How patients can control chronic pain, a new viewpoint in chronic pain management. Do we have it right?

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Chronic pain patient
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Disclosures
- Founder of ByPro Nutrition LLC
  - Nutraceutical company with products that address chronic pain and inflammation.
Objectives:
By shifting focus of chronic pain to chronic inflammation, patients have a definable control to self management of chronic pain.

1. Know difference between acute and chronic pain

2. Mechanism of immune system (inflammation) in chronic pain

3. Understandable treatments for chronic pain patients to controlling inflammation
Dr. Robert L. Bynum
Family practice physician for over 30 years.

“I never thought I needed to be humbled but God felt otherwise”
What is pain?

- **Acute** pain alerts us to possible injury and is of short duration (lasts less than 12 weeks). It gradually resolves as the injured tissues heal.

- **Chronic** pain is often defined as any pain lasting more than 12 weeks.
What is the difference?

Acute and chronic pains are very different clinical entities

- **Acute pain** is provoked by a specific disease or injury, serves a useful biologic purpose, and is self-limited.
  
  *The therapy of acute pain is aimed at treating the underlying cause and interrupting the pain signals.*

- **Chronic pain**, in contrast, may be considered a disease state. It is pain that outlasts the normal time of healing, if associated with a disease or injury.
  
  - serves no biologic purpose
  - has no recognizable end-point

  *The therapy of chronic pain must rely on a multidisciplinary approach and should involve more than one therapeutic modality.*
In this chart, we can see that pain affects more Americans than diabetes, heart disease, and cancer combined. The following table provides data on the number of chronic pain sufferers compared to other major health conditions:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Sufferers</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pain</td>
<td>100 million Americans</td>
<td>Institute of Medicine of The National Academies (2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.8 million Americans</td>
<td>American Diabetes Association (3)</td>
</tr>
<tr>
<td></td>
<td>(diagnosed and estimated undiagnosed)</td>
<td></td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>16.3 million Americans</td>
<td>American Heart Association (4)</td>
</tr>
<tr>
<td>(heart attack and chest pain)</td>
<td></td>
<td></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>

**Notes:**
5) American Cancer Society, Prevalence of Cancer: http://www.cancer.org/docroot/CRI/content/CRI_2_6x_Cancer_Prevalence_How_Many_People_Have_Cancer.asp
Chronic pain survey key findings:

➤ More than half of respondents (51%) felt they had little or no control over their pain.
➤ More than three quarters of patients (77%) reported feeling depressed.
➤ 86% reported an inability to sleep well.
➤ 70% said they have trouble concentrating.
➤ 74% said their energy level is impacted by their pain.

2006 survey conducted for the American Pain Foundation
The bravest thing I ever did was continuing my life when I wanted to die

- Juliette Lewis
The goal is not necessarily to eliminate pain, but to empower the patient to be in charge of their pain so that they may lead a full and active life.
Theories of Chronic Pain

- Gate
- Neuromatrix
- Immune system/inflammation
Theories of Chronic Pain

Gate Control Theory

asserts that non-painful input closes the "gates" to painful input, which prevents pain sensation from traveling to the central nervous system. Therefore, stimulation by non-noxious input is able to suppress pain.
Neuromatrix

- is that the central nervous system is where pain is produced and that multiple parts of the brain and spinal cord work together in response to stimuli from the body and/or the environment to create the experience of pain. It thus involves two important shifts in our understanding of pain:
  - The brain and spinal cord are what produce pain, not tissue damage
  - Various parts of the central nervous system work together to produce pain
- In this way, the location of what produces pain shifts from tissue damage in the body and the peripheral nervous system that surrounds it to the central nervous system.
Immune system/inflammation

- The release of pro-inflammatory and immunoactive substances such as cytokines, neurotrophic factors, and chemokines initiates local actions and can result in a more generalized immune response that leads to the chronic pain condition.

- Cytokines display a direct neuromodulatory role in CNS and PNS.
  - Cytokines modulate presynaptic neurotransmitter release.
  - Cytokines affect neuronal excitability also indirectly by activating glial cells.
  - Cytokines have a physiological role in synaptic transmission and plasticity.
  - Excessive cell exposure to cytokines may mediate neuropathologic effects.
Inflammatory stress

Microglia activation
- Cytotoxic cytokines
- ROS, NO, ONOO⁻
- NADPH-oxidase
- NFkB
- Glutamate

Beneficial effects
- Protective cytokines
- Differentiation factors
- Neurogenesis
- Immunoregulatory

Neuron Injury MPTP

Astrocyte activation
- Cytotoxic cytokines
- ROS, NO, ONOO⁻
- Glutamate, MPO
- NFkB

MPP⁺
- Mitochondrial dysfunction
- Inhibition of complex I
- ATP depletion
- DNA damage

Beneficial effects
- Energy substrate
- Anti-oxidant defense
- Neurotrophic factors
- Glutamate uptake
- Neurogenesis

Neuron death
THREE MAIN TYPES OF PATHOPHYSIOLOGY can be considered to result in chronic pain

NOCICEPTIVE PAIN
Examples:
Rheumatoid arthritis, osteoarthritis, gout

NEUROPATHIC PAIN
Examples:
Painful diabetic peripheral neuropathy, postherpetic neuralgia

SENSORY HYPERSENSITIVITY
Example:
Fibromyalgia

More than 1 type of pain may be present in a given patient
How does pain start?

All pain starts from inflammation

Inflammation is a vital part of the body's complex biological immune response. It is the body's attempt to heal itself after an injury; defend itself against foreign invaders, such as viruses and bacteria; and repair damaged tissue.

- Infection
- Thermal
- Chemical
- Radiation
- Immunological/Allergic
- Mechanical
- Oxygen deficiency/ischemia/hypo-perfusion
What causes Chronic Pain?

- Chronic pain comes from inflammation that goes unchecked in the body.
  - Thermostat is set but furnace keeps running out of control
- This sets off a complex cascade of chemical, physical and emotional events.
- The pathophysiology of chronic pain is multifactorial and complex and still is poorly understood.
LIVING WITH CHRONIC PAIN

Personal responsibility

- Improve your health
  - Quit smoking
  - Address diet
- Manage your stress
- Seek help for mood disorders
- Be smart on the job
What can be done for chronic pain?

Over-the-Counter Medications

- The most common types of OTC pain relievers are acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).

Topical Pain Relief

- These are often used to relieve pain associated with arthritis and muscle aches.
Prescription Medications

• Rx NSAIDs
  – Naprosyn
  – Ibuprofen
  – Mobic
  – Celebrex

Table 1.
Common Oral NSAIDs

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Max Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Advil, Motrin</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Aleve</td>
<td>1,500 mg</td>
</tr>
<tr>
<td>Prescription</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Celebrex</td>
<td>400 mg</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Voltaren</td>
<td>200 mg</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>N/A</td>
<td>1,500 mg</td>
</tr>
<tr>
<td>Etodolac</td>
<td>N/A</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Ansaid</td>
<td>300 mg</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>N/A</td>
<td>3,200 mg</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Indocin</td>
<td>200 mg</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>N/A</td>
<td>300 mg</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Toradol</td>
<td>40 mg (max 5 days of total treatment)</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Mobic</td>
<td>15 mg</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>N/A</td>
<td>2,000 mg</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Naprosyn</td>
<td>1,500 mg</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>Daypro</td>
<td>1,800 mg</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Feldene</td>
<td>20 mg</td>
</tr>
<tr>
<td>Sulindac</td>
<td>Clinoril</td>
<td>400 mg</td>
</tr>
</tbody>
</table>

max: maximum; N/A: not applicable; NSAID: nonsteroidal anti-inflammatory drug. Source: References 7, 22.
Prescription Medications

- If chronic pain is not controlled with OTC medication, people may seek medical advice. The doctor may want to prescribe something stronger. The American Chronic Pain Association (ACPA) identifies several major classes of medications used to treat chronic pain. These include:

  **Opioids**
  - Morphine
  - Codeine
  - Hydrocodone
  - Oxycodone

  **Non-Opioids**
  - Anticonvulsants
  - Antidepressants

There is no medical evidence that opioids help with the management of chronic pain.
Physician Visits

- **Surgery/procedures**, spinal cord stimulators, local electrical stimulation, brain stimulation, morphine pumps, spinal injection, trigger point injections...
Therapeutic modality

- Operant-behavioral therapy Treatment
- Cognitive-behavioral therapy (CBT) Treatment
- Mindfulness-based stress reduction
- Acceptance and commitment therapy
Therapeutic modality Description of treatments

• Operant-behavioral therapy
  Treatment focuses on extinguishing maladaptive behavioral responses and fostering of adaptive behavioral responses to pain. Behavioral responses are altered through reinforcement and punishment contingencies and extinction of associations between threat value of pain and physical behavior.
  – foster more adaptive behaviors, including graded patterns of activity, activity pacing, and time-contingent medication management
Cognitive-behavioral therapy (CBT) Treatment applies biopsychosocial approach to pain that targets behavioral and cognitive responses to pain. CBT protocols involve psychoeducation about pain, behavior, and mood, strategies for relaxation, behavioral pacing, behavioral activation, positive event scheduling, effective communication, and cognitive restructuring for distorted and maladaptive thoughts about pain.

- CBT for pain develops coping skills intended to manage pain and improve psychological functioning, including structured relaxation, behavioral activation and scheduling of pleasurable events, assertive communication, and pacing of behavior in order to avoid prolongation or exacerbation of pain flares. Unlike operant-behavioral approaches, CBT for pain also addresses maladaptive beliefs about pain and pain catastrophizing through formal use of cognitive restructuring: identification and replacement of unrealistic or unhelpful thoughts about pain with thoughts that are oriented towards adaptive behavior and positive functioning.
Mindfulness-based stress reduction Treatment promotes a nonjudgmental approach to pain and uncoupling of physical and psychological aspects of pain; teaches “nonstriving” responses to pain through experiential meditations and daily mindfulness practice intended to increase awareness of the body and proprioceptive signals, awareness of the breath, and development of mindful activities.
Acceptance and commitment therapy is based on psychological flexibility model, treatment focuses on development of acceptance of mental events and pain and ceasing of maladaptive attempts to eliminate and control pain through avoidance and other problematic behaviors; emphasizes awareness, defusion, and acceptance of thoughts and emotions as well as behavioral engagement in pursuit of personal goals.

- ACT fosters purposeful awareness and acceptance of pain, thereby minimizing the focus on reducing pain or thought content and instead directing efforts towards fulfilling behavioral functioning.
Alternative Therapies
What can you do for chronic pain?

Regular exercise Activity is important for treating chronic pain because it helps:
- strengthen muscles
- increase joint mobility
- improve sleep
- release endorphins
- reduce overall pain

Diet and healthy nutrition
- Anti-inflammatory foods
- Avoid Pro-inflammatory foods
  - processed food
  - high fructose
Relaxation techniques reduce stress and decrease muscle tension.

- Meditation
- Massage
- Yoga
- Deep breathing
- Massage
- Meditation
- Tai chi
- Yoga
- Biofeedback
- Music and art therapy
- Aromatherapy
- **Acupuncture**
  - involves the insertion of very thin needles through your skin at strategic points on your body.

- **Acupressure**
  - precise finger placement and pressure over specific points along the body.

These prompts the body to release endorphins which can block messages of pain from being delivered to the brain.
Transcutaneous Electrical Nerve Stimulation (TENS)

applies a small electric current to specific nerves. The current
interrupts pain signals, and triggers the release of endorphins.
The unit is usually connected to the skin using two or more
electrodes. A typical battery-operated TENS unit is able to
modulate pulse width, frequency and intensity
Supplements or Nutraceuticals

are formulated nutritional supplements and herbal products that provide medical or health benefits.
The major issue to be addressed:

Suppress inflammation pathways that causes pain

Remember the seven causes of inflammation
Curcumin inhibits inflammation in and around your joints, muscles, and other tissues, thus decreasing associated aches and pains.

- related to its ability to blocked IRAK thiols and enhance IL-10 (1)
- inhibit cyclooxygenase-2 (COX-2), lipoxygenase (LOX),
- curcumin may attenuate opioid tolerance and dependence by suppressing Ca2+/calmodulin-dependent protein kinase II (CaMKIIα) activity.

Alpha Lipoic Acid (ALA) is a reputable therapy for preventing nerve pain. It also detoxifies your body; fighting free-radicals and toxic metals.

- lower expression of MMP-9 and VCAM-1 through repression of NF-kappa-B.

(J Nutr. 2005 Aug;135(8):1859-64. Curcumin blocks interleukin-1 (IL-1) signaling by inhibiting the recruitment of the IL-1 receptor-associated kinase IRAK in murine thymoma EL-4 cells. Jurrmann N¹, Brigelius-Flohé B, Bol GF.
Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential.
Silymarin, found in Milk-Thistle, decreases inflammation of tissue and relieves associated pain.

- blockade and adjustment of cell transporters, p-glycoprotein, estrogenic and nuclear receptors.

Moreover, silymarin anti-inflammatory effects through reduction of TNF-α.

N-Acetylcysteine (NAC) has a protective effect against injuries caused by excessive contractile activity in muscles - preventing inflammation and reducing pain.

- Levels of tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and IL-17.

Boswellia Serrata is used clinically to treat degenerative & inflammatory joint disorders. It reduces the white blood cell count in joint fluid, and inhibits leukocyte elastase, which is released in rheumatoid arthritis.

- potent inhibitor of 5-lipoxygenase

*Molecular Pharmacology* 47(6):1212-6 · July 1995 *Mechanism of 5-lipoxygenase inhibition by acetyl-11-keto-β-boswellic acid*
Methylsulfonylmethane (MSM) is a crucial nutrient for bone health, relieving many of the symptoms associated with arthritis, osteoarthritis, and rheumatoid arthritis.

- inhibitory effect on NF-κB results in the downregulation of mRNA for interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α)

Glucosamine helps maintain the structure and function of joints in your body. Glucosamine combined with MSM can also be effective against osteoarthritis, and the pain caused by inflamed joints.

- inhibits IL-1β-induced NFκB activation, MMP-2,3,9, and PGE2
Illustration purposes only

- NSAIDs (ibuprofen, etc)
- Curcumin
- N-Acetyl Cysteine (NAC)
- Milk Thistle (Silymarin)
- Alpha-lipoic acid (ALA)
- Boswellia Serrate
- MSM
- Glucosamine
Needs to go to work... but how does it get there?

Micro-Vascular Circulation
Circulation

What does it do?

The circulatory system is a vast network of organs and vessels that is responsible for the flow of blood, nutrients, oxygen and other gases, and hormones to and from cells. Without the circulatory system, the body would not be able to fight disease or maintain a stable internal environment — such as proper temperature and pH — known as homeostasis.
Capillaries carry blood very close to the cells of the tissues of the body in order to exchange gases, nutrients, and waste products. The walls of capillaries consist of only a thin layer of endothelium so that there is the minimum amount of structure possible between the blood and the tissues. The endothelium acts as a filter to keep blood cells inside of the vessels while allowing liquids, dissolved gases, and other chemicals to diffuse along their concentration gradients into or out of tissues.
How can promoting microvascular circulation help with pain?

- Pain may be caused by poor blood flow. This deprives the cells of oxygen.
- Circulations delivers the nutrients to the cells.
- Circulation takes toxins and waste byproducts away.

Remember, you can’t lab microvascular circulation or X-ray it!
Questions?

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