

# Treatment of Neuropathic Pain

Pamela Pierce Palmer, MD PhD

Medical Director, UCSF Pain Management Center

Professor, Dept. of Anesthesia, UCSF

---

---

---

---

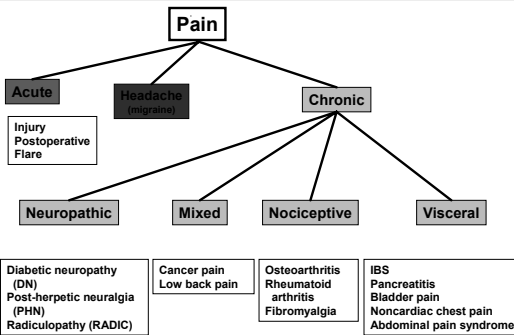
---

---

---

---

## Pain Classification



---

---

---

---

---

---

---

---

## Definitions

- **Nociceptive pain**
  - Pain transmitted by normal physiologic pathways; starting with skin or joint transducers, via peripheral nerves to the CNS (eg, arthritis, myofascial pain)
- **Neuropathic pain**
  - Pain initiated or caused by a primary lesion or dysfunction in the nervous system (eg, painful diabetic neuropathy, post-herpetic neuralgia)

---

---

---

---

---

---

---

---

## Neuropathic Pain from Breast Cancer

- Brachial plexus - radiation injury, tumor invasion
- Peripheral neuropathy - chemotherapy
- Spinal nerve compression - metastatic lesions to the spine
- Central neuropathic pain - metastatic lesions to brain
- Local breast pain - surgical nerve injury

---

---

---

---

---

---

---

---

## Characteristics of Neuropathic Pain

- Lancing, paroxysmal
- Burning, constant
- Cramping/aching
- Hyperalgesia
- Allodynia
- Hyperpathia

---

---

---

---

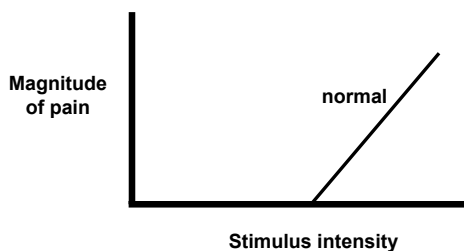
---

---

---

---

## Pathologic Pain Functions



---

---

---

---

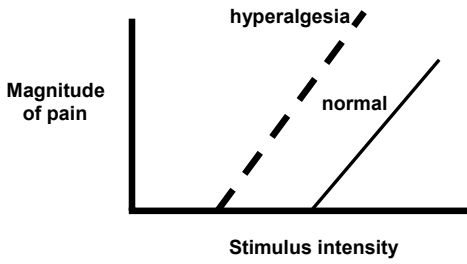
---

---

---

---

### Pathologic Pain Functions



---

---

---

---

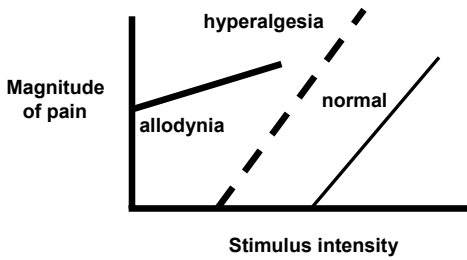
---

---

---

---

### Pathologic Pain Functions



---

---

---

---

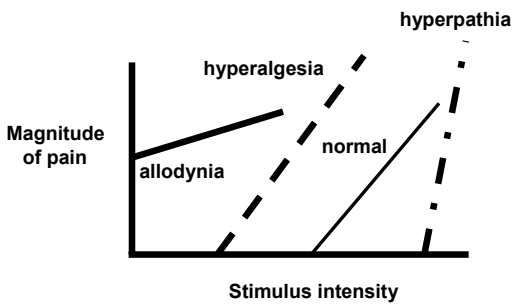
---

---

---

---

### Pathologic Pain Functions



---

---

---

---

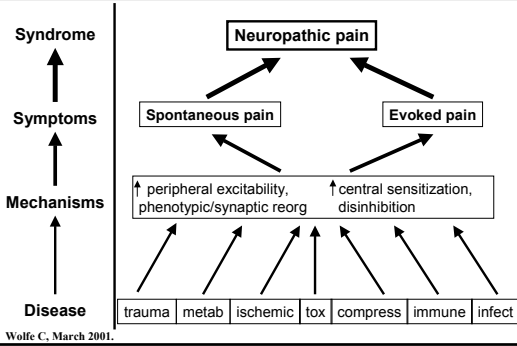
---

---

---

---

## Approach to Neuropathic Pain




---

---

---

---

---

---

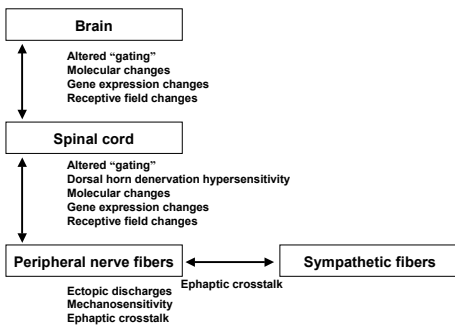
---

---

---

---

## Postulated Mechanisms Involved in Sustaining Neuropathic Pain




---

---

---

---

---

---

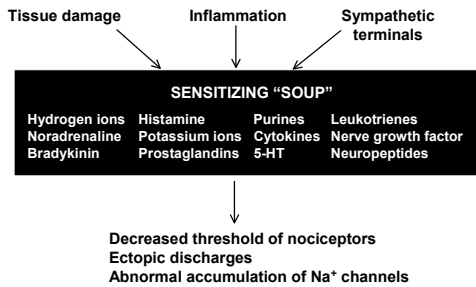
---

---

---

---

## Peripheral Sensitization



Adapted from Siddal, Cousins. In: Cousins, Bridenbaugh, eds. *Neural Blockade*. 1998:675-699.

---

---

---

---

---

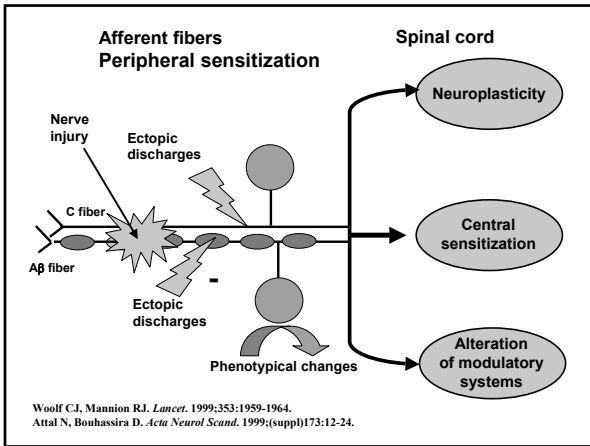
---

---

---

---

---




---

---

---

---

---

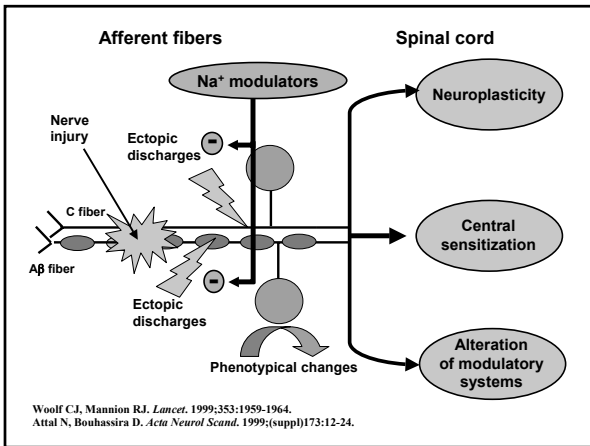
---

---

---

---

---




---

---

---

---

---

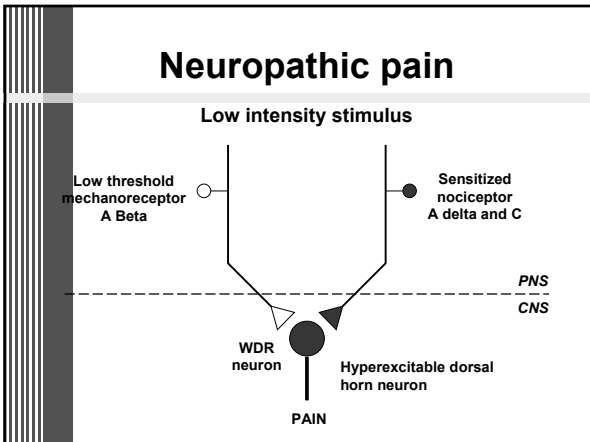
---

---

---

---

---




---

---

---

---

---

---

---

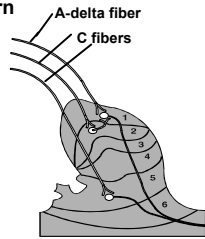
---

---

---

# Neuroanatomy of Pain Pathways

Spinal cord  
Dorsal horn




---

---

---

---

---

---

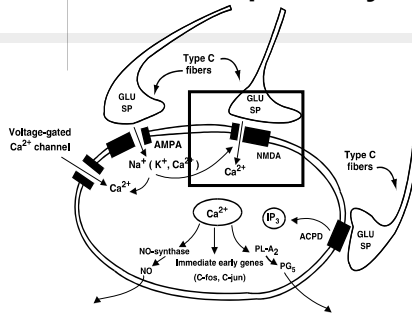
---

---

---

---

# WDR neuronal plasticity



GLU = glutamate  
SP = substance P

Oliat H, Cesaro C. *Clin Neuropharmacol.*  
1995;18:391-404.

---

---

---

---

---

---

---

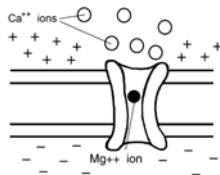
---

---

---

# NMDA Receptors

- Blocked by magnesium ions at resting membrane potential




---

---

---

---

---

---

---

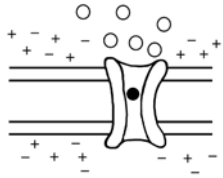
---

---

---

## NMDA Receptors

- Depolarization by C and Aδ-fiber input



---

---

---

---

---

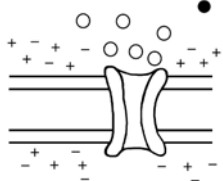
---

---

---

## NMDA Receptors

- Magnesium ion displaced in voltage-dependent manner
- Glutamate binds to activated receptor



---

---

---

---

---

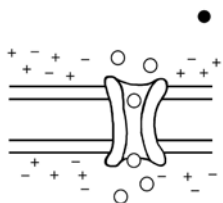
---

---

---

## NMDA Receptors

- Causes inward calcium ion flux
- Phosphorylation of NMDA receptor
- Causes decreased magnesium blockade at physiologic resting potential
- Central sensitization



---

---

---

---

---

---

---

---

## Pharmacologic Management of Neuropathic Pain

Anticonvulsants	Carbamazepine, gabapentin, lamotrigine, topiramate
Antidepressants	Amitriptyline, imipramine, desipramine, nortriptyline
Antiarrhythmics	Mexiletine
Topical formulations	Capsaicin, lidocaine
Analgesics	Opioids, NSAIDs, tramadol
Others	Levodopa, ketamine, dextromethorphan

---

---

---

---

---

---

---

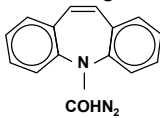
---

## Carbamazepine

Slows recovery rate of voltage-activated Na<sup>+</sup> channels, limiting repetitive firing

May inhibit release of somatostatin

Some calcium antagonistic effect



---

---

---

---

---

---

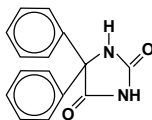
---

---

## Phenytoin

Slows recovery rate of voltage-activated Na<sup>+</sup> channels, limiting repetitive firing

May inhibit somatostatin release



---

---

---

---

---

---

---

---

## Gabapentin

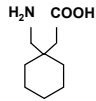
Increases GABA in brain, possibly by enhancing rate of synthesis from glutamate

Binds to alpha 2 delta subunit of voltage dependent Ca channel

Inhibits sodium currents by mechanism distinct from phenytoin and carbamazepine

No effect on GABA<sub>A</sub> or GABA<sub>B</sub> receptors

TID dosing up to 4800 mg/day



---

---

---

---

---

---

---

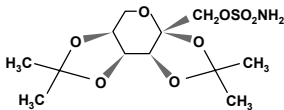
---

## Topiramate

Blocks voltage-gated sodium channels

May block kainate and AMPA subtypes of the glutamate receptor

QHS or BID dosing up to 400 mg/day



---

---

---

---

---

---

---

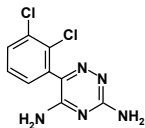
---

## Lamotrigine

Slows recovery rate of voltage-activated Na<sup>+</sup> channels, limiting repetitive firing

Inhibits neurotransmitter release mediated by sodium influx

BID dosing up to 400 mg/day



---

---

---

---

---

---

---

---

## Other Agents

- Levetiracetam - Keppra  
(N-type Ca<sup>2+</sup> channel blocker)
- Oxcarbazepine - Trileptal  
(Na<sup>+</sup> channel blocker)
- Mexiletine - Mexitil  
(Na<sup>+</sup> channel blocker)
- Tiagabine - Gabitril
- Zonisamide - Zonegran

---

---

---

---

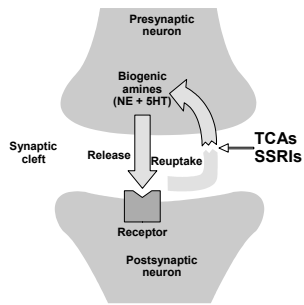
---

---

---

---

## Mechanism of Action of Antidepressants




---

---

---

---

---

---

---

---

## Common Side Effects with Tricyclic Antidepressants

	Sedation	Anti cholinergic effects	Hypo-tension	Cardiac effects	Seizure
Amitriptyline	+++	+++	+++	+++	++
Clomipramine	++	+++	++	+++	+++
Desipramine	0/+	+	+	++	+
Nortriptyline	+	+	+	++	+

---

---

---

---

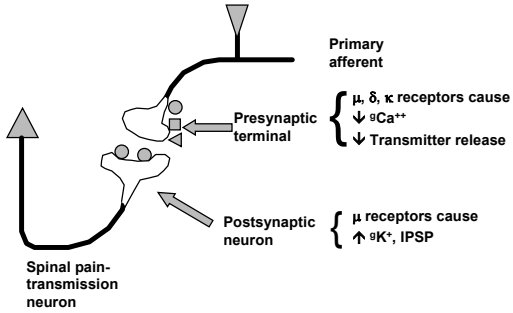
---

---

---

---

## Mechanisms of Action of Opioids




---

---

---

---

---

---

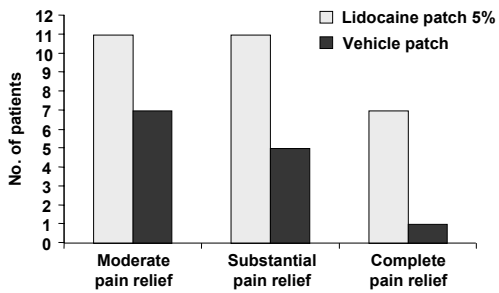
---

---

---

---

## Lidocaine Patch 5% in Post-herpetic Neuralgia




---

---

---

---

---

---

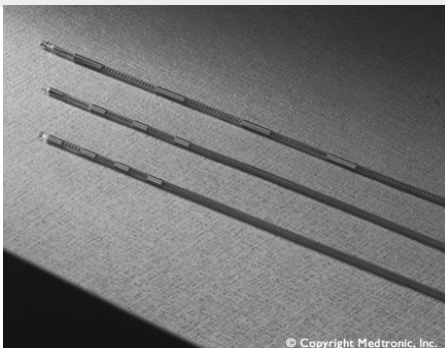
---

---

---

---

## Percutaneous Leads




---

---

---

---

---

---

---

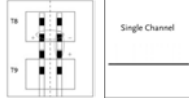
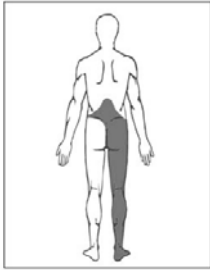
---

---

---

## Low Back and Leg Pain

2x4 SingleStim



- Access to eight electrodes
- Allows transverse stim
- Longevity similar to Itrel 3 if a similar number of electrodes are used
  - Using > 4 electrodes will reduce longevity

---

---

---

---

---

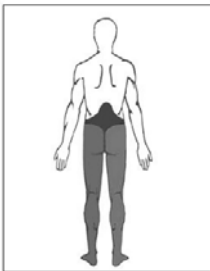
---

---

---

## Low Back and Both Legs

2x4 DualStim



- Access to eight electrodes
- Allows transverse stimulation
- Greater flexibility to target paresthesia patterns
- Longevity is a concern except at very low power settings

---

---

---

---

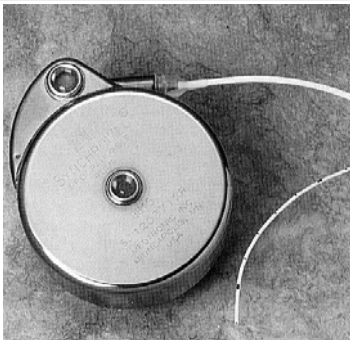
---

---

---

---

## Medtronic SynchroMed Pump



---

---

---

---

---

---

---

---

## Combining Agents Intrathecally

- Opioid
- Opioid + clonidine
- Opioid + bupivacaine
- Opioid + clonidine + bupivacaine
- Combining IT agents allows for lower opioid dosing and enhanced efficacy against neuropathic pain (J Pain Sympnt Manag, 2004)
- What's New?: Prial, midazolam

---

---

---

---

---

---

---

---

## What's New for Neuropathic Pain??

- Duloxetine - Monoamine uptake blocker
- Pregabalin - N-type Ca<sup>2+</sup> channel blocker
- Thalidomide - cytokine inhibitor
- Felbamate - anticonvulsant with NMDA receptor inhibition?
- Ketamine - NMDA receptor inhibition (review by Hocking and Cousins, 2003)
- High-dose capsaicin patch

---

---

---

---

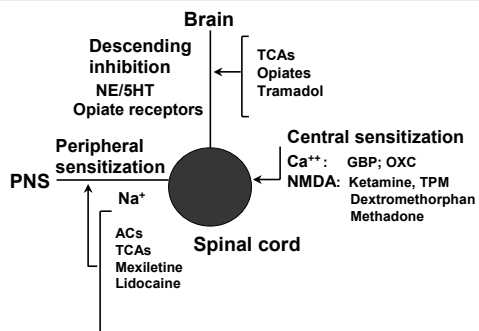
---

---

---

---

## Mechanistic Approach to Treatment



---

---

---

---

---

---

---

---

## Summary

- **Neuropathic pain is difficult to treat**
- **CNS plasticity can result in altered nociceptive pathways**
- **Oral medications can produce significant benefit but also side effects**
- **Implantable therapies can offer local, focused approach to target nociceptive pathways**

---

---

---

---

---

---

---

---