Functional Medicine Approach to Chronic Pain

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Disclosures

None
Objectives

- What is functional medicine?
- Root causes of chronic pain
- Tools for integrative medical treatment of chronic pain
FUNCTIONAL MEDICINE

A systems-oriented, patient-centered approach that aims to address the underlying causes of chronic disease, and that engages both the patient and practitioner in a therapeutic partnership.
Functional Medicine

➔ Patient-centered, rather than disease-centered
➔ Acknowledge biochemical diversity and individuality
➔ Address genetic, lifestyle, and environmental determinants of health
➔ Health as a positive vitality, not simply the absence of disease
Cost of chronic conditions, U.S.

>100 million American adults

- Chronic pain
- Cardiovascular disease
- Cancer, all sites
- Diabetes

Patients with chronic pain commonly turn to integrative approaches.

Chronic Pain Paradigm Shift:

- Treating pain, without focusing on the pain or pain treatments
- Emphasizing wellness rather than suffering
- Focus on treating the root cause (anatomic, autoimmune, neurodegenerative, metabolic, psychological disorders)
- Effective pain management integrates patient empowerment
Root causes of chronic pain:

- Primary driver is the interaction of:
  
  Genes - Lifestyle - Environment

- Imbalances that arise from how we live, work, eat, play, and move.

- Most commonly these imbalances culminate in increased inflammation.
Build confidence around your product or idea by including at least one of these slides:

➔ Milestones
What has been accomplished and what might be left to tackle?

➔ Testimonials
Who supports your idea (or doesn’t)?

➔ What’s next?
How can the audience get involved or find out more?

One Condition: Many Imbalances
- Inflammation
- Hormones
- Genetics and Epigenetics
- Diet and Exercise
- Mood Disorders

One Imbalance: Many Conditions
- Inflammation
- Heart Disease
- Depression
- Arthritis
- Cancer
- Diabetes
What to RID and GET:

- RID the most common causes of illness:
  Poor nutrition, inflammation, allergens, infections, toxins, and stress

- GET: Nutritious food, clean environment (air, food, water), regular movement, love, meaning
**Nutrition**

- GET more nutrients, antioxidants, whole foods
- RID sugars, processed foods, inflammatory foods
- Specific benefit shown for RA/OA
  - Anti-inflammatory diet

Oliviero et al. Swiss Med Wkly. 2015 Nov 2;145
Elimination Diet

- Elimination of common dietary triggers of inflammation that are unique to the individual
  - elimination/challenge remains gold standard
  - Testing is controversial
- Possible benefit for chronic pain related to migraines, fibromyalgia, arthritis.
- Multiple proposed mechanisms involving various immune pathways

Elimination Diet

- Most common foods to eliminate:
  - Wheat, dairy, soy, eggs, nuts, nightshades, citrus, yeast, corn, legumes, sugar, chocolate, coffee, tea, alcohol
- Optimal elimination trial is 3-6 weeks (I recommend 1 month)
- Re-introduce foods one by one, 3 days apart and keep a food-symptom diary
- Advise patients of risk of hypersensitivity period
Mindfulness


- 342 participants with back pain weekly for >1 year randomized to:
  - 8 weekly sessions of mindfulness training
  - 8 sessions of cognitive behavioral therapy
  - Continue current therapy

- Mindfulness (meditation, yoga instruction, CDs to use at home)
  - 43.6% had significant reduction in pain 26 weeks later

- CBT
  - 44.9% had significant reduction in pain

- Usual care
  - 26.6% improved
Mindfulness-Based Stress Reduction

Mindfulness-Based Stress Reduction is an eight week program that assists people who want to learn to use their own internal resources to respond more skillfully to stress, medical and psychological conditions, and promote healthy living. Research suggests that mindfulness practice can positively affect stress resilience; physical and mental health; academic skills; self-regulation of emotional reactivity; interpersonal skills; general well-being and happiness.

Some reasons people come to the group include, but are not limited to:

- job, school or family stress
- chronic pain
- hypertension, heart disease
- attention deficits
- enhancement of quality of life; happiness
- sleep disturbance
- mild or situational depression
- gastrointestinal disorders
- wellness and self-care
- cancer or other illness

Mindfulness Programs

- Upcoming Classes or Groups
- Mindfulness-Based Stress Reduction
- Mindfulness-Based Cognitive Therapy
- Mindfulness for Undergraduate Students
- Mindfulness Graduate Groups
- Donations for Mindfulness Programs
- Frequently Asked Questions
- Resources
- Mindful Educators
- Staff

Contact Us

Bev Klug, MA, LMFT, Director
Mindfulness Programs
UI Health Care
Heart Rate Variability Biofeedback

- High HRV - dominance of parasympathetic response (“rest and digest”)
- Low HRV - dominance of sympathetic response (“fight or flight”)
- Taught by trained therapist, or may self-teach at home using smartphone app/monitor:
  - iThlete, Bioforce HRV, Inner Balance (Heart Math) - Android and iOS
Non-pharmacological Intervention for Chronic Pain in Veterans: A Pilot Study of Heart Rate Variability Biofeedback

Melanie E. Berry, MS, United States; Iva T. Chapple, MD, United States; Jay P. Ginsberg, PhD, United States; Kurt J. Gleichauf, PhD, United States; Jeff A. Meyer, PhD, United States; Madan L. Nagpal, PhD, United States

ABSTRACT

Objective: Chronic pain is an emotionally and physically debilitating form of pain that activates the body’s stress response and over time can result in lowered heart rate variability (HRV) power, which is associated with reduced resiliency and lower self-regulatory capacity. This pilot project was intended to determine the effectiveness of HRV coherence biofeedback (HRVCB) as a pain and stress management intervention for veterans with chronic pain and to estimate the effect sizes. It was hypothesized that HRVCB will increase parasympathetic activity resulting in higher HRV coherence measured as power and decrease self-reported pain symptoms in chronic pain patients.

Study Design: Fourteen veterans receiving treatment for chronic pain were enrolled in the pre-post intervention study. They were randomly assigned, with 8 subjects enrolled in the treatment group and 6 in the control group. The treatment group received biofeedback intervention plus standard care, and the other group received standard care only. The treatment group received four HRVCB training sessions as the intervention.

Measures: Pre-post measurements of HRV amplitude, HRV power spectrum variables, cardiac coherence, and self-ratings of perceived pain, stress, negative emotions, and physical activity limitation were made for both treatment and control groups.

Results: The mean pain severity for all subjects at baseline, using the self-scored Brief Pain Inventory (BPI), was 26.71 (SD=4.46; range=21-35) indicating a moderate to severe perceived pain level across the study subjects. There was no significant difference between the treatment and control groups at baseline on any of the measures. Post-HRVCB, the treatment group was significantly higher on coherence ($P<.01$) and lower ($P<.02$) on pain ratings than the control group. The treatment group showed marked and statistically significant (t-tailed) increases over the baseline in coherence ratio (191%, $P<.04$) and marked, significant (t-tailed) reduction in pain ratings (36%, $P<.001$), stress perception (16%, $P<.02$), negative emotions (49%, $P<.001$), and physical activity limitation (42%, $P<.001$). Significant between-group effects on all measures were found when pre-training values were used as covariates.

Conclusions: HRVCB intervention was effective in increasing HRV coherence measured as power in the upper range of the LF band and reduced perceived pain, stress, negative emotions, and physical activity limitation in veterans suffering from chronic pain. HRVCB shows promise as an effective non-pharmacological intervention to support standard treatments for chronic pain.
Natural Medicines for Pain

- **Benefits:** Overall lower risk profile than NSAIDs, acetaminophen, opiates
- **Risks:** Limited dosing studies, supplement industry not regulated by the FDA (risk of contamination, variation in amount of active alkaloid compounds, etc)
Tissue Injury

Membrane phospholipids

Phospholipase A₂

Arachidonic acid

LOX
5-Lipoxygenase

5-HPETE

COX
(Cyclooxygenase)

COX-2 inhibitors
NSAIDS

COX-1,2 Inhibitors
NSAIDS

Leukotrienes
LTC₄

Thromboxanes
TXA₂

Prostacyclin
PGI₂

Prostaglandins
PGE₂
PGF₂

Leukocytes
Platelets
Endothelium
Smooth muscle

Source: Cancer Control © 2007 H. Lee Moffitt Cancer Center and Research Institute, Inc.
Alternative Therapy for Inflammation

Mechanical or chemical Injury

- Green tea
  - Turmeric
    - PGH synthase, Cyclooxygenase-1, Cyclooxygenase-2
    - Phospholipase C
    - Free Arachidonic Acid
      - Prostaglandins (PGG-2 & PGH-2)
        - Thromboxanes (Pain)
      - Leukotrienes (Cytokines)
        - Vascular permeability and Pain
          - PGF-2, PGE-2, PGD-2
            - Vasodilatation, Erythema, edema, pain, fever
            - Prostacyclin PGI-2
              - Platelet aggregation
              - Free Radical Production

- White Willow Bark
  - Phospholipase A2
  - Lipoxygenase
    - Ginger
    - Boswellia

Source: Cancer Control © 2007 H. Lee Moffitt Cancer Center and Research Institute, Inc.
Classical pathway of NF-κB activation

TNF-α

- IkB-α
- p50
- p65
- IkB kinases (IKK)
- P
- P
- Proteasome

Nucleus
- mRNA
- IkB-α

Cytoplasm
- Apoptosis regulators
  - Fas, BCL-2, c-Flip, caspases
- Chemokines
  - MCP-1, IL8, RANTES
- Cytokines
  - IL1, IL2, IL2R, IL6
- Receptors
  - TLR2, TLR4, TLR9, CD40, GPR89
- Rel/NF-κB family
  - IkB-α, p105, p100, RelB
- Growth factors
  - G-CSF, GM-CSF
- Adhesion molecules
  - ICAM-1, VCAM-1, ECAM-1, P-selectin
Natural Medicines for Pain

- **Turmeric**: 400-600 mg TID (NF-kB, COX-1, COX-2 inhibitor)
  - Standardized to 95% curcuminoids - increased bioavailability with bioperine (black pepper)
  - Can cause gastric upset at high doses

- **Omega 3 fatty acids**: 2 grams BID (DHA/EPA inhibit 5-LOX and convert COX to prostaglandin E3)
  - Risk of bleeding increases > 6 g daily

- **White Willow Bark**: 240 mg daily (salicin)
  - Avoid in children (risk of Reye’s syndrome)
  - Avoid in peptic ulcer disease (bleeding risk)

- **Boswellia**: 300 mg TID (5-LOX inhibitor)
  - Standardized to 30-40% boswellic acids
  - Can cause nausea, reflux, diarrhea
https://naturalmedicines.therapeuticresearch.com/
Low Dose Naltrexone

- Several studies suggest benefit for chronic pain as an anti-inflammatory agent in the CNS acting via microglial cells
- Small pilot studies have shown positive effects for complex regional pain syndrome, Crohn’s disease, multiple sclerosis, cancer-related pain, fibromyalgia

Dig Dis Sci. 2011 July; 56(7): 2088–2097
Low Dose Naltrexone

- Off label use - NOT FDA approved
- Available only through compounding pharmacies, not covered by insurance - $30-50/month
- Well tolerated, no common drug interactions, no withdrawal risk, no abuse potential
Low Dose Naltrexone

- 0.5 - 4.5 mg taken at bedtime
- May titrate dose up by 0.5 - 1 mg every 2 weeks until optimal dose is identified
- Most common side effects are mild:
  - Vivid dreams (tend to decrease over time)
  - Sleep disturbance
  - Headaches (rare)
  - Anxiety (rare)
Pharmacogenetics

● “Personalized pain medicine”

● Growing interest among both patients and practitioners wanting to:
  ○ Avoid ineffective drugs
  ○ Improve patient compliance
  ○ Reduce adverse side effects

● Growing popularity of direct to consumer genetic testing
  -23andme.com
Pharmacogenetics

Genes involved in the pain genome:
- COMT: catechol-o-methyltransferase
- OPRM1: mu-opioid receptor

Genes involved in drug metabolism:
- Cytochrome p450 genes
  - CYP2D6 - conversion of codeine to morphine
  - CYP2C19 - citalopram, barbiturates, diazepam
  - CYP2C9 - NSAID metabolism
Pharmacogenetics

- COMT haplotypes in TMJ:
  - TMD and fibromyalgia patients showed a dysregulation of β-adrenergic activity which contributed to altered catecholamine and pain responses, with improvement on IV beta blockers (*J Pain*. 2009;10:542–52)
  - Those **without** COMT high activity haplotype reported better pain relief with propranolol 20 mg BID (*Pharmacogenet Genomics*. 2010 Apr; 20(4):239-48.)
Pharmacogenetics

● CYP2D6 and opiates:
  ○ 4 phenotypes: poor, intermediate, extensive, and ultrarapid metabolizers
    ■ Ultrarapid metabolizers may require higher doses
    ■ Poor metabolizers are at risk for drug-related toxicity at lower doses
  ○ Ultrametabolizers do not respond to methadone therapy (*Drug Alcohol Depend. 2007 Jul 10;89(2-3): 190-4), but may respond favorably to buprenorphine (metabolized through CYP3A4, CYP2C8)

● CYP2C9 and NSAIDs:
  ○ 2 common alleles (*2 and *3) contribute to prolonged action and increase risk of acute GI bleed secondary to NSAID use (*Gastroenterology. 2007 Aug; 133(2):465-71*)
Pharmacogenetics

- Several commercial tests available to predict genetic response to pain medications.
- One common panel analyzes OPRM1, 5 CYP genes, COMT, MTHFR - Medicaid and Medicare coverage available, but not for commercial insurance.
### Opioids

<table>
<thead>
<tr>
<th>Use as Directed</th>
<th>Moderate Gene-Drug Interaction</th>
<th>Significant Gene-Drug Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine (Butrans®)</td>
<td>Meperidine (Demerol®) 1</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine/naloxone (Suboxone®)</td>
<td>Naltrexone (Revia®, Vivitrol®) 4</td>
<td></td>
</tr>
<tr>
<td>Codeine (Codeine Contin®)</td>
<td>Fentanyl (Duragesic®)</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone (Vicodin®)</td>
<td>Methadone (Dolophine®)</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid®)</td>
<td>Morphine (Avinza®)</td>
<td></td>
</tr>
<tr>
<td>Methadone (Dolophine®)</td>
<td>Oxycodone (OxyContin®)</td>
<td></td>
</tr>
<tr>
<td>Oxycodone (OxyContin®)</td>
<td>Oxymorphone (Opana®)</td>
<td></td>
</tr>
<tr>
<td>Tapentadol (Nucynta®)</td>
<td>Tramadol (Ultram®)</td>
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</tbody>
</table>

### Non-Opioids

<table>
<thead>
<tr>
<th>Use as Directed</th>
<th>Moderate Gene-Drug Interaction</th>
<th>Significant Gene-Drug Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carisoprodol (Soma®)</td>
<td>Celecoxib (Celebrex®) 1</td>
<td></td>
</tr>
<tr>
<td>Ketorolac (Toradol®)</td>
<td>Diclofenac (Voltaren®)</td>
<td></td>
</tr>
<tr>
<td>Naproxen (Aleve®, Naprosyn®)</td>
<td>Ibuprofen (Advil®, Motrin®) 1</td>
<td></td>
</tr>
<tr>
<td>Meloxicam (Mobic®)</td>
<td>Cyclobenzaprine (Flexeril®) 2.7</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical Considerations

1. Serum level of the active compound may be too high, lower doses may be required.
2. Serum level of the active compound may be too low, higher doses may be required.
3. Genotype may impact drug mechanism of action and result in reduced efficacy.
4. Serum level may be too low in smokers.

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### Patient Genotypes and Phenotypes

**Pharmacodynamic Genes**

**OPRM1**

A/A

This patient does not carry the 118A>G mutation and may be expected to experience normal analgesia with standard opioid doses.

**Pharmacokinetic Genes**

**CYP1A2**

-163C-A - A/A, 5347C-T - T/T

This genotype is most consistent with the ultrarapid metabolizer phenotype. This patient may have increased enzyme activity as compared to individuals with the normal phenotype.

**CYP2B6**

*1/*6

CYP2B6*1 allele enzyme activity: Normal
CYP2B6*6 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

**CYP2C19**

q1/q1

CYP2C19*1 allele enzyme activity: Normal
CYP2C19*1 allele enzyme activity: Increased

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

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**CYP2C9**

Intermediate Metabolizer

**CYP3A4**

-1/*1

**CYP3A4** allele enzyme activity: Normal
**CYP3A4** allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

**CYP2D6**

Extensive (Normal) Metabolizer

**CYP2D6** allele enzyme activity: Increased
**CYP2D6** allele enzyme activity: Reduced

This genotype is most consistent with the extensive (normal) metabolizer phenotype.
Functional Medicine

→ Opportunities for further learning:
  ◆ Institute for Functional Medicine
  ◆ Functionalmedicine.org
  ◆ E-courses available for AMA Category 1 CME
  ◆ 2 year certification program
Contact Info:

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