Analgesics

The treatment of pain

The treatment of pain can be causal or symptomatic.

Although causal treatment that involves removing or inactivating a primary harmful factor is the most beneficial, it is not always possible.

It is also difficult to prevent a harmful factor proper from appearing or neutralize the existing one. Because of that the symptomatic treatment of nociceptive pain is very important.

Pain can be removed by inhibiting the sensitivity of the sensory cells of the cerebral cortex that receive impulses or by paralysing sensor nerves.

The treatment of pain

Depending on the place of action two types of analgesics are distinguished:

- analgesics acting centrally
- analgesics acting peripherally, called local anesthetic drugs.

Analgesics acting centrally include:

- **opioid analgesic drugs, acting on opioid receptors (exogenic opioids)**
- nonopioid analgesic drugs, whose analgesic action involves the inhibition of transformation of arachidonic acid to prostaglandins in damaged tissues.

The treatment of pain

To relieve certain kinds of pain nonanalgesics are also used, for example:

- glycocorticoids
- antispatic drugs
- triptans (migraine pain)
- carbamazepine (trigeminal neuralgia) and others.

The treatment of pain

A group of US and Canadian scientists discovered a protein which they called DREAM. It participates in the transmission of pain impulses.

This protein is a regulatory protein, inhibiting the transmission of pain impulses to the brain and the spinal cord.

The mechanism of the action of DREAM protein is not fully known, but it is believed that it interacts with the protein of pain receptor.

It might be possible to decrease the pain sensitivity of patients with chronic diseases accompanied by pain by modifying the biosynthesis of DREAM or by inhibiting its activity.

Opioids analgesic drugs

At present exogenic opioids are classified as follows:

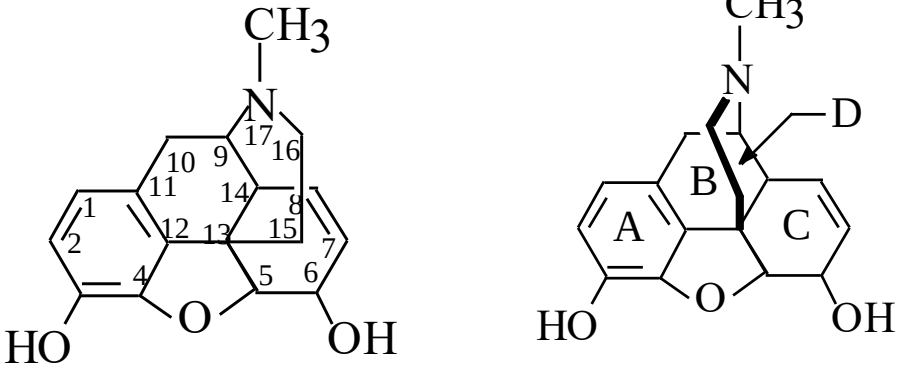
- natural opioids (morphine, codeine)
- semisynthetic opioids (dihydrocodeine, hydromorphone, hydrocodone, oxycodone, buprenorphine)
- synthetic opioids

Natural opioids - Morphine

Natural and semisynthetic opioids are derivatives of 4,5-epoxymorphinane.

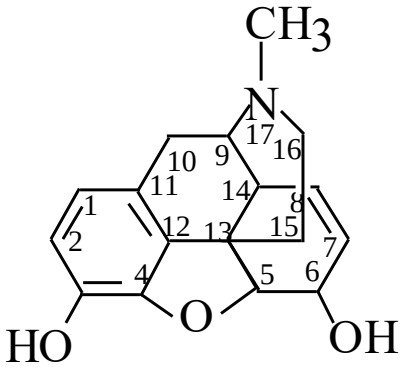
The chemical structure of morphine was defined by Sir Robert Robinson, an English chemist, in 1923.
A total synthesis of morphine, which confirmed its chemical structure, was conducted in 1952.

The formula of morphine



(5α, 6α)-4,5-epoxy-17-methylmorfin-7-eno-3,6-diol

Morphine

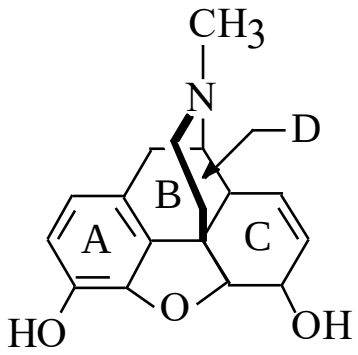


Morphine in doses of
6-9 mg administered subcutaneously,
5-6 mg intravenously and
10-25 mg orally
acts analgesically.

In patients who are not morphine addicts higher doses do not increase analgesic activity, but cause sleepiness, apathy and thinking disorders.

Morphine causes euphoria, which is a state of satisfaction and well-being accompanied by the disappearance of the ability to feel unpleasant sensations.

Morphine



High doses of morphine cause morphinic sleep, which unlike normal sleep is characterized by great sensitivity to external stimuli, especially sound.

Toxic doses of 200-400 mg administered orally or 100-200 mg subcutaneously cause much deeper sleep, up to the state of general anesthesia and even collapse, which may be deadly if medical help is not provided.

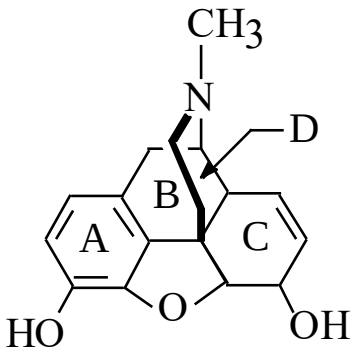
Morphine

The adverse action of morphine involves:

- depressed respiratory function
- diminished heart action
- decreased oxygen metabolism
- vomiting and constipation
- inhibited digestive function
- inhibited function of the urinary bladder leading to anuria

A typical symptom of using morphine is the narrowing of the pupils, whose size depends on dosage. In extreme cases the pupils are the size of a pinhead. No other compound is known to have such an effect.

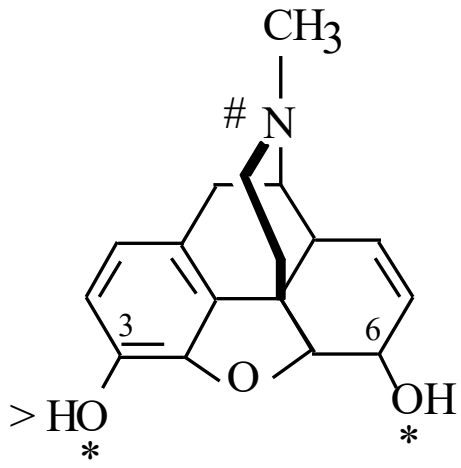
Morphine



Morphine may be administered in the following ways:

- orally (solutions, tablets and capsules with prolonged action), the longest possible use is recommended
- rectally (exceptionally)
- subcutaneously (action is twice as strong as when administered orally)
- intravenously (action three times as strong as when administered orally); the use of an infusion pump is recommended
- extrameningeal (continous administration together with local anesthetic drugs)
- externally (gel, solution)

The metabolism of morphine



\# *N*-Demethylation → normormphine

\> 3-*O*-Methylation → codeine

* Conjugation with UDPGA → M3G and M6G

* Conjugation with PAPS → M3S and M6S

* Conjugation with acetyl-CoA → 6-*O*-acetate of morphine and 3,6-diacetate of morphine (diamorphine = heroin – main metabolite)

The relationship between activity and chemical structure shown above explains the analgesic action of some metabolites of exogenic opioids.

In the liver, morphine conjugates with active acids:

(1) glucuronic (UDPGA) to 3-*O*- and 6-*O*-glucuronides (M3G or M6G),

(2) sulfuric (PAPS) to 3-*O*-or 6-*O*-sulfate (M3S or M6S) and

(3) acetate (acethyl-CoA) to 6-*O*-acetate or 3,6-diacetate of morphine (diamorphine = heroin).

N-demethylation to normorphine and 3-*O*-methylation to codeine also occur.

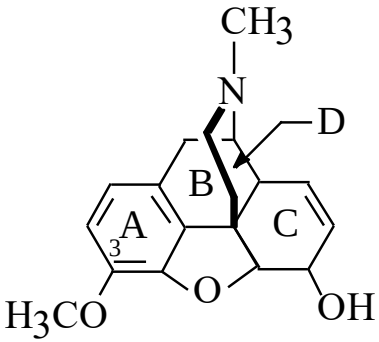
Metabolites M3G i M3S are inactive, whereas M6G and M6S are active.

The affinity of M6G for μ-receptors is similar to that of morphine, but its analgesic action, depending on the way of administration, is 3.7 times (subcutaneously) or 45 times (i.v.) greater than that of morphine.

M6S and heroin, the main metabolite of morphine, have stronger action than morphine.

O-Methylation and *N*-demethylation produce metabolites (codeine and normorphine, respectively), which act less strongly than morphine.

Natural opioids - Codeine



The analgesic action of codeine is approx. 10 times weaker than that of morphine.

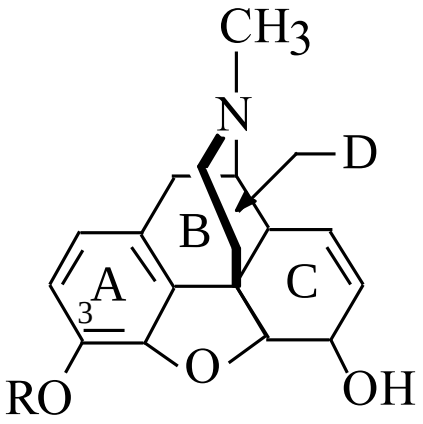
It is used as an antitussive drug:

- in monotherapy (Codeinum phosphoricum)
- together with nonopioid analgesics such as
  - paracetamol
  - ibuprofen
  - acetylsalicylic acid
- together with an expectorant drug such as sulfogaiacol (THIOCODIN).

The modification of morphine

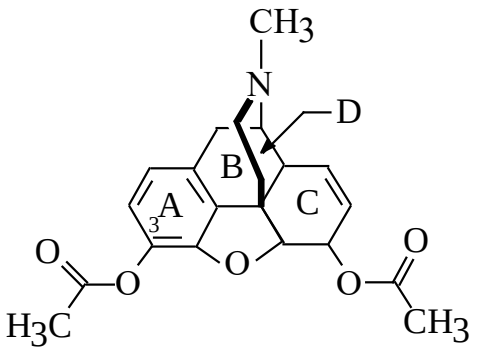
Morphine was one of the first drugs whose chemical structure was modified.

- Pharmacological activity is shown only by levorotatory isomers.
- The presence of a free phenol group is important for the drug's action. Ethers of morphine (e.g. codeine) have much weaker action.



The modification of morphine

- **The esterification or etherification of the alcohol group increases activity.**

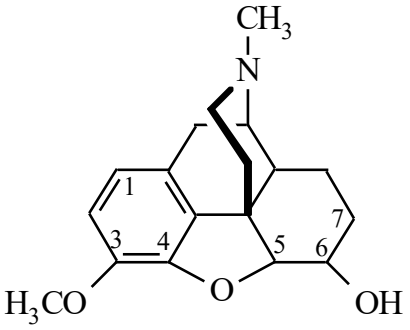


Diacetyl ester of morphine (diamorphine or heroin) is not used in medicine because of its strong addictive action.

Diacetylmorphine, which was the first synthetic pro-drug, was synthetised in 1874 and introduced into therapy as an “nonaddictive” analgesic, antidiarrhorea and antitussive agent in 1898.

- **The hydrogenation of the double bond (Δ7) increases activity.**

R = -H; Dihydromorphine
R = -CH_3; Dihydrocodeine



Dihydrocodeine tartrate is used as an analgesic.
It also has strong antitussive action.

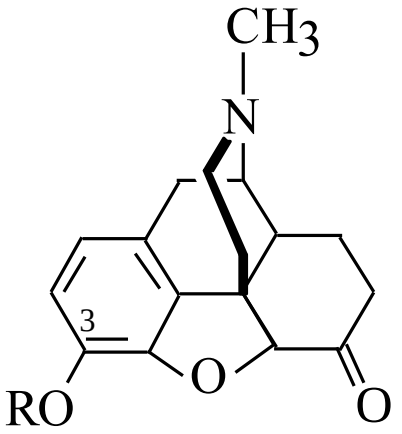
When administered in therapeutic doses, dihydrocodeine does not affect the function of the respiratory center and does not cause drug addiction.

- **The oxidation of the alcohol group of morphine or codeine to the carbonyl group together with the reduction of the double bond (Δ7) produce hydromorhone or hydrocodone, respectively, which have stronger activity than primary compounds.**

The action of hydromorphone is 7-10 times stronger than the action of morphine, while the action of hydrocodone is about twice as strong as that of codeine.

Hydromorphone, R = -H

Hydrocodone, R = -CH_3

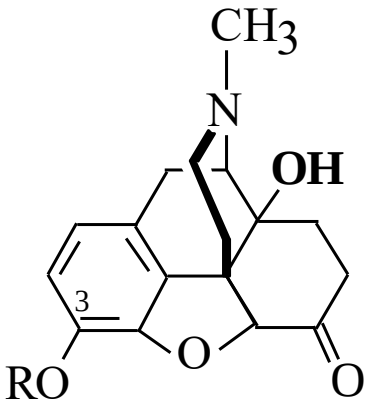


- **The introduction of the hydroxyl group at position 14 into hydromorphone or hydrocodone produces oxymorphone and oxycodone, respectively, which have stronger analgesic action.**

The action of oxymorphone is 12-15 times stronger than that of morphine.

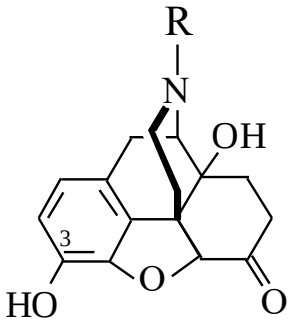
Oxymorphone; R = -H

Oxycodone, R = -CH_3



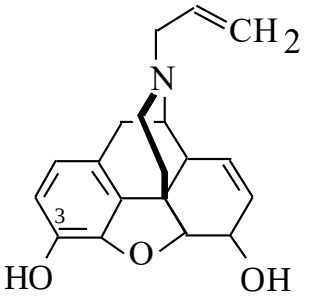
❑ **A substituent at position N17 affects activity, the kind of action (agonistic, antagonistic) and toxicity. Methyl derivatives act analgesically and antitussively.**

The elimination of the methyl group decreases action and toxicity.
The replacement of the methyl group with the allil group (naloxone), cyclopropylmethyl or cyclobutylmethyl changes agonistic action into antagonistic action.

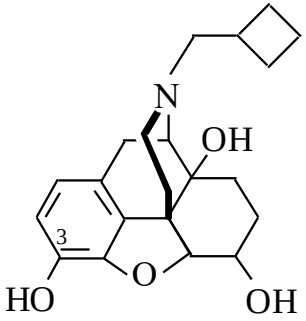


Naloxone

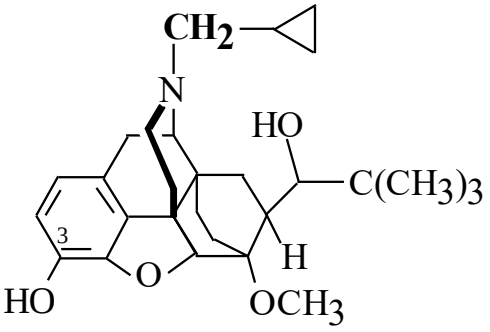
R = -CH_2-CH=CH_2



Nalorphine



Nalbuphine



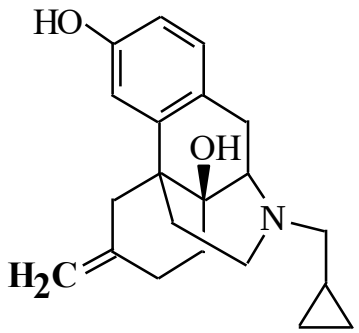
Buprenorphine

Naltrexone

R = $-CH_2$ 

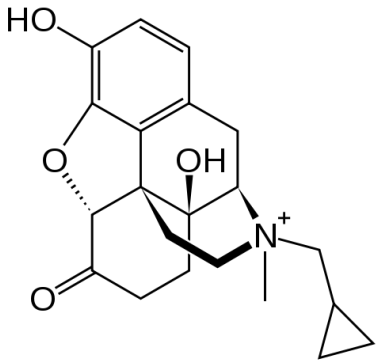
Naloxone and naltrexone act as total antagonists. Nalorphine acts as a competitive antagonist of μ-receptors, and a partial antagonist of κ-receptors and as an agonist of δ-receptors (predominance of antagonistic action).

In the case of buprenorphine and nalbuphine agonistic action is predominant.



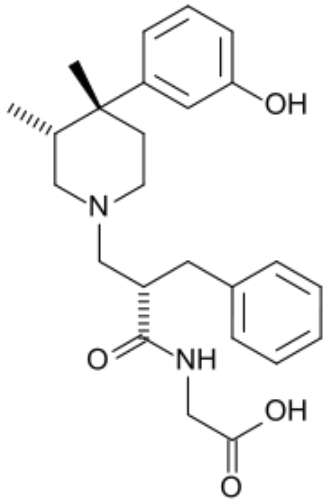
Nalmefene differs from naltrexone by substitution of the ketone group at the 6-position of naltrexone with a methylene (CH_2) group, which considerably increases binding affinity to the μ-opioid receptor.

Nalmefene also has high affinity for the other opioid receptors, and is known as a "universal antagonist" for its ability to block all three.



Methylnaltrexone (**MNTX**, trade name **Relistor**) is one of the newer agents of peripherally-acting μ-opioid antagonists that act to reverse some of the side effects of opioid drugs such as constipation without affecting analgesia or precipitating withdrawals.

Because it contains a permanently charged tetravalent nitrogen atom, it cannot cross the blood–brain barrier, and so has antagonist effects throughout the body, counteracting effects such as itching and constipation, but without affecting opioid effects in the brain such as analgesia. However, since a significant fraction (up to 60%) of opioid analgesia can be mediated by opioid receptors on peripheral sensory neurons, particularly in inflammatory conditions such as arthritis, traumatic or surgical pain, MNTX may increase pain under such circumstances.

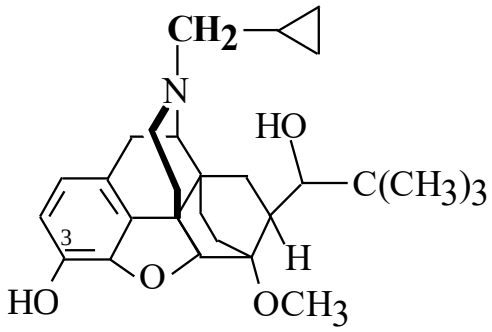


Alvimopan (trade name **Entereg**) is a drug which behaves as a peripherally acting μ-opioid antagonist.

With limited ability to cross the blood–brain barrier, many of the undesirable side-effects of the opioid agonists such as constipation are minimized without affecting analgesia or precipitating withdrawals.

The Food and Drug Administration reviewed the safety and efficacy data for alvimopan and approved its use in May 2008.

Buprenorfine



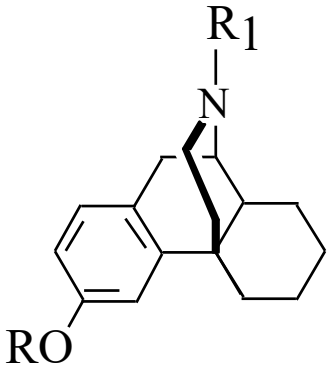
Buprenorphine is a partial agonist of μ-receptors.
It acts 60-100 times more strongly than morphine.
Buprenorphine has greater affinity for receptors than morphine, so it can push it out of its bindings with receptors. The internal activity of buprenorphine is weaker than that of morphine. Because of those properties these drug should not be administered together.
Buprenorphine is used in sublingual tablets every 8 hours.
A swallowed tablet does not have an analgesic effect.
The maximum action of buprenorphine is observed at 3-8 mg daily doses, which corresponds to 180-300 mg of morphine.
As a partial agonist, buprenorphine, has a distinct action threshold and when an individual dose is exceeded analgesic action does not increase.

- **The elimination of the epoxy bridges produces morphinane derivatives.**

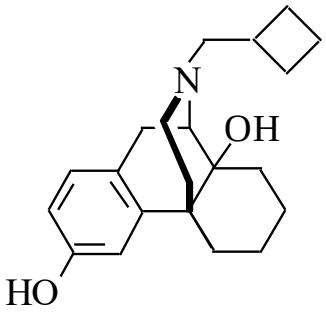
The profile of action of levorphanol is similar to that of morphine but its analgesic activity is 10 times stronger.

Dextrometorphane acts antitussively, similarly to codeine, but it does not act analgesically and does not cause drug dependence.

Levallorphan demonstrates very weak analgesic action. Butorphanol shows ago-antagonistic action and its analgesic action is 8-11 times stronger than that of morphine.



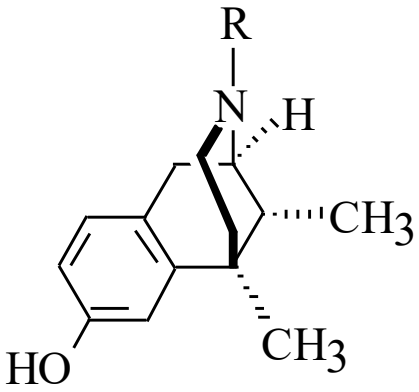
R = -H, R_1 =-CH_3; Levorphanol
R = -CH_3, R_1 =-CH_3; Dextrometorphan
R =-CH_2-CH=CH_2; Levallorphan

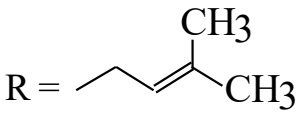


Butorphanol

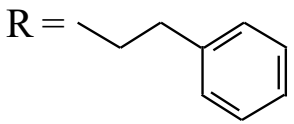
Benzomorfane (benzazocine) derivatives

- **The elimination of ring C from morphinane creates benzomorphane (or benzazocine) derivatives.**





Pentazocine

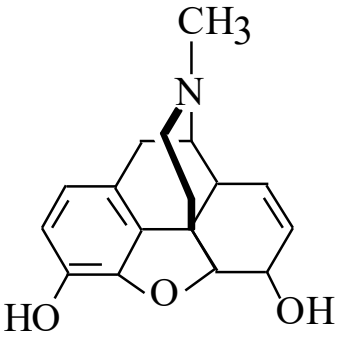


Phenazocine,

Cyclazocine

Benzazocine derivatives are weak opioid analgesics (the activity of pentazocine is about 1/3 of the analgesic activity of morphine) which have ago-antagonistic activity.

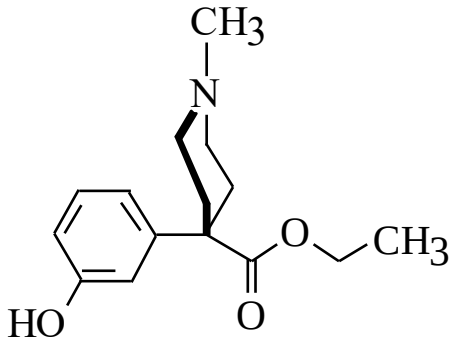
Morphine



Phenylpiperidine derivatives

- **The elimination of ring B from benzazocine produces phenylpiperidine derivatives. To retain the quaternary atom C4 of piperidine (all opioids have a quaternary carbon atom separated by 2 carbon atoms from a nitrogen atom) a carbonyl or ester group is introduced into this position.**

The analgesic activity of pethidine is 10 times weaker than that of morphine. Pethidine is metabolized in the liver and, at high doses, its toxic metabolite (norpethidine) can accumulate and cause convulsions.

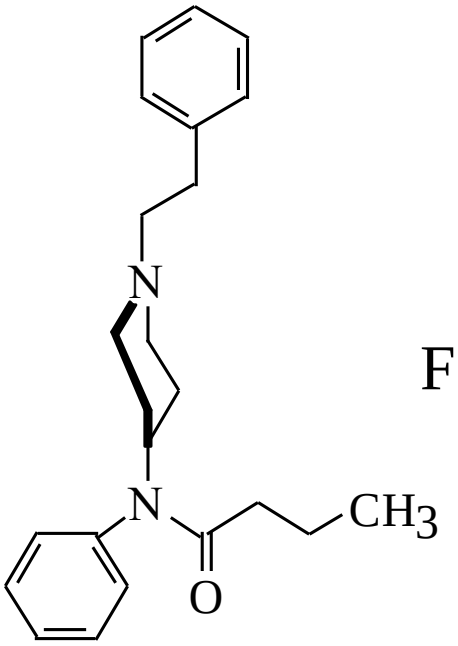


Pethidine
The agonist of μ (86%), κ (6%) and δ (8%) receptors.

Other derivatives of phenylpiperidine: Phenoperidine, Anileridine, Cetobemidone

Anilinepiperidine derivatives

- **By replacing the phenyl substituent in phenylpiperidine derivatives with an aniline substituent it is possible to receive such opioids as fentanyl, sufentanyl, alfentanyl and remifentanyl, which act 40-1000 times more strongly than morphine.**



Fentanyl, DUROGESIC, FENTANYL

Fentanyl, FENTANYL

- Fentanyl is an agonist of μ- (84%), κ- (2%) and δ- (4%) receptors. Its analgesic action is 100-300 times stronger than that of morphine.

• After intravenous administration its analgesic effect is observed almost immediately (maximum effect after 2 min) and lasts 20-30 min.

• This short time of action is determined by the distribution of fentanyl to tissues. It does not have a significant influence on the circulation system and affects the motor activity of the gastro-intestinal system less strongly than morphine.

• Fentanyl causes sleep and retrograde amnesia when used at high doses in anesthesia. It also diminishes the sensitivity of the respiratory centre and causes nausea and vomiting.

• When fentanyl is administered at equianalgesic doses, its sedative and euphoric action is weaker than that of morphine and significantly less histamine is released.

Fentanyl, DUROGESIC (plaster)

DUROGESIC plasters provide 25, 50, 75 or 100 mg/hour of fentanyl from an area of 10, 20, 30 or 40 cm^2, respectively.

Plasters are used for 72 hours.

Another plaster, after removing the previous one, is applied in another place (the same place can be used after several days).

Such plasters are used in the treatment of chronic neoplastic pain or pain of other ethiology.

Sufentanyl (the strongest opioid analgesic) and alfentanyl act 1000 times or 50 times more strongly than morphine, respectively.

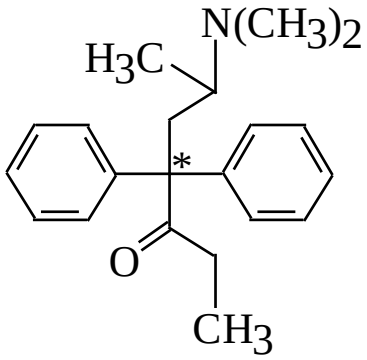
Remifentanyl, the selective agonist of μ-receptor, acts 15-20 times more strongly than alfentanyl.

Because it has very short half-time it demonstrates the best controllability among all opioids used at present in anesthesia and, as a result, its action disappears rapidly after infusion is finished.

The metabolites of remifentanyl are inactive.

Diphenylpropylamine derivatives

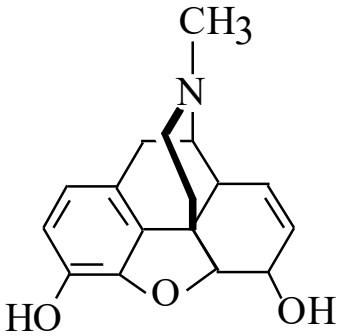
The analgesic action of methadon is 1.5 times stronger than that of morphine. It is used in the treatment of opium abstinence syndrome and as a drug of second choice in strong perioperative and neoplatsic pains.

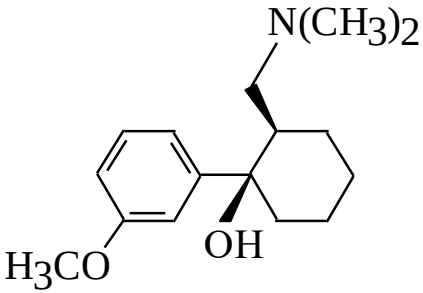


Methadone,
Methadone hydrochloride

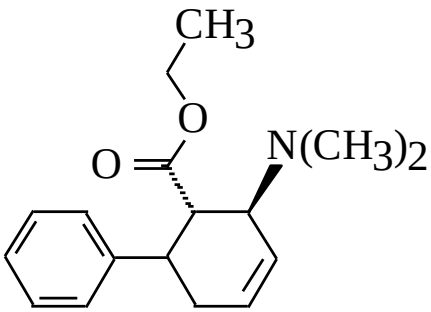
Dextromoramid acts 2-4 times more strongly than morphine.
Dextropropoxyphen is a weak agonist of μ-receptor. Its potency is only 50 per cent of the potency of morphine. It is used in monotherapy and together with NSAIDs in the treatment of mild to moderate pain. Of all isomers of dextropropoxyphen only isomer (+)-2*S*,3*R* is active.

Other opioids

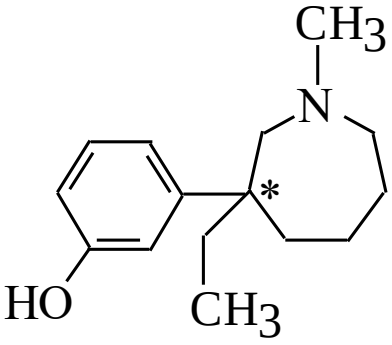




Tramadol,
SLOVADOL
TRAMADOL, TRAMAL, TRAMUNDIN

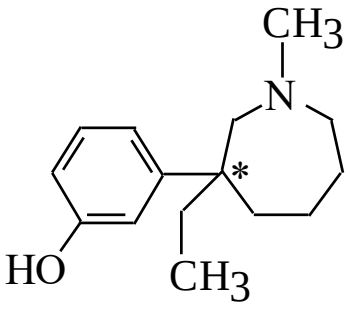


Tilidine



Meptazinol, MEPTADOL, MEPTIDOL

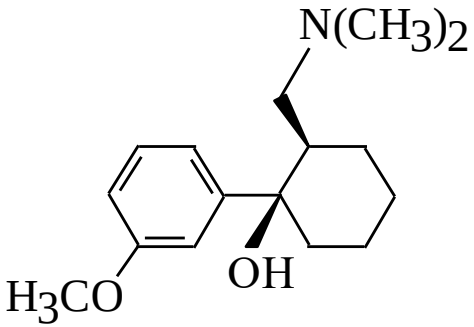
Meptazinol (Phenylazepine derivative)
MEPTADOL, MEPTIDOL



Meptazinol is a relatively selective ago-antagonist at μ_1-receptors.

Its analgesic action is quite weak, compared to pethidine and pentazocine. While meptazinol is administered, the depression of respiration is observed very rarely, which is a result of its selective action on μ_1-receptors.

Tramadol (Phenylcyclohexyl derivative)



STOVADOL, TRAMADOL, TRAMAL, TRAMUNDIN

Tramadol is an agonist at opioid receptors.

Its affinity for μ_1-receptors is 20-25 times greater than for δ- and κ-receptors.

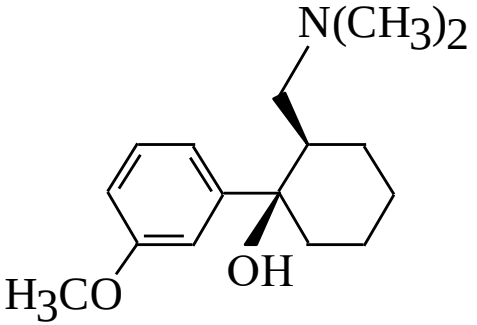
O-demethyltramadol, the metabolite of tramadol, is active and also has significantly greater affinity for μ-receptors.

The action of tramadol is only partially antagonised by naloxone because tramadol also inhibits the reuptake of NA and 5-HT in the synapses of the descending system of pain inhibition at the spinal cord level.

Drugs inhibiting the reuptake of NA and 5-HT can increase the action of opioids.

Tramadol

STOVADOL, TRAMADOL, TRAMAL, TRAMUNDIN



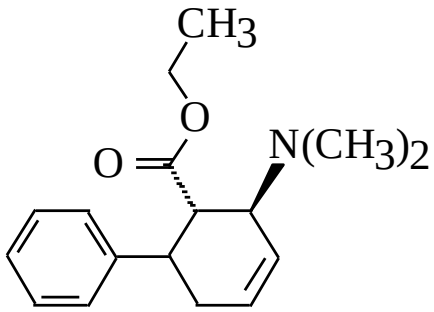
The analgesic action of tramadol is comparable to codeine and pentazocine.
At therapeutic doses tramadol does not act depressively on the respiratory center, it does not decrease blood pressure and does not cause constipation. However, it acts sedatively.

The onset of action is observed after 20 min, and the half-time of tramadol is about 5 hours.
Administration of tramadol can be combined with other drugs such as NSAIDs, spasmolytics and antidepressants, as synergism of action is observed.

Tramadol is used in the treatment of acute and chronic pain (injuries, fractures) of high and middle intensity, symptomatic pain, neuralgia, neoplastic and postoperative pain and in painful diagnostic and therapeuthic procedures.

It can be used in older patients and in pain accompanying angina pectoris.

Tilidine, VALORON



Tilidine the second derivative of phenylcyclohexyl, is used in therapy as a *trans* isomer.

It does not cause euphoria or drug dependence.

The mechanism of action

In 1973, it was discovered that **all opioids act by interacting with opioid receptors**.

Three types of opioid receptors are known at present:
mu (μ_1 and μ_2) (or MOP), *kappa* (κ) (or KOP), *delta* (δ) (or DOP) and NOP.

Sigma (σ) receptors, with which certain opioids bind, are not classified as opioid receptors.

The reaction of an agonist with a particular receptor results in the following: μ and $\delta \rightarrow$ cAMP$\downarrow$, $K^{+}\uparrow$, $\kappa \rightarrow Ca^{2+}\downarrow$.

The existence of other sub-types (δ_1, δ_2 and κ_1, κ_2, and κ_3) and types (epsilon (ε), iota (τ), lambda (λ) and zeta (ξ)) of opioid receptors is discussed in the literature.

The opioid receptors – the appearance

Opioid receptors are located in the CNS, especially

- in the limbic system,
- the medulla and
- the posterior horn of the lateral cerebral ventricle

and also outside the CNS, for example in the nerves of the autonomic system.

The endogenic agonists of the opioid receptors

In 1975, enkephalins, endorphins and dynorphins were discovered.

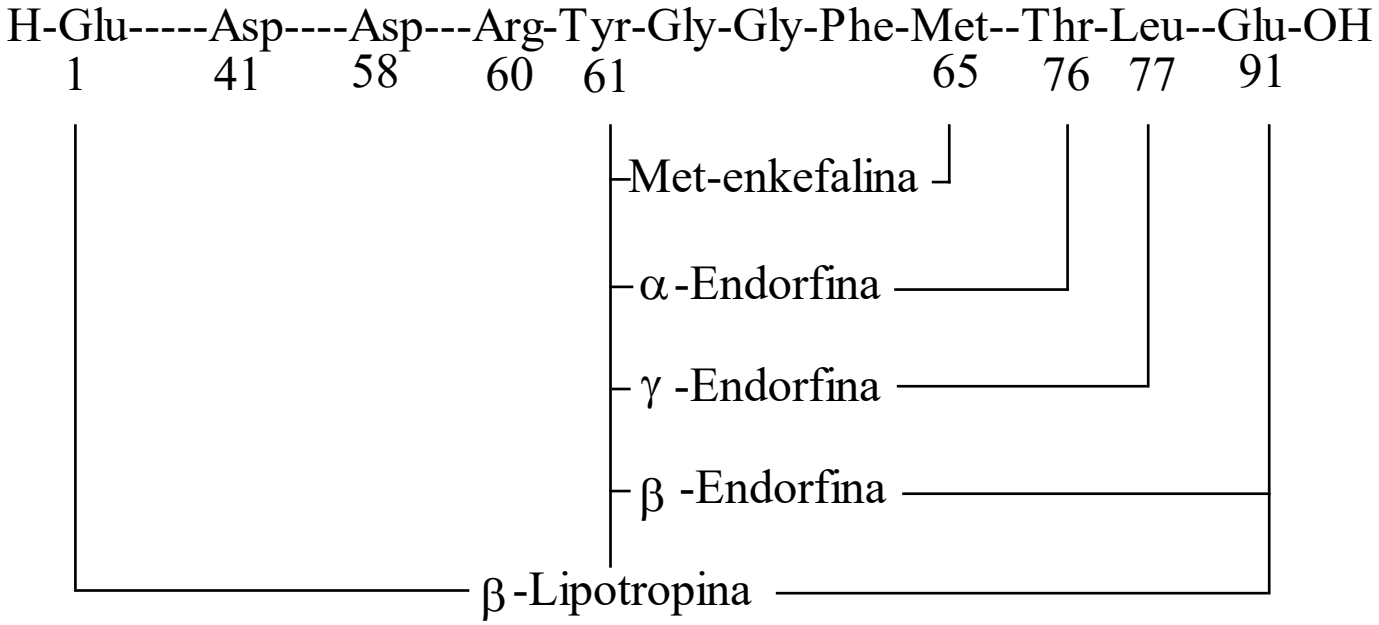
They are endogenic agonists at opioid receptors.

These three families of opioid peptides arise from three precursors:

- proopiomelanocortin (POMC),
- proenkephalin A and
- prodynorphin (proenkephalin B).

The endogenic agonists of the opioid receptors

Proopiomelanocortin (bovine) is a polipeptide consisting of 265 amino acids. The sequence of amino acids 1-91 creates β-lipoprotein, a hormone, which does not demonstrate any opioid action.



Met-enkephalin and three endorphins (α, β and γ) are parts of the β-lipoprotein sequence. Met-enkephalin is a pentapeptide (tyr-gly-gly-phe-met) and a fragment of the sequence 61-65 of β-lipoprotein.

Met-enkephalin is a pentapeptide (tyr-gly-gly-phe-met) and a fragment of the sequence 61-65 of β-lipoprotein. It is considered to be a neurotransmitter or neuromodulator of neurotransmission. It is an agonist at δ-receptors.

β-Endorphin, the most active endorphin, is a neurohormone with longer action, comprised of 31 amino acids (the sequence 61-91 of β-lipoprotein). Its physiological role has not been fully explained. It is an agonist at μ-receptors but it also acts on the δ-receptors.

α- and β-endorphins are fragments of the sequence 61-76 or 61-77 of β-lipoprotein, respectively.

Leu-enkephalin, similary to met-enkephalin, is a pentapeptide (tyr-gly-gly-phe-leu) but it has leucine as the terminal amino acid instead of methionine. It is a fragment of the sequence of dynorphins. Leu-enkephalin is an agonist at δ-receptors.

Dynorphins are probably endogenic ligands for κ-receptors.

Dynorphin A was the first isolated peptide and consists of 17 amino acids (tyr-gly-gly-phe-leu-arg-arg-ile-arg-pro-lys-leu-lys-trp-asp-asn-gln).
It contains the leu-enkephalin sequence at the terminal amine group.
In 1982 a similar peptide was isolated, which consisted of 13 amino acids. It was called dynorphin B or rymorphin.

The next dynorphins were designated as dynorphin A_{1-6}, ..., ..., A_{1-17}.

According to Goldstein, the selectivity of dynorphin A to κ-receptors is increased by a positive charge in position 7 (Arg) and 11 (Lys). That indicates that a κ-receptor has a negative charge.

The endogenic agonists of the opioid receptors

Every endogenic opioid polipeptide has specific selectivity to one of the three receptors but it also demonstrates some activity towards other receptors.

Leu- and met-enkephalin demonstrate the highest selectivity to δ-receptors, while dynorphin A to κ-receptors.

β-Endorphin has high affinity for μ and δ-receptors.

The endogenic agonists	μ	δ	κ
Leu-enkefalin	6	94	-
Met-enkefalin	9	91	-
β-Endorfin	52	47	1
$Dynorfin_{1-17}$	13	4	83

Exogenic opioids, similarly to endogenic opioids, have specific selectivity to a particular receptor but they also show some affinity for other receptors.

They may be agonists or antagonists at various types of receptors or they may act as agonists on one type of receptors and as competitive or partial antagonists on other types of receptors.

In terms of action, opioids may be classified as follows:

- full agonists
- full antagonists
- partial agonists
- ago-antagonists.

The relative affinity of opioid agonists i antagonists for the opioid receptors (%)

Drug	Receptors		
	μ	**κ**	**δ**
Morphine	Agonist (97%)	Agonist (1%)	Agonist (2%)
Fentanyl	Agonist (94%)	Agonist (2%)	Agonist (4%)
Pethidine	Agonist (86%)	Agonist (6%)	Agonist (8%)
Naloxone **Naltrexone**	Competitive antagonist (85%) Competitive antagonista (+++)	Competitive antagonist (9%) Competitive antagonist (+++)	Competitive antagonist (6%) Competitive antagonist (+)
Nalorphine	Competitive antagonist (67%)	Partial antagonist (16%)	Agonista (17%)
Pentazocine	Competitive antagonist	Agonist	Agonist
Cyclazocine	Competitive antagonist (53%)	Agonist (39%)	Agonist (2%)

Effects of the stimulation of opioids receptors

Action	μ	δ	κ
Analgesic activity			
- supraspinal	+++	-	-
- spinal	++	++	+
- peripheral	++	-	++
Breath depression	+++	++	-
Miosis	++	-	+
Inhibition of intestinal perystalsis	++	++	+
Euphoria	+++	-	-
Dysphoria	-	-	+++
Sedation	++	-	++
Physical dependence	+++	-	+

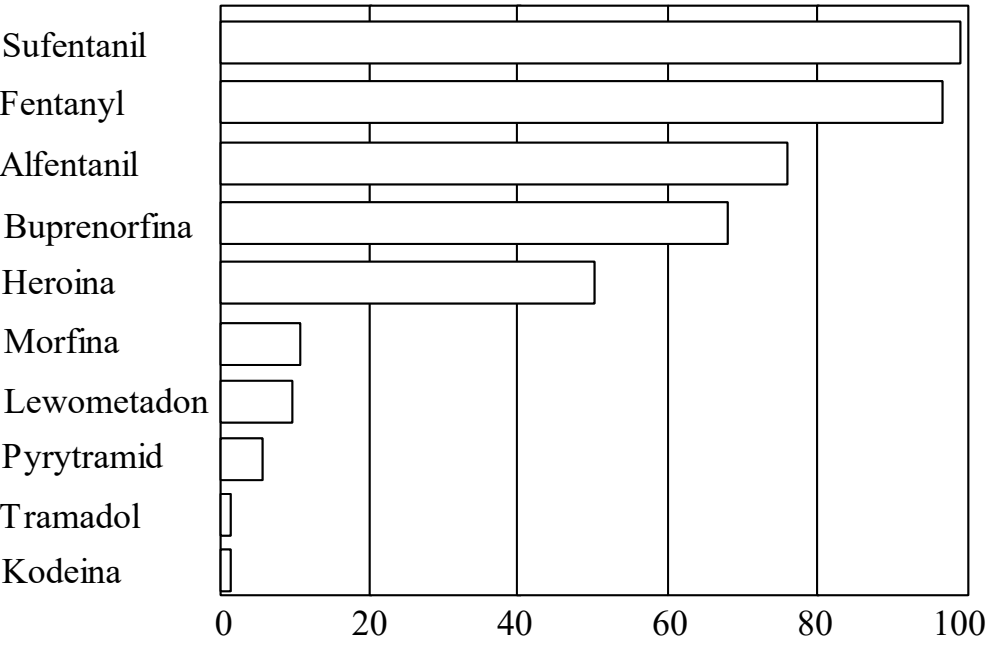
Opioids differ with regard to:

- therapeutic range (LD_{50}/ED_{50})
- relative potency of analgesic action and the duration of action
- adverse effects.

The term *relative potency of action* means the ratio of the dose of morphine to the dose of a given opioid necessary to produce analgesic effect equal to the effect of morphine.

Opioids	The potency of action
Very strong analgesia	
Sufentanil	1000
Fentanyl	100-300
Alfentanil	40-50
Oxymorfone	12-15
Strong analgesia	
Butorfanol	8-11
Hydromorfone	7-10
Dextromoramide	2-4
Methadone	1,5
MORPHINE	**1**
Nalbuphine	0,5-0,8
Weak analgesia	
Hydrocodone	0,35
Pentazocine	0,3
Codeine	0,2
Pethidine	0,1
Very weak analgesia	
Levalorphane	0,07-0,1
Naloxone	0,001

The depressive action of opioids on the respiratory center



Opioids	LD_{50}/ED_{50}
Tramadol	3
Tylidine	3
Pentazocine	4
Pethidine	11
Pirytramide	11
Methadone	12
Fenoperidine	16
Butorphanol	45
Morphine	71
Fentanyl	277
Nalbuphine	1034
Alfentanil	1082
Buprenorphine	7933
Sufentanil	27716

The therapeutic range of opioids increases as their analgesic action intensifies, but at the same time an increase in depressive action on the respiratory center is observed.

The application of opioids

Opioids as analgesics

A dose of an analgesic should be selected individually for each patient and his pain so as to ensure the desired period of painlessness. The choice of an analgesic also depends on the intensity of pain.

Analgesics should be used immediately when pain appears to prevent it from intensifying. In long-lasting pain, analgesics should be used at regular intervals to prevent pain from appearing.
Patients who receive opioids are afraid of developing addiction, losing the possibility of pain treatment in the nearest future, suffering from the depression of the respiratory center and having reduced survival time.

In neoplastic pain, the use of long-action drugs is recommended.

In Poland, pharmaceuticals containing morphine, buprenorphine, fentanyl or tramadol are the most common.

It is recommended to use oral administration of opioids for the longest time possible.

Opioids as antitussive drugs

Codeine, Hydrocodeine, Dextromethorphane

Antitussive action is not opioid action because it is not antagonized by opioid antagonists (naloxone, naltrexone); (+)-isomers demonstrate the same antitussive activity as (-)-isomers; 3-methylderivatives of morphine (codeine, hydrocodeine) have similar antitussive activity as compounds with a free phenol group.

Methoxyderivatives are preferred as antitussive drugs because of their better action when administered orally and less addictive action.

The most common antitussive drugs are codeine, hydrocodeine and dextrometorphan. Hydrocodeine is approx. 3 times more effective than codeine used as an antitussive drug. The introduction of a hydroxyl group into the structure of morphinan at position 14 (oxycodone) decreases significantly antitussive action.

Dextrometorphan, 3-methoxy (+)-isomer of levorphanol, does not demonstrate analgesic action, and does not cause breath depression or addictive influence typical of μ opioids, but retains antitussive action.
Its action is weaker than that of morphine.
Dextrometorphan is not listed by *Controlled Substance Act.*

Opioids as antidiarrheic drugs

Agonists of μ- and δ-receptors strongly inhibit the peristalsis of the intestines because they diminish the release of acetylcholine.

μ-Agonists are not used as antidiarrheic drugs because of their addictive action.
In the past, *Tinctura Opii* was used as an antidiarrheic drug.

To combat diarrhea of middle intensity codeine is sometimes used for a short time.

At present, diphenoxylate and loperamide (structural analogs of pethidine and methadone) are used as antidiarrheic drugs.

The treatment of the depression of the respiratory center

Naloxone and naltrexone, nalmefene (opioids antagonists) are used to treat breath depression caused by opioid overdose and occasionally to stop the analgesic action of opioids used during childbirth, if the newborn baby shows breathing difficulty.

Nalmefene (Revex) **is an opioid receptor antagonist used primarily in the management of alcohol dependence, and also has been investigated for the treatment of other addictions such as pathological gambling and addiction to shopping.**

Nalmefene is an opioid derivative similar in both structure and activity to the opiate antagonist naltrexone.

Advantages of nalmefene relative to naltrexone include longer half-life, greater oral bioavailability and no observed dose-dependent liver toxicity. As with other drugs of this type, nalmefene can precipitate acute withdrawal symptoms in patients who are dependent on opioid drugs, or more rarely when used post-operatively to counteract the effects of strong opioids used in surgery.

Nalmefene is extensively metabolised in the liver, mainly by conjugation with glucuronide and also by *N*-dealkylation. Less than 5% of the dose is excreted unchanged. The glucoronide metabolite is entirely inactive, while the N-dealkylated metabolite has minimal activity.

The diagnosis of addictions

In the diagnosis of addiction naloxone, naltrexone and nalmefene are used.

A rehab therapy

In a rehab therapy methadone and buprenorphine are used.

The adverse effects of opioids

Opioids show several adverse effects. Breath depression of breath is one of the main adverse effects of opioids. Other adverse effects of opioids include euphoria, dysphoria, hallucinations and addiction. Opioids also act sedatively, reduce arterial blood pressure, constrict pupils, cause nausea, vomiting and constipation. Prolonged administration of opioids leads to drug tolerance.

The depressive action of opioids on the respiratory centre involves mainly their action on μ_2-receptors and because of that research is focussed on finding analgesics that act on μ_1- and κ-receptors. It is hoped that they will demonstrate fewer adverse effects.

Opioids also act immunosupressively. The misuse of opioids diminishes the patient's immunity and increases the risk of infectious diseases.

Morphine releases histamine from mastocytes. Reactions to the release of histamine may be local (nettle rash, pruritus) or/and systemic (bronchospasm, arterial hypotension). For that reason morphine should not be used by patients with asthma.

Tolerance to opioids develops rapidly and is accompanied by the physical symptoms of the withdrawal syndrome. Tolerance is observed regardless of the type of opioid receptors. Cross tolerance occurs between different drugs acting on the same type of receptors, but not in the case of opioids acting on different types of receptors. Tolerance involves analgesic, vomiting and euphoric action as well as breath depression.

Addiction to opioids can be physical and/or psychical.

Physical dependence lasts several days after withdrawing opioids and is accompanied by the abstinence syndrome (yawning, dilation of pupils, fever, colliquative sweat, goose-flesh, nausea, diarrhea, sleeplessness). The greatest intensification of symptoms is observed on the second day and disappears after 8-10 days. Certain symptoms may occur over several weeks.

Psychical dependence, which is accompanied by a compulsion to take an opioid, may continue for months and even years. That kind of dependence rarely occurs in patients who take opioids as analgesics and is less likely when codeine, pentazocine or buprenorphine are administered.

Adverse effects of opioids

Action	Morf	Levo	Petyd	Cod	Pent	Tram	Bupr
Analgesia	+++	+++	++	+(+)	++	+(+)	++(+)
Antitussive	++	++	+	++	+	+	+(+)
Euphoria	+++	+++	++	(+)	(+)	(+)	++
Dysphoria	+	+	(+)	o	++	(+)	o(?)
Drug dependence	+++	+++	+++	(+)	+	(+)	++
Sedative	+++	+++	+++	+	++(+)	++(+)	++(+)
Breath depression	+++	+++	++(+)	++(+)	++	o	++(+)
Blood pressure ↓	+++	+++	+++	(+)	+++	o	++
Vomiting	++	+	+	(+)	+	+	+
Constipation	+++	++	(+)	++	+	o	+(?)

Morf=morphine, Levo=levomethadon, Petyd=pethidine, Cod=Codeine, Pent=pentazocine, Tram=tramadol, Bupr=buprenorphine