Chronic Pain: Signs, Symptom, Syndrome- Disease

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Disclosures

- Speakers Bureau
  - Eli Lilly
  - Allergan
  - Purdue
  - Covidien
  - Johnson & Johnson
  - Forest
  - Reckitt Benckiser
Chronic illness is a condition that is slow in progression, long in duration, and void of spontaneous resolution, often limits function, productivity, and quality of life.

Chronic illness represents 75% of the $2 trillion the US spends each year on healthcare.
“Which chronic disease should be the focus of public health efforts to reduce disability and improve functioning and quality of life?” CDC

- Emphasis on “winnable battles”
  ...chronic illnesses with cross-cutting clinical, functional, and social implications
- Exemplar approach will help identify new types of battles and population-based interventions in the management and control of chronic diseases
<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence/Impact</th>
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<tr>
<td><strong>Arthritis</strong></td>
<td>Leading cause of disability. 13% of population = 29 million</td>
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<tr>
<td><strong>Cancer survivorship</strong></td>
<td>12 million in US</td>
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<td><strong>Chronic pain</strong></td>
<td>116 million in US</td>
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<td><strong>Dementia</strong></td>
<td>5.4 million in US with Alzheimers more with other causes.</td>
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<td><strong>Depression</strong></td>
<td>~7% of population. 17% lifetime occurrence</td>
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<td><strong>Type 2 diabetes</strong></td>
<td>25.6 mil. (11.3%) leading cause of ESRD, blindness, neuropathy</td>
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<td><strong>Posttraumatic disabling conditions</strong></td>
<td>MSK, burns, fxs, with long term consequences</td>
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<tr>
<td><strong>Schizophrenia</strong></td>
<td>&gt;2 mil. in US. ETOHsim, homelessness</td>
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<td><strong>Vision and hearing loss</strong></td>
<td>15% HOH, 11% visual acuity loss in US population</td>
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Sign: objective indication of a altered process
  • Eg.: Allodynia associated with CRPS

Symptom: subjective perception of injury or perceived threat
  • Eg.: Phantom limb as a threat to the minds dichotomous perception that the brain map or somatosensory cortex should be connected to a body part

Syndrome: constellation of signs and symptoms in recurring pattern.
  • Eg.: Hemi hypesthesia and spastic tone in Dejerine–Roussy syndrome
Chronic pain as a disease:

- Consuming and progressive physical and emotional and social degradations
- Altered neuro-immune-hormonal defense mechanisms
- Changes in brain maps
- Neural plasticity
- Pain Neurobiology similar to Addiction Neurobiology
- Pathways to recovery
- Pathways to mortality
We believe pain arises in the nervous system but represents a complex and evolving interplay of biological, behavioral, environmental, and societal factors...
Chronic pain: In the US, an estimated 116 (≈ 30%) million adults deal with chronic pain, and chronic pain's prevalence on the rise worldwide.

- Racial and ethnic minorities are at greater risk of having undertreated pain.

- Disablement from chronic pain affects sufferers, their families, and their workplaces.

- Pain is part of the human condition.

- Protection from and relief of pain and suffering are a fundamental feature ... as well as a cardinal underpinning of the art and science of healing.
2.1 million—annual visits to U.S. emergency departments for headache (of 115 million total annual visits)

62%—of U.S. nursing home residents who report pain:
- arthritis is the most common painful condition

26.4%—of Americans who report low back pain lasting at least a day in the last 3 months

116 mil adults with chronic pain
Interaction of multi-level interventions and policies to achieve living well across the spectrum of health and chronic disease (i.e. Chronic Pain).

Fielding, J.E. and S.M. Teutsch JAMA 305(20) 2011.
Future Societal Direction re Chronic Pain? Pain Management in the Affordable Care Act

- HHS to convene a conference on pain. Establish an agenda for action to improve pain research, education, and clinical care in the US.
- Establishing an Interagency Pain Research Coordinating Committee to coordinate HHS efforts relating to pain research, including recommendations for expanding an aggressive program of basic and clinical research on the causes and potential treatments of pain.
- Health prof. education and training grants through HHS to develop and implement programs for improving pain care.
Cartesian Dualism: foundations of pain as a distinct sensory experience (circa 16 century)

- Mind and body are distinct
- The fire displaces the skin, which pulls a tiny thread, which opens a pore in the ventricle allowing the "animal spirit" to flow through a hollow tube, which inflates the muscle of the leg, causing the foot to withdraw.
Contemporary Models of Pain: Stimulus/receptor model of nociception

Nociception Receptor Models

Chemo receptors
Thermal receptors
Mechanico receptors
Glia as the “bad guys”: Implications for improving clinical pain control and the clinical utility of opioids.


- Glia (microglia and astrocytes) have a role in:
  - creating and maintaining enhanced pain states
  - compromising the efficacy of morphine and other opioids for pain control
Pain is amplified when glia become activated in response to repeat admin of opioids.

Leads to release of proinflammatory cytokines:
- upregulation of excitatory amino acid receptor function
- downregulation of GABA receptor function
Factors that Influence Nociceptive Inputs to Pain Perception

Tracey, I. Neuron 55, August 2, 2007
Dimensions of the pain experience: circa 1987

- **Sensory-discriminative dimension**
  - Acute pain- eudynia
  - allows patients to localize the pain exactly or to a general area

- **Affective dimension**
  - Chronic pain- maldynia
  - processed through the limbic system and produces a vague coloration and intensity to the pain

**Cognitive -evaluative dimension of chronic pain**
Pain Matrix – Pain is Processed in at Least Three Domains in CNS

- **Sensory**: where it is and how much it hurts
  - Primary and secondary somatosensory cortices
  - Thalamus
  - Posterior insula

- **Affective**: emotional valence of pain
  - Anterior cingulate cortex
  - Anterior insula
  - Amygdala

- **Cognitive**: similar to affective plus prefrontal regions

Pain Matrix: Critical structures in the mesolimbic system: reward & desire modulation

- Insula
- S1 and S2 somatosensory cortex
- Anterior Cingulate Cortex (ACC)
- Amygdala
- Prefrontal Cortex
- Thalamus
Insula “lights up” ..when people crave drugs, feel pain, anticipate pain, empathize with others, listen to jokes, see disgust on someone’s face …

- simple body states or sensations are recast as social emotions
- Craving drugs stimulated by sights, sounds, smells, situations…

Pain Matrix: Insula: where mind and body are integrated:

A Small Part of the Brain, and Its Profound Effects. Blakeslee NYTimes 2007
- most powerful of the cortical suppressor areas
- potent autonomic effector region
- ACC activity ... reflects the emotional experience that provokes our reactions to pain.
noxious and innocuous input from the somatosensory thalamus

- neurons that code spatial, temporal, and intensive aspects of innocuous and noxious somatosensory stimuli
- subserves the sensory-discriminative dimension of pain processing.
Recurrence of drug abuse / craving
Flight or fight response
Anxiety, fear, phobias
Aversive recall of withdrawal symptoms
Thalamus: Switchboard of consciousness

- Relaying sensory and motor signals to the cerebral cortex,
- Regulation of consciousness, sleep, and alertness.
- Relay of pain signals to limbic system, SSC, PFC
Diffusion tensor imaging (DTI) reveals connections between brainstem structures and prefrontal cortex, both of which are known to be involved in descending control of pain.
CNS reorganization in response to sensory and emotional experiences

Both structural and functional intrinsic changes are demonstrated

Changes occur in number / location of synapses
CNS Changes in Chronic Pain/Knee & Hip OA (PP = Pelvic Pain)

- Volumetric MRI studies
  - Decrease in gray matter
    - Cingulate cortex
    - Dorsolateral prefrontal cortex
    - ACC, insular cortex, amygdala, brainstem atrophy

- Functional MRI in CP:

  Towards a theory of chronic pain

Neuroplasticity in Chronic Back Pain
Apkarian. Progress in Neurobiology 87 (2009)

Apakarian:
5.4% - 11% decrease in gray matter vs controls
loss of PFC, SCC
Equivalent to 10-20 years of normal aging

Schmidt-Wilke:
Significant dec in gray of the SSC and brainstem
Inc. gray matter in Thalmus and Basal Ganglia

Increased activity in brain areas related to:
- anticipation of pain (FC),
- attention to pain (ACC, PFC)
- emotional aspects of pain (amygdala)
Augmented pain processing in FMS: CNS sensitization

High Intensity Pain in FM Patients: fMRI Evidence

fMRI studies show that pain processing is augmented in FM patients

Red: Activation at low intensity stimulus in FM patients

Green: Activation at high intensity stimulus in controls

Yellow: Area of overlap, i.e., area activated with low intensity stimulus in FM patients but only at high intensity stimulus in control patients

Phantom Limb Pain
- Remapping of somatosensory cortex
- Brain activity changes in ipsilateral motor cortex, thalmus, insula, forebrain, ACC
Cortical representation of the contralateral hand became smaller and shifted toward the lip area. Tactile perception / dystonia seen in post parietal cortex. Atrophy in PFC associated with poor emotional decision making.
Chronic pain after Spinal Cord Injury

- Reorganization seen in motor cortex
- Thalamic up-regulation of voltage gated Na+ channels
- Mental imagery may activate central pain processing

Stroke care

- Active physical therapy and constraint induced therapy may beneficially reorganize maladaptive plasticity

Henry, PM&R Vol 3 Dec 2011
CNS reorganization in a variety of chronic pain states: review.
Key Elements of the Neurocircuitry of Addiction

Many triggers of addiction of abuse and excessive behaviors seem to trigger a similar rise in dopamine release in the reward circuits of the brain—initial step on the way to addiction.
Cognitive Deficits Model of Addiction: PFC and pain/addiction

- Proposes ... abnormalities in the prefrontal cortex
- PFC regulates judgment, planning, and other executive functions
- Stimulant drugs ... damage specific brain circuit disrupting inhibitory signals from the PFC > mesolimbic reward system
- Opiates apparently damage the PFC itself
Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry...

- A. Inability to consistently Abstain;
- B. Impairment in Behavioral control;
- C. Craving; or increased “hunger” for drugs or rewarding experiences;
- D. Diminished recognition of significant problems with one’s behaviors and interpersonal relationships;
- E. A dysfunctional Emotional response.
**Blurred Lines - Chronic Pain Patient v. Recreational Opioid User:**

- **Recreational / Opioid Dependent**
  - Compulsion
  - Diff. controlling use
  - Withdrawal sx.
  - Tolerance
  - Neglect of alt. pleasures
  - Persist in use despite known harm

- **Chronic Pain Patient / opioid dependent**
  - Unresolved pain focus
  - Freq use of BTP meds
  - WD symptoms
  - Tolerant to potent meds
  - Altered social / occupational interactions
  - Altered insight as to benefit / harm of meds
Transition to addiction in chronic pain conditions:

Kalivas O'Brien Neuropsychopharmacology (2008)
Prescription opioid users and continuum of behavior.

Chronic pain & Opioid addiction

- Addiction ranging from 3% to 17%
- 24% in a resident physician clinic
- 31% in a Veterans Administration outpatient clinic
- High prevalence of substance misuse (32%). Chelmski *BMC Health Services Research* 2005,
PAIN PERCEPTION

- Pain is a conscious experience
- Pain cannot exist outside of consciousness
- Persistent pain is associated with a range of perceptual and regulatory dysfunctions

NOCIOCEPTION

- Nociception can exist outside consciousness
- Peripheral afferents can be activated without brain activity
- Sensitization occurs in the spinal cord and supraspinal levels
Nocioceptors are not “pain pathways”

Modulation of nocioception is required:
- Prioritization
- Meaning
- Transmission / Processing

the mislabeling of nociceptors as ‘pain fibers’ is an elegant simplification (P. Wall 1986)

‘explaining pain’ as a therapeutic strategy leads to rapid changes in pain related beliefs and attitudes, increased pain threshold during movement, better pain- and function related gains
Surge of information on CNS activity/plasticity in pain processing.

fMRI has shown beneficial reorganization after rehab therapies (stroke-constraint induced tx CIT)

fMRI may be used in biofeedback to control activity in ACC...inducing pain control

Idea of fMRI as a pain meter is unrealistic
Imaging of the brain does not explain the connection between the experience of pain and the activity of neurons
Pain is an aspect of consciousness … not neurons firing

Daniel Carr MD - The Pain Chronicles. Thernstrom, M. 2010, Farrar, Strauss & Giroux, NY
Chronic Pain cannot be perceived / treated as:

- Pain is not:
  - A simple symptom
  - Instantly curable
  - Sustainably managed by chemical means alone

- Ill conceived tx creates
  - Co-dependence
  - Passivity
  - Compliance issues
  - End of treatment failures
  - Recidivism
  - Incalculable costs…
Ongoing pain has been underreported, underdiagnosed, and undertreated in nearly all health care settings.

Because there are multiple contributors to and broad effects of chronic pain, comprehensive assessment and treatment are likely to produce the best results.
A "chronic care pain model" would acknowledge that chronic pain, like diabetes or asthma, is a condition we can treat but rarely cure (Deyo, Overtreating Chronic Back Pain JABFM 2009 22:1).

As with other chronic conditions, care of chronic pain may benefit from:

- sustained commitment from health care providers;
- involvement of patients as partners in their care;
- education in self-care strategies;
- coordination of care;
- involvement of community resources to promote exercise, provide social support, and facilitate a return to work.
- Patients need realistic expectations despite product marketing, media reports, and medical rhetoric that promise a pain-free life.
When acute pain persists and becomes chronic, it may in some cases become a disease in its own right, resulting in dysfunction in the central nervous system...