

Activity will begin momentarily.

SOWEGA-AHEC

CURE Activity

August 10, 2010

Management of Painful Diabetic Peripheral Neuropathy and Post Herpetic Neuralgia

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SOWEGA-AHEC

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Speaker Disclosures

- Speakers Bureau:
 - Pfizer
 - Forest Pharmaceuticals
 - Novartis
 - Daiichi-Sankyo

Objectives

- Describe the diagnostic evaluation process and treatment options for Diabetic Peripheral Neuropathy.
- Describe the diagnostic evaluation process and treatment options for Post Herpetic Neuralgia.

Opening Remarks

Why this subject? / Why me?

- 72 yo white female w/ Post Herpetic Neuralgia (right S2 distribution)
- 52 yo white male w/ Idiopathic Peripheral Neuropathy

Treatment Evolution

Painful Peripheral Neuropathy

Define and Classify Pain Types

- Review Neuroanatomy
- Review Normal and Abnormal Pain Mechanisms
- Focus on Diabetic Peripheral Neuropathy (DPN) and Post Herpetic Neuralgia (PHN)
 - Prevalence
 - Diagnosis
 - Treatments

Defining Pain

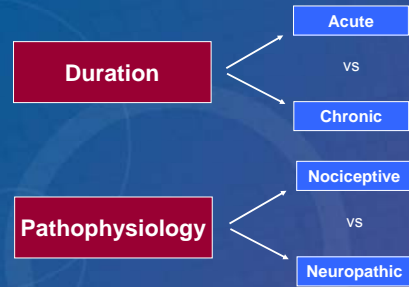
"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."



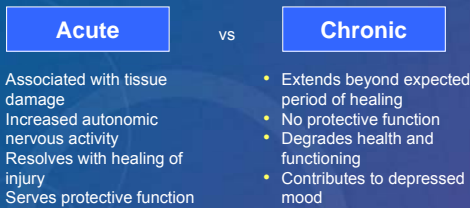
International Association for the Study of Pain (IASP)

International Association for the Study of Pain Web site.
Available at: <http://www.iasp-pain.org/terms-p.html>. Accessed September 30, 2004.

Classifying Pain

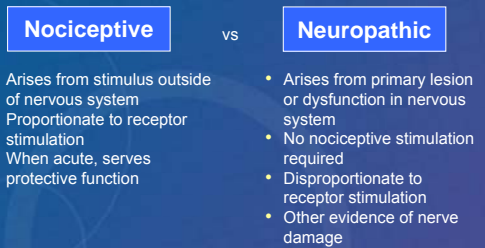


Acute vs Chronic Pain States



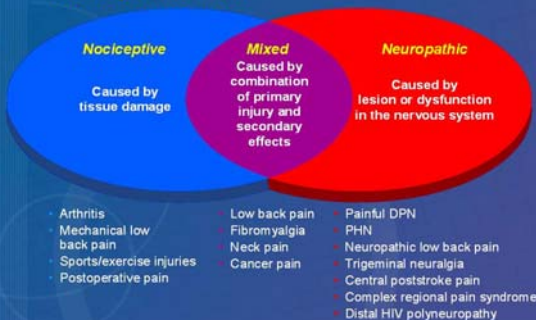
Turk, Okifuji. In: Bonica's Management of Pain, 2001; Chapman, Stollman. In: Pain and Touch, Handbook of Perception and Cognition, 2nd ed., 1996; Fields. Neuropsychiatr Neuropsychol Behav Neurol, 1991;4:83-92.

Nociceptive vs Neuropathic Pain States

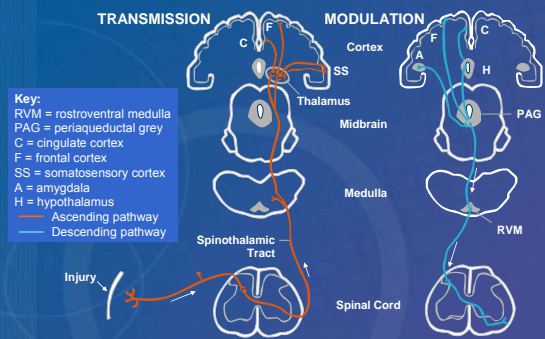


Serra. Acta Neurol Scand. 1999;173(suppl):7-11.

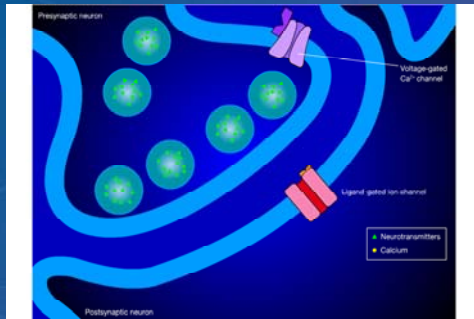
Examples of Nociceptive and Neuropathic Pain



Normal Pain Pathways



Voltage-Gated Calcium Channel Structure



Causes of Neuropathic Pain

Trauma	Surgery	Nutritional deficiency	Niacin Thiamine Pyridoxine Folic acid / B12
Complex regional pain syndrome (CRPS) type II Amputation (phantom limb pain/stump pain)	Spinal cord injury Crush injuries	Immune mediated	Multiple sclerosis Boeck sarcoidosis Guillain-Barré syndrome Some peripheral neuropathies
Infection	Herpes zoster Infectious mononucleosis Human immune deficiency syndrome Diphtheria Leprosy Syphilis	Compression/entrapment syndromes	Spinal stenosis Carpal tunnel syndrome Tarsal tunnel Plexus disorders Chronic radiculopathy

Causes of Neuropathic Pain

Vasculitis/connective tissue disorders	Churg-Strauss Cryoglobulinemia Lupus erythematosus Rheumatoid arthritis Polyarteritis nodosa Sjogren syndrome	Cancer related	Compressive Infiltrative Paraneoplastic Iatrogenic
Toxins	Chemotherapy agents, especially vincristine and cisplatinum Other drugs such as nitrofurantoin, isoniazid, phenytoin, hydralazine, thalidomide Alcohol Arsenic Lead Gold Mercury Glue sniffing	Metabolic disturbance	Diabetes mellitus Uremia Porphyria Hypothyroidism Amyloidosis
		Genetically determined	Fabry disease Hereditary sensory neuropathies
		Miscellaneous	Syringomyelia Painful epileptic crisis Chronic progressive or recurrent polyneuropathy

Peripheral Neuropathic Pain

Diabetic Peripheral Neuropathy (DPN)
Post Herpetic Neurogic (PHN)

DPN: What Is It?

- Nerve damage and dysfunction secondary to diabetes mellitus type 1 or 2
 - Consensus definition: "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes"
- A very common complication of diabetes
- A leading cause of neuropathic pain

Boulton et al. *Diabet Med.* 1998;15:508-514.

DPN Classification Based on Clinical Features

- Hyperglycemic neuropathy
- Hypoglycemic neuropathy
- Generalized neuropathies
 - Sensorimotor polyneuropathy
 - Acute painful sensory neuropathy
 - Autonomic neuropathy
 - Acute motor neuropathy
- Focal and multifocal neuropathies
 - Cranial neuropathy
 - Thoracolumbar radiculoneuropathy
 - Proximal diabetic neuropathy
- Focal limb neuropathy
- Superimposed chronic inflammatory demyelinating neuropathy

Thomas, In: *Textbook of Diabetic Neuropathy*, 2003.

DPN and PHN Produce Positive and Negative Symptoms

Positive Sensory Symptoms

- Spontaneous pain
- Dysesthesias
- Paresthesias
- Evoked pain

Negative Sensory Symptoms

- Loss/impairment of sensory quality
- Numbness, reduced sensation

Baron. *Clin J Pain*. 2000;16(2 suppl):S12-S20.

Spontaneous Symptoms

Symptom	Description
Spontaneous pain	Persistent burning pain, shocklike pain
Dysesthesias	Abnormal, unpleasant sensations (eg, shooting, lancinating, burning)
Paresthesias	Abnormal, not unpleasant sensations (eg, tingling)

Baron. *Clin J Pain*. 2000;16(2 suppl):S12-S20. International Association for the Study of Pain Website. Available at: <http://www.iasp-pain.org/terms-p.html>. Accessed September 30, 2004.

Stimulus-Evoked Symptoms

Symptom	Definition
Allodynia	Painful response to nonpainful stimulus
Hyperalgesia	Heightened response to normally painful stimulus
Hyperpathia	Explosive response to normally painful stimulus

International Association for the Study of Pain Web site. Available at: <http://www.iasp-pain.org/terms-p.html>. Accessed September 30, 2004.

Distal Symmetric Polyneuropathy

- Result of sensory nerve damage
 - Large ($A\alpha/\beta$) fibers
 - Small ($A\delta$ and C) fibers
- Most patients have mixed neuropathy
 - Large- and small-fiber symptoms
- Sock-and-glove distribution very common



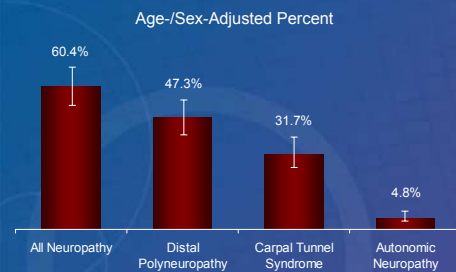
Vinik. In: *Diabetes and Carbohydrate Metabolism*. 2002.

Distal Symmetric Polyneuropathy: Small Fiber

- First: pain and hyperalgesia
- Later: loss of sensitivity
 - Heat/Cold
 - Light touch/pinprick
- Autonomic symptoms
- Predisposes to diabetic foot disease
- Electrophysiology may not detect nerve damage

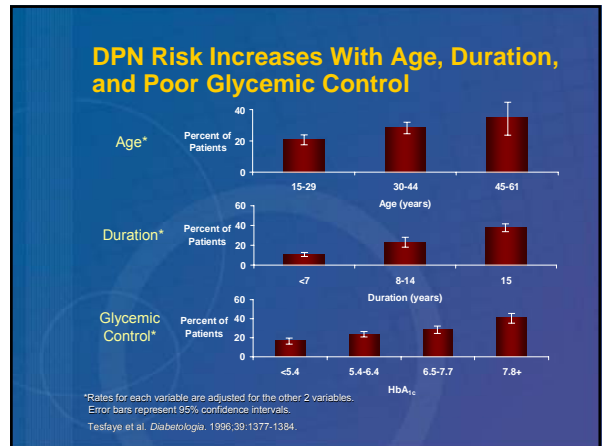
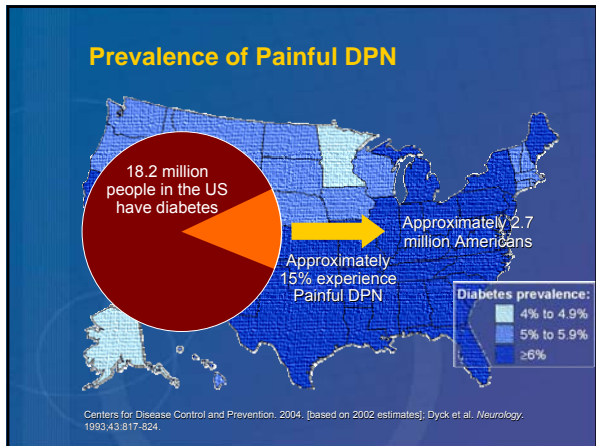


Prevalence of Neuropathy in the Rochester Diabetic Neuropathy Study, 1986

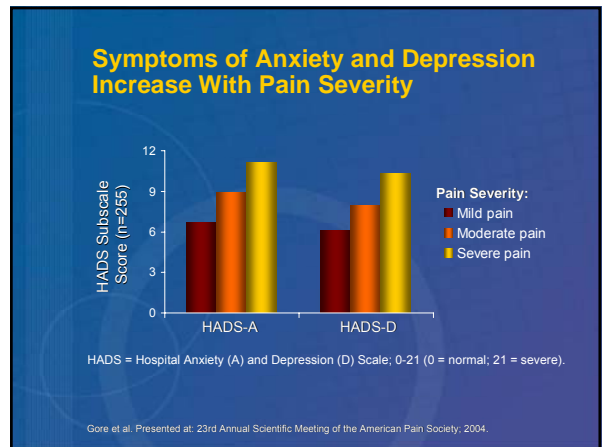
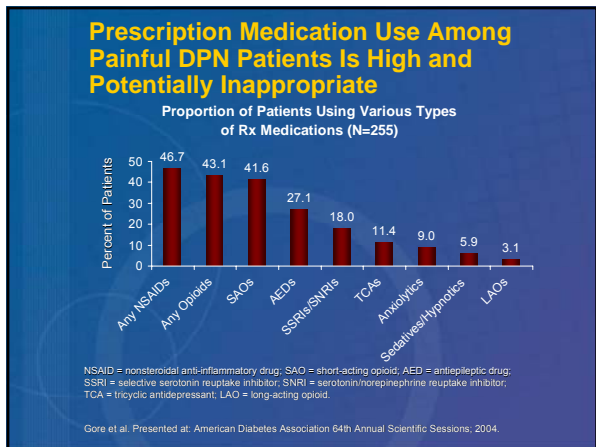
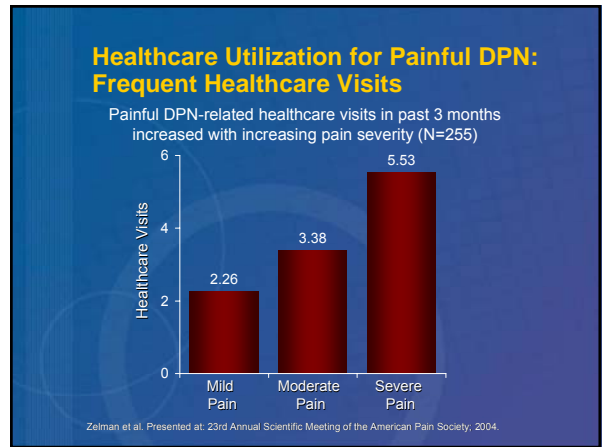


Prevalence figures are age- and sex-adjusted to the Rochester, Minn, population. Error bars represent 95% confidence intervals.

Dyck et al. *Neurology*. 1993;43:817-824.

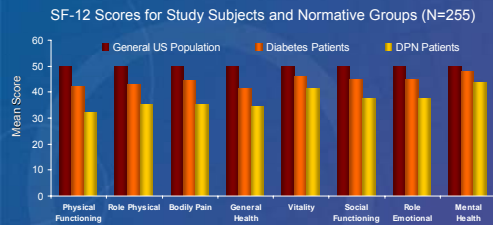


DPN: Burden of Illness Survey



Impact of Painful DPN: Physical and Mental Health Status

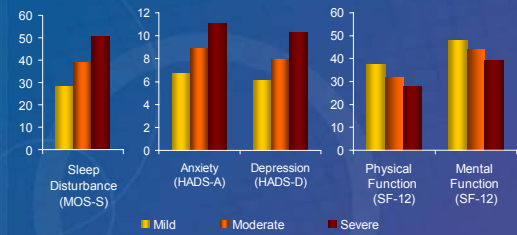
Painful DPN patients have significantly lower SF-12 scores than general US population and diabetic patients



Gore et al. Presented at: 23rd Annual Scientific Meeting of the American Pain Society, 2004.
Ware et al. How to Score Version 2 of the SF-12 Health Survey, 2002.

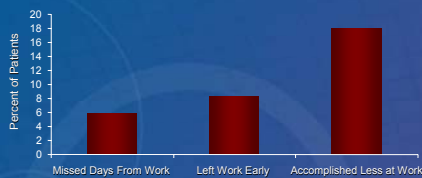
Painful DPN Impacts Multiple Domains of Patient Function

As pain increases, patient physical and emotional functioning is increasingly impaired



Gore et al. Presented at: 23rd Annual Scientific Meeting of the American Pain Society, 2004.

Painful DPN Diminishes Work Productivity



- 29% of patients surveyed with painful DPN (N=255) are part-time or full-time workers
- Data reported for part-time and full-time employed patients only

Data on file. Pfizer Inc, New York, NY.

Economic Burden of Diabetes and DPN

	Cost (US)
Diabetes (total)	\$132 billion
Direct medical	\$92 billion
Indirect (lost productivity)	\$40 billion
DPN	\$11 billion (\$4.6-\$13.7 billion)

American Diabetes Association. Diabetes Care. 2003;26:917-932 [based on 2002 estimates].
Gordois et al. Diabetes Care. 2003;26:1790-1795 [costs in 2001 US dollars].

Diabetic Foot Ulcers



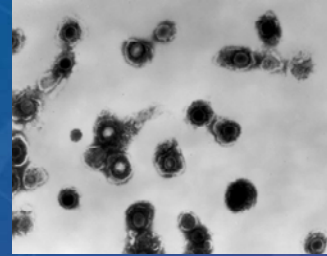
Photo Researchers. Used with permission.

Painful DPN: Summary

- Roughly 15% of diabetics affected
 - At least 2.7 million Americans
 - Risk factors: age, duration of diabetes, poor glycemic control
- Substantial impact on global health status
- Diabetes causes widespread peripheral nerve damage
 - Large fiber
 - Small fiber
 - Autonomic

PHN: An Introduction

Varicella Zoster Virus



Electron micrograph of varicella zoster virions from vesicle fluid of patient with chickenpox.

Image by Dr Erskine Palmer.

From Dormant Herpes Zoster to PHN

Acute Herpes Zoster



Image used with permission by M Oxman, MD, University of California, San Diego, Calif.

Acute Herpes Zoster



© Dr P. Marazzi, Science Photo Library. Image used with permission.

Dermatomal Distribution of Herpes Zoster Rash



Adapted with permission, from Head, Campbell. Brain. 1900;23:353-523.

PHN: What Is It?

- The medical literature contains a variety of PHN definitions
 - Pain arising or persisting in areas affected by herpes zoster at least 3 months after healing of the skin lesion
- Variety of symptom presentation
- Risk increases with age
- Patients may describe multiple pain components
 - Constant deep pain
 - Brief shooting or shocking pain
 - Cutaneous allodynia

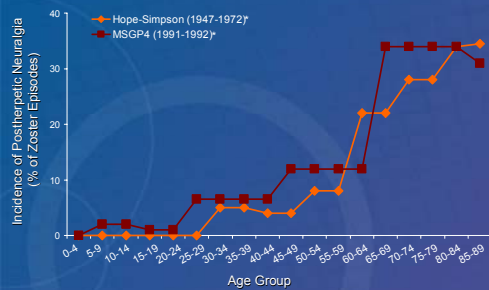
Bowsher. In: *Herpes Zoster and Postherpetic Neuralgia*. 2nd ed. 2001; Bonezzi, Demartini. *Acta Neurol Scand*. 1990;(suppl 173):25-35; Edmunds et al. *Vaccine*. 2001;19:3076-3090; Rowbotham, Fields. *Pain*. 1988;33:129-144.

Epidemiology of Herpes Zoster and PHN

Data Collected	Rate
Annual incidence of herpes zoster	
<20 years of age	0.4 to 1.6 cases per 1000
≥80 years of age	4.5 to 11 cases per 1000
Annual incidence of PHN	11 cases per 100,000
Lifetime prevalence of PHN	70 cases per 100,000
Cases of PHN in United States	Estimates range from 500,000 to 1,000,000

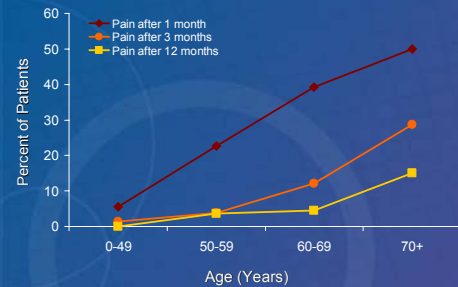
Kost, Straus. *N Engl J Med*. 1998;335:32-42; MacDonald et al. *Brain*. 2000;123:665-676; Bennett. *Acta Anaesthesiol Sin*. 1999;37:197-203; Bowsher. *Eur J Pain*. 1999;3:333-342.

Probability of PHN Among Acute Zoster Episodes Increases With Age



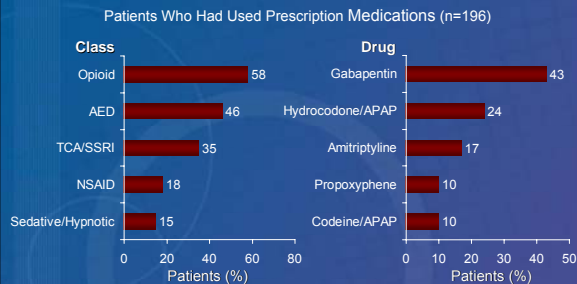
*Primary care studies in England and Wales.
Edmunds et al. *Vaccine*. 2001;19:3076-3090.

Percentage of 421 Herpes Zoster Patients With Pain After 1, 3, and 12 Months



Pain was characterized as mild to moderate.
Helgason et al. *BMJ*. 2000;321:794-796.

Prescription Medication Use in Patients With PHN



AED = antiepileptic drug; TCA/SSRI = tricyclic antidepressant/selective serotonin reuptake inhibitor; NSAID = nonsteroidal anti-inflammatory drug; APAP = N-acetyl-p-aminophenol.
Oster et al. Presented at: 22nd Annual Scientific Meeting of the American Pain Society, 2003; Oster et al. Presented at: 6th International Conference on the Mechanisms and Treatment of Neuropathic Pain, 2003.

PHN: Summary

- Caused by varicella zoster virus infection
 - Nerve damage persists after skin healing
- Risk increases with age
 - Up to 1 million Americans affected
 - Estimates vary based on PHN definition
- Need for additional treatments remains
 - High medication uses with low treatment satisfaction
 - Common medications problematic in elderly

Painful DPN and PHN:

Clinical Management

Challenges in Managing Neuropathic Pain

- Diverse symptoms
- Multiple mechanisms
- Variable response to treatment

A complete workup for neuropathic pain includes

- Physical and neurologic exam
- History
- Laboratory tests

Dworkin et al. *Arch Neurol*. 2003;60:1524-1534.

Taking a Detailed Medical History

Current

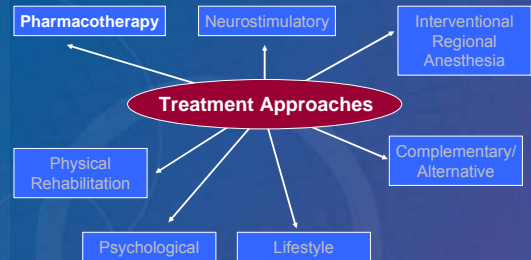
- Major complaints
- Medical comorbidities
- Psychiatric comorbidities (ie, depression, anxiety)
- Pain medications
- Sleep quality
- Work-related issues
- Rehabilitative needs and available support systems

Previous

- Medical complaints
- Toxic exposures (eg, paclitaxel, radiation)
- Pain medications

Nicholson, Verma. *Pain Med*. 2004;5(suppl 11):S9-S27. AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc*. 2002;50(suppl):S205-S224; Poncalet. *Geriatrics*. 2003;58:18-30.

Management of Neuropathic Pain Associated With DPN and PHN



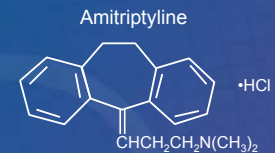
Belgrade. *Postgrad Med*. 1999;106:127-132, 135-140. Ashburn, Staats. *Lancet*. 1999;353:1865-1869; Abuaiisha et al. *Diabetes Res Clin Pract*. 1998;39:115-121.

Current Therapies for Painful DPN or PHN

- Antidepressants
 - Tricyclics
 - Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Anticonvulsants
 - First generation
 - Second generation
- Opioid analgesics
- Dermal and topical treatments

Tricyclic Antidepressants

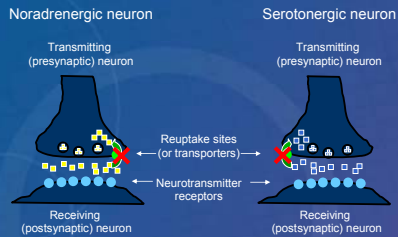
- Amitriptyline
- Imipramine
- Nortriptyline
- Desipramine
- Clomipramine
- Doxepin
- Trimipramine
- Amoxapine
- Protriptyline



Baldessarini. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. 2001.

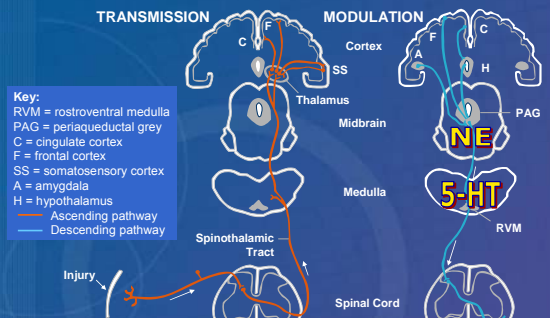
Tricyclic Antidepressants: Mechanism(s) of Action

Block reuptake of norepinephrine and serotonin



Baldessarini. In: Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 10th ed. 2001.

Normal Pain Pathways



Adapted with permission, from Fields. In: *The Placebo Effect: An Interdisciplinary Exploration*, 1997.

Tricyclic Antidepressants: Positive Controlled Trials

Study	Agent (mg/d)	N	Weeks	Primary End Point
Painful DPN				
Max	Amitriptyline (25-150, PBO)	29	12	Pain relief
Max	Desipramine (12.5-150, PBO), Amitriptyline (12.5-150, PBO)	108	14	Pain relief
Sindrup	Desipramine (50 or 200, PBO), Clomipramine (50 or 75, PBO)	26	6	Neuropathy symptoms
Max	Desipramine (12.5-250, PBO)	20	12	Pain relief
PHN				
Watson	Amitriptyline (>12.5, PBO)	24	8	Pain relief
Max	Amitriptyline (12.5-150, PBO)	58	12	Pain relief
Graff-Radford	Amitriptyline (12.5-200, PBO)	49	8	Pain intensity
Kishore-Kumar	Desipramine (12.5-250, PBO)	26	12	Pain relief
Raja	Nortriptyline (10-160, PBO)	76	24	Pain intensity, relief, cognitive function

Max et al. *Neurology*, 1987;37:588-596; Max et al. *N Engl J Med*, 1992;326:1250-1256; Sindrup et al. *Br J Clin Pharmacol*, 1990;30:683-691; Max et al. *Pain*, 1991;43:3-9; Watson et al. *Neurology*, 1992;32:671-673; Max et al. *Neurology*, 1988;38:1427-1432; Graff-Radford et al. *Clin J Pain*, 2000;16:188-192; Kishore-Kumar et al. *Clin Pharmacol Ther*, 1990;47:305-312; Raja et al. *Neurology*, 2002;59:1015-1021.

Tricyclic Antidepressants: Adverse Effects

- Most common adverse effects
 - Sedation
 - Anticholinergic effects
 - Dry mouth
 - Blurred vision
 - Increased intraocular pressure
 - Mydriasis (pupil dilation)
 - Constipation
 - Paralytic ileus
 - Urinary retention
 - Delayed micturition
 - Urinary tract dilation
 - Hyperpyrexia
 - Sinus tachycardia
- Often have unacceptable side effects in the elderly

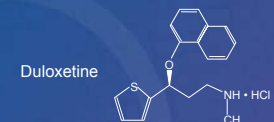
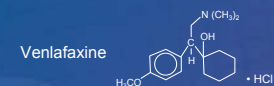
Drug Facts & Comparisons, 2004; AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc*, 2002;50(suppl):S205-S224.

Tricyclic Antidepressants: Summary

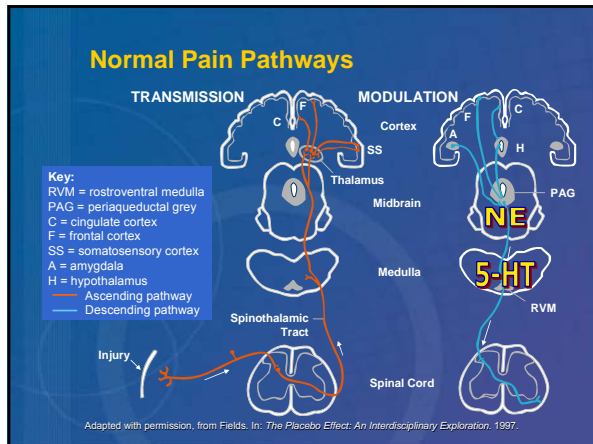
- Primary action in relieving neuropathic pain most likely increasing synaptic serotonin and norepinephrine levels
- May be effective in relieving painful DPN and PHN
- Many side effects from binding to several neurotransmitter receptors
- Utility for painful DPN or PHN may be limited by poor tolerability, particularly in the elderly

Pharmacologic Options: SNRIs

- SNRIs
 - Venlafaxine
 - Duloxetine



Baldessarini. In: Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 10th ed. 2001; Physicians' Desk Reference®, 59th ed. 2005.

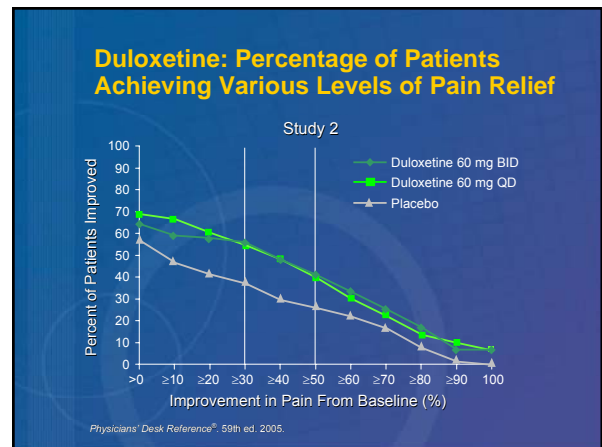
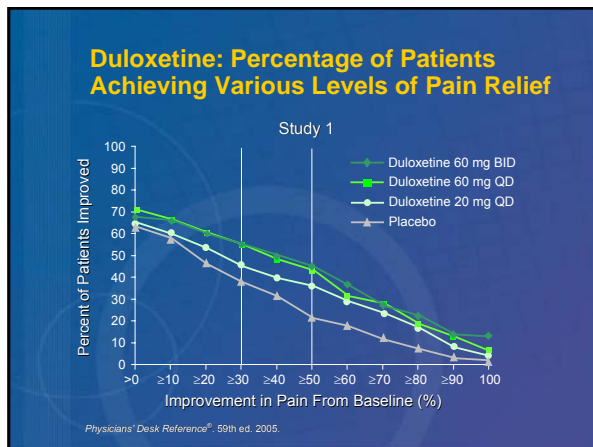


SNRIs: Positive Controlled Trials

Study	Agent (mg/d)	N	Weeks	Primary End Point
Painful DPN				
Rowbotham	Venlafaxine (75 or 150-225, PBO)	244	6	Mean change in VAS-PI, VAS-PR
Duloxetine Study 1	Duloxetine (20, 60, or 120; PBO)	457	12	End point mean pain score
Duloxetine Study 2	Duloxetine (60 or 120, PBO)	334	12	End point mean pain score

PBO = placebo; VAS-PI = Visual Analog Scale of Pain Intensity; VAS-PR = Visual Analog Scale of Pain Relief; SNRI = serotonin-norepinephrine reuptake inhibitor.

Goldstein DL, et al. *Pain*. 2005;116:109-118; Rowbotham et al. *Pain*. 2004;110:697-706; *Physicians' Desk Reference*®, 59th ed. 2005.

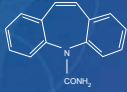


- ### Duloxetine: Summary of Adverse Events
- Most common adverse events in duloxetine-treated DPN patients*
 - Nausea
 - Somnolence
 - Dizziness
 - Constipation
 - Dry mouth
 - Hyperhidrosis
 - Decreased appetite
 - Asthenia
- *≥5% and at least twice the incidence in placebo-treated patients.
- Physicians' Desk Reference*®, 59th ed. 2005.

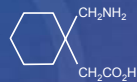
- ### Duloxetine: Additional Safety Information
- Warnings
 - Suicide risk
 - Monoamine oxidase inhibitors (MAOIs)
 - Precautions
 - Hepatotoxicity
 - Increased blood pressure (BP) (requires BP lowering and periodic monitoring)
 - Activation of mania/hypomania
 - Seizures
 - Controlled narrow-angle glaucoma
 - Increase in fasting blood glucose
 - Drug-drug interactions
 - CYP1A2 inhibitors (eg, cimetidine)
 - CYP2D6 inhibitors (eg, paroxetine)
 - Drugs metabolized by CYP2D6 (eg, amitriptyline)
 - Contraindications
 - Hypersensitivity to duloxetine
 - Patients taking MAOIs
 - Uncontrolled narrow-angle glaucoma
- Physicians' Desk Reference*®, 59th ed. 2005.

Anticonvulsants

- First generation
 - Phenytoin
 - Phenobarbital
 - Primidone
 - Ethosuximide
 - Carbamazepine
 - Valproic acid
- Second generation
 - Gabapentin
 - Lamotrigine
 - Topiramate
 - Tiagabine
 - Levetiracetam
 - Oxcarbazepine
 - Zonisamide
 - Felbamate



Carbamazepine



Gabapentin

McNamara, In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. 2001. *Physicians' Desk Reference*®, 59th ed. 2005; Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc, 2004.

Anticonvulsants: Positive Controlled Trials

Study	Agent (mg/d)	N	Weeks	Primary End Point
Painful DPN				
Wilton	Carbamazepine (600, PBO)	40	4	Pain relief
Rull	Carbamazepine (600, PBO)	30	6	Neuropathy symptoms
Backonja	Gabapentin (900-3600, PBO)	165	8	Daily pain severity
Eisenberg	Lamotrigine (25-400, PBO)	59	6	Pain intensity
PHN				
Rice	Gabapentin (1800 or 2400, PBO)	334	7	Mean daily pain
Rowbotham	Gabapentin (300-3600, PBO)	229	8	Mean daily pain

Wilton. *S Afr Med J*. 1974;48:869-872; Rull et al. *Diabetologia*. 1969;5:215-218; Backonja et al. *JAMA*. 1996;280:1831-1838; Eisenberg et al. *Neurology*. 2001;57:505-506; Rice. *Pain*. 2001;94:215-224; Rowbotham et al. *JAMA*. 1998;280:1837-1842.

Anticonvulsants: Safety and Adverse Events

	Carbamazepine*	Gabapentin†‡	Lamotrigine†§
Neuropathic pain indication	Trigeminal neuralgia	PHN	Not currently indicated
Most common adverse events	Dizziness Drowsiness Nausea Unsteadiness Vomiting	Dizziness Somnolence Peripheral edema	Vomiting Dyspepsia Dizziness Ataxia Somnolence Incoordination Insomnia Rash Diplopia Blurred vision
Black box warnings	Aplastic anemia and agranulocytosis	None	Severe rash including Stevens-Johnson syndrome

*Frequency not specified; †adverse events occurring in ≥5% of patients and with at least twice the incidence of placebo group; ‡postherpetic neuralgia; §adjunctive therapy in adults with epilepsy.

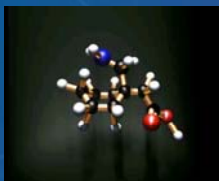
Physicians' Desk Reference®, 59th ed. 2005; Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc, 2004.

Carbamazepine: Efficacy and Dosing

- Efficacy
 - Indicated for trigeminal neuralgia
 - Significant pain relief compared with placebo shown in DPN trials
- Dosing (trigeminal neuralgia)
 - Beginning dosage: 200 mg/d (2 divided doses)
 - Titration: 100-mg increments every 12 hours
 - Maximum dosage: 1200 mg/d

Physicians' Desk Reference®, 59th ed. 2005; Wilton. *S Afr Med J*. 1974;48:869-872; Rull et al. *Diabetologia*. 1969;5:215-218.

Gabapentin: Chemical Structure



Carbamazepine is indicated for the management of PHN in adults. Gabapentin is contraindicated in patients who have a demonstrated hypersensitivity to the drug or its ingredients.

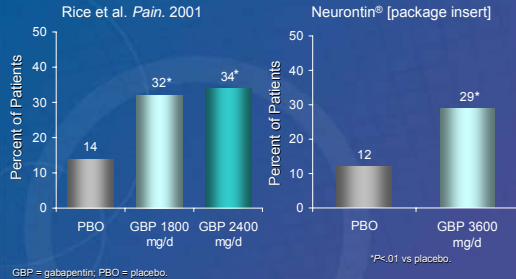
Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc, 2004.

Gabapentin: Mechanism of Action

- Interacts with $\alpha_2\text{-}\delta$ subunit of voltage-gated Ca^{2+} channels
- In animal models
 - Prevents allodynia and hyperalgesia
 - Prevents pain-related responses in models of neuropathic pain
 - Decreases pain-related responses after peripheral inflammation
- Relevance of these models to human pain is not known

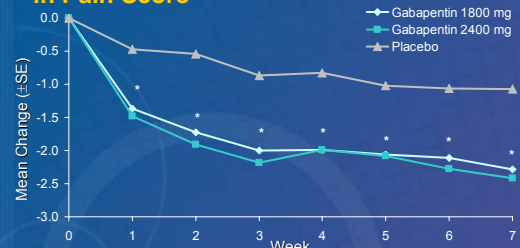
Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc, 2004.

Gabapentin: 50% Responder Rates in PHN



Percentage of patients with ≥50% reduction in pain, last observation carried forward analysis.

Gabapentin in PHN: Reduction in Pain Score



The most common observed adverse events associated with the use of gabapentin in adults compared with placebo were dizziness (28.0% vs 7.5%), somnolence (21.4% vs 5.3%), peripheral edema (8.3% vs 2.2%), asthenia (5.7% vs 4.8%), and diarrhea (5.7% vs 3.1%).

Rice, Maton. *Pain*, 2001;94:215-224.

Gabapentin: Most Common Adverse Events in Controlled Clinical Trials for PHN

	Gabapentin* N=336 % (n)	Placebo N=227 % (n)
Dizziness	28.0 (94) [†]	7.5 (17)
Somnolence	21.4 (72) [†]	5.3 (12)
Peripheral edema	8.3 (28) [†]	2.2 (5)
Asthenia	5.7 (19) [‡]	4.8 (11)
Diarrhea	5.7 (19) [‡]	3.1 (7)

*Patients receiving any dose of gabapentin; [†]incidence >5% and more than twice the rate observed with placebo; [‡]incidence >1% and numerically greater than placebo.

Adverse events were usually mild to moderate in intensity.

Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc, 2004.

Opioids: Mechanism of Action

- Bind to opioid receptors
 - G-protein-linked cell signaling molecules
 - Endogenous ligands
 - Enkephalins
 - Endorphins
 - Dynorphins
 - Physiologic role not completely understood
- Analgesia at spinal and supraspinal levels
- Enhance descending pain modulation pathway

Gutstein, Akil. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed, 2001.

Opioids: Positive Controlled Trials

Study	Agent (mg/d)	N	Weeks	Primary End Point
Painful DPN				
Gimbel	CR oxycodone (20-120, PBO)	159	6	Pain intensity
Harati	Tramadol (50-400, PBO)	131	6	Pain intensity
Watson	CR oxycodone (20-80, PBO)	45	8	Mean daily pain
PHN				
Raja	CR morphine (15-240, PBO)	76	24	Pain intensity, relief; cognitive function
Watson	CR oxycodone (20-60, PBO)	50	8	Pain intensity, relief

PBO = placebo.

Gimbel et al. *Neurology*, 2003;60:927-934; Harati et al. *Neurology*, 1998;50:1842-1846; Watson et al. *Pain*, 2002;105:71-76; Raja et al. *Neurology*, 2002;59:1015-1021; Watson, Babul. *Neurology*, 1998;50:1837-1841.

Opioids: Efficacy

- Place in neuropathic pain treatment remains controversial
- Recent evidence suggests some benefit in painful DPN and PHN
- Doses needed for neuropathic pain may be higher than for nociceptive pain

Nicholson. *Drugs*, 2003;63:17-32; Dworkin et al. *Arch Neurol*, 2003;60:1524-1534; Benedetti et al. *Pain*, 1996;74:205-211; Cherny et al. *Neurology*, 1994;44:857-861.

Opioids: Safety and Tolerability

- Most common adverse effects
 - Respiratory depression
 - Skeletal muscle rigidity
 - Apnea
 - Bradycardia
 - Lightheadedness
 - Dizziness
 - Sedation
 - Nausea
 - Vomiting
 - Sweating
 - Constipation
- Associated with tolerance, dependence, and abuse liability
- Special issues in the elderly
 - Cognitive effects
 - Mobility
 - Hip fractures

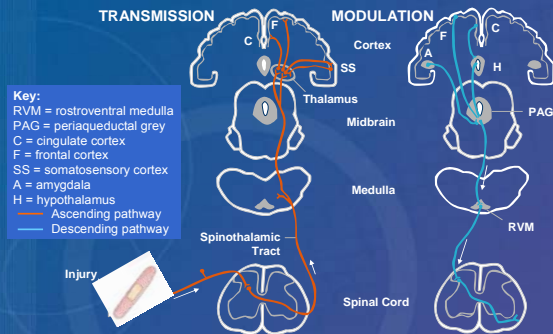
Drug Facts & Comparisons, 2004; Cutstein, Akil. In: Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 10th ed, 2001; Dworkin et al. *Arch Neurol*, 2003;60:1524-1534.

Dermal and Topical Treatments

- Lidocaine patch
 - Inhibits voltage-gated Na⁺ channels
 - Indicated for PHN
 - Suggested efficacy in open-label studies of DPN has not been confirmed in controlled trials
 - Common adverse events (localized to treatment site)
 - Erythema
 - Edema
- Capsaicin
 - One study found effective pain relief compared with amitriptyline
 - Other studies have given mixed results

Catterall, Mackie. In: Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th ed, 1996; Physicians' Desk Reference®, 59th ed, 2005; Barbano et al. *Arch Neurol*, 2004;61:914-918; Blesbroeck et al. *Adv Ther*, 1995;12:111-120; Low et al. *Pain*, 1995;62:163-168; Capsaicin Study Group. *Arch Intern Med*, 1991;151:2225-2229.

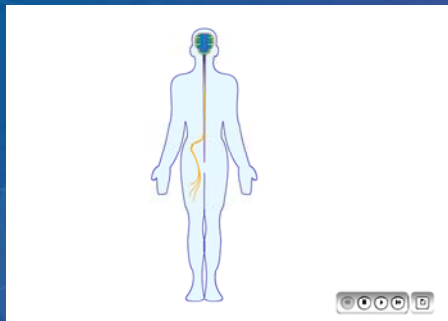
Normal Pain Pathways



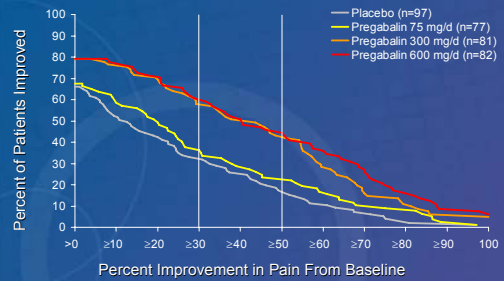
Pregabalin

Mechanism of Action and Clinical Data

Pregabalin Mechanism of Action



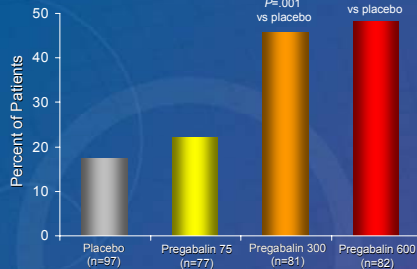
Pregabalin: Patients Achieving Various Levels of Pain Relief*



*Baseline observation carried forward (BOCF) analysis.

Lyrica® (pregabalin) Capsules CV [package insert]. New York, NY: Pfizer Inc, 2005.

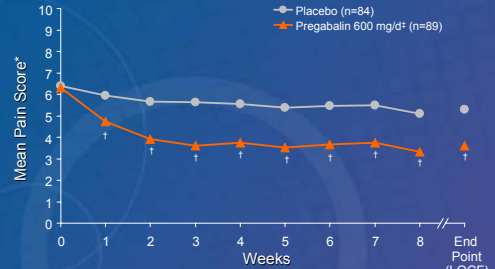
Pregabalin: Percentage of Patients With $\geq 50\%$ Reduction in Pain in Painful DPN*



*Last observation carried forward (LOCF) analysis. All pregabalin doses in mg/d.

Lesser et al. *Neurology*, 2004;63:2104-2110. Data on file. Pfizer Inc, New York, NY.

Pregabalin Effect on Mean Weekly Pain Scores in PHN

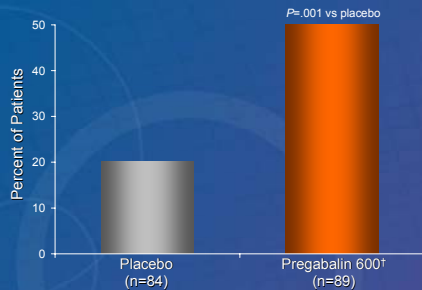


*Least squares means calculated from the model. †P < .01

‡Dose adjusted to 300 mg/d in cases of renal insufficiency.

Dworkin et al. *Neurology*, 2003;60:1274-1283.

Pregabalin: Percentage of Patients With $\geq 50\%$ Reduction in Pain in PHN*



*Last observation carried forward (LOCF) analysis. †Dose adjusted to 300 mg/d in cases of renal insufficiency. All pregabalin doses in mg/d.

Dworkin et al. *Neurology*, 2003;60:1274-1283. Data on file. Pfizer Inc, New York, NY.

Pregabalin: Efficacy Summary

- Extensive clinical trial program
- Efficacy confirmed in 6 controlled trials
 - Utilizing painful DPN and PHN models
 - Significant improvement in weekly mean pain scores
 - High responder rates
 - Efficacy sustained in 5- to 13-week controlled trials
- Fast onset of pain relief—within 1 week in some patients
- Efficacious in refractory patients, including those who failed gabapentin

In all controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (8%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. More frequent assessments should be considered for patients who are already routinely monitored for ocular conditions.

Incidence (%) of Most Common* Adverse Events With Pregabalin in All Controlled Studies

Adverse Event	Percentage of Patients				
	Pregabalin 150 mg/d (n=1164)	Pregabalin 300 mg/d (n=1224)	Pregabalin 600 mg/d (n=1802)	All Pregabalin (n=5508)†	Placebo (n=2384)
Dizziness	15.4	30.4	35.9	29.2	8.7
Somnolence	13.1	20.6	28.2	22.2	7.7
Dry mouth	5.4	6.8	11.0	9.1	3.4
Peripheral edema	4.8	8.9	7.3	6.1	1.8
Blurred vision	4.2	5.6	8.9	6.4	2.1
Weight gain	3.5	5.1	8.2	5.6	0.8
Thinking abnormal‡	2.3	2.9	8.2	5.4	1.6

*Incidence $\geq 5\%$ and at least twice the rate observed with placebo.

†Includes all doses across all controlled studies.

‡Primarily difficulty with concentration/attention.

Data on file. Pfizer Inc, New York, NY.

Adverse Events That Most Frequently Led to Discontinuation in Pregabalin Painful DPN and PHN Studies*

Reason for Discontinuation	Pregabalin† %	Placebo %
Painful DPN (n=979)		(n=459)
Any adverse event	9	4
Dizziness	3	<1
Somnolence	2	<1
PHN (n=852)		(n=398)
Any adverse event	14	7
Dizziness	4	<1
Somnolence	3	<1

*Includes data for the controlled study cohorts (painful DPN or PHN) only.

†Includes all pregabalin doses.

Lyrica® (pregabalin) Capsules CV [package insert]. New York, NY: Pfizer Inc; 2005. Data on file. Pfizer Inc, New York, NY.

Warnings for Pregabalin

- **Withdrawal from antiepileptic drugs**
 - Should be gradual and occur over a minimum of 1 week
- **Tumorigenic potential***
 - Dose-dependent increase in hemangiosarcoma, a vascular-type tumor, in 2 strains of mice
 - Clinical significance of this finding unknown
 - No evidence of carcinogenicity in 2 rat studies
 - Pregabalin is nongenotoxic (ie, it does not have DNA-damaging potential)

*Based on mouse-specific hemangiosarcoma.
Lyrica® (pregabalin) Capsules CV [package insert], New York, NY: Pfizer Inc, 2005.

Pregabalin: Drug Abuse and Dependence

	Abuse Potential	Medical Use
Schedule I	High	No
Schedule II	High	Yes
Schedule III	<I and II	Yes
Schedule IV	<III	Yes
Schedule V	<IV	Yes

- Schedule V controlled substance
 - Examples of other schedule V drugs include Robitussin A-C® and Lomotil®
 - Examples of schedule IV drugs include Ambien®

21 USC §812. Available at: <http://straylight.law.cornell.edu/uscode>. Accessed June 8, 2005. United States Department of Justice. Available at: <http://www.deadiversion.usdoj.gov>. Accessed June 23, 2005. Robitussin A-C is a registered trademark of Wyeth. Ambien is a registered trademark of Sanofi-Aventis.

Pregabalin Safety and Tolerability: Summary

- More than 10,000 patients exposed to pregabalin in clinical trials
- Majority of adverse events (AEs) were mild to moderate in intensity and dose related
- Majority of AEs resolved prior to study completion
- Low potential for pharmacokinetic drug interactions

Pregabalin may exacerbate the impairment of cognitive and gross motor function when used in conjunction with oxycodone, lorazepam, and ethanol (alcohol).

Patients with a history of drug or alcohol abuse may have a higher chance of misuse or abuse of pregabalin.

AE = adverse event.
Lyrica® (pregabalin) Capsules CV [package insert], New York, NY: Pfizer Inc, 2005.

PAINFUL PERIPHERAL NEUROPATHY: SUMMARY

- **DIAGNOSIS**
 - Accurate, specific-if possible
 - Rule out other treatable contributors (DM, Alcohol Use, B12 Deficiency, ?Heavy Metals, ?Paraneoplastic Syndrome, HIV)

PAINFUL PERIPHERAL NEUROPATHY: SUMMARY

- **TREATMENT:**
 - Eliminate the offending “toxin”
 - Control diabetes to aggressive targets
 - Cease alcohol
 - Replace B12

PAINFUL PERIPHERAL NEUROPATHY: SUMMARY

- **TREATMENT – Remember neurophysiology!**
 - Decrease pain transmission
 - Modulation of voltage gated calcium channels :Pregabalin (Lyrica), gabapentin (Neurontin)
 - Topical strategies:
 - Lidocaine patches
 - Opioid receptors:
 - Narcotics
 - Augmenting pain modulation response
 - Tricyclics (low dose)
 - NSRI – Duloxetine (Cymbalta)

FINANCIAL PAIN



QUESTIONS?

