Analgesic opioids
HISTORY:

Theophrastus (botanist) III a.C.

Arabia: use against dysentery

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

Opioid receptors (1972-73)

Different receptor types (1976)

Opioid peptides (1975)
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: $\mu$, $\delta$ and $\kappa$.

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 $\mu$, $\delta$ and $\kappa$, 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
<table>
<thead>
<tr>
<th>OPPIODI ENDOGENI</th>
<th>STRUTTURA AMINOACIDICA</th>
<th>ATTIVITÀ RECETTORIALE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MOP</td>
</tr>
<tr>
<td>Endomorfina 1</td>
<td>Tyr-Pro-Trp-Phe</td>
<td>+++</td>
</tr>
<tr>
<td>Endomorfina 2</td>
<td>Tyr-Pro-Phe-Phe</td>
<td>+++</td>
</tr>
<tr>
<td>[Leu₅]encefalina</td>
<td>Tyr-Gly-Gly-Phe-Leu</td>
<td>++</td>
</tr>
<tr>
<td>[Met₅]encefalina</td>
<td>Tyr-Gly-Gly-Phe-Met</td>
<td>++</td>
</tr>
<tr>
<td>Dinorfina B</td>
<td>Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Tyr</td>
<td>+</td>
</tr>
<tr>
<td>b-endorfina</td>
<td>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</td>
<td>+++</td>
</tr>
<tr>
<td>a-Neoendorfina</td>
<td>Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys</td>
<td>+</td>
</tr>
<tr>
<td>b-Neoendorfina</td>
<td>Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro</td>
<td>++</td>
</tr>
</tbody>
</table>
Opioids actions
Central nervous system

**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 OPIOIDS
relative potency

HYDROPHILIC

High Receptor Occupancy

LIPOPHILIC

Propoxifene, Morphine
Codeine, Ossicodone
Hydrocodone, Methadone

Fentanyl, Alfentanil Sufentanil,
Remifentanil
Carfentanil, Lofentanil
Treatment of pain based on severity of pain

1. slight
- Aspirin
- Paracetamol
- NSAD

± Adjuvants

2. moderate
- Codeine
- Idrossicodone
- Ossicodone
- Tramadole
- Tapentadolo

± Adjuvants

3. severe
- Morphine
- Hydromorphone
- Methadone
- Levorfanolo
- Fentanyl

± Adjuvants
Opioid Receptors
ENDOGENOUS OPIOID SYSTEM

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

\[ \text{G PROTEIN} \]

- Adenylate cyclase inhibition
- \( K^+ \) channel receptor-regulated, increases \( K \) conductance (post)
- Inhibition of \( Ca^{++} \) current voltage-dependent (pre)

- Hyperpolarization of cell membrane
- Limitation of \( Ca^{++} \) ions entrance

Inhibition of neurotransmitter release involved in pain transmission
# Table 41.1 Functional effects associated with the main types of opioid receptor

<table>
<thead>
<tr>
<th></th>
<th>$\mu$</th>
<th>$\delta$</th>
<th>$\kappa$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraspinal</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Spinal</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Peripheral</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td><strong>Respiratory depression</strong></td>
<td>+++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pupil constriction</strong></td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Reduced gastrointestinal motility</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Euphoria</strong></td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Dysphoria</strong></td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Sedation</strong></td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td><strong>Physical dependence</strong></td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>μ</td>
<td>δ</td>
<td>κ</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td><strong>Endogenous peptides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Endorphin</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Leu-enkephalin</td>
<td>+</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>Met-enkephalin</td>
<td>++</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>Dynorphin</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Opiate drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pure agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine, codeine, oxymorphone, dextropropoxyphene</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Methadone</td>
<td>+++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Meperidine</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Etorphine, bremazocine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Fentanyl, sufentanil</td>
<td>+++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Partial/mixed agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentazocine, ketocyclazocine</td>
<td>+</td>
<td>+</td>
<td>(++)</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>+</td>
<td>+</td>
<td>(++)</td>
</tr>
<tr>
<td>Nalorphine</td>
<td>++</td>
<td>−</td>
<td>(++)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>(++)</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td><strong>Antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>
Localization and mechanisms of opioid receptor transduction

**Trunk and brain bulb**: breathing (CO2 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

<table>
<thead>
<tr>
<th>Farmaco</th>
<th>Potenza</th>
<th>Via di somministrazione</th>
<th>Uso terapeutico</th>
<th>Emivita</th>
<th>Metabolismo</th>
<th>Tipo recettoriale</th>
<th>Effetti Collaterali</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morfina</td>
<td>++</td>
<td>i.t., i.v., s.c., p.o.?</td>
<td>Dolore Acuto e Cronico</td>
<td>$T_{1/2}$ 3-4 h</td>
<td>M-6 glucuronide</td>
<td>MOP, DOP</td>
<td>Sedazione, depre. respiratoria, nausea, vomito, tisi, euforia, tolleranza, dipendenza, prurito</td>
</tr>
<tr>
<td>Idromorfone</td>
<td>+++</td>
<td>p.o., i.m., i.v.</td>
<td>Dolore Acuto e Cronico</td>
<td>$T_{1/2}$ 2-4 h</td>
<td>Metaboliti inattivi</td>
<td>MOP</td>
<td>Come Morfina</td>
</tr>
<tr>
<td>Codeina</td>
<td>+</td>
<td>p.o., i.m.</td>
<td>Dolore moderato, Tossse</td>
<td>$T_{1/2}$ 2-4 h</td>
<td>M-6 glucuronide Morfina</td>
<td>MOP, DOP</td>
<td>Poco sensibile a naloxone, non provocazione dipendenza</td>
</tr>
<tr>
<td>Petidina</td>
<td>++</td>
<td>p.o., i.m.</td>
<td>Dolore Acuto</td>
<td>$T_{1/2}$ 2-4 h</td>
<td>Norpetidina (stimolante)</td>
<td>MOP, DOP, KOP</td>
<td>Analgesico con effetti anticolinergici; può causare eccitazione convulsioni dovute a Norpetidina</td>
</tr>
<tr>
<td>Meperidina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Come Morfina</td>
</tr>
<tr>
<td>Fentanile</td>
<td>+++</td>
<td>i.v., i.t., cerotto</td>
<td>Dolore Acuto, Anestesia</td>
<td>$T_{1/2}$ 1-1.5 h</td>
<td>Rapido</td>
<td>MOP</td>
<td>Come Morfina, non libera istamina</td>
</tr>
<tr>
<td>Remifentanile</td>
<td>++++</td>
<td>i.v.</td>
<td>Anestesia di breve durata</td>
<td>$T_{1/2}$ 10 min</td>
<td>Molto rapido</td>
<td>MOP</td>
<td>Come Fentanile</td>
</tr>
<tr>
<td>Metadone</td>
<td>++</td>
<td>p.o., i.m., s.c.</td>
<td>Dolore Cronico, Disintossicazione</td>
<td>$T_{1/2}$ 24 h</td>
<td>Metabolismo lento, entrata in azione lenta</td>
<td>MOP</td>
<td>Come Morfina, blandendo euforizzante, dipendenza diversa</td>
</tr>
<tr>
<td>Dextro</td>
<td>+</td>
<td>p.o.</td>
<td>Dolori Acuti e Cronici moderati</td>
<td>$T_{1/2}$ 4 h</td>
<td>Norpropoffinen</td>
<td>MOP, ??</td>
<td>Depr. respiratoria, convulsioni dovute Norpropoffinen</td>
</tr>
<tr>
<td>propoffinen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Convulsioni, perdita di equilibrio; non causa a) depression respiratoria; b) dipendenza; c) tolleranza</td>
</tr>
<tr>
<td>Tramadol</td>
<td>+</td>
<td>p.o., i.v.</td>
<td>Dolore Acuto postoperatorio e Cronico</td>
<td>$T_{1/2}$ 4-6 h</td>
<td></td>
<td>MOP, ??</td>
<td></td>
</tr>
<tr>
<td>Loperamid</td>
<td>+++</td>
<td>p.o.</td>
<td>Diarrea</td>
<td></td>
<td></td>
<td>MOP</td>
<td></td>
</tr>
<tr>
<td>Pentazocina</td>
<td>+</td>
<td>i.m.</td>
<td>Dolore Acuto</td>
<td>$T_{1/2}$ 2-4 h</td>
<td>Metabolizzato velocemente nel fegato</td>
<td>MOP, KOP antago</td>
<td>Ipertensione, tachicardia</td>
</tr>
<tr>
<td>Buprenorfina</td>
<td>++++</td>
<td>i.m., sublinguale, i.t.</td>
<td>Dolore Acuto e Cronico, Disintossicazione</td>
<td>$T_{1/2}$ 12 h</td>
<td>Rapida inattivazione epatica, breve durata d'azione</td>
<td>MOP, KOP ago</td>
<td>Depr. respiratoria insensibile a Naloxone</td>
</tr>
<tr>
<td>Naloxone</td>
<td>+++</td>
<td>i.v., i.m.</td>
<td>Iperdosaggio, effetti collaterali di oppioidi</td>
<td>$T_{1/2}$ 2-3 h</td>
<td>Inattivazione epatica, durata d'azione media</td>
<td>MOP, DOP, KOP</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>++</td>
<td>p.o., s.c., i.v., i.m.</td>
<td>Iperdosaggio, effetti collaterali di oppioidi</td>
<td>$T_{1/2}$ 10-12 h</td>
<td></td>
<td>MOP, DOP, KOP</td>
<td>Non permette il rimbalse</td>
</tr>
</tbody>
</table>
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
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.
Pump for erogation of morphine

La pompa è implantata all’interno della cute. Un catetere che si stacca dalla pompa è posto all’interno dello spazio del liquido spinale. La velocità della pompa può essere controllata da un dispositivo esterno di telemetria.

Spinal fluid

- Spinal cord
- Dura
- Epidural space with anesthesia
Morphine side effects

- Sedazione
- Stipsi
- Nausea e vomito
- Ritenzione urinaria
- Potenziale di tossicodipendenza
- Depressione respiratoria
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

Elimination via bile and urine
FENTANIL (Fentanest®)

Synthetic opioid, derived from pethidine. Receptor agonist $\mu$

**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

Adminstration: 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 \( \mu \) 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 (Antaxone®, Nalorex®, Narcoral ®)

Antagonist

**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 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>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
</table>
| 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 ($\alpha_2$-adrenoceptor agonist)  
Acamprosat (GABA)                   |
Effects of *buprenorfina* vs placebo