Chronic Pain Management: Are We There Yet?

Miles Belgrade, M.D.
A Tale of Two Patients

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- 47 year-old female with chronic back and left leg pain since a MVA 12 years ago.
- Works part time in retail sales. Can’t stay on her feet > 6 hrs per day
- Exercises at the Y 2 days a week
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- Her doctor gives her 30 hydrocodone per month for pain flares and she usually has some left over
- Takes citalopram for depression
- Asking what she can do to improve her endurance and QOL. She used to run marathons before her back was injured

**Paris**
- 47 year-old female with chronic back and left leg pain since a MVA 12 years ago
- Works as a PCA for her aunt 12 hrs a week doing light housework
- No exercise regimen
- Suffers from PTSD from sexual assault as a teen and early childhood trauma. Sees a psychiatrist who prescribes alprazolam 1 mg 3 X per day
- Single mother of a daughter who is currently in a treatment program for polysubstance abuse
- Paris takes hydrocodone 8 tabs per day but Rx runs out too soon so her aunt supplements with her supply
- Other pain problems include chronic headache, IBS, TMJ disorder
- Asking for something stronger for her pain
- Asking for something to take to help her sleep at night
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- No pain behaviors
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- Strength is normal
- Lumbar MRI shows left L5S1 disc bulging and mild stenosis

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- Tearful, labored movements favors left leg
- Very limited back motion
- Tender at multiple sites head to toe
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Chronic Pain: Are we there yet?

• Anatomy and physiology of pain
  • Pain transmission
  • Pain Modulation
  • Chronification of pain

• Pain Assessment
  • Physiologic pain type
  • Contributing factors
  • Barriers
  • Disease burden

• Pain Management
  • Medications including opioids
  • Interventional
  • Physical Rehab
  • Complementary/Integrative Medicine
  • Behavioral strategies

• A tale of two patients
Nociception: The Transduction of Pain Stimuli
The 1st Synapse

C-polymodal nociceptor

Post-synaptic membrane of dorsal horn neuron

Dorsal horn of the spinal cord

Ca^{2+}

NK-1 AMPA NMDA

= glutamate vesicles
= dense core vesicles with substance P, CGRP, CCK, BDNF
Pain Affect Encoded in Human Anterior Cingulate But Not Somatosensory Cortex

• Unpleasantness vs. intensity
• Unpleasantness modified by hypnosis
• PET scan localization of unpleasantness
  • Anterior cingulate
  • Rostral insula
• Pain intensity localization to SI, SII

Rainville. Science 1997
Pain Modulation: the Gate Theory
Periventricular posterior hypothalamus

Anterior cingulate gyrus

Periaqueductal gray

Descending Inhibitory Pathway for Pain

Locus ceruleus

Dopamine
Norepinephrine
Serotonin

Rostral ventromedial medulla
Dorsal horn
The *Chronification* of Pain

- Peripheral sensitization
- Central Sensitization
  - Wind-up
  - Glial activation
  - Deafferentation
- Cortical reorganization
- Connectivity

Seifert, Maihofner *Current Opinion in Anesth* 2011
Immune-Mediated Peripheral Nociception

Hist=histamine. TNF-α=tumor necrosis factor- α. IL-1β=interleukin-1β. IL-6=interleukin-6. NO=nitric oxide. ATP=adenosine triphosphate. PGs=prostaglandins. CCL2=C-chemokine ligand 2.
Mu Receptors on Pain Primary Afferents

- Upregulated in the setting of inflammation
- Topical application of morphine inhibits pain transmission
- Leukocytes are recruited from the systemic circulation into areas of inflammation
- T-lymphocytes that contain B-endorphin attach to vascular endothelium
- B-endorphin binds to mu receptors located on the terminals of peripheral afferent nerves to inhibit the release of neurotransmitters responsible for the propagation of pain impulses

Morphine 0.1% Weight-to-Weight in IntraSite Gel
Neuropathic Pain Mechanisms

Dorsal Horn

Automatic firing

Wind-up

Second order neuron

NMDA Receptor

Ectopic impulse generator

C-PMN

Ephaptic impulse

A-B
The ‘Remapping Hypothesis’ and Neural Plasticity

- Touching ‘Tom’s’ face produced sensation in his phantom hand
- Modality-specific sensations felt on hand
  - ‘Tom’ would feel water dripping down his hand if water was dripped down his face
- Complete representation of phantom hand was ‘mapped’ onto face
- Another representation mapped onto upper arm
- Hand is between arm and face on Penfield map

Figure 2. Points on the face of a patient that elicit precisely localized, modality-specific referral in the phantom limb 4 weeks after amputation of the left arm below the elbow. Sensations were felt simultaneously on the face and phantom limb.

Ramachandran & Blakeslee (1998)
Somatotopic Organization
Updating the Body Image using Visual Feedback

- Mirrored box used to create visual illusion of phantom hand
- Patients instructed to perform symmetric movements (hand clapping, etc…) with both real and phantom hands
- Visual feedback enabled patients to ‘feel’ movement in phantom hand
- Elimination of painful cramping caused by phantom hand paralysis
- In one case, after repeated practice with mirror box, phantom arm disappeared!
- Visual feedback of moving arm conflicting with muscular indication that arm is nonexistent… led to the first phantom amputation?!

Mirror therapy shows promise in amputee treatment

Posted 1/17/2008

Email story  Print story

by Donna Miles
American Forces Press Service

1/17/2008 - WASHINGTON (AFPN) -- Army Sgt. Nicholas Paupore is using a large mirror to help adjust to the loss of his leg after suffering injuries in an explosion while on duty in Iraq.

By using the mirror, the right leg that was destroyed when an explosively formed penetrator ripped through his Humvee just south of Kirkuk, Iraq, suddenly reappears before his eyes, reflecting the left leg that remains.

Sergeant Paupore said he was skeptical when Navy Cmdr. (Dr.) Jack Tsao suggested using a mirror to help him deal with excruciating pain he continued feeling in his missing right leg.

The phenomenon, called "phantom limb pain," plagues as many as half of all amputees, likely the result of a faulty signal between the brain and the missing appendage, Commander Tsao said. Neurons in the brain continue sending out signals to a limb that's no longer there. As a result, amputees can feel discomfort or pain and, in some cases, the sense that their missing limb is stuck in an uncomfortable position.

Navy Cmdr. (Dr.) Jack Tsao shows Army Sgt. Nicholas Paupore how to perform mirror therapy to treat phantom pain in his amputated right leg Jan. 15 at Walter Reed Army Medical Center in Washington, D.C. Commander Tsao conducted the first clinical trials in mirror therapy and said he hopes to advance the study to bring relief to amputees from Iraq and Afghanistan.

Commander Tsao is the associate professor of neurology at the Uniformed Services University of the Health Sciences at Bethesda, Md. (Dontea Department photo/Donna Miles)
The Neural Matrix

• Ronald Melzack
• Experiences are codified in a matrix or “web” that is activated as a unit
• Theory of phantom pain
• Pain and memory
• Possible mechanism for long-lasting response to acupuncture
Intrinsic Brain Connectivity in Fibromyalgia Is Associated With Chronic Pain Intensity

Vitaly Napadow,1 Lauren LaCount,2 Kyungmo Park,3 Sawan As-Sanie,4 Daniel J. Clauw,4 and Richard E. Harris4

Objective. Fibromyalgia (FM) is considered to be the prototypical central chronic pain syndrome and is associated with widespread pain that fluctuates spontaneously. Multiple studies have demonstrated altered brain activity in these patients. The objective of this study was to investigate the degree of connectivity between multiple brain networks in patients with FM, as well as how activity in these networks correlates with the level of spontaneous pain.

Methods. Resting-state functional magnetic resonance imaging (fMRI) data from 18 patients with FM and 18 age-matched healthy control subjects were analyzed using dual-regression independent components analysis, which is a data-driven approach for the identification of independent brain networks. Intrinsic, or resting-state, connectivity was evaluated in multiple brain networks: the default mode network (DMN), the executive attention network (EAN), and the medial visual network (MVN), with the MVN serving as a negative control. Spontaneous pain levels were also analyzed for covariance with intrinsic connectivity.

Results. Patients with FM had greater connectivity within the DMN and right EAN (corrected P [Pcorr] < 0.05 versus controls), and greater connectivity between the DMN and the insular cortex, which is a brain region known to process evoked pain. Furthermore, greater intensity of spontaneous pain at the time of the fMRI scan correlated with greater intrinsic connectivity between the insula and both the DMN and right EAN (Pcorr < 0.05).

Conclusion. These findings indicate that resting brain activity within multiple networks is associated with spontaneous clinical pain in patients with FM. These findings may also have broader implications for how subjective experiences such as pain arise from a complex interplay among multiple brain networks.

Chronic pain disorders cause significant disability and dysfunction in patients and are particularly troublesome for both researchers and clinicians. Since pain is
BRIEF REPORT

Decreased Intrinsic Brain Connectivity Is Associated With Reduced Clinical Pain in Fibromyalgia

Vitaly Napadow,1 Jieun Kim,2 Daniel J. Clauw,3 and Richard E. Harris3

Figure 1. Levels of pain in fibromyalgia patients before therapy (solid bars) and after therapy (open bars) as assessed with the short form of the McGill Pain Questionnaire. Clinical pain levels were assessed just prior to functional magnetic resonance imaging. There was a significant reduction in pain on the McGill sensory subscale and a trend toward diminished pain on the McGill affective subscale following therapy. Bars show the mean ± SEM. * = P = 0.02; + = P = 0.09.

Figure 2. Default mode network (DMN) connectivity to the anterior insula in fibromyalgia patients before and after therapy. DMN connectivity was positive at baseline, and was significantly reduced following therapy. Bars show the mean ± SEM. R Ant Insula = right anterior insula. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.34412/abstract.
Glial Activation and Pain

- Every animal model of pain facilitation causes activation of microglia and astrocytes
- Pharmacological disruption of glial activation reverses pain facilitation in every animal model tested
- Antagonism of activated glial products reverses pain facilitation
- Activation of spinal cord glia is sufficient to induce pain facilitation
- Blocking glial activation does not affect pain thresholds in control animals
- Blocking glial activation does NOT cause analgesia. It reduces the amplification of pain
Socially Mediated “Contagious” Pain Hypersensitivity (SCPH)

J. Mogul, McGill University

- Acetic Acid-Injected
- Uninjected

0.6% Acetic Acid (10 ml/kg; i.p.)
A. In C57BL/6J, DBA/2J and A/J mice

B. In CD-1 mice
SCPH: Time Course of Familiarity

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**Graph 1:**
- Y-axis: % Writhing
- X-axis: Days Housed Together (Isolated, 1, 7, 14, 21, 28)
- Bars represent observed writhing percentages with error bars.
- Stars indicate significant differences.

**Graph 2:**
- Y-axis: Observed - Expected (%)
- X-axis: Days Housed Together (0, 7, 14, 21, 28)
- Line graph showing observed writhing percentages with error bars.
- Stars indicate significant differences.
What is the Mode of Communication of SCPH?

![Graph showing writhing percentages for different conditions: Control, Anosmic, Deaf, Transparent, and Opaque with OW and BW categories.](image-url)
Pain Assessment

• Physiologic types of pain
• Acute vs. chronic pain
• Identifying co-morbid conditions
• Distinguishing opioid naïve from opioid tolerant patients
• Pain assessment tools
Pain Types by Physiology

- **Psychogenic**
  - Treat anxiety and depression
  - Stress management
  - Autonomic regulation

- **Nociceptive inflammatory**
  - NSAIDs
  - Steroids
  - Antibiotics

- **Nociceptive mechanical**
  - Stabilization
  - Surgery
  - Bracing
  - Strengthening

- **Muscular**
  - Stretching
  - Muscle balance
  - Stabilization
  - Strengthening
  - Changing activity patterns

- **Bone**
  - NSAIDs
  - Steroids
  - Osteoclast inhibitors

- **Neuropathic**
  - Anticonvulsants
  - Antidepressants

- **Psychogenic**
  - Treat anxiety and depression
  - Stress management
  - Autonomic regulation
Opioid Prescribing in the US

- 4.3% of the world’s population
- 83% of the world’s oxycodone
- 99% of the world’s hydrocodone

Rept of International Narcotics Control Board, 2008
Opioid Prescribing in the US

• Between 1997 and 2002
  • Prescriptions for oxycodone increased by 227%
  • Prescriptions for fentanyl increased by 403%

• Between 1997 and 2006
  • Oxycodone sales increased by 8-fold
  • Methadone sales increased by 9-fold
  
  Saper 2010

• In 2009, there were >250 million opioid prescriptions written
Amount of prescription painkillers sold by state per 10,000 people (2010)

Kilograms of prescription painkillers per 10,000 people

- 3.7 - 5.9
- 6.0 - 7.2
- 7.3 - 8.4
- 8.5 - 12.6

SOURCE: Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 2010
Opioid Prescribing: Informed Consent

Everyone knows:
• Constipation/nausea
• Dizziness
• Urinary retention
• Pruritis
• Respiratory depression
• Potential interactions with other controlled substances (i.e., benzo and benzo-like medications) and EtOH

Might surprise your pt:
• Disruption of sleep architecture & breathing
• Opioid –induced hyperalgesia
• Hormonal dysregulation
  • 40% men low testosterone
• Immune dysfunction
• Depression/apathy/cogniton
A Few Words On Opioid-Induced Hyperalgesia (OIH)....

- Short-term infusion can exacerbate pain
  (Ossipov, 2003)

- As little as 30 mg morphine/morphine equivalents can decrease the pain threshold and lead to OIH
  (Chang, 2007; Chu 2008; Angst 2006)

- Intra-op infusions of opioid can decrease the pain threshold

- So, let your pt know opioids may be causing MORE pain
The Risk of High Dose Opioids– Why Limit to < 100 mg Morphine?

• The risk of drug related adverse events in patients on opioids for chronic, non-cancer pain increased with increasing dose, particularly above 50 morphine equivalents per day (Bohnert, 2011)

• Patients on 50 to 99 morphine equivalents per day had a 3.7 fold increase in overdose death; those on > 100 morphine equivalents per day had an 8.9 fold increase (Dunn, 2010)
High Opioid Dose and Overdose Risk

* Overdose defined as death, hospitalization, unconsciousness, or respiratory failure.

Opioids are NOT so Great for Chronic Pain!

• Danish population-based cohort study of chronic pain showed
  • 4X higher return to work if NOT using opioids for chronic pain
  • Poorer QOL if using strong opioids for chronic pain

• A 10-year epidemiologic study found that patients on chronic prescription opioids had a lower quality of life, increased levels of depression and pain and more health care utilization
  (Jensen, 2006)
### D.I.R.E. Score Patient Selection for Chronic Opioid Analgesia

**Diagnosis**
- 1. Benign min findings
- 2. Moderate slowly progressive
- 3. Severe

**Intractability**
- 1. A lot left to try
- 2. Has done some appropriate pain management
- 3. Fully engaged in appropriate pain management

**Risk - Psych health**
- 1. Severe pathology
- 2. Mild to moderate psych
- 3. No psych issues

**Risk - Chemical Health**
- 1. Active CD
- 2. Past CD or chemical coper
- 3. No Hx of CD

**Risk - Reliability**
- 1. Non-compliant
- 2. Mostly compliant
- 3. Highly compliant

**Risk - Social roles/support**
- 1. Life in chaos
- 2. Some loss of roles/support
- 3. Life roles intact/good support system

**Efficacy**
- 1. Marginal despite moderate doses
- 2. Moderate improvement or unknown
- 3. Good improvement, stable doses, improved function

**TOTAL: D + I + R + E = _________**

**DIRE Score 7-13:** Not a suitable candidate for long-term opioid analgesia  
**DIRE Score 14-21:** May be a suitable candidate for long-term opioid analgesia
Acute vs Chronic Pain

• **Acute pain**: elicited by the injury of body tissues and activation of nociceptive transducers at site of local tissue damage. Lasts for relatively limited time and resolves with healing of underlying pathology.

• Acute pain has a beginning, a middle and a predictable end
Chronic Pain

- **Chronic pain**: May be elicited by injury or disease, but persists for a long period of time with low level of underlying pathology that does not explain the presence and extent of pain. Currently available treatments are rarely capable of totally eliminating chronic pain. Because the pain persists, it is likely that environmental, emotional, and cognitive factors will contribute to persistence of pain and associated illness behaviors. (Fishman et al, 2010)
Chronic Pain

- Chronic pain is best managed in an outpatient setting
  - Trying to solve chronic pain in the hospital is at best unsuccessful, and may lead to unrealistic expectations and chaos in the hospital course

- Chronic pain is best managed with a multidisciplinary approach over time
  - Physician
  - Nursing
  - Psychologist
  - Physical therapist
Intractable Pain

- Pain is intractable when there exist no treatments or strategies that will alleviate it.
Important Comorbidities

• Psychiatric and Personality Issues:
  • Up to half of all patient with chronic pain can have comorbid psychiatric condition (Dersh et al 2002)
  • Major depression thought to affect 30-50% (Fishbain et al 1997)
  • Anxiety disorders next most prevalent (Fishbain 1999)
Important Comorbidities

• Substance Use Disorders (SUD)
  • 10-16% of patients in general practice
  • 25-40% of hospitalized patients have problems related to drug or alcohol addiction. (Kissen 1997, Brown et al 1998)
  • 60% of hospitalized trauma patients have SUD
Pain Assessment Tools

• Numerical rating scale (NRS)
  ➢ 0 – 10 where 0 is no pain and 10 is the worst pain imaginable

• Visual analog scale (VAS)

No pain ___________________________________________ Worst possible pain

• Faces scale

• FLACC
Verne
Verne (cont.)

- 77-year-old man with PD and type 2 DM; he has burning and shooting pain in both feet; his joints ache—especially his hips and knees; pain is bad at night, but can flare up first thing in the morning and also when he walks any distance.

- He was widowed in the past year and moved to an assisted living apartment; he has fallen a few times, sustaining soft tissue injuries, but no fracture.

- Ibuprofen and acetaminophen with codeine were ineffective; hydrocodone/APAP made him confused and constipated.

- He jokes, “Might as well put me in the pine box right now”.

DM=diabetes mellitus. PD=Parkinson's disease. APAP=acetaminophen.
Verne’s Examination

- Affect discordant with his depressed mood
- Gait is shuffling and wide-based with postural instability
- Joint deformities in the hands and knees consistent with OA
- Sensory loss to pin and vibration in the feet and distal legs; positive Romberg sign; absent DTRs at the Achilles tendons; feet are sensitive to light touch
- Sacral decubitus ulcer

OA=osteoarthritis.
DTRs=deep tendon reflexes.
Contributing Factors and Barriers

• **Contributing factors** amplify or perpetuate pain
  • Depression or anxiety
  • Posture
  • Intercurrent illness

• **Barriers** interfere with pain assessment or with implementing appropriate treatment
  • Insurance noncoverage/resource access
  • Low motivation
  • Personality disorder
  • Chemical dependency
  • Language or communication difficulty
  • Conflicting medical therapies
Assess Disease Burden

Goals of Pain Management in Palliative Care vs Chronic Pain

- Return to work
- Self-care
- Patient assumes responsibility for symptom management
- Increase activity
- Functional restoration
- Minimize healthcare utilization

Priority

DISEASE BURDEN

None  Low  Medium  High  End of Life

Palliative goals

Restorative goals

Comfort
Support
Ease pain/suffering
Verne’s Case Formulation

- Painful diabetic neuropathy
- Muscular dysfunction/pain due to PD
- OA
- Inflammatory pain due to decubitus ulcer
- Contributing factors:
  - Grief and loss
  - Depression
- Barriers
  - Bradykinesia
  - Risk of falls
  - Intolerance to analgesics
- Disease burden: fairly high—take mostly palliative approach
Verne’s Plan of Care

**For DPNP**
- Optimize glucose control
- Duloxetine or venlafaxine*
- Recommend a walker
- Check and optimize shoe wear
- Tramadol for pain flares

**For OA**
- Glucosamine supplement
- Scheduled acetaminophen or NSAID
- Acupuncture

**For muscular pain**
- Pool therapy

**For decubitus ulcer**
- Topical morphine
- Local wound care
- Evaluation of sleep surface

**For contributing factors: grief/loss/depression**
- Duloxetine or venlafaxine*
- Pool therapy in group setting
- Grief group if Verne is amenable

**Manage barriers:**
- Manage PD (pramipexole)
- (Walker)
- Choose intermediate analgesic (tramadol)

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*Duloxetine and venlafaxine are the choice for this patient, but other neuropathic pain medications may also substitute for these choices. DPNP = diabetic peripheral neuropathic pain. NSAID = non-steroidal anti-inflammatory drugs.*
What Does the Future Hold?
Turning Straw into Gold

• Brain and spinal cord plasticity—making it work for us instead of against us
• Glial cell de-activation
• Making the connection between Pain and the mind
• Breaking down the barriers to interdisciplinary treatment that addresses the biopsychosocial components of pain
• Preventing pain through education, public health measures, occupational health measures
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