The Modern Science of Pain

A View From the Frontline

Science Board to the FDA Meeting

March 1, 2016

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SCOPE of Pain
Safe and Competent Opioid Prescribing Education

CARE
Clinical Addiction Research and Education

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Disclosures

I serve as faculty and course director for safe opioid prescribing CME funded by unrestricted educational grants awarded to Boston University by:

- Substance Abuse and Mental Health Services Administration
- REMS Program Companies as part of the FDA's ER/LA Opioid Analgesic REMS program

I did not receive any direct payment from industry for these activities

Pain

René Descartes. *Treatise of Man*, 1664

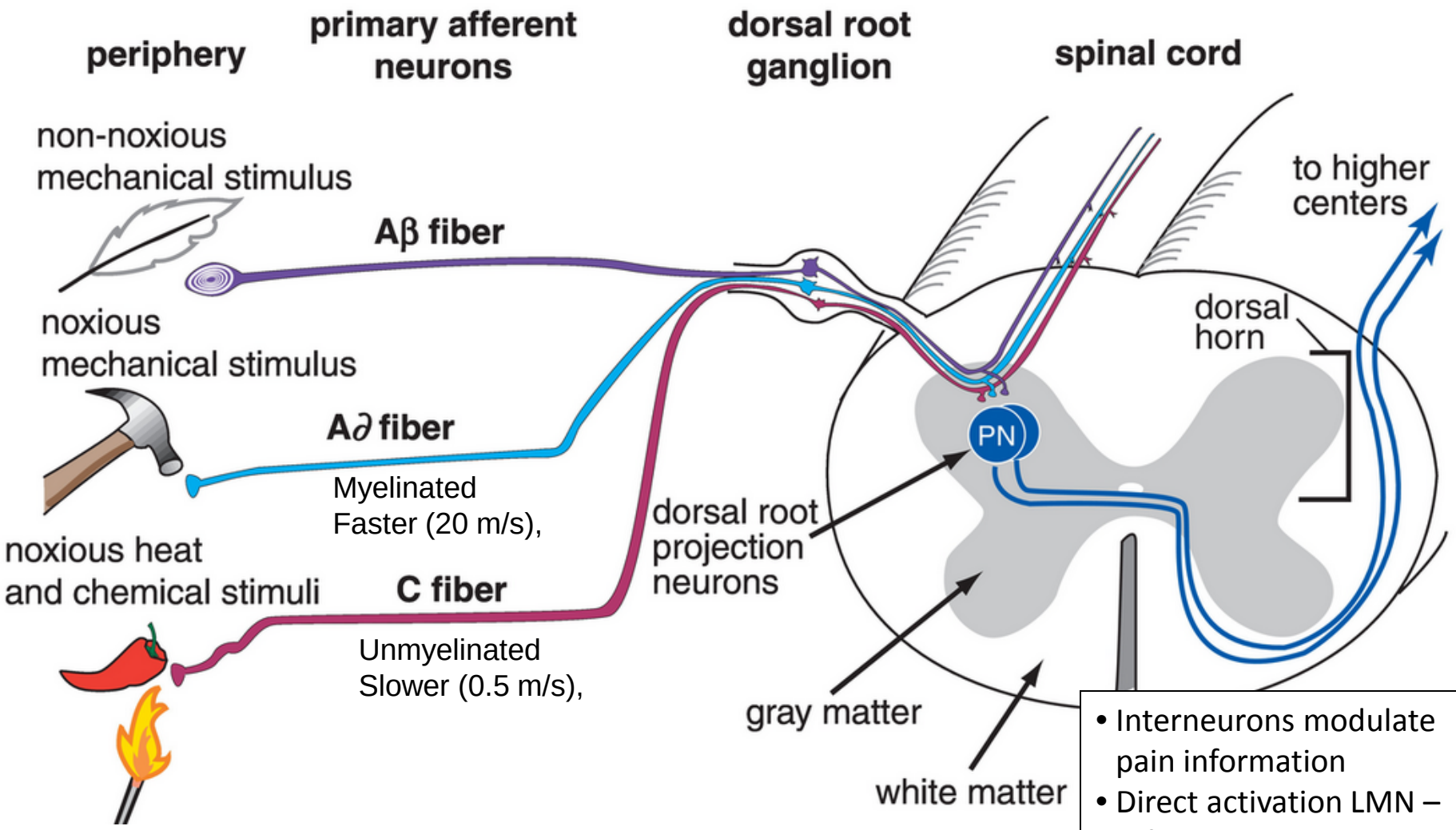
"an **unpleasant sensory and emotional experience** associated with **actual or potential tissue damage** or described in terms of such damage" *International Association for the Study of Pain*. 1994

PAIN has an element of blank;
It cannot recollect when it began,
Or if there were a day when it was not.

It has no future, but itself,
Its infinite realms contain its past,
Enlightened to perceive new periods of pain.

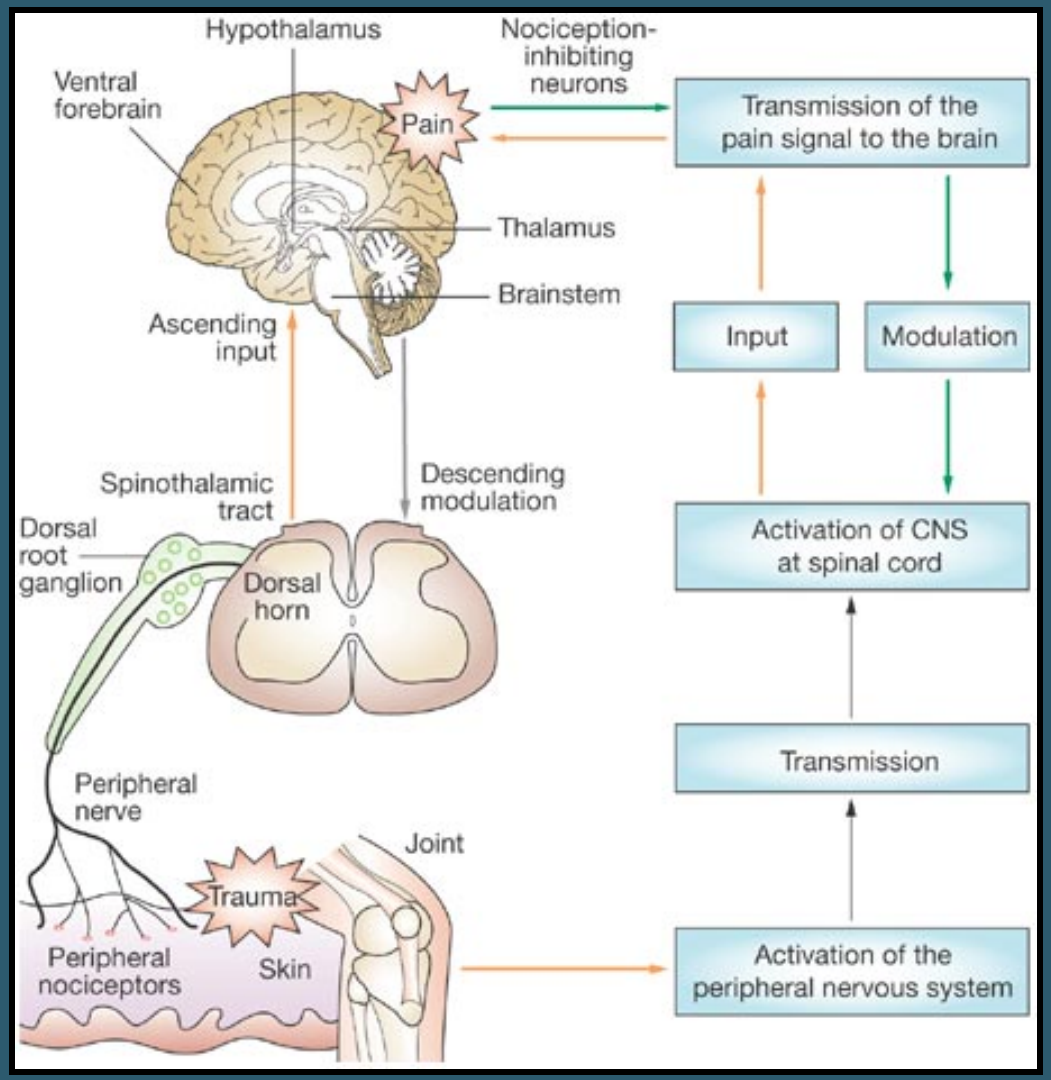
- Emily Dickinson (1890)

Nociception:
Transduction, Conduction, Transmission, Perception



- Interneurons modulate pain information
- Direct activation LMN – reflex withdrawal

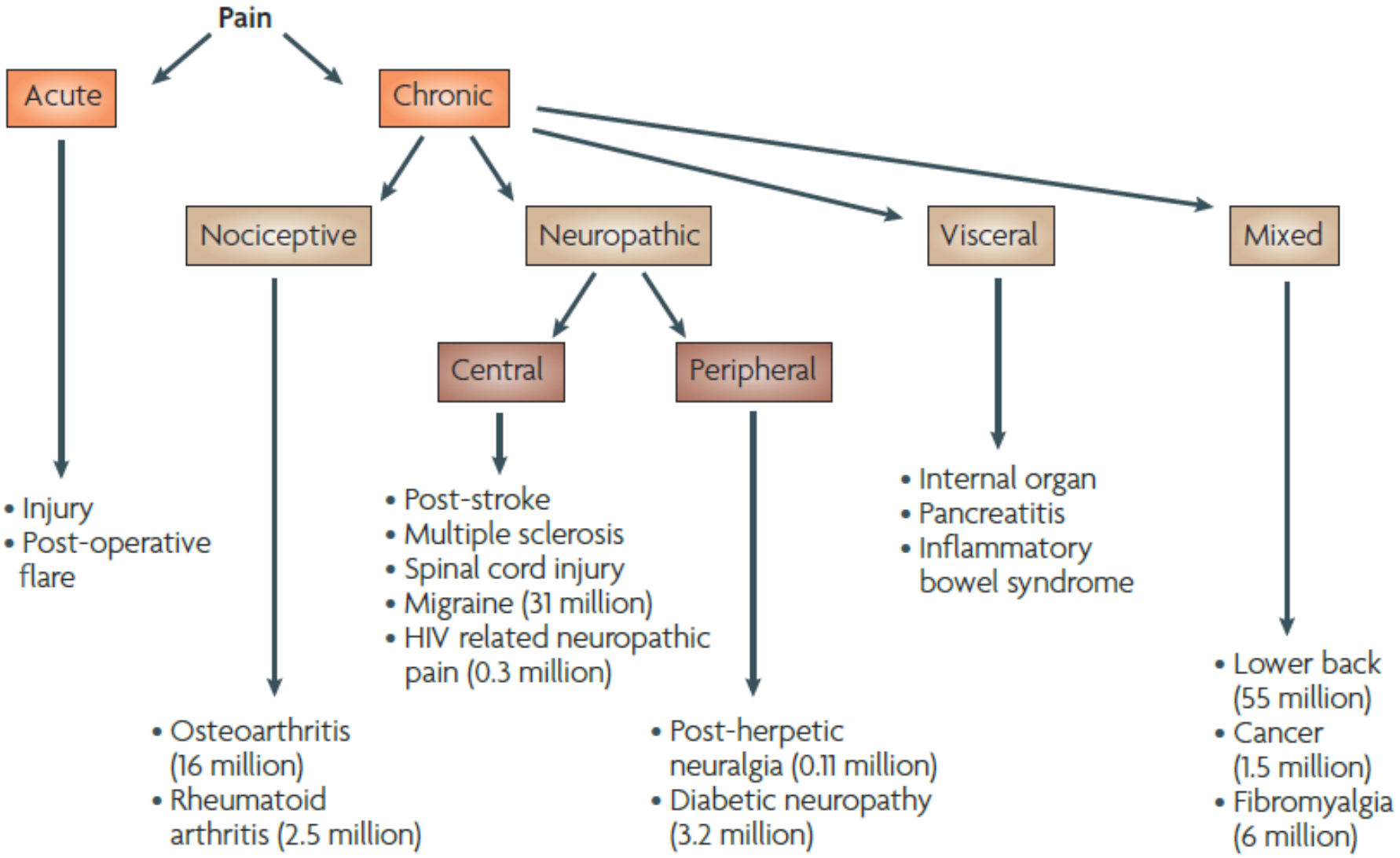
Acute Pain: A Life Sustaining Symptom



- Protective role by eliciting reflex and motivation to minimize harm
- Signal subject to physiologic modulation (fight or flight)

Argoff CE, et al. *Pain Med.* 2009

Pain Types



Melnikova I. *Nature Reviews Drug Discovery* 2010

Chronic Pain

- Pain that persists for more than 3 month or beyond the expected time for healing
- Prevalence in the US:

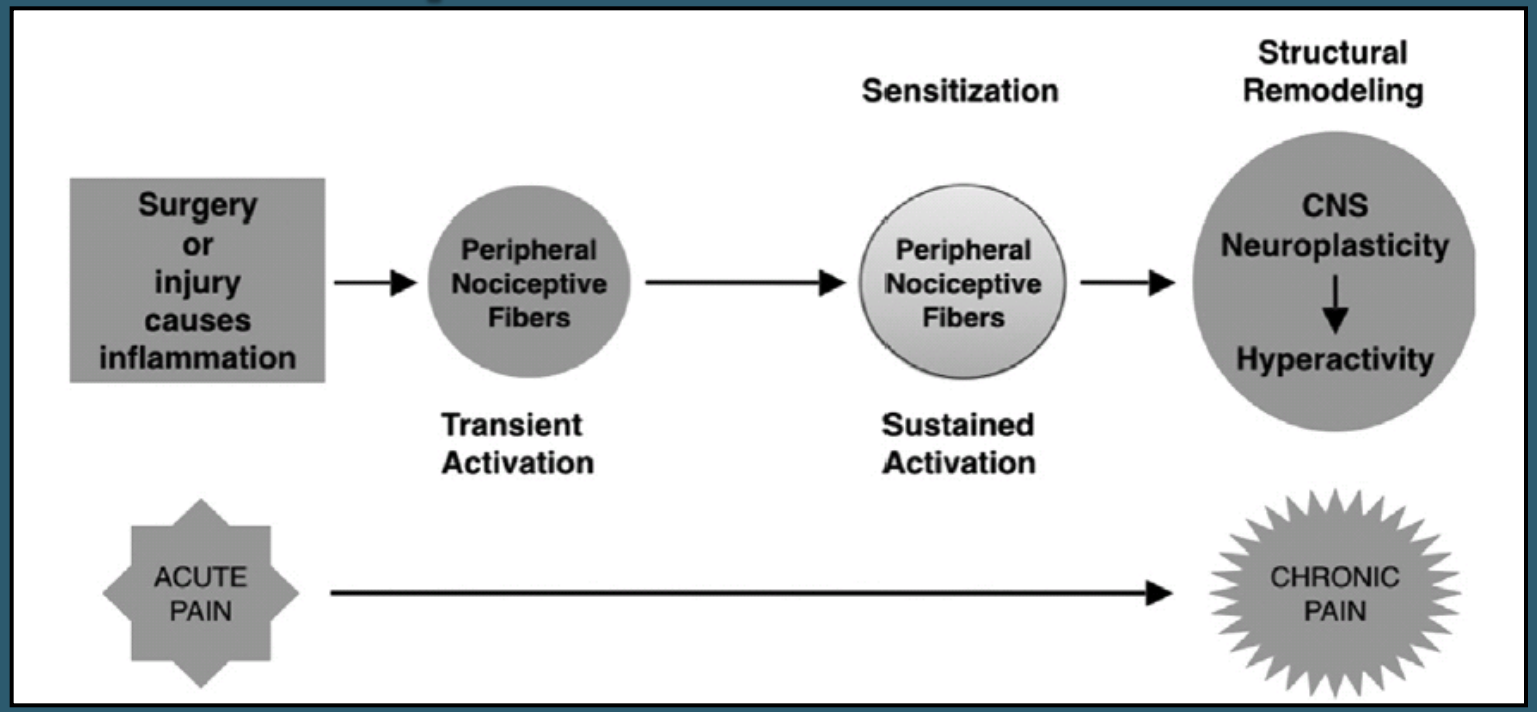
  ~11-31% (100 million) annually

  ~8% (25 million) with moderate to severe chronic pain

Nahin RL. *J Pain* 2015
IOM. *Relieving Pain in America*. 2011
Boudreau D et al. *Pharmacoepi Drug Safey*. 2009

Dzau VJ, Pizzo PA. *JAMA* 2014
Reuben DB et al. *Ann Intern Med*. 2015

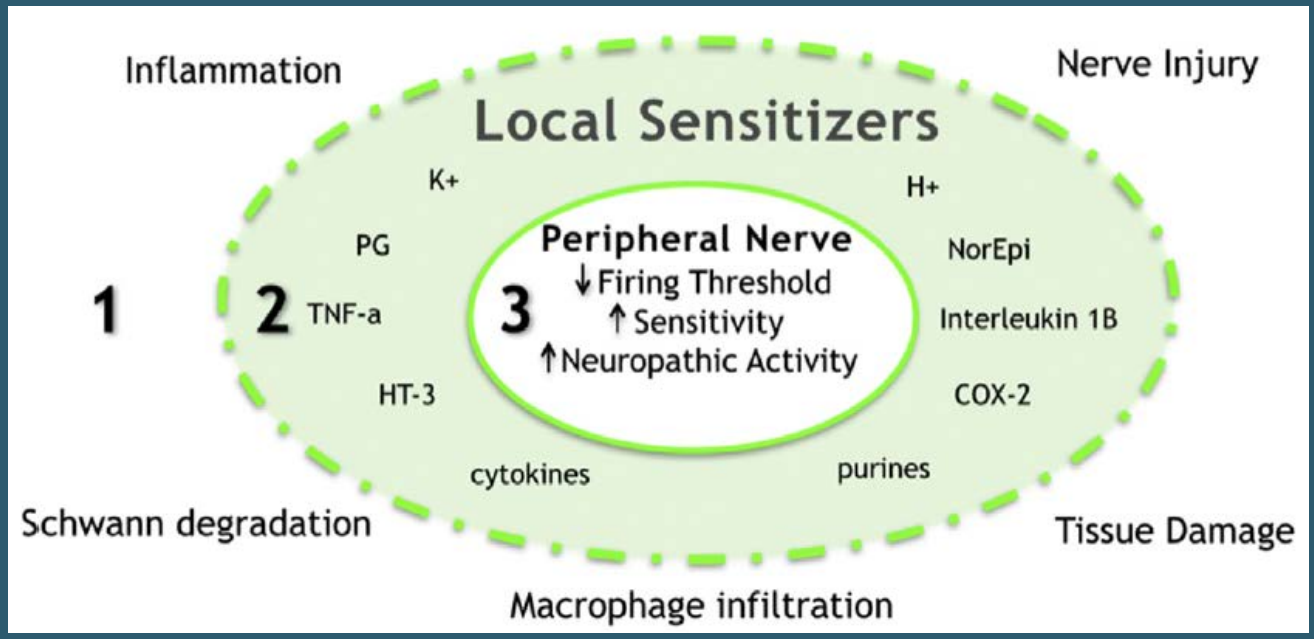
Development of Chronic Pain



- Exact mechanism unknown
- Alterations in expression of transmitters, receptors and ion channels, and in structure, connectivity and survival of neurons
- Risk factors – younger, female, psychosocial, genetic (variations of Na+ channels, μ-opioid receptors, single-nucleotide polymorphisms

Voscopoulos C, Lema M. *Brit J Anaesth.* 2010

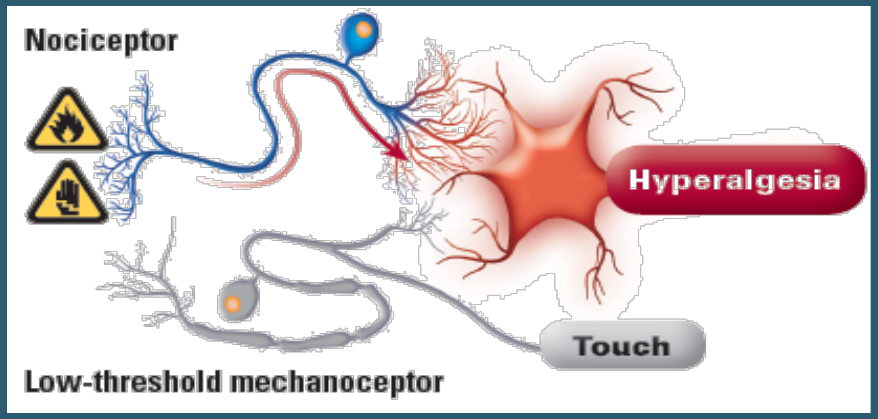
Peripheral Sensitization

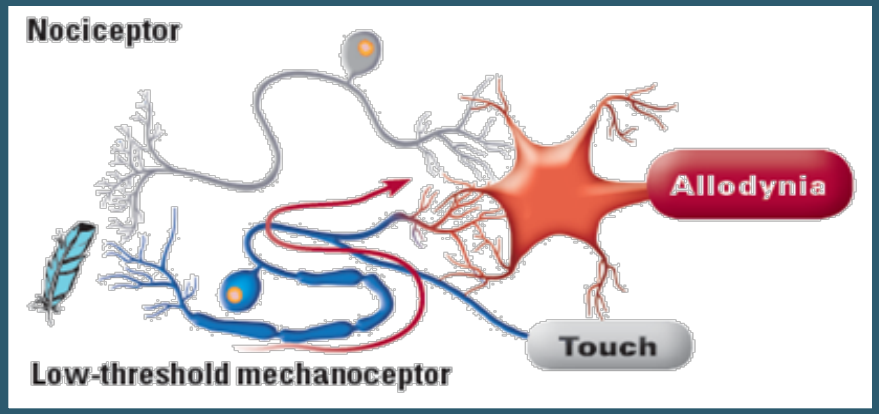


1. Inflammation, nerve injury, etc
2. Release of local sensitizers
3. Neurotransmitters promote increase nociceptor sensitivity

John-Paul J, et al. *Med Clin N Am.* 2016

Central Sensitization

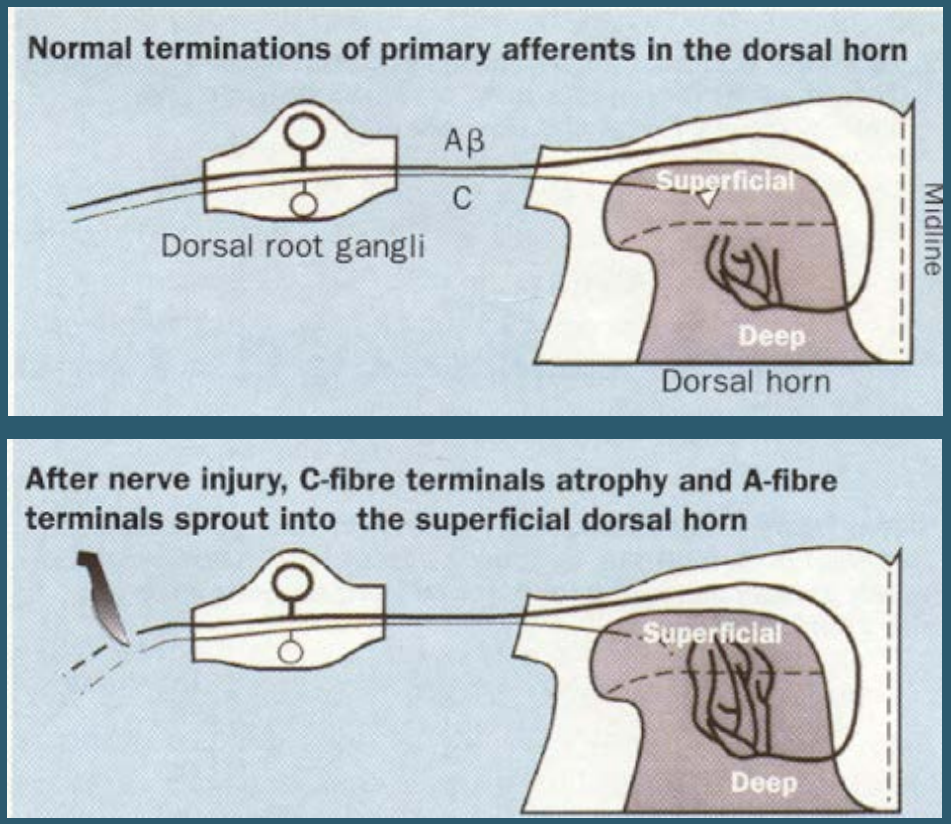




- A state if excitability of the central nociceptive circuits in the absence of inflammation or an acute neural lesion
- Spontaneous activity
- Reduced thresholds for activation by peripheral stimuli
- Increased receptive fields
- Reduced activity in descending inhibitory pathways

Latremoliere A, et al. *J Pain*. 2009; Woolf CJ. *Pain*. 2011

Neuroplasticity: Structural Reorganization



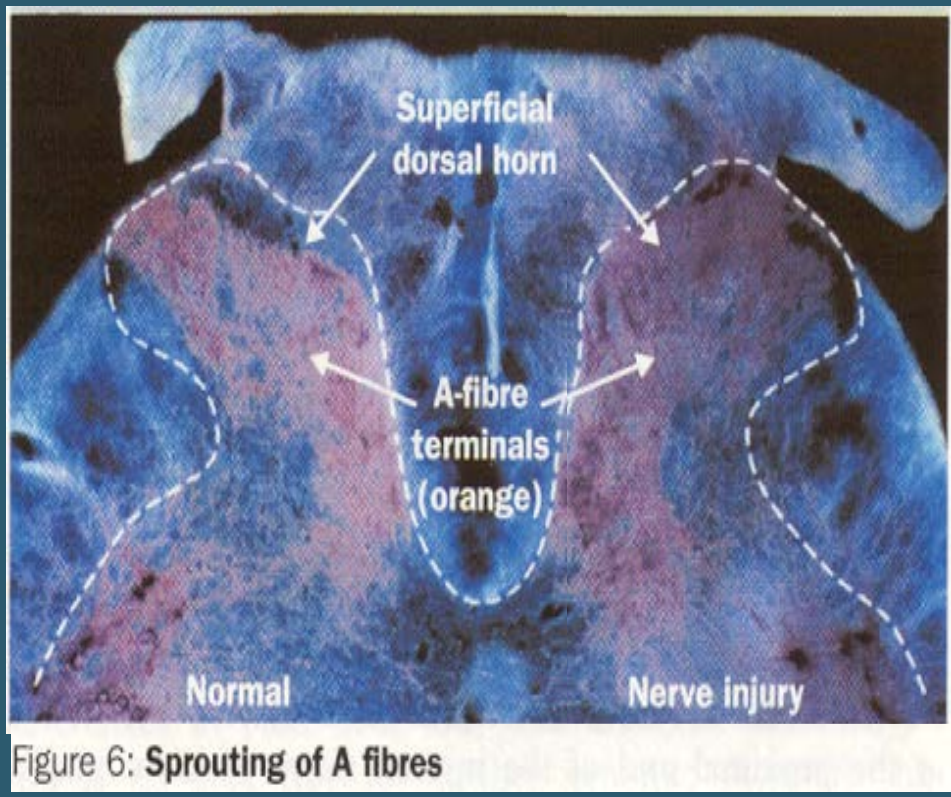
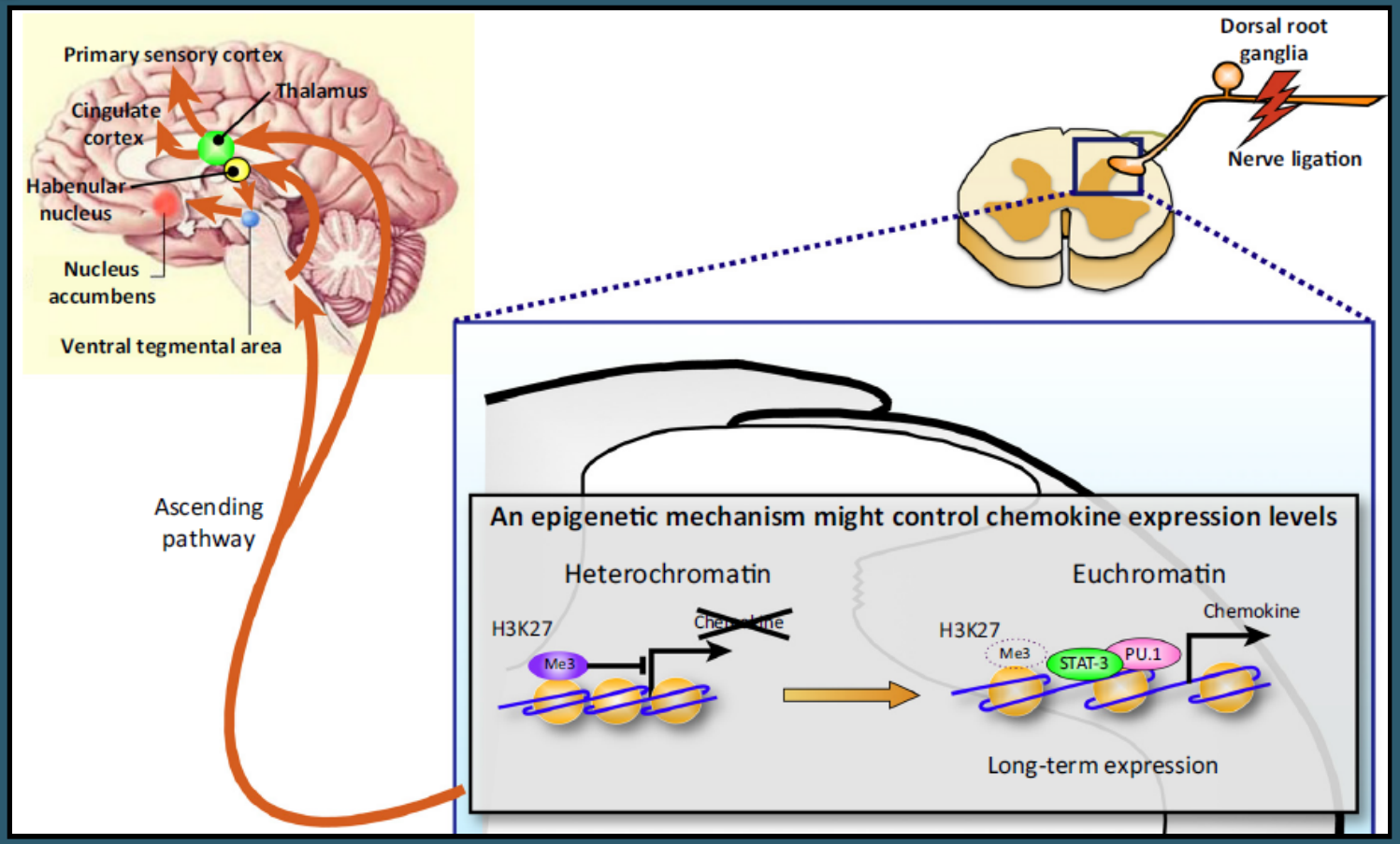


Figure 6: **Sprouting of A fibres**

Peripheral nerve injury → recruitment of macrophages and glial cells → dysregulated nerve regeneration of both Aβ and C-fibers

Woolf CJ, Mannion RJ. *Lancet*. 1999
Woolf CJ. *Ann Intern Med*. 2004

Epigenetics Can Mediate Chronic Pain



- Dynamic long-term changes in gene expression that alter cellular activity
- Activation of secondary neurons by long-term chemokine expression can induce central sensitization leading to neuropathic pain

Descalzi G et al. *Trends Neurosciences.* 2015

Chronic Pain as a Disease State

- Pathologic, maladaptive disorders of somatosensory - pain signaling pathways
- Acute pain conditions can lead to maladaptive sensitization that persists well after the acute injury
- Genetic and epigenetic factors that predispose to sensitization of pain pathways

Therefore, management approaches designed for acute, self-limited pain are inadequate and inappropriate for treating chronic pain

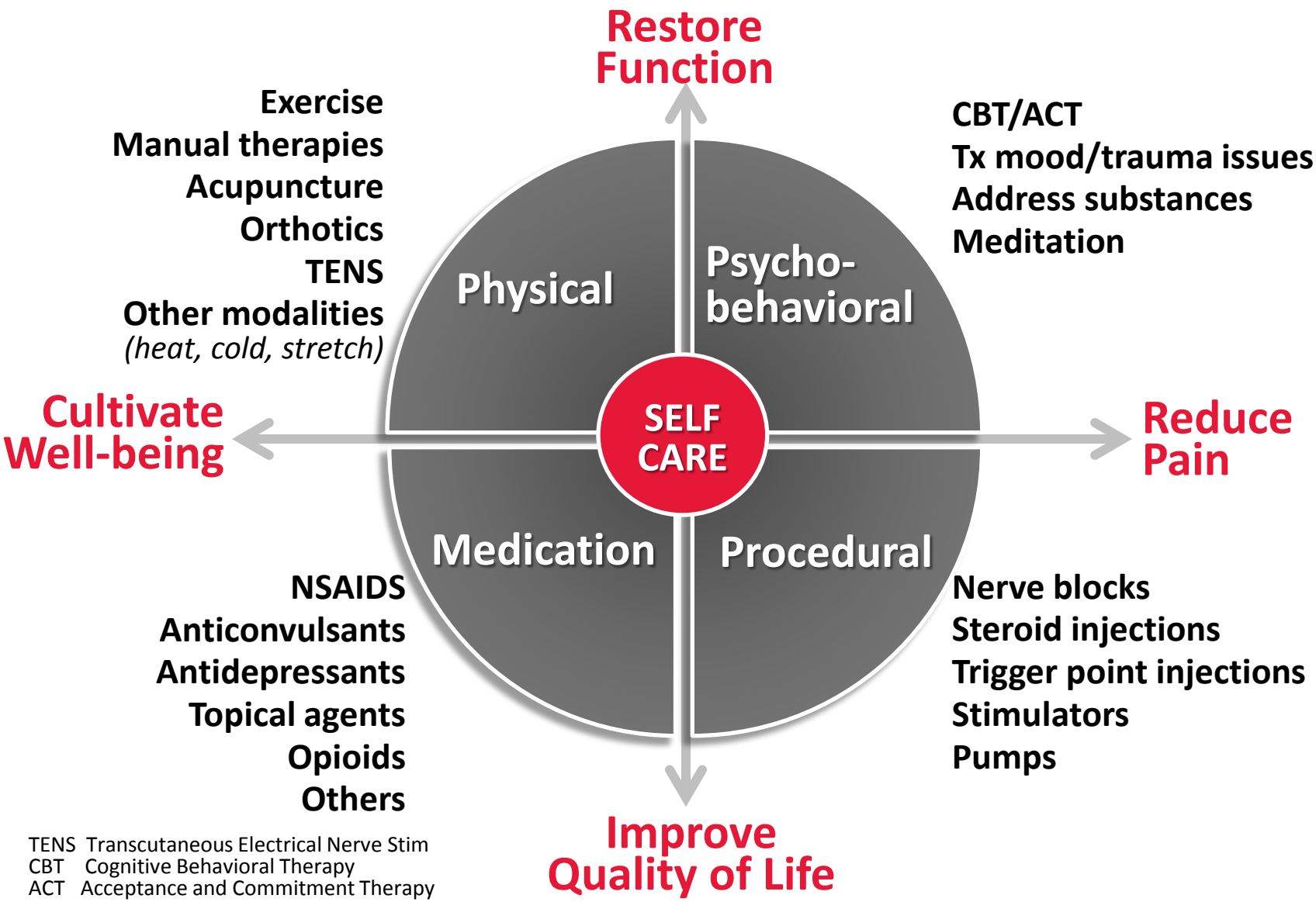
Walk D, Poliak-Tunis M. *Med Clin N Am*. 2016

Chronic Pain Terminology

- Pain mechanisms do not discriminate between **cancer** and **noncancer** pathophysiology
- Patients with cancer and those without cancer have same pain-generating physiology
- Terms “cancer” and “noncancer” does not help better understand mechanism underlying pain or guide to appropriate treatment strategies

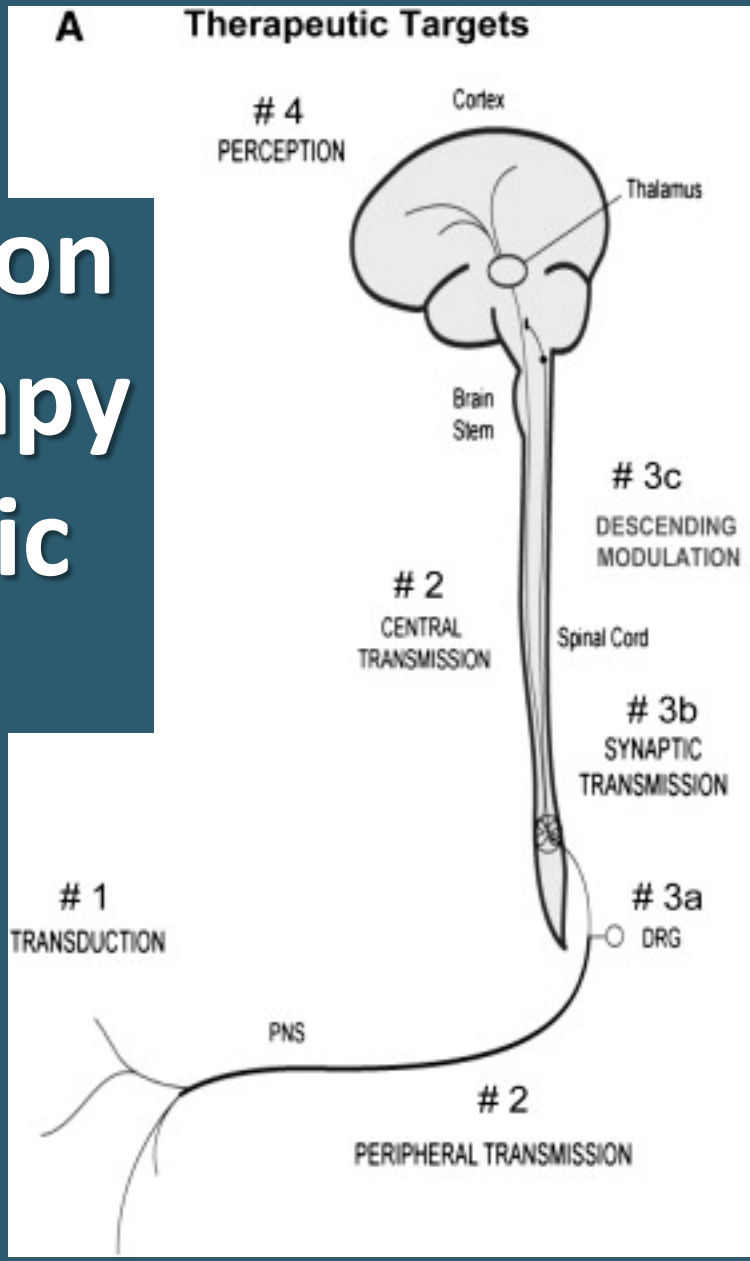
Peppin JF, Shatman ME. *J Pain Res.* 2016

Chronic Pain Management



TENS Transcutaneous Electrical Nerve Stim
CBT Cognitive Behavioral Therapy
ACT Acceptance and Commitment Therapy

Combination Drug Therapy for Chronic Pain



B Target-directed Drugs

#1: Transduction
Capsaicin, local anesthetic, NSAID, steroid, opioid, anti-TNFα agent

#2: Transmission - action potential propagation
Local anesthetic, TCA

#3a: Plasticity – DRG ectopic activity
Local anesthetic, TCA, anti-TNFα agent, NSAID

#3b: Plasticity – synaptic transmission
Ion channel blocker, NMDA receptor antagonist, opioid, tramadol, α-adrenergic receptor agonist, COX-2 inhibitor, anti-TNFα agent, ziconotide

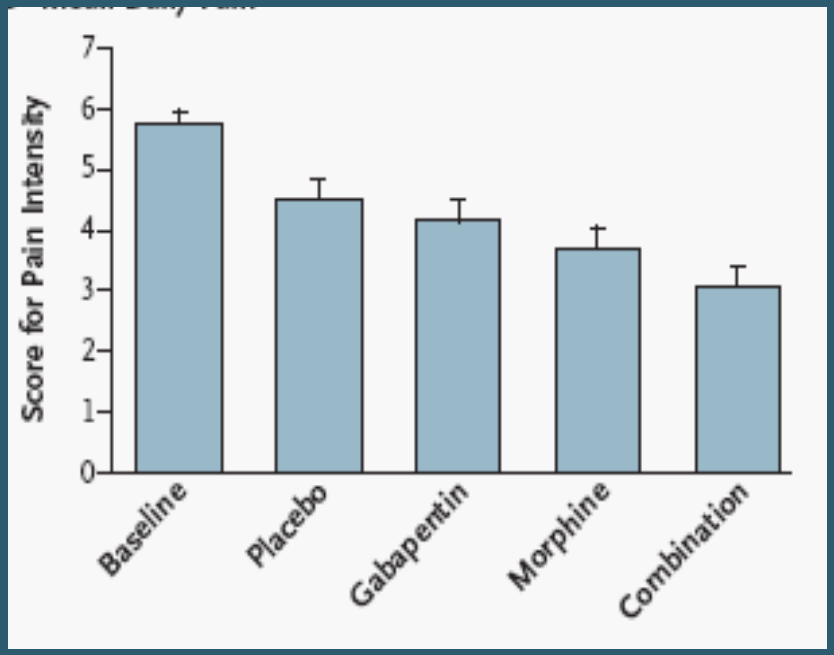
#3c: Plasticity - descending modulation
TCA, SNRI, opioid, tramadol

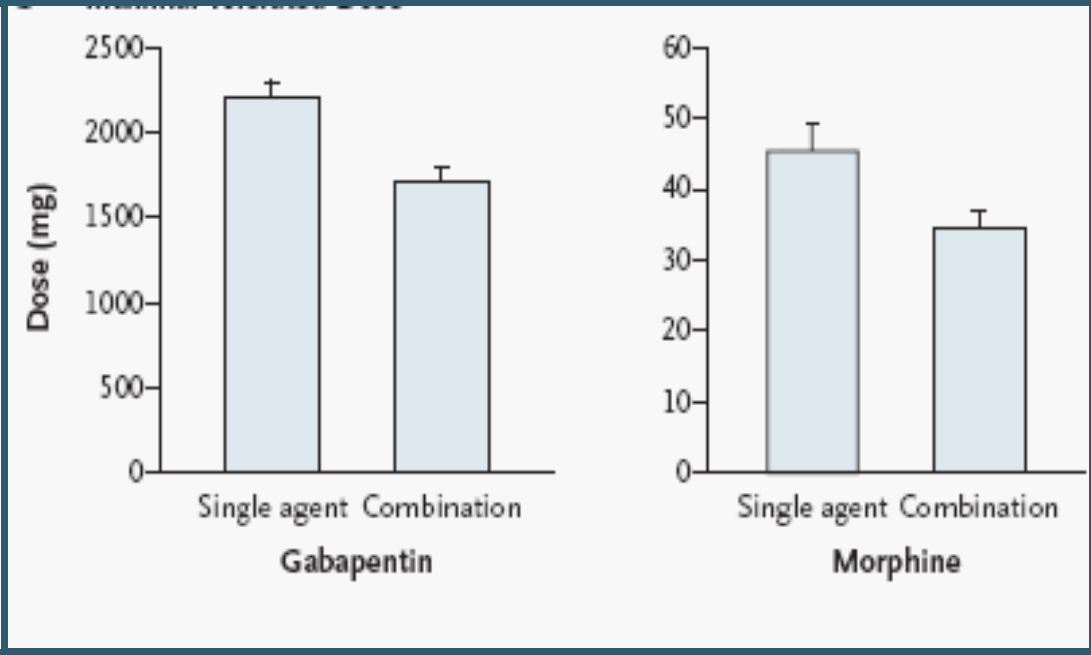
#4: Perception
TCA, SNRI, opioid, tramadol, ion channel blocker

Mao J et al. *J Pain*. 2011

Morphine, Gabapentin, or Their Combination for Neuropathic Pain

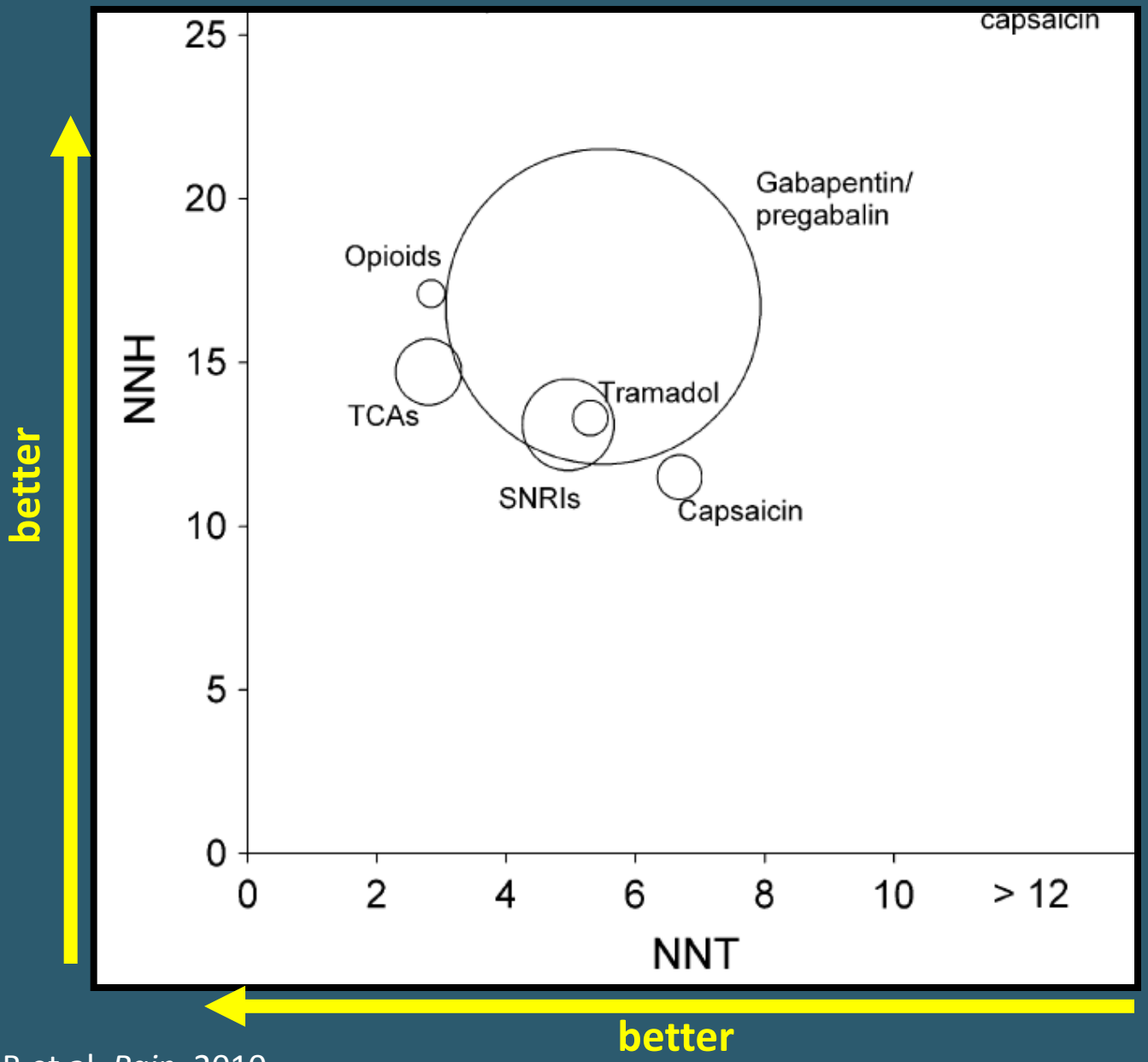
- Randomized, double-blind, active placebo–controlled, four-period crossover trial
- N=57, 5 week treatment





Gilron I et al. *N Engl J Med.* 2005

Comparing Pharmacotherapies



Finnerup NB et al. *Pain.* 2010

Chronic Pain Assessment is Complicated

- **"Pain can only be measured as it is reported"** (Walk D, Poliak-Tunis M. *Med Clin N Am* 2016)
- Pain is subjective to both the patient and the provider
- Pain cannot always be visualized even with sophisticated diagnostic imaging tests
- Pain is influenced by psychiatric co-morbidities and environmental stressors
- It is difficult to distinguish…
  - inappropriate drug-seeking from…
  - appropriate pain relief-seeking

Measuring Chronic Pain

An fMRI-Based Neurologic Signature of Physical Pain

Tor D. Wager, Ph.D., Lauren Y. Atlas, Ph.D., Martin A. Lindquist, Ph.D., Mathieu Roy, Ph.D., Choong-Wan Woo, M.A., and Ethan Kross, Ph.D.

CONCLUSIONS

It is possible to use fMRI to assess pain elicited by noxious heat in healthy persons. Future studies are needed to assess whether the signature predicts clinical pain.

N Engl J Med. 2013

Benefit is Difficult to Measure

- How does one measure pain, function, and quality of life?

- How much improvement in pain, function and quality of life is enough?
  - Is a decrease in pain from a 9 → 7 on a 10 point scale enough?
  - Is walking 2 blocks to the store once per week enough?

Opioids for Chronic Pain

The Backdrop

- Over the past 1 ½ decades chronic pain management has become "opiocentric"
  - Effectiveness of long-term opioid therapy has not been adequately studied
  - High dose opioids associated with increased overdose deaths
  - There is a prescription opioid misuse epidemic (overdose - deaths, addiction, diversion)
- Many providers have become "opiophobic"

*Dzau VJ, Pizzo PA. *JAMA* 2014; 312 (15):1507-1508

“The pain medication conundrum”

Opinion The New York Times

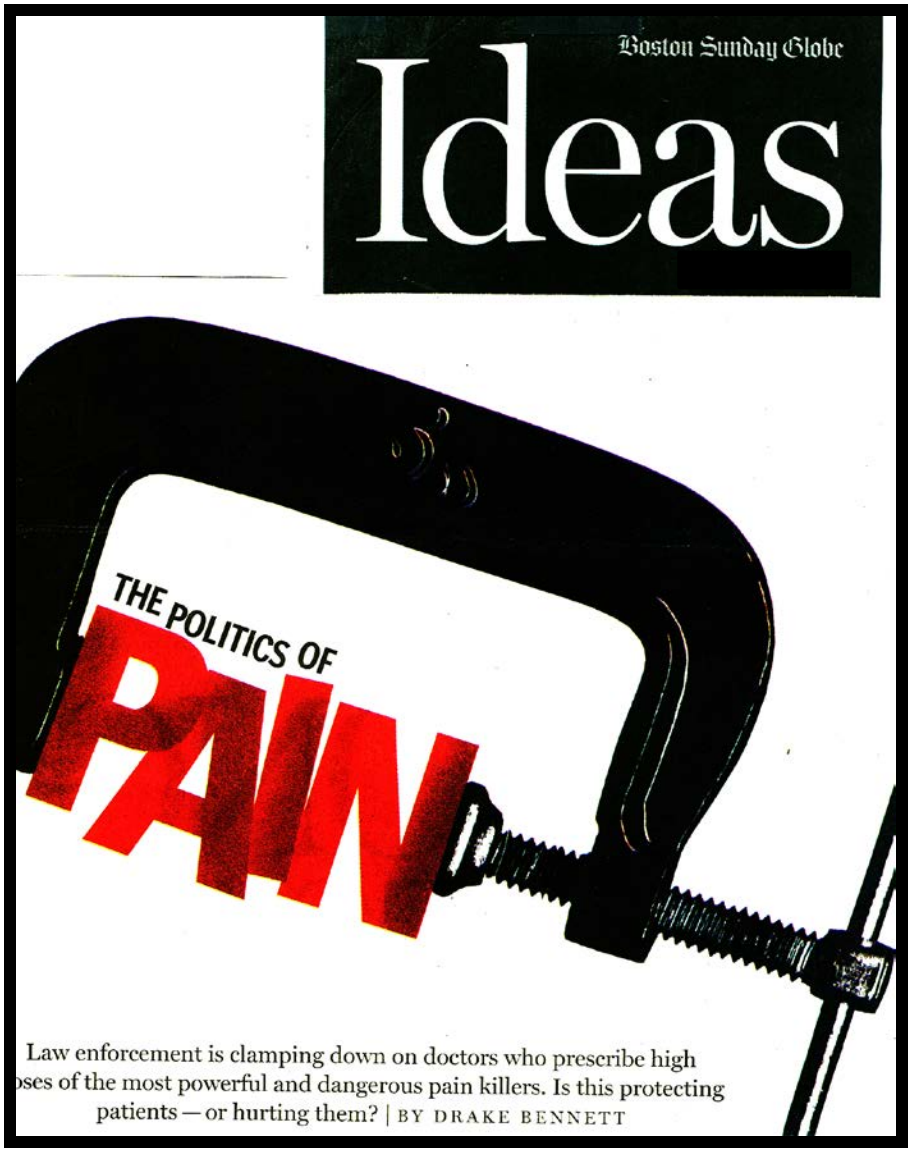
- Undertreating pain, we are admonished…it violates the basic ethical principles of medicine. On the other hand, we are lambasted for overprescribing pain medications… creating an epidemic of overdose deaths.

- For patients with chronic pain, especially those with syndromes that don’t fit into neat clinical boxes, being judged by doctors to see if they “merit” medication is humiliating and dispiriting. This type of judgment, with its moral overtones and suspicions, is at odds with the doctor-patient relationship we work to develop.

> *“As Mr. W. and I sat there sizing each other up, I could feel our reserves of trust beginning to ebb. I was debating whether his pain was real or if he was trying to snooker me. He was most likely wondering whether I would believe him…”*

Danielle Ofri, MD, faculty NYU and Bellevue Hospital *Aug 13, 2015*

Opioid Over-Prescribing



- Lack of training in pain and addiction at all levels of health professional education
- Societal medication mania
- Patients (families) overly focused on opioids
- Providers' confrontation phobia
- Lack of pain specialists offering comprehensive pain management

Mezei L et al. *J Pain* 2011
Watt-Watson J et al. *Pain Res Manage* 2009
Morely-Forster PK et al. *J Pain Res* 2013

"Universal Precautions"

(not evidence-based but has become "standard" of care)

- Opioid misuse risk assessment
- Patient Provider Agreements ("contracts"), informed consent
- Monitor for adherence, addiction and diversion
  - Urine drug testing
  - Pill counts
  - Prescription Drug Monitoring Program data

Gourlay DL, Heit HA. *Pain Med.* 2005

“My chronic pain isn’t a crime”

Opinion The Boston Globe

- I will be in chronic pain until I die…I accept it.
- Pain medication is inadequate. But with it I am more consistently functional (homeowner, spouse, parent, teacher, writer, editor).
- Abuse of prescription pain medications is a serious problem; people are dying.
- Ever-tighter regulations…are of dubious value in reducing [abuse] – while causing grave harm to those of us in chronic pain, to the overwhelming majority who take medications for appropriate reasons.
- Increasingly I am a suspect, treated less as a patient and more as a criminal.

Donald N.S. Unger, MFA, PhD, faculty English Department, College of the Holy Cross *Feb 03, 2015*

Chronic Pain Workforce Issues

Pain Medicine Expert & Education Gap

- Chronic pain is managed primarily in primary care
  - Only 5% of patients ever receiving pain specialist consultation
- Only 6 board certified pain physicians per 100,000 adult patients with chronic pain
- US Medical Schools
  - Average of 10 hours of pain management education
  - Of 104 medical schools only 4% required a pain course
- Canadian veterinary schools devote 5x more hrs (87) to pain management than Canadian medical schools (16)

Breuer B et al. *J Pain* 2007
IOM. *Relieving Pain in America*. 2011
Mezei L et al. *J Pain* 2011
Watt-Watson J et al. *Pain Res Manage* 2009
Morely-Forster PK et al. *J Pain Res* 2013

Pain Medicine Education

The Good News…

Pain Medicine 2013; 14: 971–981
Wiley Periodicals, Inc.

Review Articles

Core Competencies for Pain Management: Results of an Interprofessional Consensus Summit

Pain Medicine 2013; 14: 345–350
Wiley Periodicals, Inc.

Recommendations for a New Curriculum in Pain Medicine for Medical Students: Toward a Career Distinguished by Competence and Compassion

Pain Medicine 2015; 16: 2090–2097
Wiley Periodicals, Inc.

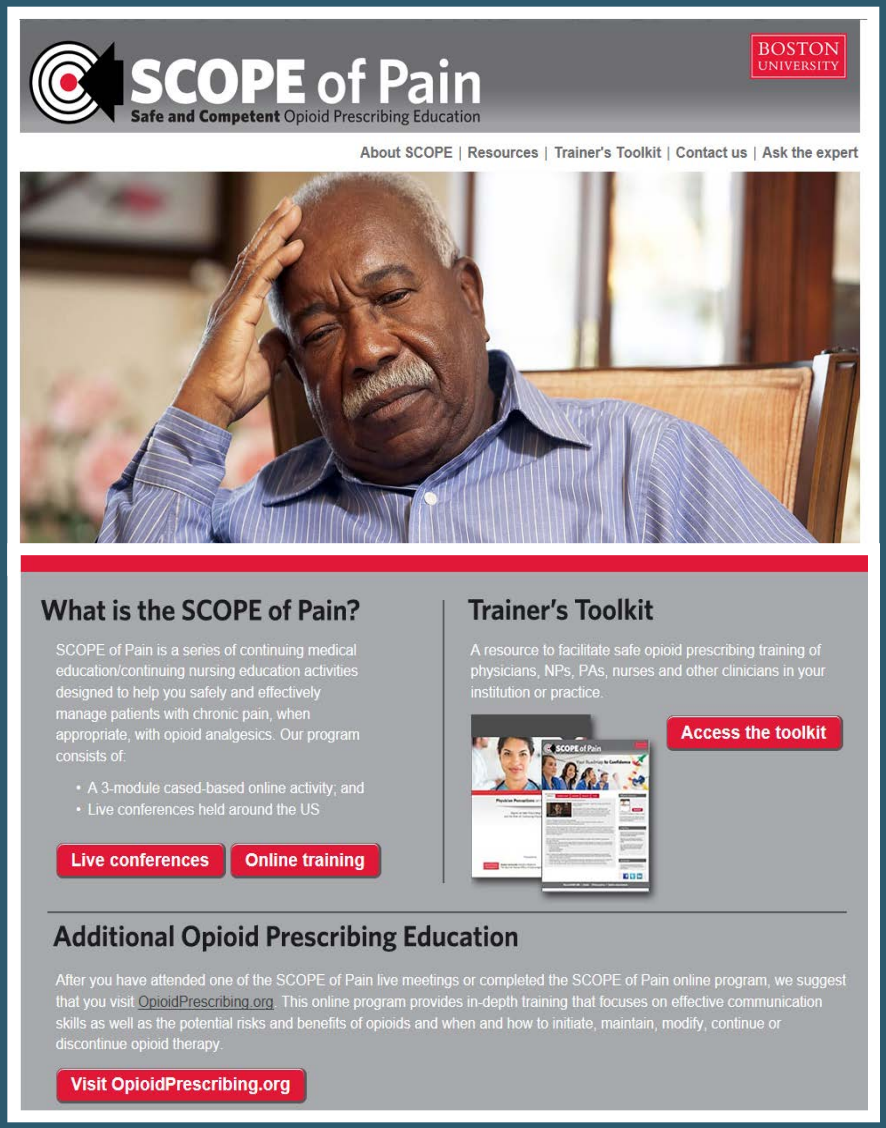
EDUCATION & TRAINING SECTION

Original Research Article

Core Competencies in Integrative Pain Care for Entry-Level Primary Care Physicians

Original Research Article

SCOPE of Pain: An Evaluation of an Opioid Risk Evaluation and Mitigation Strategy Continuing Education Program

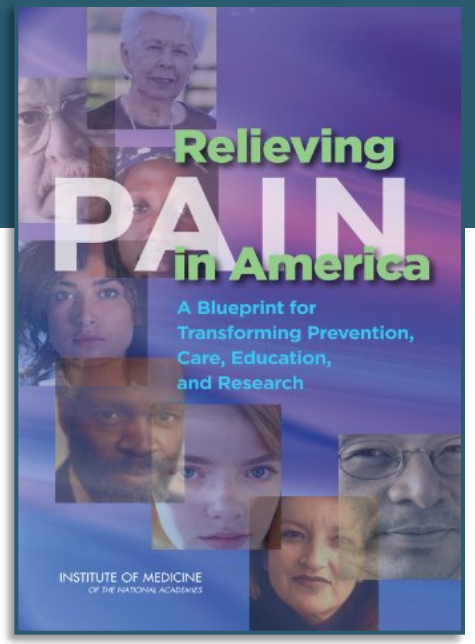


2 M Post-Program (n=476)

- Significant increase in knowledge
- 67% increased confidence in applying safe opioid prescribing care
- 86% implemented guideline-based practices changes
- Increased alignment of desired attitudes toward safe opioid prescribing

Alford DP et al. *Pain Med* 2016

Barriers to Chronic Pain Care



- Negative attitudes, stigma and disparities in pain care
- Lack of decision support for chronic pain management
- Financial misalignment favoring use of medications
- Poor support for team-based care and specialty clinics
- Over-burdened primary care system

"Addressing the enormous burden of pain will require a cultural transformation in the way pain is understood, assessed and treated."

IOM. *Relieving Pain in America*. 2011