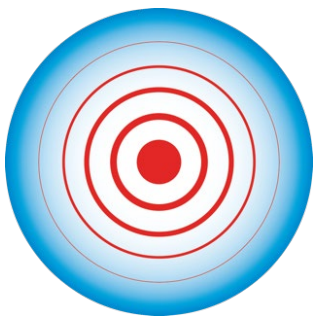
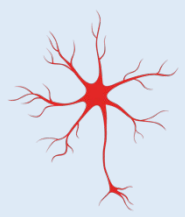


What is Pain? [1, 2, 3]

Pain is defined by the *International Association for the Study of Pain* as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". It can be classified according to cause or duration.

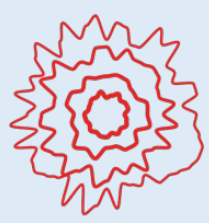


Nociceptive pain arises in the tissues and is transmitted to the brain by the nervous system. This is the type of pain that most people are familiar with (ex. bee stings, burns, and repetitive strain injuries).

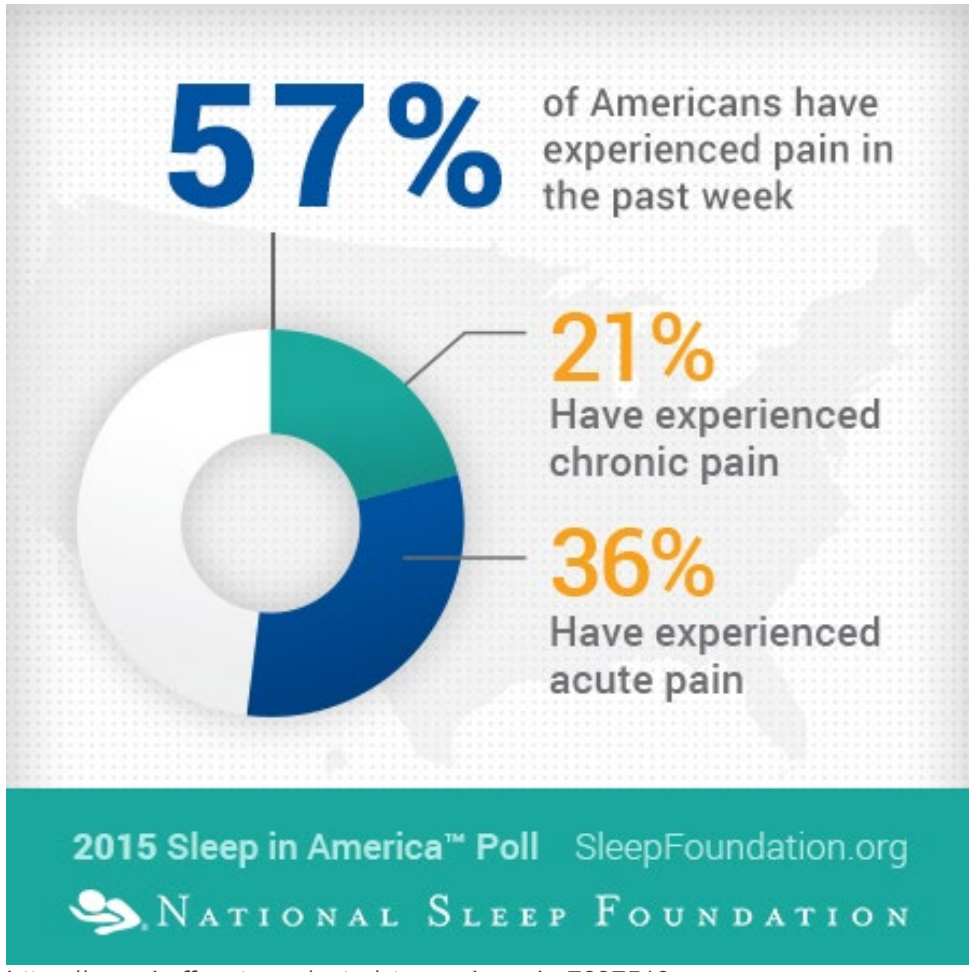
Inflammatory pain results from the activation of the nociceptive pain pathway by mediators released at the site of inflammation

Neuropathic pain originates in the nervous system itself. Anything that damages neurons, such as multiple sclerosis, chemotherapy and alcoholism can result in this type of pain. Since nerves do not heal well, neuropathic pain is likely to result in chronic pain.

Acute pain is associated with sudden onset and limited duration (lasts up to weeks or months). It usually resolves with the healing of the underlying cause. However, acute pain may not always resolve, and it result in chronic pain. This is common when the pain is due to a more serious disease or condition, or when the injury is not treated in time.



Chronic pain is ongoing pain that usually last longer than 6 months. It can continue even after the underlying injury has healed. However, some people do suffer from chronic pain without having a past injury. This type of pain is linked to conditions such as nerve pain, back pain, arthritis and cancer.

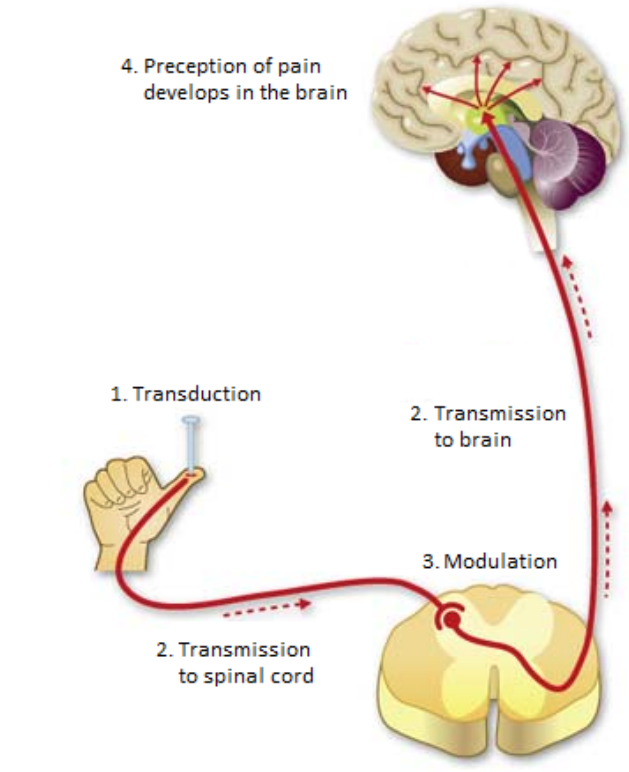


https://www.huffpost.com/entry/stress-sleep_b_7637510

Mechanism of Pain: [4]

The pain pathway consists of 4 steps:

1. **Transduction** is the process by which the stimulus (ex. pricking of needle) activates the nerve endings.
2. **Transmission** is when the nerve impulses are sent to the spinal cord and brain.
3. **Modulation** is the process of amplifying OR dampening the pain-related neural signals.
4. **Perception** is the *subjective* experience of pain that results for an individual.



https://www.change-pain.com/grt-change-pain-portal/change_pain_home/chronic_pain/physician/physician_tools/picture_library/en_EN/312500026.jsp

Importance of mitigating pain: [5, 6]

Pain is the most frequent reason for physician consultation in the US. Also, it is the 2nd leading cause of medically-related work absenteeism in the US, resulting in more than 50 million lost workdays yearly. According to a study by the World Health Organization (WHO), individuals who live with persistent pain are 4 times more likely than those without pain to suffer from depression or anxiety, and more than 2 times as likely to have difficulty working. Chronic pain, specifically, has been linked to restrictions in mobility & daily activities, dependence on opioids, anxiety, depression, and ultimately reduced quality of life. [1]

Oral/Systemic Treatment Options:

OTC Non-Opioids[7]

NSAIDs (ex. naproxen, aspirin, ibuprofen, celecoxib, diclofenac, meloxicam, ketoprofen, nimesulide)

- NSAIDs work by inhibiting cyclooxygenase (COX) enzymes. COX-1 is needed for the normal functioning of the GI, kidneys and platelets. COX-2, on the other hand, is more associated with pain and inflammation. NSAIDs differ in their selectivity for the COX enzymes, which causes variation in their side-effect profiles.
- Adverse events include nausea, GI risk (ulceration, bleeding), cardiovascular risk (increased risk of MI and stroke), increased blood pressure, decreased renal clearance, increased risk of a CV event after coronary artery bypass graft (CABG) surgery, premature closure of the ductus arteriosus in the third trimester of pregnancy, and CNS effects (e.g. dizziness)
- COX-2 selective NSAIDs (celecoxib, diclofenac, meloxicam) are known to have a lower risk of GI complications, but a higher risk of cardiovascular complications, as compared to non-selective NSAIDs (naproxen, ibuprofen)

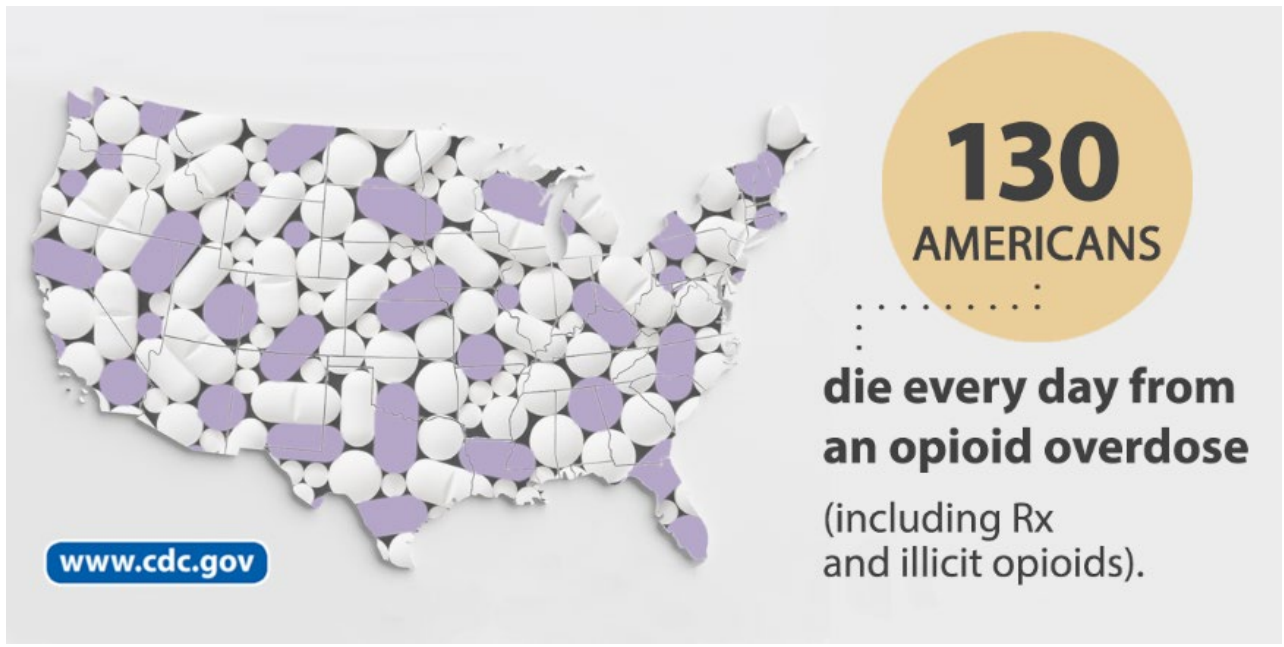
Acetaminophen

- The mechanism of action is not completely understood.
- One of the main differentiating factors between acetaminophen and NSAIDs is that acetaminophen is not an anti-inflammatory agent.
- Acetaminophen has a boxed warning of hepatotoxicity.
- Adverse events include severe skin rash and nephrotoxicity (rare – usually with chronic overdose)

Pain Reliever	Analgesic	Antipyretic	Anti-inflammatory
NSAID	✓	✓	✓
Acetaminophen	✓	✓	⊘

Prescription Opioids[8]

- Opioids produce pain relief by blocking mu receptors in the central nervous system (CNS)
- Opioids are usually reserved for mild to severe pain
- Boxed warnings include addiction, abuse, misuse, respiratory depression, and increased risk of death if used with benzodiazepines
- From 1999 to 2017, almost 400,000 people died from an opioid (prescription or illicit use) overdose
- If opioids are used for chronic pain, it is recommended to combine them with nonpharmacologic therapy and nonopioid pharmacologic therapy (ex. NSAIDs, acetaminophen)



https://www.cdc.gov/drugoverdose/epidemic/index.html

Adjuvants[7]

Prescription medications that can be used for pain, even though they are not indicated for pain (ex. antidepressants, antiepileptics, muscle relaxants)

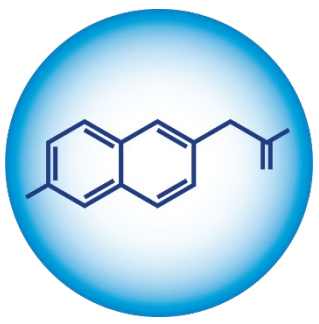
Topical Treatment Options:

Classes of topical pain medications	Brands	Available OTC
NSAIDs (diclofenac)	Voltaren®	✓
Counterirritants (capsaicin, menthol, camphor, salicylates): create a	Biofreeze®; Bengay®; Salonpas®; Icy	✓

warming or cooling sensation that distracts from the sensation of pain	Hot®; Aspercreme®	
Local Anesthetics (lidocaine): dampen peripheral nociceptor sensitization	Salonpas®; Icy Hot; Aspercreme®	✔
	Lidoderm®	
Opioids (fentanyl, buprenorphine)	Duragesic®; Butrans®	
α_2-adrenergic agent (clonidine hydrochloride)	Catapres®	

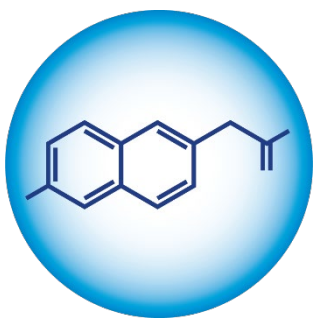
Absorption, Distribution, Metabolism, and Excretion: A Summary of Pharmacokinetics[9]

Naproxen sodium quickly dissolves and is rapidly and completely absorbed from the GI tract. It builds up in the blood plasma and begins working within 30-60 minutes after taking the medication. Naproxen sodium reaches peak blood plasma levels approximately 1 hour after intake. It is metabolized by the liver and mostly excreted by the kidneys, meaning that kidney disease or impairment can prevent naproxen elimination and cause a buildup of the medication in the body. It should be noted, however, that no significant risk of kidney damage by naproxen sodium has been observed when it is taken at low, non-prescription doses,[10] especially when taken for the duration recommended on the drug facts label.[11]



Naproxen Vs. naproxen sodium. What's the difference?[9]

As previously described, naproxen is an NSAID. It is a nonselective COX inhibitor, meaning it inhibits both COX-1 and COX-2. Two forms of naproxen are readily available: naproxen as a free acid (known as "naproxen") or a sodium salt (known as "naproxen sodium"). The body reaches peak levels of naproxen free acid in 2–4 hours and naproxen sodium in 1–2 hours, meaning that it absorbs naproxen sodium from the GI tract faster than regular naproxen.



Currently Available Formulations

Naproxen sodium exists in numerous forms, including an immediate-release liquid gel capsule, tablet, caplet (a capsule-shaped tablet), capsule, and most recently an extended-release tablet. The dosage of the different formulations also vary. Naproxen sodium is generally available in 220 mg capsules and tablets over the counter (US), 275 mg and 550 mg tablets, and in combination with other ingredients such as diphenhydramine (sleep aid), used for pain relief and occasional sleeplessness due to minor pain in the United States. It is also available in combination with pseudoephedrine for the treatment of nasal congestion and other common cold and flu symptoms

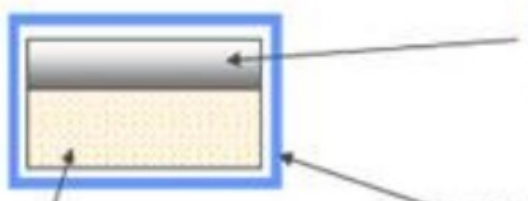
A new formulation, naproxen sodium 660 mg extended release tablet, became available in recent years. This product is different from immediate release naproxen sodium. In this formulation, the tablet is made up of two layers. The first layer releases the drug immediately upon ingestion, while the second layer is surrounded by a special coating that controls the rate of dissolution of the tablet, providing a slower release of the drug over 16 hours. The goal of this formulation was to develop a single dose tablet capable of providing 24 hours of pain relief, with the convenience of once-daily dosing. Other immediate release naproxen sodium products require patients to re-dose after 8-12 hours, and certain pain conditions may require the use of a pain medication for 24 hours or more.

See below for the attributes of this extended release formulation of naproxen sodium:

Bi-layer tablet (40% IR and 60% ER) – total of 660 mg

Immediate release layer – 264 mg

Extended release layer – 396 mg



Immediate-release (IR) layer
Contains 40% of total dose (264 mg)

Film coating

Extended-release (ER) layer
Contains 60% of total dose (396 mg)
Formulated with 30% hypromellose (HPMC), which controls the rate of dissolution
Designed to release over a period of approximately 16 hours

[1] Katz N. Cleveland Clinic. (2020). *Acute Pain vs. Chronic Pain*. [online] Available at: https://my.clevelandclinic.org/health/articles/12051-acute-vs-chronic-pain.
[2] International Association for the Study of Pain. IASP Terminology. Available at: https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Neuropathicpain.
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[6] Dahlhamer J, Lucas J, Zelaya, C, et al. Prevalence of chronic pain and high-impact chronic pain among adults, 2016. MMWR Morb Mortal Wkly Rep 2018;67:1001–1006. Available from: http://dx.doi.org/10.15585/mmwr.mm6736a2.
[7] Portenoy RK. Current pharmacotherapy of chronic pain. J Pain Symptom Manage. 2000 Jan;19(1):S16-20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10687334.
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[9] Naproxen Oral (Drug Facts And Comparisons). *Facts and Comparisons.* 2020 Feb 13.
[10] Watson WA, Freer JP, Katz RS, Basch C. Kidney function during naproxen therapy in patients at risk for renal insufficiency. Seminars in Arthritis and Rheumatism. 1988;17(3):12-16. Available from: http://doi:10.1016/0049-0172(88)90039-x.
[11] Bayer HealthCare. Aleve Tablets. *Drug Facts Label.* Accessed 2020 Feb 18.