Pain Management

Siamak Rahman, MD
Associate Clinical Professor
Director of UCLA Acute Pain Management Service
In 2010 Patient Protection and Affordable Care Act required the Department of Health and Human Services (HHS) to enlist the IOM in examining pain as a public health problem.
Every year, about 100 million adult Americans experience chronic pain, a condition that costs the nation between $560 billion and $635 billion annually.

The committee called for coordinated, national efforts of public and private organizations to create a cultural transformation in how the nation understands and approaches pain management and prevention.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Sufferers</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pain</td>
<td>116 million Americans</td>
<td>Institute of Medicine of The National Academies (2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.8 million Americans (diagnosed and estimated undiagnosed)</td>
<td>American Diabetes Association (3)</td>
</tr>
<tr>
<td>Coronary Heart Disease (heart attack and chest pain)</td>
<td>16.3 million Americans</td>
<td>American Heart Association (4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>7.0 million Americans</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>11.9 million Americans</td>
<td>American Cancer Society (5)</td>
</tr>
</tbody>
</table>
Figure  Duration of Pain, 1999-2002

- **≥1 year**
  - 20-44 years of age (25% reported pain)
  - 45-64 years of age (30% reported pain)
  - 65 years of age and over (21% reported pain)

- **<1 month**

- **1-3 months**

- **3 months-1 year**

Sources: CDC, National Center for Health Statistics, Health, United States, 2006. Figure 29. Data from the National Health and Nutrition Examination Survey.
• The report recommends that NIH designate a lead institute to move pain research forward and increase the scope and resources of its existing Pain Consortium.

• The committee called on the Department of Health and Human Services (HHS) to develop a comprehensive population-based strategy for addressing pain prevention as well as pain management and research.
• Pain management curriculum resources
  – Development
  – Evaluation
  – Distribution
PAIN IS MULTIDIMENSIONAL AND SUBJECTIVE

- Chronic Pain:
  - Casual link not necessarily present

- Pain is an unpleasant sensory and emotional experience accompanied by actual or potential tissue damage or described in terms of such damage

- Subjective perception
- Objective lesion, stimulus may be absent in chronic pain

- Of equal standing
  - Emotional component
  - Sensorial component
Assessing Pain in Practice

<table>
<thead>
<tr>
<th>Nociceptive Pain</th>
<th>Inflammatory Pain</th>
<th>Neuropathic Pain</th>
<th>Dysfunctional Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noxious stimuli</td>
<td>Inflammation</td>
<td>Neuronal damage</td>
<td>No noxious stimulus No inflammation No neuronal damage</td>
</tr>
</tbody>
</table>

- **Protective**
  - High pain threshold

- **Healing/Repair/Pathological**

- **Pathological**
  - Low pain threshold
Classification According to Pathogenesis

- **Nociceptive pain syndromes**
  - Somatic pain
  - Visceral pain
- **Psychosomatic pain**
- **Neuropathic pain syndromes**
  - Continuous dysthesias
  - Paroxysmal pain
Overlapping Components in Chronic Pain

Primary nociceptive
(For example)

- Osteoarthritis
- Visceral pain
- Headache
- Ischemic pain
- Cancer pain (without nerve injury)
- Back pain (without nerve injury)

Pain including both nociceptive and neuropathic component

- Chronic back pain (nerve lesion/dysfunction + nociceptive activation from ligaments, joints, muscles, tendons)
- Cancer pain (with nerve infiltration)
- CRPS I (without nerve injury)

Primary neuropathic
(For example)

Peripheral
- Back pain (due to nerve injury/dysfunction)
- PHN
- Trigeminal neuralgia
- HIV
- CRPS II
- Phantom pain

Injured / irritated somatic or visceral structure

Nociceptive and neuropathic components

Injury of the neural structure

Central
- Post stroke
- Multiple sclerosis
- Spinal cord Injury
Biopsychosocial Pain Models

source: Gatchel et al. 2007 [1]
Depression
Anxiety
Disturbed sleep
Limited social function
Limited work function
Reduced mobility

REDUCED QUALITY OF LIFE
<table>
<thead>
<tr>
<th>Acute Pain</th>
<th>Chronic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>... is caused by external or internal injury or damage</td>
<td>... in uncoupled from the causative event</td>
</tr>
<tr>
<td>... its intensity correlates with the triggering stimulus</td>
<td>... its intensity no longer correlates with the causal stimulus</td>
</tr>
<tr>
<td>... can be clearly located</td>
<td>... becomes a disease in its own right</td>
</tr>
<tr>
<td>... has a distinct warning and protective function</td>
<td>... has lost its warning and protective function</td>
</tr>
<tr>
<td></td>
<td>... is a special therapeutic challenge</td>
</tr>
</tbody>
</table>
Acute/ Chronic pain

- Adaptive
- Reversible
- Protective

- Autonomous
- Irreversible
- Maladaptive
<table>
<thead>
<tr>
<th>Location</th>
<th>Focal, Multifocal, Generalized, Referred, Superficial, Deep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Character/quality</td>
<td>Aching, Throbbing, Stabbing, Burning</td>
</tr>
<tr>
<td>Intensity/Impact of pain</td>
<td>Apply rating scales (e.g. NRS), Multidimensional tools, Impact on physical &amp; mental function, Impact on quality of life</td>
</tr>
<tr>
<td>Temporal features</td>
<td>Onset, Duration, Course, Pattern</td>
</tr>
<tr>
<td>Influential factors</td>
<td>Aggravating factors, Relieving factors</td>
</tr>
<tr>
<td>Patient concept</td>
<td>Purely somatic?, Impact on activity/quality of life</td>
</tr>
<tr>
<td>Associated factors</td>
<td>Mood, Emotional distress, Poor sleep</td>
</tr>
<tr>
<td>Secondary signs / symptoms</td>
<td>Neurological deficit, Hyperalgesia, alldynia</td>
</tr>
<tr>
<td>Treatment response</td>
<td>Type of treatment, Dosages, Duration, Side effects, Reasons for stopping</td>
</tr>
</tbody>
</table>
Measuring improvements in pain management

- Improved numeric rating scale
- Higher patient satisfaction ratings
- Improved functional ability, fewer side effects from treatment, and shorter hospital lengths of stay

From the mostly practiced to pragmatic
IMPROVED POSTOPERATIVE PAIN MANAGEMENT

MONITORING AND REEVALUATING

BENCHMARKING

PARTICIPATION OF ALL CLINICIANS AND STAFF

ADOPTING THE DEVELOPED PLAN
FIGURE 10-2  The McGill Pain Questionnaire

Part 1  Where Is Your Pain?
Please mark on the drawing below, the areas where you feel pain. Put E if external, or I if internal, near the areas which you mark. Put E if both external and internal.

Part 2  What Does Your Pain Feel Like?

1. Flickering
2. Jumping
3. Pricking
4. Sharp
5. Guivering
6. Flashing
7. Boring
8. Cutting
6. Pulsing
7. Shooing
8. Drilling
9. Throbbing
10. Stabbing
11. Lancinating
12. Pounding
13. Pinching
14. Twanging
15. Hot
16. Tingling
17. Pressing
18. Pulling
19. Burning
20. Itchy
19. Gnawing
20. Wrenching
21. Scalding
22. Smarting
23. Camping
24. Searing
25. Stinging
26. Crushing
27. Splinting
28. Sickening
29. Dull
30. Tender
31. Exhastening
32. Sore
33. Taut
34. Suffering
35. Hurting
36. Raspings
37. Exhausting
38. Aching
39. Splitting
40. Heavy
41. Terrifying
42. Mean
43. Frightful
44. Terrifying
45. Torturing
46. Fearful
47. Cruel
48. Piteous
49. Tearing
50. Piercing
51. Squeezing
52. Numb
53. Cooling
54. Freezing
55. Spreading
56. Tigh
57. Cool
58. Radiating
59. Numb
60. Napping
61. Penetrating
62. Drawing
63. Nauseating
64. Piercing
65. Squeezing
66. Agonizing
67. Tearing
68. Dreadful
69. Torturing
70. How Does Your Pain Change With Time?
1. Which word or words would you use to describe the pattern of your pain?
2. Continuous
3. Rhythmic
4. Brief
5. Steady
6. Periodic
7. Momentary
8. Constant
9. Intermittent
10. Transient

Part 3  How Does Your Pain Change With Time?

1. What kind of things relieve your pain?
2. What kind of things increase your pain?

Part 4  How Strong Is Your Pain?

People agree that the following 5 words represent pain of increasing intensity. They are:

1. Mild
2. Discomforting
3. Distressing
4. Horrible
5. Excruciating

To answer each question below, write the number of the most appropriate word in the space beside the question.

1. Which word describes your pain right now?
2. Which word describes it at its worst?
3. Which word describes it when it is least?
4. Which word describes the worst toothache you ever had?
5. Which word describes the worst headache you ever had?
6. Which word describes the worst stomach-ache you ever had?

Source: Reprinted from McGill Pain Questionnaire from PAIN, VI: 277-299, ©1975 with permission from International Association for the Study of Pain.
Over 17,000 sensory corpuscles have been reported in the human face.

Four different types of receptors have been described in the hairy skin of the face:
- Ruffini corpuscles
- Meissner corpuscles
- Merkel cell disks
- Hair receptors.
Mechanoreceptors

- Ruffini corpuscles,
  - Skin stretch
- Meissner corpuscles,
  - Stroking
  - Fluttering of the skin
- Merkel receptors detect
  - Pressure
  - Texture of objects
- Hair follicle
  - Light stroking
Pain and temperature

- Intaepidermal free nerve endings terminate in different cellular layers
- Face has the highest distribution density of free nerve endings
- Transmitted by small myelinated (A[DELTA]) and small unmyelinated fibers (C fibers)
<table>
<thead>
<tr>
<th>Fiber type</th>
<th>Function</th>
<th>Diameter (μm)</th>
<th>CV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A α</td>
<td>Proprioception, somatomotor</td>
<td>12 - 20</td>
<td>100</td>
</tr>
<tr>
<td>β</td>
<td>Touch, pressure</td>
<td>5 - 12</td>
<td>30 - 70</td>
</tr>
<tr>
<td>γ</td>
<td>Motor to muscle spindle</td>
<td>3 - 6</td>
<td>15 - 30</td>
</tr>
<tr>
<td>δ</td>
<td>Pain esp. cold, touch</td>
<td>2 - 5</td>
<td>12 - 30</td>
</tr>
<tr>
<td>B</td>
<td>Preganglionic autonomic</td>
<td>&lt; 3</td>
<td>3 - 15</td>
</tr>
<tr>
<td>C</td>
<td>Thermal pain, mechanoreceptor</td>
<td>0.4 - 1.2</td>
<td>0.5 - 2</td>
</tr>
<tr>
<td></td>
<td>Postganglionic autonomic</td>
<td>0.3 - 1.3</td>
<td>0.7 - 2.3</td>
</tr>
</tbody>
</table>
Figure 7  Individual Pathophysiology Requires Personalized Treatment  Etiology, genotype, and environmental factors lead to individual pathophysiological changes and individual neuropathic pain profiles. Precise clinical examination and diagnostic tools are...

Christian A. von Hehn, Ralf Baron, Clifford J. Woolf

Deconstructing the Neuropathic Pain Phenotype to Reveal Neural Mechanisms

Neuron, Volume 73, Issue 4, 2012, 638 - 652

http://dx.doi.org/10.1016/j.neuron.2012.02.008
Figure 1  The Nociceptive Pain Circuit  High-threshold nociceptors are activated by intense mechanical, thermal, or chemical stimuli and feed this information to nociceptive neurons in the spinal cord, which project via the thalamus to cortical areas genera...

Christian A. von Hehn, Ralf Baron, Clifford J. Woolf

Deconstructing the Neuropathic Pain Phenotype to Reveal Neural Mechanisms

Neuron, Volume 73, Issue 4, 2012, 638 - 652

http://dx.doi.org/10.1016/j.neuron.2012.02.008
Peripheral sensitization

• Nerve injury changes;
  – the expression, distribution, and phosphorylation of many ion channels in sensory neurons
    – Potassium channels
    – Sodium channels
  – generation of “membrane potential oscillations” resulting in rhythmic firing bursts in the absence of a stimulus
• Multiple sodium channel blockers used to treat neuropathic pain, e.g., local anesthetics, mexilitine, and carbamazepine
• However, the currently available nonselective blockers come at the cost of cardiovascular and CNS side effects
Central Sensitization

- Why is there a spread of hyperalgesia beyond areas of tissue injury or outside a damaged nerve territory?
- Why can a repeated stimuli at a fixed intensity lead to a progressive increase in pain?
- Why pain may long outlast a peripheral stimulus?
Christian A. von Hehn, Ralf Baron, Clifford J. Woolf

Deconstructing the Neuropathic Pain Phenotype to Reveal Neural Mechanisms

Neuron, Volume 73, Issue 4, 2012, 638 - 652
Neuroplasticity

• Physical remodeling of neuronal cytoarchitecture,
• Occurs shortly after the onset of persistent acute pain and leads to chronic pain state
• Inhibitory interneurons responsible for modulating painful nerve transmission impulses eventually die
• Glial cells remodel neuronal synapses to intensify nociceptive transmission
• Neurons become more sensitive, react more intensely to stimuli, and grow more connections to second-order neurons
Long term potentiation LTD

• Long lasting enhancement in signal transduction between 2 neurons.

• NMDA receptors also are required for this form of activity-dependent enhancement of synaptic transmission and has been intensively studied as a cellular correlate of memory formation in the brain.
• The NMDA receptor is both a ligand-gated and voltage-gated ion channel
• NMDA itself displays no voltage-dependency, the magnesium block confers voltage dependency to the channel
• At resting membrane potentials the NMDA receptor is inactive due to magnesium ions block of the channel pore
Descending pathway

- involves the release of norepinephrine in the dorsal horn from the locus coeruleus, acting at $\alpha_2$-adrenoceptors,
- inhibit primary afferent terminals and suppress firing of projection neurones,
- Descending facilitatory pathways, primarily involving a serotonergic mechanism
Figure 5  Spinal Disinhibition  Excitatory nociceptive signals are enhanced after nerve injury by a reduction in normal inhibitory regulation through a loss of local inhibitory interneurons, a depolarized anion reversal potential and reduced descending inhi...
Nerve injury

• Maladaptive changes along the entire nociceptive pathway within the CNS
• lead to spontaneous pain or pain hypersensitivity
• present as a complex combination of negative and positive symptoms
• Symptoms vary enormously from individual to individual
  – etiological,
  – genotypic,
  – environmental factors
Nerve damage

- Sensory Nerve Damage Produces Negative Symptoms
  - Numbness
  - Elevated heat threshold

- Peripheral Sensitization after Nerve Lesions Increases Pain Sensitivity
  - Innocuous stimuli; light touch, warm or cool temperatures, being perceived as painful (allodynia),
  - Stimuli that usually are felt as uncomfortable or slightly painful, such as a pinprick, becoming extremely painful (hyperalgesia)

- Ectopic Activity after Nerve Injury Generates Spontaneous Pain
  - Pain occurring in the absence of any external stimulus
Figure 6  Immune Contribution to Neuropathic Pain  Innate and adaptive immune cells in the periphery and spinal cord can sensitize primary nociceptors and secondary nociceptive neurons respectively to produce pain hypersensitivity.

Christian A. von Hehn, Ralf Baron, Clifford J. Woolf

Deconstructing the Neuropathic Pain Phenotype to Reveal Neural Mechanisms

Neuron, Volume 73, Issue 4, 2012, 638 - 652

http://dx.doi.org/10.1016/j.neuron.2012.02.008
Annu. Rev. Pharmacol. Toxicol. 52:111–33
Key points

• The transition from acute to chronic pain occurs in discrete pathophysiological steps involving multiple signalling pathways.

• The duration and intensity of the initial stimulus leads to both peripheral and central sensitization that synergistically exacerbate pain perception.

• A multimodal therapeutic approach is best suited to target the complex mechanisms leading to the transition from acute to chronic pain.
Although many details remain to be elucidated, the current data suggest that:

- opioid-induced desensitization (pharmacological tolerance) and
- sensitization (opioid-induced pain sensitivity)

may share common cellular mechanisms in part mediated through activation of the **central glutamatergic system**.
opioid-induced hyperalgesia (OIH).

• A phenomenon that cause new or paradoxically worsening pain.
• May be more formally defined as “increased nociceptive sensitization” caused by exposure to opioids.
• One of the chief problems in properly diagnosing OIH is the condition's close resemblance to opioid tolerance.
Common Characteristics of Opioid-Induced Hyperalgesia

• Worsening pain over time in spite of, or because of, increases in opioid dose
• Nociceptive sensitization
• Area of pain more diffuse
• Pain of lesser quality and harder to pinpoint
Does Opioid Induced Hyperalgesia Exist?

• Randomized controlled trial – Acute Opioid Tolerance: Intraoperative Remifentanil Increases Postoperative Pain and Morphine Requirement. (Guignard 2000)
• Randomized controlled trial - “Does Intrathecal Fentanyl Produce Acute Cross-Tolerance to IV Morphine?” (Copper 1997)
• Animal Model - Progressive Enhancement of Delayed Hyperalgesia Induced by Repeated Heroin Administration: A Sensitization Process. (Celebrier 2001)
What is the Mechanism behind Opioid Induced Hyperalgesia?

• Central Glutaminergic System - Inhibition of Morphine Tolerance and Dependence by the NMDA Receptor Antagonist MK-801. (Trujillo 1991)

• Spinal Dynorphins - Dynorphin promotes abnormal pain and spinal opioid antinociceptive tolerance. (Vandareh 2000)

• Descending Facilitation
Opioid Induced Hyperalgesia

- Definition

1. Nociceptive sensitization caused by exposure to opioids
2. Opioid effects lessens in the absence of disease progression
3. Reports of pain or allodynia unrelated to original pain
4. Increased levels of pain with increased dosages of opioids
5. Pain is improved by reducing or eliminating the opioid

- Distinguish from Tolerance

1. Progressive lack of response to a drug, requiring increased dosing, which occurs in a variety of drugs not limited to opioids.
2. Tolerance can be overcome by increasing the dose
What is the Mechanism behind Opioid Induced Hyperalgesia?

- Central Glutaminergic System
- Spinal Dynorphins
- Descending Facilitation
Assessment of OIH

• Once a practitioner sees a lack of efficacy with administration of opioids,
  – clinical exacerbation of preexisting pain,
  – tolerance,
  – OIH.

• Distinguishing factors include
  – increase pain intensity above preexistent pain levels with no disease progression,
  – diffuse, undefined pain extending to areas away from pre-existing pain.
  – Increasing opioid dosage may worsening OIH.
Treatment Of OIH

• Utilize non-opioid medications
• Rotation of opioids from phenanthrene class to alternatives
• Consider:
  – methadone, a NMDA antagonist
  – buprenorphine, a kappa receptor antagonist
• Escalate opioid dosing and evaluate for efficacy.
Identify patients at risk
Inform patients adequately about pain management
Regularly administered analgesics
When possible, use a multimodal approach
Pain is controlled and measured to a degree that facilitates function and quality of life
Post-operative pain

- Systemic Analgesic
- Alternative pain management
- Thoracic Epidural
- Truncal blocks
- Extremity nerve blocks
“Pain is a more terrible lord of mankind than even death itself.”

Albert Schweitzer
The Future
NEXT EXIT
Thank you

sirahman@mednet.ucla.edu