
ANALGESICS INFLUENCE MECHANISMS AND THEIR CLASSIFICATION

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Annotation: Analgesic, any drug that relieves pain selectively without blocking the conduction of nerve impulses, markedly altering sensory perception, or affecting consciousness. This selectivity is an important distinction between an analgesic and an anesthetic.

Key words: Analgesic, blood, disease, arthritis, ache, head ache.

Analgesics may be classified into two types: anti-inflammatory drugs, which alleviate pain by reducing local inflammatory responses; and the opioids, which act on the brain. The opioid analgesics were once called narcotic drugs because they can induce sleep. The opioid analgesics can be used for either short-term or long-term relief of severe pain. In contrast, the anti-inflammatory compounds are used for short-term pain relief and for modest pain, such as that of headache, muscle strain, bruising, or arthritis.

Analgesics are medications that relieve pain. They work either by reducing inflammation or by changing the way the brain processes and perceives pain. Side effects include heartburn, nausea, and headaches.

Some types of analgesics are available over the counter. However, stronger variants are available only with a prescription. This is because strong analgesics are more likely to cause side effects such as dependence, addiction, and withdrawal symptoms.

This article outlines what analgesics are, including their uses, the different types available, and how they work. It also discusses the risks and side effects of analgesics and provides information on their availability.

Analgesics are pain-relieving medications. These medications relieve pain but do not address its underlying cause. Typically, they work either by reducing inflammation at the site of pain or by changing the brain's perception of pain.

Analgesics are available in many forms, including:

- oral medications such as tablets, capsules, and liquids
- topical creams, gels, and ointments
- suppositories

Analgesics are medications that relieve pain. There are three main types: non-opioid analgesics, opioid analgesics, and compound analgesics that combine the two previous forms.

Most non-opioid analgesics work by reducing inflammation at the site of pain. In comparison, opioid analgesics work by interacting with opioid receptors to change the way the brain processes and perceives pain.

Many non-opioid analgesics are available over the counter, whereas opioids are available only via prescription. The latter have a higher likelihood of causing dependence and addiction. People taking opioid medications require careful monitoring and a regular review of their medications to reduce the risk of these side effects.

Most anti-inflammatory analgesics are derived from three compounds discovered in the 19th century—salicylic acid, pyrazolone, and phenacetin (or acetophenetidin). Although chemically unrelated, the drugs in these families have the ability to relieve mild to moderate pain through actions that reduce inflammation at its source. Acetylsalicylic acid, or aspirin, which is derived from salicylic acid, is the most widely used mild analgesic. It is considered the prototype for anti-inflammatory analgesics, the two other major types of which include acetaminophen (a derivative of phenacetin) and the aspirin-like drugs, or nonsteroidal anti-inflammatory drugs (NSAIDs), which include compounds such as ibuprofen, naproxen, and fenoprofen. Pyrazolone derivatives, with some exceptions, are no longer widely used in many countries, because of their tendency to cause an acute infection known as agranulocytosis.

Aspirin and NSAIDs appear to share a similar molecular mechanism of action—namely, inhibition of the synthesis of prostaglandins (natural products of inflamed white blood cells) that induce the responses in local tissue that include pain and inflammation. In fact, aspirin and all aspirin-like analgesics, including indomethacin and sulindac, which are derived from a heterocyclic organic **compound** known as indole, inhibit prostaglandin synthesis and release. All these agents can be further divided into nonselective COX inhibitors and selective COX inhibitors. COX, or cyclooxygenase, is an **enzyme** responsible for the synthesis of prostaglandins and related compounds. It has two forms, COX-1, which is found in most normal tissues, and COX-2, which is induced in the presence of inflammation. Because COX-2 is not normally expressed in the **stomach**, the use of COX-2 inhibitors (e.g., rofecoxib, celecoxib) seems to result in less gastric ulceration than occurs with other anti-inflammatory analgesics, particularly aspirin. However, COX-2 inhibitors do not reduce the ability of **platelets** to form clots, a benefit associated with aspirin and other nonselective COX inhibitors.



Preferences in COX selectivity and the possibility of additional molecular actions of NSAIDs may explain differences in the therapeutic effects between aspirin, acetaminophen, and NSAIDs. For example, while aspirin is effective in reducing **fever**, as well as relieving inflammation, acetaminophen and NSAIDs are more potent antipyretic (fever-reducing) analgesics. Acetaminophen, on the other hand, possesses inferior anti-inflammatory activity compared with aspirin and NSAIDs and thus is relatively ineffective in treating inflammatory conditions such as **rheumatoid arthritis**. Despite this, **acetaminophen** is a popular mild analgesic and antipyretic and is a suitable **alternative** to aspirin for patients who develop severe symptoms of stomach irritation, because it is not as harmful to the **gastrointestinal tract**.

As might be expected from their common mechanisms of action, many of the anti-inflammatory analgesic drugs share similar side effects. Hypersensitivity responses to aspirin-like drugs are thought to be due to an accumulation of prostaglandins after the pathways that break down prostaglandins are blocked. These responses can be fatal when very strong anti-inflammatory compounds are given. Inhibition of prostaglandin synthesis may result in other serious side effects, such as **peptic ulcers** and a reduced ability of platelets in the **blood** to **aggregate** and form clots. The latter effect, however, has given aspirin an added use as a prophylactic antithrombotic drug to reduce chances of cardiac or **cerebral** vascular **thrombosis**—the formation of a clot in a **blood vessel** in the heart or brain. Some aspirin-like analgesics also have specific toxic effects: **liver** damage occasionally occurs after administration of acetaminophen, and renal toxicity is sometimes seen with use of NSAIDs. Aspirin itself, taken in overdose, can cause **deafness**, ringing in the **ears**, **diarrhea**, **nausea**, and headache, which disappear when the dose is reduced or stopped. Aspirin is also thought to be a causative agent of **Reye syndrome**, a rare and serious degenerative disease of the brain and **fatty tissue** of the liver that accompanies certain viral infections in children and young adults.

The term opioid has been adopted as a general classification of all those agents that share chemical structures, sites, and mechanisms of action with the endogenous opioid agonists (endogenous substances are those produced inside the human body). Opioid substances **encompass** all the natural and **synthetic** chemical compounds closely related to **morphine**, whether they act as agonists (cellular activators) or **antagonists** (substances that block the actions of agonists). Although interest in these drugs had always been high because of their value in pain relief and because of problems of abuse and addiction, interest intensified in the 1970s and '80s by discoveries about the naturally occurring morphinelike substances, the endogenous opioid neuropeptides. **Opium** is the powder from the dried juice of the poppy *Papaver somniferum*. When taken orally, opium produces sleep and induces a state of peaceful well-being. Its use dates back at least to Babylonian civilization. In the early 19th century opium **extract** was found to contain more than 20 distinct complex organic bases, called **alkaloids**, of which morphine, **codeine**, and papaverine are the most important. These pure alkaloids replaced crude opium extracts in **therapeutics**.

In the 1950s several new morphinelike drugs were developed. Despite the increase in the number of compounds available for pain relief, however, little was understood of their sites and mechanisms of action. The first real breakthrough came from the discovery, by neuroscientists John W. Hughes and Hans W. Kosterlitz at the University of Aberdeen in Scotland, of two potent naturally occurring analgesic pentapeptides (peptides containing five linked amino acids) in extracts of pig brain. They called these compounds **enkephalins**, and since then at least six more have been found. Larger peptides, called **endorphins**, have been isolated, and these contain sequences of **amino acids** that can

be split off as enkephalins. There are at least three types of receptors on brain **neurons** that are activated by the enkephalins. Morphine and its congeners are thought to exert their effects by activating one or more of these receptors.

Opioid drugs are useful in the treatment of general postoperative pain, severe pain, and other specific conditions. The use of opioids to relieve the pain associated with **kidney stones** or **gallstones** presumably depends on their ability to affect opioid receptors in these tissues and to inhibit contractility. By a similar mechanism, opioids are also able to relieve the abdominal distress and fluid loss of **diarrhea**. Central receptors appear to account for the ability of morphine and **analogs** to suppress coughing, an effect that requires lower doses than those needed for **analgesia**. Low doses of opioids are also used for relief of the respiratory distress that accompanies acute cardiac insufficiency complicated by the buildup of fluid in the **lungs**.

Several commonly used natural or synthetic derivatives of morphine are used in drug therapeutics. **Codeine**, a naturally occurring opium alkaloid that can be made synthetically, is a useful oral analgesic, especially when used in combination with aspirin. **Meperidine** was an early synthetic **analog** of morphine, marketed under the trade name Demerol, that was originally thought to be able to provide significant short-lasting analgesia and little or no addiction because of its shortened duration of action; however, this belief proved false. **Methadone**, a synthetic opioid analgesic, has long-lasting analgesic effects (six to eight hours) when taken orally and is used to moderate the effects of **withdrawal** from **heroin** addiction. Among the opioid **antagonist** drugs, naloxone and its longer-lasting orally active version, naltrexone, are used primarily to reverse morphine overdoses and to reverse the chemical stupor of a wider variety of causes, including alcohol intoxication and anesthesia. In opioid overdoses, these drugs provide recovery within minutes of injection. They can, however, also precipitate severe withdrawal reactions in a person addicted to opiates.

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