The Modern Science of Pain
A View From the Frontline

Science Board to the FDA Meeting

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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. 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)

René Descartes. *Treatise of Man*, 1664
Nociception:
Transduction, Conduction, Transmission, Perception

- Unmyelinated: Slower (0.5 m/s), Myelinated: Faster (20 m/s),
- 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)

Pain Types

Acute

- Injury
- Post-operative flare

Chronic

Nociceptive

- Post-stroke
- Multiple sclerosis
- Spinal cord injury
- Migraine (31 million)
- HIV related neuropathic pain (0.3 million)

Neuropathic

- Central
- Peripheral

Visceral

- Internal organ
- Pancreatitis
- Inflammatory bowel syndrome

Mixed

- Lower back (55 million)
- Cancer (1.5 million)
- Fibromyalgia (6 million)

Melnikova I. *Nature Reviews Drug Discovery* 2010
Chronic Pain

• Pain that persists for more than 3 months 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
Dzau VJ, Pizzo PA. *JAMA* 2014
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

Central Sensitization

- A state of 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

Peripheral nerve injury $\rightarrow$ recruitment of macrophages and glial cells $\rightarrow$ dysregulated nerve regeneration of both A$\beta$ and C-fibers

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

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

Chronic Pain Terminology

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

Chronic Pain Management

**Restore Function**
- CBT/ACT
- Tx mood/trauma issues
- Address substances
- Meditation

**Psycho-behavioral**
- Exercise
- Manual therapies
- Acupuncture
- Orthotics
- TENS
- Other modalities (heat, cold, stretch)

**Physical**
- Meditation
- SELF CARE

**Procedural**
- Nerve blocks
- Steroid injections
- Trigger point injections
- Stimulators
- Pumps

**Medication**
- NSAIDS
- Anticonvulsants
- Antidepressants
- Topical agents
- Opioids
- Others

**Cultivate Well-being**
- Physical
- Psycho-behavioral
- Medication
- Procedural

**Improve Quality of Life**
- Reduce Pain

TENS  Transcutaneous Electrical Nerve Stim
CBT  Cognitive Behavioral Therapy
ACT  Acceptance and Commitment Therapy
Combination Drug Therapy for Chronic Pain

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

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.

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
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
“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

“My chronic pain isn’t a crime”

Opinion

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

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

EDUCATION & TRAINING SECTION
Original Research Article
Core Competencies in Integrative Pain Care for Entry-Level Primary Care Physicians
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

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