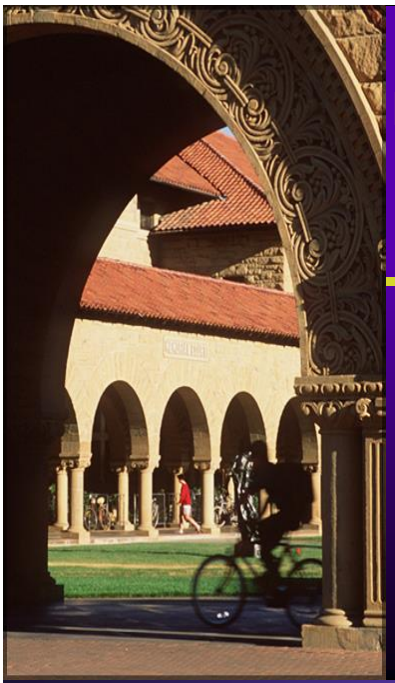

Neuropathic Pain and Pain Treatments – Focus on Over the Counter Agents

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Disclosures – Funding Sources

- National Center of Complementary and Alternative Medicine
  - P01 AT006651-01
- National Institutes of Drug Abuse (NIDA)
  - K24 DA029262, R21 DA026092
- National Institutes of Neurological Diseases and Syndromes
  - R01 NS053961
- National Institutes of Diabetes and Digestive and Kidney Diseases
  - U01 DK082316
- Dodie and John Rosekrans Pain Research Endowment
- Redlich Pain Research Endowment
- *No industry conflicts*

What Americans Know about Science

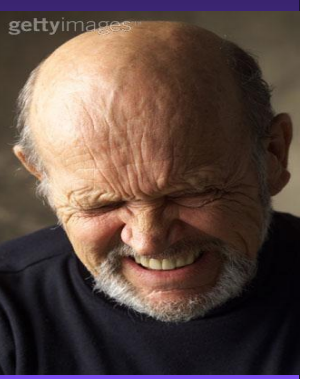
- "H_20 is hot water, $C0_2$ is cold water"
- "Water is composed of two gins, Oxygin and Hydrogin. Oxygin is pure gin. Hydrogin is gin and water"
- "Three kinds of blood vessels are arteries, vanes, and caterpillars
- "Gonads: a tribe of wandering desert people."
- "To keep milk from turning sour: Keep it in the cow"

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 – Institute of Medicine Report

- Affects 100 Million Americans
  - More than heart disease, diabetes and cancer combined
- Indirect/direct medical expenses US $560-$630 Billion/year
- Chronic pain can become a disease in its own right

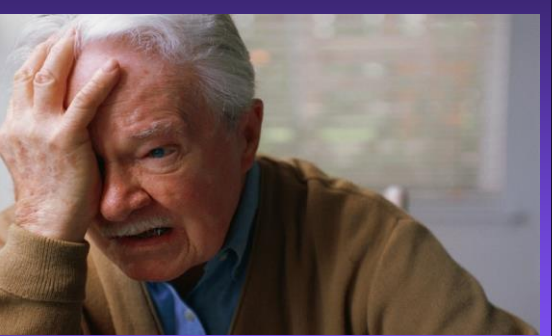


INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Institute of Medicine – Relieving Pain In America 2011

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

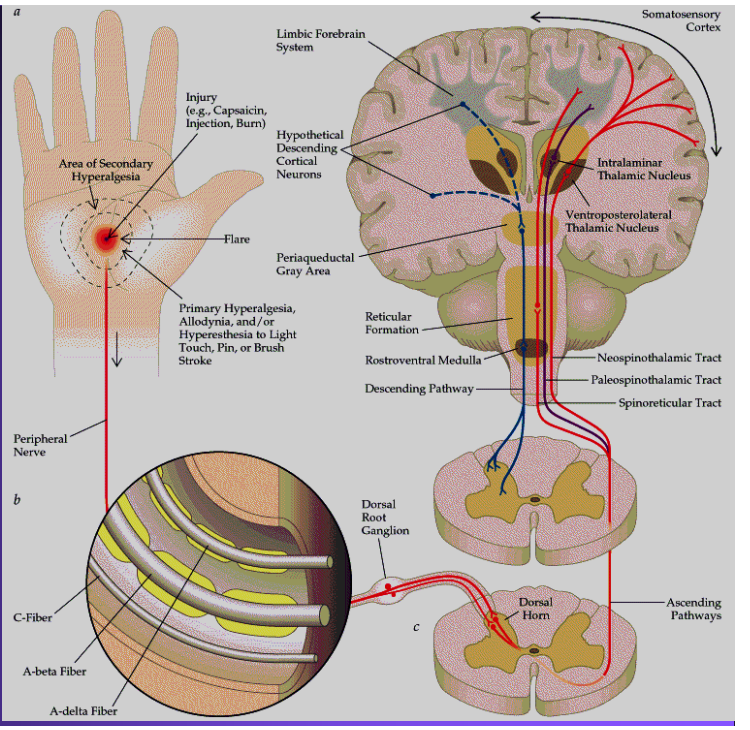
- IASP Definition of Neuropathic Pain: “Pain initiated or caused by a primary lesion or dysfunction in the nervous system. “
- Pain resulting from lesions of the peripheral nerves has sometimes been termed deafferentation pain.
- Pain resulting from injury to the spinal cord or brain, especially when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

Neuropathic Pain - Deleterious Effects

- Negative emotions
  - Depression
  - Anxiety
  - Anger
- Poor Sleep
- Immune impairment
- Decreased quality of life

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

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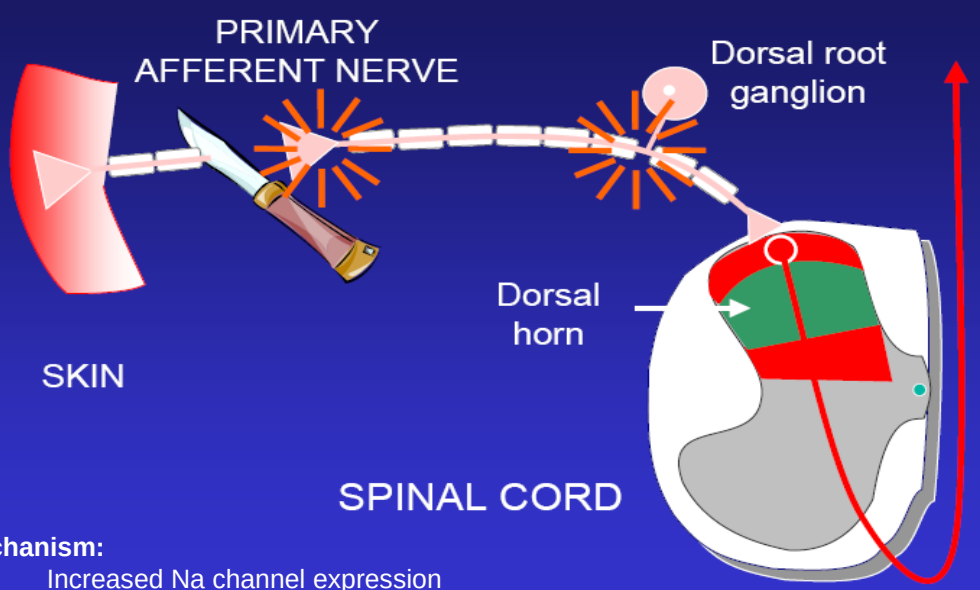
Ectopic activity in primary afferents following injury



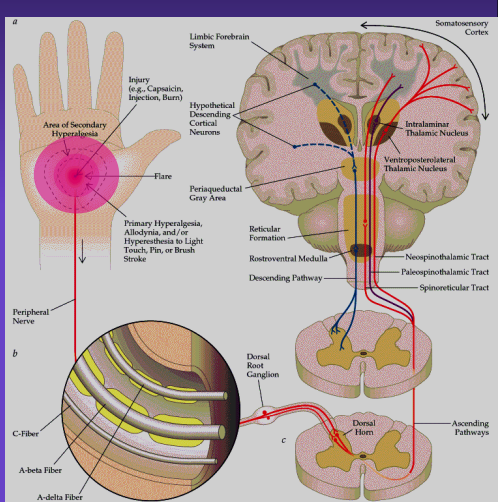
Mechanism:

Increased Na channel expression
Locally activates membrane of neuroma/DRG

Adapted from Cousins

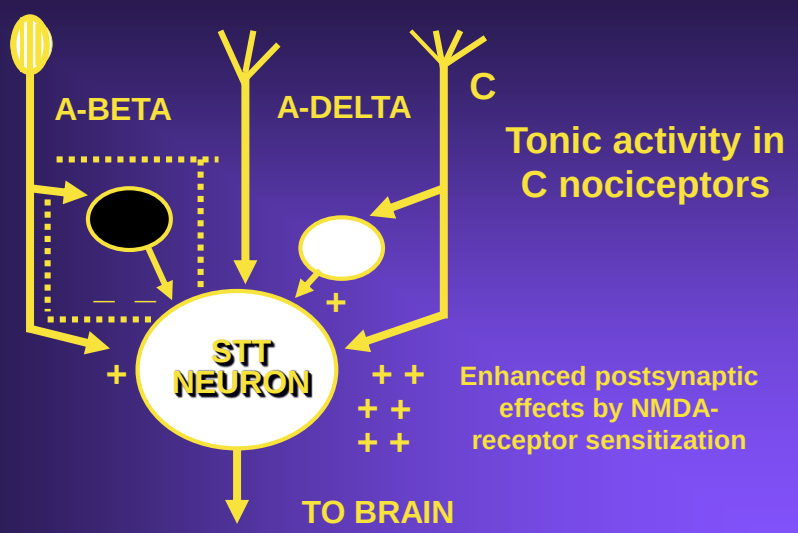
Central Sensitization (Secondary Hyperalgesia)

- 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



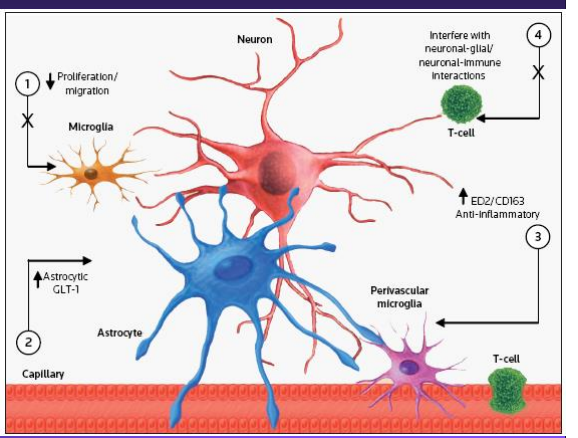
Scientific American Medicine

Loss of Inhibitory Interneuron Function



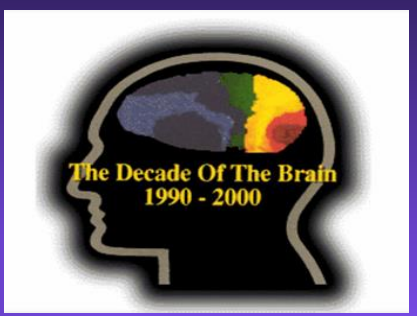
Glial Cells and Neuropathic Pain

- 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.



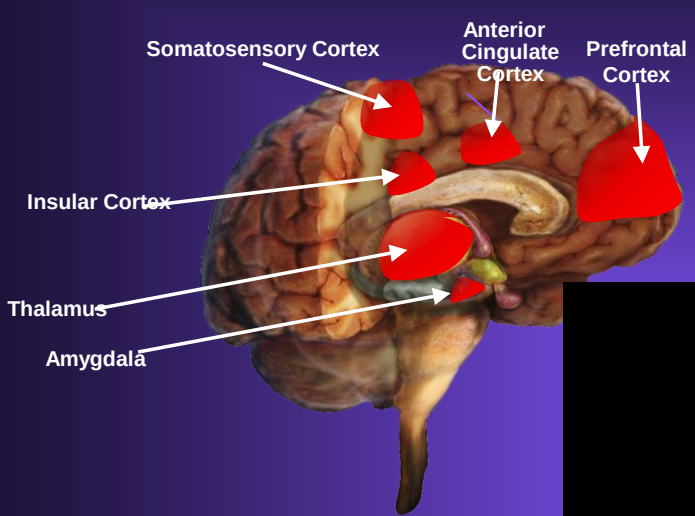
Current Opinion in Investigational Drugs 2008 9(7):726-734

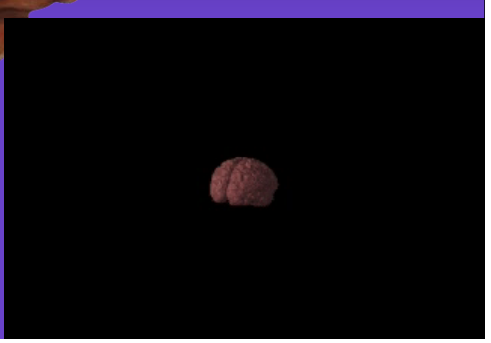
Functional Magnetic Resonance Imaging (fMRI)



A method of observing brain activation

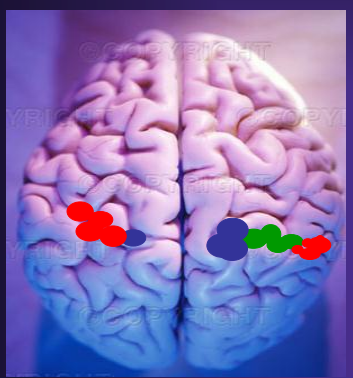
Brain Regions Involved in Pain Perception





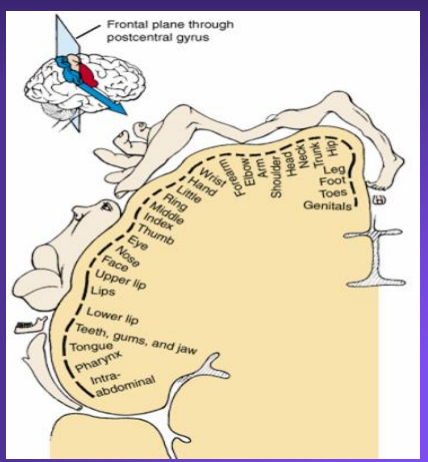
Apkarian AV, et al. *Eur J Pain.* 2005;9:463-484.
Brain image courtesy of ATI
LONI

Right arm amputation below elbow



Face
Hand
Upper Arm

Lip pursing and phantom limb pain (PLP):



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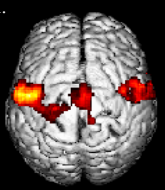
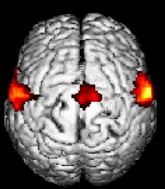
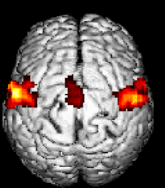


patients with PLP



patients without PLP

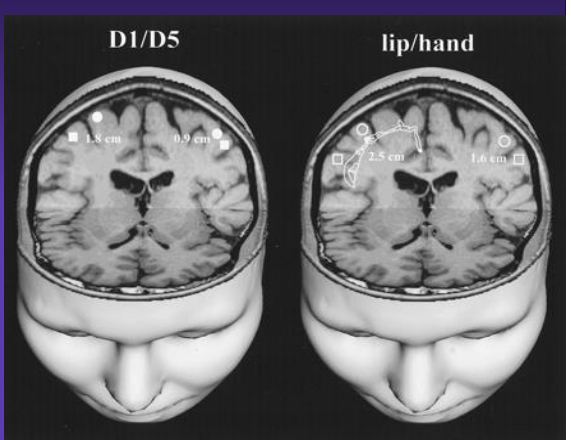


healthy controls

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

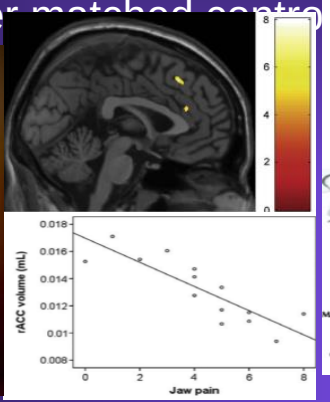
- Participants
  - 12 upper limb CRPS
- Methods
  - Non-painful air puffs to digit 1 and 5 and lower lip
  - Cortical responses recorded with MEG
- Results
  - Shrinkage of hand representation contralateral to affected side
  - Reorganization correlated with amount of pain and mechanical hyperalgesia

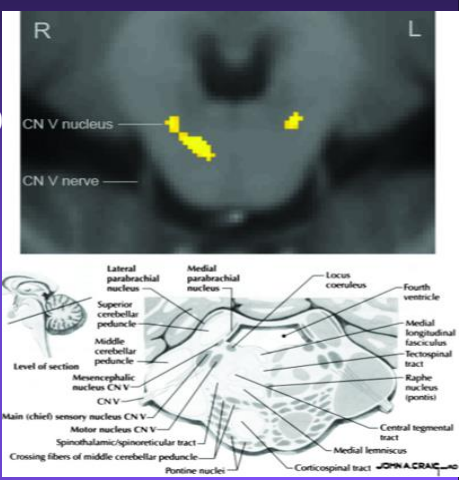


Maihofner, C. Neurology. 2003; 61: 1707-1715

Temporomandibular (TMD) Pain Alters Gray Matter in the Brain

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

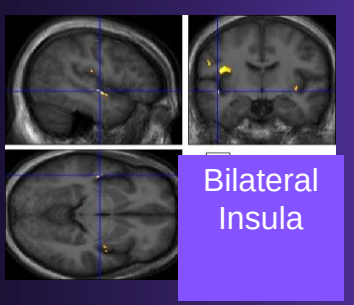


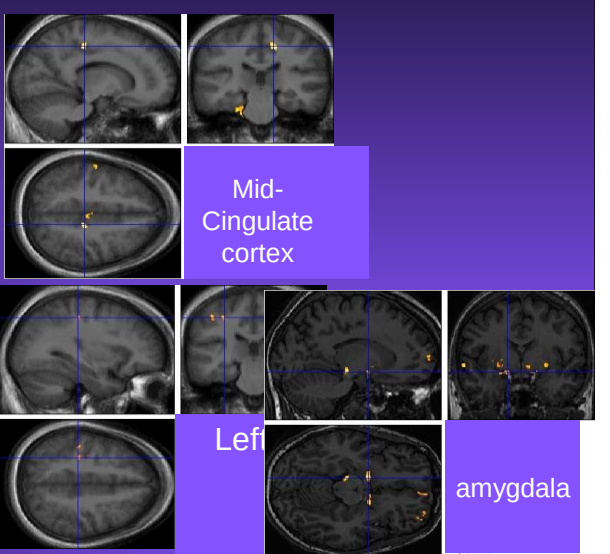


Younger JW, Shen Y, Goddard G, Mackey S. PAIN (2010)

Neuropathic Pain Associated with Gray Matter Reductions

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

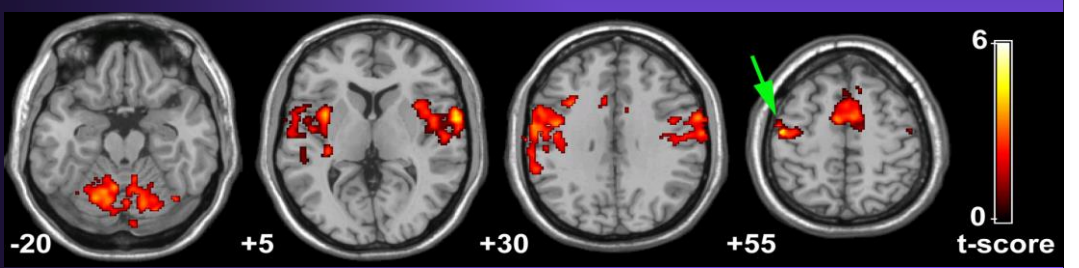




In Preparation

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



IASP 2008

Therapeutic Approaches to Neuropathic Pain

Chronic pain management

- Multidisciplinary treatment
  - Pharmacologic
  - [illegible]
  - [illegible] Therapy
  - [illegible]
  - Complementary and Alternative Medicine

Integration

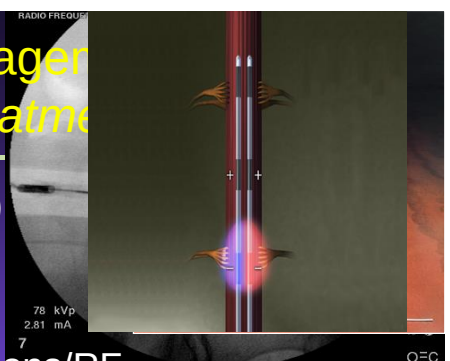
Neuropathic Pain Management – *Physical Therapy, Occupational Therapy, Rehab*

- 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 Manager
Procedural Treatme

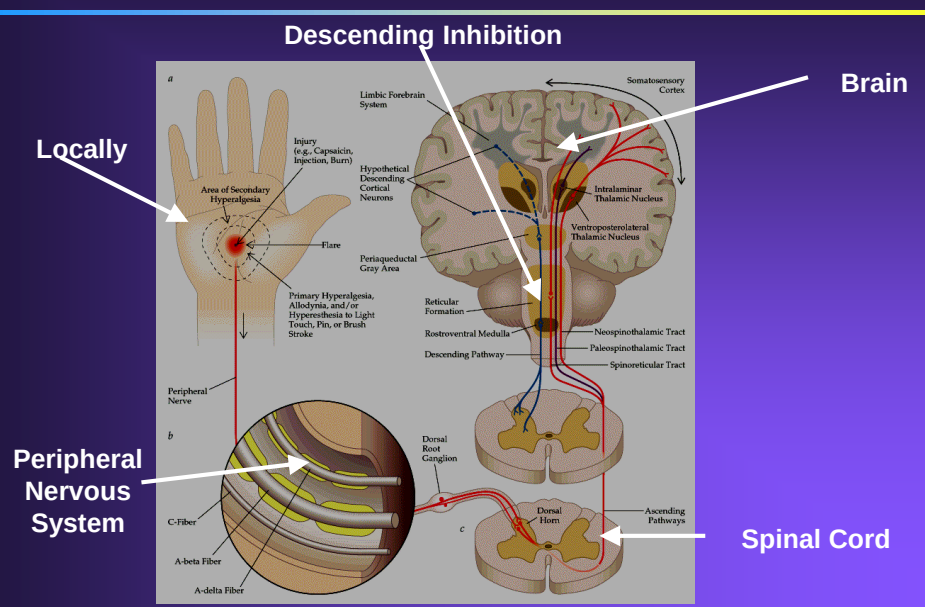


- Trigger point injections (local/Botox)
- Nerve blockade
  - Epidural steroids
  - Medial branch blocks/facet injections/RF rhizotomy
  - Sympathetic blockade
  - Peripheral nerve blockade
  - Neurolytic blockade – chemical an
- Spinal drug delivery systems
- Spinal cord stimulation

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

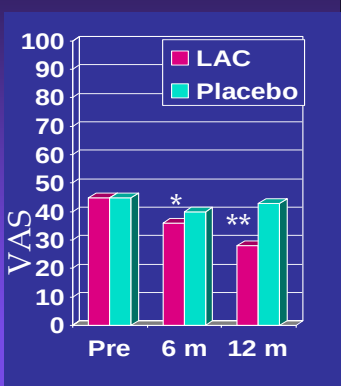
Acetyl-L-Carnitine and Neuropathies

$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

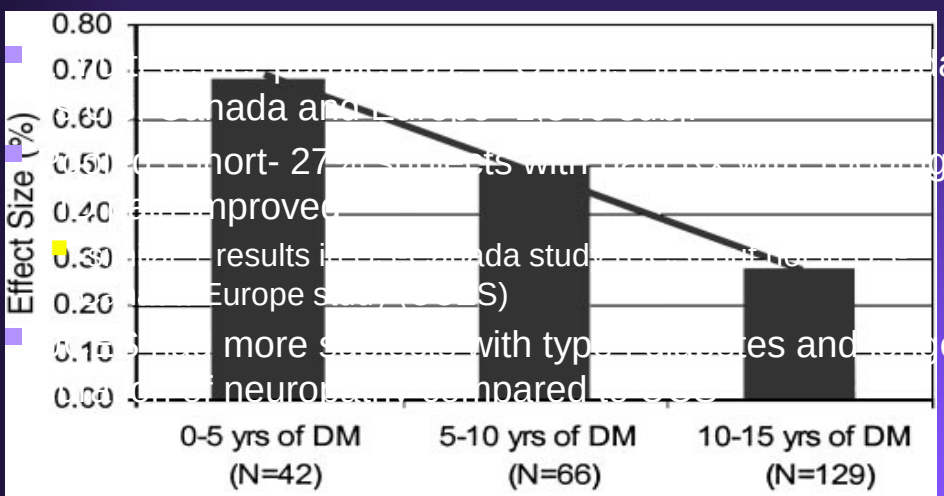
Acetyl-L-Carnitine in Diabetic Neuropathy

- Double-blind placebo-controlled RCT in 333 subjects, 1 yr follow-up
- 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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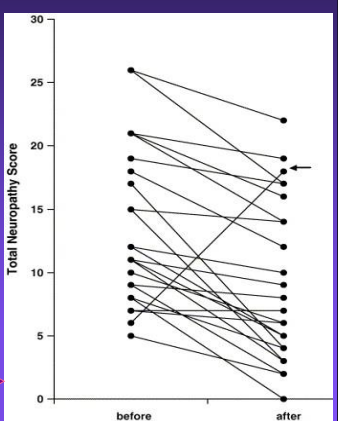
Sima et al, Diabetes Care 2005;28;89

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

- 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)

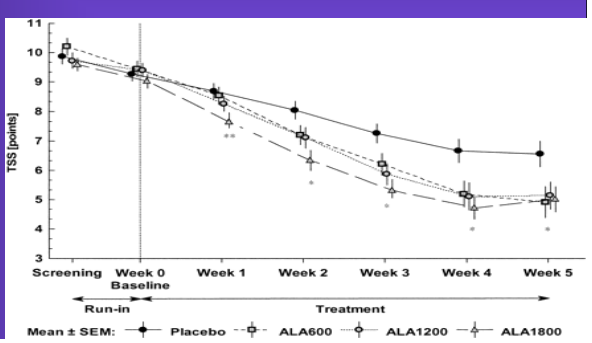
- Improves nerve blood flow, distal nerve conduction and increases endoneurial glucose uptake and energy metabolism
- Has also been used to reduce oxidative damage
- Approved in Germany for diabetic neuropathy
- S/E mild- headache, skin rash, stomach upset at high doses (600 mg/d) and possible hypoglycemia

$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

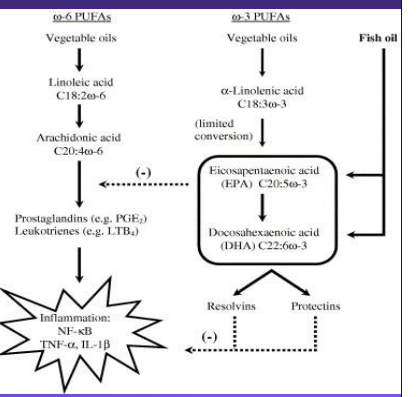
ALA for Treatment of Oxaliplatin-Induced Polyneuropathy

- 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

STANFORD SCHOOL OF MEDICINE
Stanford University Medical Center

- Major tertiary comprehensive Pain Management Center
- Comprehensive chronic pain in-patient unit
- Started in 1989.
- Over 12,000 patient visits (FY11)
- 21 Clinical Pain Faculty
  - Anesthesiology
  - Internal Medicine
  - Physiatry
  - Neurology
  - Addiction Medicine
  - Acupuncture
- 4 Pain Psychologists Faculty
- 7 Clinical ACGME pain fellows
- PT/OT, Nutrition, Nursing

Centers Excellence
AMERICAN PAIN SOCIETY
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Common Pain Conditions We Treat

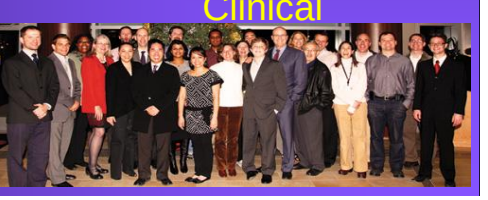
- Neuropathic pain
  - Post traumatic, post surgical
  - Post-herpetic neuralgia
  - Complex regional pain syndrome/RSD
  - Diabetic neuropathy
- Back and neck pain
- Headache
- Abdominal and pelvic pain
- Cancer pain
- Work related

Unique Aspects of Stanford Pain Center

- 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.