Neurobiology of Pain and the Homeless Patient

Barry Zevin, MD
Barbara Wismer, MD, MPH
Tom Waddell Health Center
San Francisco Department of Public Health

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Outline

• Why is this important?
• Neurobiology of pain
• Biopsychosocial spiritual model of pain
• Treatments/rationale
• Communicating with patients
• Next Steps
Why is this important?

• Chronic pain is common + costly
• It’s hard + stressful to treat
• There are increasing harms from opioids
• The neurobiology of pain + the biopsychosocial spiritual model applied to pain suggest an interdisciplinary approach
• It is challenging to talk with patients about causes/treatment of chronic pain
Chronic pain is common + costly

- Affects ~100 million adults
- Reduces quality of life
- Affects different groups disparately
- Costs $560-635 billion annually

Chronic pain is hard + stressful to treat

• National survey of HCH clinicians in 2010 (n=101)
• Results showed clinicians:
  – Lacked resources for optimal pain management
  – Lacked access to non-pharmacologic pain interventions
  – Were uncomfortable prescribing opioids, especially if substance use disorders
  – Found successful pain management gratifying

There are increasing harms from opioids

Rates* of opioid pain reliever (OPR) overdose death, OPR treatment admissions, + kilograms of OPR sold --- United States, 1999--2010

*Age-adjusted rates per 100,000 population for OPR deaths, crude rates per 10,000 population for OPR abuse treatment admissions, + crude rates per 10,000 population for kilograms of OPR sold.
There are increasing harms from opioids

- Mortality study among Boston Health Care for the Homeless Program patients seen 2003-2008
- Leading cause of death: drug overdose (17%)
  - Opioids implicated in 81% - of these:
    - Heroin in 13%
    - Opioid analgesics in 31%
    - Other/unspecified narcotics in 60%
  - Increased 3 fold from 1993-1998

Pain Definitions

• Pain: An unpleasant sensory + emotional experience associated with actual or potential tissue damage, or described in terms of such damage

• Chronic Pain: Pain that persists beyond normal tissue healing time, which is presumed to be 3 months

(International Association for the Study of Pain)
Pain Definitions

- **Acute pain** usually reflects an injury or illness and serves to alert us to protect ourselves or change our behavior to remove the threat or allow healing.
- **Chronic pain** does not generally serve this purpose.
Neurobiology

- Nervous system (NS)
- Peripheral/central NS
- Voluntary/involuntary NS
- Sympathetic/parasympathetic NS

Neurobiology

• Neuron
• Sensory, motor, interneuron
• Neurotransmitters, neuromodulators

http://users.tamuk.edu/kfjab02/Biology/AnimalPhysiology/B3408%20Systems/BIOL%203408%20Chapter%2011%20Neurons.htm
Neurobiology

- **Nociception**
  - Neural processes for sensing + processing noxious stimuli
- **Nociceptor**
- **C fiber, A-delta fiber nerves**
- **Spinal cord**
- **Neuromodulation**
- **Brain**
- **Pain Perception**
  - Awareness of pain, activation of memory + associations when pain present – occurs in brain

[Diagram of pain perception and processing]

http://medical-dictionary.thefreedictionary.com/nociception
Neurobiology - Neuromodulation

- "Amazing Pain Story:" soldiers in the field do not always feel pain from significant war wounds
- Inhibitory spinal neurons
- Inhibitory descending pathways
- Gate Control Theory

http://www.amazon.com/Photographic-control-Science-Photo-Library/dp/images/B008ZBIV2K
• “Nociception is neither sufficient nor necessary to cause pain”
Neurobiology - Neuromodulation

- Descending inhibitory pathways affect ascending pain pathways
  - periaqueductal gray (PAG) in midbrain
  - rostroventral medulla (RVM)
  - dorsolateral funiculus (DLF)

- Controlled by prefrontal, anterior cingulate, insular cortices

- Main inhibitors
  - Endorphins (produced in hypothalamus, PAG, spinal cord, PNS)
  - Serotonin (produced in PAG, RVM, spinal cord)
  - Norepinephrine (appears to work at spinal cord level)
  - GABA (appears to work at RVM, spinal cord level)

- Also can be facilitative
Neurobiology - Modulation

• Cognitive modulation
  – Attention (DLPFC/ACC)
  – Expectations (DLPFC/VLPFC)
  – Reappraisal (coping resources, perceived control) (VLPFC)

• Example: placebo effect

Neurobiology

• Neuropathic pain
  – Injury or disease (toxin, infection, inflammation) to sensory system, peripherally or centrally
  – Symptoms: burning, shooting, stabbing, piercing, electric shock - spontaneous pain, allodynia (pain from stimulus not normally painful), hyperalgesia (exaggerated response to painful stimulus)
  – Pain may spread to neighboring nerve distribution or other side of body
  – Sensitization of nociceptive neurons (both primary/secondary order) occurs
Neurobiology

• Peripheral sensitization - hyperalgesia
  – Decreased threshold, increased responsiveness of nociceptors when exposed to inflammatory mediators/damaged tissue
  – Mechanism: changes in receptors, ion channels, proteins, in nociceptor
  – Restricted to site of injury
  – Generally requires ongoing peripheral pathology
Neurobiology

• Central Sensitization
  – “Abnormal state of responsiveness or increased gain of the nociceptive system”
  – Triggered by nociceptive inputs; centrally mediated
  – Shift from high threshold nociception to low threshold pain hypersensitivity
  – Not coupled with presence, intensity, duration of peripheral stimuli
  – Increased sensitivity persists after peripheral cause resolved
  – Development/increases in spontaneous activity, reduction in threshold for activation, increased response to suprathreshold stimulation, enlargement of receptive fields
  – Secondary pain hypersensitivity (unaffected tissue) by changing response to normal inputs
  – Target for treatment: central nervous system

Neurobiology – Sensitization
• Stress/endocrine/system
  – Pain considered a threat, body engages mechanisms to restore homeostasis
  – Major consequence of homeostatic imbalance is stress
  – Stressors activate autonomic NS (epinephrine release) + hypothalamus/pituitary/adrenal axis (cortisol release – glucose/metabolism increase to restore homeostasis)
  – If prolonged, can affect muscles (atrophy), tissues (growth/repair), immune system (suppression), brain (changes in hippocampus) – can lead to conditions for development/maintenance of chronic pain syndromes
“Amazing Pain Story:” Many people who lose a limb experience a phantom limb; some have chronic pain in the phantom limb.

Neuromatrix

- Central anatomical “substrate” of the body-self
- Widespread network of neurons, with loops between thalamus/cortex, cortex/limbic system
- Genetically determined, modified by sensory inputs
- Loops diverge/converge – parallel processing, interactions of outputs of processing – in characteristic patterns: neurosignature
- Neurosignature patterns diverge
  - Sentient neural hub: converts flow of neurosignatures into awareness
  - Action neuromatrix: activation provides pattern of movements
- “widespread network of neurons which generates patterns, processes information that flows through it, + ultimately produces the pattern that is felt as a whole body”
Neuromatrix Theory of Pain

• “pain is a multidimensional experience produced by characteristic “neurosignature” patterns of nerve impulses generated by... [the] neuromatrix”

• “neurosignature patterns may be triggered by sensory inputs, but they may also be generated independently of them”

Neuromatrix Theory of Pain

Fig. 1.3 Factors that contribute to the patterns of activity generated by the body-self neuromatrix, which is composed of sensory, affective, and cognitive neuromodules. The output patterns from the neuromatrix produce the multiple dimensions of pain experience, as well as concurrent homeostatic and behavioral responses. (From Melzack R: Pain and the neuromatrix in the brain, J Dent Educ 65:1378–1382, 2001.)
• “Nociception is neither sufficient nor necessary to cause pain”
Neurobiology – what this all means

• Pain is a product of the brain
• Pain does not necessarily represent a threat
• The amount of pain does not necessarily relate to the amount of tissue damage
• When pain persists, the nervous system becomes more sensitive + excitable
• When pain persists, the brain (including thoughts + feelings) + response systems (e.g., stress) become more involved + can contribute to (or reduce) the pain
• Nociception contributes less over time to pain perception
Biopsychosocial Spiritual Model of Pain

• Pain (like other illnesses) is the result of the ongoing interaction of physiological, psychological, social, + spiritual factors, all of which affect + may worsen symptoms, function, + disability

• Pain a unique experience for each individual

• Pain treatment calls for interdisciplinary approach

Biopsychosocial Spiritual Model of Pain

Treatment

• Pain has multiple components
• Optimal treatment will reflect this
• No clear data on which combinations are best
  – Weigh harms/benefits
  – Consider co-existing conditions (e.g., mental illness/substance abuse)
  – Consider other potential benefits of non-pharmacologic treatments (e.g., improved self efficacy, physical fitness)
Brain and CNS Basic Principles

• Inhibition and stimulation
• Homeostasis: generally if something affects the system there is a reaction that tries to put the system back in balance
• Short term stress responses
• Long term neuroplasticity
• Allostasis
  – Excessive inhibition and excessive stimulation may be difficult for the system to balance and unexpected negative effects can occur
Brain and CNS Basic Principles

- The thinking Part of the brain is connected to everything else fortunately not directly
- the emotional part of the brain is connected to everything else fortunately not directly
- Memory is connected to everything else fortunately not directly
  - Habit is a closely related phenomenon
Focus topics

- Topical therapy
  - Local anesthetics
  - Capsaicin
- Opioids
- TCA’s and SNRI’s
- AED’s
- Cannabinoids
- Transcranial and deep brain stimulation
- Physical Activity / Exercise
- Acupuncture
- Psychotherapy

- Pain education
- Mindfulness
- Placebo
- Nocebo
- Depression treatment
- Pain and Pleasure
- Chemical and other dependency
- Traumas and Losses
- Spiritual Approaches
Local Anesthetic:

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

- Inhibition
- Facilitation
- Restore homeostasis
- Decrease stress
- Increase neuroplasticity

- Na+ channels
- Neurotransmitters
Topical Anesthetic
e.g. lidocaine patch

• Patches or gels effective for some neuropathic pain
• May be effective for deeper (e.g. joint pain, low back pain)
• Could relief of pain this way lead to longer term relief by decreasing central sensitization and helpful neuroplasticity?
Topical therapy: Capsaicin

- Nerve endings
- Nerve fibers
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neurotransmitters

- Substance P
- TRPV1 channels (endovanilloids, nonselective cation & various physical and chemical stimulation)
Capsaicin

• 8% patch provides long term effect by “defunctionalization” of nociceptor fibres.
• Repeated applications of lower concentration Capsaicin has same effect
• This is interesting example of using peripheral neuroplasticity for therapeutic effect
opiates

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neurotransmitters

- Beta-Endorphin – mu receptors
- Enkephalins – delta receptors
- Dynorphins – kappa receptors
- Extensive interaction with dopamine, serotonergic, and endogenous cannabinoid systems in the CNS
- Extensive interaction with the immune system and neuro-endocrine stress response in the periphery
opiods

• Analgesic effect of opioids much more complex than simply causing a stop sign for pain impulses in the brain
  – Effects are modulated by placebo and nocebo effects – that is cognitive systems
• Effective opioid analgesics that just work at a peripheral level would be very desirable if they can be developed
• Effective combination medications that use cannabinoid and opioid activity at levels not causing adverse effects would be very desirable if they can be developed
• Opioid Induced Hyperalgesia
TCA’s and SNRI’s

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

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- Increase neuroplasticity

- NA
- 5HT
- Adenosine
- Na⁺ channels
- Ca²⁺ channels
- Complex interaction with endogenous opioid systems
TCA’s and SNRI’s

• Any effective anti-depressant (medication or psychotherapy) is likely to be very effective for pain in a depressed pain patient
• Strong Placebo component
• Difficult Adverse effects profile
• Start Low Go Slow
• Drug-drug interactions caused by Cyp 2D6 inhibition
  – Failure to metabolize codeine
  – Risk with tramadol (risk of serotonin syndrome)
AED’s

- Nerve endings
- Nerve fibers
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neurotransmitters

- Na+ channels (VGSCs / Nav)
- Ca++ channel (\(\alpha_2-\delta\) Ligands Gabapentin and Pregabalin)
- Glutamate and NMDA
- GABA and Glycine

neurotransmitters
AED’s

- Gabapentin, Pregabalin, Topiramate, Lamotrigine, Carbamazapine, Oxcarbazepine, others
  - Some are FDA approved for some pain indications others are not.
  - Evidence is mixed
  - When using watch out for adverse effects, drug interactions, and establish endpoints for effectiveness
Cannabinoids

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

- Inhibition
- Facilitation
- Restore homeostasis
- Decrease stress
- Increase neuroplasticity

neurotransmitters

- Anandamide
- Other endocannabinoids
- Extensive interaction with opioid systems and with acetylcholine, noradrenaline, dopamine, 5-hydroxytryptamine, γ-aminobutyric acid, glutamate, D-aspartate and cholecystokinin
Cannabis

• Very strong theoretical reasons to think cannabinoids would be beneficial for pain
• Very active area for pharmaceutical development
• Pros and cons of medical marijuana for pain are complex
Transcranial and Deep Brain Stimulation

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

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Neuro-anatomy
- Sensorimotor cortex, ACC
- PAG, thalamus
Brain Techniques

• Non-invasive transcranial magnetic and transcranial direct current
• Invasive deep brain stimulation
• Stay tuned for more...
Physical Activity / Exercise

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

- Inhibition
- Facilitation
- Restore homeostasis
- Decrease stress
- Increase neuroplasticity

neurotransmitters
- Opioid peptides
- DA
- NA
- Many others
Physical Activity

• “any body movement that works...muscles + requires more energy than resting” (NHLBI)
• Some evidence to support benefits of:
  – Aerobic exercise
  – Anaerobic/strengthening exercise
  – Stretching/flexibility (yoga, pilates, Tai Chi)
    • These also affect mind-body awareness

Physical Activity

- Exercise activates endogenous analgesia (release of opioids from pituitary/hypothalamus), increases supraspinal nociceptive inhibitory mechanisms via norepinephrine + opioids (via hypothalamus/periadueductal grey)
- May also increase body awareness (distract attention from pain)
- Other possible benefits: deconditioning may worsen pain; exercise may improve other aspects of health
- May have effects through anti-depressant effect and general cognitive effects of activation
Physical Activity

- In some types of chronic pain, analgesia/inhibition do not occur
  - Tailor recommendations
  - Focus on preventing flares

Acupuncture

• Nerve endings
• Nerve fibers
• Spine and brain stem
• Thinking systems of brain
• Emotional systems of brain
• Memory

• Inhibition
• Facilitation
• Restore homeostasis
• Decrease stress
• Increase neuroplasticity

neurotransmitters

• Opioid peptides
• CCK-8
• 5-HT
• NA
• Glutamate
• GABA
• SP
• adenosine
Psychotherapy

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

- Inhibition
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- Opioid peptides
- Many others

neurotransmitters
Psychotherapy

- Decreasing Catastrophizing Thinking
- Focus of attention
- Re-appraisal changes pain experience
  - Of experience of pain
  - Of meaning of pain
- Empathy reduces pain
- Thoughts, emotions, and behaviors are all amenable to treatment
Cognitive, Affective, and Behavioral Pain Coping Strategies

• “Active” strategies activate opioid peptides and other systems and inhibit pain mechanisms
  – Distraction, Reappraisal, certain types of meditation and religious practice, relaxation strategies

• Passive strategies that reinforce sense of helplessness suppress opioid peptide function and facilitate pain mechanisms
  – Catastrophizing – rumination, pessimism,

• CBT, guided imagery, hypnosis – fair to good evidence, behavioral therapy – evidence against effectiveness, psychodynamic, interpersonal, DBT – inadequate evidence

• Suggestion of long term benefit with positive neuroplasticity
Pain Education

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

- Inhibition
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- Increase neuroplasticity

neurotransmitters
Pain Education

• Presumed to work through:
  – Cognitive re-appraisal processes
  – Addressing catastrophizing
  – Increasing movement
Education

• Neuroscience education has positive effects on pain, function/disability, catastrophization

• May affect movement, exercise, ability to tolerate discomfort

• Cognitive-based education:
  – Neurobiology/physiology of pain, pain processing of nervous system
  – How modulation, sensitization, brain processing interpret information from tissues, affect pain experience
  – Pain experience determined by nervous system processing of injury including psychosocial aspects
  – Pain not always a true representation of status of tissues

• Combining education with movement can increase physical capacity, reduce pain, improve quality of life

Mindfulness

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

- Inhibition
- Facilitation
- Restore homeostasis
- Decrease stress
- Increase neuroplasticity

Neuro-anatomy

- ACC via PAG
Mindfulness

- Focused Attention (FA) and Open Appraisal (OA) meditation may have different effects
- Differences in experienced meditators and newly trained
Placebo

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

- Inhibition
- Facilitation
- Restore homeostasis
- Decrease stress
- Increase neuroplasticity

Neuro-anatomy / neurotransmitters
- DLPFC via ACC
- Opioid systems
- Endocannabinoid systems
- Dopamine systems
Placebo

- Words and rituals, symbols and meanings
- Always related to the treatment context
- Acts in thinking parts of brain
- Closely related to reward systems
- Patients with Alzheimer's disease and possibly other conditions affecting pfc have less placebo response
- It is appropriate to do whatever is possible to potentiate placebo effects
Nocebo

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

- Inhibition
- Facilitation
- Restore homeostasis
- Decrease stress
- Increase neuroplasticity

Neuro-anatomy / neurotransmitters

- Thalamus, Insula, PFC, ACC
- CCK-1, CCK-2
Nocebo

• Based on expectations, past experience,
• Disclosure of adverse effects may cause harm to some patients and new ethical paradigms may need to be developed
Depression Treatment and Pain

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory
- Inhibition
- Facilitation
- Restore homeostasis
- Decrease stress
- Increase neuroplasticity

neurotransmitters
- 5HT
- NA
- DA
Depression Treatment and Pain

• Pain and depression frequently co-occur and outcomes are worse
• Depression may be more amenable to treatment than pain
Pain and Pleasure

- Nerve endings
- Nerve fibers
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- Thinking systems of brain
- Emotional systems of brain
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- Increase neuroplasticity

neurotransmitters
- DA
- EC
- OP
Pain and Pleasure

• Overlapping systems anatomically and neurotransmitters
• Brain needs to decide between competing pleasant and aversive events
• Always modulated by meaning and context
Chemical (and other) Dependence and Pain

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

- Inhibition
- Facilitation
- Restore homeostasis
- Decrease stress
- Increase neuroplasticity

neurotransmitters
- OP
- DA
- EC
Chemical (and other) Dependence and Pain

Traumas and Losses

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory

- Inhibition
- Facilitation
- Restore homeostasis
- Decrease stress
- Increase neuroplasticity

neurotransmitters
Traumas and Losses

- Shared vulnerabilities, Mutual maintenance, Fear-Avoidance, Triple Vulnerability
- Partial overlap in stress processing and pain modulation areas of the brain
  – ACC
- Considering prevalence of PTSD and co-morbid pain needs much more research
Spiritual Approaches

- Nerve endings
- Nerve fibers
- Spine and brain stem
- Thinking systems of brain
- Emotional systems of brain
- Memory
- ???

- Inhibition
- Facilitation
- Restore homeostasis
- Decrease stress
- Increase neuroplasticity

neurotransmitters
Prayer

• One of the most common pain management strategies globally
• Prayer is a complex of activities not easily reducible or studied
• Prayer when studied for pain management has had mixed results
• Some forms of prayer activate or deactivate brain activity in areas related to pain modulation
Meditation and Contemplation

• Religious meditation and contemplation adds principle of “meaning” to similar secular activities

• In limited studies meaningfulness had added benefit on pain coping
  – Fmri studies of devout Catholics contemplating BVM
  – Various meditation studies
Communicating with Patients

Communicating – What’s Going On

• “When pain persists, the danger alarm system becomes more sensitive.”
• “The danger messenger neurone becomes more excitable.”
• “The brain starts activating neurones that release excitatory chemicals.”
• “Response systems become more involved + start contributing to the problem.”
• “Thoughts + beliefs become more involved + start contributing to the problem.”
• “Danger sensors in the tissues contribute less + less to the danger message arriving at the brain.”
Communicating – What To Do

• “Modern management models incorporate the current scientific knowledge + do not focus solely on tissues.”
• “These models recognise the importance of alarm system sensitivity, fears, attitudes + beliefs in a chronic pain state.”
• “How you understand + cope with pain affects your pain as well as your life.”
• “Many people with persistent pain relate to the ‘pain is your guide’ or ‘boom-bust’ cycles.... [T]hese cycles are not helpful + lead to drastic limitation of activity + meaning in life.”
Communicating – What To Do

• “Education + understanding are critical for you to overcome pain + return to life.”
• “A key is to understand why your hurts won’t harm you + that your nervous system now uses pain to protect at all costs, not to inform you about damage.”
• “Purposefully seek out activities that produce danger-reducing chemicals.”
• “By mastering your situation + then planning your return to normal life, you will be able to do so. The research shows that it can work.”
Thank You to All My Colleagues at Tom Waddell Health Center and Our Many Partners

Thank You to My Patients Who I Learn From Every Day
Next Steps

• Based on this talk, think about 1 thing you can do when you return to work to improve your care of patients with chronic pain.

• Share with someone sitting near you.