

Chronic Pain Overview

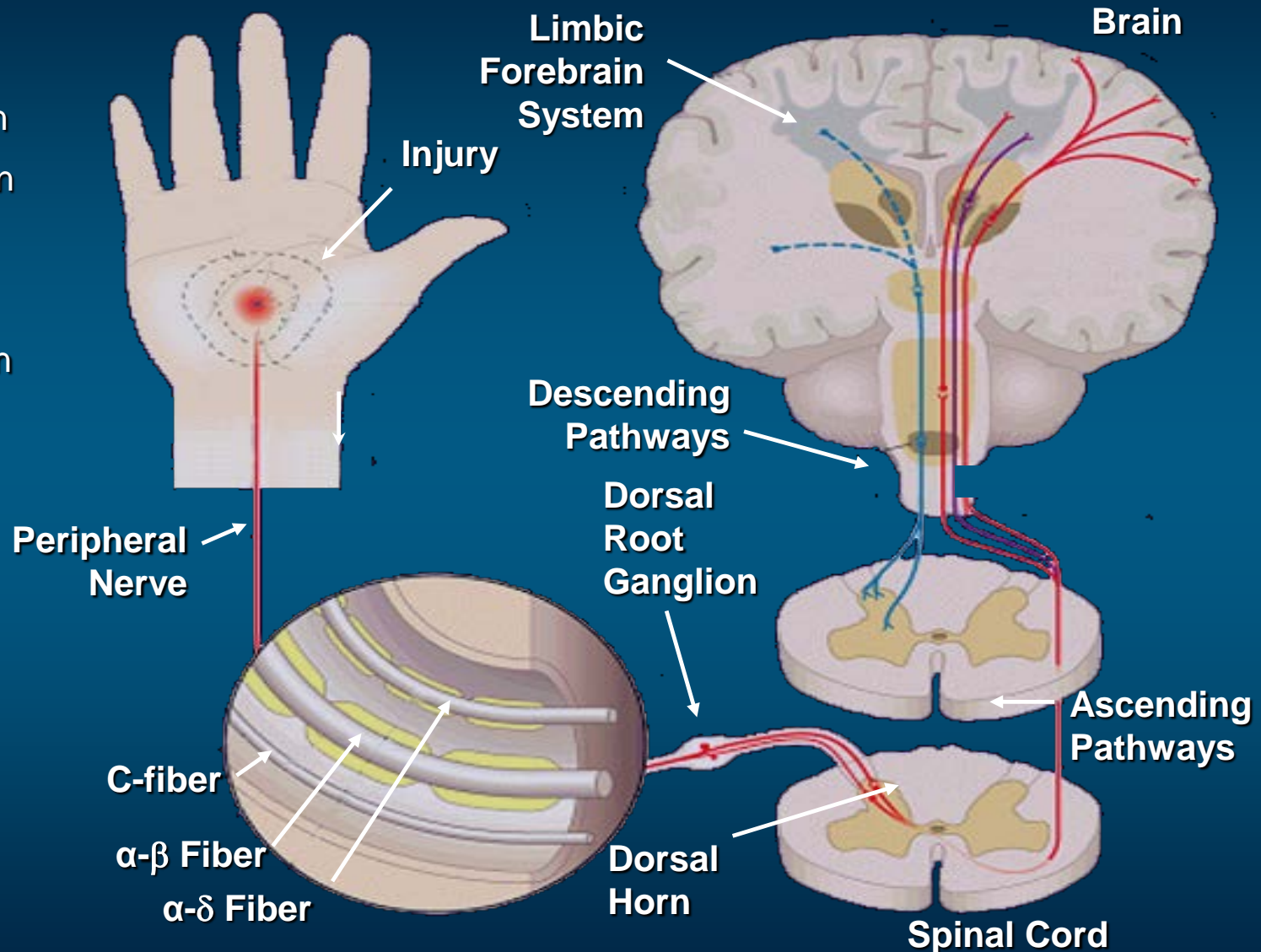
Mark S. Wallace, M.D.

Professor of Clinical Anesthesiology

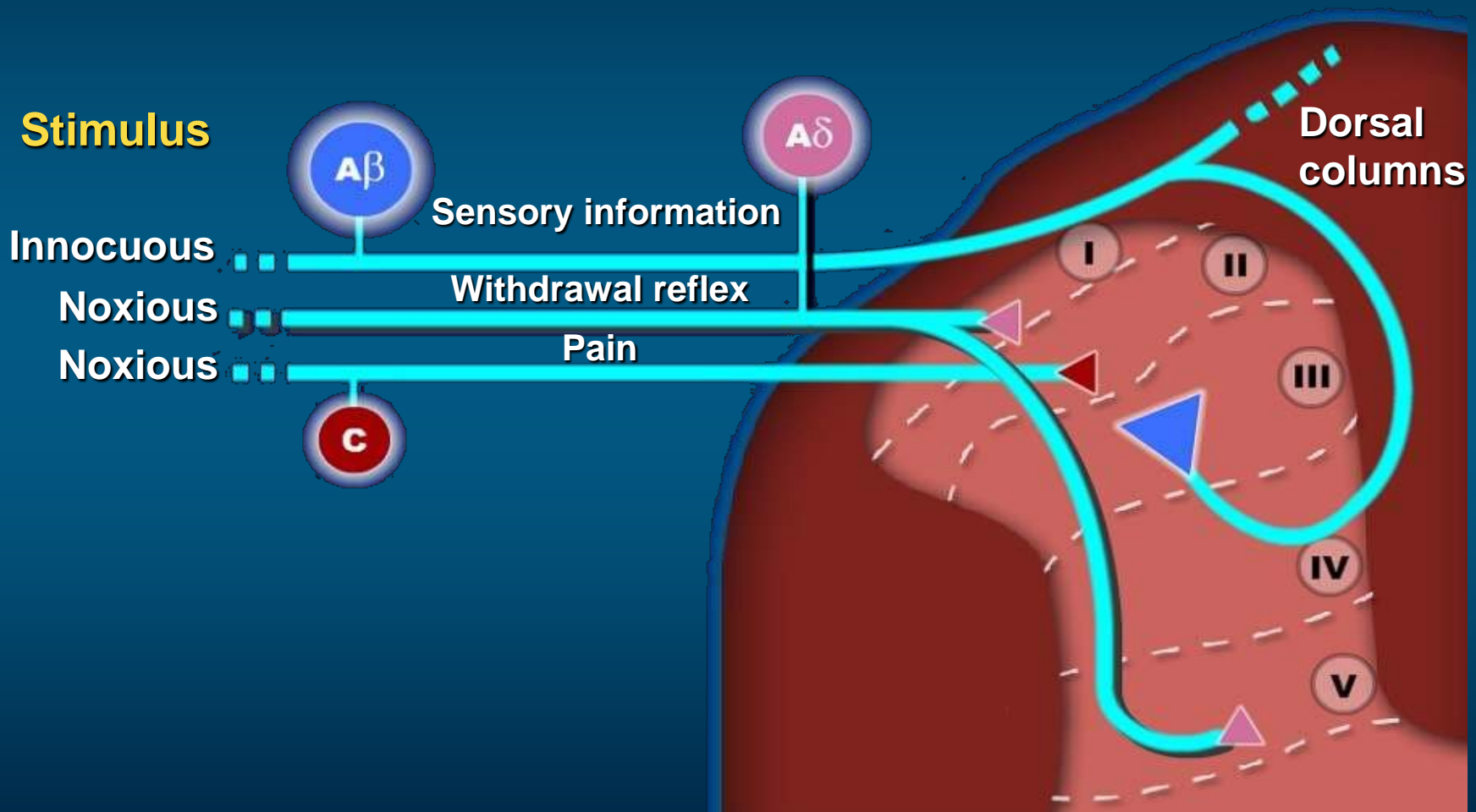
University of California, San Diego

Physiology of Pain Perception CORE

- ◆ Transduction
- ◆ Transmission
- ◆ Modulation
- ◆ Perception
- ◆ Interpretation
- ◆ Behavior

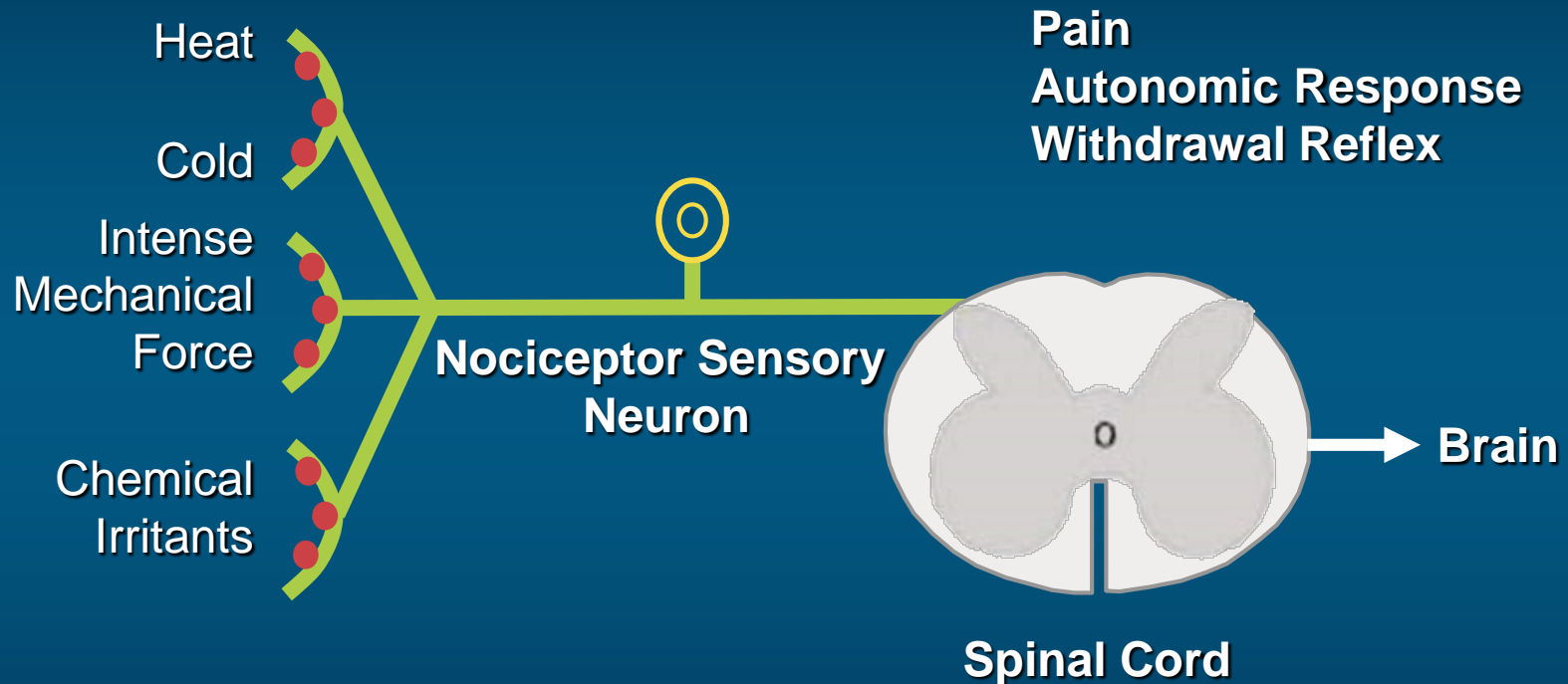


Normal Pain Pathways in the Dorsal Horn



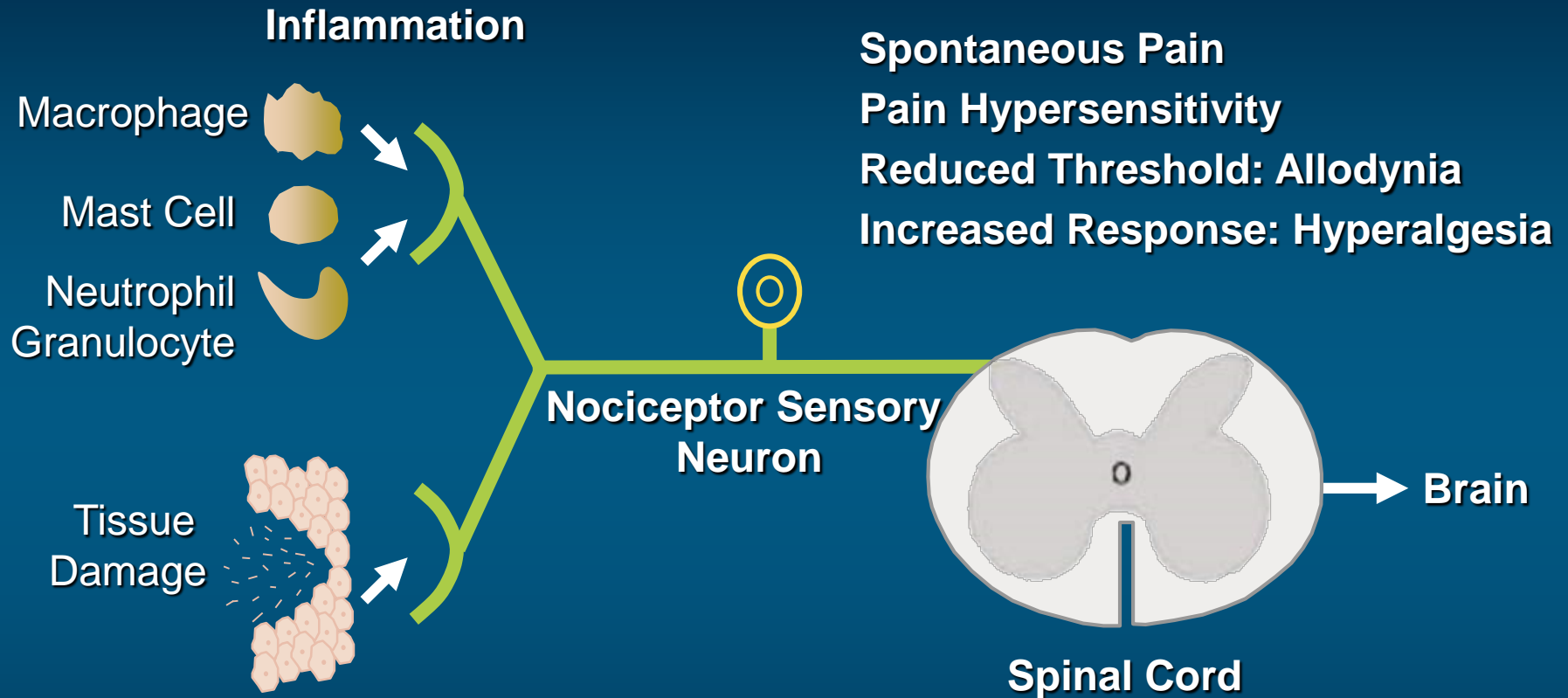
Nociceptive Pain

Noxious Peripheral Stimuli



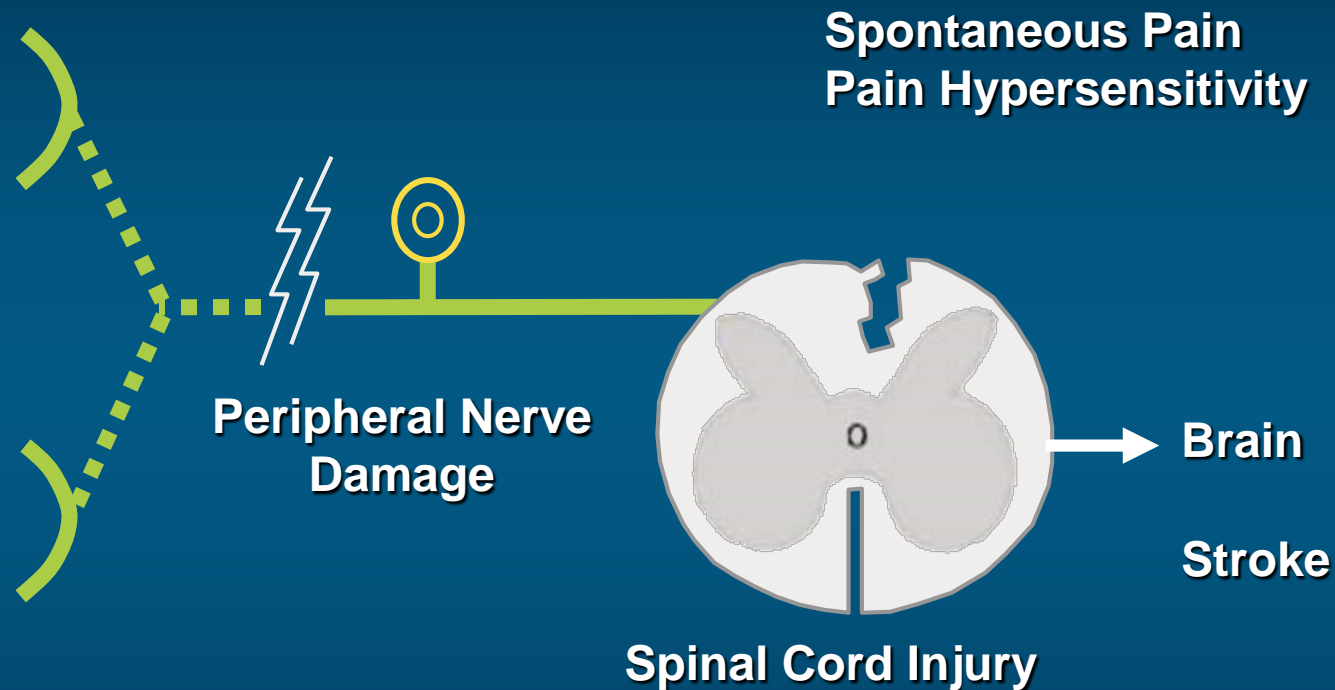
Transient pain in response to a noxious stimulus
High threshold, protective

Inflammatory Pain



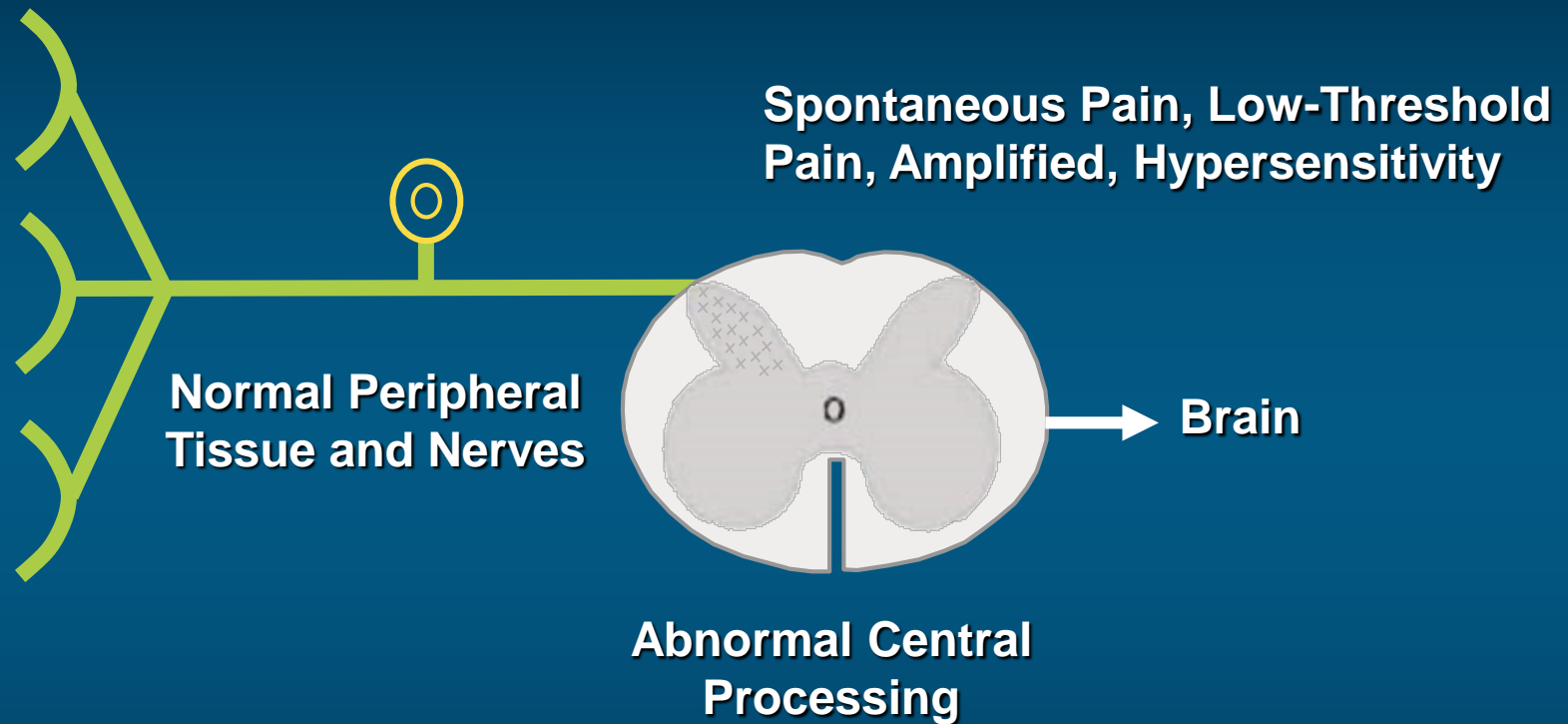
Spontaneous pain and hypersensitivity to pain in response to tissue damage and inflammation (postop pain, trauma, arthritis)—healing and repair

Neuropathic Pain



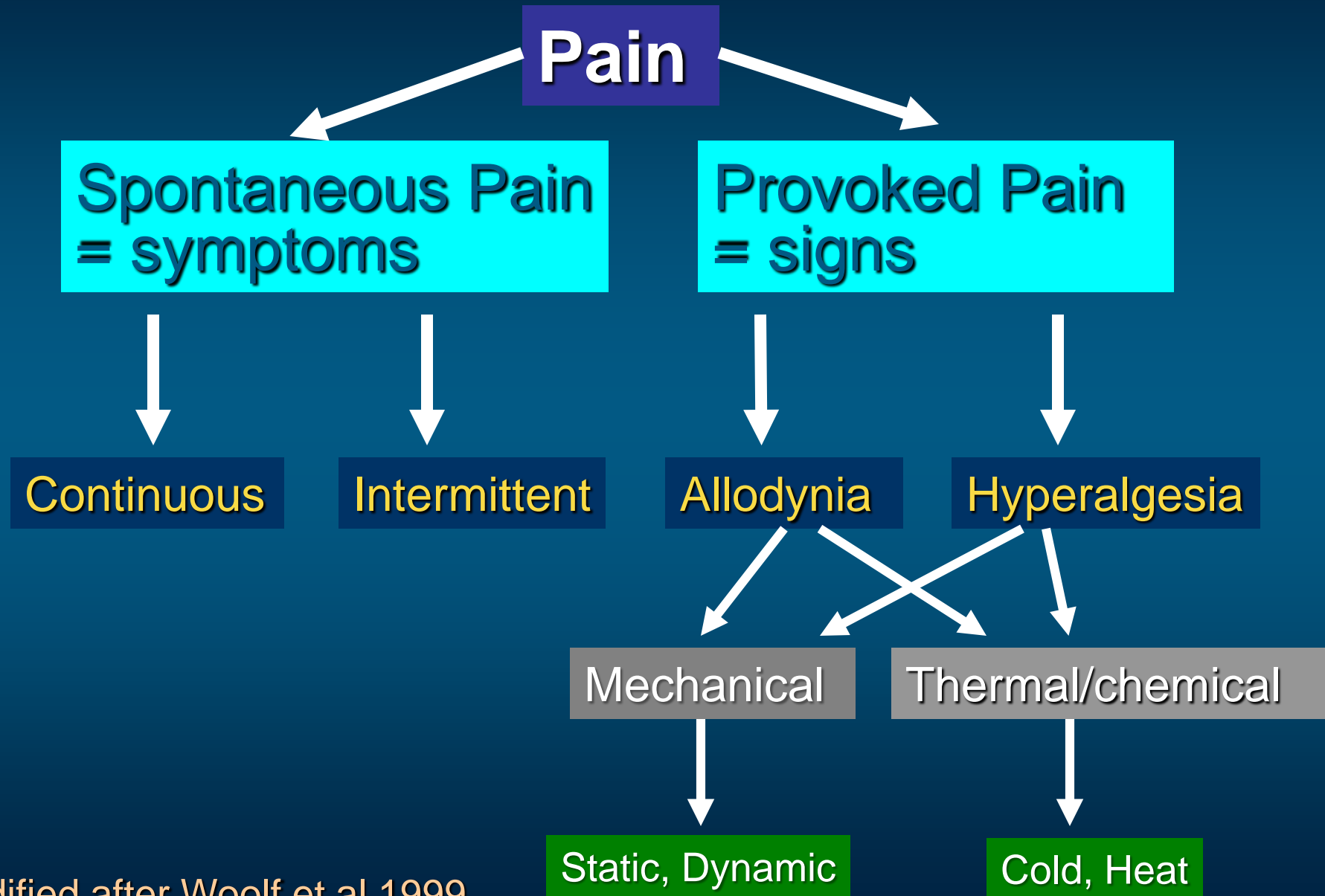
Spontaneous pain and hypersensitivity to pain in association with damage to or lesion of the nervous system—pathological pain

Functional Pain



Hypersensitivity to pain resulting from abnormal central processing of normal input—pathological IBS, fibromyalgia

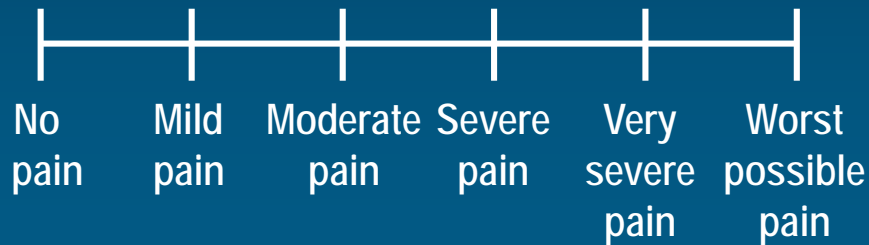
Neuropathic Pain: Clinical characteristics



Modified after Woolf et al 1999

Pain Assessment Scales

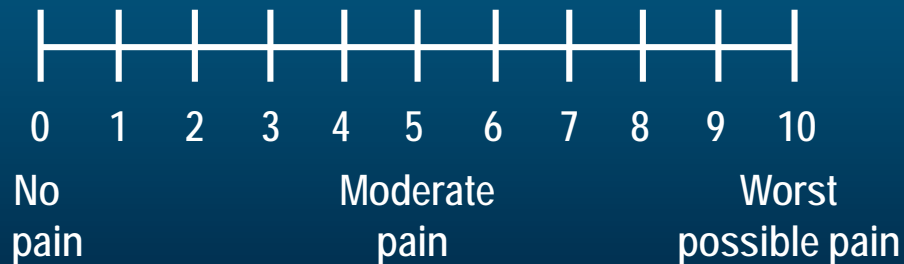
Verbal Pain Intensity Scale¹



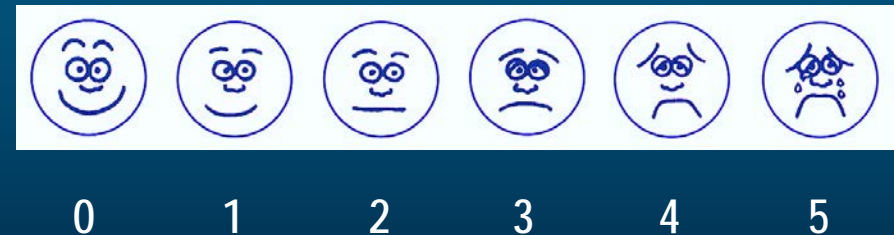
Visual Analog Scale¹



0–10 Numeric Pain Intensity Scale²



“Faces” Scale³



1. Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. 1996:8-10.

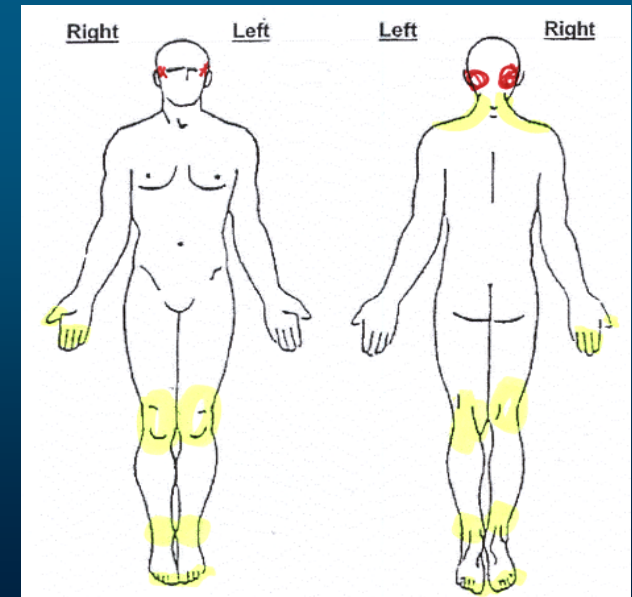
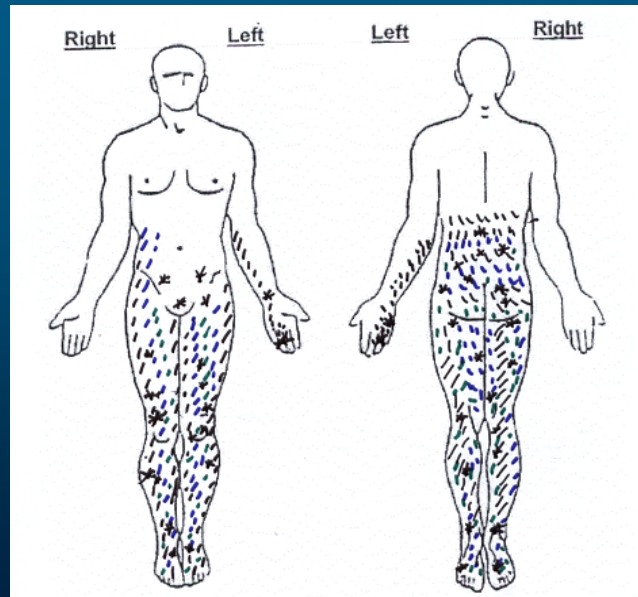
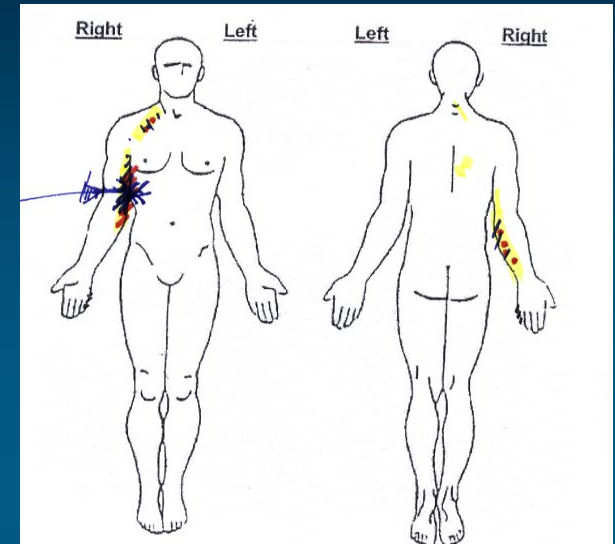
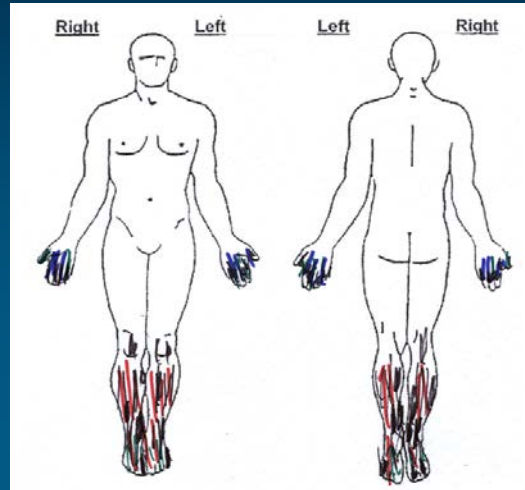
2. McCaffery M, Pasero C. *Pain: Clinical Manual*. Mosby, Inc. 1999:16.

3. Wong DL. *Waley and Wong's Essentials of Pediatric Nursing 5th ed*. 1997:1215-1216.

Neuropathic Pain Symptoms Distribution

Mapping NP symptoms: *Colored pain diagrams*

yellow = ache
blue = burning
red = stabbing
black = numb
green = tingling



Neuropathic Pain (NP) Symptoms Assessment and Measurement Tools

♦ Differentiation between NP vs. non -NP

- Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)
- Neuropathic Pain Questionnaire (NPQ)
- Neuropathic Pain Diagnostic Questionnaire (Douleur Neuropathique en 4 questions, DN4)
- painDetect
- ID-Pain

♦ Measurements of NP Characteristics

- Neuropathic Pain Scale (NPS)
- Neuropathic Pain Questionnaire (NPQ)
- Neuropathic Pain Symptom Inventory (NPSI)
- painDetect

Neuropathic Pain Patients Suffer from a Variety of Sensory Phenomena

Positive Signs (+)

Hyperalgesia

stimulus-evoked increased response to painful stimulus

Allodynia

stimulus-evoked painful response to non-painful stimulus

Hyperesthesia

Increased sensitivity to stimulation excluding special senses

Paresthesia

Abnormal, not unpleasant sensation

Dysesthesia

Abnormal, unpleasant, non-painful sensation

Negative Signs (-)

Hypoalgesia

stimulus-evoked decreased response to painful stimulus

Analgesia

Absence of pain to normally painful stimulus

Hypoesthesia

Decreased sensitivity to stimulation excluding special senses

Neuropathic Pain Patients Suffer from Spatial and Temporal Sensory Abnormalities

Spatial

Dyslocalization

Extraterritorial spread

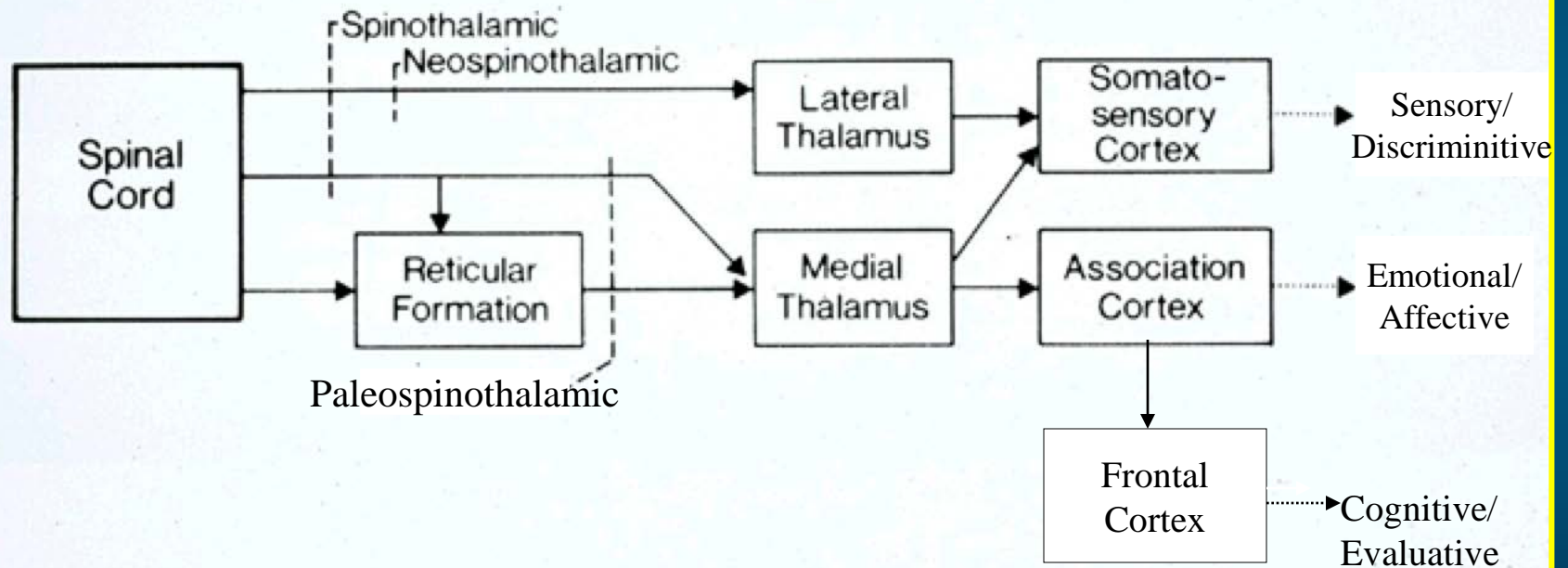
Radiation

Temporal

Afterensation

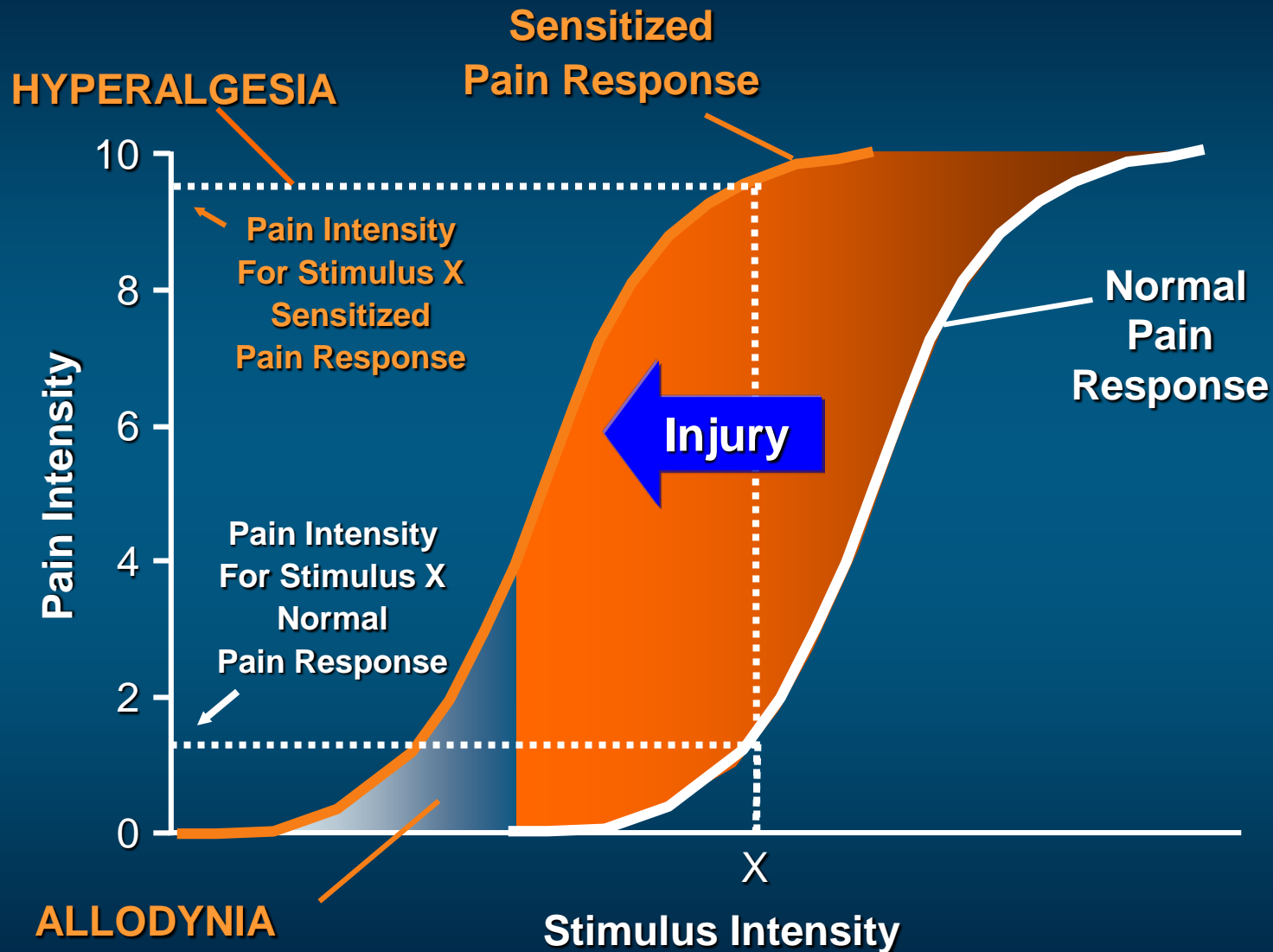
Abnormal latency

The Pain Experience



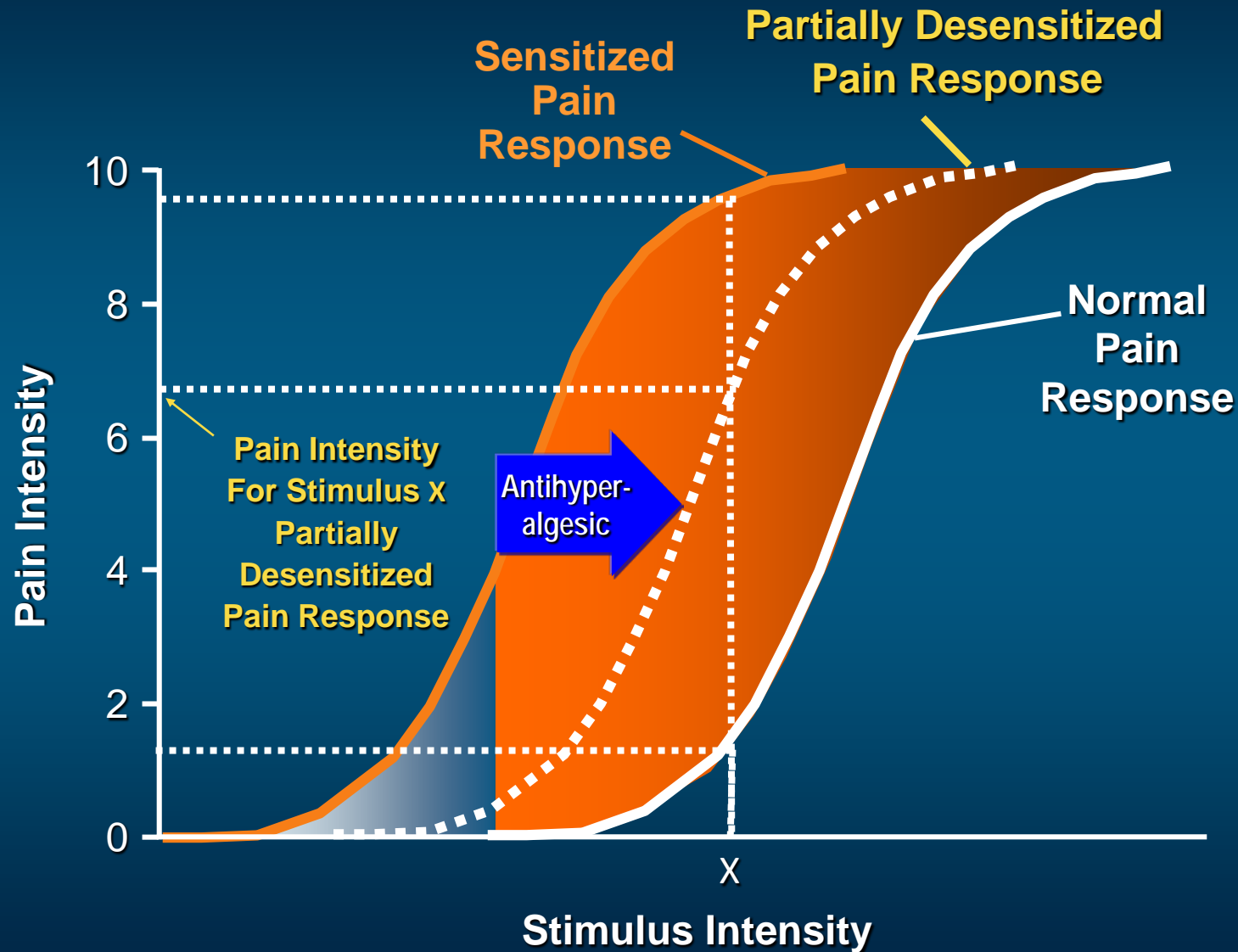
Pain Sensitization

CORE



Antihyperalgesic Therapy

CORE



Multiple Pathophysiologies May Be Involved in Neuropathic Pain

- ◆ More than one mechanism of action likely involved
- ◆ Neuropathic pain may result from abnormal peripheral nerve function and neural processing of impulses due to abnormal neuronal receptor and mediator activity
- ◆ Combination of medications may be needed to manage pain: topicals, anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and opioids
- ◆ In the future, ability to determine the relationship between the pathophysiology and symptoms/signs may help target therapy

Acute vs Chronic Pain States

Acute

vs

Chronic

- Associated with tissue damage
- Increased autonomic nervous activity
- Resolves with healing of injury
- Serves protective function

- Extends beyond expected period of healing
- No protective function
- Degrades health and functioning
- Contributes to depressed mood

Effects of Chronic Pain on the Patient

Physical Functioning

- ◆ Ability to perform activities of daily living
- ◆ Sleep disturbances

Psychological Morbidity

- ◆ Depression
- ◆ Anxiety
- ◆ Anger
- ◆ Loss of self-esteem

Social Consequences

- ◆ Relationships with family and friends
- ◆ Intimacy/sexual activity
- ◆ Social isolation

Societal Consequences

- ◆ Healthcare costs
- ◆ Disability
- ◆ Lost workdays

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.

Analgesic Options

- ◆ Acetaminophen
- ◆ NSAIDs/COX-2 inhibitors
- ◆ Local anesthetics
- ◆ Central analgesics (tramadol)
- ◆ Opioids
 - Codeine, hydrocodone, oxycodone, propoxyphene
 - Morphine, hydromorphone, methadone

Adjunct Analgesics

- ♦ TCAs
 - Amitriptyline, nortriptyline, desipramine, trazodone, doxepin
- ♦ SNRIs
 - Duloxetine, milnacipran, venlafaxine
- ♦ Anticonvulsants
 - Gabapentin, pregabalin, carbamazepine

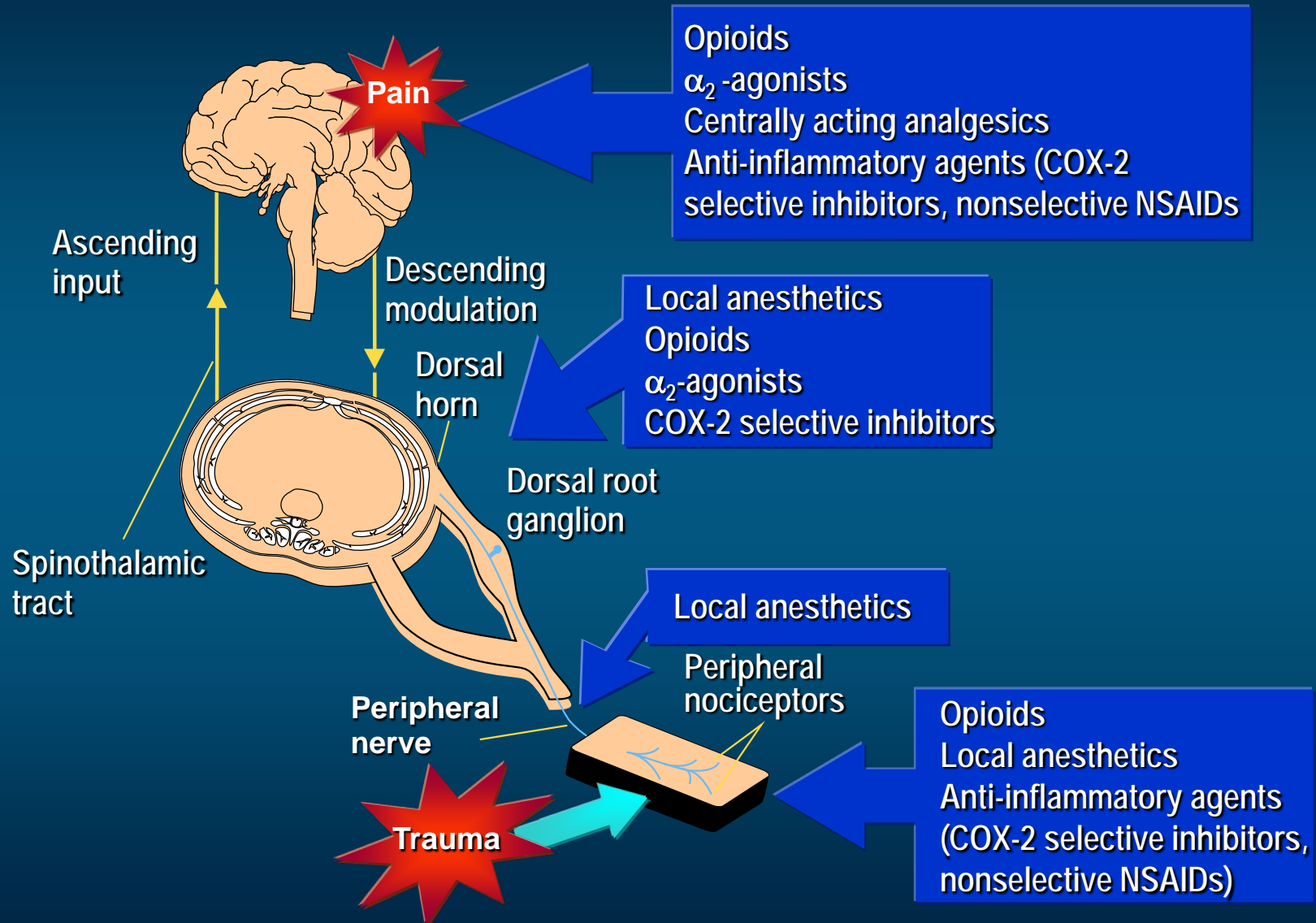
Adjunct Analgesics

- ◆ Muscle relaxants
- ◆ NMDA antagonists
 - Ketamine, dextromethorphan
- ◆ α_2 -agonists
 - Clonidine, tizanidine
- ◆ Sedative/anxiolysis
- ◆ Topical therapy
 - Capsaicin, lidocaine#, NSAIDs
- ◆ Intra-articular therapy
 - Corticosteroids, hyaluronan

#FDA approved for postherpetic neuralgia

Analgesia and the Pain Pathway

CORE



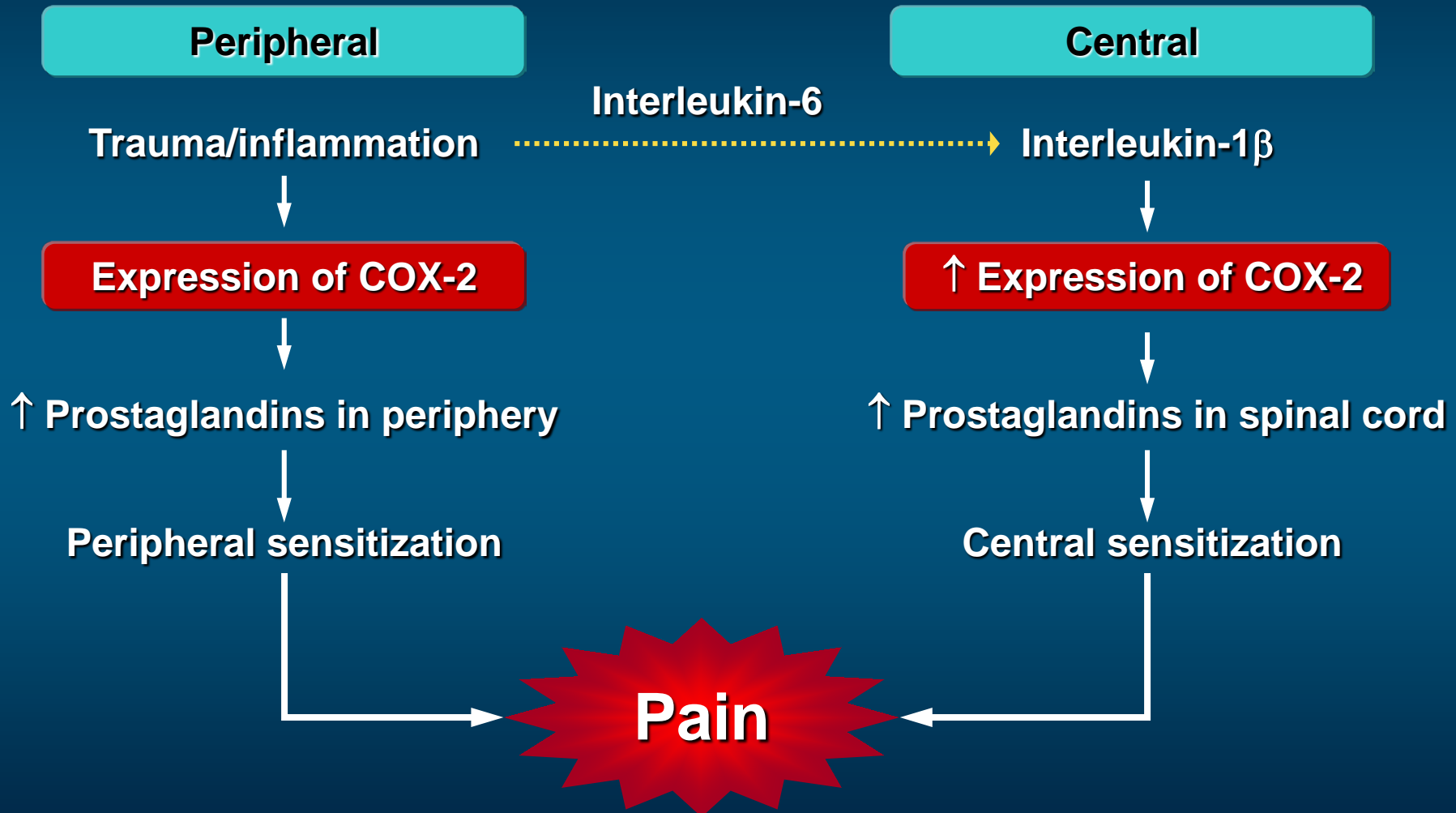
Adapted from Gottschalk et al. *Am Fam Physician*. 2001;63:1979-1984.

Acetaminophen: Mechanisms

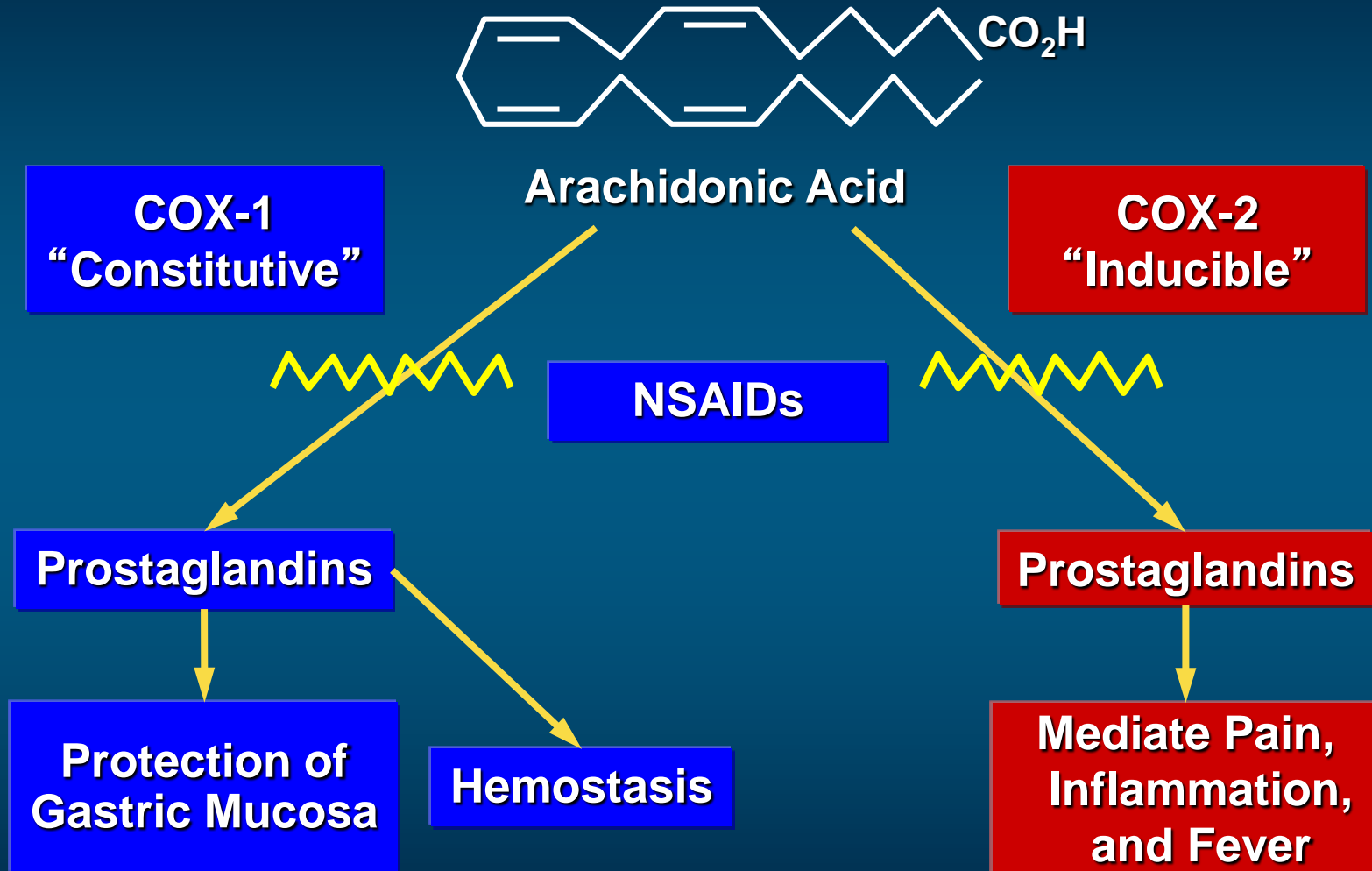
- ◆ Mechanism of action unclear
- ◆ Inhibits COX-3, a cyclooxygenase-1 variant
- ◆ Cyclooxygenase isoenzymes are known to catalyze the rate-limiting step of prostaglandin synthesis and are targets of nonselective NSAIDs

Peripheral and Central Prostaglandins and COX-2

CORE



Mechanism of Action of NSAIDs



NSAID Analgesic Properties

- ◆ Target peripheral pain pathways (peripheral sensitization)
- ◆ Anti-inflammatory and analgesic effects
- ◆ Selectively inhibit C-fiber (“second pain”) and not A- δ fiber (“first pain”)
- ◆ Analgesic ceiling effect
- ◆ Reversibly inactivate the COX enzyme (except aspirin)

Benefits

- ◆ No addiction
- ◆ Decrease or eliminate opioid use
- ◆ Lower side-effect profile than opioids

Risks

- ◆ Bleeding
- ◆ PUD
- ◆ Renal impairment
- ◆ Wound/bone healing
- ◆ Analgesic ceiling effect

Tramadol: Mechanism

- ◆ A weak μ opioid agonist
- ◆ A norepinephrine and serotonin reuptake inhibitor

Tramadol: Dosing and Administration

- ◆ In RCTs the optimum dosage self-selected by patients was 250 mg/d
- ◆ Initiate at low dosages 50 mg/d or bid
- ◆ Titrate every 3 to 7 d by 50 to 100 mg/d in divided doses as tolerated
- ◆ An adequate trial requires 4 wk at maximum dosage
- ◆ Initiate tramadol ER at 100 mg/d and increase every 5 days to maximum of 300 mg/d

Harati et al. *Neurology*. 1998;50:1842-1846; Sindrup et al. *Pain*. 1999;83:389-400. ULTRAM ER (tramadol HCl) Extended-Release Tablets [package insert]. Raritan, NJ: PriCara Unit of Ortho-McNeil, Inc. 2005.

Tramadol: AE

- ◆ Nausea
- ◆ In polypharmacy, increased risk with rapid dose escalation
 - Dizziness
 - Somnolence
 - Orthostatic hypotension
 - Serotonin syndrome with MAOIs or SSRIs
- ◆ Dosage adjustment required for renal/hepatic disease
- ◆ Lowers the seizure threshold
- ◆ Increased risk of addiction in patients with history of substance abuse

Tramadol ER

- ◆ Extended-release formulation created to help moderate-to-moderately severe chronic pain in adults who need round-the-clock pain treatment for extended periods of time
- ◆ Lag in drug absorption; reaches peak in 12 to 15 hours; steady state in 4 days
- ◆ As yet unstudied adverse event profile in patient population over 65 years of age; not to be used in severe renal or hepatic disease

Are Opioids Overprescribed?

- ◆ In the past 10 years, opioid prescribing has increased 400%
- ◆ Balance of opioid abuse and overdose shifted toward prescription opioids in the late 90s
- ◆ Opioids are now the most widely prescribed class of drugs in the U.S.
- ◆ Vicodin is the single most commonly prescribed medication in the U.S.
- ◆ Although the U.S. is the #1 consumer of opioids in the world, there is no evidence that pain outcomes are better

Methodone Overdose

- ◆ Methadone appears to be involved in approximately one third of all prescription opioid-related deaths, exceeding hydrocodone and oxycodone despite being prescribed one-tenth as often
- ◆ Several possible reasons
 - Prescribed as maintenance for addicts who often abuse other illicit drugs
 - Pharmacokinetic differences
 - Possible cardiac effects

Opioids in Chronic Pain: Review of Randomized, Controlled Clinical Trials

- ◆ Efficacy of opioids in chronic noncancer pain established in a number of randomized, controlled trials, including placebo-controlled trials of:
 - codeine
 - tramadol
 - oxycodone
 - morphine
 - fentanyl
- ◆ **However, there are no long-term studies demonstrating benefits**

State of Washington Opioid Law

- ◆ The first state to pass a bill that established an upper limit on the opioid dose a primary care physician can prescribe for chronic non-cancer pain
- ◆ If this upper limit is reached, a pain consultation is required
- ◆ Other states have followed

The Food and Drug Administration has:

- ◆ Issued a recommendation for special certification for prescribing long-acting opioids
 - 2012
- ◆ Reclassified scheduled III opioids to scheduled II
- ◆ Relabeled all long acting and extended release opioids (September, 2013)
 - Recommending failure of short acting opioids before resorting to LA/ER.
 - Raise the bar required (treatment failures) before resorting to chronic opioid therapy.
 - Require that the industry conduct more postmarketing studies to address long term safety.
 - Warn about the risks of maternal use and affects on the newborn

The Center for Disease Control has:

- ◆ Adopted a set of 12 Guidelines for the Primary Care Physician to consider when using opioids to treat chronic non-cancer pain
- ◆ Not intended to be standard of care
- ◆ There are situations for some patients to be treated outside the guidelines

The Food and Drug Administration is Considering:

- ◆ Removing all acetaminophen containing products from the market
- ◆ Removing acetaminophen and NSAIDs from over the counter sales

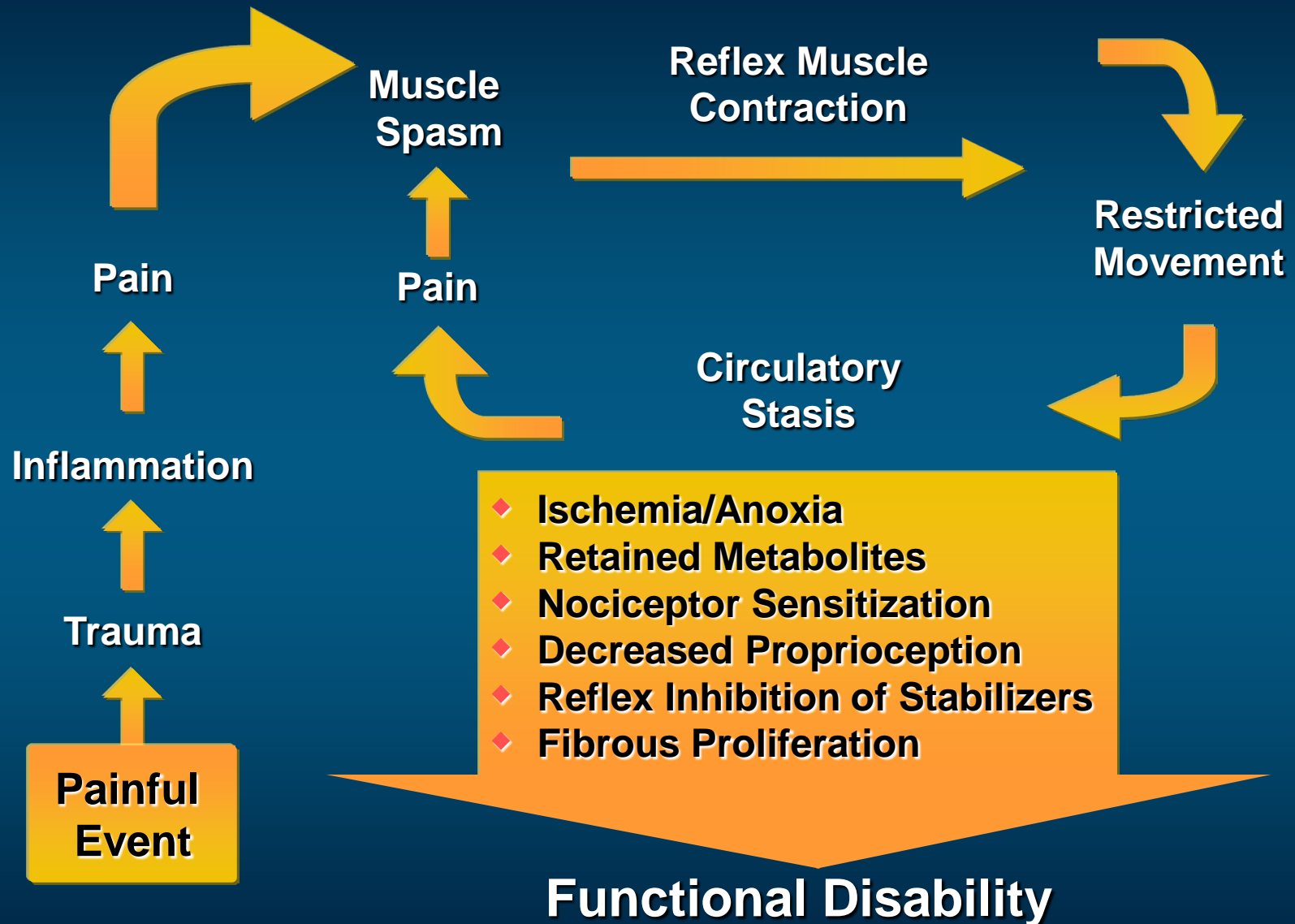
FDA-Approved Treatments for Neuropathic Pain

- ◆ Capsaicin Patch 8%
 - Postherpetic neuralgia
- ◆ Duloxetine
 - Peripheral diabetic neuropathy
 - Fibromyalgia
- ◆ Gabapentin (1 short acting and 2 extended release)
 - Postherpetic neuralgia
- ◆ Lidocaine Patch 5%
 - Postherpetic neuralgia
- ◆ Milnacipran
 - Fibromyalgia
- ◆ Pregabalin
 - Peripheral diabetic neuropathy
 - Postherpetic neuralgia
 - Fibromyalgia
 - Spinal Cord Injury
- ◆ Carbamazepine
 - trigeminal neuralgia

Human Models for Neuropathic Pain

- ◆ Diabetic neuropathy (DN) and postherpetic neuralgia (PHN) are the most prevalent neuropathic pain disorders
- ◆ Majority of randomized controlled trials data are in PHN/DN
- ◆ PHN has been the most commonly used model for treating neuropathic pain in clinical trials

Spasm-Pain-Spasm Cycle



Muscle Relaxants: AEs

- ◆ CNS side effects
 - Sedation
 - Dizziness
 - Confusion
 - Blurred vision
- ◆ Potential for abuse with carisoprodol (Schedule IV*)
- ◆ GI AEs
 - Nausea, epigastric distress, vomiting
- ◆ Anticholinergic properties: dry mouth, urinary retention

*In 10 states.

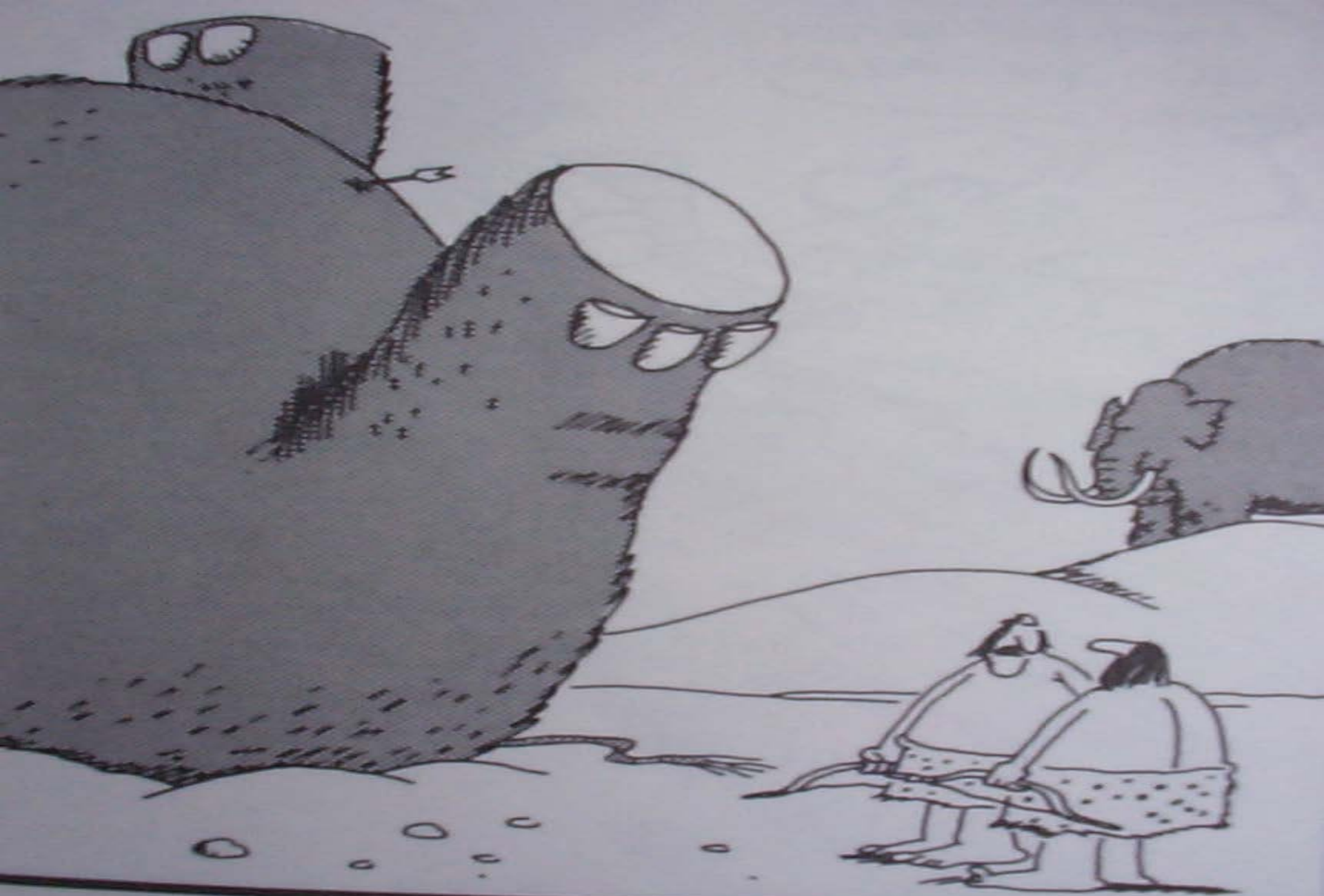
Waldman. *J Pain Symptom Manage*. 1994;9:434-441 (B); Toth et al. *Clin Ther*. 2004;26:1355-1367 (A); van Tulder et al. *Spine*. 2003;28:1978-1992 (A).

Nonpharmacologic Options CORE

- ◆ TENS: electrical stimulation of the skin to relieve pain by interfering with the neural transmission of signals from underlying pain receptors
 - 3 controlled studies
 - 66% experienced immediate symptomatic improvement and 44% maintained improvement for 1 year¹
- ◆ Acupuncture: specific body areas associated with peripheral nerves are pierced with fine needles to produce anesthesia, relieve pain, and promote therapy
 - 10-week randomized study
 - Relieved pain and primary and secondary symptoms in 77% of the patients²

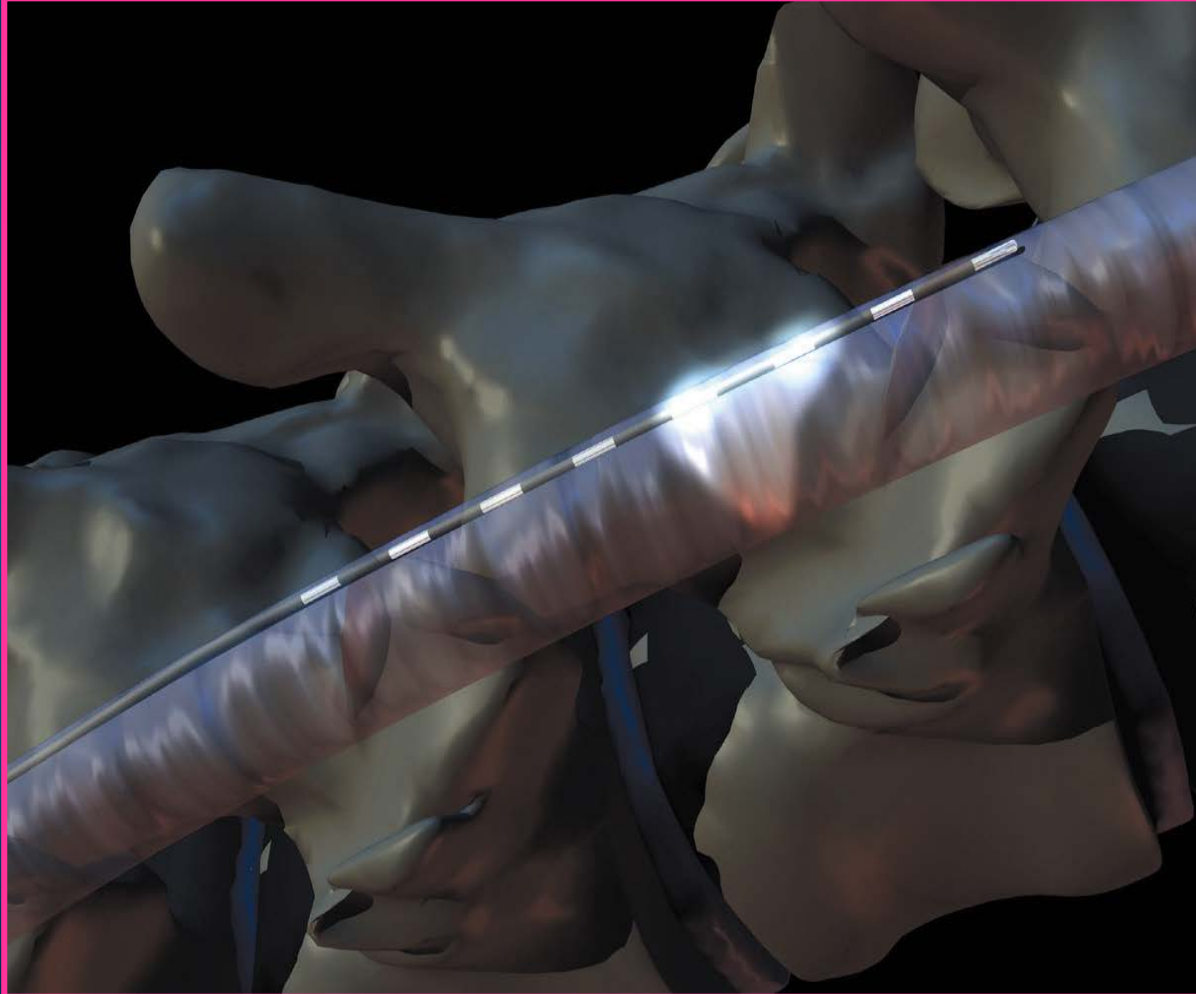
Nonpharmacologic Options (cont' d)

- ◆ PT/massage/desensitization¹
- ◆ Ice¹
- ◆ Biofeedback: the technique of using monitoring devices to furnish information regarding an autonomic bodily function, such as heart rate or blood pressure, in an attempt to gain some voluntary control over that function²
- ◆ Relaxation techniques²
- ◆ Cognitive behavioral therapy²



"Maybe we should write that spot down."

Spinal Cord Stimulation



Spinal Drug Delivery

- ◆ Opioids
- ◆ Clonidine
- ◆ Bupivacaine
- ◆ Baclofen
- ◆ Ziconotide
- ◆ Drug Compounding

