Overview of Neuropathic Pain and Pharmacological Approaches

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Peripheral Neuropathy Patient Conference Foundation for Peripheral Neuropathy

AGENDA

8:30 AM Welcome: David M. Simpson, MD, FAAN 8:35 AM: Opening Remarks: Louis Mazawey; Lindsay Colbert 8:45 AM: Overview of Neuropathic Pain and Pharmacologic Approaches: David M. Simpson, MD, FAAN 9:15AM: Controlled Substances: What are the Roles of Opioids and Medical Marijuana in the Treatment of Neuropathic Pain: Jessica Robinson-Papp, MD 9:45AM: Q and A/Round Table 10:15 AM: Break **10:30 AM: Optimizing Communication With Your Provider and Beyond: Drugs: Non-Pharmacological Management of Neuropathic Pain:** Shanna Patterson, MD 11:00 AM: Research and Technology for Possible Options to Neuropathic Pain Treatment: Mary Catherine George, PhD 11:30 AM: Q and A/Round Table 12:15 PM: Adjourn

Nociceptive vs Neuropathic Pain

Nociceptive Pain

Caused by activity in neural pathways in response to potentially tissue-damaging stimuli

Mixed Type

Caused by a combination of both primary injury and secondary effects

Neuropathic Pain

Initiated or caused by primary lesion or dysfunction in the nervous system

Postoperative pain

> Mechanical low back pain

Arthritis

Sickle cell crisis

Sports/exercise injuries

Neuropathic low back pain

Postherpetic

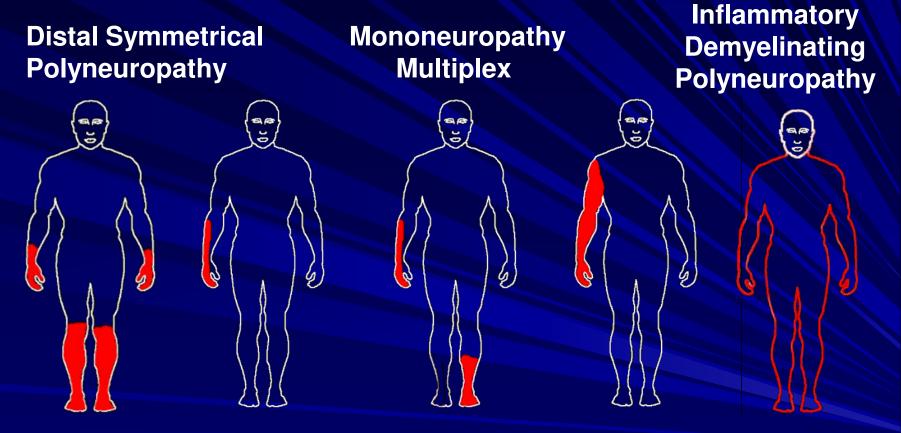
neuralgia

Trigeminal neuralgia

Central post-Distal stroke pain polyneuropathy (eg, diabetic, HIV)

*Complex regional pain syndrome.

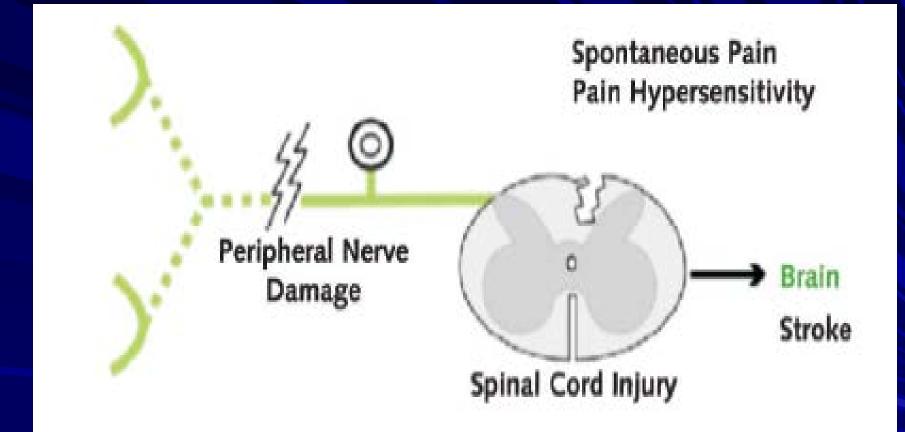
Types of Neuropathy



Mononeuropathy

Brachial Plexopathy

Neuropathic Pain



Woolf CJ. Ann Intern Med. 2004;140:441-451.

Common Causes of Neuropathic Pain

Disease Process

- Infection/inflammation
- Tumor infiltration
- Metabolic abnormality

Therapeutic Intervention

- Surgery
- Chemotherapy
- Irradiation

Neuropathic Pain Trauma
External injury
Nerve compression
Inflammation

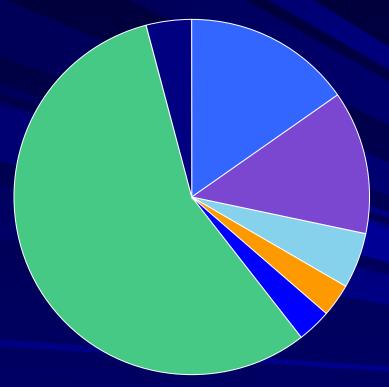
Genetic Predisposition

- Inherited
 neurodegeneration
- Metabolic/endocrine abnormalities

Adapted from Dworkin RH et al. Arch Neurol. 2003;60:1524-1534.

Estimated Prevalence of Neuropathic Pain in the United States*

Total Number of Cases of Neuropathic Pain: 3,780,000



DPN (600k)
PHN (500k)
Cancer-associated (200k)
Spinal cord injury (120k)
Spinal cord injury (120k)
CRPS (100k)
Low-back pain (1200k)
Other (160k) Multiple sclerosis (50k) Phantom pain (50k) Poststroke (30k)
HIV-associated (15k) Trigeminal neuralgia (tic douloureux) (15k)

DPN = diabetic peripheral neuropathy; PHN = postherpetic neuralgia; CRPS = complex regional pain syndrome. *Based on population of 270 million.

Bennett GJ. Hosp Pract (Off Ed). 1998;33:95-98, 101-104, 107-110.

Pain is a more terrible master of humankind than death itself

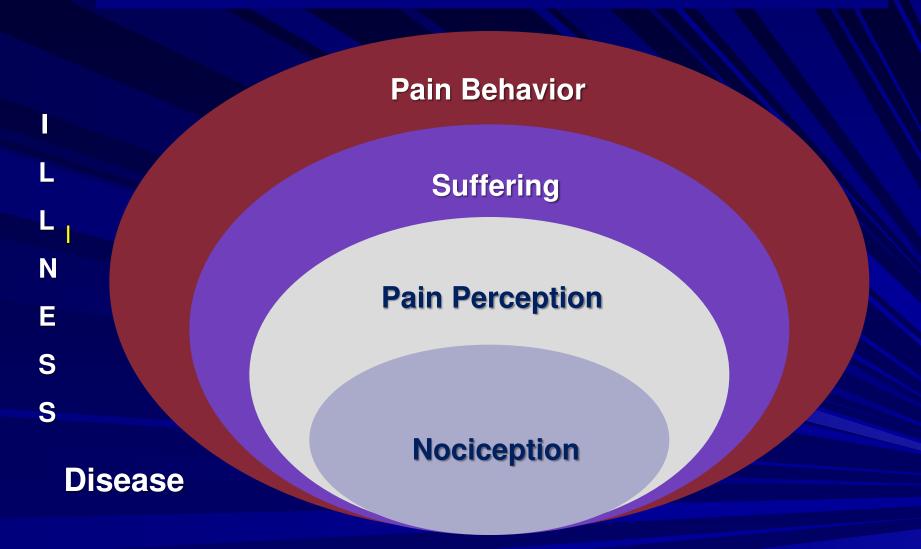
Albert Schweitzer (1922), On the Edge of the Primeval Forest



Pain: Issues and Challenges

Most common type of medical symptom -25% to 50% of all clinic visits Underassessment and undertreatment Patient not believed Complex pathophysiology Treatment choices suboptimal Interpatient variability in response to Rx

The Complex Nature of Pain

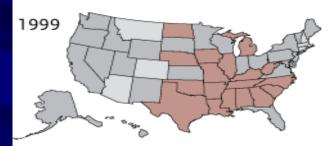


Adapted from: Loeser J, et al. Bonica's Wanagement of Pain. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins. 2001;241-254.

Obesity and Diabetes in US



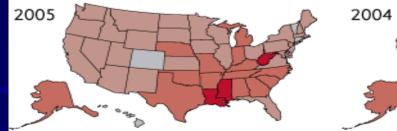




OBESITY

No data 10-14 15-19 20-24 25-29











Percent prevalence in adult population

30+

Prevalence of Diabetes, Diabetic Neuropathy, and Diabetic Peripheral Neuropathic Pain



- 1. NDIC. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/#7. Accessed May 30, 2008.
- 2. Schmader KE. Clin J Pain. 2002;18(6):350-354.
- 3. Boulton AJ, et al. Diabetes Care. 2004;27(6):1458-1486.
- 4. CDC. Available at: http://www.cdc.gov/diabetes/statistics/prev/state/fPrev1994and2004.htm. Accessed May 30, 2008.

Diabetic Neuropathy: Risk Factors

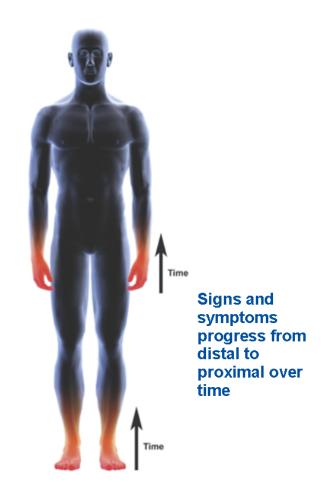
Aging

- Duration of diabetes
- Poor glycemic control
- Diastolic hypertension
- Reduced HDL cholesterol
- Increased triglycerides
- Hypertension
- Smoking

Gimbel JS et al. *Neurology.* 2003;60:927-934.
 Schmader KE. *Clin J Pain.* 2002:18:350-354.
 Tesfaye S et al. *Diabetologia.* 1996;39:1377-1384.

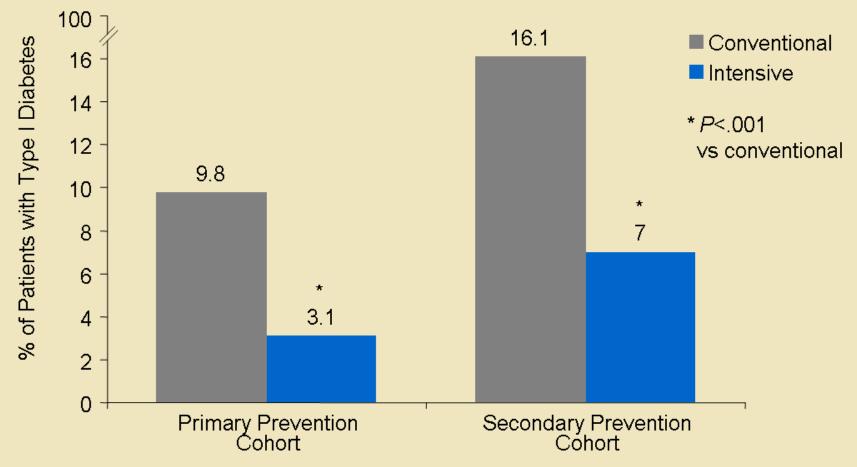
Clinical manifestations of diabetic peripheral neuropathy (DPN)^{1,2}

- Distal symmetrical sensorimotor polyneuropathy is the most common form of DPN
- Patients frequently complain of:
 - -Pain (e.g. burning, shooting, stabbing)
 - Exacerbated by activities
 - Typically worse at night
 - -"Pins and needles" (paresthesias)
 - -Increased sensitivity (allodynia, hyperalgesia)
 - -Numbness
 - -Impaired balance (loss of proprioception)



Glycemic control can decrease the risk of diabetic neuropathy

Effect of Diabetes Treatment on the Prevalence of Clinical Neuropathy at 5 years (from the Diabetes Control and Complications Trial)

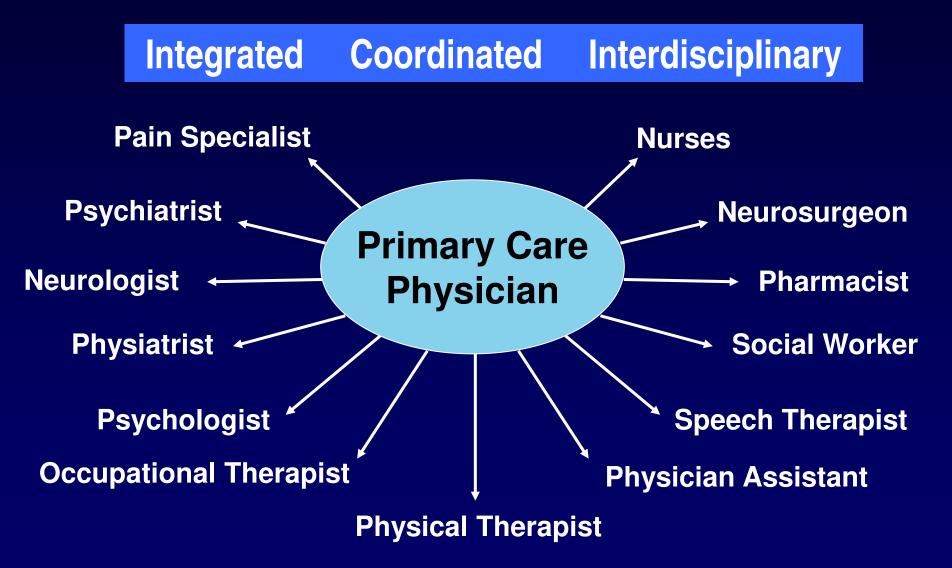


Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329(14):977-986.

What Are the Goals of Clinical Assessment?

Achieve diagnosis of pain Identify underlying causes of neuropathy Identify comorbid conditions Evaluate psychosocial factors Evaluate functional status (activity levels) Set goals Develop a targeted treatment plan Determine when to refer to specialist or multidisciplinary team (pain clinic)

Coordination of the Multidisciplinary Team



Can We Reliably Measure Pain?



Pain Assessment Process

Physicians should address

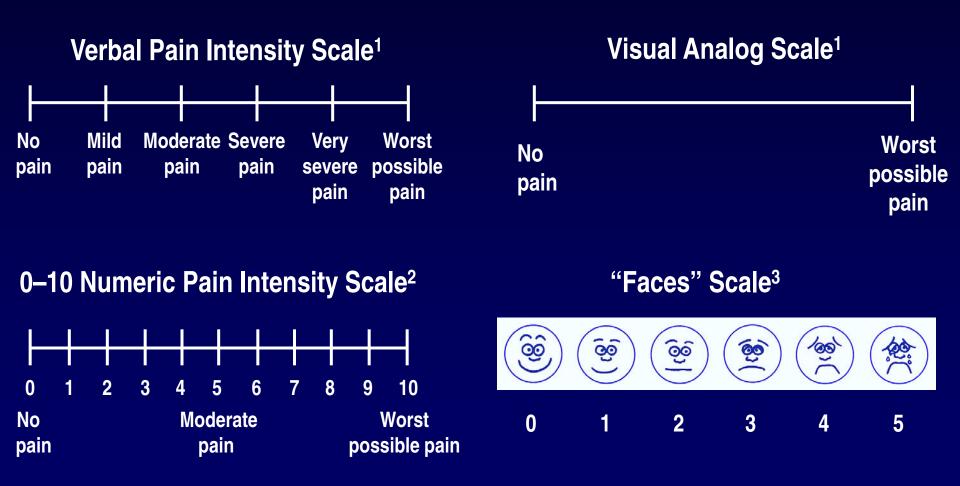
- -Types of pain
- Distribution of pain
- -Patient's current pain state
- -Effects of patient's current treatment
- Appropriate tools available for pain evaluation

Pain Intensity: How Much It Hurts



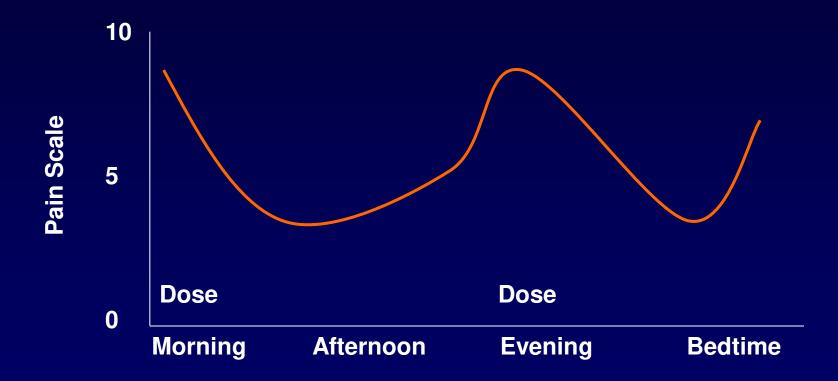
"Ouch," "D*#mn!," and "G*% D*#mn!" Courtesy of M Jensen

Pain Assessment Scales



Patient Pain Diary

Utility of manual versus electronic diaries?



Pain Quality: How it Feels







Sharp/stabbing

Hot/burning

Electrical/ shocking

Courtesy of M Jensen

Diagnostic Studies and Limitations

Studies

- Blood studies
 X-ray, CT, MRI
 Electromyography (EMG)
 Nerve conduction velocity (NCV)
- Quantitative sensory testing (QST)
 Epidermal skin biopsy
- Epidermal skin biopsy

Limitations of EMG/NCV

Insensitive in acute injury
 Normal result does not rule out neuropathic pain
 Cannot assess function of small-fiber nerves involved in most neuropathic pain

Treatment of Neuropathic Pain

"Undertreatment of acute and chronic pain persists despite decades of efforts to provide clinicians with information about analgesics."

Amer Pain Society Quality of Care Committee. JAMA 1995

Attitudes on Pain

To experience pain is to have certainty; to hear about pain is to have doubt

~ Elizabeth Scary

Courtesy of M Jensen

THE NEW YORK TIMES, TUESDAY, MAY 14, 2013

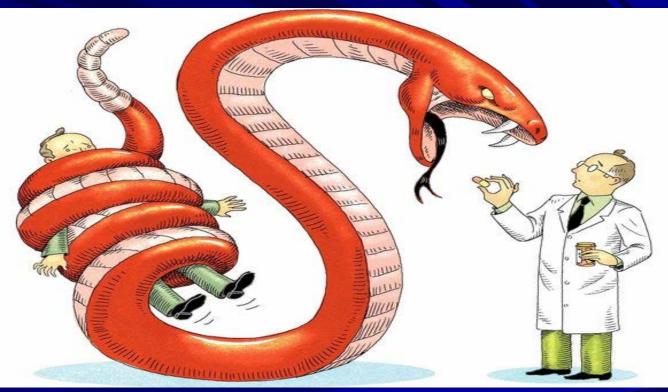


HARD CASES | ABIGAIL ZUGER, M.D.

The Traps of Treating Pain

Doctors are rarely trained to manage discomfort, so they wind up following general guidelines. measured or monitored, and varies wildly and unpredictably from person to person. We hate it because it can drag us closer to the perilous zones of illegal practice than any other complaint.

And we hate it most of all because unless we specifically seek out training in how to manage pain, we get virtually none at all, guidelin fuller th ples, an do any o One o heartfe written ternal



Neuropathic Pain Barriers to Management

Patient-related

- Reluctance to report pain
- Substance abuse
- Health care provider
 - Fear of addiction
 - Fear of being "scammed"
- Health care system
 - Triplicates, narcotic restrictions

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OxyContin D	eaths May Top Early Count
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Doctor Given Long Prison Term For 4 Deaths Tied to OxyContin

MILTON, Fin., March 22 (AP) - A doctor convicted of manslaughter in the deaths of four patients who overdosed on the painkiller OxyComin was sentenced today to nearly 63 years in prison.

The doctor, James Graves, 55, was the first in the United States to be found guilty of manslaughter or murder in an OxyContin death.

The defense said it would appeal. Dr. Graves remained deflant today, telling the prosecutor that one day both of them would have to "stand before God."

Speaking of the prosecutor, Dr. Graves told Judge Kenneth Bell of Circuit Court, "I pray to God something will change and somehow he will come to know Christ."

Prosecutors said Dr. Graves ran a "pill mill" that dispensed the painkiller to addicts and dealers. He was convicted last month of manslaughter, unlawful delivery of a controlled substance and racketeering. Thejudge said state guidelines called for a sentence of as much as 138 years. Dr. Graves testiled that patients

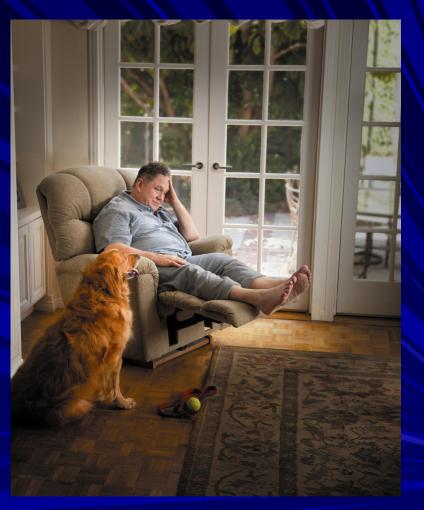


Dr. James Graves was fingerprinted vesterday after his sentence.

To the Patient, the Impact of Pain Rx Goes Far Beyond the Pain

- Pain broadly interferes with daily functioning and quality of life¹⁻⁵
 - General activity, walking
 - Energy level
 - Social and leisure activities
 - Ability to sleep
 - Change in mood, ↑ feelings of depression and anxiety
 - Overall enjoyment of life





Overall Objectives of Treatment of Neuropathic Pain

Diagnosis and assessment

If possible, treat underlying condition with disease-modifying therapy

Reduce Pain

Improve overall health-related quality of life

Improve physical functioning (e.g., sleep, mobility) Improve emotional functioning (e.g., anxiety, depression)



Opioids, nonopioids, adjuvant analgesics

Therapeutic Approaches to Pain as a Disease State

Lifestyle Change

Exercise, weight loss

Physical Medicine and Rehabilitation

Assistive devices, electrotherapy

Complementary and Alternative Medicine

Massage, supplements

Interventional Approaches

Injections, neurostimulation

Psychological Support

Psychotherapy, group support

Fine PG, et al. *J Support Oncol.* 2004;2(suppl 4):5-22; Porteney FK, et al. In: Lowinson JH, et al. eds. Substance Abuse: A Comprehensive Textbook. 4th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2005:863-903.

Pain Treatment Continuum

Least invasive

Most invasive

Continuum not related to efficacy

Psychological/physical approaches

Topical medications

Systemic medications*

Interventional techniques*

*Consider referral if previous treatments were unsuccessful.



- Classes of systemic agents with efficacy demonstrated in multiple, randomized, controlled trials for neuropathic pain
 - Anticonvulsants (e.g. Gabapentin/Neurontin, Pregabalin/Lyrica)
 - Antidepressants (e.g. Amitriptyline/Elavil, Duloxetine/Cymbalta)
 - Opioids (e.g. Morphine, Oxycodone/Oxycontin, Percocet, Vicodin)

The Perils of Placebo

Of course, parachute design and testing should always be done with the **utmost** scientific rigor and diligence.



FDA-Approved Treatments for Neuropathic Pain (Oct 2018)

- Lidocaine patch 5%
 PHN
- Gabapentin– PHN
- Carbamazepine

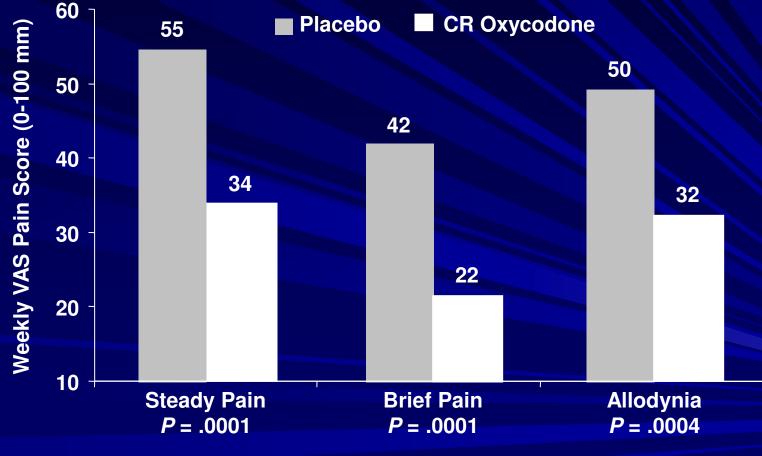
 Trigeminal neuralgia

 Duloxetine

 PDN
- Pregabalin – PHN - PDN High-conc capsaicin patch - PHN (US FDA) – Periph PN x DM EMEA) Tapentadol – DPN

Opioid Analgesics: Efficacy in Postherpetic Neuralgia

VAS Scores During Final Week of Treatment



N = 38

Reproduced with permission from Watson CPN, Babul N. Neurology. 1998;50:1837-1841.

Combination Therapy for Peripheral Neuropathic Pain

Possible Advantages

Decreased adverse effects¹

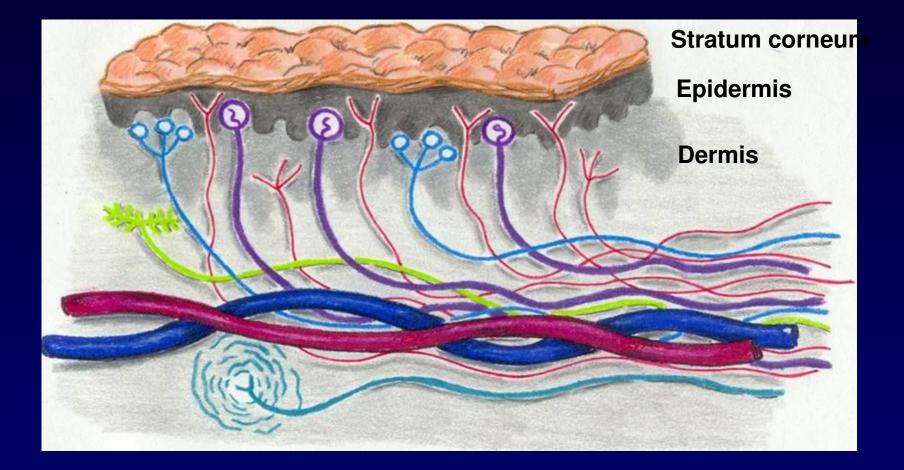
Increased efficacy^{1,2,4}

Possible Disadvantages

- Increased adverse effects^{3,4}
- Increased drug–drug interactions^{1,4}
- Complex drug regimens⁴
 Difficulty in determining
 - cause of adverse effects^{3,4}

- 1. Namaka M et al. *Clin Ther*. 2004;26:951-979.
- 2. Dworkin RH et al. Arch Neurol. 2003;60:1524-1534.
- 3. Dworkin RH, Schmader KE. *Clin Infect Dis.* 2003;36:877-882.
- 4. Harden N, Cohen M. J Pain Symptom Manage. 2003;25:S12-S17.

Sensory System in Skin



Courtesy of K Bley

Topical Treatments for Pain





Lidocaine Patch 5%



Capsaicin Patch Neuropathy Treatment Procedure







Take Home Points

Patients who present to their primary care physicians with pain require:

- -A thorough diagnostic evaluation
- -Targeted diagnostic testing
- Aggressive cause-specific treatment
- -Lifestyle modification
- -Pain control

Summary

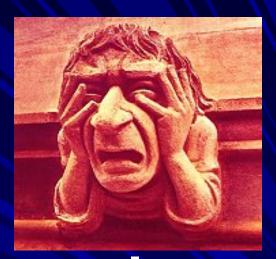
- Neuropathic pain is common, and a major cause of chronic pain and suffering
- Pain is underdiagnosed and undertreated
- A rational, mechanism-based approach to treatment of pain provides substantial improvement in quality of life
- Successful treatment requires long term close relationships with patients
- Successes are not measured by eliminating painbut by improving ability to function.

Mount Sinai Neuropathy Research Program

<u>Neurology</u>

David M. Simpson, MD, FAAN Jessica Robinson-Papp, MD Shanna Patterson, MD

<u>Neuropathy Research Team</u> Mary Catherine George, Program Coordinator Alexandra Nmashie, MD



<u>Neuropsychology</u> David Dorfman, PhD



