FUNCTIONAL MEDICINE
Continuing Education

Chronic Pain Cases

A Functional Medicine Approach for Fibromyalgia, Neuropathy and OA/DJD

Frank Bodnar, DC, MS

@thenutrientfix

Frank.Bodnar.dc@gmail.com

Disclosures

- Dr. Bodnar is affiliated with Ortho Molecular Products. CEImpact has taken appropriate action for conflict resolution, including external peer review.

Objectives

- Discuss natural product mechanisms of action for addressing pain and inflammation.
- Recommend appropriate dietary interventions to address pain and inflammation.
- Determine when to incorporate nutrient supplementation alongside dietary approaches.

Polling Question

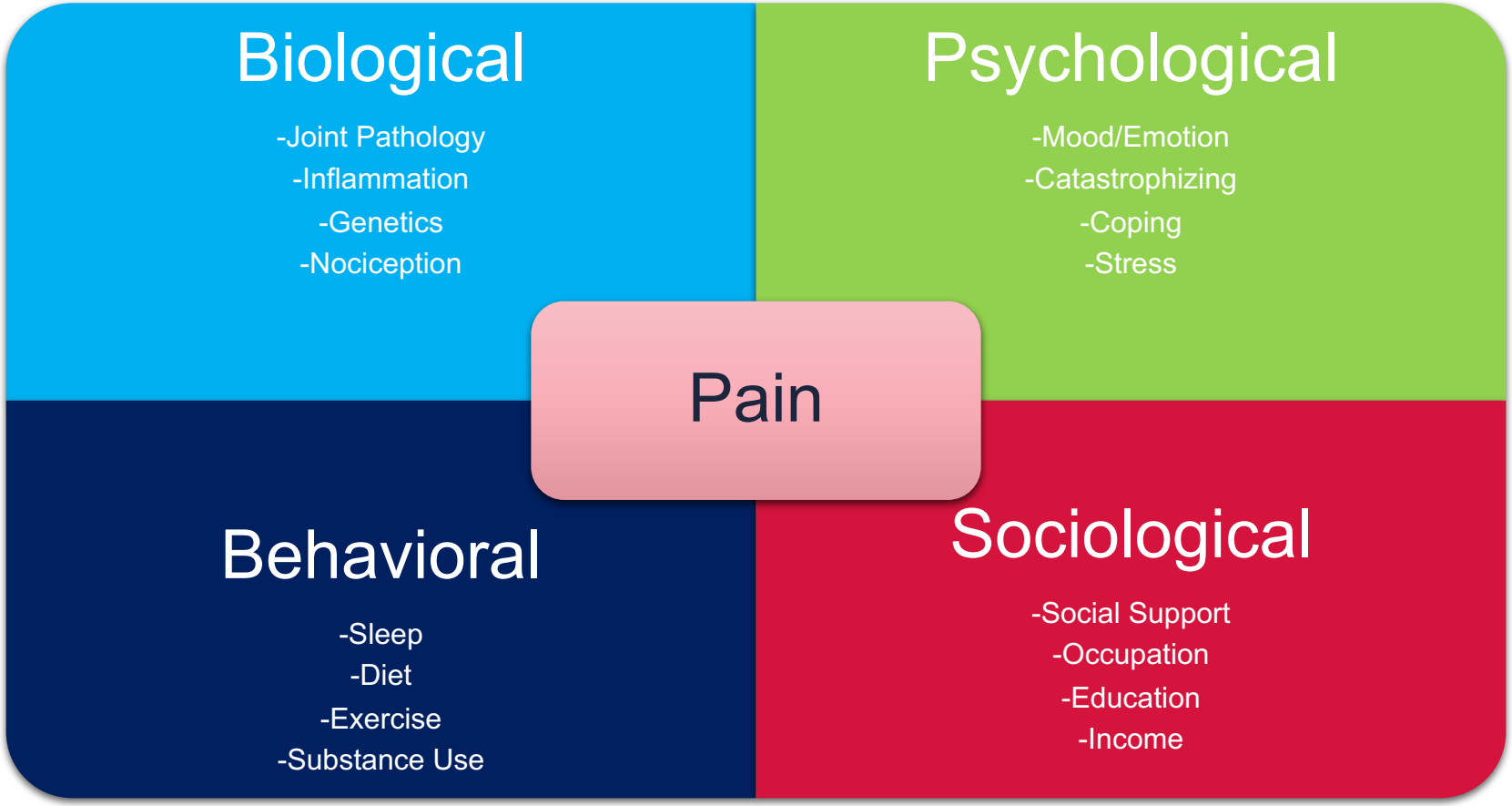
- What has your experience been thus far with treating pain patients from a Functional Medicine perspective?

The State of Pain

- Pain is a Problem[1]
  - 126 million US adults reported some pain in the previous 3-4 months
  - About 30% of those reported moderate to severe pain
  - 25.3 million (11.2%) reporting daily chronic pain
  - 39.5 million adults report facing pain on all or nearly all days. (>10% US pop.)
- High proportion of primary care visits involve (at least in part) management of chronic pain.
  - Over half are musculoskeletal in nature
- Over 49,000 deaths due opioids in 2017[2]
  - Now more likely to die from opioid overdose than a motor vehicle accident
  - Decline in prescriptions and deaths since 2017, however still a big problem

1. CDC. NCHS Statcast. 2019; September 11.
2. Dahlhamer J et al. CDC MMWR Weekly. 2016; 67(36);1001–1006.

Biopsychosocial Model = Highly Individual



What is Pain?

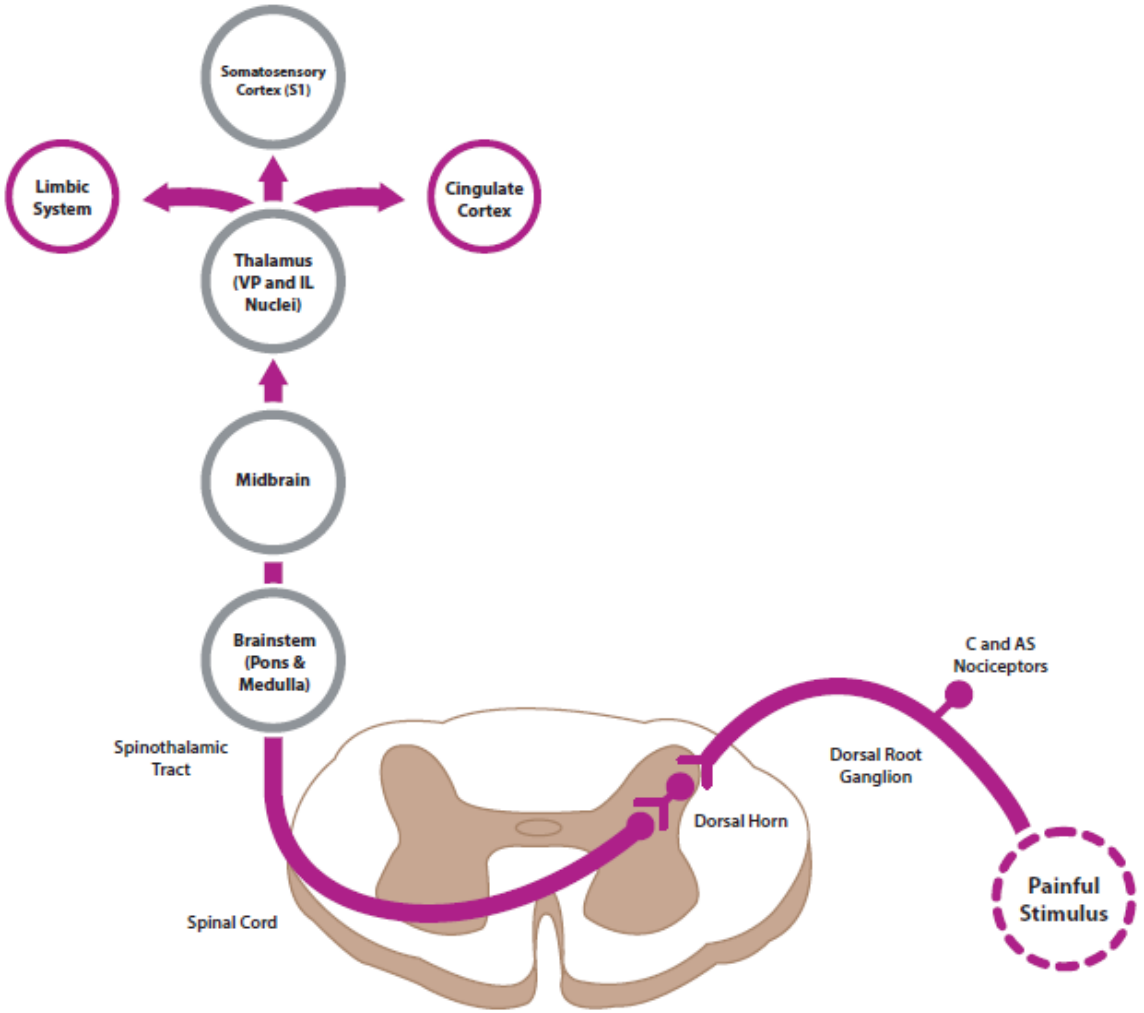
Pain" is defined by the International Association for the Study of Pain (IASP) as:

“An unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage”

4 Recognized Types of Pain Categories

- Nociceptive
- Inflammatory
- Neuropathic
- Functional

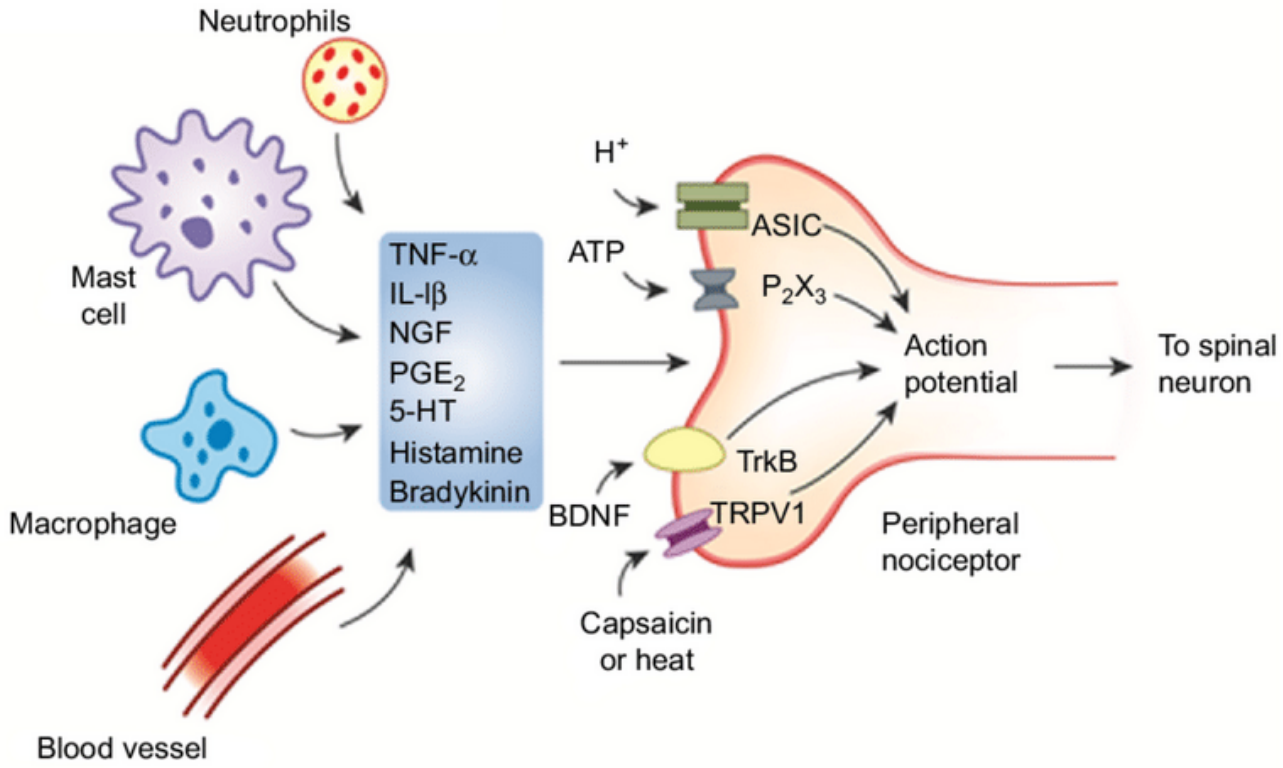
Acute Pain


Somatosensory Cortex (S1)
Limbic System
Cingulate Cortex
Thalamus (VP and IL Nuclei)
Midbrain
Brainstem (Pons & Medulla)
Spinothalamic Tract
C and AS Nociceptors
Dorsal Root Ganglion
Dorsal Horn
Painful Stimulus
Spinal Cord

ACUTE VS. CHRONIC PAIN

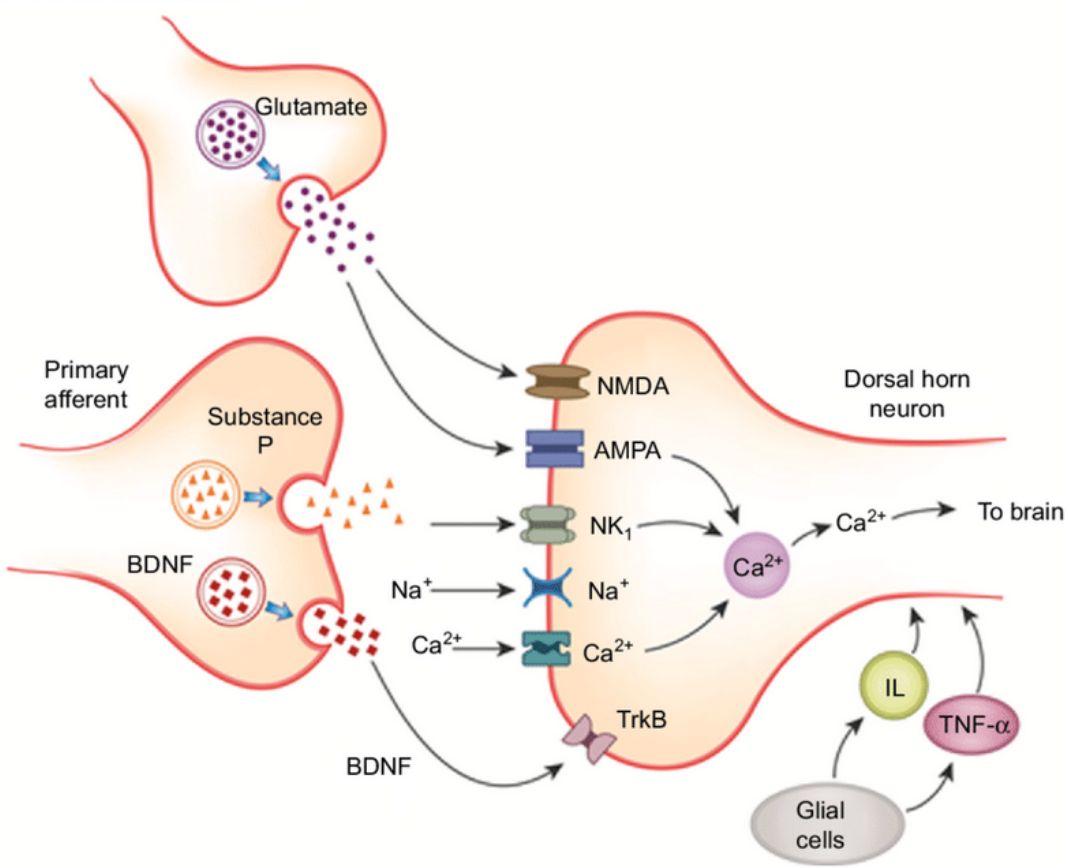
	Acute Pain	Chronic Pain
Duration	Time-limited	Lasts for more than 3-6 months
Intensity	Often intense	Varies in intensity from mild to excruciating
Location	One area of the body	One area or multiple areas of the body
Function	Has survival value; warns of danger and harm	Has no survival value; no longer warns of immediate danger
Cause	Biological mechanisms of acute pain are well-understood	Mechanisms of persistent pain are not well-understood
Emotional response	Associated with anxiety and fear	Form of chronic stress
Treatment	Cure is common	Cure is not common
Role of activity & exercise	Rest is often best for acute pain	Activity balanced with rest is best for chronic pain
Role of health care provider(s)	Diagnose and treat	Teach and advise
Role of person with pain	Follow treatment advice	Partner in health care responsible for daily management

Peripheral Sensitization



Dureja G et al. *Journal Of Pain Research*, 2017;(*10*), 709-736.

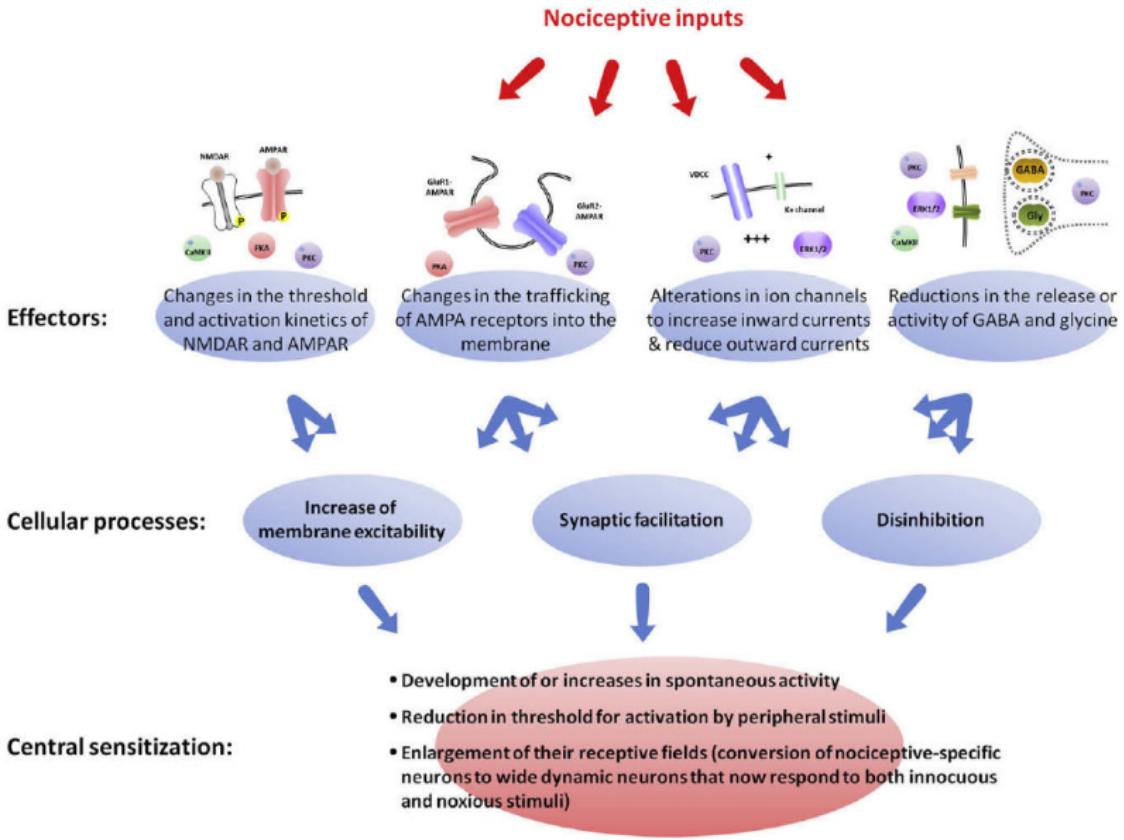
Central Sensitization



Dureja G et al. *Journal Of Pain Research*, 2017;(*10*), 709-736.

FUNCTIONAL MEDICINE
Continuing Education

Chronic Pain Mechanisms (Functional)



Latremoliere A, Woolf C.et al. *The Journal of Pain*, 2009;10 (*9*), 895-926.

FUNCTIONAL MEDICINE
Continuing Education

What is true about Pain?

Polling Question

- With a basic understanding of some key differences between Acute and Chronic pain, how does this change your approach with Chronic pain patients?

Fibromyalgia Overview

- October 1, 2015 ICD-10 M79.7 officially a diagnosis
- Women account for more than 75-85% of Fibromyalgia patients
- Peak Incidence: ages 20 to 60 years old
  - Incidence increases with age
- Most common rheumatic cause of chronic diffuse pain
  - Most common cause of Chronic Pain in women ages 20 to 55 years old

Fibromyalgia Overview

- **Pathophysiology**
  - Increased central sensitivity to peripheral sensation (as with other functional pain syndromes)
  - Pain system dysfunction related to abnormalities in the forebrain
- **Risk Factors**
  - Post-Traumatic Stress Disorder (present in up to 45% of Fibromyalgia patients)
  - Sexual abuse or rape, Care-taker
- **Associated Conditions: Common Comorbid Chronic Conditions: Rheumatic, Endocrine, Neurologic**
  - Rheumatoid Arthritis
  - Osteoarthritis
  - Lyme Disease
  - Sleep Apnea

Case Study: Fibromyalgia

- 49yo female, BMI 29, recently divorced, Dx with FM 7 years prior by rheumatologist
  - Rx: duloxetine (SSRI), pregabalin, gabapentin and occasional OTC acetaminophen
- Presents with widespread diffuse pain in upper back, shoulders, neck and hips bilaterally pain is 8/10 VAS
  - *"It hurts all over"*
- Mild but constant bloating, occasional diarrhea with stress
- Previous history of occasional migraine HAs
- Frequent periods of unexplained anxiety, brain fog, dizziness and fatigue, intermittent bouts lasting a week, no trigger identified
- Stopped exercising due to knee pain, shoulder pain and excess soreness
- Sleep is frequently disrupted, waking up 3-4x's per night
- *"I'll give you 6 months to get me better."*

Past Traditional Assessment

- Hx and Physical Exam
  - No neurological deficits, BP high (142/92), vitals WNL, normal reflexes
  - 14/18 trigger point sites, weak muscle strength extremities but equal bilaterally
- Previous Labs:
  - CBC with differential: WNL
    - No indication of infection, anemia, bleeding/clotting disorders, cirrhosis
  - ESR (chronic) / hs-CRP (acute):
    - both elevated over last 6 years, no success lowering with anti-inflammatory meds
  - CCP Antibody: negative
  - RF: negative
  - Thyroid function tests (TSH): WNL
  - ANA (lupus): negative

Functional Assessment

- Physical Exam
  - Gait, posture, shoe wear pattern, paraspinal palpation, respiratory patterns
  - HRV, Sleep quality (wearable tech)
  - Social and Family Support
- Further Lab Testing Considerations – Order of Most Common
  - IBS (most common comorbidity)
    - SIBO / Intestinal hyperpermeability?
    - Gluten and Dairy sensitivities?
  - Key Nutrient deficiencies: B-vitamins, Zinc, Vitamin D, Mg+, Essential Amino Acids, 5-HT*
  - Thyroid/HPA-axis: commonly associated with low HPA-axis function, lesser degree thyroid association
  - Common Detoxification and Energy Production Pathways
    - Mycotoxins?
    - Mercury toxicity?
    - MTHFR and CYP450 mutations?
    - Glutathione?
    - Mitochondrial dysfunction?
  - Genomic SNPs – MTHFR, **COMT**, TNF-α, and APOE?

Testing: Organic Acids/Nutrient Panel and CAR

- Clinical questions we needed answered:
  - Is there excessive growth of bacteria/fungi in the gut?
  - Is mitochondrial energy production dysfunctional?
  - Functional nutrient needs present?
  - Undue toxic load/Detoxification capacity?
- Organic Acids in Urine, Whole Blood, RBC, Plasma:
  - Metabolic Analysis (organic acids in urine)
    - Malabsorption and Dysbiosis Markers
    - Mitochondrial and Cellular Energy Metabolites
    - Neurotransmitter Metabolites
    - Vitamin Markers

Testing Continued - CAR

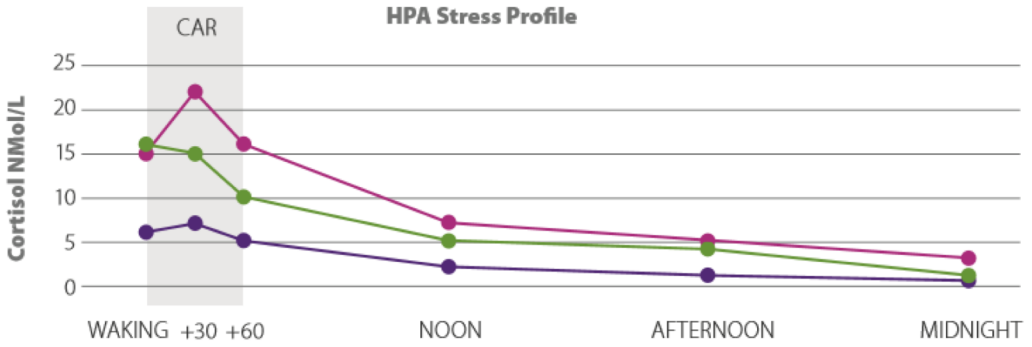
- Nutrient Panel – Continued:
  - Essential and Metabolic Fatty Acids (RBC):
    - omega 3,6,9,7 and ratios
  - Oxidative Stress / Elements (whole blood, urine, plasma):
    - toxins, detox pathways
- Cortisol Awakening Response (salivary): HPA-axis
  - 3 awakening samples and 1 evening sample

Lab Results

- Bacterial Dysbiosis – need for Probiotics
  - H – 4-Hydroxyphenylacetic Acid
- Mitochondrial Dysfunction – need for energy support: Mg, B-vitamins, Zn, Mn
  - H – Lactic Acid
  - H – Pyruvic Acid
  - H – α-Ketoglutaric Acid
  - H – Malic Acid
- Neurotransmitter Metabolites – Tryptophan
  - L – 5-OH-indoleacetic Acid (5-HIAA) = low serotonin production
  - H – Kynurenic Acid = oxidative stress
- B-Vitamin Markers – need energy, serotonin and Histamine biosynthesis
  - H – Isovalerylglycine = B2
  - H – Xanthurenic Acid = B3,B6
- Detoxification Pathway – need for antioxidant support
  - L – Pyroglutamic Acid = oxidative stress, Phase II detox support

Lab Results

- Urine Amino Acid Analysis
  - L – Histidine, Isoleucine, Tryptophan, Alanine, Glutamine = Serotonin, B-Vitamin, Histamine, BCAA and Skeletal Muscle Catabolism, Detoxification and GI barrier function
  - H - α-Amnoadipic Acid = Tryptophan and lysine catabolism
  - H – 3-Methylhisidine = methylated histidine means increased muscle/protein breakdown
- Essential and Metabolic Fatty Acids:
  - low EPA, DPA, DHA and elevated AA/EPA ratio = pro-inflammatory eicosanoids and cytokines
- Elemental Markers:
  - no heavy metal toxicity, low zinc
- CAR: low AM pattern, moderate elevation PM
  - Future considerations: Diurnal Test is Sx persist
    - Glycemic dysregulation
    - Advanced thyroid testing
    - Advanced GI testing/infection



FUNCTIONAL MEDICINE
Continuing Education

Treatment Protocol

- Chiropractic and Acupuncture 2x/week and decreasing PRN
- Sleep and gratitude journals – weekly check-in with health coach
- Gut Healing Diet:
  - Started with a 2-Day fast for a quick reset, meal plans and shopping list for first month
  - Eliminated: gluten, most dairy (yogurt), all grains, processed/packaged foods and added sugars/sweeteners
  - Added: collagen peptides, glutamine (beef, chicken), nuts, seeds, green smoothies (cabbage, kale, spinach), and used maple syrup and honey as sweeteners if needed

Controlled Clinical Trial › Altern Ther Health Med, 17 (2), 36-44 Mar-Apr 2011

A Program Consisting of a Phytonutrient-Rich Medical Food and an Elimination Diet Ameliorated Fibromyalgia Symptoms and Promoted Toxic-Element Detoxification in a Pilot Trial

Joseph J Lamb [1], Veera R Konda, David W Quig, Anura Bouillon, Jyh-Lurn Chang, Alex Hsi, Robert H Lerman, Ja
Affiliations + expand
PMID: 21717823

Abstract

Background: An effective treatment for fibromyalgia (F

Objective: To assess the efficacy ofa lifestyle program supplemental medical food on clinical symptoms of FM Questionnaire (FIQ), FibroQuest Symptoms Survey (Fibr (MSQ), metallothionein mRNA expression, and urinary

Methods: Eight women (aged 48-74 years) were enrol sequential design. During the initial 4-week Program A Department of Agriculture food pyramid diet and a ric basic macronutrient support. During the second 4-wee consumed a modified elimination diet and a phytonutr

Results: Compared to baseline, both programs showe MSQ total score, and FibroQuest total score, FIQ stiffn Compared to Program A, Program B resulted in a sign and stiffness score. Participants also had better pain tc than during Program A. Higher metallothionein mRNA increase in creatinine-adjusted mercury excretion and s arsenic excretion were noted when Program B was con concentrations were inversely associated with FIQand F

Conclusions: Program B was shown to be a safe and treatment program for the amelioration of FM sympto

Review › J Nutr Metab, 2015, 760689 2015

Modulation of Metabolic Detoxification Using Foods and Food-Derived Compon Scientific Review With Clinical Applicat

Romilly E Hodges [1], Deanna M Minich [2]
Affiliations + expand
PMID: 26167297 PMCID: PMC4488002 DOI: 10.1155/2015/760689

Abstract

Research into human biotransformation and elimination systems continues tc and in vivo studies have been undertaken to evaluate the effects of foods an components on the activity of detoxification pathways, including phase I cyto phase II conjugation enzymes, Nrf2 signaling, and metallothionein. This revie research in this area to date, highlighting the potential for foods and nutrient modulate detoxification functions. Clinical applications to alter detoxification improve patient outcomes are considered, drawing on the growing understa between detoxification functions and different disease states, genetic polymc nutrient interactions. Some caution is recommended, however, due to the limitations of current research as well as indications that many nutrients exert biphasic, dose-dependent effects and that genetic polymorphisms may alter outcomes. A whole-foods approach may, therefore, be prudent.

Review › Biomed Pharmacother, 103, 531-538 Jul 2018

Fibromyalgia and Nutrition: Therapeutic Possibilities?

Geir Bjørklund [1], Maryam Dadar [2], Salvatore Chirumbolo [3], Jan Aaseth [4]
Affiliations + expand
PMID: 29677539 DOI: 10.1016/j.biopha.2018.04.056

Abstract

Fibromyalgia (FM) is a complex chronic condition of unknown etiology, characterized by deep and widespread pain, sleep problems, cognitive impairment, fatigue, and other well-known functional symptoms. Recently, it has been proposed that an imbalance of nutritive components, including essential metal ions and vitamins, might play a critical role in the development of FM. Muscle pain has been associated with deficiencies in amino acids, magnesium, selenium, vitamins B and D, as well as with the harmful effects of heavy metals, such as mercury, cadmium, and lead. Research indicates that patients deficient in certain essential nutrients may develop dysfunction of pain inhibitory mechanisms together with fatigue and other FM symptoms. Additionally, mercury and other toxic elements may interfere with the bioavailability of essential nutrients. This review examines the many effects of metals and vitamins in pain evaluation of FM patients. Dietary guidance is therefore critical for FM patients to help them in correcting a suboptimal or deficient intake of essential nutrients. When optimal levels of nutrition are achieved, pain levels are usually lowered. Additional research is recommended in the field of FM and nutrition to disclose further possible relationships.

Nutrient Protocol

- 6-Months:
  - Combo Nutrients (daily):
    - Micronutrient blend supporting NT production: 5-HT, L-Theanine, GABA
    - Complete Turmeric Matrix (660mg), quercetin (240mg), rutin (50mg), bromelain (240mg)
    - GABA (250mg), Glycine (225mg), and muscle-relaxing herbs Cramp bark (200mg) and Dong Quai (150mg)
    - High quality multivitamin Pack: B-Vitamins (methylated folate), Zinc (10mg), EPA+DHA+DPA (950mg), Broccoli Seed Extract, Resveratrol, *Andrographis paniculata*
  - Single Nutrients:
    - Vitamin D3 (5,000 IU / 125 mcg per day)
    - Magnesium (glycinate) 470mg/day
    - 5-HTP 300 mg/day
    - Recommended 225 billion CFU product but patient did not comply

Review › PLoS One, 12 (4), e0176631 2017 Apr 28 eCollection 2017

Vitamin and Mineral Status in Chronic Fatigue Syndrome and Fibromyalgia Syndrome: A Systematic Review and Meta-Analysis

Monica L Joustra [1], Isidor Minovic [2 3], Karin A M Janssens [1], Stephan Rosmalen [1]

Affiliations + expand

PMID: 28453534 PMCID: PMC5409455 DOI: 10.1371/journal.pone.017

Abstract

Background: Many chronic fatigue syndrome (CFS) and fibromyalgia sy (35-68%) use nutritional supplements, while it is unclear whether deficie contribute to symptoms in these patients. Objectives were (1) to determ in CFS and FMS patients as compared to healthy controls; (2) to investig vitamin and mineral status and clinical parameters, including symptom s (3) to determine the effect of supplementation on clinical parameters.

Methods: The databases PubMed, EMBASE, Web of Knowledge, and P eligible studies. Articles published from January 1st 1994 for CFS patien till March 1st 2017 were included. Articles were included if the status of minerals were reported, or an intervention concerning vitamins or mine reviewers independently extracted data and assessed the risk of bias.

Results: A total of 5 RCTs and 40 observational studies were included i which 27 studies were included in the meta-analyses. Circulating concen in patients compared to controls (pooled standardized mean difference -0.05; p = .042). However, this difference was not present when restricti subgroup of studies with high quality scores. Poor study quality and a s most studies was found. No vitamins or minerals have been repeatedly parameters. In addition, RCTs testing supplements containing these vita result in clinical improvements.

Discussion: Little evidence was found to support the hypothesis that vitamin and mineral deficiencies play a role in the pathophysiology of CFS and FMS, and that the use of supplements is effective in these patients.

Review › Nutrients, 8 (6) 2016 Jun 4

Vitamin D in Fibromyalgia: A Causa Confounding Biological Interplay?

Spyridon Karras [1], Eleni Rapti [2], Stauros Matsoukas [3], Kalliopi Kot

Affiliations + expand

PMID: 27271665 PMCID: PMC4924184 DOI: 10.3390/nu8060343

Abstract

Fibromyalgia (FM) is a chronic syndrome with an increasing prevale musculoskeletal pain in combination with a variety of cognitive symp scientific evidence that has accumulated during the last decades, res of the understanding of the pathophysiology of the disease. Howev in patients with FM remains a multidimensional approach including therapy, exercise, pain management, and relief of chronic symptom therapies, based on the mechanisms of disease development. Vitam mainly from skin synthesis through ultraviolet radiation, has been re extraskeletal actions, apart from its fundamental role in skeletal and modulation of cell growth, neuromuscular actions, and potential ant findings indicate that hypovitaminosis D to be highly prevalent in pa studies are limited so far, indicating potential beneficial effects on p however specific recommendations are lacking. This review aims to data regarding the pathophysiological interplay between vitamin D observational and supplementation studies so far, with a clinical dis and future research agenda.

Randomized Controlled Trial › Antioxid Redox Signal, 20 (8), 1169-80 2014 Mar 10

NLRP3 Inflammasome Is Activated in Fibromyalgia: The Effect of Coenzyme Q10

Mario D Cordero [1], Elísabet Alcocer-Gómez, Ognjen Culic, Angel M Carrión, Manuel de Miguel, Eduardo Díaz-Parrado, Eva M Pérez-Villegas, Pedro Bullón, Maurizio Battino, José Antonio Sánchez-Alcazar

Affiliations + expand

PMID: 23886272 PMCID: PMC3934515 DOI: 10.1089/ars.2013.5198

Abstract

Aims: Fibromyalgia (FM) is a prevalent chronic pain syndrome characterized by generalized hyperalgesia associated with a wide spectrum of symptoms such as fatigue and joint stiffness. Diagnosis of FM is difficult due to the lack of reliable diagnostic biomarkers, while treatment is largely inadequate. We have investigated the role of coenzyme Q10 (CoQ10) deficiency and mitochondrial dysfunction in inflammasome activation in blood cells from FM patients, and in vitro and in vivo CoQ10 deficiency models.

Results: Mitochondrial dysfunction was accompanied by increased protein expression of interleukin (IL)-1β, NLRP3 (NOD-like receptor family, pyrin domain containing 3) and caspase-1 activation, and an increase of serum levels of proinflammatory cytokines (IL-1β and IL-18). CoQ10 deficiency induced by p-aminobenzoate treatment in blood mononuclear cells and mice showed NLRP3 inflammasome activation with marked algesia. A placebo-controlled trial of CoQ10 in FM patients has shown a reduced NLRP3 inflammasome activation and IL-1β and IL-18 serum levels.

Innovation: These results show an important role for the NLRP3 inflammasome in the pathogenesis of FM, and the capacity of CoQ10 in the control of inflammasome.

Conclusion: These findings provide new insights into the pathogenesis of FM and suggest that NLRP3 inflammasome inhibition represents a new therapeutic intervention for the disease.

First Month

- First week – felt terrible
  - Very tired, very bad migraine and pain 8/10 all week
  - Stopped taking pregabalin on own accord
  - Acid reflux gone (within 1 week) – never mentioned during exam or consult ☺
  - Less gas, less bloating, less frequent diarrhea
- Second week
  - Felt more energy, slightly less pain 6/10 on average
  - Tolerated chiro and acupuncture but said it was very painful
  - Completed gratitude journal, sleep back to where it was previously
- Fourth week
  - No reflux, no diarrhea, still occasional bloating
  - No headaches the past 2 weeks, pain 6/10
  - Energy and mood felt much better, best week of sleep she's had in years
  - Started going for walks
  - Chiro care still painful but feels like it is helping keep her active

2-Month Follow Up

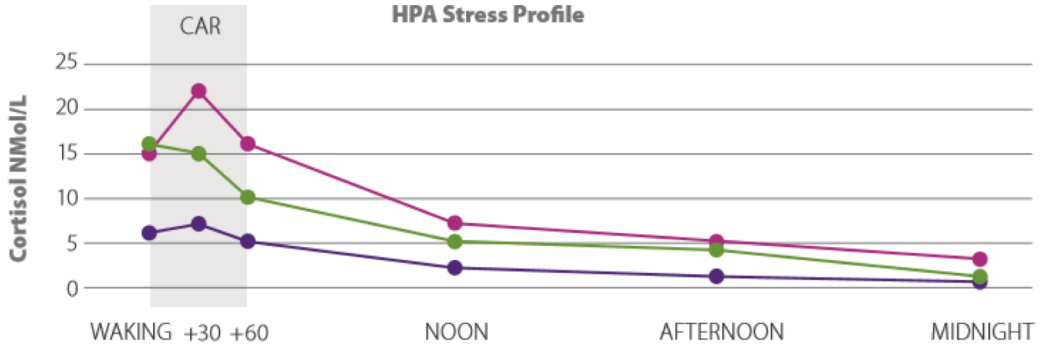
- Bloating, diarrhea and reflux once per week
- Pain is 4/10 on average
- One migraine HA over last month
- Walking at least 20 minutes 4x/week
- Still getting dizzy – referred to Rheumatologist regarding medication
- Fatigue and brain fog are improved, still has occasional anxiety
- Occasionally wakes up around 2-3am, but able to fall back asleep
- Protocol remained the same
- Hired health coach for diet accountability

4-Month Follow Up

- Occasional bloating, no diarrhea or reflux in last month
- Pain is still 4/10 on average
- No migraine HAs over last 2 months
- Dizziness and anxiety has improved since taken off gabapentin
- Fatigue is also improving and has been walking 4-5x/day with the warmer weather
- Sleep is about the same
- Monthly chiro and acupuncture to help manage muscle soreness
- Protocol and coaching remained the same

6-Month Follow Up

- Pain is 3/10 on average and very surprised with no migraine HAs in last 4 months
- Still has 11/18 trigger points but much less tender
- Would like to get off duloxetine
- Energy has improved still occasionally fatigued, she joined a fitness class 3x/week, happy with sleep quality
- Monthly chiro and acupuncture to help manage muscle soreness, treatments are very tolerable
- BMI 26
- Labs
  - hs-CRP – normal
  - Triglycerides, LDL and HDL improved
  - CAR: increased AM, decreased PM pattern



Long-term Maintenance

- Continue maintenance chiro/acupuncture
- Continue to work with health coach for diet adherence to address GI Sx
- Discuss duloxetine options with prescribing physician
- Nutraceuticals:
  - Combo Nutrients (daily):
    - Micronutrient blend supporting NT production: 5-HT, L-Theanine, GABA
    - Complete Turmeric Matrix (660mg), quercetin (240mg), rutin (50mg), bromelain (240mg)
    - High quality multivitamin Pack: B-Vitamins (methylated folate), Zinc (10mg), EPA+DHA+DPA (950mg), Broccoli Seed Extract, Resveratrol, *Andrographis paniculata*
  - Single Nutrients:
    - Vitamin D3 (5,000 IU / 125 mcg per day)
    - Magnesium (glycinate) 470mg/day
    - 100 billion CFU probiotic

Which of the following is true about Fibromyalgia?

Question

- What is one assessment or treatment strategy you'll be implementing with your Fibromyalgia patients?
  - Type your answer in the chat box!

Diabetic Neuropathy Overview

- CDC – 1/3 of US population will be Diabetic by 2050
- Chronic complications of Diabetes
  - Microvascular (hyperglycemia – retina, kidneys, peripheral nerves) and macrovascular (accelerated atherosclerosis) damage
  - Insulin resistance / Hyperglycemia
    - HbA_{1C} - full RBC lifecycle (120 days) = ideally < 7%
    - Fasting blood glucose: 70-100 mg/dL
  - Co-morbidities
- Up to 50% of diabetics overall have peripheral neuropathy clinically, and up to 80% of those who have had the disease for more than 15 years. Affects both peripheral and autonomic nerves
- Higher association with greater abdominal adiposity
- Most common pattern: ***distal symmetric polyneuropathy*** **of the lower extremities that affects both motor and sensory function** (glove and stocking patterns, foot and wrist drop, bladder and bowel dysfunction, ED)
  - balance, loss of pain sensation, paresthesia

Primary Mechanisms of Diabetic Neuropathy

1. **Formation of Advanced Glycation End Products (AGEs) accelerated**
   - AGE receptors on T cells and macrophages, endothelial and vascular smooth muscle cells = trigger inflammation, generate ROS, procoagulants, (+) ECM and muscle cell proliferation
   - AGEs cross-link ECM proteins decreasing elasticity, encourages protein build up, and enhances LDL deposition in vessel wall
2. **Activation of Protein Kinase C (PKC)** = procoagulant vascular actions
3. **Oxidative Stress** = increased intracellular glucose in nerves, blood vessels, lenses of eye and kidney (do not require insulin) uses up NADPH, also cofactor for glutathione reductase activity thereby limiting GSH regeneration
   - Primary mechanism of cataract formation
4. **Hexosamine Pathway**: Fructose-6-Phosphate Generation – excess proteoglycans, TGFβ and end-organ damage

Case Study: Peripheral Diabetic Neuropathy

- 82yo male, Type 2 Diabetes (15 years) – Dx with peripheral neuropathy 6 years ago, hypercholesteremia (25 years). Diabetes continues to progress.
  - Rx: statin (25 years), metformin (10 years) and insulin (7 years) – 50 units/day
  - Rx Celebrex and gabapentin – mild relief
  - Frequent OTC ibuprofen
- Presents with constant pain in both anterior-lateral thighs 7/10, worsening balance issues, similar pain now in both shoulders
- Very limited ADLs – must use can or walker to walk, stopped driving, and noted he gets very tired when walking having to stop every 20 yards to rest
- Intense brain fog, forgetfulness
- *"Wants a different approach. He isn't progressing even after following doctor's orders after all these years."*

First Office Visit

- Physical exam, orthopedic evaluation
  - Biomechanical dysfunctions in sacroiliac joints, lumbar spine, cervico-thoracic region
  - Hypertonic pectoralis, upper traps and suboccipital muscles
  - Forward head posture - excessive thoracic kyphosis, anteriorly rounded shoulders and obvious decreases in shoulder range-of-motion (ROM) bilaterally
  - Sensory: two-point discrimination failed in feet
  - Oral cavity showed geographic tongue – suggests yeast overgrowth
  - Palpation of liver – tender and slightly enlarged suggesting inflamed

Initial Lab Assessment

Lab Value	Normal	Abnormal	Units	Reference Range
Hemoglobin (Hgb)		11.8	g/dL	Male: 13.8 - 17.2 Female: 12.1 - 15.1
MCV		77.8	fL	80-95
RDW		17.9	%	11.5-14.5
HDL	48		mg/dL	High >= 60 Low <= 39
LDL		138	mg/dL	1 - 99
Triglyceride		230	mg/dL	<= 149
Glucose		126	mg/dL	70 to 100
Total Cholesterol	186		mg/dL	<= 199
HbA1c		9.2% (217)	% and mg/dL	4% = 68 (normal) 5.7% = 117 (pre-diabetic) 6.5% = 139 (diabetes) 14% = 355 (very high)

Treatment Plan: 6-12 months

- Chiropractic care:
  - 3x/week
- Strict Paleo Diet (no cheat days):
  - Low carb
  - Nutrient dense
  - High fiber
  - Higher good fats
- Nutrient Protocol

Nutrient	Dose	MOA
Coenzyme Q10 (CoQ10)	300 mg /day for 60 days	Antioxidant that is essential for ATP production via electron transport chain; also activates AMPK, reduces hsCRP, balances blood sugar and repletes CoQ10 levels via enhancing HMG-CoA reductase activity that is depleted from statin therapy
N-acetyl Cysteine	600 mg /day for 60 days	Increases production of glutathione, providing systemic oxidation support
Alpha Lipoic Acid	200 mg /day for 60 days	Recycles and recharges other antioxidants and minimizes oxidative damage
Acetyl L-carnitine	500 mg /day for 60 days	Increases medium chain fatty acid oxidation and mitochondrial energy production
L-Glutathione	250 mg /day for 60 days	Intracellular antioxidant, detoxification (phase II), regenerates vitamin E

Nutrient Protocol Continued

Nutrient	Dose	MOA
Complete Turmeric Matrix (Standardized to contain 45-55% Curcuminoids, 3-8% Volatile Oil, 2-6% Turmerin Protein)	500-1,000 mg /day for 60 days	Curcumin's NFkB-modulation decreasing cytokine production and provides anti-inflammatory and antioxidant support
Bromelain	240 mg (560 GDU) /day for 60 days	Protease that inhibits inflammation by modulating leukocyte activation, PGE2 activation and inhibiting bradykinin synthesis.
Quercetin and Rutin	240 mg /day and 50 mg /day for 60 days	Modulates diamine oxidase and prevents mast cell degranulation, decreasing histamine release and the inflammatory cascade. Also act as potent antioxidants and protect connective tissue from degradation
trans-Resveratrol (from Plygonum cuspidatum (Roots))	10 mg /dayfor 60 days	Polyphenol that has shown antioxidant that reduces lipid peroxidation, anti-inflammatory activity of COX-1, COX-2 and has been shown to reduce CRP
Broccoli Seed Extract (Standardized to contain 13% Glucoraphanin)	40 mg /dayfor 60 days	Sulforaphane that shows antioxidant activity via Nrf2 modulation, increasing glutathione, and boosting cytochrome P450 and detoxification activity
Berberine Hydrochloride Hydrate	1 g /day for 60 days	Alkaloid that activates AMP kinase (AMPK), which regulates blood sugar and blood lipids; also inhibits chronic inflammation by modulating NFkB and decreasing IL-1 and TNFa, and exhibits antioxidant activity via increased superoxide dismutase activity
Chromium (as O-polynicotinate)	200 mcg /day for 60 days	Niacin-bound mineral that enhances insulin sensitivity, glucose tolerance and plays a role in appetite control

Progression: Months 1-6

- Key Notes / Milestones
  - Patient discontinued statin on own accord – did not notify physician
  - Signs of liver inflammation still present, however no rebound tenderness on palpation
  - Brain fog, energy and geographic tongue improved, but still present
  - Walking distance improved, still slow but without walker, physically shoulders still painful and posture still needs improvement however upper back tension improved – less tender
    - Began rotator cuff exercises – gained strength, reduced pain
  - 2-Point Discrimination improved in lower extremities
  - Pain improved to 3/10 VAS – stopped ibuprofen use, was able to reduce gabapentin and reduce Celebrex use
  - Overall nutrition (diet/supplements) adherence was great, with help of daughter
  - Endocrinologist removed insulin Rx, remains on lower dose of metformin

Follow Up Labs: 6 Months

Lab Value	Normal	Abnormal	Units	Reference Range
Hemoglobin (Hgb)	14.2		g/dL	Male: 13.8 - 17.2 Female: 12.1 - 15.1
MCV	82		fL	80-95
RDW	11.6		%	11.5-14.5
HDL	48		mg/dL	High >= 60 Low <= 39
LDL	65		mg/dL	1 - 99
Triglyceride	165		mg/dL	<= 149
Glucose		126	mg/dL	70 to 100
Total Cholesterol	186		mg/dL	<= 199
HbA1c		6.5% (139)	% and mg/dL	4% = 68 (normal) 5.7% = 117 (pre-diabetic) 6.5% = 139 (diabetes) 14% = 355 (very high)

Review › Singapore Med J, 57 (2), 55-9 Feb 2016

Vitamin B Supplementation for Diabetic Peripheral Neuropathy

Bhavani Jayabalan [1], Lian Leng Low [2]
Affiliations + expand
PMID: 26892473 PMCID: PMC4759374 [

Abstract

Vitamin B12 deficiency has been associate
peripheral neuropathy. This review aims to
vitamin B12 supplementation for the treatr
and the Cochrane Central Register of Cont
conducted in December 2014. Any type of
assessed for efficacy and safety in diabeti
perception thresholds, neuropathic sympt
effects of vitamin B12 therapy, were asses
criteria. This review found no evidence tha
improvement in the clinical symptoms of c
reported no improvement in the electroph

Review › Cochrane Database Syst Rev, 6 (6), CD011265 2019 Jun 15

Acetyl-L-carnitine for the Treatment of Diabetic Peripheral Neuropathy

Luiz Csp Rolim [1], Edina Mk da Silva, Ronald Lg Flumignan, Marcio M A
Affiliations + expand
PMID: 31201734 PMCID: PMC6953387 (available on 2020-06-15)
DOI: 10.1002/14651858.CD011265.pub2

Abstract

Background: Diabetic peripheral neuropathy (DPN) is a common and
50% of people with diabetes. Painful DPN is reported to occur in 16%
A complete and comprehensive management strategy for the preventi
whether painful or not, has not yet been defined.Research into treatme
characterised by a series of failed clinical trials, with few noteworthy ac
peripheral nerve regeneration and restore neurological function in pec
are needed. The amino acid acetyl-L-carnitine (ALC) plays a role in the
into mitochondria for β-oxidation. ALC supplementation also induces n
neurotrophic effects in the peripheral nervous system. Therefore, ALC
mechanisms relevant to potential nerve repair and regeneration, and c
potential. There is a need for a systematic review of the evidence from

Review › Altern Med Rev, 11 (4), 294-329 Dec 2006

Peripheral Neuropathy: Pathogenic Mechanisms and Alternative Therapies

Kathleen A Head [1]
Affiliations + expand
PMID: 17176168

Abstract

Peripheral neuropathy (PN), associated with diabetes, neurotoxic chemotherapy, human immunodeficiency virus (HIV)/antiretroviral drugs, alcoholism, nutrient deficiencies, heavy metal toxicity, and other etiologies, results in significant morbidity. Conventional pain medications primarily mask symptoms and have significant side effects and addiction profiles. However, a widening body of research indicates alternative medicine may offer significant benefit to this patient population. Alpha-lipoic acid, acetyl-L-carnitine, benfotiamine, methylcobalamin, and topical capsaicin are among the most well-researched alternative options for the treatment of PN. Other potential nutrient or botanical therapies include vitamin E, glutathione, folate, pyridoxine, biotin, myo-inositol, omega-3 and -6 fatty acids, L-arginine, L-glutamine, taurine, N-acetylcysteine, zinc, magnesium, chromium, and St. John's wort. In the realm of physical medicine, acupuncture, magnetic therapy, and yoga have been found to provide benefit. New cutting-edge conventional therapies, including dual-action peptides, may also hold promise.

Which of the following is true about Diabetic Neuropathy?

Question

- What nutrient recommendation will you be offering to your Diabetic Neuropathy patients in the future?
  - Type your answer in the chat box!

Osteoarthritis / DJD Overview

- OA/DJD impacts > 30 million Americans
- A top reason to see physician
- First-line therapies:
  - patient education
  - OTC analgesics (acetaminophen) and anti-inflammatories (NSAIDs)
  - braces/supports, topicals
  - walking or light exercise program
  - weight management or nutrition program
  - referral to a physical therapist or chiropractor - symptom management
- Steroid injection
- Surgery/Joint Replacement

OA/DJD: Whole Joint Failure

- Associated with aging
- More than “wear and tear” of cartilage (1/2 of the story)
  - loss of joint space, cartilage degeneration, osteophytes, loss of mobility and function
- Inflammatory mechanisms:
  - Subchondral bone, synovial membrane and fluid, tendons, muscles, nerves, nociceptor sensitivity, metabolic factors (TIMP/MMP activity)
- Knees, hips, lumbar spine, cervical spine, fingers and toes
- Risk factors:
  - Obesity, joint deformity, diabetes, gout, traumatic injury

Diet and OA Progression / Prevention

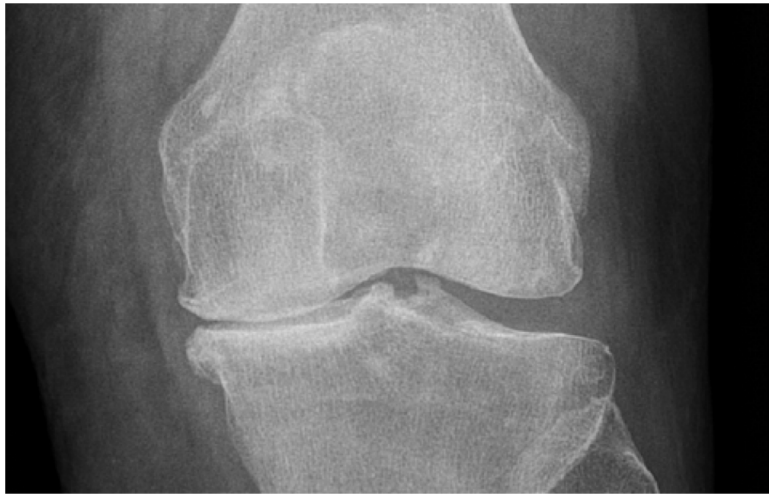
"Adherence to a Western dietary pattern was associated with increased radiographic and symptomatic KOA progression, while following a prudent pattern was associated with reduced progression. In general, for people already diagnosed with KOA, eating a diet rich in fruits, vegetables, fish, whole grains, and legumes may be related to decreased radiographic and symptomatic disease progression."

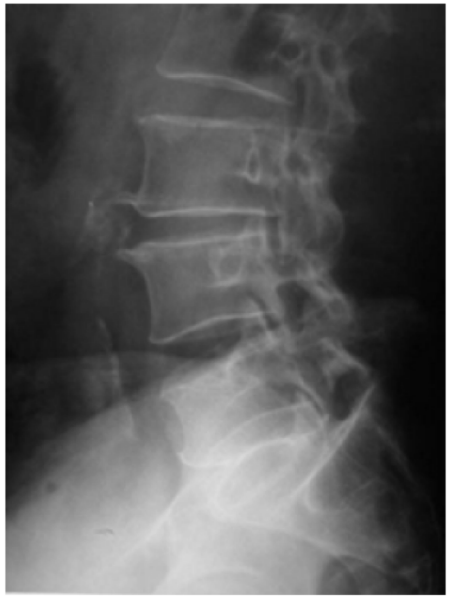
Case Study: Osteoarthritis/DJD

- 70yo male, chronic LBP and knee pain
- Avid runner and track/cross-country coach
- Slipped and fell landing on ice and has pain down leg to his knee that he rates at a 6/10 VAS
  - Saw physical therapists for 4 months with no improvement but continued core exercises and icing over SIJ and knee
  - OTC ibuprofen, helped but has GI issues with medication
- Noted that pain in back is worse with sitting and forward lean
- Reflexes, sensory and motor function all normal
- Has taken anti-inflammatories and analgesics in past with success
- *"I'm concerned the pain is not resolving and want to be able to run again."*

Initial Assessment

- Physical Exam / Orthopedic Exam
  - R Straight Leg Raiser (+): pain down hamstring, not below knee
  - R External rotation painful: glute/hip dysfunction
  - (+) R Kemp's: facet pain
- X-rays:





Differential Diagnosis

- **Lumbar Disc Herniation**
- **OA of Knee / DJD and DDD in Lumbar Spine**
- **SIJ Dysfunction**
- Hamstring Syndrome
- Gluteal Artery Insufficiency
- **Myofascial Pain syndrome due to Piriformis Trigger Points**
- Osteopenic changes

Treatment Plan

- Chiropractic manipulation to lumbar spine and R SIJ
- Cold Laser, K-Tape, IASTM/manual therapy to piriformis
- Glute medius/maximus, quad and groin stabilization exercises
- Patient education on inflammatory mechanisms and diet
- Anti-inflammatory Diet: Mediterranean/Paleo

Nutrient Protocol: Acute/Subacute

Nutrient	Dose	MOA
Complete Turmeric Matrix (Standardized to contain 45-55% Curcuminoids, 3-8% Volatile Oil, 2-6% Turmerin Protein)	500-1,000 mg /day for 60 days	Curcumin's NFkB-modulation decreasing cytokine production and provides anti-inflammatory and antioxidant support
Bromelain	240 mg (560 GDU) /day for 60 days	Protease that inhibits inflammation by modulating leukocyte activation, PGE2 activation and inhibiting bradykinin synthesis.
Quercetin and Rutin	240 mg /day and 50 mg /day for 60 days	Modulates diamine oxidase and prevents mast cell degranulation, decreasing histamine release and the inflammatory cascade. Also act as potent antioxidants and protect connective tissue from degradation

Nutrient Protocol: Long-term Support

Nutrient	Dose	MOA
Omega-3 Fish Oil (triglyceride form) EPA, DHA, DPA	3 g /day continued	Anti-inflammatory effects via COX, LOX, PLA2 inhibition and lowering of inflammatory cytokines and CRP
Glucosamine Sulfate	1,500 mg /day continued	Mucopolysaccharide that increases sulfate levels, inhibits IL-1B, and inhibits MMP enzymes which degrade cartilage. Provides shock-absorbing quality to cartilage and maintains joint space
Chondroitin Sulfate	900 mg /day continued	GAG that reduces IL-1, modulates NF-kB and limits cytokine production overall. Also provides precursors for cushioning and lubricating qualities in joints, helping to maintain range-of-motion and decreases synovial inflammation and joint capsule irritation
Hyaluronic Acid (+precurors and cofactors)	40-80 mg /day continued	Increases hyaluronic acid concentration in synovial fluid and stimulates synoviocytes to increase HA production for joint and connective tissue hydration and lubrication

Treatment Progression: 3 months

- Manual therapy reduced trigger points significantly
- Low back pain 1-2/10 VAS, no pain down hamstring
- Knee pain 1-2/10
- Ran first 5k in 6 months, although not happy with time very happy to be running again
- Noted cholesterol improved at his last doctor's appointment
- Has continued diet on his own and continues to take long-term supplements as he feels that they are helping

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 23, 2006 VOL. 354 NO. 8

Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis

Daniel O. Clegg, M.D., Domenic J. Reda, Ph.D., Crystal L. Harris, Pharm.D., Marguerite A. Klein, M.S., James R. O'Dell, M.D., Michele M. Hooper, M.D., John D. Bradley, M.D., Clifton O. Bingham III, M.D., Michael H. Weisman, M.D., Christopher G. Jackson, M.D., Nancy E. Lane, M.D., John J. Cush, M.D., Larry W. Moreland, M.D., H. Ralph Schumacher, Jr., M.D., Chester V. Oddis, M.D., Frederick Wolfe, M.D., Jerry A. Molitor, M.D., David E. Yocum, M.D., Thomas J. Schnitzer, M.D., Daniel E. Furst, M.D., Allen D. Sawitzke, M.D., Helen Shi, M.S., Kenneth D. Brandt, M.D., Roland W. Moskowitz, M.D., and H. James Williams, M.D.

ABSTRACT

BACKGROUND

Glucosamine and chondroitin sulfate are used to treat osteoarthritis. The multicenter, double-blind, placebo- and celecoxib-controlled Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) evaluated their efficacy and safety as a treatment for knee pain from osteoarthritis.

METHODS

We randomly assigned 1583 patients with symptomatic knee osteoarthritis to receive 1500 mg of glucosamine daily, 1 glucosamine and chondroitin sulfate, 2 weeks. Up to 4000 mg of acetaminoph Assignment was stratified according to vs. moderate to severe [N=354]). The p decrease in knee pain from baseline to

RESULTS

The mean age of the patients was 59 year cosamine and chondroitin sulfate were ducing knee pain by 20 percent. As com (60.1 percent), the rate of response to glu (P=0.30), the rate of response to chondr er (P=0.17), and the rate of response to co higher (P=0.09). The rate of response in t age points higher than that in the plac with moderate-to-severe pain at baseline, er with combined therapy than with place Adverse events were mild, infrequent, a

CONCLUSIONS

Glucosamine and chondroitin sulfate al effectively in the overall group of patier atory analyses suggest that the combin fate may be effective in the subgroup of (ClinicalTrials.gov number, NCT00032

From the University of Utah School of Medicine, Salt Lake City (D.O.C., C.G.J., A.D.S., H.J.W.); the Hines Veterans Affairs Cooperative Studies Program Coordinating Center, Hines, Ill. (D.J.R., H.S.); the Clinical Research Pharmacy Coordinating Center, Albuquerque, N.M. (C.L.H.); the National Center for Com-

Molecules **2015**, *20*, 4277-4289; doi:10.3390/molecules20034277

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Review

Discrepancies in Composition and Biological Effects of Different Formulations of Chondroitin Sulfate

Johanne Martel-Pelletier [1,*], Aina Farran [2], Eulàlia Montell [3], Josep Vergés [3] and Jean-Pierre Pelletier [1]

[1] Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC H2X 0A9, Canada; E-Mail: dr@jppelletier.ca

[2] Unitat de Recerca en Inflamació i Cartílag, Institut Mar d'Investigacions Mèdiques (IMIM)

OPEN ACCESS

EXTENDED REPORT

Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to plac symptomatic knee osteoarthritis: the ChO versus CElecoxib versus Placebo Trial (CO

Jean-Yves Reginster,[1] Jean Dudler,[2] Tomasz Blicharski,[3] Karel Pavell

[1]Department of Public Health, Epidemiology and Health Economics, Liège State University, Liège, Belgium [2]HFR Fribourg, Hôpital Cantonal, Fribourg, Switzerland [3]Lublin Medical University, Åświdnik, Poland [4]Institute of Rheumatology, Charles University, Prague, Czech Republic

Correspondence to Professor Jean-Yves Reginster, Department of Public Health, Epidemiology and Health Economics, Liège State University, Liège, Belgium, Quartier Hôpital – CHU B23, avenue Hippocrate, 13, 4000

ABSTRACT

Objectives Chondroitin sulfate 800 mg/day (CS) pharmaceutical-grade in the management of symptomatic knee osteoarthritis consistent with the European Medicines Agency guideline.

Methods A prospective, randomised, 6-month, 3-arm, double-blind, double-dummy, placebo and celecoxib (200 mg/day)-controlled trial assessing changes in pain on a Visual Analogue Scale (VAS) and in the Lequesne Index (LI) as coprimary endpoints. Minimal-Clinically Important Improvement (MCII), Patient-Acceptable Symptoms State (PASS) were used as secondary endpoints.

Results 604 patients (knee osteoarthritis) diagnosed according to American College of Rheumatology (ACR) criteria, recruited in five European countries and followed for 182 days. CS and celecoxib showed a greater

management of knee OA cological and non-phar and numerous scientific recommendations for the n of knee OA.[5–9] Although observed between these ev mostly reflecting heteroger involved, geographical diff of chemical entities [10 11] th general consensus that ana etamol and non-steroidal (NSAIDs) have demonstrat profile when used to treat s However, recent publica challenged the use of parac of symptomatic OA becau and a considerable degree the upper end of the stan Similarly, safety profiles a concern and caution i selecting the preparation Therefore, recent guideli nance therapy to be cond slow-acting drugs for OA drugs that is recognised t safety and tolerability.[5] can be found in the liter mendations on SYSADOA knee OA,[10 11] higher quali provided for patented, p of chondroitin sulfate (CS amine sulfate (GS).[9]

Chondroitin sulfate (CS noglycan composed of cha curonic acid and N-acety is available as pharmaceut tical-grade products, the variations in preparatio as well as clinical effects. explain why, whereas pharmaceutical-grade CS (ie, the 4&6isomer of sodium CS) was shown to improve pain and function and/or delay structural progression of knee OA in several well-conducted

RESEARCH ARTICLE Open Access

Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study

Jean-Pierre Pelletier[1*], Jean-Pierre Raynauld[1,2], André D. Beaulieu[3], Louis Bessette[4], Frédéric Morin[5], Artur J. de Brum-Fernandes[6], Philippe Delorme[7], Marc Dorais[8], Patrice Paiement[7], François Abram[7] and Johanne Martel-Pelletier[1]

Abstract

Background: In osteoarthritis (OA) treatment, although chondroitin sulfate (CS) was found in a number of studies using radiography to have a structure-modifying effect, to date CS use is still under debate. A clinical study using quantitative magnetic resonance imaging (qMRI) is therefore of the utmost importance. Here we report data from a 24-month, randomised, double-blind, double-dummy, controlled, comparative exploratory study of knee OA. The primary endpoint was to determine the effect of CS 1200 mg/day versus celecoxib 200 mg/day on cartilage volume loss (CVL) in the lateral compartment over time as measured by qMRI. Secondary endpoints included assessment of the OA structural changes and signs and symptoms of OA.

Methods: qMRI was performed at baseline and at 12 and 24 months. CVL, bone marrow lesion size, and synovial thickness were evaluated using qMRI. The primary statistical analysis was carried out on the modified intention-to-treat (mITT) population ($n = 138$) using chi-squared, Fisher's exact, Wilcoxon Mann–Whitney, and Student's t tests and analysis of covariance. Analyses were also conducted on the according-to-protocol (ATP; $n = 120$) population.

Results: In the adjusted mITT analysis, compared with celecoxib treatment, patients treated with CS had a significant reduced CVL at 24 months in the medial compartment (celecoxib −8.1 % ± 4.2, CS −6.3 % ± 3.2; $p = 0.018$) and medial condyle (−7.7 % ± 4.7, −5.5 % ± 3.9; $p = 0.008$); no significant effect was seen in the lateral compartment. In the ATP population, CS reduced CVL in the medial compartment at 12 months (celecoxib −5.6 % ± 3.0, CS −4.5 % ± 2.6; $p = 0.049$) and 24 months (celecoxib −8.4 % ± 4.2, CS −6.6 % ± 3.3; $p = 0.021$), and in the medial condyle at 24 months (celecoxib −8.1 % ± 4.7, CS −5.7 % ± 4.0; $p = 0.010$). A trend towards a statistically reduced synovial thickness (celecoxib +17.96 ± 33.73 mm, CS −0.66 ± 22.72 mm; $p = 0.076$) in the medial suprapatellar bursa was observed in CS patients. Both groups experienced a marked reduction in the incidence of patients with joint swelling/effusion and in symptoms over time. Data showed similar good safety profiles including cardiovascular adverse events for both drugs.

Conclusion: This study demonstrated, for the first time in a 2-year randomised controlled trial using qMRI, the superiority of CS over celecoxib at reducing CVL in knee OA patients.

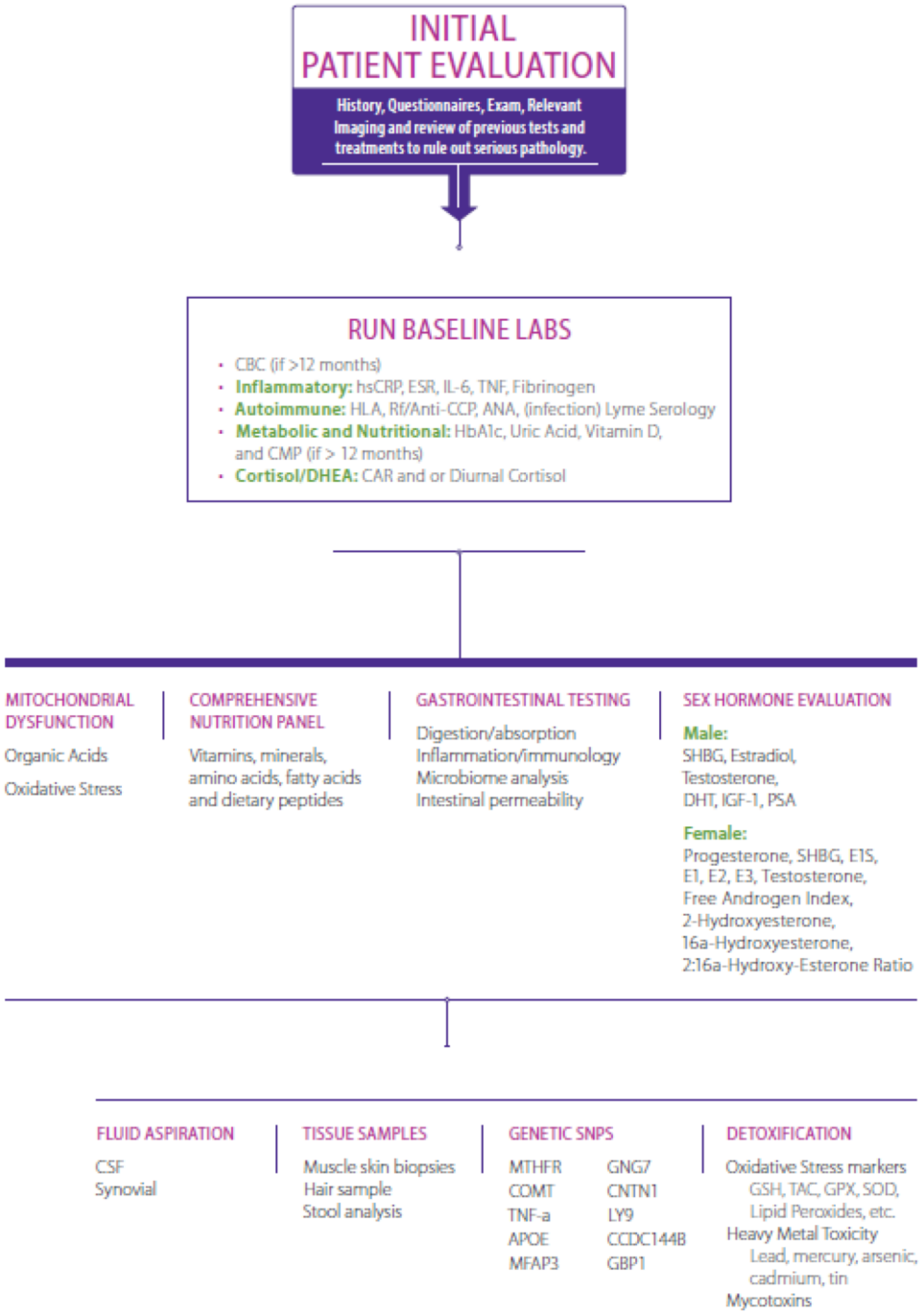
Trial registration: ClinicalTrials.gov NCT01354145. Registered 13 May 2011.

Keywords: Chondroitin sulfate, Symptomatic slow-acting drug in osteoarthritis, Osteoarthritis, Knee, Celecoxib

Which of the following is true about Osteoarthritis?

Question

- What is one way your dialogue with OA patients will change in the future?
  - Type your answer in the chat box!

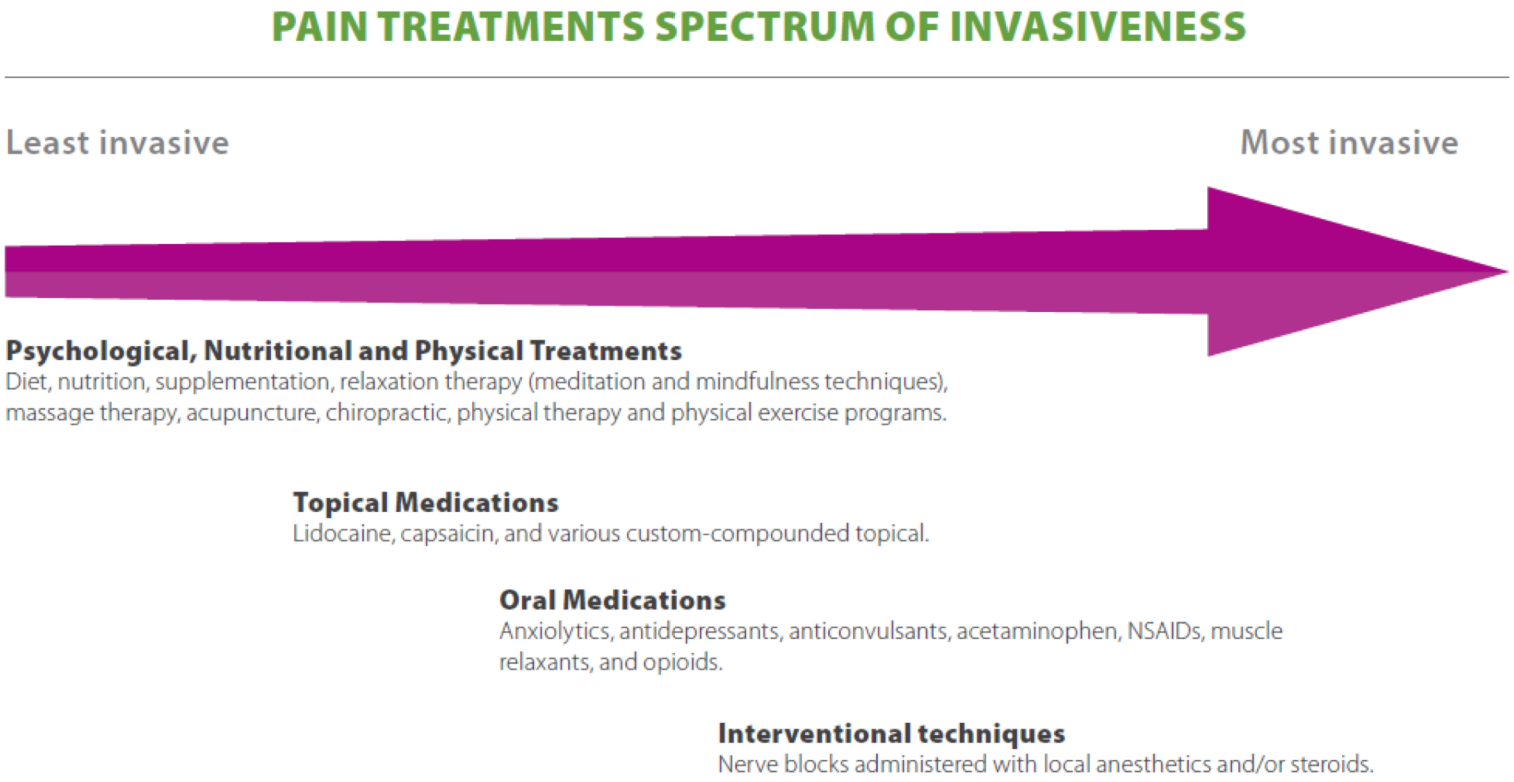


Testing for Pain?

- Chronic Pain Decision Tree:

1. Initial Evaluation
2. Baseline Labs
3. Functional Labs
4. Further Testing

Treating Pain: *"First Do No Harm"*



Drug-Induced Side Effects and Nutrient Depletions

Nerve / Pain Drug Class	Side Effects		Nutrient Depletion
NSAIDs	• GI bleeding – especially with stomach ulcers, older than 65, or on blood thinners or corticosteroids (prednisone) • Increased risk of heart attack and stroke • Reversible kidney damage		• Glutathione • Vitamin b12 • Folic acid (vitamin b9) • Vitamin c • Iron • Sodium
Acetaminophen	• Serious liver damage at high doses • Liver damage when combined with alcohol		• Glutathione • Vitamin b12 • Folic acid • Vitamin c
Opioids / Narcotics	• Risk of misuse and abuse, addiction, overdose, and death. • Common side effects include drowsiness, dizziness, nausea, vomiting, constipation, and slowed or difficult breathing. • Can interact with antidepressants and migraine medicines.	• Risks increase if taking opioids along with benzodiazepines (medicines for anxiety, insomnia and seizers) or other central nervous system depressant medicines, including alcohol. • May cause respiratory depression that in some cases can lead to death.	• Addiction and abuse is highly associated with nutritional deficiency and poor dietary choices.
Muscle relaxants (benzodiazepines)	• Drowsiness • Impaired breathing		• Melatonin
Anti-anxiety (hydroxyzine, beta-receptor blockers)	• Dizziness • Drowsiness • Blurred vision	• Dry mouth • Stomach upset • Headache	• Potassium • Vitamin b6 • Coq10 • Melatonin
Antidepressants (tricyclics, SNRIs, SSRIs)	• Drowsiness • Nausea • Dry mouth	• Dizziness • Reduced sexual desire or difficulty reaching orgasm or inability to maintain an erection (erectile	• Folic acid (vitamin b9) • Melatonin

Drug-Induced Side Effects and Nutrient Depletions

Tendon / Arthritis Drug Class	Side Effects	Nutrient Depletion
NSAIDs	• GI bleeding – especially with stomach ulcers, older than 65, or on blood thinners or corticosteroids (prednisone) • Increased risk of heart attack and stroke • Reversible kidney damage	• Glutathione • Vitamin B12 • Folic acid (B9) • Vitamin C • Iron • Sodium
Acetaminophen	• Serious liver damage at high doses • Liver damage when combined with alcohol	• Glutathione • Vitamin B12 • Folic acid • Vitamin C
Corticosteroids	• Increased appetite, weight gain • Sudden mood swings • Muscle weakness • Blurred vision • Increased growth of body hair • Easy bruising • Lower resistance to infection • Swollen, "puffy" face • Acne • Osteoporosis (bone weakening) • Worsening of diabetes • High blood pressure • Stomach irritation • Nervousness, restlessness • Having difficulty sleeping • Cataracts or glaucoma • Water retention, swelling	• Calcium • Chromium • Magnesium • Vitamin D • Zinc • Selenium • Strontium
Fluoroquinolones (antibiotic)[83]	• Inflamed or torn tendon • Muscle and joint pain • Nerve pain • Walking difficulty • Pins and needles • Tiredness • Depression • Memory • Sleep • Vision and hearing • Altered taste and smell	• Calcium • Magnesium • Potassium • Thiamine (B1) • Riboflavin (B2) • Niacin (B3) • Pantothenic acid (B5) • Pyridoxine (B6) • Folic acid (B9) • Vitamin K
Disease-modifying antirheumatic drugs (DMARDs/Biologics) (prescribed for RA)	• Nausea, vomiting, or diarrhea • Liver enzyme elevation • Increased risk of infection • Lower white blood cell counts • Lower red blood cell counts (anemia)	• Niacin (B3) • Vitamin K

Osteoporosis Drug Class	Side Effects	Nutrient Depletion
Bisphosphonates	• nausea • difficulty swallowing • heartburn • irritation of the esophagus • gastric ulcer • flu-like symptoms • fever • headache • pain in muscles or joints • rare reports of osteonecrosis of the jaw	• Calcium • Magnesium • Phosphorus
Estrogenic Agents (Premarin)	• stomach upset or cramps • nausea • vomiting • bloating • breast tenderness or swelling • headache • weight or appetite changes • freckles or darkening of facial skin • increased hair growth • loss of scalp hair • vaginal itching or discharge • changes in your menstrual periods • decreased sex drive • nervousness • dizziness • tired feeling	• Vitamin B6 • Vitamin C • Zinc • Vitamin A • Vitamin D • Folic Acid • Vitamin B_{12}
SERMs	• abnormal vaginal bleeding or discharge • pain or pressure in the pelvis • leg swelling or tenderness • chest pain • shortness of breath • weakness, tingling, or numbness in your face, arm, or leg • sudden difficulty seeing • dizziness • sudden severe headache	• Unknown drug-induced nutrient deficiencies, but should supplement with vitamin D, calcium and magnesium
Corticosteroids[173]	• long-term use increases risk of osteoporosis and fracture • See complete list in connective tissue chart • Depression • Memory • Sleep • Vision and hearing • Altered taste and smell	• Calcium • Chromium • Magnesium • Vitamin D • Zinc • Selenium • Strontium
Proton Pump Inhibitors[163]	• Long-term use increases risk of osteoporosis and fracture • headache • nausea • vomiting • diarrhea • stomach pain • gas • constipation • fever • cold symptoms (stuffy nose, sneezing, and sore throat)	• Folic acid[164] • Beta-carotene • Chromium • Vitamin C • Iron • Zinc • Vitamin B_{12} • Magnesium • Calcium
Calcitonin	• runny nose • nose bleeds • nasal irritation • dry nose with crusting • headache • dizziness • nausea • vomiting • loss of appetite • stomach pain	• Calcium recommended as support nutrient • No known nutrient depletions
Parathyroid Hormone (PTH)	• muscle cramps or spasms • leg cramps • joint pain • cough • sore throat • runny nose • headache • neck pain • nausea • constipation • diarrhea	• Phosphorus

FUNCTIONAL MEDICINE
Continuing Education

Take-Aways

1. Mitochondrial dysfunction is commonly overlooked in chronic pain
   - Look for fatigue, depression and amplified or hypersensitive pain responses
   - Poor response to traditional anti-inflammatory and opioid medications
2. The gut is a common source of chronic inflammation
   - Intestinal permeability, poor absorption, poor detoxification
   - Source of neuroinflammation
   - Start with the gut – AIP Diet
3. HPA-axis function gives us a snap-shot of the healing potential in pain patients
   - Slow healing, poor sleep, hormone imbalances
   - CAR test as initial assessment in functional chronic pain