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Mechanisms Of Opioid-Induced Hyperalgesia: Implications For Chronic Pain Management

Krisli Serani[1], Hira Aslam[2], Syed Hyder Raza Naqvi[3], Shaheryar Shafqat[4], Avrina Kartika Ririe[5], Prof. Dr. Sudhair Abbas Bangash[6]

[1]Anaesthesia and Reanimation Specialist, Anaesthesia and Intensive Care Unit, University of Medicine Tirana Albania/ University Hospital Mother Theresa Tirana, Albania

Email: krisliserani@yahoo.com

[2]Pharmacy Student, Department of Pharmacy, University of Sargodha, Pakistan

Email: hirahassan1000@gmail.com

[3]Professor, Department of Pharmacology & Therapeutics, Niazi Medical & Dental College, Sargodha, Pakistan, Email: hyder.raza891@gmail.com

[4]Graduate Research Assistant, University of Memphis, School of Public Health

Email: shaheryarshafqat55@outlook.com

[5]UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, California, USA

Email: saravinamd@gmail.com

[6]Faculty of life sciences, Department of Pharmacy, Sarhad University of Science and Information Technology, Peshawar, Pakistan, Email: sudhair.fls@suit.edu.pk

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ABSTRACT

Background: Our understanding of opioid pharmacology has expanded significantly in recent years. Both naturally occurring and synthetic opioids bind to specific receptor types, which play a key role in their effects and mechanisms of action.

Objective: To provide an overview of the opioid receptor types, their classifications, associated pharmacological effects, mechanisms of dependence, and key aspects of opioid pharmacokinetics, interactions, and therapeutic uses.

Methods: A comprehensive analysis of opioid receptor families, including nociceptin, mu, kappa, and delta, and their pharmacological interactions. Opioids are categorized as agonists, antagonists, partial agonists, or agonist-antagonists based on their affinity and efficacy.

Results: Opioid administration commonly leads to side effects such as sedation, euphoria, analgesia, nausea, vomiting, miosis, respiratory depression, cough suppression, stiffness, constipation, facial redness and itching, urinary retention, and the potential for dependence (tolerance and abstinence). The development of tolerance and physical dependency is linked to elevated cAMP and adenyl cyclase levels. Long-term use can result in increased transcription factors, such as CREB and ΔFosB, which are associated with relapses and sustained effects.

Conclusion: This study outlines the pharmacokinetics, drug interactions, and therapeutic applications of commonly used opioids, providing a comprehensive understanding of their clinical and pharmacological profiles.

Keywords: *endogenous opioids, exogenous opioids, opioid receptors, pharmacology*

1. INTRODUCTION

The poppy (a drowsy poppy) is a plant whose capsules contain the active ingredient opium. A small cut is made in the capsule to release the juice, which is also known as (Simon and Lizarraga 2024), Opioids, both synthetic and those found in nature, bind to different receptors. On the opioid receptor family, there are four types: nociceptin, mu, kappa, and delta. All of these

are protein G-bound receptors on cell membranes. In terms of the efficiency and affinity of their receptors, opioid drugs can be categorized into four groups: agonists, antagonists, partial agonists, and agonist-antagonists. Illnesses such as lethargy, euphoria, analgesia, nausea, vomiting, miosis, suppressed cough, respiratory depression, constipation, truncal rigidity, flushing of the face and pruritus, retention of urine, dependence, and withdrawal are among the most common agonist-induced pharmacological effects. It seems that an increase in activity along the AMPc pathway is the cause of tolerance and withdrawal symptoms. The induction of long-term brain alterations linked to the synthesis of specific transcription factors, such as CREB and ΔFosB, suggests that opioid agonists contribute to relapse. Therapeutic indications, drug interactions, and pharmacokinetics are some of the topics covered. (Sumpton 2024). Opium was traditionally administered in opium dens by smoking it, which requires cooking. The common method for extracting liquid opium involves boiling the plant and straining it through a sieve to remove impurities. It is ready to smoke opium when the water has evaporated, at which point it is roasted until it turns brown. Isolating morphine requires first precipitating off the non-morphine alkaloids from a solution of dried opium in boiling water using calcium oxide, hydroxide, or carbonate. The liquid that is produced is then filtered through a cloth. The morphine is subsequently precipitated by re-disposing the solution in hot water with ammonium chloride. It is filtered and let to dry after cooling. The morphine base consists of 50–70% codeine and morphine. Making morphine hydrochloride is as simple as mixing morphine base with hydrochloric acid and sifting the resulting liquid. The next step is to mold the material into brick-shaped bundles, each weighing 1.6 kilograms. One milligram of morphine hydrochloride requires thirteen kilograms of opium and one day of labor. (Johnson and Egan 2024). The hydrochloride or base form of morphine can be converted into heroin. The first method involves heating acetic anhydride and adding it to the mixture. The heroin base is obtained after various processes and filtering. Based on its intended usage, it can be further processed into various forms. Injectable heroin (heroin hydrochloride, white heroin) and smoked heroin (heroin number 3, brown heroin) are two examples. White heroin is better suited for intravenous injection, while brown heroin is smoked because it is less soluble. 2. Substance usage habits in Spain have changed due to the introduction of many heroin varieties and the spread of AIDS, with the majority of users now opting to smoke the drug rather than inject it. White heroin is more prevalent in the eastern and northern regions of Spain, whereas brown heroin is more common in the middle and southern regions.(Li, Huang et al. 2024).

Heroin can have anywhere from 5% to 35% purity, with the most recent data coming from the National Drug Plan showing a 25% purity level. Glucose, starch, or lactose is what it's typically sold cut with. Medications including caffeine, paracetamol, strychnine, quinine, procaine, and piracetam are frequently seen in their contaminated forms. To smoke (pipe or cigarette) or inhale (chasing the dragon or Chinese) heroin is the most prevalent method of administration, followed by intranasal and, less commonly, intravenous injections. To prepare the powder for intravenous administration, dissolve it in a small amount of water. To make it more soluble, add a few drops of lemon or vinegar. Heat the mixture in a teaspoon. Then, use a cigarette or cotton filter to load it into the syringe. "Speedball" refers to an intravenous mixture of heroin and cocaine or amphetamine. *(Edwards 2024).* Because they were created in underground labs, several synthetic opioids are considered designer medicines. Once more, to evade the narcotic drug listings. In this way, drug trafficking convictions can be evaded. Among these, three fentanyl derivatives—alpha-methyl fentanyl, also known as china white, and 3-methyl fentanyl—stand out as particularly lethal in overdose cases. The byproduct 1methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was created in one of the phases of the manufacture of 1-methyl-4-phenylpropionoxypiperidine (MPPP), a pethidine derivative. Hundreds of people saw the onset of permanent Parkinsonism in heroin addicts who shot the drug. Not long after that, it was found that MAO metabolizes MPTP to MPP+, a chemical that specifically kills the zone compacta of the substantia nigra.(Archambault, Bertrand et al. 2024).

2. HISTORICAL ASPECTS OF OPIOIDS

Evidence of opium's analgesic and antidiarrheal effects can be found in ancient texts from Sumer and Egypt. The Greeks and Romans provided the most detailed accounts of opium preparation and usage. Opium or laudanum tinctures were the standard medical treatment for a long time. It was in the nineteenth century that opium was first used for recreational reasons in Europe. Thomas de Quincey, in his 1821 article "Confessions of an English opium consumer," was the leading advocate for opium use. Friedrich Sertürner, a German pharmacy student, named the compound he isolated from opium "morphine" in 1805, after the Greek deity of dreams Morpheus. (Mann, Meshkin et al. 2024).

As a result of the English and Portuguese bringing opium to China, opium dens began to spring up. The so-called "Opium War" broke out in 1842 as a result of Chinese imperial authorities' attempts at control and import prohibitions; the Treaty of Nanking, which limited the opium trade to certain ports, ended the war. The legalization of opium led to the proliferation of opium dens. In 1855, parenteral therapy was made possible by Alexander Wood's creation of the hypodermic syringe. Both the American Civil War (1861–1865) and the Franco-Prussian War (1869–1971) made extensive use of morphine. Morphine dependence became so common that it was dubbed "soldier's disease." Consequently, many service members were addicted to the drug. Diamorphine, apomorphine, and diacetylmorphine were among the several byproducts of the 1874 boiling of morphine and acetic acid that the English chemist C.R. Wright created. (Karunarathna 2024).

Strübe released his findings on heroin's effects on TB patients in 1898. The German pharmaceutical firm Bayer started making and selling heroin in the same year to relieve coughs. Following evidence of heroin's high addictive capacity, the United States outlawed its import, production, and sale in 1920. The League of Nations followed suit, effectively outlawing the drug in most countries. Even though heroin was once illegal in the UK, its usage as an analgesic and a substitute treatment for opioid dependence has persisted under strict regulation. Heroin as a treatment for heroin dependence has recently been the subject of controlled programs and clinical trials (Switzerland, Holland, Spain)(Bakare, Uzoeto et al. 2024).

American involvement in the Vietnam War, which lasted from 1963 to 1973, brought in the so-called "modern heroin epidemic" in the US. In addition to widespread consumption by troops on the battlefield, the gold triangle also served as the hub for massive worldwide distribution networks. He eventually made it to Europe and eventually Spain after a few years. By the late 1970s, heroin's negative effects were already noticeable in Spain, and by the 1980s, they had reached their peak. Many of the first heroin users died from complications related to the AIDS virus. There may be as many as 9 million individuals worldwide who rely on heroin. In 2003, Afghanistan, Burma, and Laos accounted for about 90% of the world's illicit opium production. Mexico, Colombia, Pakistan, and Thailand were among the other producing nations with smaller volumes.(Pagare, Flammia, et al. 2024).

3. TERMINOLOGY

Opiates and opioids mean different things, despite their frequent interchangeability. Opioids comprise both naturally occurring and artificial substances that bind particularly to opioid receptors, a property known as affinity. Any drug derived from the poppy plant is called an opiate. The Greek term anesthetic—meaning "drowsiness" or "clumsiness"—is the origin of the English word narcotic. It doesn't seem right to use it to describe opiates because it is more commonly used to describe drugs of abuse in the legal and policy fields.(Binder Jr, Stearns, et al. 2024).

Table 1. Characteristics of opioid receptors (+/+++ = magnitude of action; - = no action).

Nomenclature	In (m, OP3, MOR)	Delta (δ, OP1, DOR)	Kappa (κ, OP2, KOR)	Nociceptin (N/OFQ,OP4, NOR)
effector system	Protein G	Protein G	Protein G	Protein G
Endogenous ligand	β-endorphin, endomorphin	Enkephalin (yr and leu-enkephalin)	Dinorfina A	Nociceptin/ orphanin' FQ
Precursor	POMC (ACTH, MSH, β-lipotropin)	Proencephalina	Prodynorphin/	Pronociceptin/ orphanin' FQ
Analgesia: Supraspinal Spinal Peripheral	+++ ++ ++	— ++ —	-/hiperalgesia + ++	hiperalgesia +
Apr. respiratory	+++	++	—	
Miosis	++	—	+	
Reduction digestive motility	++	++	+	
Sedation	++	—	++	

Euphoria	+++	—	—	
Dysphoria	—	—	+++	
Dependence	+++	—	+	
Agonist	Morphine	Morphine	Pentazocine	Ro 64-6198
Antagonist	Naloxone	Naloxone	Naloxone	
POMC = proopiomelanocortina; ACTH = corticotropina; MSH = melanotropina				

About the same time in 1973, teams headed by Snyder in Baltimore, Terenius in Uppsala, and Simon in New York found opioid receptors. A brief description of the many kinds was provided. Hughes and Kosterlitz of Aberdeen found endogenous opioid peptides in 1975. Opioid receptors in the brain are specific to both endogenous and exogenous opioids; these receptors are widespread throughout the brain but are particularly concentrated in certain regions, including the spinal cord's periaqueductal grey matter and the myenteric plexuses in the periphery. gastrointestinal and musculoskeletal(Garza-Carbajal, Bavencoffe, et al. 2024). The human body has four different opioid receptor subtypes: mu (OP3, MOR), delta (OP1, DOR), kappa (OP2, KOR), and nociceptin (nociceptin/orphanin' FQ, OP4, NOR). Note that kappa receptors have three subclasses whereas mu and delta receptors have at least two. At this time, the sigma receptor is not thought of as an opioid. They are all G protein-coupled membrane receptors with very similar structures; nevertheless, they each have their own unique set of endogenous ligands and perform somewhat comparable functions. (Monico, Eastlick et al. 2024).

And other different ones (see Table 1).

Table 2. The action of different opioid drugs on opioid receptors (Ag = agonist; An = antagonist; AP = partial agonist; +/+++ = magnitude of the action; - = weak or no action) [1,7,11].

Morphine	At +++	At +	At +
Petidina Ag ++ Ag + Ag + Metadona Ag +++ Ag+ -			
Fentanyl Ag +++ Ag + Pentazocina An+ Ag + Ag ++ Butorphanol An+ Ag+ Ag ++			
Buprenorphine	AP+++	-	At ++
Naloxone	An+++	An+	An++
Naltrexone	An+++	An+	An+++

At the opioid receptor or receptors, opioids can take one of three forms: agonist, partial agonist, or antagonist. This so-called pharmacological dualism is present with exogenous opioids. This occurrence occurs when two opioid medications, for instance, analgesia, have the same pharmacological action while acting on separate receptors (mu, kappa). However, due to their unique interaction, the same medications might bind to two receptors in opposite ways, producing opposing effects (see Table 2)(Gaertner, Boehlke, et al. 2024). Among the many physiological roles played by the endogenous opioid system are the control of gastrointestinal, endocrine, and autonomic processes; learning and memory; and pain regulation (the inhibition of the response to painful stimuli). Its function in the reward and addiction circuit of the brain is highly significant. The same neurological basis that underlies the reinforcing effects and physical dependence of the majority of addictive substances is represented by opioid receptors. The primary mechanism by which opioids, like all addictive substances, cause dopamine release in the nucleus accumbens is by blocking GABA interneurons in the tegmental region.ventral (Kozell, Eshleman, et al. 2024). Traditionally, researchers have used medicines with varying degrees of potency on various opioid receptors to learn more about their roles in the effects of these drugs. A more precise method has recently been made possible with the development of transgenic (knockout) mice devoid of opioid receptor expression. Since it is recognized that there are compensation mechanisms to keep physiological functioning and life going when a crucial receptor is suppressed, it is important to note that these studies have limitations. These research findings are helpful, but they don't prove anything. (Levinstein, De Oliveira et al. 2024).

There is no evidence of physical dependency or location preference (reinforcement) in studies of morphine administration in mu-opioid receptor knockout mice. Also, these animals do not experience withdrawal symptoms when given naltrexone, an

antagonist of these receptors. The fact that these mice do not experience any analgesic effects from morphine is demonstrated in an experimental pain test. In a study by Knockout In terms of the kappa opioid receptor, the location preference test results and morphine-induced analgesia are comparable to those of wild-type, non-transgenic animals. But the condition (McCurdy, Sharma, et al. 2024)

Table 3. Result of morphine administration in mice *knockout* for the different opioid receptors in different analgesia tests and phenomena involved in addiction (self-administration, place preference, withdrawal syndrome) [13].

Opioid receptor *knockout*	Analgesia	Self-administration	Preference of place	Syndrome of abstinence
Mu receptor	No	No	No	No
Delta receptor	Yes	?	?	Yeah
Receptor coat	Yeah?	Yeah	Yes (reduction of symptoms)	

4. MECHANISM OF ACTION OF OPIOIDS

G proteins (Gαi/αo) link with opioid receptors, as previously stated. Adenyl cyclase activity is inhibited after opioid receptor stimulation, leading to a drop in cAMP concentration and cAMP-dependent protein kinase (PKA) activity, which in turn reduces protein phosphorylation (Figure 1). Postsynaptic neurons open potassium channels (GIRK), leading to membrane hyperpolarisation and, consequently, reduced activation, and presynaptic neurons close calcium channels more easily, reducing neurotransmitter release. Thus, they mediate inhibitory activities like receptors. (Gérard, Bailly, et al. 2024).

Tolerance, dependence, and withdrawal are all symptoms of molecular and gene expression alterations brought about by chronic opioid treatment. Afterwards, we will elucidate these occurrences. (Lane, Tomedi, et al. 2024).

Tolerance, dependence, and withdrawal are all symptoms of molecular and gene expression alterations brought about by chronic opioid treatment. Afterwards, we will elucidate these occurrences. (Drakopoulos 2024):

–Pure agonists: opioid agonists, mainly of the mu receptor, with high efficacy (intrinsic activity). Morphine, heroin, pethidine, methadone, fentanyl, and their derivatives belong to this group.

–Mixed agonists-antagonists: they act as agonists at one receptor (kappa) and as partial agonists or even antagonists at another (mu). When administered together with a pure mu agonist they can antagonize its effects and can reduce or suppress its analgesic effect. In subjects dependent on opioid agonists (heroin), they cause withdrawal syndrome. They are pentazocine, butorphanol, or nalorphine.

–Partial agonists: they act on mu receptors with lower efficacy than pure agonists. They are analgesics when administered alone, but antagonize the effects of a pure agonist. The most characteristic drug is buprenorphine.

–Pure antagonists: they have an affinity for the receptors but are not effective. They prevent or reverse the action of agonists and lack analgesic effects. They are naloxone and naltrexone.

Some of the most popular opioids used in clinical practice have their receptor action properties summarised in Table 2. One component of the hallucinogenic Sage of the Divine plant, Salvinorin A, is a kappa receptor agonist. (Bowe and Kerr 2024).

5. PHARMACOLOGICAL EFFECTS OF PURE AGONISTS

The prototype drug is morphine. The effects can be divided into central and peripheral. Some of them decrease after repeated administration (tolerance). Continued administration can produce addiction (opioid dependence) that causes physical dependence and withdrawal syndrome, tolerance, uncontrollable desire to consume despite the damage, as well as the abandonment of personal, family, and social activities other than those related to the drug. Obtaining and consuming the substance (Naji, Dennis, et al. 2024).

Central effects

Sedation. In general, pure agonists produce sedation, which will be expressed more or less depending on the patient's condition (degree of pain and insomnia). At higher doses, they produce stupor, deep sleep, and coma. Therefore, psychomotor performance worsens. If very high doses are administered, seizures may occur. In other species (cats, horses, cows, and pigs) they paradoxically cause excitement (Karunarathna 2024).

Euphoria. They produce euphoria, pleasure, and a feeling of well-being, with an anxiety reduction. This effect is very intense intravenously *(rush)* and, less by smoking or inhaling. It is the basis of its abuse, although it is often not observed in the first administrations since nausea and vomiting appear. In abstinence, however, dysphoria, restlessness, and general discomfort appear. Agonist-antagonists produce dysphoria at high doses (Gooding and Whistler 2024).

Analgesia. Pain has sensory and affective (emotional) components. Opioids reduce both components. Analgesia is the most important therapeutic property of opioids, being dose-dependent. They relieve or suppress pain of great intensity (acute or chronic) and any location. However, they are not useful in pain due to deafferentation (certain neuralgia). Analgesia is due to the action of mu receptors that control the afferent and efferent nociceptive systems. On the afferent system, which conveys nociceptive information, they reduce spinal ascending activity. On the efferent or descending system, which controls or regulates the transmission of nociceptive information in the spinal cord from cortical centers, midbrain, and medulla, they activate the inhibitory neuronal system (system *off* of the bulb) and inhibits an exciter system (system *on* of the bulb), both with downward projection (Spoleti, George, et al. 2024).

This is expressed as a descending inhibitory action in the posterior horns of the spinal cord. They also have actions on the limbic and cortical systems, attenuating the perception of the unpleasant or distressing tone of pain. More recently, the action on peripheral nerve endings (nociceptors) has been described, after local administration in places where there is an inflammatory component, such as, for example, in joints *respiratory depression (Ferrante and Blendy 2024)*.

They depress the activity of the bulbopontine respiratory center. Reduce sensitivity to CO_2 and hypoxia. They decrease the respiratory minute volume, mainly affecting the frequency more than the amplitude. Therefore, a reduction in the number of breaths per minute is observed, which can lead to apnea. As a consequence, respiratory acidosis may appear. This effect is dose-dependent and seems related to the action of the mu receptor. It may be clinically relevant in subjects with respiratory pathology (Ferrante and Blendy 2024).

Cough suppression. They suppress the cough reflex, possibly by affecting the set of respiratory neurons that integrate and direct the convulsive cough movements. The exact mechanism is not known, but antitussive actions do not correlate with analgesics or respiratory depression. One of the most used antitussives, dextromethorphan, is almost free of opioid actions. Codeine reduces cough at lower doses than analgesics. Suppression of cough can cause an accumulation of bronchial secretions (Herman, Cascella, et al. 2024).

Miosis. Pupillary constriction is a typical effect of almost all opioids. This miosis is due to its disinhibitory action on the Edinger-Westphal nucleus of the oculomotor. It can be blocked by opioid antagonists and by antimuscarinics such as atropine. Miosis does not present tolerance and is therefore useful in predicting recent opioid use and acute intoxication. In cases of severe hypoxia, miosis develops into paralytic mydriasis. Pethidine, due to its antimuscarinic action, does not produce miosis (Green, Veltri et al. 2024).

Nausea and vomiting. By activation of the chemoreceptor zone of the area postrema. They are observed more frequently after the first administration. In heroin addicts, vomiting is not interpreted as a negative effect. *Neuroendocrine actions*. Due to their action on the hypothalamus and pituitary gland, they stimulate the secretion of ACTH, growth hormone, β-MSH, and antidiuretic hormone, and inhibit the secretion of TSH and gonadotropins (LH and FSH). *Other central effects*. They can cause hypothermia of hypothalamic origin muscle hypertonia and rigidity (Damiescu, Dawood, et al. 2024).

Peripheral effects

Gastrointestinal. Opioid agonists cause an increase in myogenic tone in the gastrointestinal tract, including the sphincters, and an inhibition of neurogenic activity with reduced motility. As a consequence, gastric emptying is delayed, intestinal peristalsis decreases, and the sphincters contract. Clinically it manifests itself with the appearance of constipation and an increase in pressure in the bile ducts with hypertonia of the sphincter of Oddi, decreasing bile and pancreatic secretion. These actions have a central and a peripheral component and fundamentally involve mu receptors (Kheirabadi, Minhas et al. 2024).

Cardiovascular. They can cause hypotension by action on the vasomotor center, as well as by arterial and venous vasodilation, with a reduction in afterload and preload. The release of histamine may contribute to this effect. Bradycardia of vagal origin may also appear. Due to increased pCO_2, cerebral vasodilation occurs with elevation of intracranial tension. Pethidine, due to its antimuscarinic action, can

cause tachycardia (Withey, Bergman et al. 2024).

It occurs in areas of the face and upper part of the trunk. As a consequence, a feeling of

heat, facial redness, and itching. Histamine release may produce some degree of bronchoconstriction. *Kidney and urinary*. They increase the tone of the detrusor muscle of the bladder with a feeling of urinary urgency and increase the tone of the sphincter, making urination difficult (urinary retention). They reduce renal flow and have an antidiuretic effect (Hochrainer, Serafin, et al. 2024).

Others. They reduce uterine tone and therefore prolong labor. Chronically administered opioids are immunosuppressive.

Pharmacological tolerance

It is manifested by a decrease in the intensity of the response or by the shortening of the duration of action, which requires increasing the dose or administering it at shorter intervals. In general, it develops relatively quickly for depressant actions, such as analgesia, respiratory depression, euphoria, sedation, and hypotension, and much less so for miosis and gastrointestinal action. There is cross-tolerance between opioids that activate the same receptor, which facilitates their exchanges, especially in the treatment of dependence. The tolerance that heroin addict patients have to opioids is very important. As an example, in clinical trials in which intravenous heroin has been used for dependence maintenance treatment, patients injected around 500 mg per day, spread over two or three occasions. In comparison, for pain treatment in non-addicted people, the recommended dose of heroin would be 4-5 mg every 6 hours (Carter 2024).

The molecular basis of tolerance is pharmacodynamic. One of the most recognized theories is that of the upregulation of cAMP (*up-regulation*). As mentioned, acutely, opioids decrease the concentration of cAMP and the activity of PKA. After repeated administration, the activity of adenyl cyclase and PKA progressively increases (*up-regulation*) and, as a consequence, cAMP concentrations gradually increase. Thus, increasingly higher doses of opioids are needed to maintain the decrease in cAMP (tolerance) (Barakat, Munro et al. 2024).

When the opioid is stopped or an antagonist such as naloxone is administered, a rebound increase in cAMP occurs. This large increase in cAMP increases the excitability of neurons and is the molecular basis of the signs and symptoms of withdrawal (see Figure 1). This phenomenon has been demonstrated in the locus coeruleus, nucleus accumbens, ventral tegmental area, and periaqueductal gray matter. It seems that the cause of the upregulation of the cAMP system is the increase in the production of a transcription factor called CREB (a protein that binds to cAMP response elements). In addition, CREB increases the synthesis of dynorphin, a substance that activates kappa receptors in the neurons of the ventral tegmental area, which produces a decrease in the release of dopamine in the nucleus accumbens. This reduction contributes to the negative emotional state (dysphoria and anhedonia) characteristic of withdrawal. The advantage of this theory is that it relates to the phenomena of tolerance and abstinence (Mariani, Diebolt et al. 2024).

Another theory of tolerance postulates that repeated administration of opioids produces a desensitization of the receptors due to their phosphorylation by kinases (G protein receptor kinase or GRK) and their binding to β-arrestin, which can internalize it, thereby decreasing the density of receptors in the membrane. Most agonists cause these actions rapidly, while morphine produces less and slower internalization. Therefore, the exact molecular basis of morphine tolerance is not known (Huang, Ho et al. 2024).

Withdrawal syndrome. Dependence

Table 4. DSM-IV-TR diagnostic criteria for opioid withdrawal (F11.3).

A.	Any of the following possibilities:
(1)	stopping (or tapering off) heavy, prolonged (several weeks or more) opioid use
(2)	administration of an opiate antagonist after a period of opiate use
B.	Three or more of the following signs and symptoms, appear within a few minutes to several days after Criterion A.
(1)	dysphoric mood
(2)	nausea or vomiting
(3)	muscle pain
(4)	tearing or rhinorrhea
(5)	pupillary dilation, piloerection or sweating
(6)	diarrhea
(7)	yawns
(8)	fever
(9)	insomnia
C.	Criterion B symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of the individual's functioning.
D.	The symptoms are not due to a medical illness nor are they better explained by the presence of

The repeated administration of opioids can produce dependence, which consists of a lack of control over the substance, its compulsive use, drug-seeking behavior, and the presence of medical and social problems. Abrupt discontinuation of the

opioid triggers a withdrawal syndrome (physical dependence, see Table 4). Withdrawal resembles a flu-like state, with yawning, mydriasis, rhinorrhea, muscle pain, sweating, piloerection, nausea and vomiting, diarrhea, fever, and insomnia. There is restlessness and anxiety. In addition, there is a very intense desire to consume the drug (psychological dependence or *craving*) (Sandhu and Calcaterra 2024). The symptoms seem related to rebound noradrenergic hyperactivity in the locus coeruleus. May be attenuated or disappear with short-term administration of α-receptor agonists.$_2$, such as clonidine or with the administration of opioid agonists (e.g., methadone). For short-elimination half-life agonists, it appears rapidly with a maximum of 24–72 hours and resolves spontaneously in just over a week (Table 5). With longer-lasting agonists, such as methadone or buprenorphine, withdrawal is less intense and appears more delayed. The administration of an antagonist to dependent subjects produces the appearance of a very intense acute withdrawal syndrome (Goudsward, Ruiz-Velasco, et al. 2024).

At a therapeutic level, dependence is very rare in non-addicted patients (four cases in 11,882 patients treated with opioids). It is more common in former addicts, so they must be closely monitored so that they do not relapse. In cancer patients treated with morphine at high doses, limited tolerance, and a withdrawal syndrome appear when consumption ceases, but definitive dependence is not observed since the psychological and behavioral components that require it do not appear (Shi, D. Langleben, et al. 2024).

Table 5. Time course of heroin withdrawal symptoms. Many of the symptoms persist and worsen until the phase of maximum expression (24-36 hours).

Grade I 4-8 hours appear.	Grade II They appear from 8-12 pm.	Grade III They appear in 12-24 hours.	Grade IV They appear 24-36 hours.
Intense drug craving *craving*) Anxiety Concern Irritability yawns Sweating tearing Rhinorrhea Insomnia	Grade I symptoms with greater intensity, plus: Mydriasis Piloerection Tremors Hot/cold sensation Myalgias Arthralgias Anorexia	Grade I symptoms with greater intensity, plus: Hypertension Tachycardia Hyperthermia Concern Nausea Insomnia	Grade I symptoms with greater intensity, plus: You look feverish Vomiting Diarrhea Weight loss Spontaneous ejaculation spontaneous orgasm

The molecular mechanism of withdrawal has been explained in part in the tolerance section. The upregulation of the cAMP and CREB system causes the lack of opioids to trigger the synthesis of cAMP and increase neuronal excitability, especially in the noradrenergic neurons of the locus coeruleus, which causes the symptoms of withdrawal syndrome (Figure 1). Similarly, the synthesis of corticotropin-releasing hormone (CRF) is increased, which also seems to be involved in the stress associated with withdrawal and negative symptoms (Verret, Lam, et al. 2024).

Opioids and other drugs appear to produce long-lasting neuronal changes that facilitate relapse into addiction, even after many years, during which the patient has not used drugs, and therefore could consider himself cured of his substance dependence disorder. It has been suggested that during repeated consumption of opioids, there is an increase in the synthesis of another transcription factor called deltaFosB (ΔFosB), which, unlike other factors, remains activated for prolonged periods. After chronic use, very significant amounts of ΔFosB would accumulate, which could even remain for years ΔFosB increases, among others, the production of NMDA glutamate receptors, involved in long-term potentiation phenomena, memory, and learning. These changes would produce a state of acquired vulnerability, and seem responsible for the *craving* (irresistible desire to consume the drug), which appears after detoxification and also in relapses. In the latter case, new consumption of the substance would facilitate relapse into addiction (Tsai, Chen, et al. 2024).

6. PHARMACOLOGICAL EFFECTS OF AGONISTS-ANTAGONISTS

The prototype is pentazocine. They are opioids that have a high efficacy on kappa receptors, but little or no effectiveness on mu receptors, where they act as partial agonists or antagonists. Therefore, they exert less respiratory depression and fewer

effects on gastrointestinal motility, but they have an analgesic ceiling that limits their therapeutic efficacy. Kappa activation produces dysphoria with a feeling of tiredness, drowsiness, disorientation, drunkenness, dizziness and vertigo, nervousness, and anxiety. When administered at somewhat higher doses, pseudohallucinations (psychotomimetic effects) may appear. They are capable of inducing a withdrawal syndrome in patients who chronically receive pure mu agonists, by acting as antagonists. Although the possibility of creating dependency is less, there are also

you are addicted (Serra, Alcedo, et al. 2024).

7. PHARMACOLOGICAL EFFECTS OF PARTIAL AGONISTS

The most characteristic drug is buprenorphine, which is 25 times more potent than morphine. Its actions are predominantly mu in nature, although it also shows an affinity for kappa receptors. It binds intensely and lastingly to mu receptors, for this reason, its action is longer. Naloxone does not completely antagonize its effects. Causes less respiratory depression. It can create dependence, although its withdrawal is less intense and appears more delayed (Shahbazi Nia, Ortiz et al. 2024).

PHARMACOLOGICAL EFFECTS OF PURE ANTAGONISTS

Table 6. Pharmacokinetic properties of the main opioids.
Used in the clinic.

Drug	Bioavailability oral (%)	$t_{1/2}$ (hours)	UP (%)	Duration (hours)	Equianalgesic doses 10 mg morphine IM im			
Morphine	25	2-3	35	3-6	10	30-60	Heroin	25	0.1	35	3-6
Codeine	50	2-4	7	4	130	75	Methadone	90	15-40	80	4-6	10	20
Dextropropoxifeno			60		6-12	78		4-6	--	130	
Petidina	50	3-5	70	2-4	100	300	Fentanilo	90 (td)	2-7	83	1	0.2	-
Tramadol	68	6	4	4-6	100	100					
Buprenorphine			50 (sl)/90 (td)		3-5	96		6-8	0.3	0.8 (sl)	
Pentazocine			40		4-5	65		3-4	60	150	

t1/2 = elimination half-life time; UPP = plasma protein binding; po = oral route; im = intramuscular route; sl = sublingual route; td = transdermal route

The best-known drugs are naloxone and naltrexone. They are antagonists of all three types of receptors. They block both the action of endogenous and exogenous opioids. They reverse the effects of agonists and agonist-antagonists (Tsang, Kang, et al. 2024).

Naloxone is used in case of poisoning or overdose. In patients treated with high doses of opioids, the acute reversal of depressant actions can cause a hypertensive crisis, with tachycardia and even ventricular fibrillation and acute pulmonary edema. It is therefore recommended to administer low doses at the beginning and monitor the cardiovascular response. In healthy individuals, high doses produce pharmacological effects, including endocrine disruption (hypercortisolemia), sweating, yawning, anxiety, and confusion. Naltrexone is used to block the effects of opioids after detoxification and in the treatment of alcoholism (Duque, Vallavoju, et al. 2024).

8. PHARMACOKINETICS

Table 6 summarizes the pharmacokinetic properties of the main opioid analgesics. [1,7]. There are preparations for parenteral use (intravenous, subcutaneous, intramuscular) for many of them. Most opioids are well absorbed from the oral mucosa

(buprenorphine, fentanyl) and the skin (buprenorphine, fentanyl). There are also transnasal preparations of butorphanol. Heroin is administered parenterally (mainly intravenously, but also subcutaneously and intramuscularly), intrapulmonary by smoking or inhaling ("Chinese"), and intranasally (snorting) (Greenhouse, Hayes et al. 2024).

Orally, most have low bioavailability (<50%) due to first-pass hepatic metabolism. After absorption, they are distributed rapidly in the body, varying their volume of distribution between 1.5 and 4.7 L/kg. The main mechanism of inactivation is hepatic metabolism, which usually consists of microsomal oxidation and conjugation with glucuronide acid. Demethylation by the cytochrome P450 2D6 enzyme system, cytochrome (CYP2D6), is relevant in the metabolism of codeine, tramadol and dextromethorphan. They are excreted mainly through urine (so doses should be lower in patients with renal failure because it accumulates) and also through bile, undergoing enterohepatic circulation. The presence of morphine in urine at concentrations greater than 300 ng/ml is considered positive and indicative of recent heroin or morphine consumption. After administration of an opioid, urine may present concentrations above the positive threshold for about 3-4 days (Neelamegam and KUMAR 2024).

Its elimination half-life is generally short, except for buprenorphine and methadone. In the case of morphine, its effects are prolonged with the administration of sustained or delayed release preparations. The same occurs in the case of fentanyl delayed-release patches (Cohen and Gorman 2024).

Morphine is transformed into two glucuronides, the majority being morphine 3-glucuronide (M3G) and 10% being morphine 6-glucuronide (M6G) (Figure 1). M6G has a longer elimination half-life than morphine (4 hours versus 2 hours) and has greater analgesic action than morphine. Therefore, it contributes substantially to the pharmacological effect and its toxicity. It has been suggested that M3G could antagonize the analgesic effects. In single-dose studies, a potency ratio between parenteral and oral morphine has been established as 1:6 (10 mg: 60 mg), while after multiple doses of oral morphine, the potency ratio is reduced to 1: 2 or 1:3 (10 mg: 30 mg). This is possibly due to the increased production of M6G after repeated doses (Table 4) (Sima, Lapkin et al. 2024)

Heroin (diacetylmorphine, diamorphine) is transformed by deacetylation by plasma esterases and hepatic carboxylesterase into 6-monoacetylmorphine (6-MAM) and then into morphine (Figure 2). It appears that the effects of heroin are due to 6-MAM and morphine. Heroin and 6-MAM have a greater lipid solubility than morphine, so if heroin is administered parenterally it can reach the brain sooner and achieve higher concentrations of morphine there. The elimination half-lives of heroin and 6-MAM are 3-5 min. and 3-12 min., respectively. When heroin is administered intravenously the maximum concentrations of heroin, 6-MAM, and morphine are observed at 1 min., 1 min. And 1-5 min., respectively· If heroin is administered by smoking, maximum concentrations of heroin, 6MAM, and morphine are observed at 1-2 min., 2 min., and 1-7 min., respectively (Denton 2024).

When heroin is administered intranasally, peak concentrations of heroin, 6-MAM, and morphine are observed at 5 min., 5 min. And 12 min., respectively. If heroin is administered orally, no plasma concentrations of heroin or 6-MAM are detected, and only levels of morphine and its metabolites are observed. The bioavailability of heroin, measured by morphine concentrations, is 80% intranasally when smoked 89%, in the case of inhalation from a Chinese (*chasing the dragon*) of 45%, and orally 20-50%. Illegal heroin contains residues of other opioids, including acetylcholine, which are not found in pharmaceutical-grade heroin (the one used therapeutically). The presence of acetylcholine in urine makes it possible to differentiate the consumption of legal heroin from illegal (Laffont, Purohit, et al. 2024).

Codeine (3-methoxy morphine) is transformed into morphine after being demethylated by the cytochrome CYP2D6, which accounts for most of its pharmacological activity (Figure 2). It is necessary to mention that up to 10% of the Caucasian population has a deficiency of this enzyme (genetic polymorphism), so these subjects (slow metabolizers) will have fewer pharmacological and medicament effects. Nor therapeutic efficacy. La pethidine (meperidine) is metabolized to norpethidine, which is also active. It presents neurological and cardiac toxic effects after repeated administration due to the accumulation of the metabolite. It also has antimuscarinic properties (Ghoshal, Damani et al. 2024).

Fentanyl and derivatives (sufentanil, remifentanil) are characterized by their great potency (50-150 times more than morphine) and low cardiotoxicity, as they are very fat-soluble and penetrate quickly into the CNS. They are the drugs of choice for anesthesia and in intensive care units. Among its derivatives, remifentanil can be highlighted, which is hydrolyzed in plasma with a very rapid elimination half-life (5 minutes) (Dalgarno, Turnnidge, et al. 2024).

Methadone is slightly more potent than morphine. In addition to activating opioid receptors, it antagonizes the NMDA glutamate receptor. In chronic treatment, it is widely fixed to the tissues where it accumulates as a reservoir and from where it is redistributed to the plasma. Methadone is metabolized mainly by the cytochrome CYP3A4 to its most important metabolite, 2-ethylene1,5-dimethyl-3-3-diphenylpyrrolidine or EDDP and, to a lesser extent, by the cytochromes CYP2D6 and CYP1A2. Methadone occurs as a racemic mixture (R-methadone, S-methadone), but the pharmacological activity appears to reside in the R-enantiomer, l-methadone. Its long elimination half-life allows its additional ministration once a day (Ellison, Hutton et al. 2024).

Buprenorphine is metabolized by hepatic cytochrome CYP3A4 to norbuprenorphine. Given its low oral bioavailability, it is administered parenterally, sublingually, and in the form of transdermal patches. Its high receptor binding and prolonged elimination half-life allow, in the maintenance treatment of opioid dependence, its sublingual use every other day (three times a week) (Qiu and Wang 2024).

Dextropropoxyphene is an optical enantiomer of methadone with less activity than methadone and less potency than codeine. It is metabolized to nor propoxyphene, which has a longer elimination half-life and can accumulate causing neurological toxicity (tremors, seizures) (Bilel 2024).

Tramadol (codeine analog) is a weak opioid that possibly acts by non-opioid mechanisms (inhibits the reuptake of serotonin and norepinephrine at the spinal level). It is transformed by cytochrome CYP2D6 into an active metabolite (O-desmethyl tramadol or M1) that has opioid action. Again, polymorphisms of this enzyme will modify the concentrations of the active metabolite and the pharmacological and therapeutic effects. Tramadol occurs as racemic, the (+) enantiomer binds to the mu-opioid receptor and inhibits serotonin reuptake, while the (-) enantiomer inhibits norepinephrine reuptake and stimulates α2-adrenergic receptors (Gisemba, Ferracane, et al. 2024).

Dextromethorphan does not appear to have opioid action. By itself, it is inactive but is metabolized by cytochrome CYP2D6 to dextrorphan, which is an antagonist of NMDA glutamate receptors. The polymorphisms of this isoenzyme, already explained for codeine, will apply to this substance. Thus, slow metabolizers will not present an antitussive response.

Tilidine is transformed by hepatic metabolism into an active metabolite, nortilidine, which is why it has greater opioid action orally than parenterally. Loperamide crosses the blood-brain barrier poorly and, therefore, does not exert central actions at usual doses. It is used as an antidiarrheal (Ni, Gao et al. 2024).

9. UNDESIRABLE EFFECTS AND INTOXICATION

The main undesirable effects are related to its pharmacological effects and are, therefore, dose-dependent. For some of them, especially sedatives, tolerance develops after repeated administration (respiratory depression, euphoria, sedation, hypotension, analgesia). There appears to be no tolerance for miosis and constipation (Rysztak, Hoying, et al. 2024).

The most common adverse reactions after acute use of a mu agonist are nausea and vomiting (20-60%), drowsiness, dizziness, and instability and confusion. After repeated use, the most common undesirable effect is constipation. In addition, they can cause respiratory depression, urinary retention, dry mouth, diaphoresis, pruritus, muscle hypertonia, myoclonus, and euphoria. Respiratory depression is the most worrying effect, especially in the elderly and patients with chronic respiratory problems. Also, postural hypotension may occur. Abuse, tolerance, withdrawal, and dependence should be considered undesirable effects. The administration of partial agonists and even agonist-antagonists can cause dependence.

Pethidine, in addition to the above, causes neurological reactions (such as disorientation, tremors, delirium, hallucinations, and seizures) and cardiac reactions (ventricular arrhythmias). It can also produce anticholinergic effects (dry mouth and blurred vision) (Stove 2024).

Methadone at high doses and l-alphaacetylmethadol (LAMM) can increase the QTc interval and cause ventricular arrhythmias (*Torsades de pointes*) (Giorgi, Sarzi-Puttini, et al. 2024).

Tramadol may cause nausea, vomiting, sedation, confusion, dizziness, dry mouth, irritability, orthostatic hypotension with tachycardia, and gastrointestinal upset. It can also cause dependence, although less frequently than an agonist. As mentioned above, agonist-antagonists produce dysphoric reactions, drowsiness, disorientation, feelings of intoxication, dizziness and instability, nervousness, and anxiety. At higher doses or in susceptible subjects, they cause pseudohallucinatory symptoms. They induce less respiratory depression and sphincter spasms.

Off (Jalali 2024).

Naloxone and naltrexone, when administered to patients receiving agonist opioids, can produce an acute and severe withdrawal syndrome. Naloxone can cause high blood pressure, tachycardia, and acute lung edema. Naltrexone increases transaminases without definite liver injury (Marchand 2024).

Intoxication or overdose by opioids produces a typical picture of stupor or coma accompanied by respiratory depression and intense or punctate miosis (classic triad). Table 7 shows the DSM-IV-TR diagnostic criteria for opioid intoxication. The treatment of acute poisoning is carried out with parenteral naloxone, which is the antidote and drug of choice. Intoxication may be due to an actual overdose or to altered behavioral tolerance phenomena (administration outside the usual environment or in a different way). It must be remembered that the majority of heroin addicts are multiple users, and it is most common to find various substances in the blood and urine of those intoxicated. In addition, the possibility of effects caused by adults must be taken into account (Fong, Lewis, et al. 2024).

Table 7. DSM-IV-TR diagnostic criteria for opioid intoxication (F11.0).

A. Recent use of an opiate.

B. Clinically significant maladaptive psychological or behavioral changes (e.g., initial euphoria followed by apathy, dysphoria, psychomotor agitation or inhibition, impaired judgment, or social or occupational impairment) occurring during or shortly after opioid use.

C. Miosis (or anoxia mydriasis in severe poisoning) and one (or more) of the following signs, appearing during or shortly after opiate use:

(1) drowsiness or coma

(2) gibbering language

(3) impairment of attention or memory

D. The symptoms are not due to a medical illness nor are they better explained by the presence

The intravenous administration of heroin is generally carried out in unhygienic conditions and, therefore, is a vehicle for the transmission of serious infectious diseases such as hepatitis C and B or AIDS. For the last twenty years, the main cause of death for heroin addicts has been AIDS. Also, endocarditis, sepsis, and abscesses may appear (Cahill 2024).

Agonist opioids should be administered with caution in the elderly, in case of renal and hepatic failure (elimination decreases, concentrations increase) or associated chronic lung pathology, as well as in case of head trauma or pregnancy (risk of producing dependence in the newborn) (Birgül Iyison, Abboud, et al. 2024).

10. PHARMACOLOGICAL INTERACTIONS

The sedative actions of opioids are enhanced by the administration of other central sedatives (benzodiazepines, hypnotics, antipsychotics, MAOIs, tricyclic antidepressants, antihistamines, or alcohol, among others). Its analgesic effect can be enhanced with the administration of amphetamine, tricyclic antidepressants, and some calcium antagonists (Di Ianni, Ewbank et al. 2024).

Opioids can reduce the rate of absorption of other drugs through their digestive actions. MAOIs increase the toxicity of pethidine (hypotension, rigidity, hyperthermia, coma) and tramadol, so their combined use should be avoided. Drugs that inhibit or induce cytochrome CYP3A4 metabolism may modify the pharmacokinetics and effects of methadone. Thus, methadone concentrations may increase if it is co-administered with metabolic inhibitors such as macrolides (erythromycin), antifungals (ketoconazole, fluconazole), benzodiazepines (diazepam, midazolam), ciprofloxacin or grapefruit juice (Harrison 2024).

Methadone concentrations may be reduced (causing withdrawal symptoms) if coadministered with metabolic inducers such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, antiretrovirals (ritonavir, lopinavir-ritonavir, nelfinavir, efavirenz, nevirapine), or St. John's wort. Juan). Furthermore, drugs such as amitriptyline, due to inhibition or competition for cytochrome CYP2D6, fluoxetine, and fluvoxamine, due to inhibition of cytochromes CYP3A4 and CYP2D6, and moclobemide, due to inhibition of CYP1A2, may increase their plasma concentrations. The patient's therapeutic response should, therefore, be monitored to determine whether methadone doses should be decreased or increased (Rhee, Sager, et al. 2024).

In the case of buprenorphine, which is also metabolized by cytochrome CYP3A4, if substrates or inhibitors of this isoenzyme are administered, the precautions described above should be taken. Tramadol can interact with CYP2D6 substrates and inhibitors, among which quinine, fluoxetine, paroxetine, and amitriptyline stand out since all of them decrease the formation of the Metabolite (Gillies, Chadwick et al. 2024).

In some countries, different fixed-dose combinations of opioids with other drugs are marketed. Codeine or dextromethorphan stand out in preparations for the symptomatic treatment of colds and flu. For the treatment of mild-moderate pain, codeine, tramadol, or dextropropoxyphene are combined with paracetamol, acetylsacylycyl acid, or ibuprofen. Buprenorphine and pentazocine are associated with naloxone in formulations for sublingual or oral use to reduce their abusive use. Through these routes of administration, naloxone is not absorbed and therefore does not interfere with the opioid effects, but if the preparation is used intravenously, it can cause withdrawal syndrome. Morphine is associated with dextromethorphan since it seems to enhance the opioid effect and reduce tolerance (Clements, Kochan, et al. 2024).

11. PHARMACOGENETICS AND OPIOIDS

Another chapter of this monograph specifically addresses the relevance of molecular genetics in opioid abuse and dependence. Here, we just want to highlight that polymorphic changes in metabolic enzymes (CYP2D6) have great relevance

in the pharmacokinetics and effects of some opioids. Among the genetic variations that affect opioid receptors, the single nucleotide polymorphism (SNP, *single nucleotide polymorphism*) that affects the mu receptor at position 118 (A118G, substitution of adenine for guanine), seems to be one of the most clinically relevant. Carriers of this mutation require higher doses of opioids to obtain analgesia (Liu, Patanwala et al. 2024).

12. CLINICAL USE OF OPIOIDS

The main therapeutic indications for opioids are listed in Table 8. For each clinical condition, the most effective drug and the most relevant route of administration must be selected. It is of choice in the case of acute pain, mainly for the treatment of mild-moderate pain (codeine, tramadol) or when chronic pain. In addition, the sublingual route is used in the maintenance treatment of neoplastic or using oral morphine. The path of dependency.buccal, sublingual and transdermal are used (Weisman, Ciavarra et al. 2024).

arenteral routes are used in severe acute conditions, especially in severe pain intensity. Intramuscular and subcutaneous routes are appropriate in most of these cases. The intravenous route is reserved for emergencies or the establishment of infusion pumps or analgesia pumps controlled by the patient. In the treatment of neoplastic pain and palliative care units, subcutaneous infusion pumps are used. The oral route Morphine is the drug of choice in the treatment of acute and chronic pain of severe intensity. In addition, it is used in acute lung edema, acute myocardial infarction, and severe dyspnea in terminal patients to relieve respiratory effort. Pethidine is more toxic and only a few doses are recommended.

Pentazocine is practically out of use due to its ceiling effect and psychotomimetic properties. In some countries, heroin is used for pain treatment and relapse prevention (agonist maintenance programs). Codeine is used orally as an analgesic, antitussive, and antidiarrheal. Fentanyl and derivatives are used in anesthesia and for the treatment of pain.

Table 8. Main therapeutic indications for opioids.

Agonists
Acute and chronic pain
Those
Diarrhea
Acute lung edema
Dyspnea of terminally ill patients
Analgesia during anesthesia
Opioid detox
Prevention of opioid relapses (maintenance programs with agonists)
partial agonists for Acute and chronic pain
Opioid detox
Opioid relapse prevention (maintenance programs with partial agonists)
Antagonists
Acute opioid poisoning
Opioid relapse prevention (maintenance programs with antagonists) Alcoholism treatment

13. CONCLUSIONS

Methadone is used as an analgesic and, above all, for detoxification and relapse prevention (maintenance programs with agonists). Buprenorphine, at high doses, is used in detoxification and relapse prevention (maintenance programs with agonists) while, at low doses, it is used as an analgesic. Dextropropoxyphene is used for pain treatment and detoxification. Tramadol is used as an analgesic. Loperamide is used in diarrhea. Dextromethorphan is used as a cough suppressant. Naloxone, in opioid poisoning and to check the effectiveness of detoxification. Naltrexone is used in the prevention of relapses (maintenance programs with antagonists) and also, in alcoholism.

Racecadotril (acetorphan) is an inhibitor of intestinal enkephalinases responsible for the degradation of endogenous opioid peptides and, as a consequence, increasing their concentrations. It is a lipophilic prodrug, which is rapidly hydrolyzed to the active metabolite, thiorphan. It is used, in some countries, in the treatment of acute diarrhea. It produces a reduction in the

hypersecretion of water and metabolites into the intestinal lumen. Does not affect motility or act on the CNS.

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