Neuropathic Pain:

Insights Into the Spectrum and Innovative Approaches to Treatment

A CME CD-ROM

Jointly sponsored by the Dannemiller Memorial Educational Foundation and Embryon, Inc.

Supported through an unrestricted educational grant from Pfizer

Neuropathic Pain

- Neuropathic pain is represented by a broad spectrum of patients and is an increasingly significant and costly healthcare problem.
- Neuropathic pain is a chronic condition and often misunderstood and misdiagnosed by physicians.
- In the rehabilitation setting, it is important to address pharmacotherapy and its role in treating the neuropathic pain patient.
- Recent research provides opportunities for more effective management of neuropathic pain patients.

Neuropathic Pain (cont'd)

- Neuropathic pain affects 3.5 to 4 million Americans
- Basic clinical research is revealing new treatment paradigms
- The Joint Commission on Accreditation of Healthcare Organizations has mandated pain as the Fifth Vital Sign
  1. Temperature
  2. Respiration
  3. Blood pressure
  4. Pulse
  5. *Pain*

Decade of Pain Control & Research

Federal Government Recognition

- Implemented by US Congress
  - Began January 1, 2001
- Aims
  - To focus on pain in both the public and private sectors
  - To stimulate research, education, and clinical management
- *This is only the second-ever Congressionally declared medical decade (1990s: Decade of the Brain)*

American Academy of Pain Medicine, 2000.

Mandatory Physician CME in California

State Government Recognition

- California legislation requires physicians to complete pain management training
  - Treating physicians required to complete 12 hours of CME in pain management and end-of-life care in order to renew their medical license
- Sponsored by Compassion in Dying Federation and Americans for Death With Dignity
- Legislation AB 487 passed October 4, 2001

www.compassionindying.org/releases/AB487.html

Peripheral and Central Mechanisms of Neuropathic Pain

Bruce Nicholson, MD

Clinical Associate Professor of Anesthesia
Penn State School of Medicine
Director, Division of Pain Medicine/Hospice
Greater Lehigh Valley Health Network
Allentown, PA

Normal CNS Function

Excitation

Inhibition

Glutamate,
Aspartate

GABA

Abnormal Excitation

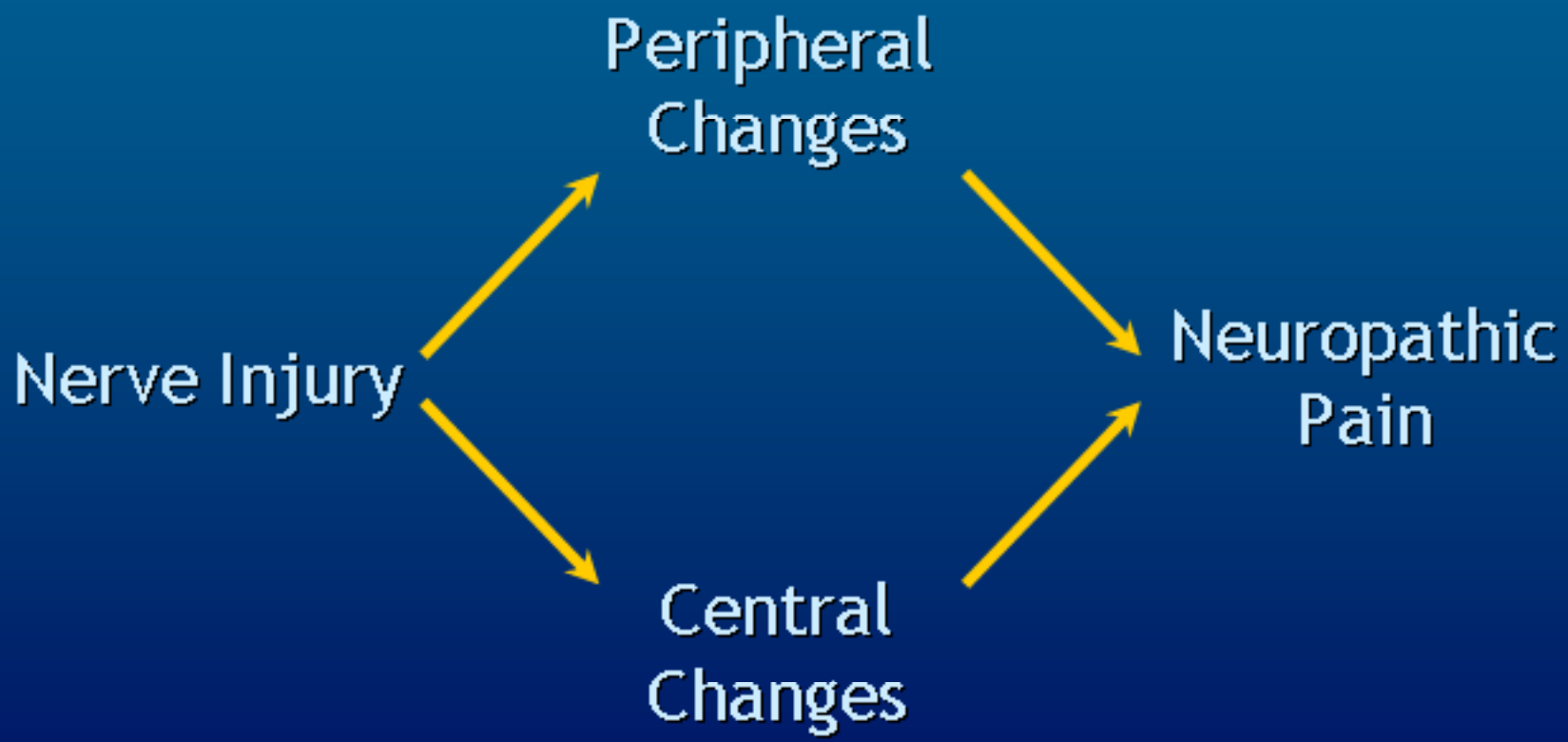
Glutamate,
Aspartate

Inhibition

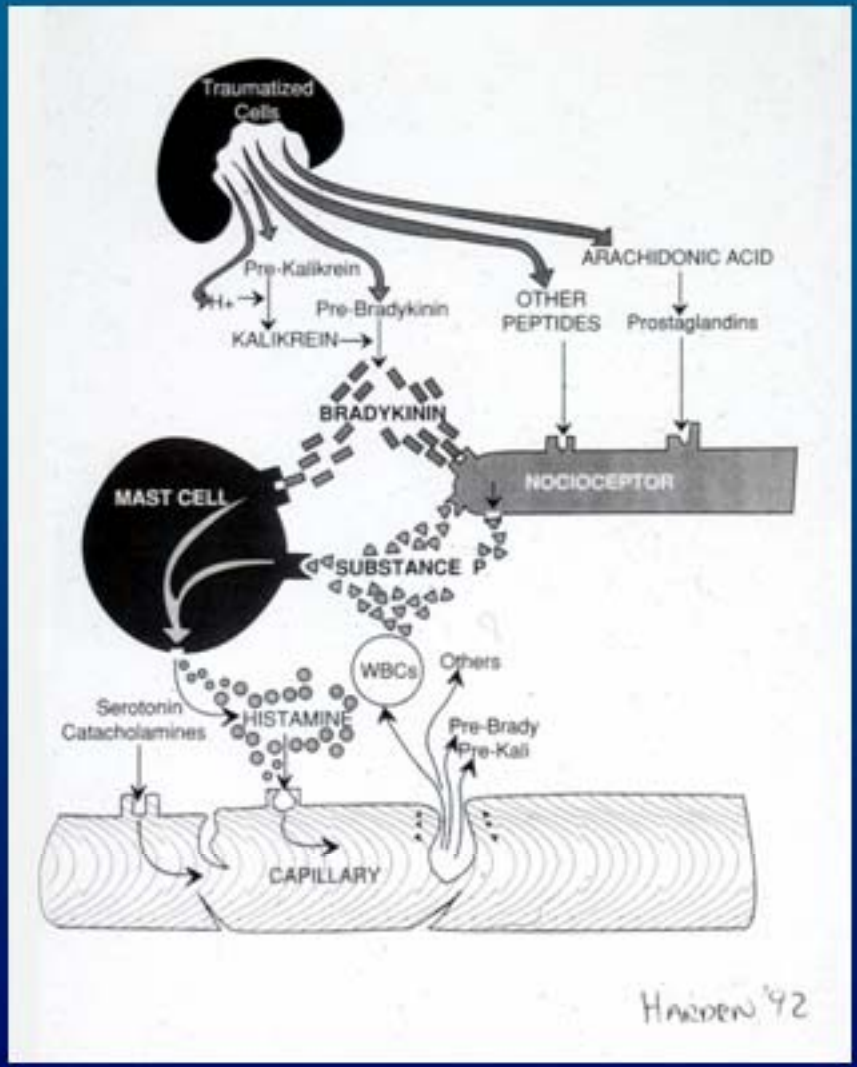
Excitation

GABA

Nerve Injury Leads to Peripheral and Central Changes



Mediators Released After Peripheral Tissue Injury



Peripheral Sensitization

Tissue damage

Inflammation

Sympathetic terminals

SENSITIZING "SOUP"

Hydrogen ions	Histamine	Purines	Leukotrienes
Noradrenaline	Potassium ions	Cytokines	Nerve growth factor
Bradykinin	Prostaglandins	5-HT	Neuropeptides

Woolf CJ, Chong, M - . *Anesth Analg* 1993; 77:1-18.

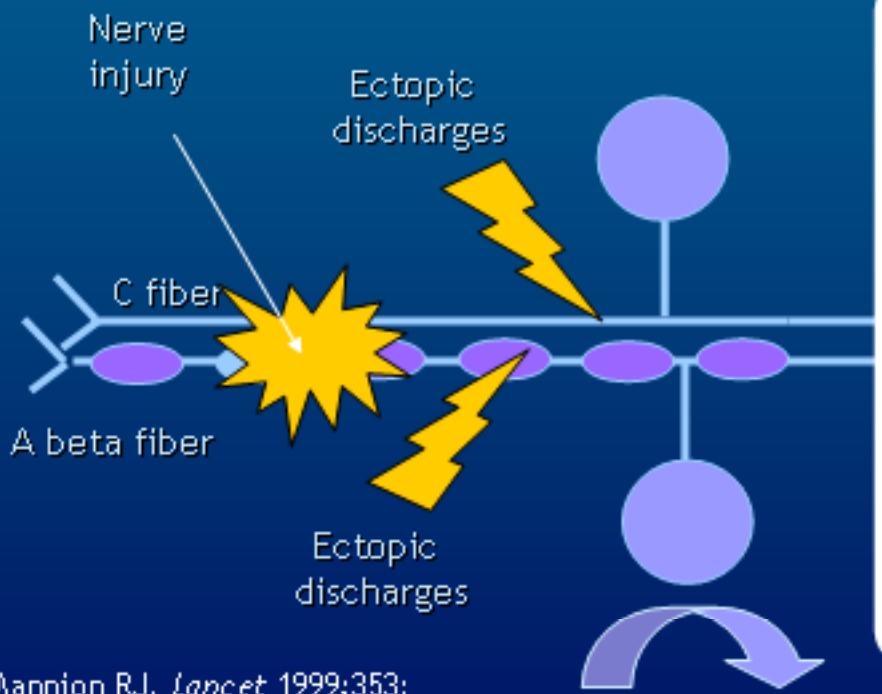
Fiber Types

Type	Function	Diameter (μm)	Velocity (ms)
C	Pain, mechanical stimuli	1 (no myelin)	0.2-1.5
B	Preganglionic/autonomic	1	3-14
Aδ	Pain, mechanical, thermal	1	5-15
Aγ	Touch, muscle tone	4	15-40
Aβ	Touch, proprioception	8	40-70
Aα	Motor	13	70-120

Effect of Nerve Injury at the Spinal Cord

Afferent fibers
Peripheral sensitization

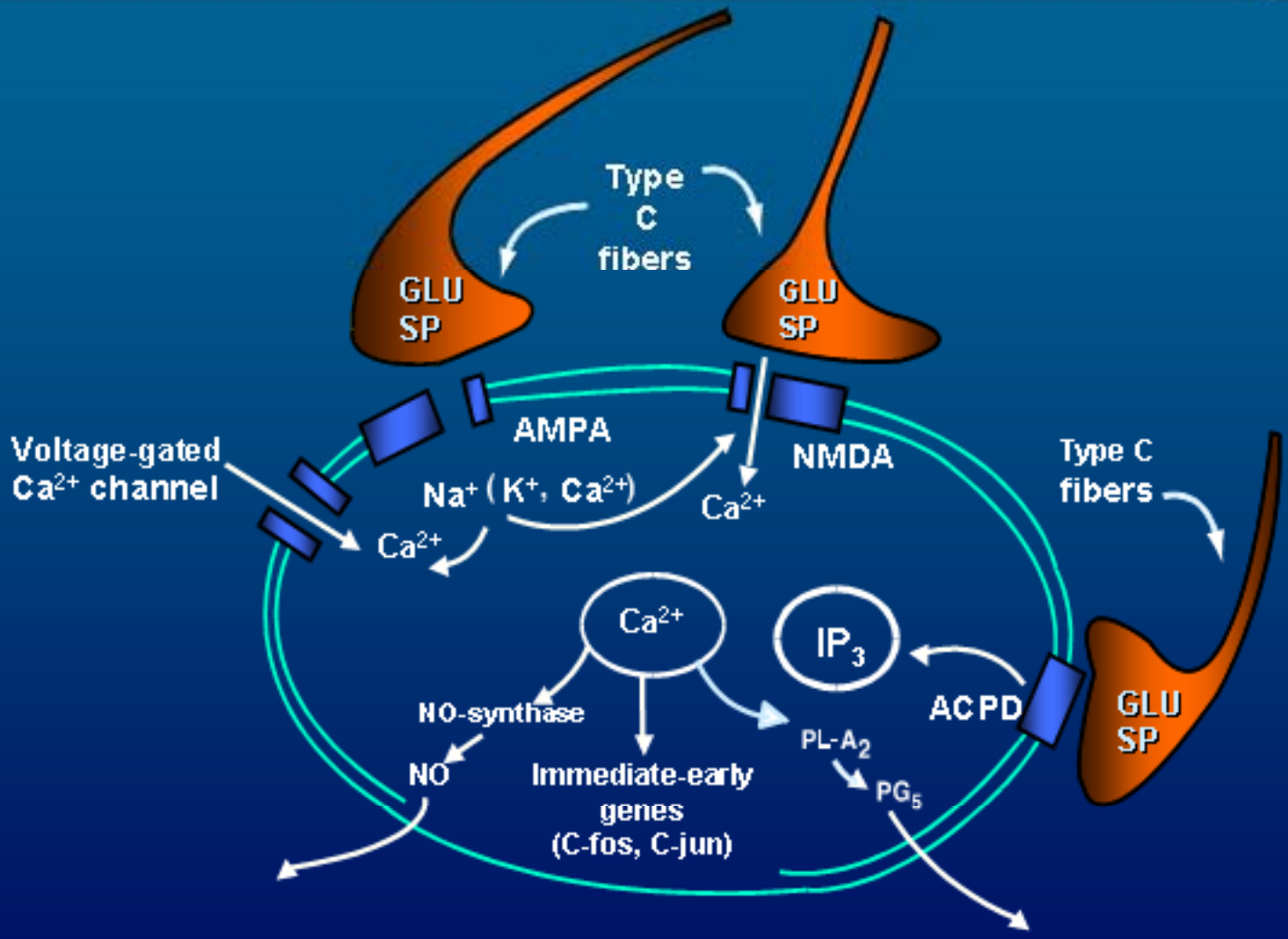
Spinal cord



- Neuroplasticity
- Central sensitization
- Alteration of modulatory systems

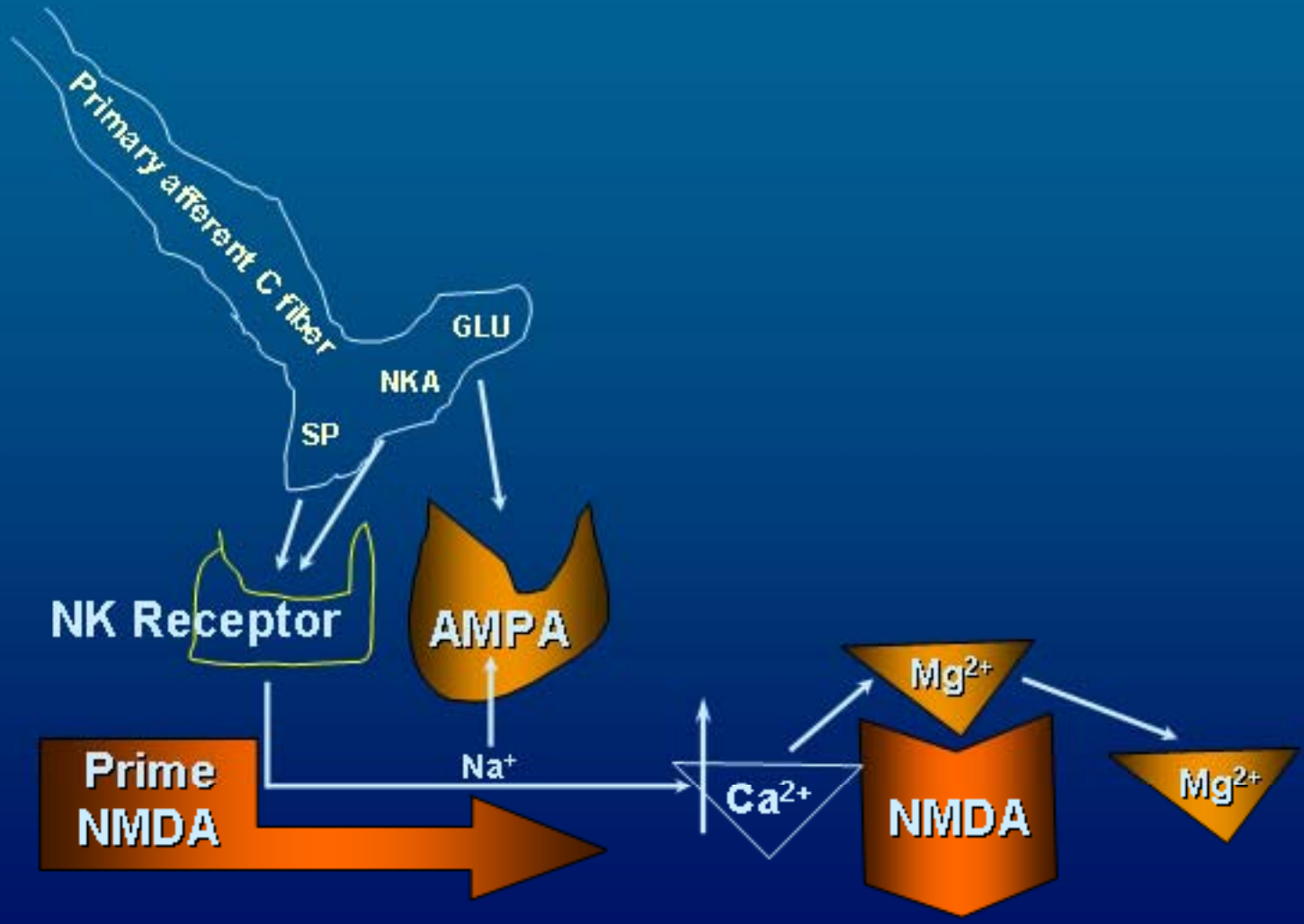
Woolf CJ, Mannion RJ. *Lancet* 1999;353: 1959 - 1964.
Attal N, Bouhassira D. *Acta Neurol Scand* 1999; 100 (Suppl 173): 12 - 24.

Mechanisms of Neuropathic Pain

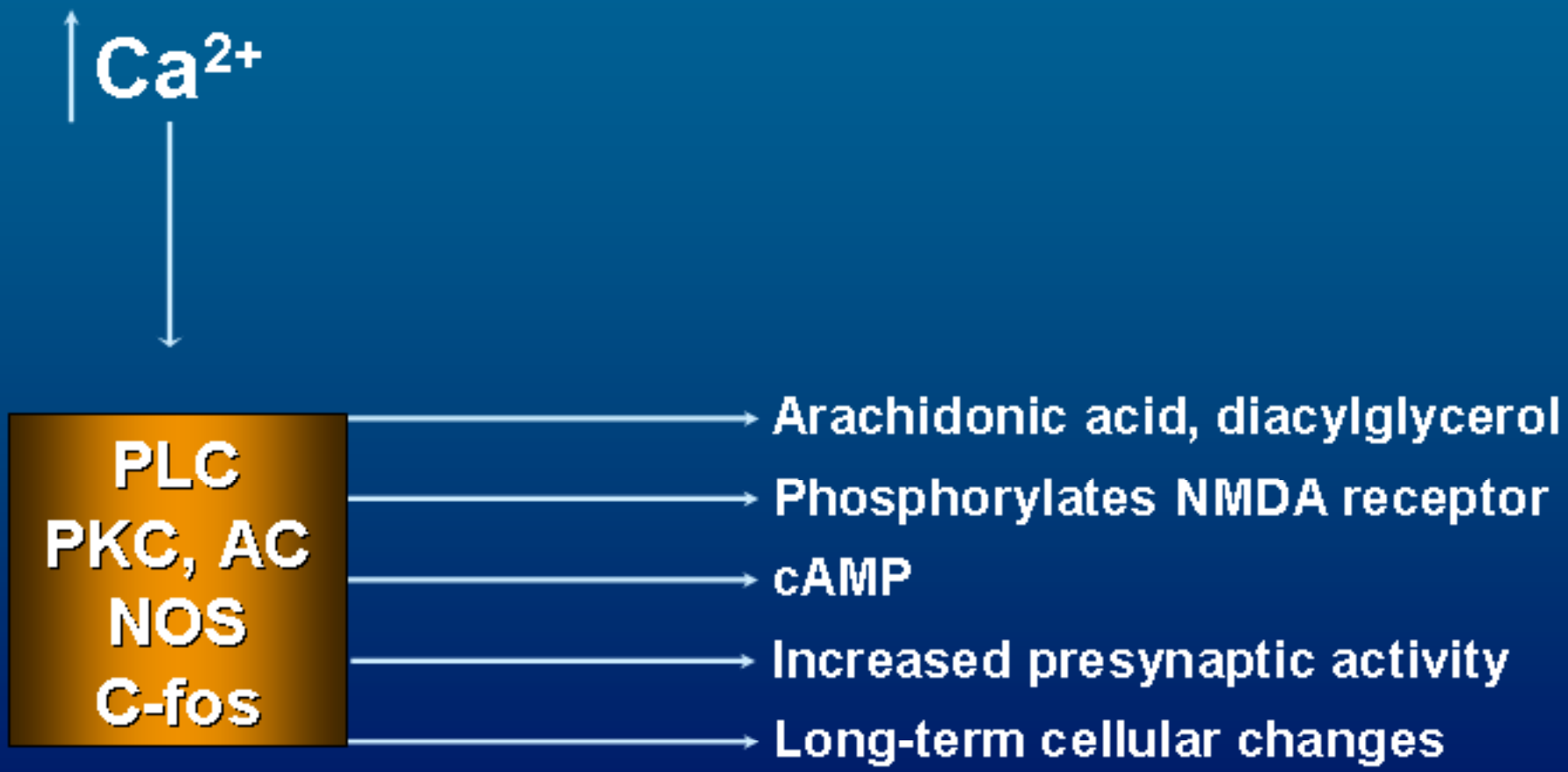


Ollat H, Cesaro P. *Clin Neuropharmacol* 1995;18:391-404.

Mechanisms of Neuropathic Pain (Cont'd)

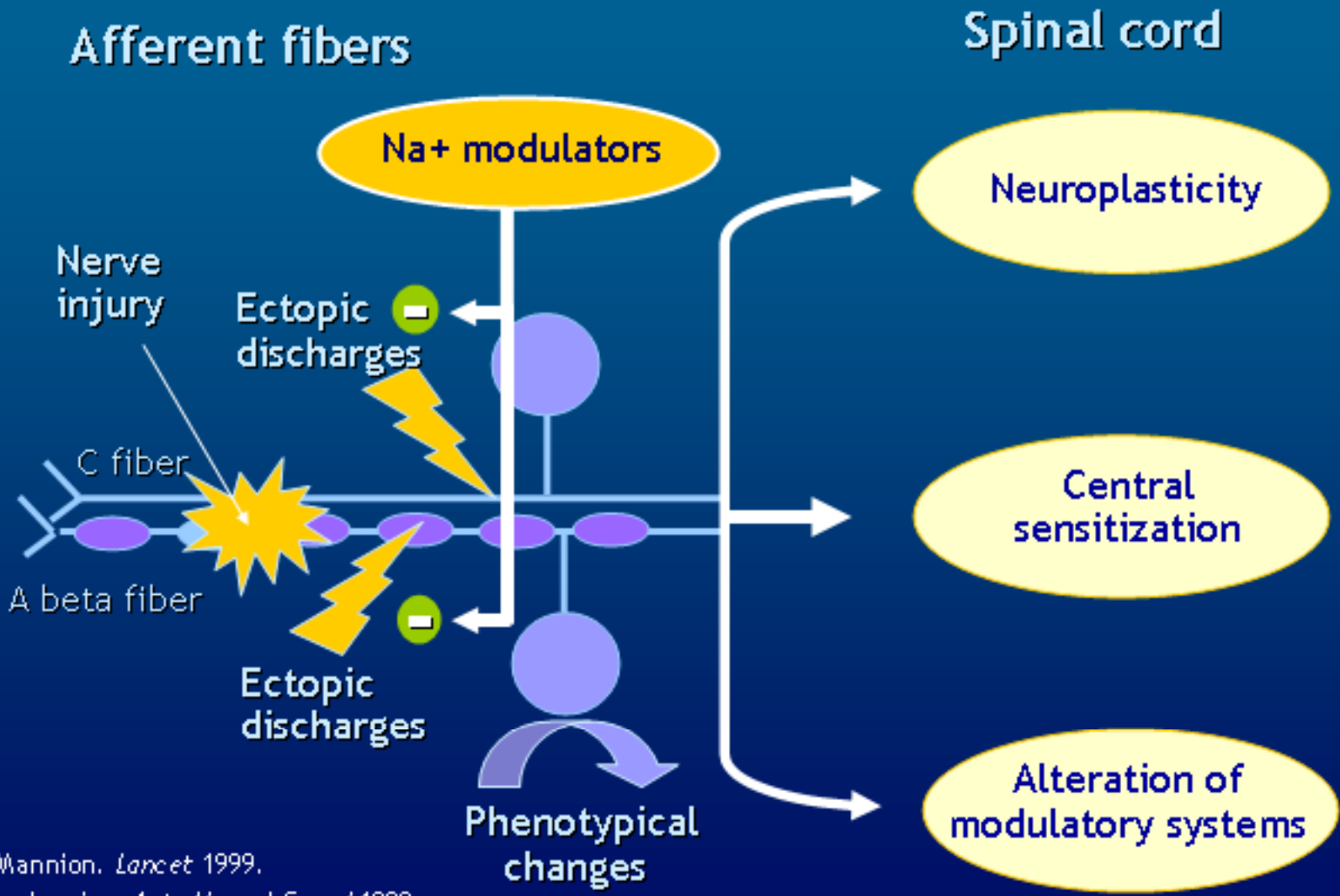


Mechanisms of Neuropathic Pain (Cont'd)



PLC = phospholipase C; PKC = protein kinase C; AC = adenyl cyclase; NOS = nitric oxide synthase; cAMP = cyclic adenosine monophosphate.

Altered Sodium Channels and Central Sensitization



Woolf & Mannion. *Lancet* 1999.
Attal & Bouhassira. *Acta Neurol Scand* 1999.

Peripheral and Central Mechanisms

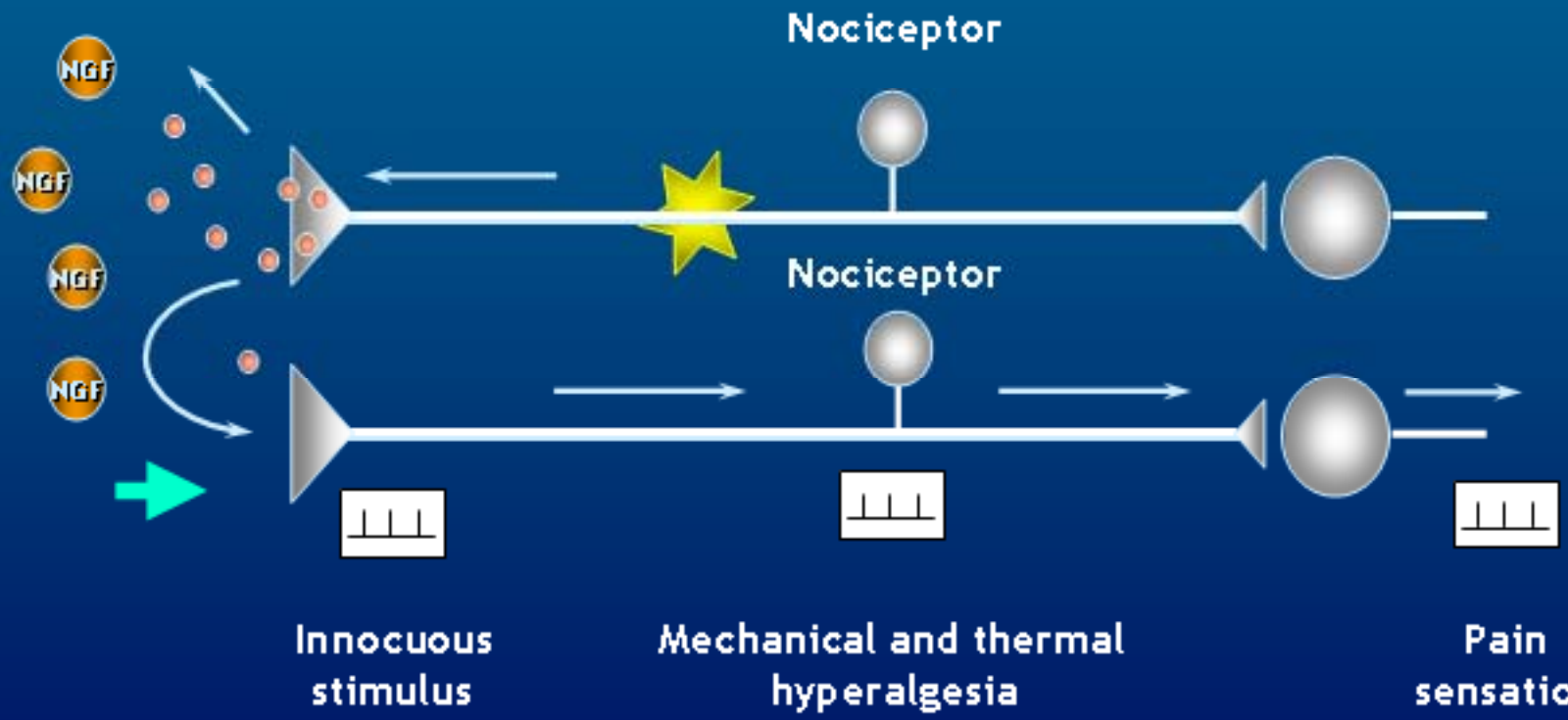
- Peripheral
  - Sensitization of peripheral neurons
  - Collateral sprouting of A fibers
  - Increased activity of damaged axons and their sprouts
- Central
  - Central sensitization
  - Reorganization of synaptic connectivity
  - Disinhibition

Hyperalgesia

- Increased response to a painful stimulus
  - Pinprick pain
  - Heat

Peripheral Sensitization

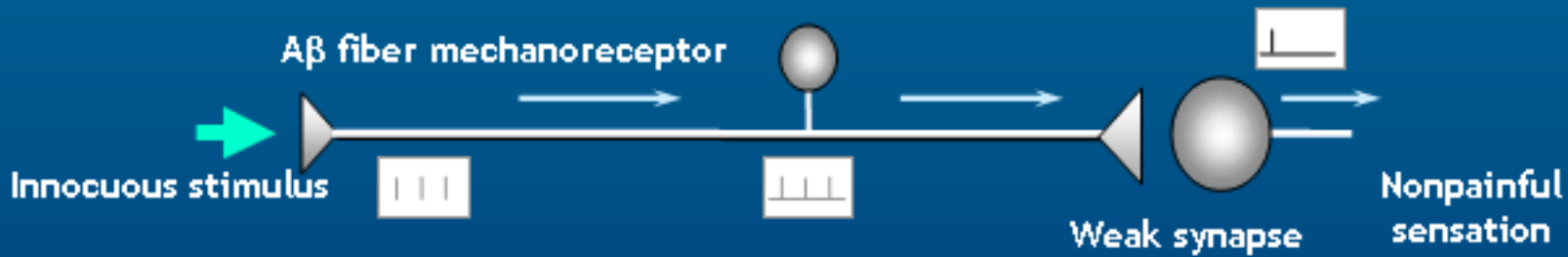
Results from antidromic activation, neurogenic inflammation, or exposure to molecules such as nerve growth factor (NGF)



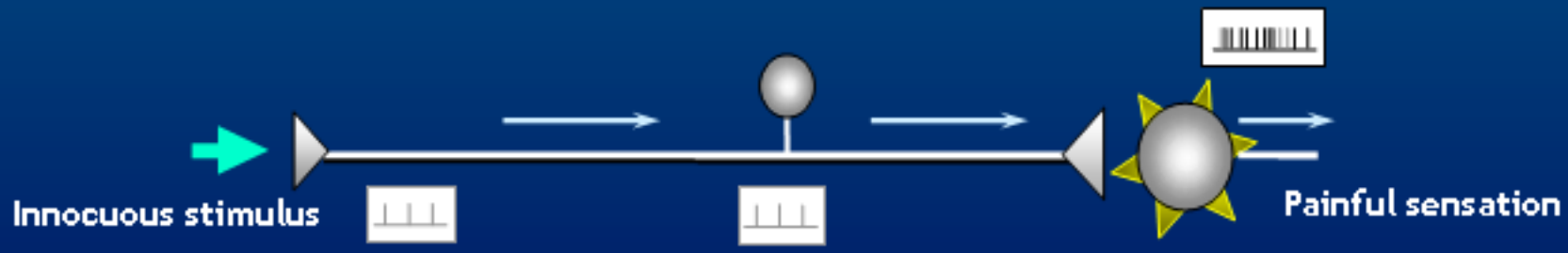
Woolf CJ, Mannion RJ. *Lancet* 1999;353:1959-1964.

Central Sensitization

Normal sensory function: Aβ fiber activation by low-threshold stimuli is unable to activate dorsal horn pathways



Increased nociceptor drive leads to central sensitization of dorsal horn neurons. Aβ fiber input is now sufficient to activate spinal cord pain pathways.



Brush-Evoked Mechanical Hyperalgesia

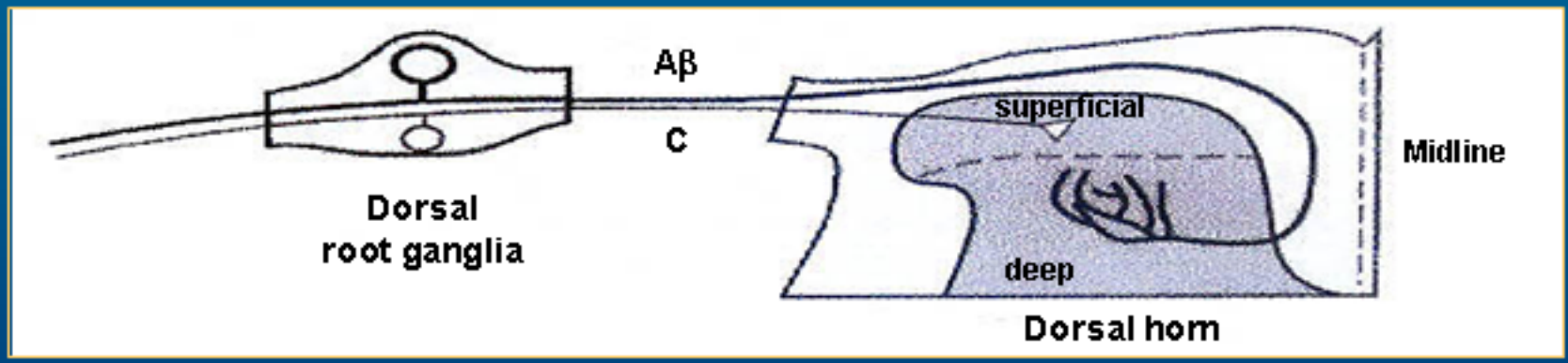
Woolf CJ, Mannion RJ. *Lancet* 1999;353:1959-1964.

Allodynia

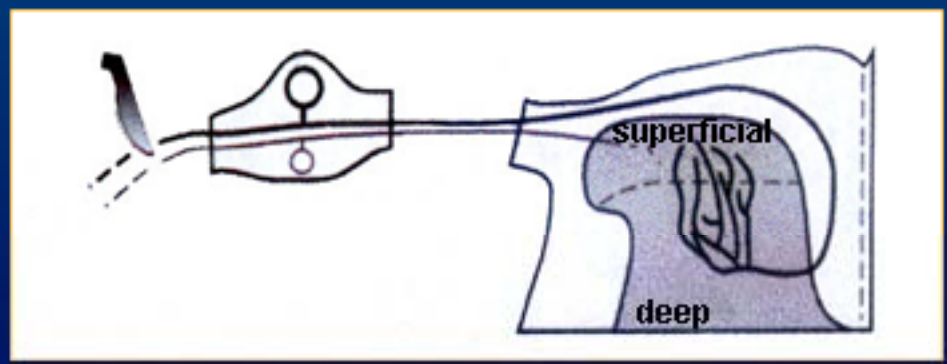
- The interpretation of a non-painful stimulus as being painful
- The result of a qualitative change in the interpretation of a stimulus
  - Dynamic Aß fiber mediated
  - Static C fiber mediated

A Fiber Sprouting

Normal terminations of primary afferents in the dorsal horn



After nerve injury, C fiber terminals atrophy and A fiber terminals sprout into the superficial dorsal horn



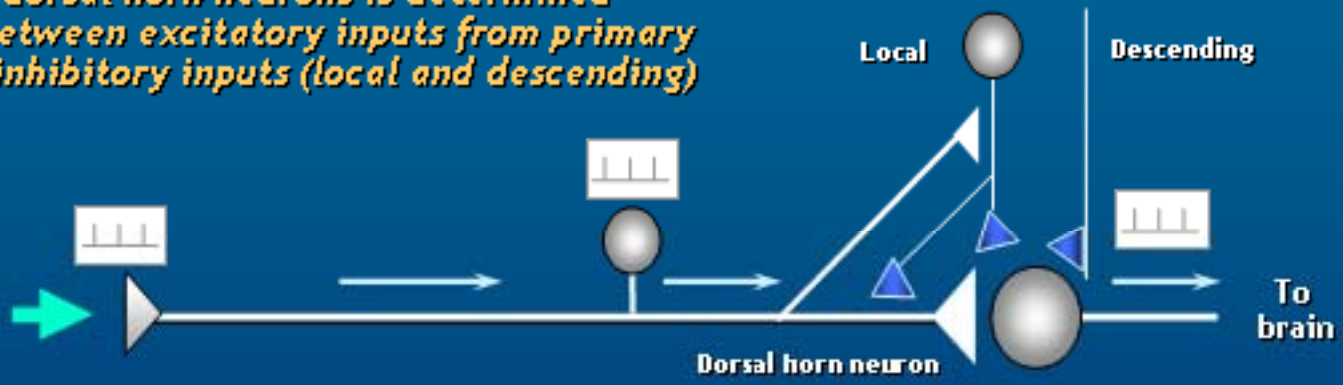
Woolf CJ, Mannion RJ. *Lancet* 1999;353:1959-1964.

Hyperpathia

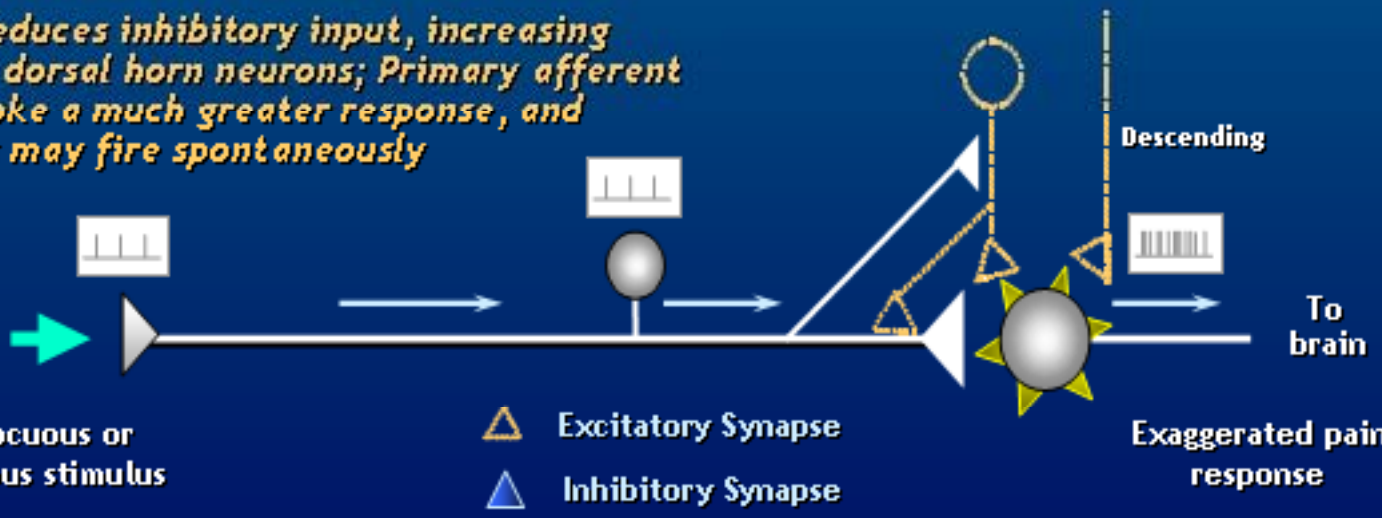
- An exaggerated and prolonged response to a painful stimulus
- A quantitative change in the interpretation of a stimulus

Disinhibition

Excitability in dorsal horn neurons is determined by a balance between excitatory inputs from primary afferents and inhibitory inputs (local and descending)



Nerve injury reduces inhibitory input, increasing excitability in dorsal horn neurons; Primary afferent inputs now evoke a much greater response, and dorsal neurons may fire spontaneously



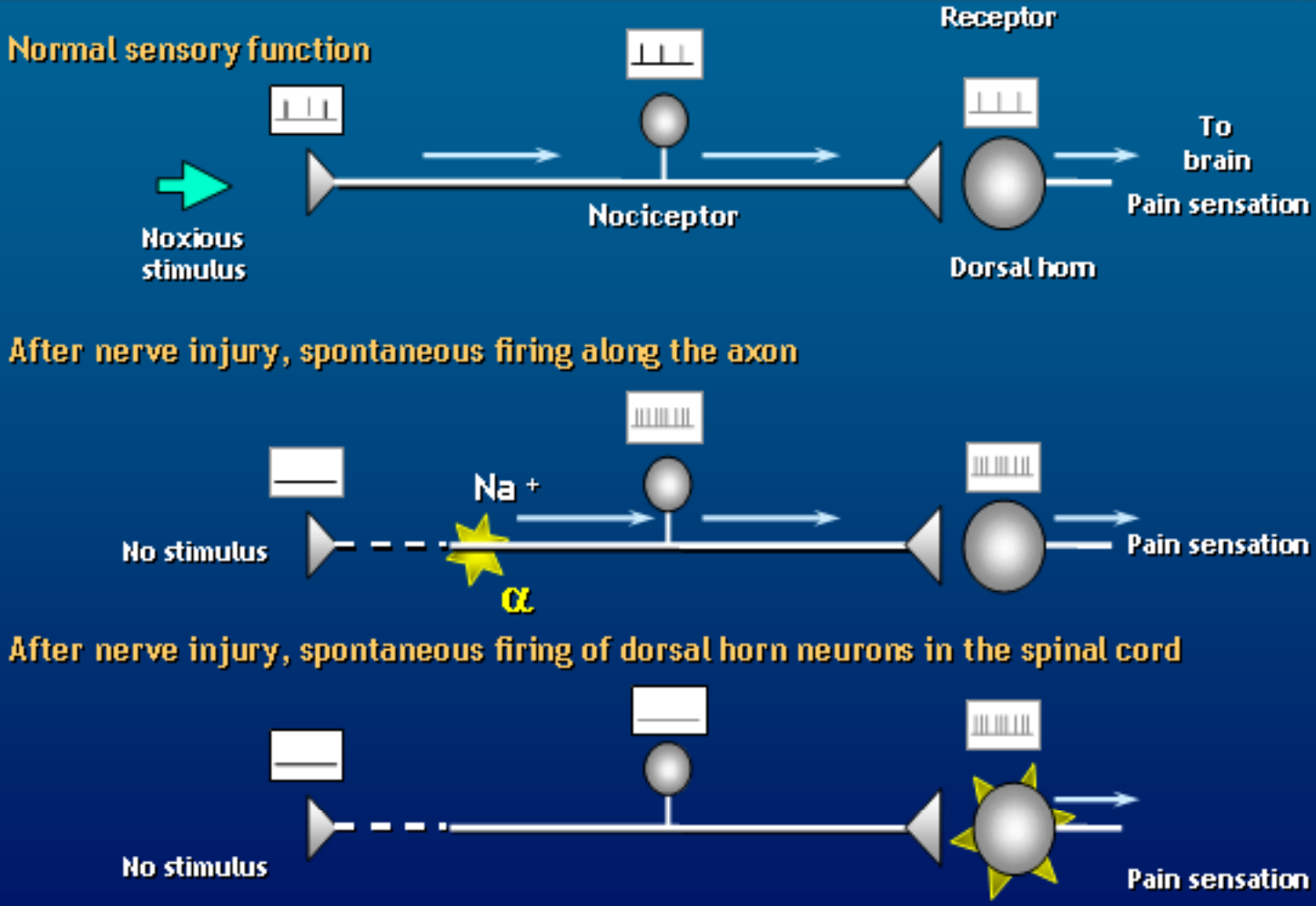
Woolf CJ, Mannion RJ. *Lancet* 1999;353:1959-1964.

Spontaneous Stimuli

- Peripheral/DRG sodium channel function
  - Sprouting of sympathetic nerve terminals
- Paresthesia
  - Nonpainful
- Dysesthesia
  - Painful or unpleasant

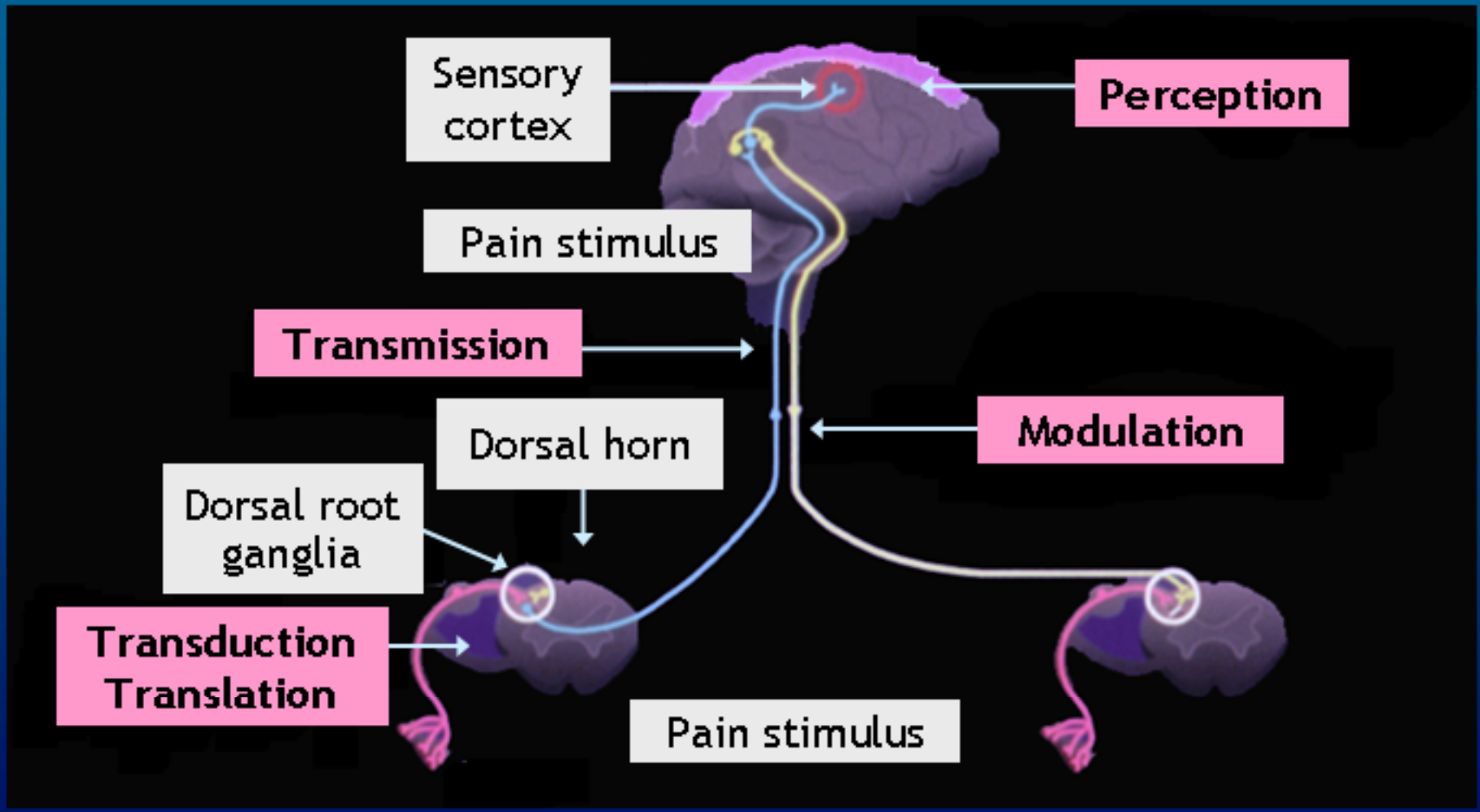
DRG = dorsal root ganglia.

Stimulus-independent Pain

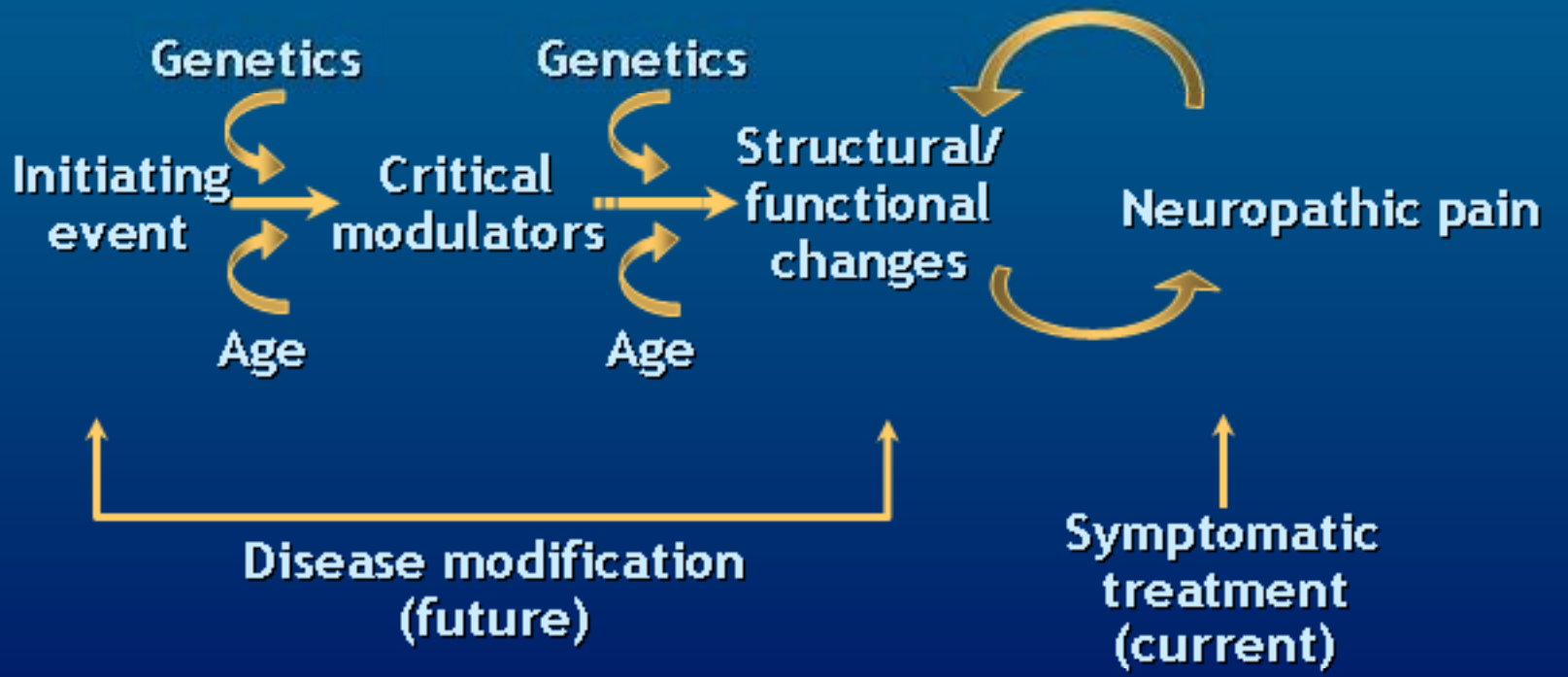


Woolf CJ, Mannion RJ. *Lancet* 1999;353:1959-1964.

The Pain Pathway



Functional Cascade of Neuropathic Pain



Sander JW, White HS. In: Pellock JW, Dodson WE, Bourgeois BFD, eds. *Pediatric Epilepsy: Diagnosis and Therapy*. 2nd ed. New York, NY: Demos Medical Publishing Inc; 2001:301-316.

Restoring Balance

Increase inhibition

Excitation *Inhibition*

Reduce excitation

Clinical Manifestations of Neuropathic Pain in the Rehabilitation Setting

Misha-Miroslav Backonja, MD
Associate Professor
Departments of Neurology, Anesthesiology, and Physical Medicine & Rehabilitation
Director of Education & Research, University of Wisconsin Pain Center
University of Wisconsin Hospital and Clinics
Madison, WI

Pain! Which Pain?

Inflammatory pain (e.g., rheumatoid arthritis)

- Nociceptor activation
- Severity of pain = severity of disease

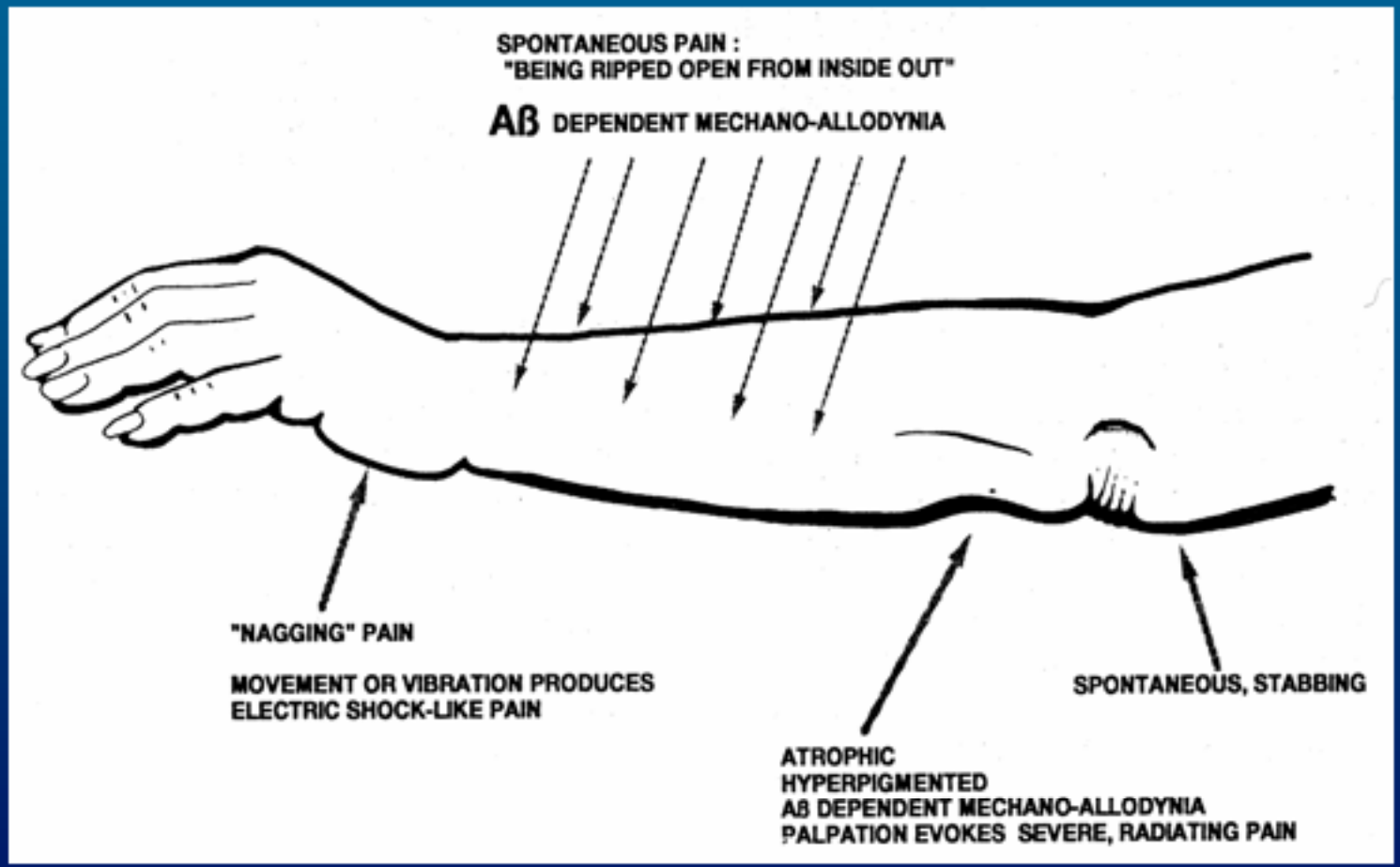
Physiology of pain

Chronic neuropathic pain (e.g., post-stroke central pain)

- Nervous system is changed
- Severity of pain = degree of neuroplasticity

Pathophysiology of pain

Pain Symptoms



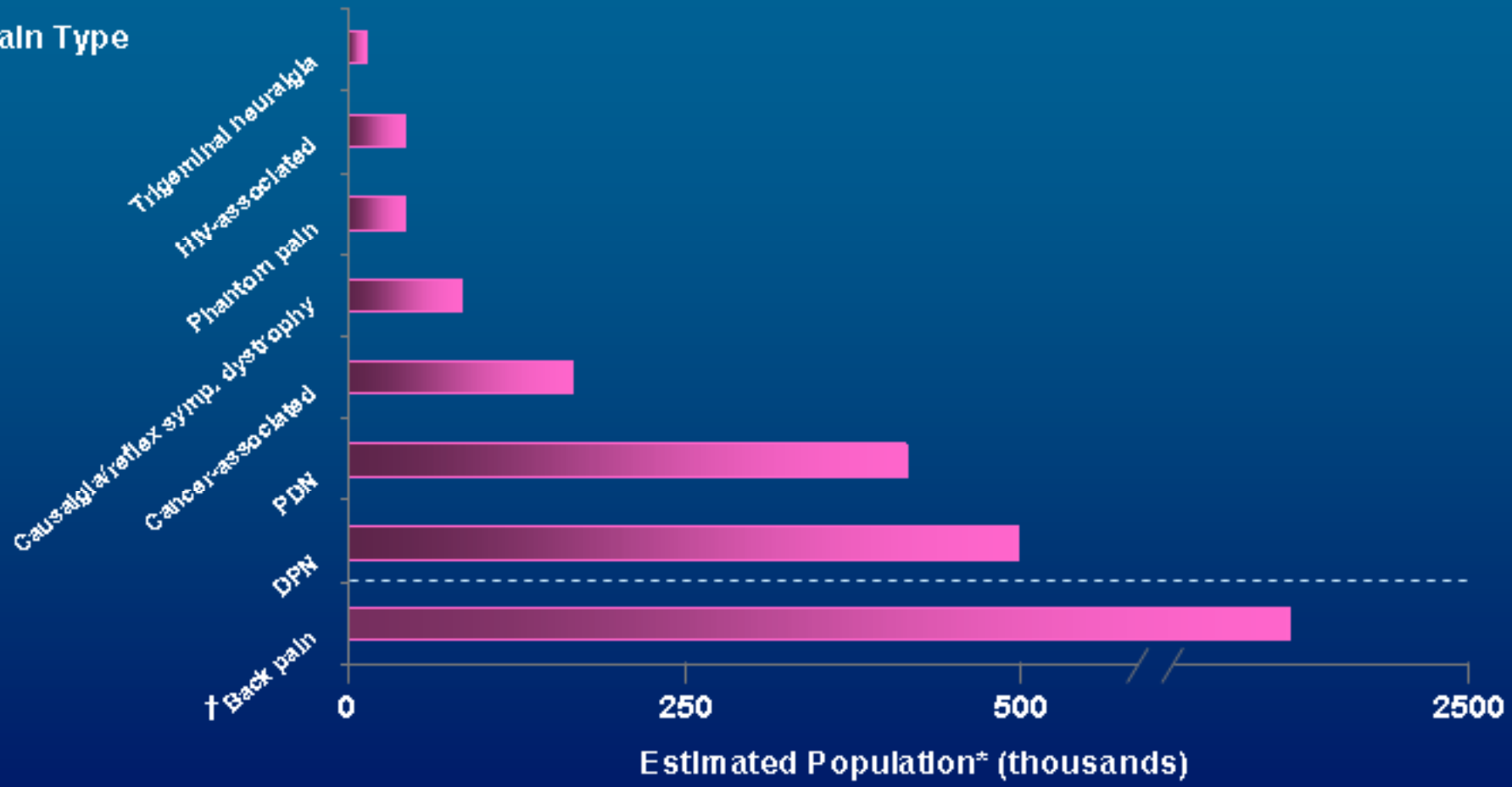
Gracely RH et al. *Pain* 1992;51:175-194.

Neuropathic Pain

Syndromes (common examples)

- Painful diabetic neuropathy
- Postherpetic neuralgia
- Traumatic neuralgia — complex regional pain syndrome/reflex sympathetic dystrophy (CRPS/RSD), post-amputation
- Radiculopathies (cervical, thoracic, lumbosacral)
- Cancer-related neuropathic pain
- Trigeminal neuralgia
- Central pain syndrome — spinal cord, brainstem, brain (thermonociceptive pathways and relays)

Prevalence of Neuropathic Pain in the US



*Estimates are believed to be conservative.

†Assumes 1 in every 10 patients with lower back pain has a component of neuropathic pain.

PDN=painful diabetic neuropathy; PHN=postherpetic neuralgia.

Bennett GJ. *Acta Anaesthesiol Sin* 1999; 37:197-203.

Neuropathic Pain

Pattern

- Peripheral examples
  - Mononeuropathy
  - Mononeuropathy multiplex
  - Brachial plexopathy
  - Lumbosacral plexopathy
  - Monoradiculopathy
  - Polyradiculopathy
  - Polyradiculoneuropathy

Neuropathic Pain (Cont'd)

Pattern (cont'd)

- Central examples
  - Hemicord (Brown-Sequard) syndrome
  - Complete transection = transverse myelitis
  - Disseminated myelopathy
  - Brainstem syndromes
  - Thalamic lesions
  - Cortical lesions

Neuropathic Pain (cont'd)

Pathologic mechanisms

- Injury
- Compression
- Inflammation
- Ischemia
- Infections
- Demyelination
- Axonopathies
- Metabolic/toxic
- Neoplasm

Complexity of Neuropathic Pain

Sensory abnormalities

- Positive sensory phenomena
  - Ongoing spontaneous pain
  - Spontaneous paroxysms
  - Hyperalgesia
- Negative sensory phenomena
  - Sensory deficits at varying degrees to any or all sensory modalities (light touch, pain…)

Complexity of Neuropathic Pain (cont'd)

Motor abnormalities

- Negative motor phenomena
  - Weakness
  - Clumsiness
  - Fatigue
- Positive motor phenomena
  - Tremor
  - Dyskinesiae
  - Ataxia
  - Dystonia

Neuropathic Pain (cont'd)

Rehabilitation medicine-related pain syndromes (cont'd.)

- Spinal disorders
  - Spinal segmental instability
  - Radiculopathy
  - Spinal stenosis
- Spinal cord injury
  - Instability-related
  - Transitional zone-related pain
  - Central pain
- Central post-stroke and other pain and dysesthesia syndromes

Neuropathic Pain Scales

Galer and Jensen 1997

- Quantitative
- Validated in clinical trials

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale

- Qualitative
- Relies on physical exam as well

Galer BS, Jensen MP. *Neurology* 1997;48:332-338.
Bennett M. *Pain* 2001;92:147-157.

Clinical Importance of Changes in Chronic Pain Intensity

- A consistent and close relationship between changes in pain intensity NRS and PGIC was demonstrated
  - Pain can be reliably measured with easy-to-use validated rating scales
- On average, a reduction of ≈ 2 points or ≈ 30% on the pain intensity NRS represented a clinically important improvement as determined by PGIC assessment
  - Modest changes in pain rating scale scores (2 to 3 points) are associated with clinically meaningful changes in patient and physician impressions of overall improvement

NRS=numerical rating scale; PGIC=Patient Global Impression of Change.

Farrar JT et al. *Pain* 2001;94:149-158.

Pain Assessment

Items/Issues	Questions
Onset	When and how did the pain start?
Location(s)/site(s)	Where is (are) pain(s) located?
Temporal profile	What has happened since onset?
Characteristics/quality of pain(s)	Describe the pain.
Severity	How severe is the pain?
Unpleasantness/distress	How unpleasant is the pain?
Associated symptoms	Are there any other symptoms, such as numbness, weakness, bowel/bladder dysfunction, or insomnia?
Psychological factors	Does patient suffer from depression? Anxiety?
Aggravating factors	What makes the pain(s) worse?
Alleviating factors	What makes the pain(s) better?
Impact on function and activities	How are work and daily activities affected? Is the patient active in recreational pursuits?
Response to past treatments	What prior treatments has patient received?
Habits	Does patient smoke? Drink? Use illegal drugs? If yes, how much and how often?
Coping skills	How is patient coping with pain?

Neuropathic Pain

Rehabilitation medicine-related pain syndromes

- Traumatic neuropathies
  - Causalgia
  - CRPS/RSD
- Amputation
  - Stump pain
  - Phantom pain

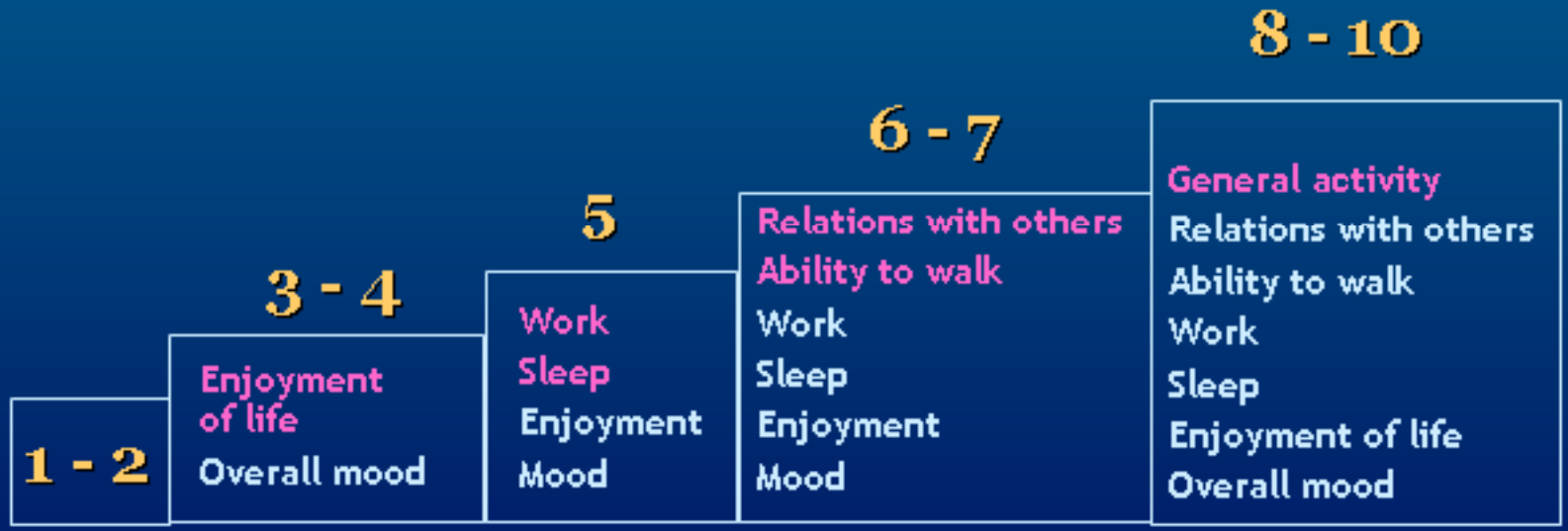
Neuropathic Pain

Pain Assessment and Evaluation

- Establishment of neuropathic pain = H&P
- Differentiation from other sources and mechanisms of pain:
  - Bony and ligamentous pain = instability, irritation
  - Secondary myofascial pain syndromes
  - Referred pain from distant and visceral sources

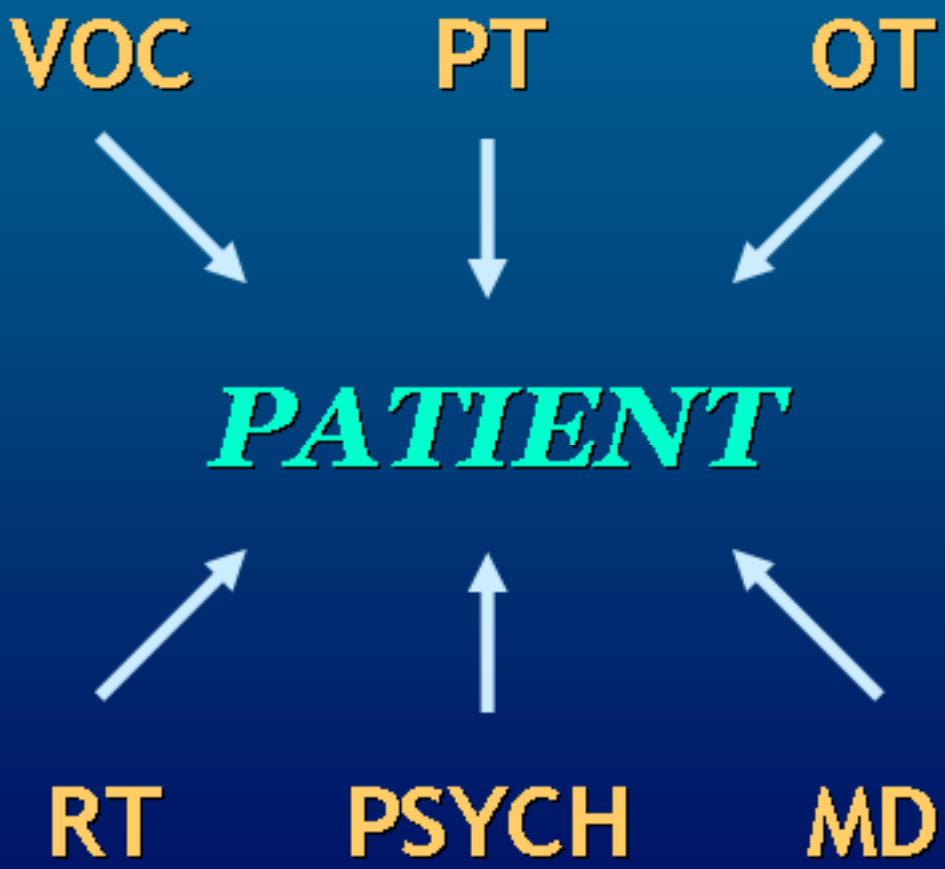
Pain Intensity and Functional Interference

Functional impact is significantly correlated with pain severity ($P<0.0001$)



Breitbart W et al. *Pain* 1996;68:315-321.

An Interdisciplinary Approach to Neuropathic Pain



Rehabilitation Medicine and Neuropathic Pain

Conclusions

- Determination of mechanisms - neuropathic vs inflammatory
- Specific pain diagnosis should lead to specific pain therapy

Approaches to the Management of Neuropathic Pain:

Targeting the Putative Mechanisms

Norman Harden, MD

Program Chair

Associate Professor

Physical Medicine and Rehabilitation

Northwestern University

Director, Center for Pain Studies

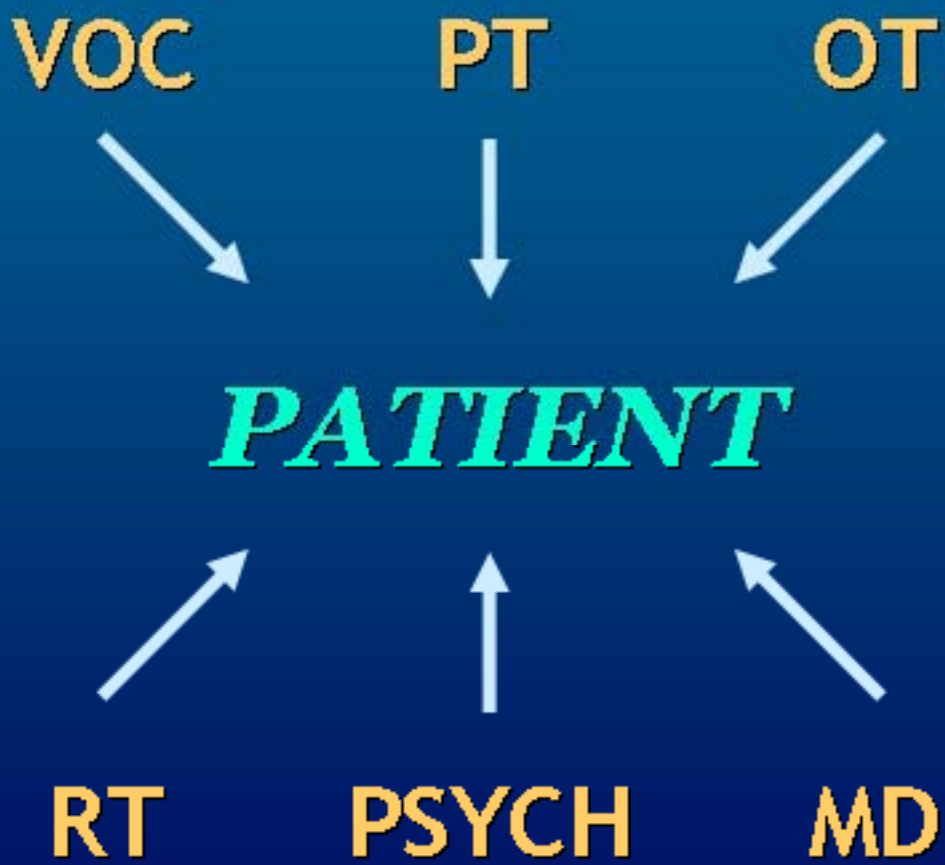
Rehabilitation Institute of Chicago

Chicago, IL

Treatment of Neuropathic Pain

- Targeting the underlying cause
- Targeting pain characteristics
- Targeting putative pathophysiological mechanisms

Bio-psycho-social Disease



Nonpharmacologic Treatment

Thermal Biofeedback Heat Massage

Herbal Medicine Progressive Muscle Relaxation (PMR)

Blood letting

Trephining Acupuncture Diaphragmatic Breathing

Occlusal Adjustment Placebo

TENS ***BIOFEEDBACK***

YOGA Physical Therapy Mesmerism Relaxation

Galvanic Skin Response (GSR)

Electromyography (EMG) Biofeedback ***Hypnosis*** Autogenics

Chiropractic Adjustment Ice Occlusal Splint

Treatment of Neuropathic Pain

Patient with trigeminal postherpetic 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 O, Bucy PC. *Arch Neurol Psychiatry* 1951;61:131-145.

Neuropathic Pain Agents and Their Actions

Brain

NE
Serotonin
Endogenous opiates

- Tricyclic Antidepressants
- Selective Serotonin Reuptake Inhibitors

Na^+

PNS

Spinal Cord

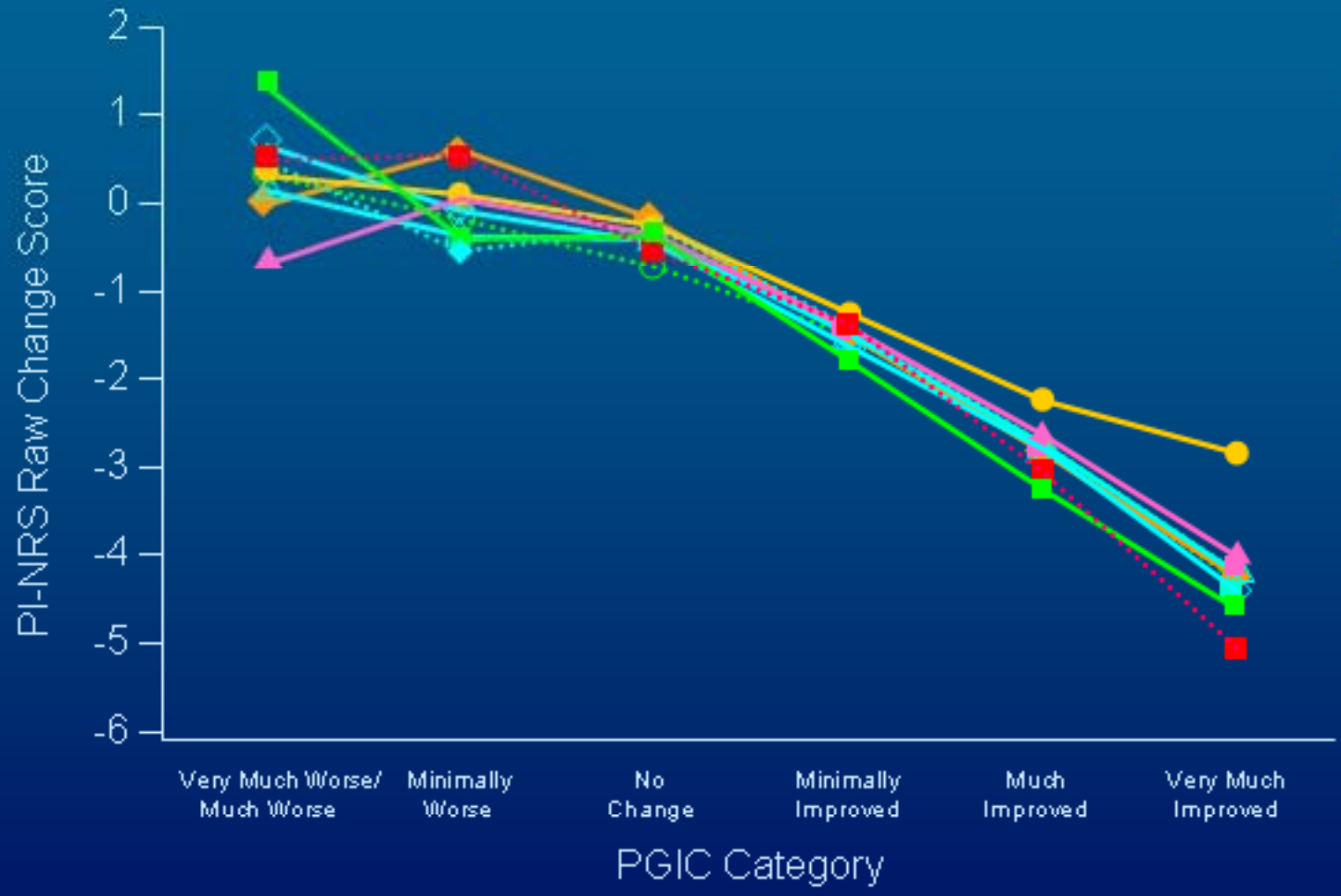
- Ca^+ + channels: Gabapentin, Oxcarbazepine
- NMDA antagonists: Ketamine, Dextromethorphan, Topiramate

- Carbamazepine
- Oxcarbazepine
- Phenytoin
- Mexiletine
- Lidocaine
- Lamotrigine, Topiramate

Pharmacologic Management of Neuropathic Pain

Antidepressants	Amitriptyline, imipramine, desipramine, nortriptyline
Anticonvulsants	Carbamazepine, oxcarbazepine, clonazepam, gabapentin, lamotrigine, phenytoin, valproic acid, topiramate
Antiarrhythmics	Lidocaine, mexiletine
Topical formulations	Capsaicin, lidocaine, aspirin
Others	Tramadol, NMDA antagonists, clonidine, opioids

Clinical Importance of Changes in Chronic Pain Intensity



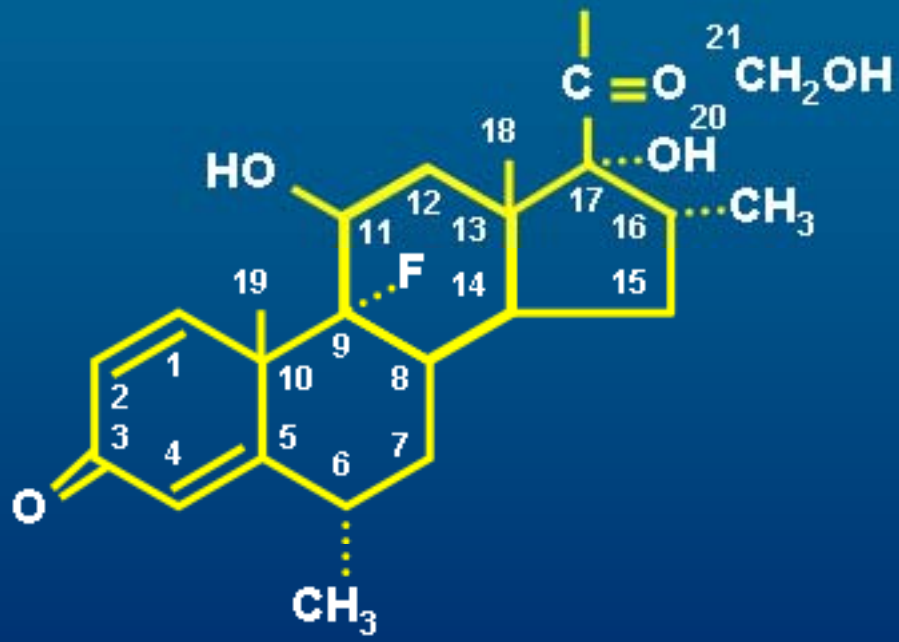
CLBP-chronic low-back pain; FIB=fibromyalgia; OA=osteoarthritis; PDN=painful diabetic neuropathy; PHN=postherpetic neuralgia; PI-NRS=Pain Intensity-Numerical Rating Scale.

Farrar JT et al. *Pain* 2001;94:149-158.

Nonsteroidal Anti-inflammatory Agents (NSAIDs) by Class

Class	Drug	
	Generic	Trade Name
Salicylic acids	Choline magnesium Trisalicylate	Trilisate®
Indoleacetic acids	Sulindac Indomethacin Etodolac	Clinoril® Indocin® Lodine®
Pyrrolacetic acids	Tolmetin sodium Ketorolac tromethamine	Tolectin® Toradol®
Propionic acids	Ketoprofen Ibuprofen Naproxen	Orudis®, Oruvail® Motrin® Naprosyn®
Naphthylalkanones	Nabumetone	Relafen®

Steroids



Adrenocorticosteroids

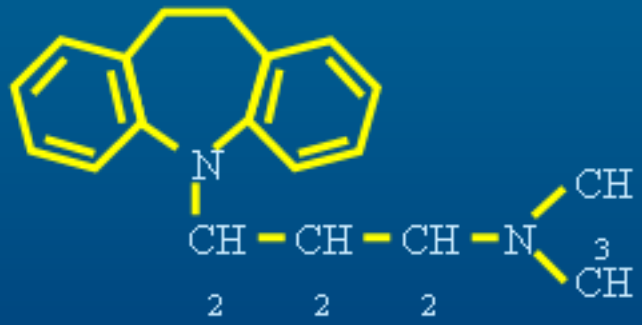
Prednisone high dose, rapid taper

IE: 80 mg x 3 days, 60 x 3,
40 x 3, 20 x 3, 10 x 3, 5 x 3

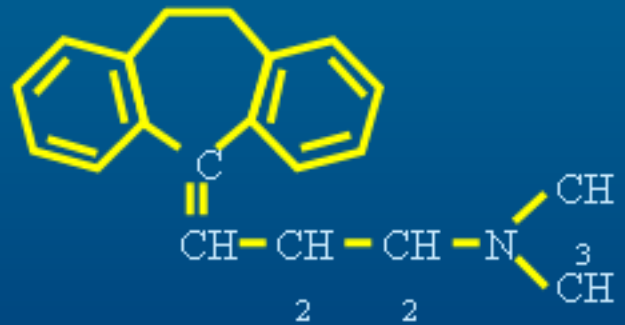
Not for chronic use

Chemical Structure of Tricyclic Antidepressants (TCAs)

Tertiary amines

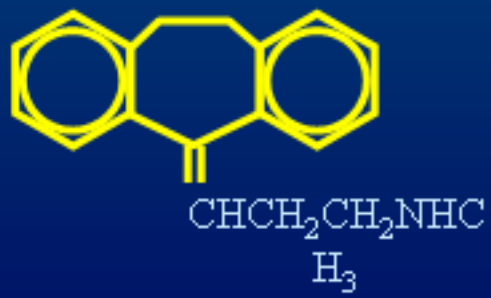


Imipramine

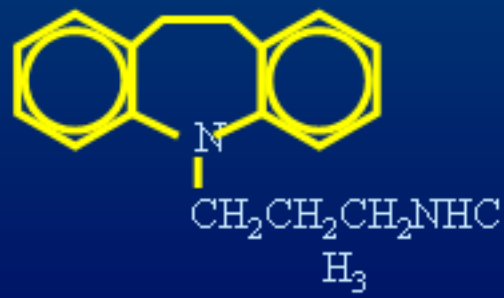


Amitriptyline

Secondary amines



Nortriptyline



Desipramine

TCAs in Postherpetic Neuralgia

Study	n	Response	
Watson et al (1982) Amitriptyline vs placebo	24	A: 67%	P: 5%
Max et al (1988) Amitriptyline vs placebo	24	A: 47%	P: 16%
Kishore-Kumar et al (1980) Desipramine vs placebo	19	D: 63%	P: 11%
Watson et al (1992) Amitriptyline vs maprotiline	32	A: 44%	M: 18%
Watson and Evans (1985) Amitriptyline vs zimeldine (SSRI)	15	A: 60%	Z: 7%

SSRI=selective serotonin reuptake inhibitor.

Max MB. *Ann Neurol* 1994;35(Suppl):S50-S53.

Common Side Effects Associated with TCAs

	Sedation	Anti-cholinergic effects	Hypo-tension	Cardiac effects	Seizures	Weight gain
Amitriptyline	+++	+++	+++	+++	++	++
Clomipramine	++	+++	++	+++	+++	+
Desipramine	0/+	+	+	++	+	+
Nortriptyline	+	+	+	++	+	+

0/+=minimal; += mild; ++=moderate; +++=moderately severe.

Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds.
Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw - Hill, 1996.

SSRIs in Painful Diabetic Neuropathy (PDN)

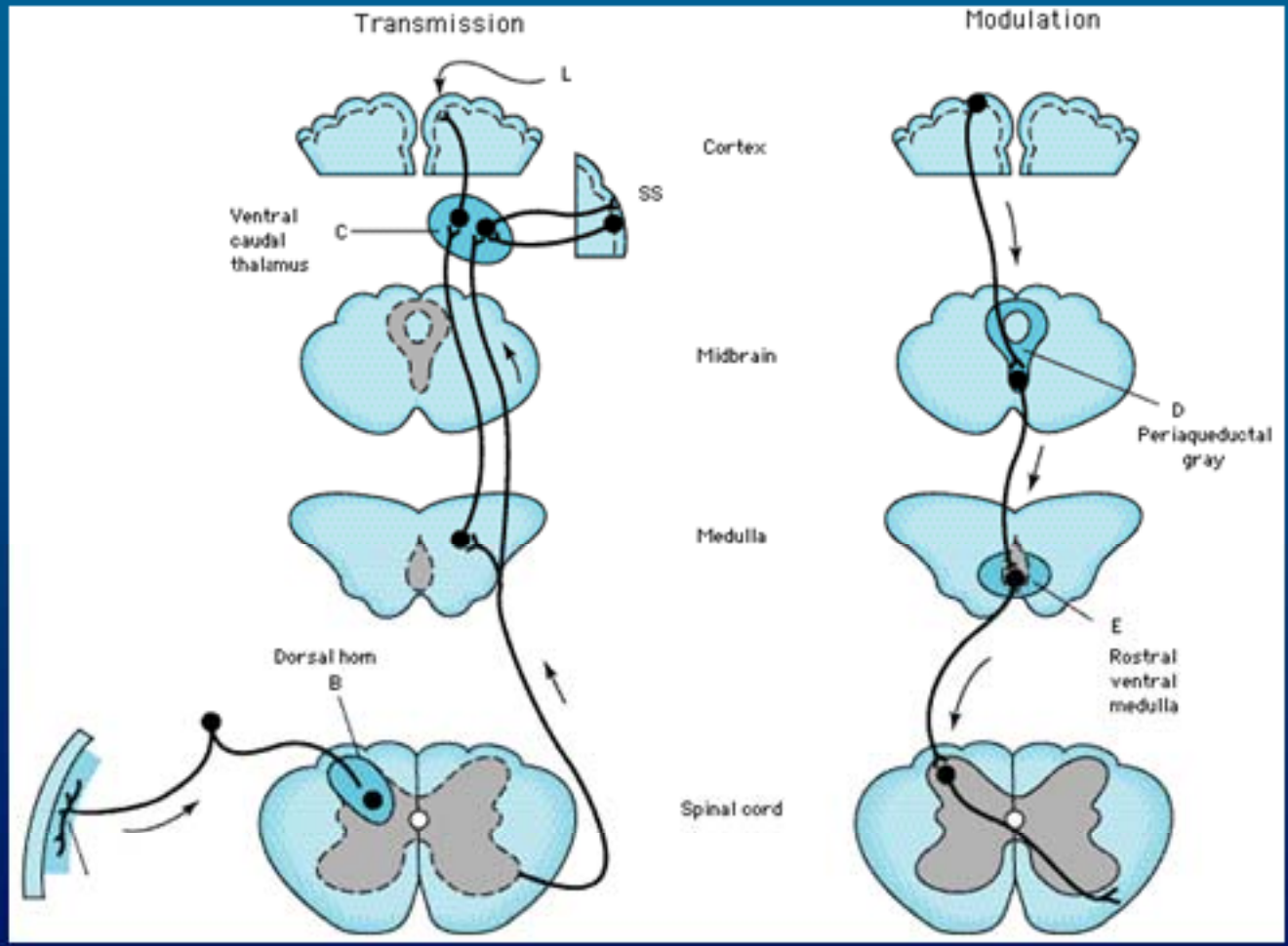
- A comparative trial showed that paroxetine led to significantly better pain relief than placebo in patients with PDN
- Although paroxetine was better tolerated, it had significantly less efficacy compared with imipramine
- A randomized, double-blind, crossover design trial showed that citalopram induced slight relief of pain for patients with PDN

Venlafaxine and PDN

- Randomized, placebo-controlled trial of 224 patients with PDN and no depression
- Venlafaxine (VLF) XR administered at 75 mg and at 150 mg to 225 mg for up to 6 weeks
- Venlafaxine (150 mg to 225 mg) resulted in significantly better pain relief at weeks 2 to 6 and significantly decreased pain intensity at weeks 4 and 6
- At week 6, 56%, 39%, and 35% of patients on VLF 150 mg to 225 mg, VLF 75 mg, and placebo, respectively, reported significantly reduced pain intensity

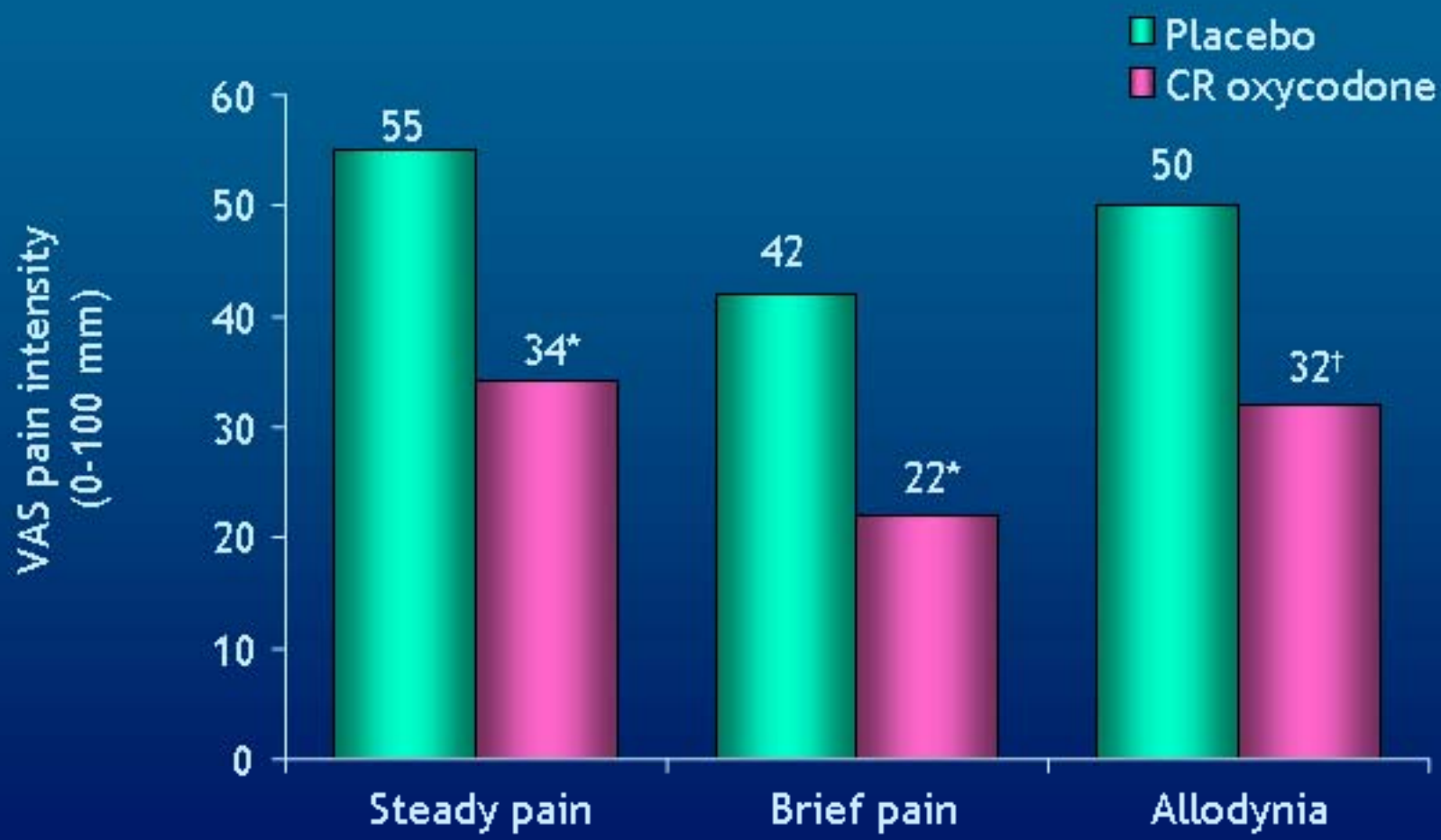
Kunz N. et al. Presented at the 60th annual meeting of the ADA, San Antonio, TX, 2000.

Opioid Analgesics: Sites of Action



Katzung BG, ed. *Basic and Clinical Pharmacology*. 8th ed. Lange Publishers, 2001.

Efficacy of Controlled-release Oxycodone in Postherpetic Neuralgia



*P=0.0001; †P=0.0004.

Watson CP, Babul N. *Neurology* 1998;50:1837-1841.

NMDA Antagonists and PDN

- Animal and pilot data suggest that NMDA receptor blockade may alleviate neuropathic pain
- Significant side effects from NMDA antagonists (MK 801, ketamine, phencyclidine)
- High doses of low-affinity, noncompetitive, NMDA-receptor antagonists (dextromethorphan, remacemide) may have a better therapeutic ratio

NMDA = *N*-methyl-D-aspartate.

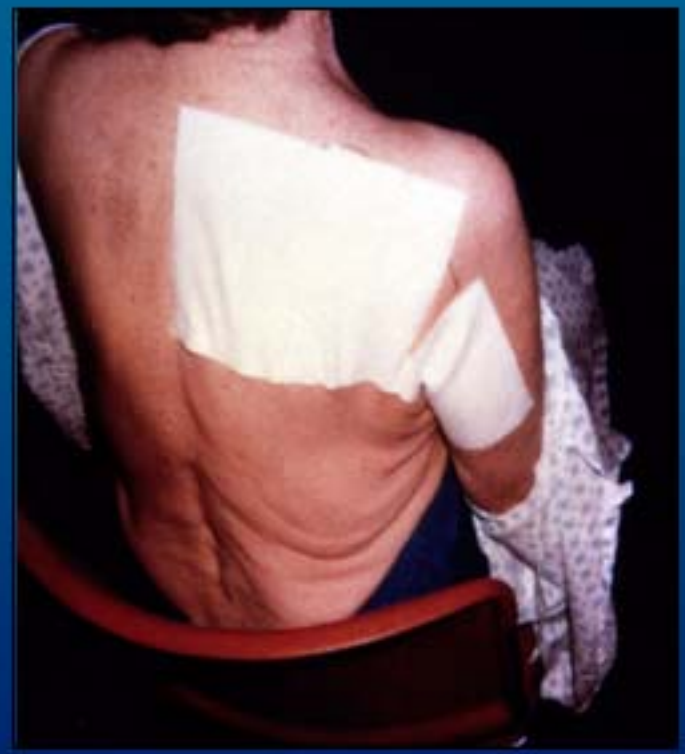
Oral Dextromethorphan and PDN

- Randomized, placebo-controlled, 2-period, crossover design trial (1-week baseline, two 6-week Rx periods, 1-week washout period)
- Dextromethorphan started at 120 mg/day and titrated to a maximum of 960 mg/day (by 30 to 60 mg every 3 days)
- 14 patients (mean dose 381 mg); dextromethorphan reduced pain by 24% compared with placebo
- Most common AEs were sedation, dizziness, and lightheadedness

Nelson KA et al. *Neurology* 1997;48:1212-1218.

Topical Treatments for Neuropathic Pain

Capsaicin



Lidocaine patch 5%

Capsaicin and PDN

- Multicenter, double-blind, vehicle-controlled trial
- 252 patients on topical 0.075% capsaicin vs vehicle cream applied 4x daily for 8 weeks
- Statistically significant improvement in pain favoring capsaicin (69.5% vs 53.4%), pain intensity (38.1% vs 27.4%), and pain relief (58.4% vs 45.3%)
- Capsaicin caused transient burning, sneezing, and coughing

Topical Medications

Capsaicin

- Inconsistent trial results; potential burning upon application

EMLA Cream

- May help some patients with allodynia

Clonidine gel

- Pilot studies suggest efficacy; controlled trial in progress

Unstudied custom compounds

- Doxepin, other TCAs, gabapentin, opioids, ketamine, guanethidine

Anticonvulsant Drugs and Neuropathic Pain

First-generation

- Carbamazepine[A]
- Divalproex sodium[B]
- Phenytoin[A]
- Valproic acid[B]
- Clonazepam[B]
- Phenobarbitol[B]

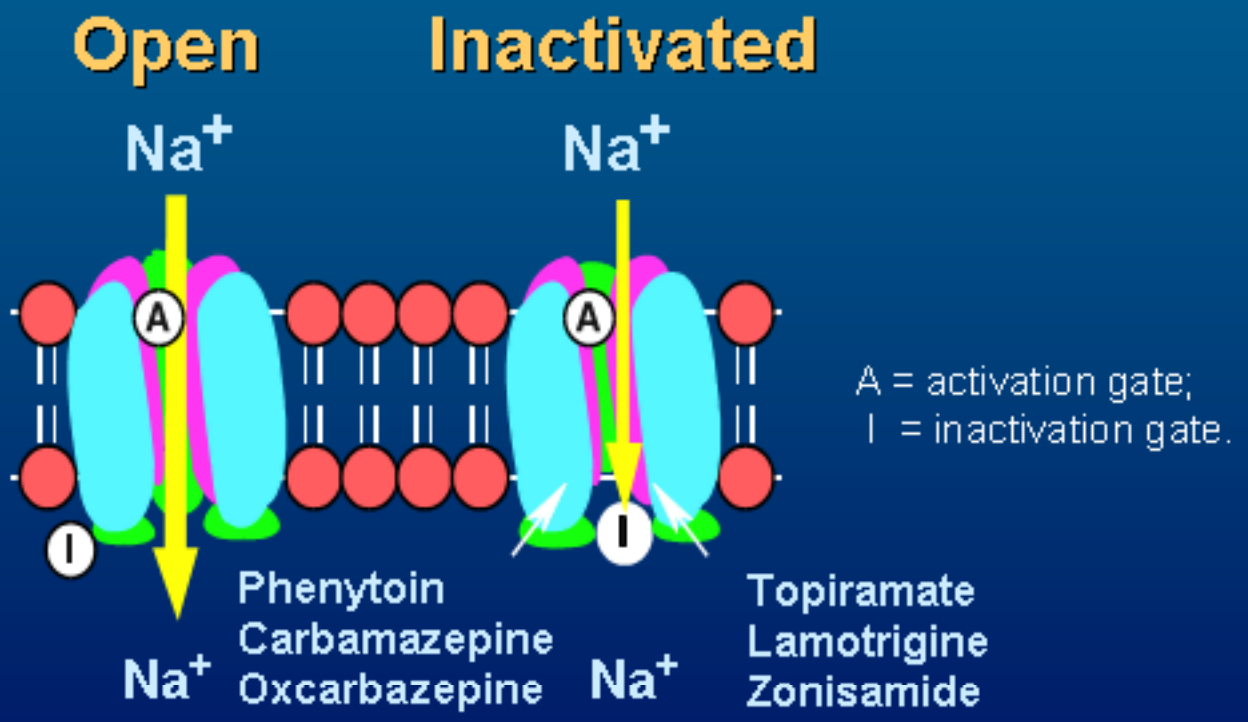
Second-generation

- Gabapentin[A]
- Lamotrigine[A]
- Levetiracetam[B]
- Oxcarbazepine[A]
- Tiagabine[B]
- Topiramate[B]
- Zonisamide[B]

[A] Published randomized controlled trials.
[B] Clinical anecdotes and/or published case series.

Anticonvulsants: Mechanisms of Action

Voltage-gated sodium channel

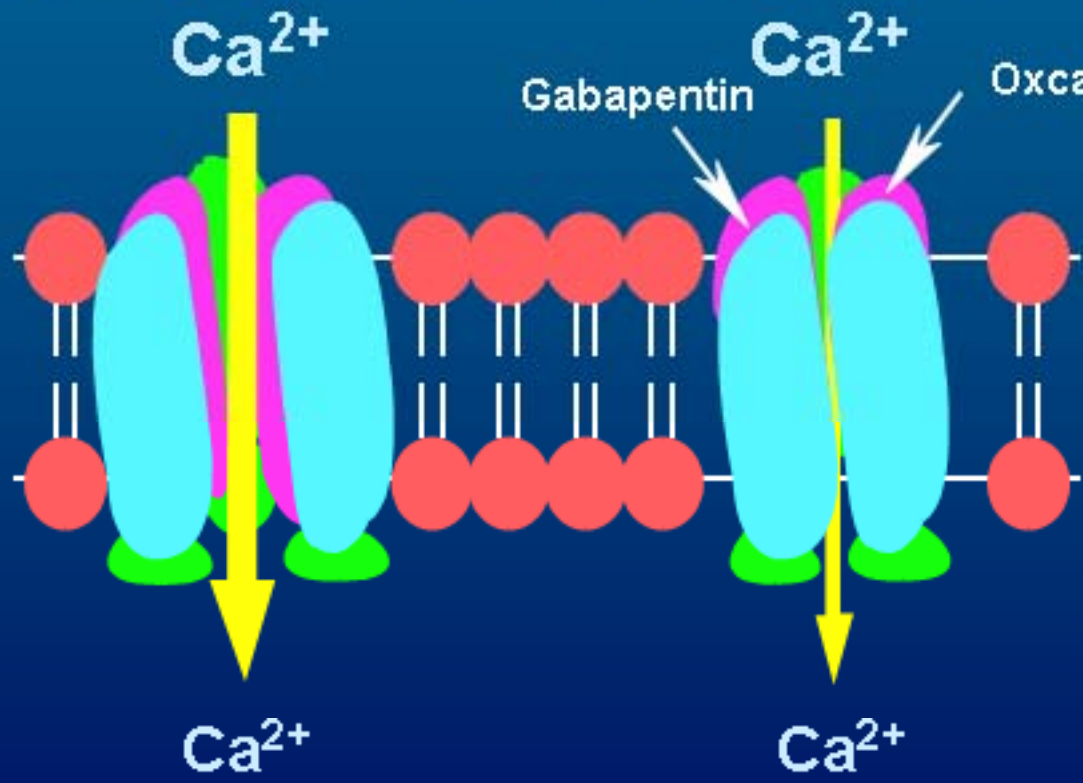


Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds.
Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw - Hill, 1996.

Anticonvulsants: Mechanisms of Action (cont'd)

Voltage-gated calcium channel

Subtypes
L-type
T-type
N-type*
P-type*

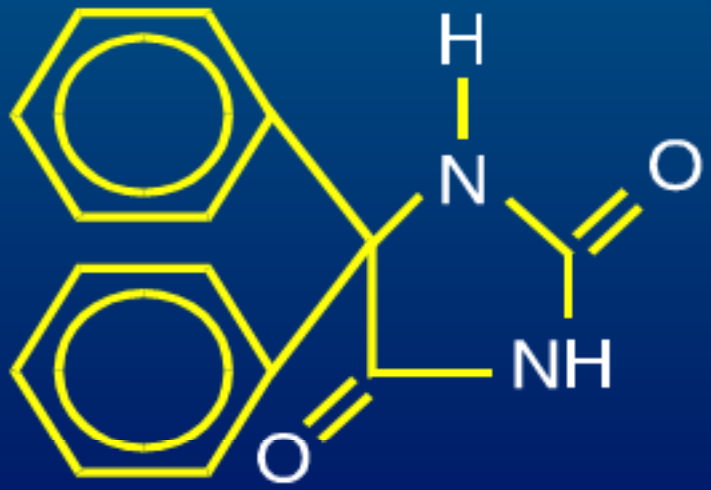


* Found in neuronal tissue.

Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York: McGraw - Hill, 1996.

Mechanisms of Action of Phenytoin

- Slows recovery rate of voltage-activated Na+ channels, limiting repetitive firing
- May inhibit somatostatin release



Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York: McGraw - Hill, 1996.
Reichlin S, Mothon S. *Ann Neurol* 1991;29:413-417.

Phenytoin in PDN

Conflicting data

- Saudek et al, 1977
  - Double-blind, placebo-controlled, crossover trial of 4 weeks; 12 patients
  - Pain relief on linear analog scale
  - No significant difference between phenytoin and placebo
- Chadda and Mathur, 1978
  - Double-blind, placebo-controlled, crossover trial of 5 weeks; 38 patients
  - Categorical scale of improvement
  - Significant improvement with phenytoin

Saudek CD et al. *Clin Pharmacol Ther* 1977;22: 196 - 199.
Chadda VS, Mathur MS. *J Assoc Physicians India* 1978;26: 403 - 406.

Pharmacologic Properties of First-generation Anticonvulsants

Carbamazepine

- Slows recovery rate of voltage-activated Na+ channels, limiting repetitive firing
- May inhibit release of somatostatin
- Some calcium antagonistic effect

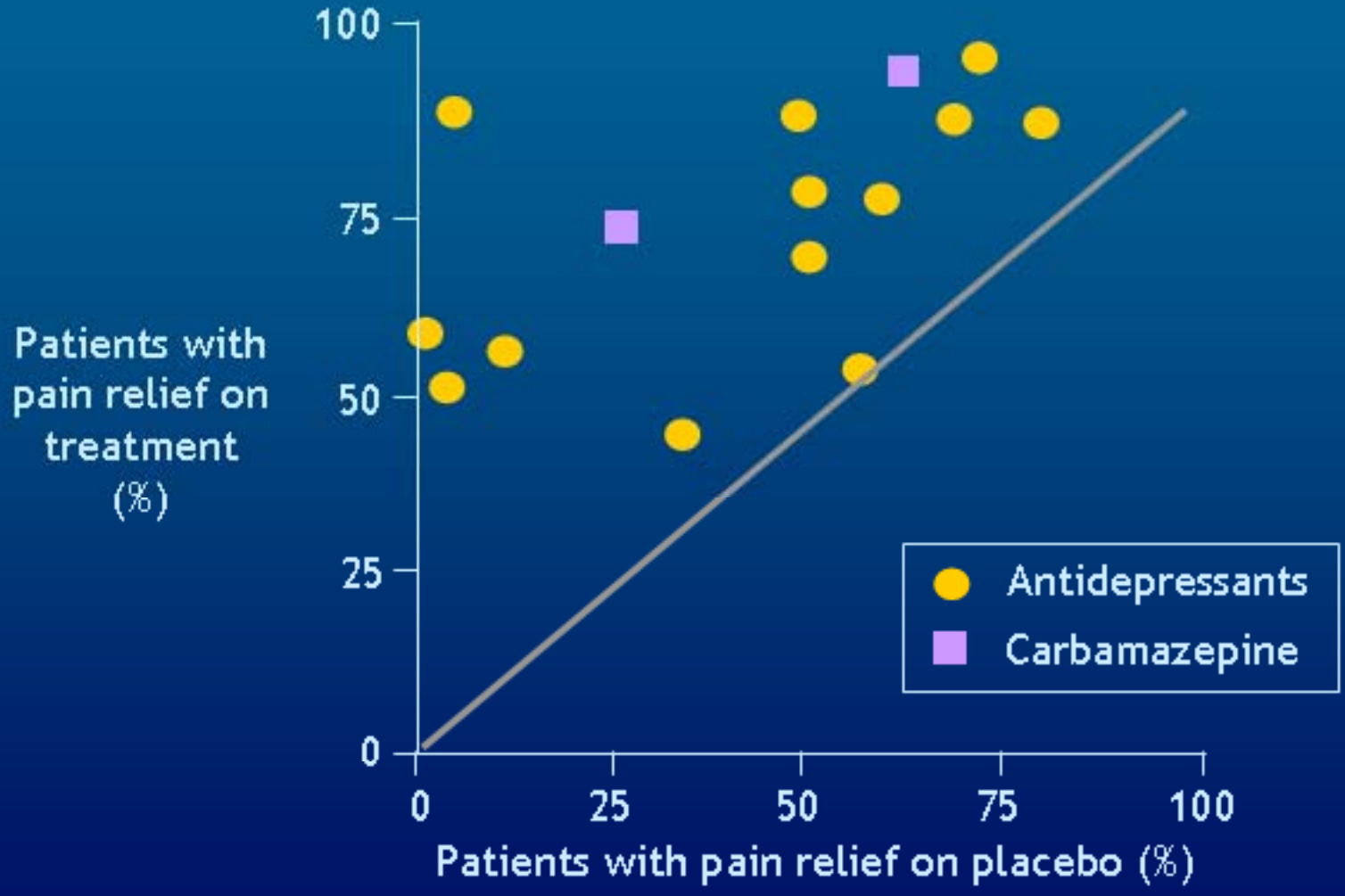
McNamara JO. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. 1996:461-486.
Reichlin S, Mothon S. *Ann Neurol* 1991;29:413-417.
Walden J et al. *Eur Neuropsychopharmacol* 1992;2:455-462.

Carbamazepine (CBZ) in PDN

- Double-blind, placebo-contolled, crossover trial of 6 weeks (three 2-week periods); 30 patients
- Pain relief on a categorical scale
- 63% of patients on carbamazepine had moderate to complete relief vs 20% of patients on placebo ($P<.05$)
- Median carbamazepine dose 600 mg

Rull JA et al. *Diabetologia* 1969; 5:215-218.

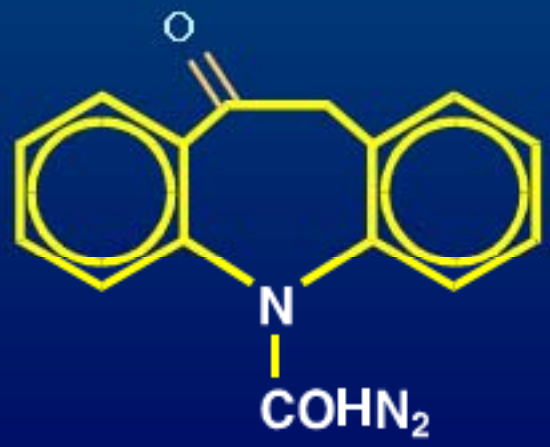
CBZ in PDN (con'd)



McQuay HJ et al. *Pain* 1996;68:217 - 227.

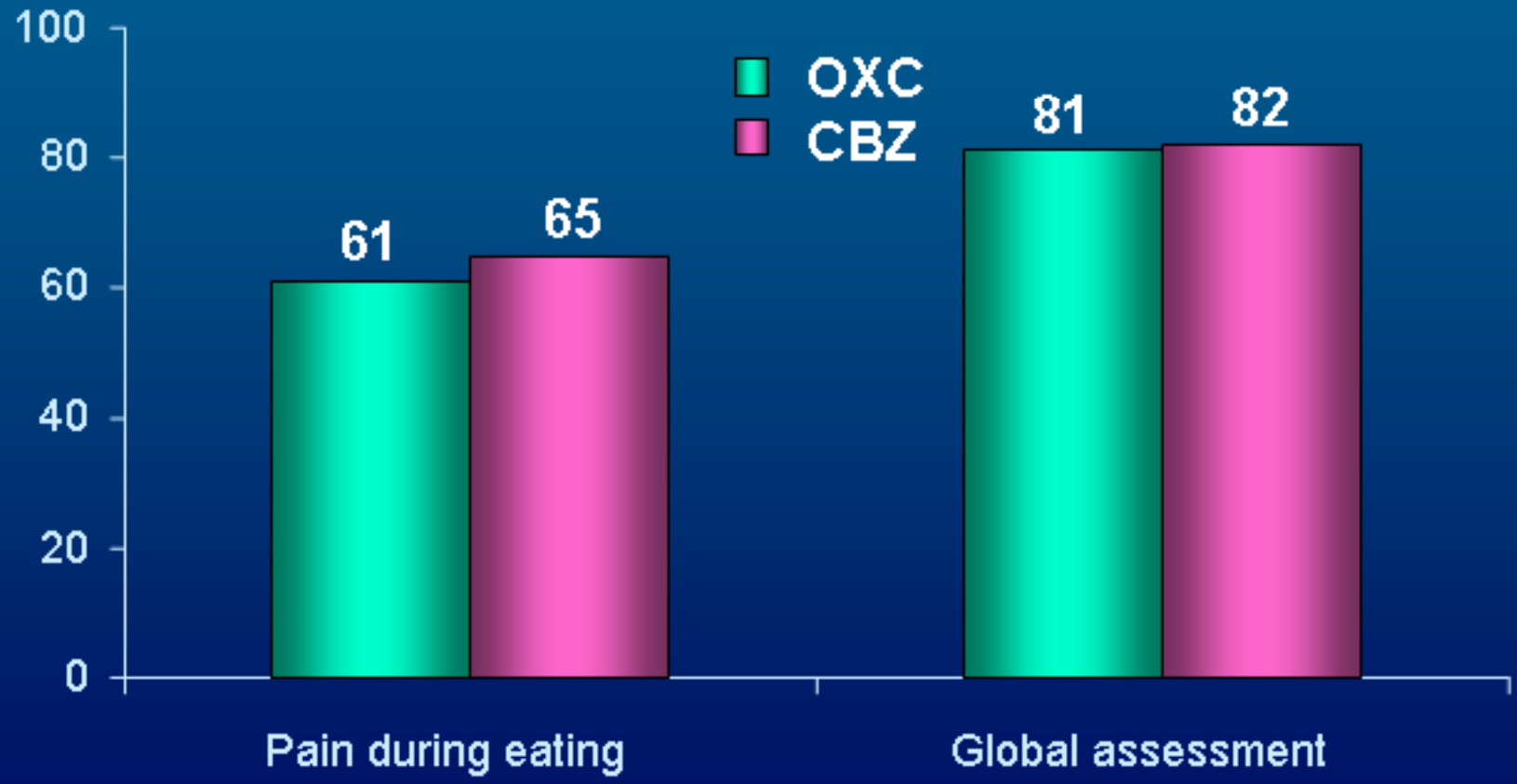
Mechanisms of Action of Oxcarbazepine (OXC)

- Slows recovery rate of voltage-activated Na+ channels, limiting repetitive firing
- Modulates high-threshold N- and P-type calcium channels
- Reduces glutamatergic transmission



OXC vs CBZ in Trigeminal Neuralgia (TN)

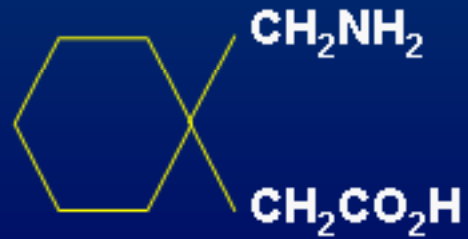
Results



Pharmacologic Properties of Second-generation Anticonvulsants

Gabapentin

- Increases GABA in brain, possibly by enhancing rate of synthesis from glutamate
- Binds to alpha 2 delta subunit of voltage dependent Ca+ channel
- Inhibits sodium currents by mechanism distinct from phenytoin and carbamazepine
- Inhibits branched-chain amino acid transferase, possibly reducing glutamate concentration
- No effect on $GABA_A$ or $GABA_B$ receptors



Upton N. *Trends Pharmacol Sci* 1994;15:456-463.
Chadwick D. *Lancet* 1994;343:89-91.
Petroff O et al. *Ann Neurol* 1996;39:95-99.
Goldlust A et al. *Epilepsy Res* 1995;22:1-11.

Gabapentin in Neuropathic Pain
Double-blind, placebo-controlled studies

Study/ year	Indication	N	Dose (mg/day)	Duration (weeks)	Results
Backonja 1998	DPN	165	900-3600	8	Positive
Rowbotham 1998	PHN	225	1200-3600	8	Positive
Rice 2001	PHN	334	1800 or 2400	7	Positive
Serpell In Press	Neuropathic pain	305	900-2400	8	Positive

Gabapentin in PDN

- Multicenter, randomized, double-blind, 8-week, placebo-controlled, parallel design trial in 165 patients titrated up to 3600 mg/day
- Average daily pain score dropped from 6.4 to 3.9 on gabapentin compared with a drop from 6.5 to 5.1 for placebo ($P<.001$)
- Most common adverse events of GBP were dizziness and somnolence

Backonja M, et al. *JAMA*. 1998;280:1831-1836.

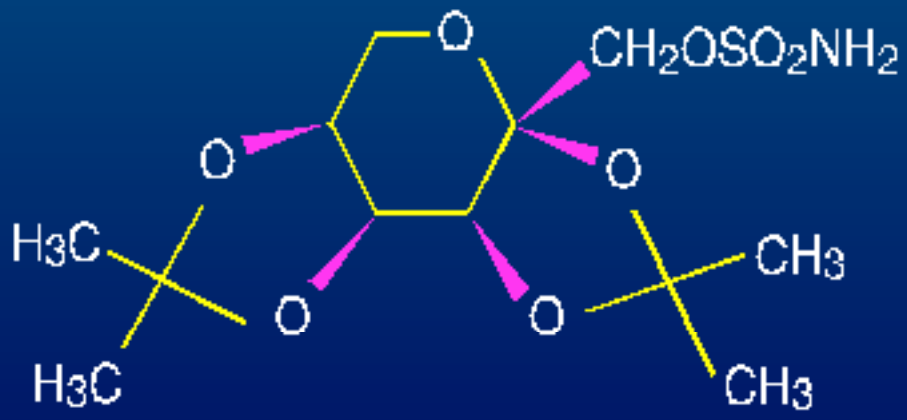
Gabapentin in Postherpetic Neuralgia

- Multicenter, randomized, double-blind, 8-week, placebo-controlled, parallel-design trial in 229 patients titrated up to 3600 mg/day
- Average daily pain score dropped from 6.3 to 4.2 on gabapentin compared with a drop from 6.5 to 6.0 for placebo (P<.001)
- Somnolence, dizziness, ataxia, peripheral edema, and infection more frequent in gabapentin group

Rowbotham M et al. *JAMA* 1998;280:1837-1842.

Mechanisms of Action of Topiramate (TPM)

- Blocks voltage-gated Na+ channels
- Blocks kainate and AMPA subtypes of the glutamate receptor
- Enhances $GABA_A$ receptor actions by interaction with a nonbenzodiazepine receptor



Ben-Menachem E. In: *Antiepileptic Drugs*. 4th ed. New York: Raven Press, 1995:1063-1070.

Topiramate (TPM) in PDN

- Double-blind, placebo-controlled (2:1) trial of 13 weeks duration in 27 patients
- TPM titrated over 9 weeks up to 400 mg/day
- Average daily pain score dropped from 6.9 to 4.1 on TPM compared with an increase from 6.5 to 7.0 for placebo (P=.007)
- 5/18 patients (28%) on TPM vs 1/9 patients (11%) on placebo exited because of intolerable adverse events

Edwards KR et al. Presented at the 18th Annual Scientific Meeting of the American Pain Society; October 21-24, 1999; Fort Lauderdale, FL.

Mechanisms of Action of Lamotrigine (LMG)

- Slows recovery rate of voltage-activated Na+ channels, limiting repetitive firing
- Inhibits neurotransmitter release (glutamate, aspartate, acetylcholine, GABA) mediated by sodium influx

Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds.
Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw - Hill, 1996.

LMG in Neuropathic Pain
Double-blind, placebo-controlled studies

Study/ year	*Indication*	*N*	*Dose (mg/day)*	*Duration*	*Results*
Zakrzewska 1997	Trigmenial Neuralgia	14	400	31-day	positive
Simpson 1999	HIV neuropathy	42	25→300	7 weeks	positive
McCleane 1999	Neuropathic pain	100	200	8 weeks	negative
Vestergaard 2001	Central post stroke pain	30	25→200	8 weeks	positive

Antihyperalgesics/Anticonvulsants Neuromodulators?

Mechanisms of Action	Drugs	
Na^+ channel blocker	• Carbamazepine • Lamotrigine • Oxcarbazepine	• Phenytoin • Valproate • Zonisamide
Ca^{++} channel blocker	• Ethosuximide • Oxcarbazepine	• Gabapentin • Zonisamide
GABA receptors	• Barbiturates	• Benzodiazepines
GABA metabolism	• Vigabatrin • Valproate	• Tiagabine • Gabapentin
Glutamate receptors	• Carbamazepine • Felbamate	• Lamotrigine • Topiramate
Glutamate metabolism	• Gabapentin	

"RATIONAL POLYPHARMACY"

"Today's dogma will be tomorrow's heresy..."

D.J. Dalessio

Neuropathic Pain: A Brief Recap

- Neuropathic pain affects 3.5 to 4 million Americans
- Basic clinical research is revealing new treatment paradigms
- The Joint Commission on Accreditation of Healthcare Organizations has mandated pain as the Fifth Vital Sign
  1. Temperature
  2. Respiration
  3. Blood pressure
  4. Pulse
  5. *Pain*

Neuropathic Pain: A Brief Recap

- The very nature of neuropathic pain makes it difficult to diagnose. Therefore, it is often misdiagnosed, and is underreported
- Chronic pain is a combination of inflammatory and neuropathic mechanisms
- Treating only the inflammatory (nociceptive) component will be ineffective

Conclusion: Treating the Patient to Goal

- The triad of pain - mood disorders and functional impairment, including sleep disorders, must be addressed
- Modest improvements in pain scores reported by a patient can mean improved quality of life - the ultimate goal of treatment

Conclusion: Comprehensive Management of Neuropathic Pain

- No one agent is approved
- Medications are often prescribed without careful consideration of intended effect
- Patients are often sub-optimally treated
- Rational polytherapy may be necessary

Conclusion: The New Treatment Paradigm

- As a result of the shifting treatment paradigm from a mechanism- to an evidence-based approach, clinicians are diagnosing patients according to specific signs and symptoms
- The patient and clinician can develop a treatment strategy specifically targeted to the individual patient's signs and symptoms