

Analgesics

The terms *analgesics* and *analgetic drugs* are often used interchangeably to describe a diverse group of pain medications such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and triptans, each with very different mechanisms of action for relieving pains of a wide array of causes.

Analgesics can be broadly categorized, according to their therapeutic use, into several drug classes: (a) the opioids (or narcotic analgesics), which play a major role in the relief of acute pain and in the management of moderate to severe chronic pain; (b) the NSAIDs and acetaminophen, which are the most widely used analgesic drugs for relieving mild to moderate pain and reducing fever; (c) the triptans (the antimigraine medications), which are specifically designed and targeted for acute treatment of migraine and cluster headaches; and (d) a new emerging class of analgesics known as analgesic adjuvants that include tricyclic antidepressants such as amitriptyline, anticonvulsants such as gabapentin and pregabalin, and topical analgesics such as lidocaine patches that can be used to treat neuropathic pains.

Acute and Chronic pain:

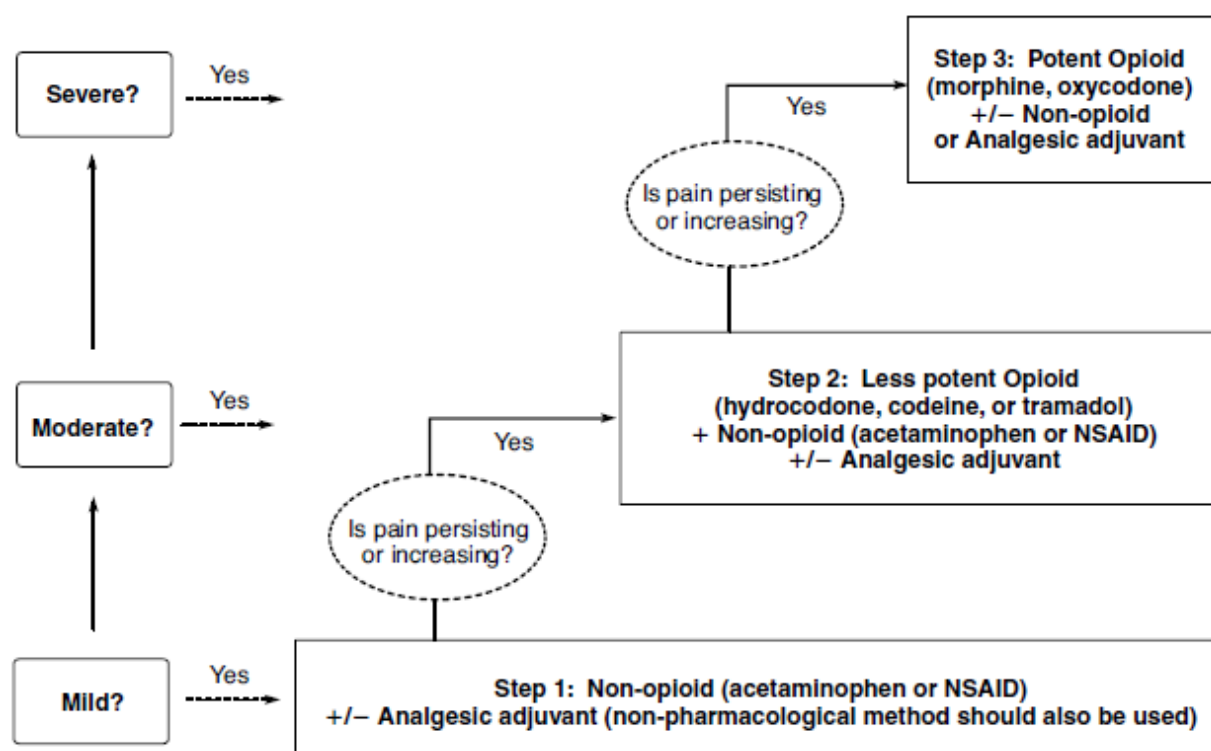
Pain may be acute or chronic. Acute pain is often severe but usually lasts only until the removal of the source that triggered the pain. Acute pain includes nociceptive, somatic, or visceral pain, postoperative and posttraumatic pain, burn pain, acute headache, etc. Acute and postoperative pains are most often treated with the opioid analgesics.

Chronic pain, on the other hand, is defined as a pain lasting longer than 6 months that persists even when the initial cause has been resolved through appropriate medical intervention. Chronic pain can be further divided into chronic malignant pain (e.g., cancer, amyotrophic lateral sclerosis, multiple sclerosis, end-stage organ failure) and chronic nonmalignant pain (e.g., lower-back pain, osteoarthritis (OA), rheumatoid arthritis (RA), migraine and chronic headache). Pain therapy in patients with chronic pain only provides transient pain relief but does not resolve the underlying pathological process.

Approaches to pain management:

According to the analgesic ladder model, the choice of analgesic therapy is based on assessment of pain intensity. Thus, nonopioid analgesics such as acetaminophen and NSAIDs are the drugs of choice for mild pain. The patients should continue on this regimen for as long as they are receiving adequate pain control, although an analgesic adjuvant may be added to help relieve the side effects associated with pain medications. For moderate pain, a combination of an NSAID (or acetaminophen) and a weak opioid such as codeine should be used.

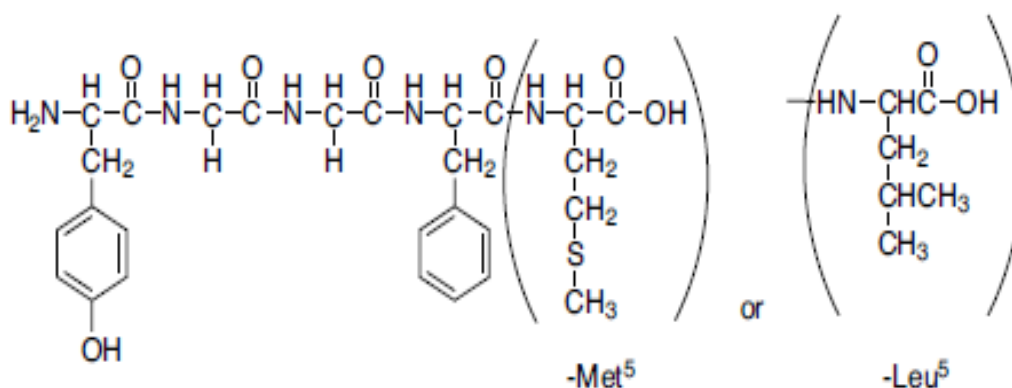
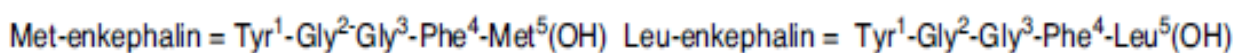
Morphine, fentanyl, and other potent opioids are reserved only for severe pain, especially in patients who are terminally ill, to control pain and to improve their quality of life.



World Health Organization (WHO) 3 steps Analgesic Ladder.

Opioid receptor and endogenous ligands:

The discovery and identification of endogenous substrates for the opioid receptor by Hughes in 1975 further confirmed the existence of an opioid receptor and intensified the SAR studies of the analgesic opioids. The first endogenous peptide was termed *enkephalin*, which was found to be a mixture of the two pentapeptides that only differ in their terminal amino acid: methionine-enkephalin (Met-enkephalin) and leucine-enkephalin (Leu-enkephalin)



SARs of Enkephalins:

TYR¹ (Tyrosine)

The first amino acid of the pentapeptide shows a distinct preference for tyrosine. Most changes to this amino acid, either by substituting with other amino acids or masking the phenolic hydroxyl (OH) or amino function, produce an inactive or weakly active peptide.

GLY² (Glycine)

Replacing the naturally occurring L-Gly with various D-amino acids produces a peptide that is resistant to peptide cleavage by aminopeptidases. Replacement with D-Ser (serine) is the most effective replacement, and all L-amino acid analogs had low activities. Substituting D-amino acids for L-amino acids produces stable peptides. Replacing the Gly² with D-Ala² (Alanine) while simultaneously replacing the L-Leu⁵ with D-Leu⁵ produces the peptide known as D-Ala², D-Leu⁵ enkephalin (DADLE), which is commonly used as a selective δ agonist.

GLY³

Almost all changes to this amino acid result in a drop in potency, unless they are also accompanied by another change such as replacing the Gly² with D-Ala² as described above.

PHE⁴ (phenylalanine)

The aromatic nature of the fourth residue is required for high activity. When combined with the D-Ala² replacement, the addition of an electron withdrawing, lipophilic substituent (e.g., NO₂, Cl, and Br) in the para position of Phe⁴ greatly increases activity. Para substitutions with electron donating, hydrophilic functional groups (e.g., NH₂ and OH) abolish activity.

MET⁵/LEU⁵

Position 5 appears to tolerate more residue changes than the other positions. Many amino acid substitutions at this position maintain activity (e.g., Ala, Gly, Phe, Pro: Proline)

Even the loss of the fifth residue to yield the tetrapeptide Tyr¹-Gly²-Gly³-Phe⁴ maintains weak activity.

Opioid Receptors:**The μ - Receptor:**

Mu receptors are found primarily in the brainstem and medial thalamus. Endogenous peptides for the μ - receptor include endomorphin-1, endomorphin-2, and β -endorphin. Exogenous agonists for the μ -receptor include drugs from the five structural classes (4,5-epoxymorphinan, morphinan, benzomorphan, 4-phenyl/4-anilido piperidines, and the diphenylheptanes) and exogenous peptides such as dermorphin isolated from the skin of South American frogs.

In general, agonists at the μ -receptor produce analgesia, respiratory depression, decreased gastrointestinal (GI) motility, euphoria, feeding. Agonists are also responsible for the addictive effects of the opioid analgesics. Most clinically used opioid drugs bind to the μ - opioid receptor.

The δ - Receptor:

Opioid peptides for the δ -receptor include the endogenous peptides described previously, Met and Leu enkephalin, as well as some synthetic peptides.

In addition, δ -receptor agonist shows antidepressant activity in rat models. These results suggest that ligands targeting this receptor may represent new leads for the treatment of schizophrenia, bipolar disorders, and depression.

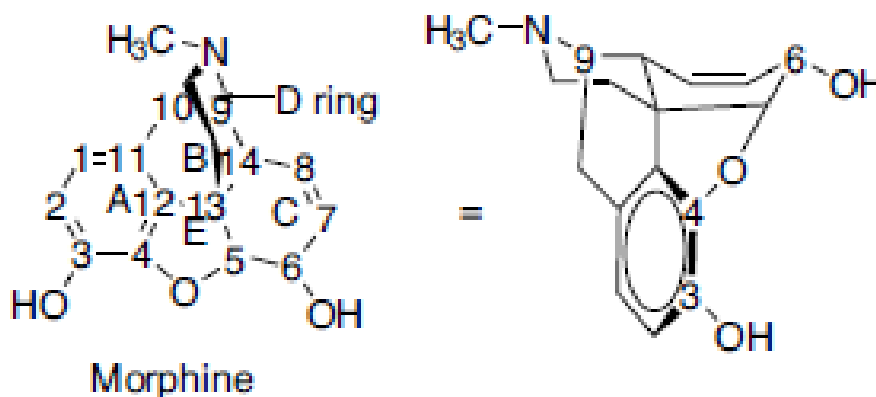
The κ - Receptor:

Kappa receptors are primarily found in the limbic, brain stem, and spinal cord. The κ -receptor shows less structural homology to the μ -receptor than the δ -receptor does. In clinical trials, most κ -agonists produce dysphoria and thus may be less psychologically addicting but also less acceptable to patients.

Drug monographs:

4, 5- Epoxymorphinans:

A summary of the SARs of the 4,5-epoxymorphinan structure can be seen below:



Changes on Morphine that increase analgesic activity

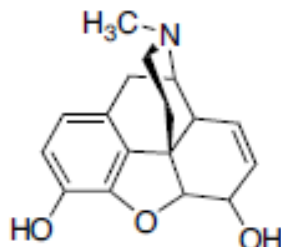
C6 - OH to OAc
C3 and C6 - OH to OAc
C6 - OH to O-Sulfate or O-glucuronide
C6 - OH to =O and C7-C8 single bond
C6 - OH to H and C7-C8 single bond
C14 - H to β OH
N - CH₃ to CH₂CH₂Ph
N - CH₃ to CH₂CH₂furan
N - CH₃ to CH₂C=OPh
Removal of C4-C5 ether link

Changes on Morphine that produce antagonists

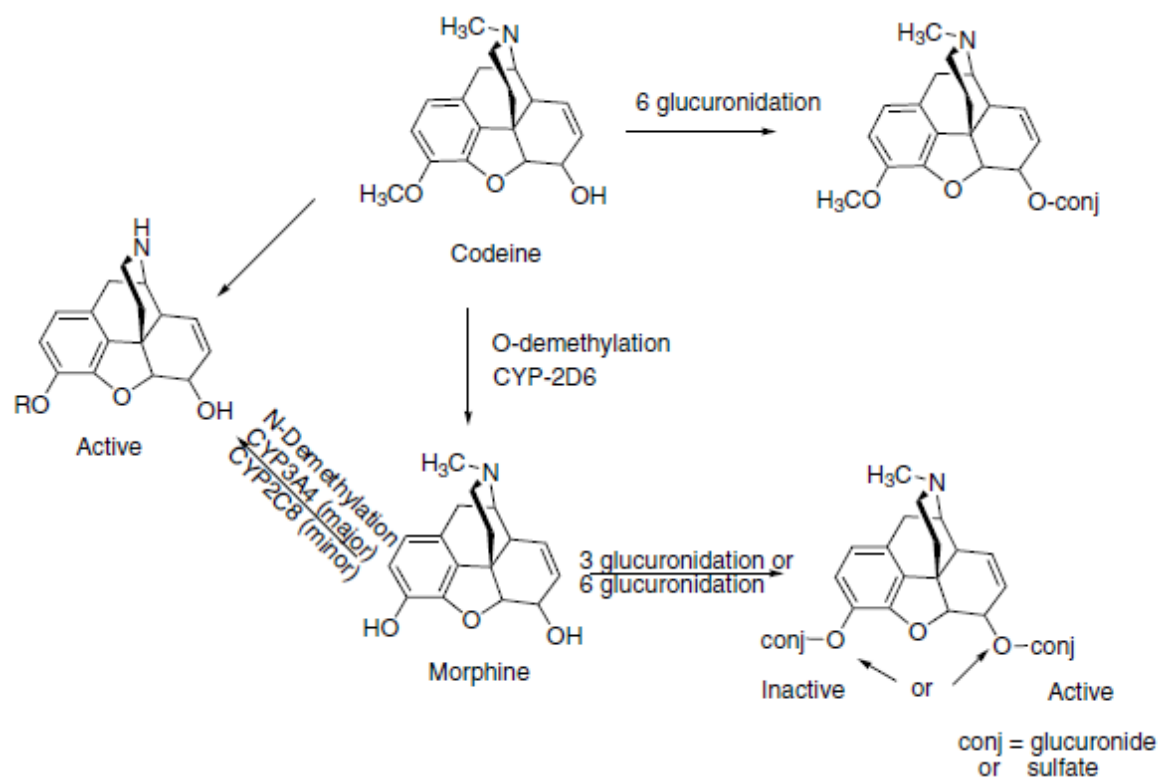
N - CH₃ to CH₂CH=CH₂
N - CH₃ to CH₂—

Summary of functional group changes on morphine structure**Morphine:**

The prototype ligand for the μ -receptor is morphine.

**Structure of Morphine**

Morphine is extensively metabolized via phase II conjugation to morphine-3-glucuronide (60%), morphine-6-glucuronide (9%), and, to a lesser extent, the *N*-demethylated metabolite (3%). Much controversy exists on the contribution of the metabolites of both codeine-6-glucuronide and morphine-6-glucuronide to their analgesic effect. In some studies, the 6-glucuronide metabolite of both drugs contributes significantly to their potency. In other studies, the 6-glucuronide metabolites of morphine and codeine produces very little analgesic effect. Morphine, or another potent opioid drug, is introduced in the WHO stepladder when pain is severe and no relief is obtained from NSAIDs or a combination of NSAIDs and a less potent opioid.

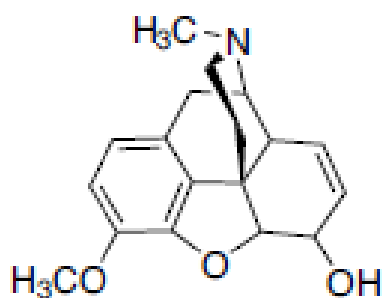


Metabolism of Morphine and Codeine

Codeine:

Codeine is an alkaloid that occurs naturally in opium, but the amount present is usually too small to be of commercial importance. Consequently, most commercial codeine is prepared from morphine by methylating the phenolic OH group.

The general pharmacological action of codeine is similar to that of morphine, but it does not possess the same analgesic potency. Approximately 5% of codeine is metabolized to morphine via *O*-demethylation.



Structure of Codeine