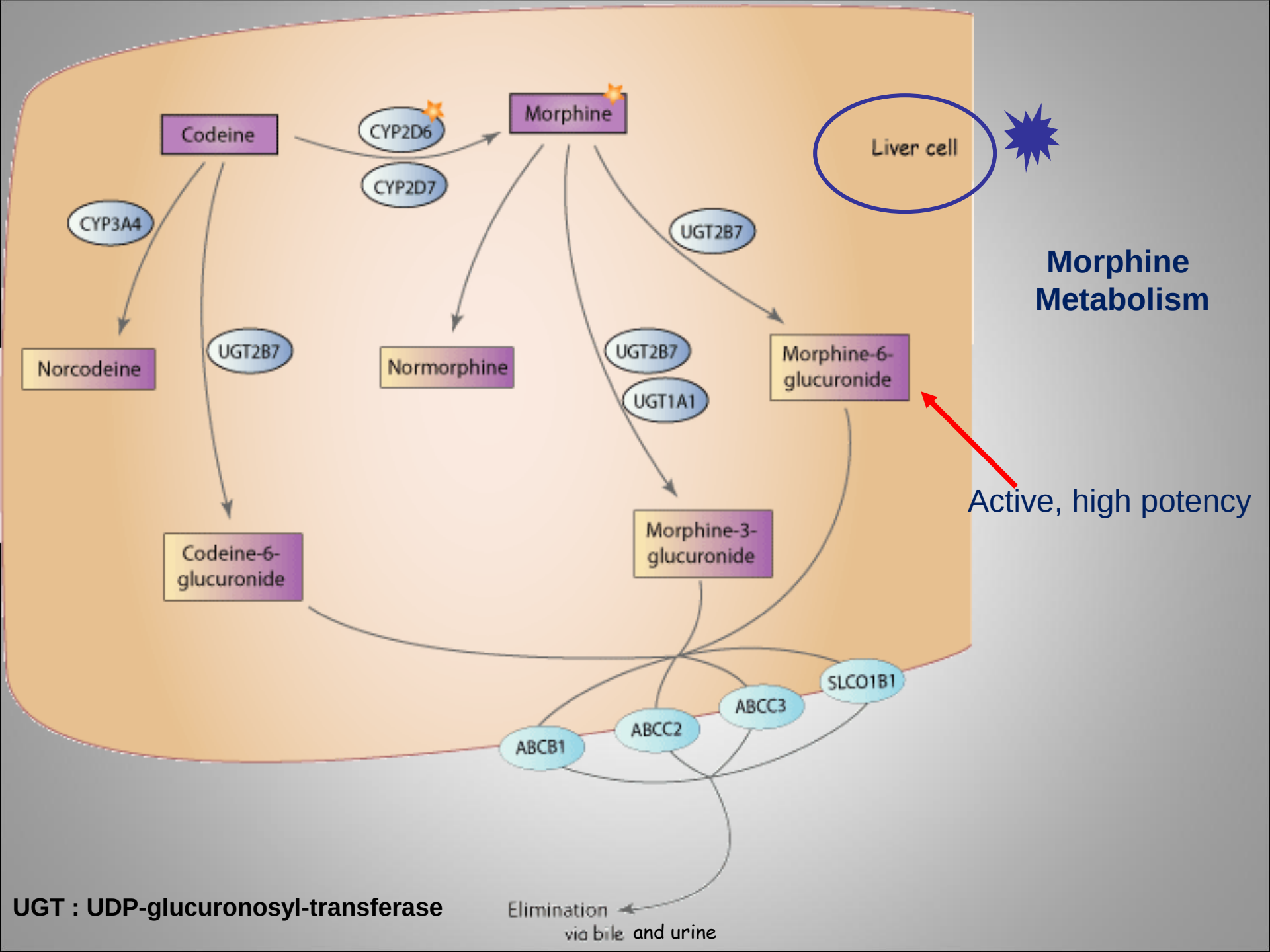
Administration:
Morphine sulphate / hydrochloride
Oral; IM; SC, EV, Epidural; Intrathecal; Intraarticular

Absorption:
Oral bioavailability 25%

Distribution:
Protein binding: 30%
Cross the BBB and placenta. Plasma half-life: 2 - 3 hours

Metabolism:
Hepatic: Glucuronidation → morphine-6-glucuronide (active metabolite) → Morphine-3-glucuronide

Elimination:
Renal: metabolites (morphine-3-glucuronide)
Biliary, fecal: glucuronides (10%)



Morphine Metabolism

Active, high potency

UGT : UDP-glucuronosyl-transferase

Actions of morphine

- The main pharmacological effects are:
  - —analgesia. Infarto, edema polmonare,
  - —euphoria and sedation
  - —respiratory depression and suppression of cough
  - —nausea and vomiting
  - —pupillary constriction
  - —reduced gastrointestinal motility, causing constipation. Motilità vie biliari
  - —histamine release, causing bronchoconstriction and hypotension.
- The most troublesome unwanted effects are constipation and respiratory depression.
- Morphine may be given by injection (intravenous or intramuscular) or by mouth, often as slow-release tablets.
- Acute overdosage with morphine produces coma and respiratory depression.
- Morphine is metabolised to morphine 6-glucuronide (M6G), which is more potent as an analgesic.
- Morphine and M6G, are the active metabolites of diamorphine and codeine.

Decrease sensitivity to Co2

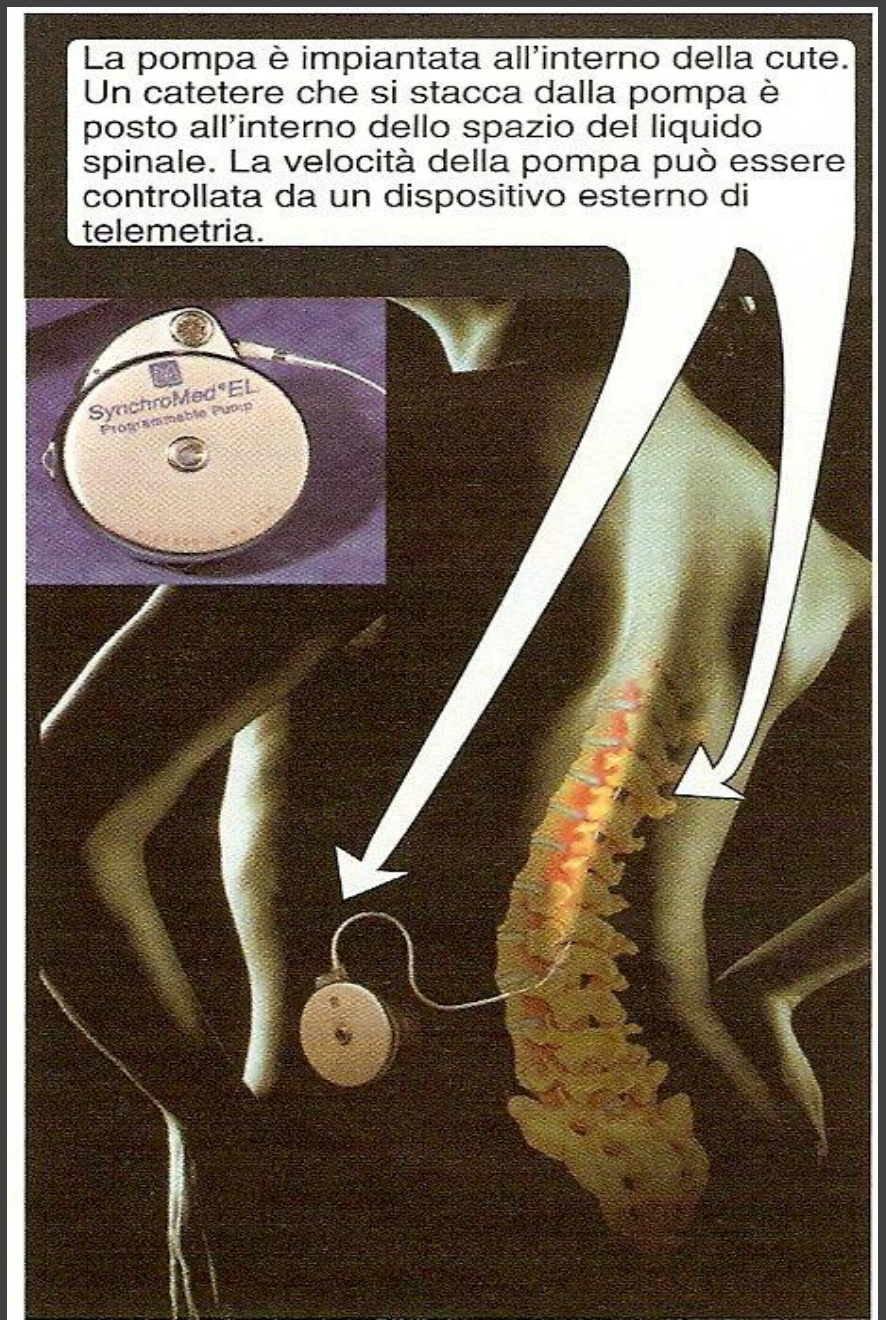
CTZ

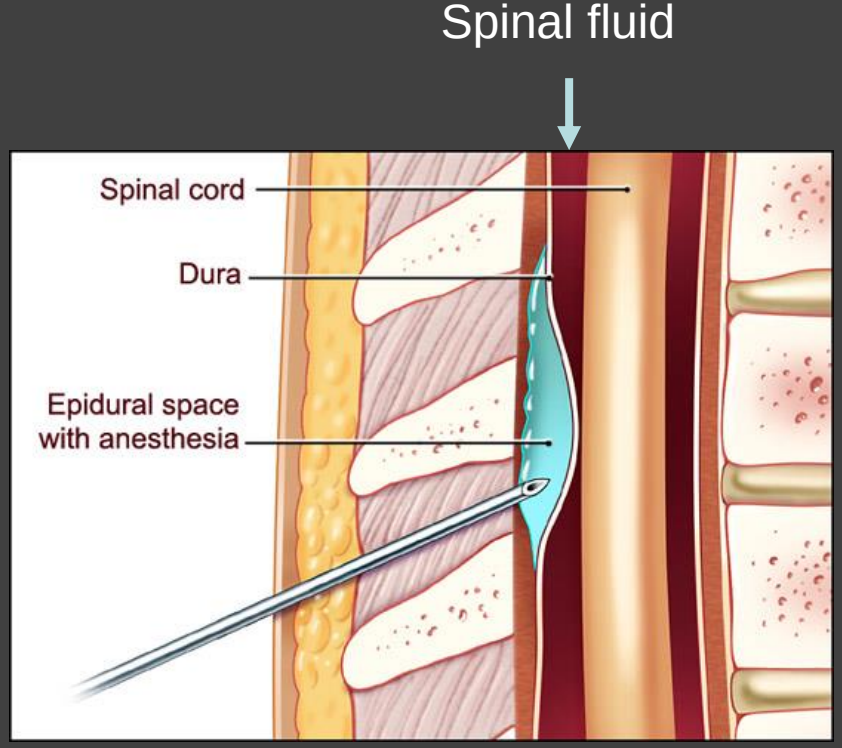
Parasympathetic stimulation

Inhibition of NA, ACh

Allergic reaction (high dosage)

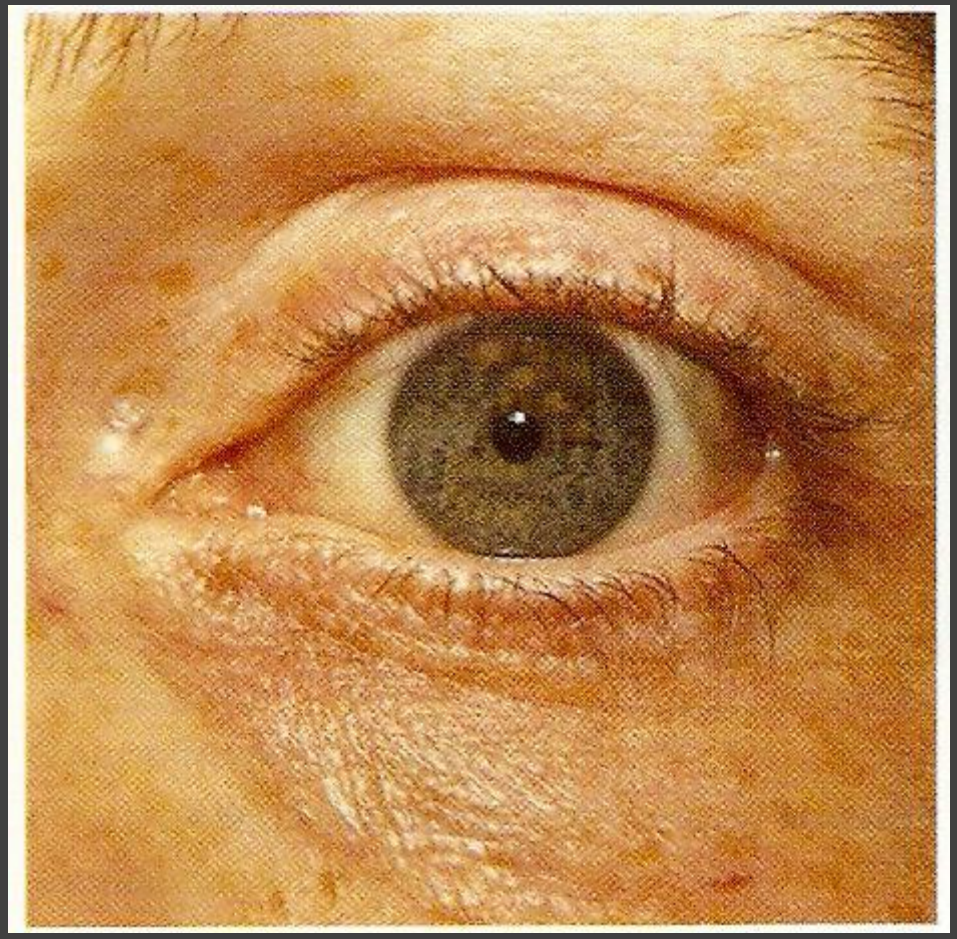
Pump for erogation of morphine

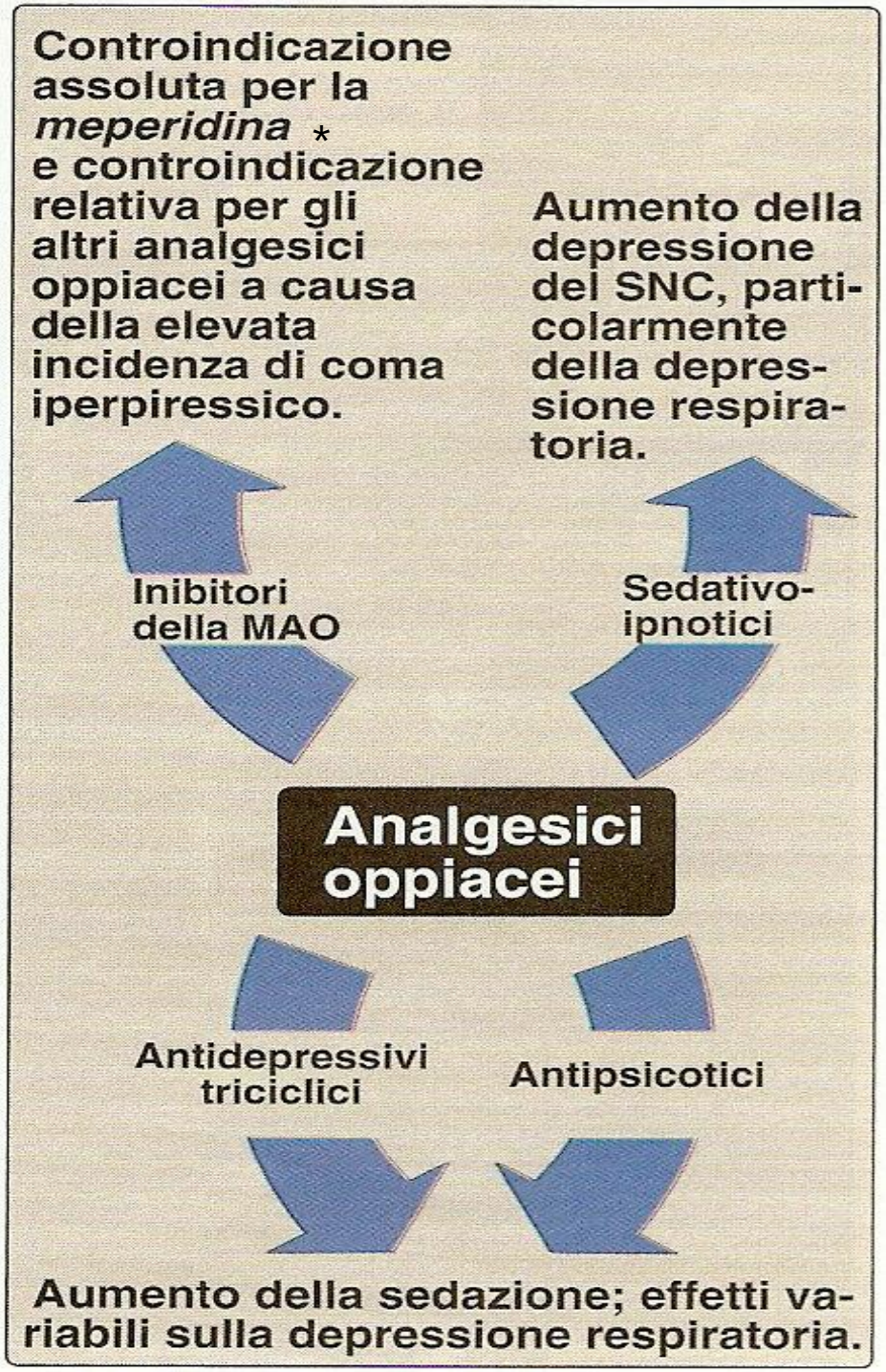




Morphine side effects

Strengthening of parasympathetic eye stimulation caused by morphine





Drugs that interact with opioid analgesics

* **Meperidine** or pethidine blocks reuptake 5HT (pyrexia), intravenously decreases peripheral resistance and increases blood flow, dilates cerebral vessels such as morphine, does not contrast cough and diarrhea is used in obstetrics (for its brief action is used in childbirth and labor). Effective orally (as opposed to morphine) and intramuscularly

Other Opioids

Codeine

Dextromethorphan (5HT)

(no analgesic effects)

CODEINE PHOSPHATE (metabolite: ⟶ morphine)

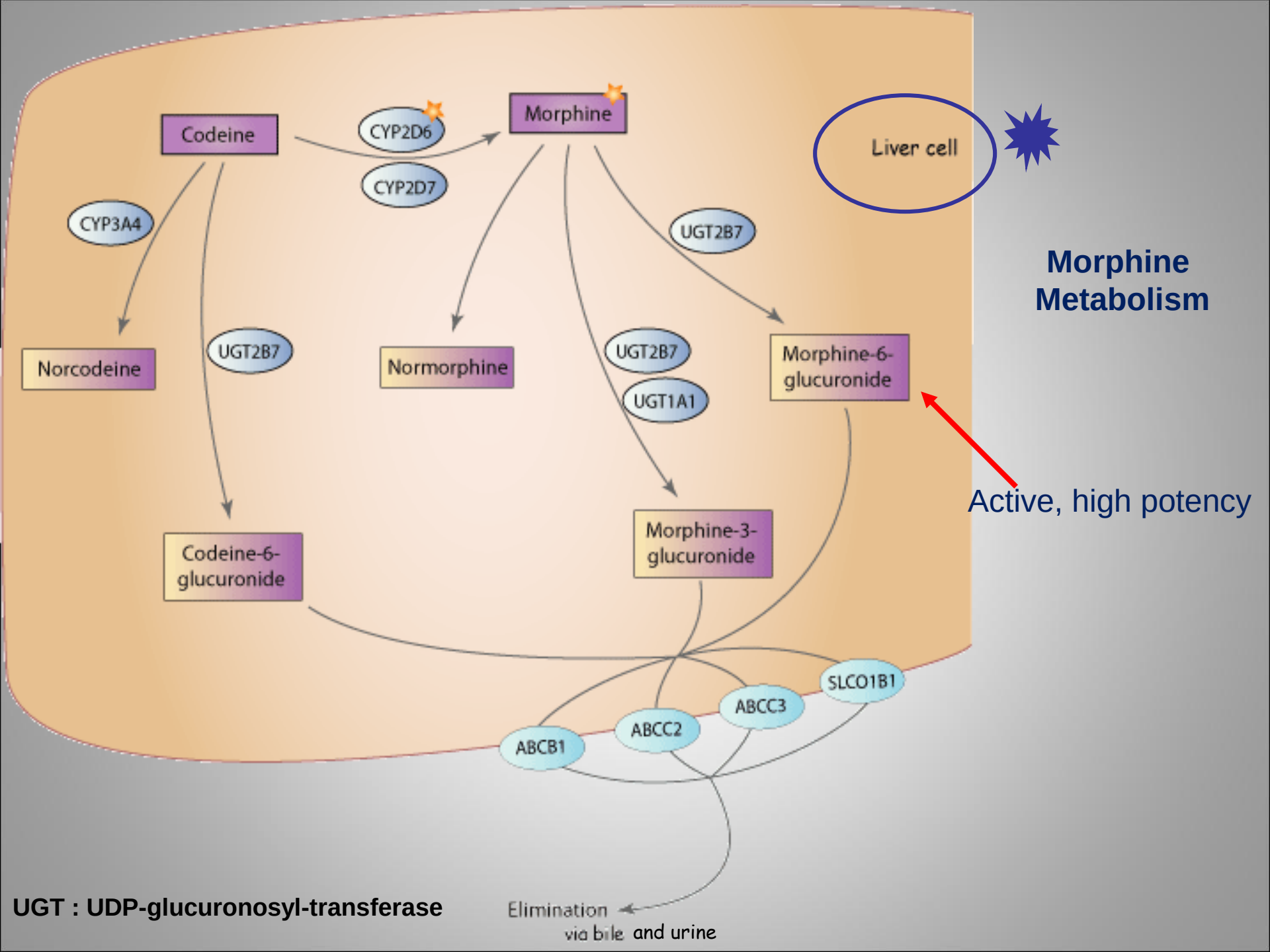
Indications: Cough suppression (dry or painful cough)

Not recommended for children; Asthma; alterations of the hepatic and renal function

CHLORIDATED LOPERAMIDE (Imodium®)

Indications: Symptomatic treatment of acute diarrhea

in addition to rehydration

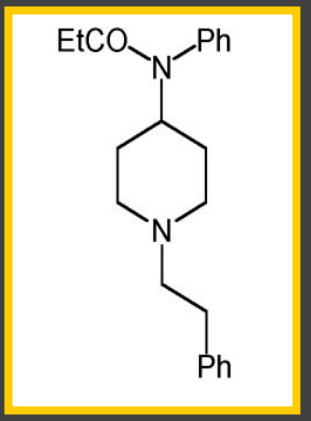


Morphine Metabolism

Active, high potency

UGT : UDP-glucuronosyl-transferase

FENTANIL (Fentanest®)



Synthetic opioid, derived from pethidine. Receptor agonist μ

Pharmacokinetics

Administration: Citrate injectable solution. 5 mg / ml EV, IM, EPI,
Transdermal Absorption: rapid
Distribution: Binding to protein: 80% Plasma half-life: 4 hours
Metabolism: Hepatic: dealkylation, hydroxylation
Elimination: Renal: (85% met. 8% no mod.) Fecal: biliary

INDICATIONS

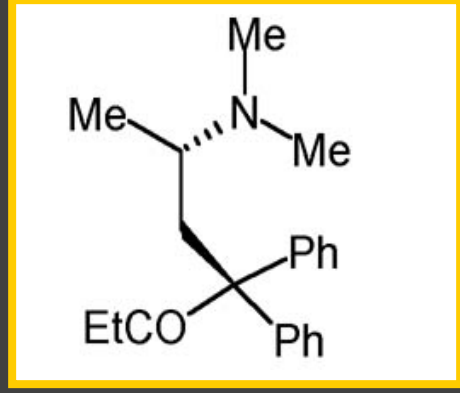
Preoperative medication. Chronic intractable pain (transdermal systems 25-100 mg / hour)

TOXICITY

Respiratory depression, dizziness, tremors, myoclonus, convulsions. Nausea, vomiting, constipation. Pharmacodynamic interaction with BZD.
Induction and inhibition of the metabolism of other drugs

METADONE (Eptadone®)

Syntetic Opioid, long acting



PHARMACOKINETICS

Administration: Oral 2.5-10mg - 40mg / day (drug addiction)
Absorption: rapid
Distribution: Protein binding: 70-80% Plasma half-life: 23 hours
Metabolism: Hepatic demethylation - conjugation
Elimination: Renal 21% unchanged Fecal: biliary

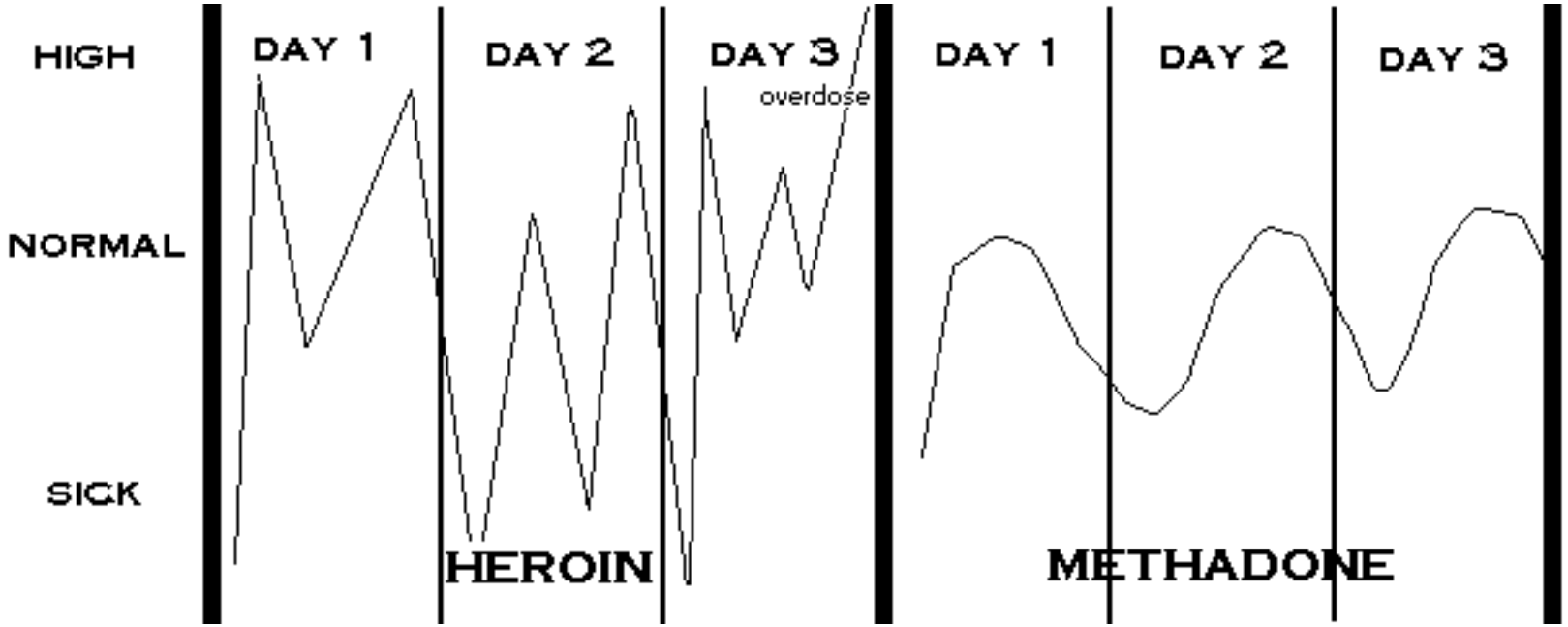
INDICATIONS

Treatment of acute and chronic pain. Treatment of opioid addiction

TOXICITY

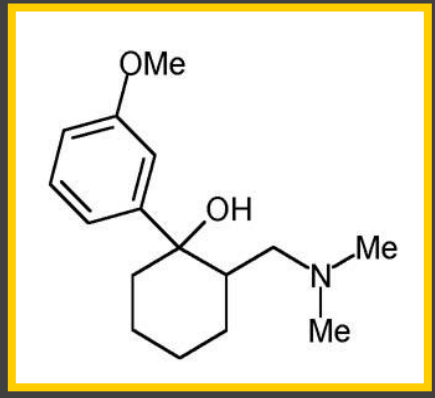
Respiratory depression, nausea, vomiting

Stabilizing effect of methadone



TRAMADOL (Contramal®)

Synthetic opioid



Low binding μ receptors- inhibits **NA** and 5-HT reuptake

PHARMACOKINETICS

Administration: IM 50-100 mg x4 / day Oral, EV Absorption: large (2 h)
Distribution: Protein binding 20% Plasma half-life 6 hours
Metabolism: Hepatic conjugation demethylation
Elimination: Renal 60% met 30% immod Fecal 10%

INDICATIONS

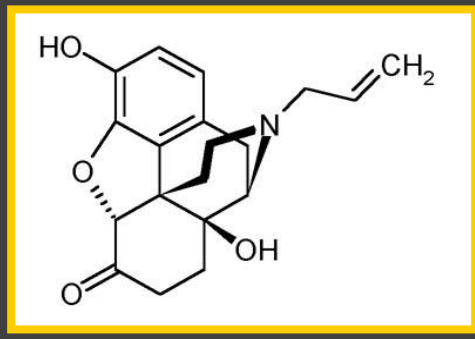
Postoperative pain treatment. Obstetric analgesia. Neoplastic pain. It is NOT indicated as an analgesic in balanced anesthesia for intraoperative consciousness increase

TOXICITY

Low incidence of respiratory and cardiac depression and low potential for addiction

Antagonists of opioid receptors

NALOXONE (Narcan®) Direct Antagonist



PHARMACOKINETICS

Administration: EV 0.4-2 mg up to a maximum of 10 mg
Absorption: Bioavailability oral low
Distribution: Plasma half-life 30-80 min
Metabolism: Hepatic large Glucuronidation
Elimination: Renal glucuronides

INDICATIONS

Diagnosis and treatment of opioid overdose

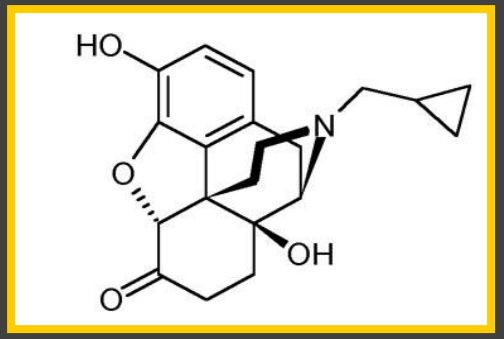
TOXICITY

Hypotension, hypertension, cardiac arhythmias. Pulmonary edema. Opioid withdrawal symptoms

NALTREXONE

Antagonist

(Antaxone®, Nalorex®, Narcoral ®)



PHARMACOKINETICS

Administration: Oral 50 mg / 100 mg
Absorption: Bioavailability oral 40%
Distribution: Protein binding 21% Half-life 4 h
Hepatic metabolism: extensive conjugation
Elimination: Renal 60% conjugated. Fecal 3%

INDICATIONS

Treatment of opioid addiction

TOXICITY

Nausea, vomiting, abdominal pain. Constipation. Anxiety, nervousness, irritability

Withdrawal Syndrome

8-12 hrs

lachrymation
rhinorrhea
yawning
sweating
mydriasis
anorexia
restlessness
irritability
tremor

24-72 hrs

pupillary dilation,
tremor
anorexia

intestinal spasms, vomiting, diarrhea, weight loss, chills, skin redness, abdominal cramps, bone and muscle pain

7-10 days

Lack of food intake; vomiting, sweating, and diarrhea cause dehydration; ketosis, acid-base balance disturbance insomnia, increased arterial blood pressure and body temperature

Opioid dependence and abuse

Definition of “Abuse”

Non-therapeutic use of the substance

Self-administration of a substance in ways that deviate from shared medical and social norms

Definition of “DRUG ADDICTION”

Pathological condition characterized by loss of control of consumption behavior and serious consequences on the social life of the individual

DRUG ADDICTION IS RELATED TO THREE FACTORS

1) The substance of abuse

2) The consumer

3) The social environment in which the meeting between the substance and the consumer takes place

DRUG ADDICTION

Drug addiction must be considered as a "chronic disease" of a recurring nature and development

A drug addict is an individual who, as a result of repeated administration of a substance of abuse, becomes:

1) Dependent on the effects of the substance taken

2) Has an uncontrollable desire to continue taking it (CRAVING)

3) It shows a marked tendency to increase the dose

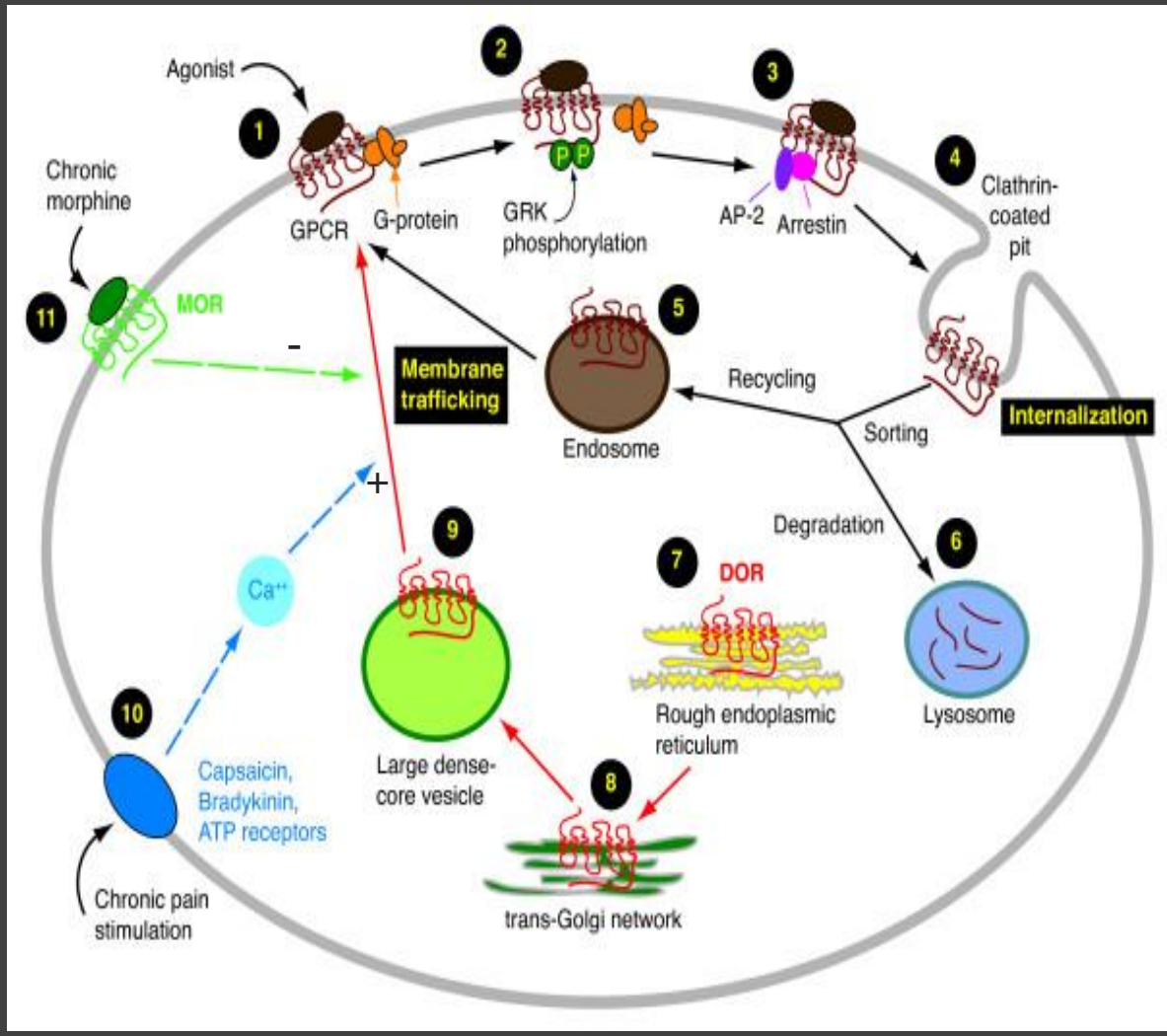
Opioids Tolerance

Opioids Tolerance

Hypothesized Mechanisms

- Short term:
reduction of the coupling between the opioid receptor and the G protein, with loss of the ability to exchange GDP with GTP.

- Long-term:
receptor desensitization, receptor internalization, phosphorylation of the intracellular receptor loops and reduction of the opioid agonist's efficacy



- reduction in intracellular sodium levels with reduced activity of Na/K-ATPase

OVERDOSE

SYMPTOMS

Pupil miosis with non reactive pupils to a light stimulus
Superficial respiration with 2/3 breaths / min

Body temperature: hypothermia
Reduced or absent osteo-tendon reflexes
Rhabdomyolysis
Acute cyanosis
Cardiovascular system bradycardia / severe hypotension
Central nervous system severe respiratory depression
absence of response to external stimuli; brain anoxia

EVOLUTION

acute cardiorespiratory failure
coma - death

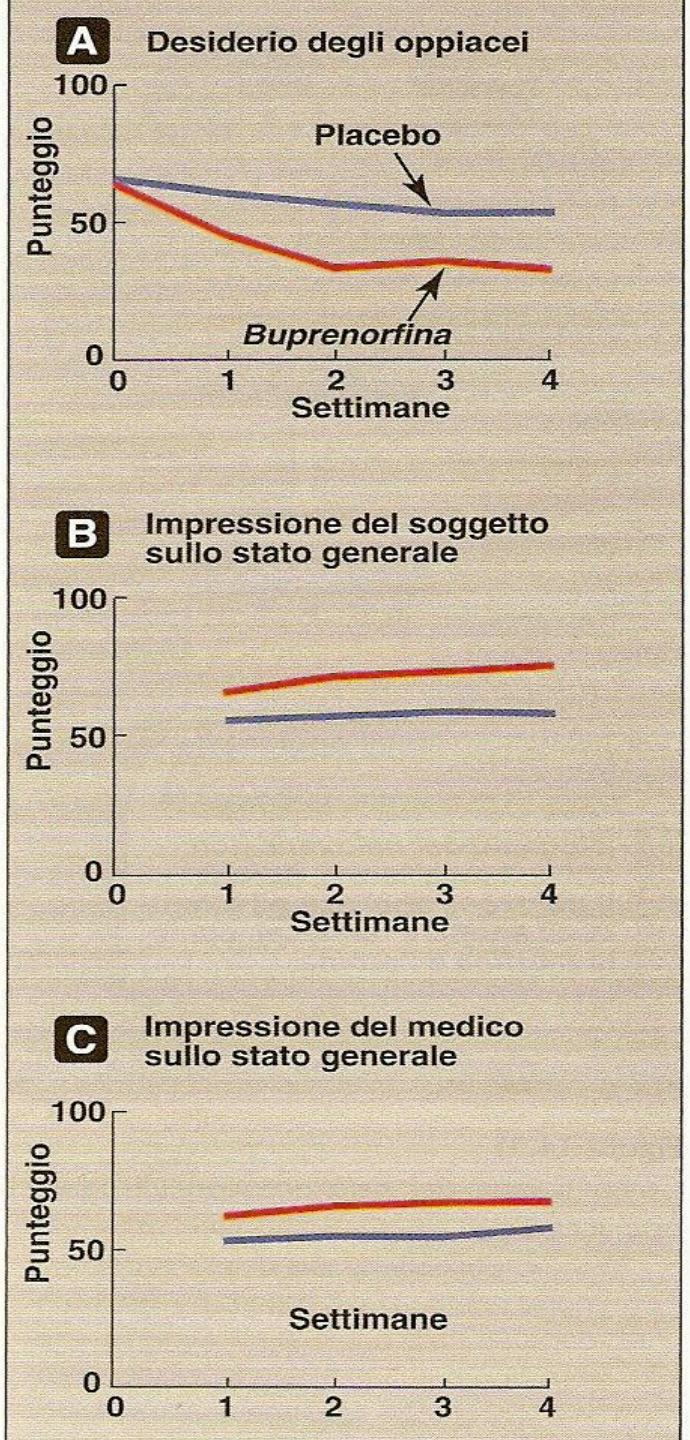
THERAPY

Opioid antagonists maintenance of airway patency (assisted ventilation, oxygen) maintenance of circulation, contrast of convulsions

Weaning

Table 42.2 Pharmacological approaches to treating drug dependence

Mechanism	Examples
Substitution, to alleviate withdrawal symptoms	Methadone, used short-term to blunt opiate withdrawal **Buprenorphine**
Long-term substitution	Methadone substitution for opiate addiction **Buprenorphine, levo-acetilmetadolo LAAM,**
Blocking response	Naltrexone to block opiate effects
Modification of craving	Bupropion (antidepressant) Naltrexone (blocks opiate receptors—also of value in treating other addictions) Clonidine (α_2-adrenoceptor agonist) Acamprosat (GABA)



Effects of *buprenorfina* vs placebo