



Because pain is universally understood as a signal of disease, it is the most common symptom that brings a patient to a physician's attention.

The function of the pain sensory system is to protect the body and maintain homeostasis.

The quality, time course, and location of a patient's pain complaint and the location of tenderness provide important diagnostic clues and are used to evaluate the response to treatment.

It does this by detecting, localizing, and identifying tissue-damaging processes.

Once this information is obtained, it is the obligation of the physician to provide rapid and effective pain relief.

PAIN: PATHOPHYSIOLOGY AND MANAGEMENT



THE PAIN SENSORY SYSTEM



- Pain is an unpleasant sensation localized to a part of the body.
- It is often described in terms of a penetrating or tissue-destructive process (e.g., stabbing, burning, twisting, tearing, squeezing) and/or of a bodily or emotional reaction (e.g., terrifying, nauseating, sickening).



THE PAIN SENSORY SYSTEM



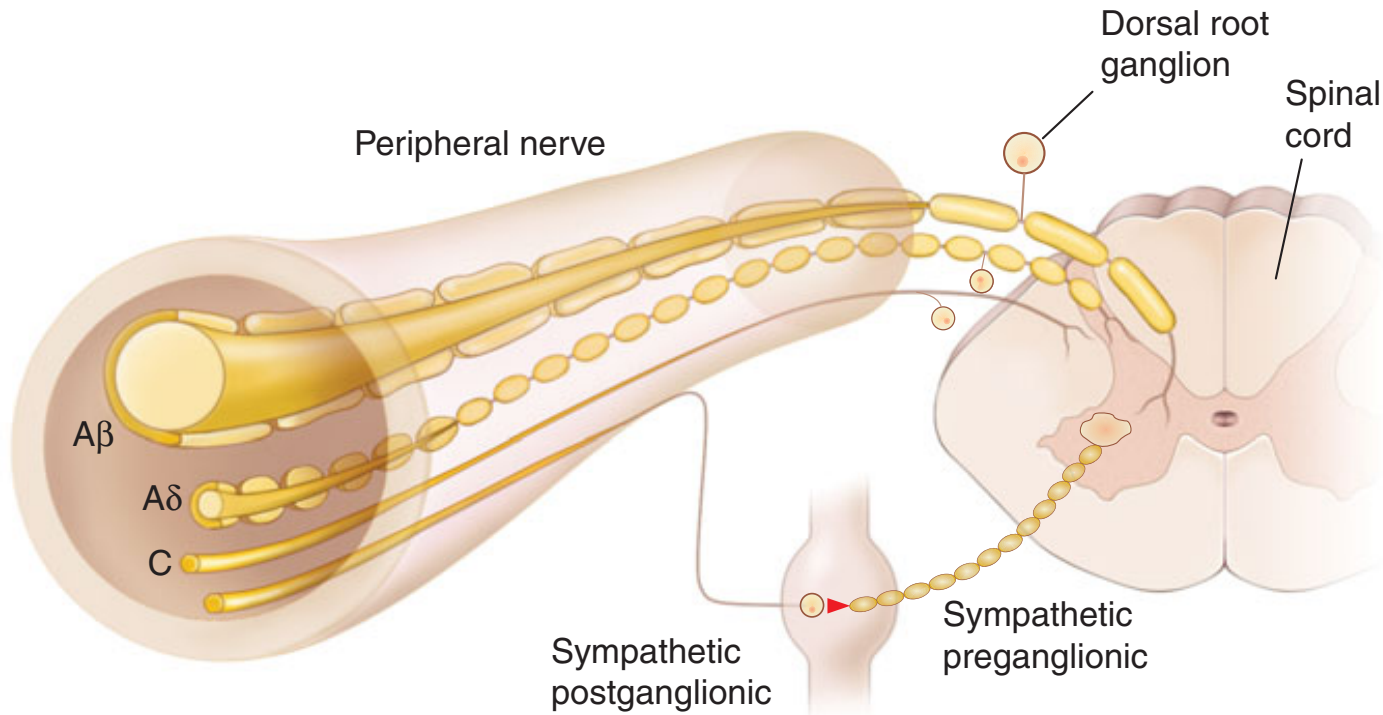
- Any pain of moderate or higher intensity is accompanied by anxiety and the urge to escape or terminate the feeling.
- These properties illustrate the duality of pain: it is both sensation and emotion. Fear is a constant companion of pain.





PERIPHERAL MECHANISMS

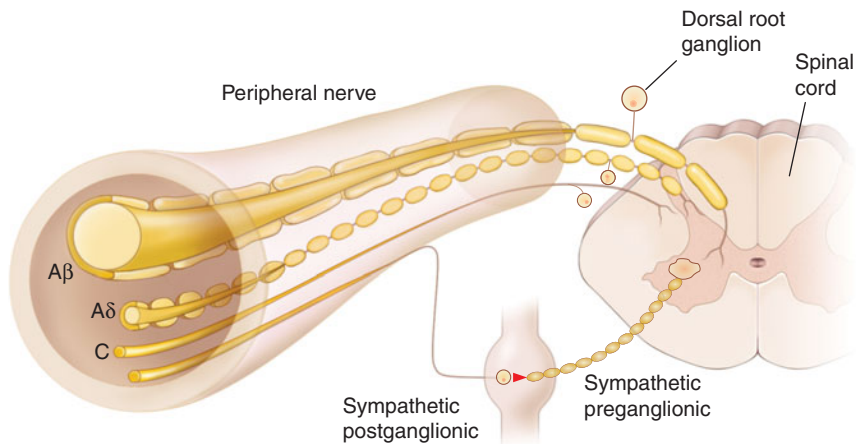
The Primary Afferent Nociceptor



Components of a typical cutaneous nerve



The Primary Afferent Nociceptor



- The largest-diameter fibers, A-beta ($A\beta$), respond maximally to light touch and/or moving stimuli; they are present primarily in nerves that innervate the skin.
- The small-diameter myelinated A-delta ($A\delta$) and the unmyelinated (C fiber) axons are present in nerves to the skin and to deep somatic and visceral structures.



PERIPHERAL MECHANISMS

Sensitization

- A large proportion of A δ and C afferents innervating viscera are completely insensitive in normal noninjured, noninflamed tissue.
- However, in the presence of inflammatory mediators, these afferents become sensitive to mechanical stimuli. Such afferents have been termed ***silent nociceptors***.
- Low pH, prostaglandins, leukotrienes, and other inflammatory mediators such as bradykinin play a significant role in sensitization.



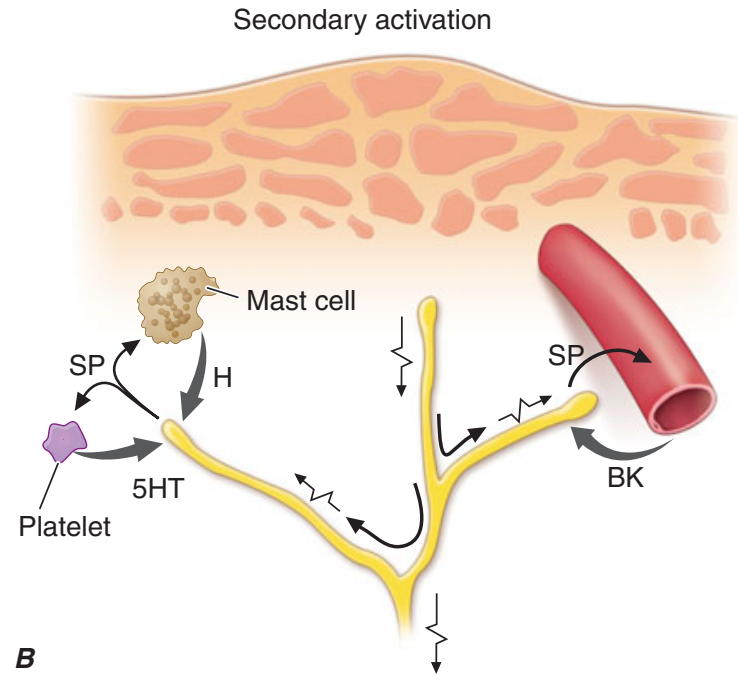
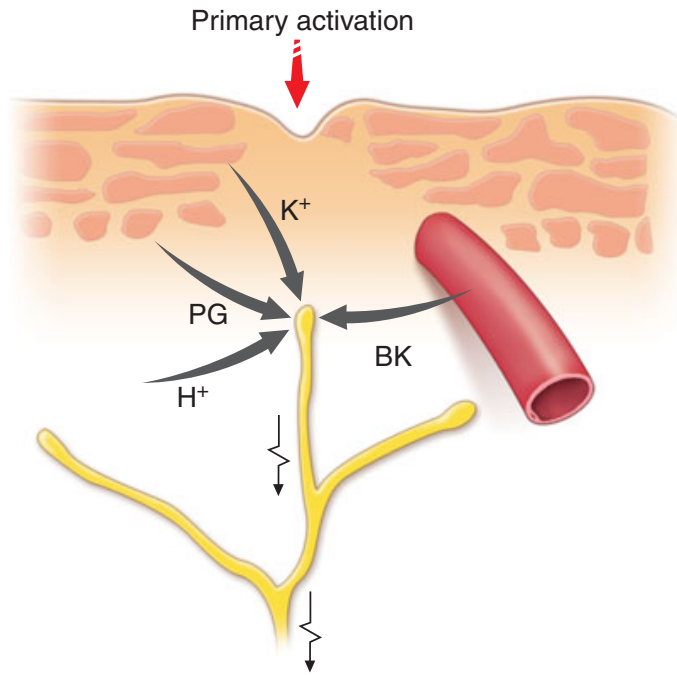


PERIPHERAL MECHANISMS



A. Primary activation

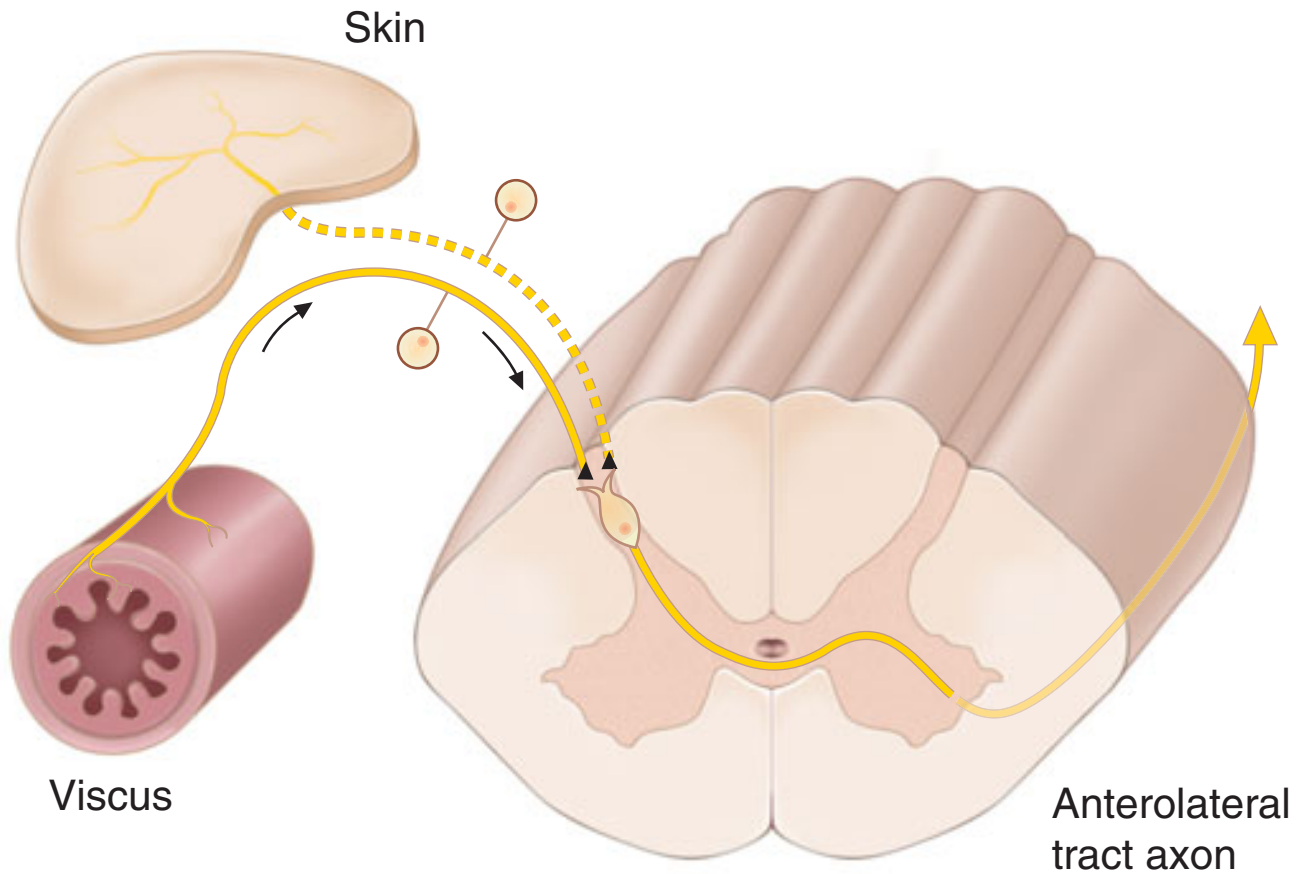
B. Secondary activation.





CENTRAL MECHANISMS

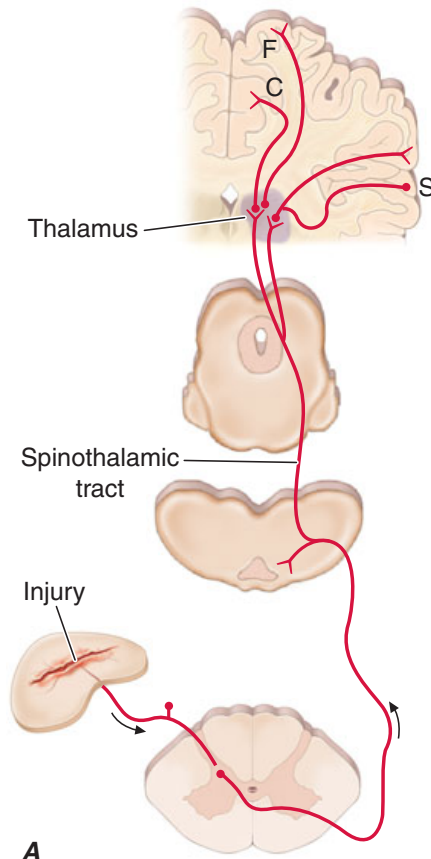
The Spinal Cord and Referred Pain



GLUTAMATE!

+ Pain transmission and modulatory pathways

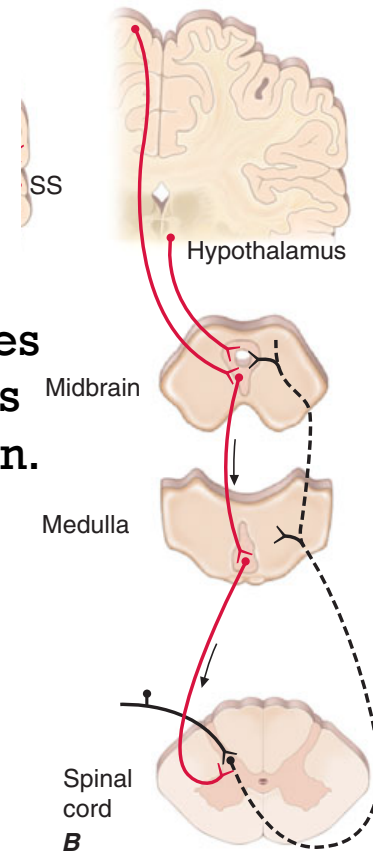
A. Nociceptive transmission system



B. Pain-modulation network.

OPIOID RECEPTORS

endogenous opioid peptides
- enkephalins
- β -endorphin.



+ NEUROPATHIC PAIN

- Neuropathic pains typically have an unusual burning, tingling, or electric shock–like quality and may be triggered by very light touch.
- On examination, a sensory deficit is characteristically present in the area of the patient's pain.
- Hyperpathia is also characteristic of neuropathic pain; patients often complain that the very lightest moving stimuli evoke exquisite pain (allodynia).

+ NEUROPATHIC PAIN

Sympathetically Maintained Pain

- Patients with peripheral nerve injury can develop a severe burning pain (**causalgia**) in the region innervated by the nerve.
- The pain typically begins after a delay of hours to days or even weeks.
- The pain is accompanied by swelling of the extremity, periarticular osteoporosis, and arthritic changes in the distal joints.
- The pain is dramatically and immediately relieved by blocking the sympathetic innervation of the affected extremity.

+ NEUROPATHIC PAIN

Sympathetically Maintained Pain

- Damaged primary afferent nociceptors acquire adrenergic sensitivity and can be activated by stimulation of the sympathetic outflow.
- A similar syndrome called ***reflex sympathetic dystrophy*** can be produced without obvious nerve damage by a variety of injuries, including fractures of bone, soft tissue trauma, myocardial infarction, and stroke.
- The pain is accompanied by swelling of the extremity, periarticular osteoporosis, and arthritic changes in the distal joints.
- This implies that sympathetic activity can activate undamaged nociceptors when inflammation is present.



Treatment :

ACUTE PAIN



- The ideal treatment for any pain is to remove the cause; thus, diagnosis should always precede treatment planning.
- Sometimes treating the underlying condition does not immediately relieve pain.
- Furthermore, some conditions are so painful that rapid and effective analgesia is essential (e.g., the postoperative state, burns, trauma, cancer, sickle cell crisis).
- Analgesic medications are a first line of treatment in these cases, and all practitioners should be familiar with their use.



Treatment :

ACUTE PAIN

ASPIRIN, ACETAMINOPHEN, AND NON-STEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)

These drugs are considered together because they are used for similar problems and may have a similar mechanism of action.

All these compounds inhibit cyclooxygenase (COX), and, except for acetaminophen, all have anti-inflammatory actions, especially at higher dosages.

They are particularly effective for mild to moderate headache and for pain of musculoskeletal origin.





DRUGS FOR RELIEF OF PAIN

Nonnarcotic Analgesics: Usual Doses and Intervals

GENERIC NAME	DOSE, mg	INTERVAL	COMMENTS
Acetylsalicylic acid	650 PO	q 4 h	Enteric-coated preparations available
Acetaminophen	650 PO	q 4 h	Side effects uncommon
Ibuprofen	400 PO	q 4-6 h	Available without prescription
Naproxen	250–500 PO	q 12 h	Delayed effects may be due to long half-life
Fenoprofen	200 PO	q 4-6 h	Contraindicated in renal disease
Indomethacin	25–50 PO	q 8 h	Gastrointestinal side effects common
Ketorolac	15–60 IM/IV	q 4-6 h	Available for parenteral use
Celecoxib	100–200 PO	q 12 – 24 h	Useful for arthritis
Valdecoxib	10–20 PO	q 12 – 24 h	Removed from U.S. market in 2005



Treatment :

ACUTE PAIN



OPIOID ANALGESICS

- Opioids are the most potent pain-relieving drugs currently available.
- Furthermore, of all analgesics, they have the broadest range of efficacy, providing the most reliable and effective method for rapid pain relief.
- Although side effects are common, they are usually not serious except for respiratory depression and can be reversed rapidly with the narcotic antagonist naloxone.

+ DRUGS FOR RELIEF OF PAIN

Narcotic Analgesics: Usual Doses and Intervals

GENERIC NAME	PARENTERAL DOSE, mg	PO DOSE, mg	COMMENTS
Codeine	30-60 q 4 h	30-60 q 4 h	Nausea common
Oxycodone	-	5-10 q 4-6 h	Usually available with acetaminophen or aspirin
Morphine	10 q 4 h	60 q 4 h	
Morphine sustained release	-	30-200 bid to tid	Oral slow-release preparation
Hydromorphone	1-2 q 4 h	2-4 q 4 h	Shorter acting than morphine sulfate
Levorphanol	2 q 6-8 h	4 q 6-8 h	Longer acting than morphine sulfate; absorbed well PO
Methadone	10 q 6-8 h	20 q 6-8 h	Delayed sedation due to long half-life
Meperidine	75-100 q 3-4 h	300 q 4 h	Poorly absorbed PO; normeperidine a toxic metabolite Intranasal spray
Butorphanol	-	1-2 q 4 h	Removed from U.S. market in 2005
Fentanyl	25-100 µg/h	-	72-h Transdermal patch
Tramadol	-	50-100 q 4-6 h	Mixed opioid/adrenergic action



Treatment :

ACUTE PAIN



OPIOID ANALGESICS

- Opioids produce analgesia by actions in the central nervous system.
- They activate pain-inhibitory neurons and directly inhibit pain-transmission neurons.
- Most of the commercially available opioid analgesics act at the same opioid receptor (μ -receptor), differing mainly in potency, speed of onset, duration of action, and optimal route of administration.



Treatment :

ACUTE PAIN



OPIOID ANALGESICS

- *The most common error made by physicians in managing severe pain with opioids is to prescribe an inadequate dose. Since many patients are reluctant to complain, this practice leads to needless suffering.*
- In the absence of sedation at the expected time of peak effect, a physician should not hesitate to repeat the initial dose to achieve satisfactory pain relief.



CHRONIC PAIN



- Managing patients with chronic pain is intellectually and emotionally challenging.
- The patient's problem is often difficult to diagnose; such patients are demanding of the physician's time and often appear emotionally distraught.
- The traditional medical approach of seeking an obscure organic pathology is usually unhelpful.

+ Treatment :

CHRONIC PAIN

- Important is to identify specific and realistic functional goals for therapy, such as getting a good night's sleep, being able to go shopping, or returning to work.
- A multidisciplinary approach that utilizes medications, counseling, physical therapy, nerve blocks, and even surgery may be required to improve the patient's quality of life.
- There are no set criteria for predicting which patients will respond to these procedures.

+ Treatment :

CHRONIC PAIN



ANTIDEPRESSANT MEDICATIONS

- The tricyclic antidepressants [*amitriptyline, imipramine, nortriptyline, desipramine* (TCAs)] are extremely useful for the management of patients with chronic pain.
- TCAs has a more rapid onset and occurs at a lower dose than is typically required for the treatment of depression.
- Furthermore, patients with chronic pain who are not depressed obtain pain relief with antidepressants.



DRUGS FOR RELIEF OF PAIN

Antidepressants^a

GENNERIC NAME	UPTAKE BLOCKADE		SEDATIVE POTENCY	ANTI-CHOLINERGIC POTENCY	ORTHO-STATIC HYPO-TENSION	CARDIAC ARRHYH-MIA	AVE. DOSE, mg/d	RANGE, mg/d
	5-HT	NE						
Doxepin	++	+	High	Moderate	Moderate	Less	200	75-400
Amitriptyline	++++	++	High	Highest	Moderate	Yes	150	25-300
Imipramine	++++	++	Moderate	Moderate	High	Yes	200	75-400
Nortriptyline	+++	++	Moderate	Moderate	Low	Yes	100	40-150
Desipramine	+++	++++	Low	Low	Low	Yes	150	50-300
Venlafaxine	+++	++	Low	None	None	No	150	75-400
Duloxetine	+++	+++	Low	None	None	No	40	30-60

^a *Antidepressants, anticonvulsants, and antiarrhythmics have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain.*

^b *Gabapentin in doses up to 1800 mg/d is FDA approved for postherpetic neuralgia.*
Note: 5-HT, serotonin; NE, norepinephrine.



PAINFUL CONDITIONS THAT RESPOND TO TRICYCLIC ANTIDEPRESSANTS

Postherpetic neuralgia^a

Diabetic neuropathy^a

Tension headache^a

Migraine headache^a

Rheumatoid arthritis^{a,b}

Chronic low back pain^b

Cancer

Central post-stroke pain

^a**Controlled trials demonstrate analgesia.**

^b**Controlled studies indicate benefit but not analgesia.**

+ Treatment :

CHRONIC PAIN

ANTICONVULSANTS AND ANTIARRHYTHMICS

- These drugs are useful primarily for patients with neuropathic pain. Phenytoin (Dilantin) and carbamazepine (Tegretol) were first shown to relieve the pain of trigeminal neuralgia.
- Newer anticonvulsants, gabapentin (Neurontin) and pregabalin (Lyrica), are effective for a broad range of neuropathic pains.
- Antiarrhythmic drugs such as low-dose lidocaine and mexiletine (Mexitil) can also be effective for neuropathic pain. These drugs block the spontaneous activity of damaged primary afferent nociceptors.



DRUGS FOR RELIEF OF PAIN

Anticonvulsants and Antiarrhythmics^a

GENERIC NAME	PO DOSE, mg	INTERVAL
Phenytoin	300	daily/qhs
Carbamazepine	200–300	q 6 h
Oxcarbazepine	300	bid
Clonazepam	1	q 6 h
Gabapentin ^b	600–1200	q 8 h
Pregabalin	150–600	bid

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+ Treatment :

CHRONIC PAIN

CHRONIC OPIOID MEDICATION

- The long- term use of opioids is accepted for patients with pain due to malignant disease.
- Although opioid use for chronic pain of nonmalignant origin is controversial, it is clear that for many such patients opioid analgesics are the best available option.
- Therefore, before embarking on opioid therapy, other options should be explored, and the limitations and risks of opioids should be explained to the patient.

+ Treatment :

CHRONIC PAIN

CHRONIC OPIOID MEDICATION

- With long-term outpatient use of orally administered opioids, it is desirable to use long-acting compounds such as levorphanol, methadone, or sustained-release morphine.
- Transdermal fentanyl is another excellent option.
- The pharmacokinetic profile of these drug preparations enables prolonged pain relief, minimizes side effects such as sedation that are associated with high peak plasma levels, and reduces the likelihood of rebound pain associated with a rapid fall in plasma opioid concentration.

+ TREATMENT OF NEUROPATHIC PAIN

- It is important to individualize treatment for patients with neuropathic pain.
- The first is to move quickly to provide relief.
- A second is to minimize drug side effects.
- A primary responsibility of all physicians is to minimize the physical and emotional discomfort of their patients.





Q & A

