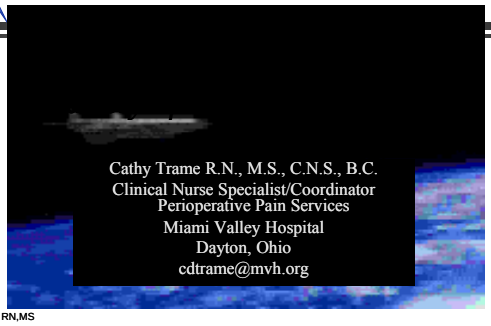
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Myths

- Pain is a simple algorithmic process
- Opioids are the drug of choice for pain treatment
- Cancer pain and surgical pain are both well managed
- Chronic pain is being decreased with increased knowledge of pain pathophysiology
- Physicians are better educated in pain management than 20 years ago

Epidemiologic Statistics

- Obesity affects 33.3% American males, 35.3 % females, and 16.3% children (National Center for Health Statistics, 2007)
- Global aging (50 year trends) –UN Population Division
  - Fertility decline from 5 to 2.7 children/woman, 1.5/woman 2000-2005
  - 20 year increase in life expectancy (developed countries increased by 24 years)
  - Current life expectancy in women of developed countries will exceed 80 years; Japan, 85 years
- 76.5 million Americans (26%)have chronic pain (American Pain Foundation, 2009)
- 40% of chronic pain patients do not have adequate pain relief (Heit, Kieber, & Nicholson, 2009)
- 3% U.S. Medical Schools offer separate courses in pain management (Khazzoom, 2009)

Pain Prevalence Study (Sawyer et.al., 2008)

- 600 bed hospital with **acute, palliative and chronic pain teams**
- 71% of patients reported having pain- random mix of surgical (n=72) and medical patients (n=42)
- 11.4% reported “severe pain”
- 31.5% reported “moderate to severe pain”
- Some stats comparable to older reviews of literature from 1973 through 2005

Trauma (Barclay et.al., Archives of Surgery, 2008)

- N=3,047 hospitalized patients involved in trauma- University of Washington study
- At 12 months after injury, 62.7% of patient reported injury-related pain.
- Mean severity 5.5 on a 10 point scale
- Pain at 3 months was predictive of presence and severity at 12 months

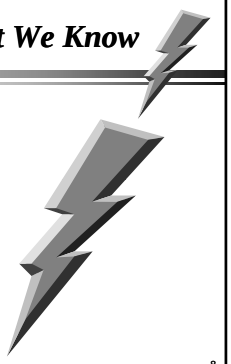
What is going on?

- Are we doing a poorer job?
- Is there more awareness and monitoring?
- Has patient perception changed?
- National Pain Care Policy Act of 2009(H.R. 756 and S.660)
  - Improve pain care research, education, training, access, outreach, and care
  - Institute of Medicine Conference on Pain Care
  - Pain research at NIH
  - Pain Care Education and Training for Healthcare workers
  - Pain Management Public Awareness Campaign

Pain Process – What We Know

- Transduction
- Transmission
- Perception
- Modulation

(Fields, 1987)



Types of Pain

- Nociceptive - normal pain processing
  - Somatic - bone, joint, muscle, skin, or connective tissue
  - Visceral - arises from visceral organs, such as GI tract and pancreas
    - Tumor
    - Obstruction of hollow viscous
- Neuropathic -abnormal pain processing
  - Centrally mediated -
    - peripheral or central nervous system injury
    - Sympathetically mediated - autonomic nervous system dysregulation
  - Peripherally generated
    - Polyneuropathies
    - Mononeuropathies

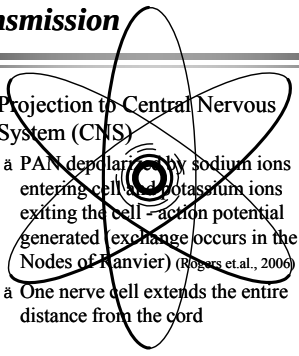
Transduction

- Cell damage (Orstavik et.al., 2006; Schaible, 2006)
  - Release of phospholipids & other substances into the intracellular space
  - Initiates the the arachidonic acid cascade:
    - 5-lipooxygenase and cyclooxegenase synthesize leukotrienes and prostaglandins respectively (New research beyond COX-1 - Brenneis et.al.,2006; Zeilhofer & Brune, 2006)
  - Sensitize PAN to be activated
    - Release of substance P, dilates nearby blood vessels, release of histamine from mast cells
  - Activation of autonomic nervous system
    - Release of norepinephrine and prostaglandins

Transduction

- Mechanical, thermal, or chemical stimulus converted into a neuronal action potential
  - Peripheral nerve fibers stimulated
  - A-delta and C fibers (primary afferent nociceptors) are stimulated
  - Transverse to dorsal root ganglia and sympathetic fibers into the dorsal horn of the spinal cord along with A-alpha (sensory skin) and A-beta (sensory muscle) fibers - synapse or communication of fibers occurs at this level

Transmission



- Projection to Central Nervous System (CNS)
  - PAN depolarized by sodium ions entering cell and potassium ions exiting the cell - action potential generated (exchange occurs in the Nodes of Ranvier) (Rogers et.al., 2006)
  - One nerve cell extends the entire distance from the cord

Pathophysiology – Transmission may be the key…

Genetic Abnormalities

- Mutations found in gene that encodes the voltage-gated sodium channel (expressed in nociceptive dorsal root ganglion and sympathetic ganglion neurons)(Waxman & Dib-Hajj, 2005)
  - Decreases threshold for nerve transmission
  - More frequent firing of nerve impulses
  - Keeps channels open for longer periods of time
  - Can be inherited (as in erythermalgia) or caused by mutations
  - Autosomal dominant
  - Present in mice with hyperalgesia

Transmission cont'd.

- Processing in dorsal horn - dermatomes
  - Release of neurotransmitters (nt) into synaptic cleft
  - Binding of nt to receptors on nearby cell bodies and dendrites of cell

Transmission cont'd.

- *Neurotransmitters include excitatory amino acids **(glutamate** and aspartate), fluoride resistant acid phosphatase (FRAP), and peptides, **substance P**, VIP, somatostatin, cholecystokinin, gastric releasing peptide, calcitonin, gene related peptide, angiotensin II, leu-enkaphalin, and dynorphin (McDougall et.al., 2006), .
- Produce activation or inhibition
- Cells excited by PAN release GABA and glycine

Glutamate Induced Muscle Spasm (Ge et al., 2008)

- Laboratory human study of injection of myofascial trigger points with glutamate versus isotonic saline in normal human subjects (n=14)
- Increased electrical activity measured by EMG on both
- 92.86% glutamate injected developed muscle cramps vs. 0% of isotonic saline

Transmission cont'd.

- Dendrites within the cells of the laminae communicate with each other
- A-beta stimulation can have an inhibitory effect on cells transmitting the nociceptive message (Gate control, TENS)
- Smaller slower fibers inhibited by heat or cold
- WDR (wide dynamic range neurons) have large receptive fields from A-delta and C fibers making discrimination of source difficult (*referred pain)*

Concept of Neuroplasticity

- Repetitive transmission of nociceptive signals results in changes in dorsal horn processing – AMPA receptors activated due to prolonged stimulus →NMDA receptors enabled, alter calcium conduction, profound changes in neural processing of afferent stimuli (Alexander et.al., 2006; Pace et.al., 2006; Campbell & Meyer, 2006)
  - Enlarged receptive field of peripheral neuron
  - Activation of normally inactive receptors
  - "Wind-up" of C fibers
  - Allodynia (RSD or CRPS)
  - New research – glial cells, peroxynitrite (Salvemini, D., 2007)

Development and Modulation of Nociceptive Circuitry (Zhang & Bao, 2006)

- Nociceptive sensory neurons have distinct circuits at spinal and brain levels
- Sensitivity is regulated by:
  - Phosphorylation of receptors
  - Ion channels
  - Associated regulatory proteins
  - Cell surface expression of **G-protein coupled receptors** – stimulus induced

Opioid-Induced Hyperalgesia

(DuPen et.al., 2007)

- Paradoxic increase in pain unrelated to the nociceptive source
- Tolerance to opioids (7 mu receptor sub-types so trial rotation first; variants in genes encoding the mu receptor)
- Activation of G proteins leads to decreased neuronal excitability- alteration in sodium and calcium channels.
- Glutamate-associated activation of NMDA receptors resulting in spinal neuron sensitization.
- Amplified neuronal activity in spinal cord due to increased excitatory peptide neurotransmitters (CCK -cholecystokinin upregulates spinal dynorphin which amplifies the signal).
- Studies to treat include low dose opioid antagonists to suppress G protein switching, CCK antagonists, NMDA antagonists, adjuvant medications for opioid sparing.

Pain Perception *(Mobascher et al., 2009; Pujol et al., 2009)*

- Where pain is perceived:
  - Thalamus
  - Somatosensory and motor cortices
  - Operculoinsular cortices
  - **Posterior sector of the anterior cingulate cortex***
  - **Basal ganglia***
- All three of these areas interact with:
  - Dorso-lateral prefrontal cortices
  - Amygdalae
  - Hippocampus (memory by association)
- Embedding of pain signal in CNS (Alexander et.al., 2006; Pace et.al., 2006; Campbell & Meyer, 2006)

(emotion-related, increased with fibromyalgia)

Brain Correlation with Subjective Pain Ratings (Nir et al., Journal of Pain, November 2008)

- Activation magnitude of the somatosensory cortex consistently and predictably correlates with subjective pain ratings based on standardized low-resolution brain electromagnetic tomography.
- Sole and most significant predictor, so preferred marker for research.

Mechanisms of Cancer Pain

Journal of the National Cancer Institute, Vol. 95, No. 11, June 4, 2003

- Astrocytes in spinal cord increase, communicate with each other and with nerve cells, altering normal processes causing chronic pain
- Cytokines increased (released from astrocytes) causing immediate pain
- Increase in acidic environment opening ion channels and causing neurons to fire
- Bone cancer will increase osteoclasts with increased acidity
- Growth factor or endothelin – 1 released by tumor causing inflammatory pain
  - Treatment involves endothelin-1 receptor antagonists (Antrasentan), receptor for RANK ligand which inhibits osteoclast production, or target ion channels via acid sensing ion channel (ASIC), receptors; or vanilloid receptors.

Mysteries

- Mixed findings in literature
- Why don't NMDA antagonists always work in the chronic patient?
- Why don't SSRI's mediate pain signals as well as TCA's and SNRI's?
- Can re-circuiting eliminate chronic pain?
- Why is abdominal pain so difficult to manage?
- Can we eliminate phantom pain?

Modulation (Descending Pathway)

- Nociceptive fields are inhibited in the dorsal horn by stimulation in the brainstem.
- Modulation includes inhibition and enhancement fired from the medulla Endogenous analgesia produced by:
  - Periventricular & periaqueductal grey
  - Rostral ventral medulla
  - Spinal cord

Neuromodulators

- Mu, kappa, & delta opioid*
- Alpha 2 adrenergic*
- Serotonin (5HT)*
- Adenosine
- GABA
- Neuropeptide Y
- Calcitonin
- Somatostatin
- Neurotensin receptors

Inhibit nociceptive cells in dorsal horn. Neuro-chemicals unclear.

Neuromodulation

- Descending fibers release serotonin, norepinephrine, & enkephalins thereby inhibiting release of neurotransmitters in PAN
- New evidence that TCA's inhibit tumor necrosis factor (TNF) in brain, which increases production of norepinephrine (Spengler, 2003)
- Opioids, tricyclic antidepressants, alpha2 agonists, placebos, heat, hypnosis, acupunture, imagery, & distraction all enhance inhibition

Physiologic Sex Differences

- Pain Perception – overall women more sensitive to pain of all types (Fillingim etal., 2009)
- Pain Modulation

Literature review 1887-2005: (Rhudy & Williams, 2005)

- Males have reduced pain in combination with sexual/erotic stimuli
- Females have increased pain with fear/threat or high emotional arousal
- No differences between males and females in the presence of anxiety

Exposure to deep tissue pain produced more endogenous analgesia in males than females

- Traced by PET scan in anterior thalamus, ventral basal ganglia, and amygdala (Zubieta et.al., 2002)

Testosterone correlated positively with increased macrophage migration inhibitory factor which is a neuroendocrine mediator; whereas estradiol correlated negatively (Aloisi et.al., 2005)

Human Studies – Response to pain treatments

- Comprehensive literature review found opioids to be more effective in women than men; men needed 24-40% more. Kappa receptor agonists more effective in women than men (Miaskowski & Levine, 2004)
- Gender variance for morphine requirements disappeared in patients >75 years old (Aubrun et.al., 2005)
- Vibratory stimulation experimentally applied to mitigate pain increased pain thresholds for women but not men (Dahlin et.al., 2006)

Anticonvulsants

- Pregabalin 100 mg po pre-op for minor gynecologic surgery **did not** reduce NRS or total fentanyl use for up to 24 hours post-op (Paech et.al., 2007).
- Gabapentin 800 mg 2 hours pre-op for brachial plexus injury (n=20) significantly **reduced** VAS at rest and with movement, and interoperative fentanyl consumption (Prabhaker et.al., 2007).
- Gabapentin 300 mg 2 hours pre-op for lower extremity orthopaedic surgery (n=70), revealed **reduced** morphine consumption and VAS for 1st 24 hours (Montazeri, Kashefi & Honarmand, 2007).
- Gabapentin 800 mg pre-op in combination with interscalene brachial plexus block for shoulder arthoscopy **did not** augment analgesia (Adam et.al, 2007).
- Gabapentin 1200 mg 2 hours pre-op thyroidectomy significantly **reduced** NRS and morphine use postoperatively (Al-Mujadi et.al., 2006).

Studies (Medications)

- Pramipexole (Mirapex®) – Dopamine D2 receptor agonist – traditionally used for Parkinson's disease. Start 0.25-0.5 mg nightly up to 3-4.5 mg nightly (increase by 0.5 mg weekly), for treatment of fibromyalgia (Wood, 2007).

Non-pharmacologic Adjuvants

- Non-dominant unilateral ECT treatment for CRPS – 6-12 treatments benefited 2 out of 3 patients (Michaels, 2008)