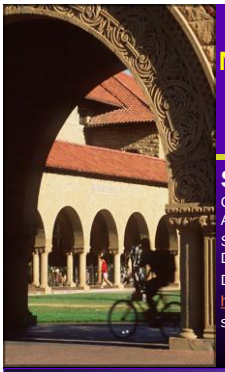

Neuropathic Pain and Pain Treatments – Focus on Over the Counter Agents

Sean Mackey, M.D.,Ph.D.
Chief, Pain Management Division
Associate Professor
Stanford University
Department of Anesthesia
Division of Pain Management
http://paincenter.stanford.edu
smackey@stanford.edu

Centers of Excellence
AMERICAN PAIN SOCIETY
Award Recipient

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- National Institutes of Neurological Diseases and Syndromes
  - R01 NS053961
- National Institutes of Drug Abuse (NIDA)
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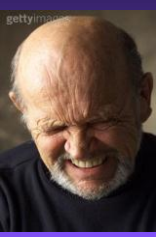
  - U01 DK082316
- NCCAM
  - PO1 pending
- Rosekran's Pain Research Endowment
- Redlich Pain Research Endowment

Overview

- Impact of neuropathic pain
- Taxonomy of pain
- Characteristics and mechanisms of neuropathic pain
- Tools to manage neuropathic pain with a focus on over the counter agents

Experiences With Pain

- >50% of Americans live with chronic or recurrent pain
- 20% suffer chronic pain (ongoing pain ≥3 months). Over 60 million Americans
- Many of the chronic pain conditions started with an acute injury or surgery.
- More than 300 million prescriptions for analgesics (125 million for Vicodin) are written each year for pain.
- #1 reason people out of work
- Indirect/direct medical expenses $200B



Suffering

Gureje O, et al. JAMA 1998;280: 147-151
Morb Mortal Wkly Rep., 2002;51:948-50

Experiences with pain. ABC News/USA Today/Stanford University Medical Center poll.

Pain – definition

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"

IASP 1979.

Types of Pain

- Nociceptive
  - Activation of nociceptors in cutaneous and deep musculoskeletal tissues.
  - Accurately localize pain to the site of pathology; it may be felt in superficial cutaneous or deeper musculoskeletal structures
- Visceral
  - Poorly localized.
  - Often associated with nausea, vomiting, and diaphoresis.
  - Ischemia, infiltration, compression, distention, and torsion or stretching of thoracic, abdominal, and pelvic viscera.
- Neuropathic

Neuropathic Pain

- IASP Definition of Neuropathic Pain: “Pain initiated or caused by a primary lesion or dysfunction in the nervous system. “
- Pain resulting from lesions of the peripheral nerves has sometimes been termed deafferentation pain.
- Pain resulting from injury to the spinal cord or brain, especially when complicating cerebrovascular, demyelinating, or traumatic CNS injury is involved, is usually termed central pain.

Neuropathic Pain - Deleterious Effects

- Negative emotions
  - Depression
  - Anxiety
- Poor Sleep
- Decreased quality of life
- Weight loss

Estimated Prevalence of Neuropathic Pain in the US*

Condition	Number of Cases
Painful diabetic neuropathy	600,000
Postherpetic neuralgia	500,000
Cancer-associated	200,000
Spinal cord injury	120,000
Causalgia and reflex sympathetic dystrophy (CRPS)	100,000
Multiple sclerosis	50,000
Phantom pain	50,000
Poststroke	30,000
HIV-associated	15,000
Trigeminal neuralgia (tic douloureux)	100,000
Low-back pain–associated	2,100,000
Total (excluding back pain)	**1,775,000**
Total (including back pain)	**3,865,000**

Adapted from Bennett GJ. *Hosp Pract*. October 15, 1998.
*Based on population of 270 million.

How we have thought about pain

Approaches to Understanding and Treating Pain

Etiological Factors

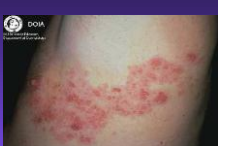
↓

Pain Symptoms

Pain Syndromes

Approaches to Understanding and Treating Pain

Etiological Factors



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Pain Symptoms

Pain Syndromes

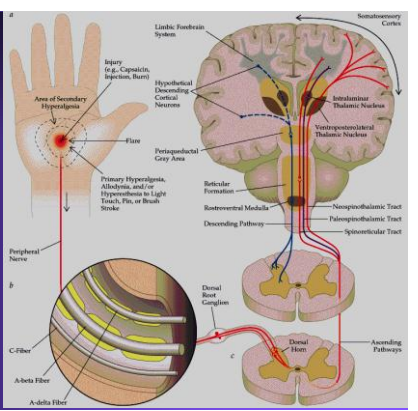
Post Herpetic Neuralgia

Approaches to Understanding and Treating Pain

- Etiological Factors
- Pain Mechanisms
- Pain Symptoms
- Pain Syndromes

Pain – Where does it all start and why is it bad for our patients?

Neuroanatomy of Pain Pathways

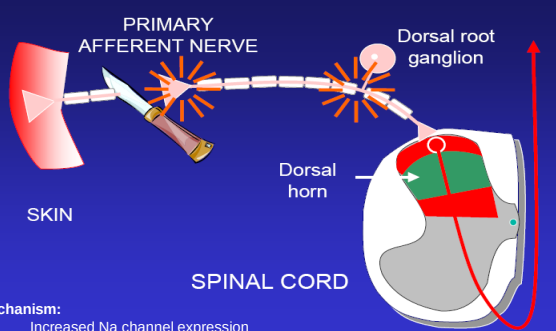


Scientific American Medicine

Peripheral vs Central Mechanisms of Neuropathic Pain: Experimental Effects

Peripheral Effects	Central Effects
• Ectopic and spontaneous discharge • Nonsynaptic conduction • Alterations in ion channel expression • Collateral sprouting of primary afferent neurons • Sprouting of sympathetic neurons in dorsal root ganglion • Nociceptor sensitization • Neurogenic inflammation	• Central sensitization • Spinal reorganization • Cortical reorganization • Changes in inhibitory pathways • Changes in glial cell functioning

Ectopic activity in primary afferents following injury



Mechanism:
Increased Na channel expression
Locally activates membrane of neuroma/DRG

Adapted from Cousins

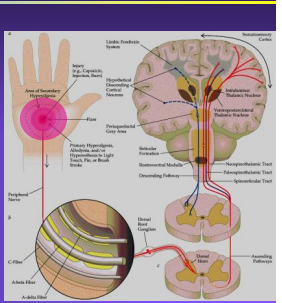
Central Mechanisms of Neuropathic Pain

Peripheral vs Central Mechanisms of Neuropathic Pain: Experimental Effects

Peripheral Effects	Central Effects
• Ectopic and spontaneous discharge • Nonsynaptic conduction • Alterations in ion channel expression • Collateral sprouting of primary afferent neurons • Sprouting of sympathetic neurons in dorsal root ganglion • Nociceptor sensitization • Neurogenic inflammation	• Central sensitization • Spinal reorganization • Cortical reorganization • Changes in inhibitory pathways • Changes in glial cell functioning

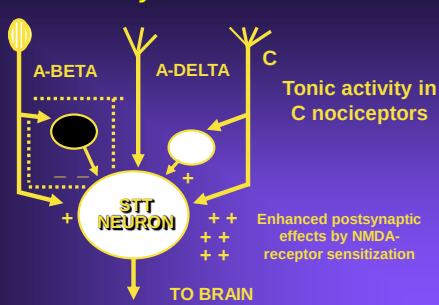
Central Sensitization (Secondary Hyperalgesia)

- Repeated impulse activity in C nociceptive neurons produces sensitization of spinothalamic tract neurons over time
- Previously subthreshold inputs reach threshold and initiate action potential (allodynia)
- Increases in spontaneous activity
- Spinal and supraspinal mechanisms
- Enlargement of the area in periphery where stimulus will activate neurons



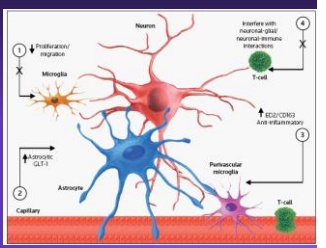
Scientific American Medicine

Loss of Inhibitory Interneuron Function



Glial Cells and Neuropathic Pain

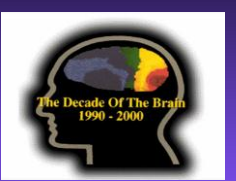
- Parenchymal (resident) microglia, perivascular microglia, astrocytes and oligodendrocytes, constitute > 70% of the total cell population in the brain and spinal cord
- Key neuromodulatory, neurotrophic and neuroimmune elements in the CNS.



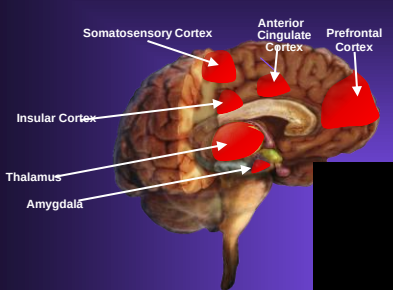
Current Opinion in Investigational Drugs 2008 9(7):726-734

Functional Magnetic Resonance Imaging (fMRI)

A method of observing brain activation

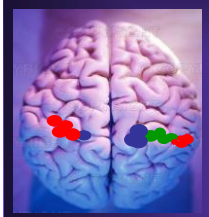


Brain Regions Involved in Pain Perception "Pain Matrix"



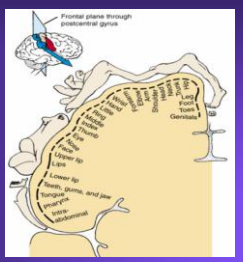
Apkarian AV, et al. *Eur J Pain.* 2005;9:463-484.
Brain image courtesy of ATI

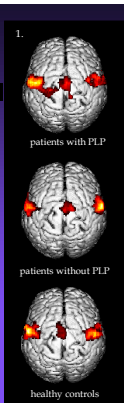
Right arm amputation below elbow



Face
Hand
Upper Arm

Lip pursing and phantom limb pain (PLP):

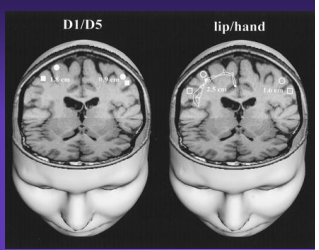




1. Reprinted with permission from M. Lotze, MD. Inst of Medical Psychology & Behavioral Neurobiology, Univ. of Tübingen, Germany. Lotze M, et al. Brain. 2001;124(pt 11):2268-2277.

Cortical Reorganization in Complex Regional Pain Syndrome

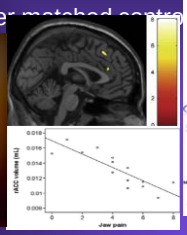
- Participants
  - 12 upper limb CRPS
- Methods
  - Non-painful air puffs to digit 1 and 5 and lower lip
  - Cortical responses recorded with MEG
- Results
  - Shrinkage of hand representation contralateral to affected side
  - Reorganization correlated with amount of pain and mechanical hyperalgesia

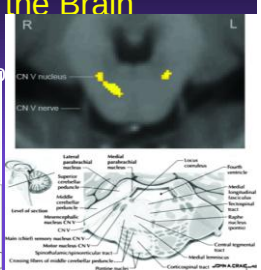


Maihofner, C. Neurology. 2003; 61: 1707-1715

Temporomandibular (TMD) Pain Alters Gray Matter in the Brain

- 15 women with TMD pain
- 15 age/gender matched contro

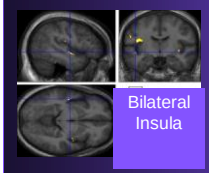




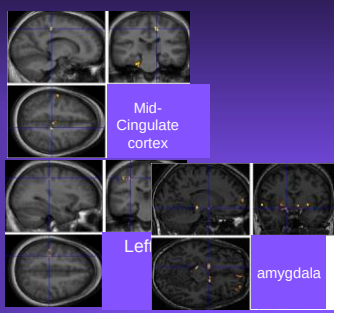
Younger JW, Shen Y, Goddard G, Mackey S. PAIN

Neuropathic Pain Associated with Gray Matter Reductions

- Reductions noted in:
  - Mid-posterior Cingulate
  - S2
  - Posterior Insula
  - Left S1



Bilateral Insula



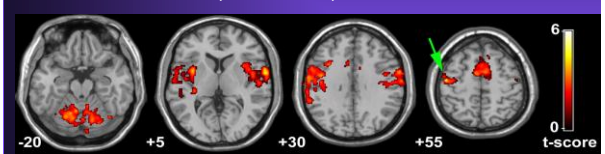
Mid-Cingulate cortex

Left amygdala

In Preparation

Resting State Brain Networks – Abnormalities in Neuropathic Pain

- No significant differences between groups in visual or default-mode networks.
- CRPS patients had significantly more connectivity in "salience" network (Seeley, 2007)
  - Dorsal ACC and insula (salience network) but ALSO cerebellum, and S1

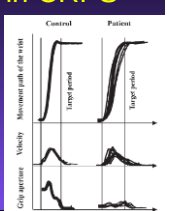


Submitted

Presented at IASP 2008

Changes in CNS Motor Systems in CRPS

- 12 CRPS patients, 12 healthy controls
- Kinematic analysis during target reaching and grasping
- CRPS patients showed prolonged target phase
- fMRI and finger tapping task
- CRPS patients showed reorganization of central motor circuits
  - Increased activity of primary motor and SMA
  - Regressed against tapping performance



Malhofner, et al. , Brain (2007), 130, 2

Therapeutic Approaches to Neuropathic Pain

Chronic pain management

- Multidisciplinary treatment
  - Pharmacologic
  - ...ional Therapy
  - ...ural

Integration

Neuropathic Pain Management – *Physical Therapy, Occupational Therapy, Rehab*

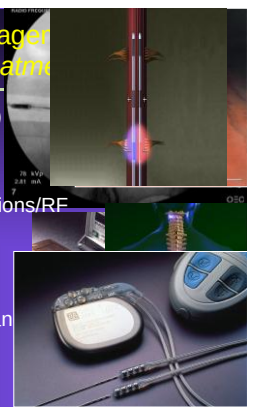
- Setting goal oriented paced activities
- Aerobic exercises, weight loss
- Re-education (e.g. body mechanics, back school, ergonomics)
- Muscle group strengthening (e.g. flexion, extension, range motion)
- Transcutaneous electrical nerve stimulation

Neuropathic Pain Management – Psychological and Behavioral Therapy

- Positive reinforcement for healthy behavior
- Time contingent instead of pain contingent pain management
- Spousal involvement
- Modification of:
  - Meaning of pain and disability
  - Expectations regarding control of pain
  - Catastrophizing
- Respondent treatment
  - Hypnosis
  - Visualization
  - Relaxation
  - Biofeedback

Chronic Pain Manage
Procedural Treatm

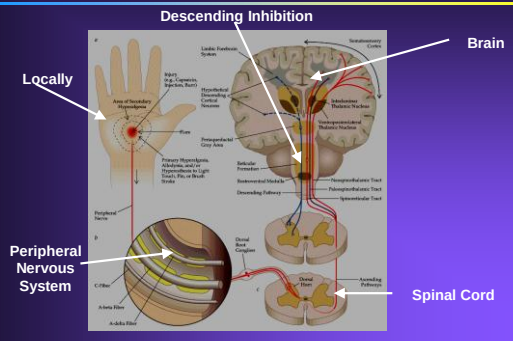
- Trigger point injections (local/Botox)
- Nerve blockade
  - Epidural steroids
  - Medial branch blocks/facet injections/RF rhizotomy
  - Sympathetic blockade
  - Peripheral nerve blockade
  - Neurolytic blockade – chemical an
- Spinal drug delivery systems
- Spinal cord stimulation



Pharmacologic Management of Neuropathic Pain

Antidepressants	**Amitriptyline, imipramine, desipramine, nortriptyline, duloxetine, venlafaxine, SSRIs**
Anticonvulsants	**Carbamazepine, oxcarbazepine gabapentin, lamotrigine, phenytoin, topiramate, levetiracetam, pregabalin**
Antiarrhythmics	**Mexiletine**
Topical formulations	**Capsaicin, lidocaine, aspirin**
Analgesics	**NSAIDs, Cox inhibitors, tramadol, opiates**
Others	**Levodopa, ketamine, dextromethorphan**

Pharmacologic Approach to Treatment



Importance of Randomized Clinical Trials

- Patient with trigeminal post-herpetic neuralgia treated with:
  - Alcohol injection into supra-orbital nerve
  - Division of the sensory root
  - Alcohol injection into trigeminal ganglion
  - Stellate ganglion block
  - Electroconvulsive therapy
  - Extirpation of contralateral then ipsilateral sensory cortex
  - Prefrontal lobotomy

Sugar and Bucy. *Arch Neurol Psychiatry.* 1951;61:131-145.

Over the Counter Agents for Neuropathic Pain

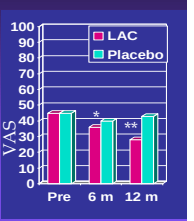
Acetyl-L-Carnitine and Neuropathies

$14/60 cap

- Diabetic peripheral neuropathy
- Chemotherapy-induced neuropathy
- HIV neuropathy
- In mitochondria ensures availability of acetyl-co-A for elimination of toxic metabolites,
  - Involved in acetylation of proteins- tubulin- role in neuronal protection;
  - Enhances neuronal NGF response and possibly regulation of gene expression

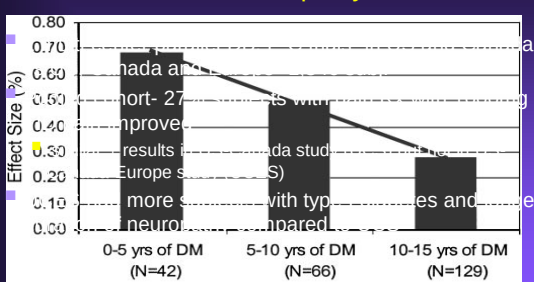
Acetyl-L-Carnitine in Diabetic Neuropathy

- Double-blind placebo-controlled RCT in 333 subjects, 1 yr followup
- 1 gm IM for 10 d, 2 gm orally for 355 d
- Nerve conduction velocity (NCV; motor and sensory) and amplitude primary outcome measure, pain secondary
- 12 month NCV increased in active group in all nerves, decrease or no change in placebo; 6 month similar trend
- 199 pts had pain at baseline. 39% decrease at 12 month



De Grandis and Minardi Drugs R&D 2002; 3:223

ALC and Diabetic Neuropathy



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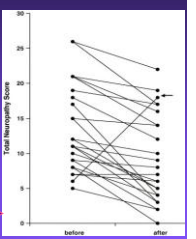
Sima et al, Diabetes Care 2005;28;89

ALC in other NP pain states

- HIV-associated neuropathy:
  - Open label studies 1500 mg x2/d for up to 33 m improvement in neuropathy (?pain) in 76%
  - Small, 3 wk study- 0.5-1 g iv/im daily, pain intensity decreased in 10, no change in 5, 1 worse
- Chemotherapy-induced neuropathy
  - Open label 8 wk trial in 25 pt, total neuropathy score improved in 23 pt. symptoms and neurophys measures



Hart AM et al. AIDS 2004;18:1549; Scarpini E et al. J Peripher Nerv Syst 1997;2:250; Bianchi et al. Eur J Cancer 2005; 41:1746

Vitamin E for Prevention of Cisplatin Neurotoxicity

- Neurotoxicity is the major dose-limiting toxicity for cisplatin
- Peripheral sensory polyneuropathy, ototoxicity, focal encephalopathy
  - Signs and symptoms often not reversible
  - Mechanism of toxicity not fully understood
  - Mechanisms: free radical damage to nerves; possible vitamin E depletion

J Clin Oncol 2003;21:927-931

Vitamin E for Prevention of Cisplatin Neurotoxicity

- Medication: Vitamin E as alpha-tocopherol
- Dose: 300 mg (447 IU)/day
- Protocol: Vitamin E administered before cisplatin therapy and continued for 3 months after cessation of cisplatin treatment
- Patients were randomized to receive vitamin E plus cisplatin (Group 1) or cisplatin alone (Group 2)
- Median time between start of vitamin E and cisplatin was 4 days (range, 1 to 8 days)

J Clin Oncol 2003;21:927-931

Vitamin E for Prevention of Cisplatin Neurotoxicity

- 27 patients with solid tumors (15 lung; 3 ovarian; 2 rhinopharinx, 2 uretheral; and 1 each gastric, testicular, esophageal, ethmoidal, tongue) completed six cycles of cisplatin therapy
  - Neurotoxicty: Group 1 was 30.7% vs. 85.7% in Group 2
  - Severity of neurotoxicity was 79% less in Group 1 compared to Group 2
  - **Overall there was a 64% decreased risk in developing neurotoxicity with Vitamin E**
- No differences between groups in response to cisplatin treatment were noted (eg, tumor weight inhibition, tumor growth delay, life span)

J Clin Oncol 2003;21:927-931

Alpha-Lipoic Acid (ALA)

- Improves nerve blood flow, distal nerve conduction and increases endoneurial glucose uptake and energy metabolism
- Has also been used to reduce oxidative damage
- Approved in Germany for diabetic neuropathy
- S/E mild- headache, skin rash, stomach upset at high doses (600 mg/d) and possible hypoglycemia

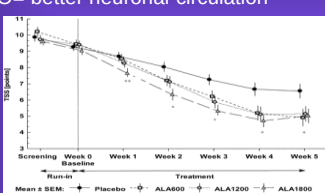
$12.95/60 cap

Halat CE & Dennehy KM
J Am Board Fam Pract 2003;16:47–57

Alpha-Lipoic acid and neuropathy

- Meta-analysis of 4 PCRT in diabetic N, n=1,258
- 600 mg ALA IV for 3 wk
- Improvement in symptom score starting day 8 of Rx
- Smaller studies- similar symptomatic improvement
- Normalizes plasma nitrates and nitrites- a surrogate for NO production, increased NO= better neuronal circulation

Ziegler et al. Diabet Med 2004;21:114



ALA for Treatment of Oxaliplatin-Induced Polyneuropathy

- Dose-limiting toxicity of oxaliplatin is cumulative peripheral sensory neuropathy (PNP)
- Peripheral neuropathic pain symptoms:
  - Paresthesias with or without functional impairment of the extremities
- Develop in 10-18% of patients when a cumulative dose of about 800 mg/m2 is reached

J Clin Oncol 2002;20:3359-3361

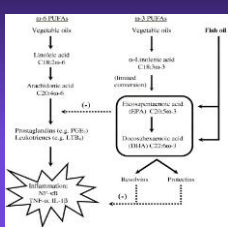
ALA for Treatment of Oxaliplatin-Induced Polyneuropathy

- 15 patients with oxaliplatin –induced cumulative PNP
- Treatment:
  - Alpha-lipoic acid 600 mg I.V. weekly for 3-5 weeks
  - Followed by 600 mg orally three times daily until full recovery or for a maximum of 6 months
- 8 of 15 patients (53%) experienced reduction in severity of symptoms
  - Median response time: 4 weeks (range 3-12 wks)
  - Median treatment duration: 2 months (range 1-4 months)

J Clin Oncol 2002;20:3359-3361

Essential fatty acids

- Omega-6 FA: gamma-linonelic acid
  - Evening primrose oil, borage and black currant, Efamol oil
  - 2 RCTs in diabetic neuropathy
- Omega-3 FA: eicosopentaenoic and docosahexaenoic acid- Fish oil
  - Reduced pain in RA, inflammatory bowel disease, dysmenorrhea, and musculoskeletal injury



*Coste et al. Cellular and Molecular Biology*TM 2004;**50:**845
Goldberg RJ, Katz J. Pain 2007;129:210

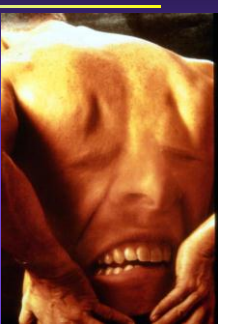
Stanford Pain Management Center

- Major tertiary comprehensive Pain Management Center
- Started in 1989.
- Over 10,000 patient visits (FY08)
- 18 Clinical Pain Faculty
  - Anesthesiology

Centers Excellence AMERICAN PAIN SOCIETY Award Recipient

Common Pain Conditions We Treat

- Neuropathic pain
  - Post traumatic, post surgical
  - Post-herpetic neuralgia
  - Complex regional pain syndrome/RSD
  - Diabetic neuropathy
- Back and neck pain
- Headache
- Abdominal and pelvic pain
- Cancer pain
- Work related



Unique Aspects of Stanford Pain Center

Centers Excellence AMERICAN PAIN SOCIETY Award Recipient

- True comprehensive interdisciplinary clinical program with national and international reputation
- State of the art therapies with proven outcomes
- Only in patient program in Western US (SCIPP)
- Collaborative translational research with world class resources
- Integration of research programs with clinical care – part of the culture

Research ↔ Clinical

Summary

- Neuropathic pain is a tremendous burden on the individual and society.
- Neuropathic pain represents a complex mixture of peripheral and central mechanisms.
- Multidisciplinary treatment approaches are the most effective.
- A number of over the counter agents have demonstrated efficacy in neuropathic pain.
- Look for the Institute of Medicine report on Pain on June 29th!!!